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Review

Medicated Chewing Gums: Development Challenges and Expansion of SeDeM-MCG-Based Preformulation Screening

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Abstract

Medicated chewing gums (MCGs) are a promising dosage form for systemic and local delivery of active substances; however, their development is complicated by an underdeveloped regulatory framework and the absence of systematic preformulation approaches. In this review, we present a critical analysis of 42 original studies from 2005 to 2026 devoted to the design, technology, and standardization of MCGs. It is shown that pharmacopeial tests, including the "Dissolution" test, exhibit limited predictive ability due to the use of standardized mechanical parameters and buffer media that do not account for the enzymatic activity of saliva, variability of chewing forces, and mucosal adsorption. It was revealed that the choice of manufacturing method (direct compression or melting) determines structural–mechanical properties and release kinetics, with direct compression being preferable for hydrophilic thermolabile compounds and melting favored for lipophilic ones. A reliable in vitro–in vivo correlation is lacking, which is associated with systematic discrepancies in testing conditions. To bridge the methodological gap, a hypothetical expanded SeDeM-MCG-based preformulation assessment system is proposed, including three additional parameters: the granulometric compatibility index (Δd), elastic recovery index (ERI), and wetting contact angle (θ). Preliminary threshold values for the parameters are substantiated by data from the literature; however, their universality requires mandatory experimental validation. This review can serve as a conceptual foundation for developers of MCGs and for planning experimental studies to verify the proposed criteria.

Keywords: medicated chewing gums; direct compression; melting method; SeDeM diagram; dissolution test; IVIVC

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1. Introduction

Medicated chewing gums (MCGs) are a unique solid dosage form that combines properties of compressed solid preparations and food products. In recent years, interest in MCGs has increased significantly due to their clinical advantages: the possibility of rapid delivery of active substances through the buccal epithelium, bypassing hepatic first-pass metabolism; high patient adherence owing to favorable organoleptic properties; convenience of use in patients with dysphagia, children, and the elderly; and local action in dental diseases [1–4]. According to market analyses, the global market for MCGs is steadily growing, which stimulates the development of new formulations with a broad spectrum of APIs—from analgesics and antihistamines to antibiotics and peptides [5–8]. The number of scientific publications on medicated chewing gums is steadily increasing. The majority of these publications have appeared since the early 2000s (Figure 1).

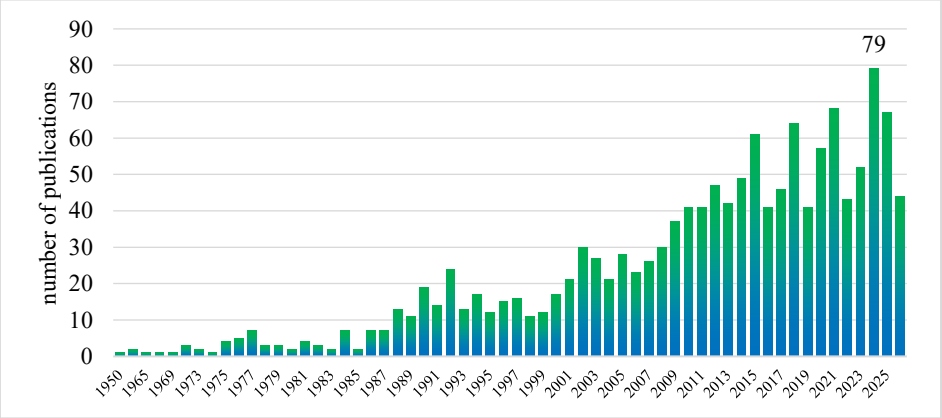

Figure 1. Number of publications according to PubMed data for the query "Medicated Chewing Gums" (date of access 20 September 2026).

Despite the obvious potential, the design of pharmaceutical development of medicated chewing gums is associated with technological challenges that distinguish this form from conventional tablets. A chewing gum must simultaneously be sufficiently hard to withstand compression and storage, yet become elastic in the mouth during mastication; release a therapeutically effective amount of the active pharmaceutical ingredient (API) within a specified time, yet not disintegrate; mask an unpleasant taste, yet not hinder release; remain stable, yet not irritate the mucosa [9,10]. Addressing these tasks requires a systems approach that integrates polymer physics, pharmaceutical technology, and biopharmaceutics.

