

CAFFEINE-LOADED MEDICATED CHEWING GUM: A Critical Review of Formulation Variables, Quality Evaluation, and In-Vitro Drug Release

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Abstract—Medicated chewing gum is an oral drug-delivery system in which an active pharmaceutical ingredient is released from a gum matrix during mastication. Caffeine is a methyl xanthine stimulant associated with temporary improvements in wakefulness and selected aspects of attention. Incorporating caffeine into chewing gum may offer a convenient dosage form, but formulation development requires control of drug distribution, bitterness, excipient compatibility, mechanical properties, content uniformity, release behavior and stability. This narrative review discusses the pharmaceutical principles of caffeine-loaded medicated chewing gum, including formulation components, manufacturing approaches, quality evaluation and in-vitro drug-release testing. The available literature on caffeine gum is considered alongside broader research on medicated chewing-gum technology and caffeine pharmacology. The review emphasizes that in-vitro release, systemic exposure and clinical effects are distinct outcomes. A formulation with acceptable laboratory release cannot be assumed to improve alertness without appropriate pharmacokinetic and clinical evidence. Important research priorities include reproducible release methods, validated analytical procedures, acceptable taste, batch consistency and the relationship between formulation attributes and human outcomes. This review provides a foundation for Pharmacy students studying the formulation and evaluation of caffeine-loaded medicated chewing gum

Keywords— Caffeine; medicated chewing gum; formulation development; quality evaluation; in-vitro drug release; oral drug delivery.

I. INTRODUCTION

Oral drug delivery is widely used because it is convenient, familiar and suitable for many active pharmaceutical ingredients. Conventional forms include tablets, capsules, solutions and suspensions. Alternative dosage forms are also investigated to address administration preferences, product performance and patient acceptability. Medicated chewing gum is a solid dosage form in which an active ingredient is incorporated into a gum base and released during chewing. The released drug mixes with saliva and may be absorbed through the oral mucosa or swallowed and absorbed from the gastrointestinal tract [1,2].

Caffeine is a methyl xanthine compound with central nervous system stimulant activity. It is also used in functional and pharmaceutical goods and is ingested in beverages. Its effects can include increased wakefulness and temporary improvement in selected attention-related outcomes, although responses vary with dose, habitual intake, sleep status and individual sensitivity [3,4].

Caffeine-containing gum combines a familiar chewable format with the potential for drug release during mastication. However, incorporation of caffeine into a gum base does not automatically produce a suitable dosage form. The formulation must provide consistent drug content, acceptable taste and texture, reproducible release and adequate stability. The testing method must also distinguish drug released under laboratory conditions from drug absorbed by a person.

An experimental study by Aslani and Jalilian provides a direct starting point for research on caffeine chewing-gum formulation and evaluation [1]. Broader reviews describe the formulation components, manufacturing approaches and

quality tests used for medicated chewing gum [2]. This review focuses on formulation variables, quality evaluation and in-vitro release, while considering the limits of evidence related to alertness.

II. REVIEW METHODOLOGY

This manuscript is structured as a narrative review of literature on caffeine chewing gum, medicated chewing-gum technology, pharmaceutical evaluation and caffeine pharmacology. Relevant records can be searched in PubMed, Google Scholar, Europe PMC and publisher websites using combinations of the terms “caffeine chewing gum,” “medicated chewing gum,” “formulation and evaluation,” “drug release,” “content uniformity,” “taste masking,” “caffeine pharmacokinetics” and “alertness.”

Original experimental studies are important for specific formulation procedures and measured outcomes. Review articles provide broader context, while pharmacokinetic and clinical studies address systemic exposure and human performance. These different sorts of proof address various concerns and should not be considered interchangeable.

Before submission, the student should complete and document the actual database searches, search dates, full search strings, eligibility criteria, screening process and number of papers included. Search counts must not be invented. If the work is intended to be a systematic review, the methods and reporting should be expanded in accordance with PRISMA 2020; otherwise, it should be accurately described as a narrative review.

III. CAFFEINE: RELEVANT PROPERTIES AND PHARMACOLOGY

3.1 Physicochemical properties

Caffeine has the molecular formula $C_8H_{10}N_4O_2$ and a molecular mass of approximately 194.19 g/mol [3]. Its solubility, particle characteristics and distribution within the gum matrix are relevant to formulation performance. The drug must be incorporated consistently and remain compatible with the selected excipients and processing conditions. Caffeine has a bitter taste, making sensory acceptability a formulation consideration. Sweeteners and flavouring agents may help mask bitterness, but their effects on texture, stability and release should also be assessed.

3.2 Pharmacological relevance to alertness

Caffeine's central effects are primarily associated with antagonism of adenosine receptors. Adenosine signalling contributes to sleep pressure and reduced neuronal activity; receptor antagonism by caffeine can temporarily increase wakefulness and influence attention [3,4]. The magnitude of effect varies among individuals and depends on factors such as dose, habitual caffeine use, sleep deprivation, sensitivity and the task being assessed.

Studies of caffeine gum have investigated outcomes such as mood and attention [5]. Such findings may support the rationale for studying this dosage form, but they do not establish that every gum formulation produces the same effect. Clinical claims should be tied to the dose, formulation and outcomes actually studied.

IV. MEDICATED CHEWING GUM AS A DRUG-DELIVERY SYSTEM

4.1 Principle of drug release

During mastication, the gum matrix is repeatedly deformed and exposed to saliva. Drug can move from the gum matrix into saliva, dissolve or disperse, and become available for absorption. A portion may cross the oral mucosa, while another portion may be swallowed and absorbed through the gastrointestinal tract. The relative contribution of these pathways depends on drug properties, formulation design, chewing behaviour and physiological conditions.

4.2 Potential advantages

Possible benefits include portability, waterless administration, an option for those who don't want to take traditional solid dosage forms, and the potential for drug release during chewing. The gum can also be removed when chewing is complete, although this does not reverse drug already released or absorbed. These advantages are product-dependent and do not by themselves demonstrate greater efficacy or safety than other caffeine products.

4.3 Limitations

Drug release may vary with chewing intensity, duration, salivary flow and gum composition. Bitter taste can reduce acceptability, and a gum matrix may retain part of the active ingredient. Mechanical properties must balance elasticity and

chewability with consistent release. Laboratory methods should therefore be sufficiently standardized to support meaningful comparison between formulations [1,2].

V. FORMULATION COMPONENTS

5.1 Active pharmaceutical ingredient

Caffeine is the active ingredient intended to provide the stimulant effect. The selected material should meet appropriate identity and purity requirements. The amount per unit must be justified by the intended use and relevant safety considerations, rather than copied uncritically from another formulation. Uniform distribution is important because a product may have an acceptable average content while individual units differ.

5.2 Gum base

The gum base provides cohesion, elasticity and chewability. Depending on the material, it may contain elastomers, resins, waxes and other permitted constituents. Base composition can influence mixing, mechanical strength, drug retention, release and sensory characteristics. A base that produces a pleasant texture does not necessarily provide optimal release, so mechanical and pharmaceutical performance should be assessed together.

5.3 Sweeteners and flavouring agents

Sweeteners and flavouring agents improve palatability and may reduce the perception of caffeine bitterness. Selection depends on sweetness, flavour profile, compatibility, moisture behaviour, processing requirements and product design. Sensory acceptability should be evaluated using an appropriate method; it should not be inferred from the ingredient list alone.

5.4 Softening agents and other excipients

Softening agents or plasticizers may modify flexibility and mechanical behaviour. Excessive softening can produce a sticky gum, while insufficient flexibility may produce a hard or unpleasant product. Other excipients may be included for a defined processing or stability purpose. Every component should have a justified function, and compatibility with caffeine and the other ingredients should be considered.

Component	Main function	Key consideration
Caffeine	Active pharmaceutical ingredient	Content uniformity and release
Gum base	Matrix, elasticity and chewability	Drug retention and mechanical properties
Sweetener	Palatability	Compatibility and texture
Flavouring agent	Taste and aroma	Acceptability and stability
Softening agent	Flexibility adjustment	Hardness and stickiness
Other excipients	Processing or stability support	Justified purpose and compatibility

VI. MANUFACTURING APPROACHES

6.1 Conventional softening and mixing

Conventional approaches involve conditioning or softening the gum base, incorporating the active ingredient and other excipients, mixing the mass, and forming individual units. Ingredient-addition sequence, temperature, mixing efficiency and conditioning can influence content uniformity and mechanical properties. The procedure should be selected and optimized based on the materials and equipment available. Processing conditions should not be assumed suitable without testing.

6.2 Compression-based approaches

Compression-based approaches may be possible when the selected materials have suitable processing and recovery properties. These methods may offer process-control advantages, but ordinary tablet-manufacturing assumptions cannot automatically be applied to every gum formulation. The final units must be assessed for integrity, texture, uniformity and release.