The literature underlying this review was identified through a structured search of PubMed/MEDLINE, Scopus and Google Scholar, supplemented by the Russian-language database eLibrary. The following combinations of terms were used: "medicated chewing gum", "chewing gum drug delivery", "chewing gum formulation", "direct compression chewing gum", "melting method chewing gum", "dissolution testing chewing gum", "in vitro–in vivo correlation chewing gum" and "SeDeM". In addition, the reference lists of the retrieved review articles were screened to identify further primary studies. Records published between September 2005 and May 2026 in English or Russian were considered. The search returned 104 records. Of these, 68 reported the assessment of at least one physical—as opposed to purely organoleptic—parameter, such as flowability, compressibility, texture, mechanical strength or release behavior; studies confined to organoleptic and sensory evaluation alone were not considered further. Full text was accessible for 42 of these records, and these 42 original studies constitute the final set analyzed in the present review. Narrative and systematic reviews, editorials, conference abstracts, book chapters

and patents were excluded, as were studies of confectionery chewing gum without an active substance and studies reporting no original experimental data. Screening was performed in two stages, by title and abstract and subsequently by full text, and the eligible records were supplemented by the additional sources cited in the retained papers. Given the pronounced heterogeneity of apparatuses, dissolution media and chewing frequencies, no quantitative synthesis was attempted; data on the active substance, gum base, manufacturing route, testing conditions and reported release values were extracted and compared descriptively. The final set of 42 original studies forms the evidentiary basis of the present review.

An analysis of 42 original studies conducted in the present review identifies three principal barriers to the effective development of medicated chewing gums. The first is associated with imperfections in the regulatory framework. The European, United States, Japanese, and Russian pharmacopoeias take different approaches to regulating medicated chewing gums. Only the European Pharmacopoeia contains a detailed description of the Dissolution test. However, even this test is essentially a mechanical simulation of chewing in phosphate buffer, without accounting for enzymatic activity, variability of masticatory forces, or mucosal adsorption. As shown in [11–13], in vitro release often substantially exceeds in vivo release, which casts doubt on the predictive value of standard methods. The second barrier to standardization is the technological heterogeneity of approaches. Two fundamentally different methods—direct compression and the melting method—are used to produce medicated chewing gums; each not only requires its own gum base but also yields different release profiles [10,14,15]. At the same time, there is no unified methodological platform for selecting the optimal technology at early development stages. The third, and most significant, barrier is the absence of systematic preformulation screening. For tablets, the SeDeM diagram evaluates 12 parameters of flow and compressibility [9,16]. However, SeDeM is not designed to account for factors specific to medicated chewing gums: granulometric (particle-size) compatibility of components (leading to segregation during blending and dose nonuniformity) [2,9,17], elastic recovery after compression (affecting the stability of geometry and hardness) [18–20], and wettability of the powder blend (correlating with the release of hydrophilic substances) [21–23]. These parameters are not included in standard assessments, creating a methodological gap.

Thus, there is now a need to revise approaches to the design of medicated chewing gum development from the standpoint of Quality by Design (QbD), as codified in ICH Q8–Q11. The aim of the present review is to analyze and systematize current data on the design of medicated chewing gums, identify the limitations of existing methods, and propose a conceptual expansion of preformulation screening. To achieve this aim, the following objectives were pursued: a critical analysis of regulatory requirements with extension to the USP and JP; systematization of nonpharmacopoeial quality attributes with an in-depth technological description; synthesis of data on in vitro and in vivo release; and the justification and introduction of an expanded SeDeM-MCG system with three new parameters (Δd, ERI, Θ) proposed as a candidate tool for predicting critical quality attributes.

2. Regulatory Foundations and Their Methodological Boundaries

Recognition of medicated chewing gums as an official dosage form in the leading pharmacopoeias—the European (Ph. Eur.), United States (USP), Japanese (JP), State Pharmacopoeia of the Russian Federation (Ph.RF), and the Pharmacopoeia of the Eurasian Economic Union (EEUPh)—is accompanied by substantial differences in the depth and nature of regulatory specifications. These differences determine not only the scope of quality requirements but also the methodological basis that guides the developer in creating a new

product. The absence of harmonized approaches among pharmacopoeias creates additional barriers to international registration and requires developers to orient predominantly toward European standards.

The European Pharmacopoeia contains a general monograph defining medicated chewing gums as solid single-dose preparations with a base intended for chewing but not swallowing [24]. The key element of the European approach is the Dissolution test, which is the only pharmacopoeial method modeling the release of the active substance during chewing. The monograph also regulates tests for dose uniformity, content uniformity, mass, microbiological quality, and loss on drying (not more than 7.0% as per Ph.RF).

While permitting two fundamentally different manufacturing methods—direct compression and the melting method—the European Pharmacopoeia establishes a single, common set of release-testing requirements for products obtained by either route. Since these routes yield bodies with markedly different internal architecture, and therefore with different mechanisms of release, the same formal criteria may differ appreciably in their discriminating power when applied to the two types of product.

In contrast to the European approach, the USP does not contain a general monograph on chewing gums as a class. Mentions of medicated chewing gums are limited to general chapters devoted to dosage forms and mucosal products. The only official monograph is a private monograph for nicotine-containing chewing gum, in which identification and assay are specified; however, the Dissolution test is not described as an independent method. Instead, the USP refers to the European test 2.9.25 as a possible method for assessing release, effectively delegating to Ph. Eur. methodology. A similar situation is observed in the JP, where medicated chewing gums are assigned to the category of "chewable preparations" and defined as oral tablets that release the active substance upon chewing; however, detailed methods for finished-product release testing are absent.