6.3 Choosing a method

Method selection should consider reproducibility, equipment needs, drug distribution, mechanical quality, release behaviour, cost and scale. For a college project, feasibility within the approved laboratory and the ability to measure product quality reliably are important considerations.

Approach	Potential advantage	Important limitation
Softening and mixing	Flexible ingredient incorporation	Temperature and mixing may affect uniformity
Compression-based processing	Potentially controlled unit formation	Requires suitable material properties
Specialized processing	May improve process control	May require specialized equipment and validation

VII. EVALUATION OF CAFFEINE-LOADED MEDICATED CHEWING GUM

7.1 Appearance and physical characteristics

Appearance, colour, surface consistency and visible defects should be recorded. Unit weight and dimensions may be assessed when relevant. Physical differences can indicate processing inconsistency, but an acceptable appearance does not establish chemical quality or dose uniformity.

7.2 Weight variation

Weight variation assesses differences in mass between units. It is useful for monitoring unit formation, but it cannot replace drug-content testing because equal weights do not guarantee equal caffeine content. The number of units, method and acceptance criteria should be chosen according to an applicable standard or justified protocol.

7.3 Drug content and content uniformity

Drug-content testing estimates the amount of caffeine in a unit. Content uniformity assesses variation among individual units and is important for dose consistency. A suitable

extraction and analytical procedure is required. UV-visible spectrophotometry may be appropriate when matrix interference is adequately controlled; chromatography such as HPLC may be preferred when greater selectivity is needed. The analytical method should be suitable for the intended purpose, with appropriate validation or verification.

7.4 Mechanical properties

Mechanical properties may include hardness, elasticity, cohesiveness, adhesiveness and chewability. Texture analysis can support comparison of formulations prepared with different bases or excipient proportions. Measurements should be interpreted alongside sensory observations and release profiles, since a formulation with acceptable hardness may still have poor taste or release.

7.5 Organoleptic evaluation

Sensory characteristics include taste, aroma, texture, mouthfeel and aftertaste. Caffeine bitterness makes palatability a relevant development challenge. Any evaluation involving human participants should follow applicable institutional ethics requirements and a defined protocol for recruitment, assessment and recording of responses.

7.6 In-vitro drug-release testing

In-vitro release testing measures the amount of caffeine released under defined laboratory conditions. A suitable chewing apparatus or justified simulation may be used to reproduce selected aspects of mastication. The protocol should describe the apparatus, medium, temperature, chewing or agitation conditions, sampling times and analytical method. Results may be expressed as cumulative amount released or percentage of measured content released over time.

The method should be reproducible enough to support comparison. Release data from different studies should not be compared without considering differences in apparatus, medium and experimental conditions. In-vitro release describes laboratory performance; it does not directly establish absorption or clinical effectiveness.

7.7 Stability evaluation

Stability studies assess whether a formulation maintains acceptable quality during storage. Relevant attributes may include caffeine content, appearance, texture, moisture-related changes, sensory properties and release behaviour. Storage parameters and research duration must be selected using the appropriate guidance and the target product. Accelerated results should not be used in isolation to make unsupported shelf-life claims.

Evaluation	Purpose
Appearance	Identifies visible defects
Weight variation	Assesses consistency of unit mass
Drug content	Estimates caffeine amount
Content uniformity	Assesses drug variation between units
Mechanical testing	Evaluates texture and chewability
Organoleptic assessment	Assesses sensory acceptability
In-vitro release	Measures release under defined conditions
Stability studies	Assesses quality during storage

VIII. FACTORS AFFECTING DRUG RELEASE

8.1 Gum-base composition

The gum base may affect partitioning of caffeine between the matrix and saliva. Its structure and elasticity also influence the response to mastication. Different bases can therefore produce different release profiles even when nominal drug content is similar.

8.2 Drug distribution and particle characteristics

Uneven distribution can cause variation in drug content and release between units. Particle characteristics and the incorporation method may affect dispersion and contact with saliva. Appropriate mixing and sampling procedures are needed to investigate these potential sources of variation.

8.3 Salivary conditions and mastication

Salivary volume, composition and flow can influence dissolution and transport of released drug. Chewing frequency, intensity and duration also affect mechanical exposure of the gum to saliva. Laboratory tests should define these variables, while acknowledging that laboratory conditions may not fully represent actual use.

8.4 Excipients and testing method

Excipients are able to modify texture, matrix structure and sensory properties, and may thus influence release. Variations in apparatus, medium, temperature, sampling and analytical methods could also account for differences between published profiles. Formulation effects should not be inferred unless experimental conditions are sufficiently comparable.

IX. PUBLISHED EVIDENCE AND CRITICAL INTERPRETATION

Aslani and Jalilian reported an experimental investigation specifically addressing the design, formulation and evaluation of caffeine chewing gum [1]. This paper serves as a key primary source for a review centred on caffeine-gum formulation. Its formulation design, excipients, preparation method, analytical procedures and results should be extracted directly from the original article before numerical values are included in a comparison table.

Reviews of medicated chewing gum provide broader context for composition, manufacturing, evaluation and factors influencing release [2]. They help identify additional primary sources, but specific experimental findings should be traced to original studies whenever possible.

Human pharmacokinetic studies have examined caffeine administered in chewing gum compared with other dosage forms and have investigated repeated administration [6,7]. Such studies are relevant to systemic exposure, but their results should not be generalized automatically to a new formulation. Caffeine content, formulation composition, chewing conditions and study design must be considered.

Research has also examined effects of caffeine gum on mood and attention [5]. An effect on one measured task does not establish a broad improvement in all cognitive functions. Results should be interpreted according to the population, dose, comparator and outcome measured.

The available literature can differ in gum-base composition, drug content, processing conditions, release apparatus and analytical procedures. These differences limit direct comparisons. In-vitro release, pharmacokinetic exposure and clinical performance should be treated as distinct endpoints, and claims about alertness should be supported by appropriately designed human studies.

Reference	Study type	Relevance to this review
Aslani and Jalilian [1]	Original formulation study	Directly relevant to caffeine-gum formulation and evaluation
Bobe et al. [2]	Review article	General formulation and evaluation principles
Kamimori et al. [6]	Human pharmacokinetic study	Caffeine delivery by gum compared with capsules
Syed et al. [7]	Human pharmacokinetic study	Repeated administration of caffeine gum
Smith [5]	Human experimental study	Attention and mood outcomes

X. FORMULATION CHALLENGES AND RESEARCH GAPS

10.1 Taste masking

Bitterness can limit acceptability. Sweeteners and flavouring agents may improve palatability, but their concentrations and combinations need to be optimized without compromising release, stability or mechanical properties. Sensory outcomes should be measured using a suitable protocol rather than inferred.

10.2 Reproducible release and analytical reliability

Differences in gum composition, drug distribution and mastication can influence release. Standardized laboratory methods and transparent reporting are needed for comparison. A reliable caffeine assay is also essential; matrix interference should be investigated, and the method should be shown to be suitable for the relevant concentration range.

10.3 Connection to clinical performance

Acceptable drug content and in-vitro release do not demonstrate clinical effectiveness. Further work would need to establish whether formulation differences affect pharmacokinetic behaviour and whether any such differences translate into meaningful human outcomes. Human studies require appropriate design and ethical oversight.

10.4 Stability and manufacturing consistency

A useful formulation must maintain quality during storage and show reproducibility between batches. Future studies should connect processing conditions with content uniformity, mechanical properties, release and stability. Manufacturing feasibility, packaging and cost should be considered early in development

XI. FUTURE PERSPECTIVES

Future research should prioritize formulation optimization, reproducible drug release, sensory acceptability and robust analytical procedures. Systematic investigation of gum-base composition and excipient concentrations may identify the variables that most strongly affect performance. Suitable

experimental designs can reduce unnecessary trial-and-error work.

Standardized release testing would improve comparability between studies. Reports should describe apparatus, medium, temperature, chewing conditions, sampling schedule and analytical method in enough detail for the work to be understood and reproduced. Researchers should also examine whether in-vitro differences correspond to meaningful differences in systemic exposure.

Clinical claims should not be inferred from formulation testing alone. In addition, stability, manufacturing reproducibility, packaging and cost should be considered when evaluating the practical value of a formulation.

XII. CONCLUSION

Caffeine-loaded medicated chewing gum is a dosage-form concept that combines the stimulant properties of caffeine with administration through mastication. Successful development depends on appropriate formulation components, a reproducible manufacturing process and reliable quality evaluation. Important attributes include appearance, unit consistency, caffeine content, content uniformity, mechanical properties, sensory acceptability, in-vitro drug release and stability.

Gum-base composition, excipient selection, drug distribution, salivary conditions and mastication may all influence release. Published studies provide a foundation for examining formulation, pharmacokinetics and attention-related outcomes, but pharmaceutical quality, systemic exposure and clinical effectiveness are separate questions requiring different

evidence. Future work should emphasize standardized release testing, analytical reliability, batch consistency and a careful assessment of the relationship between laboratory performance and human outcomes.

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