Additional approaches to standardizing medicated chewing gums are offered by Ph.RF and EEUPh. In addition to other tests, they set a limit on loss on drying (≤7.0%), which directly indicates the possibility of producing the dosage form by the melting method, where residual moisture represents a potential risk, in contrast to compression. Also, Ph.RF most thoroughly describes the mechanism of action of medicated chewing gums with separation into local and systemic effects, and EEUPh notes that this dosage form may be coated.

Thus, with the exception of Ph.RF and EEUPh, the European Pharmacopoeia remains the only source of a dedicated instrumental methodology for testing medicated chewing gums, whereas the USP and JP recognize this dosage form but do not offer independent solutions for evaluating release. This has a substantial practical consequence: a developer seeking international registration is compelled to rely predominantly on European standards, which indicates the incomplete maturation of the regulatory framework for medicated chewing gums.

3. Technological Approaches to the Production of Medicated Chewing Gums: Structure Formation and Its Biopharmaceutical Implications

Contemporary approaches to the manufacture of medicated chewing gums can be divided into two fundamentally different strategies, each based on distinct physical principles of material formation and, consequently, predetermining both the mechanical properties of the final product and the release kinetics of the API. Understanding these fundamental differences is not only technologically but also biopharmaceutically important, since the choice of method largely determines the therapeutic profile of the product and patient compliance. The two fundamentally different manufacturing strategies, the resulting matrix structures, and their implications for API release are summarized in Figure 2.

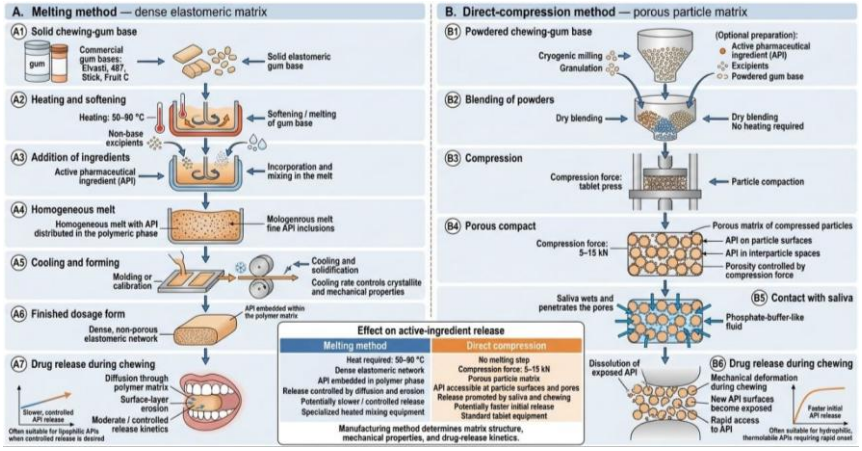

Figure 2. Methods for obtaining medicated chewing gums (AI-generated).

3.1. Components of MCGs and Their Functional Roles in Shaping Properties

Excipients in MCGs are divided into components of the water-insoluble chewing gum base and water-soluble additives [24,25]. The base must be insoluble, pharmacologically inert, resilient, elastic, and plastic. It typically comprises elastomers (natural or synthetic), plasticizers, texturizers, and emulsifiers.

The choice of elastomer depends on the manufacturing method. In direct compression, polyvinylpyrrolidone is used [19,26–28]; in the melting method, polyisobutylene [10,11] and polyvinyl acetate [29] are used. Experimental formulations employed alternative bases derived from natural polymers—wheat prolamin [30], zein [31], and compositions with xanthan gum in combination with wax and emulsifiers [23]; in this case, xanthan gum served as a structure-forming agent rather than a classical elastomer. Chicle, a biodegradable polymer from sapodilla sap, is used for both methods [4,32].

Plasticizers (glycerol, polyethylene glycol, waxes, vegetable oils) increase dosage form flexibility and must be compatible with the elastomer [24]. Fillers (calcium carbonate, talc) reduce tackiness and increase tensile resistance [11,19,26–28,32]. Emulsifiers (lecithin, glyceryl monostearate) improve hydration and component compatibility [11,23,32].

Most authors used commercial co-processed blends: for direct compression—Health in Gum [2,9,17,33–35] and Pharmagum S [3,14–16]; for the melting method—a mixture of Elvasti, 487, Stick, and Fruit C [1,6,7,12,13,36].

The water-soluble phase includes sweeteners, flavors, colorants, and antioxidants [37]. For direct compression, glidants and lubricants are critical. Colloidal silicon dioxide (Aerosil 200) has been used to improve flowability [2,3,8,9,19,33,34,38], reduce cohesion [9], and as a moisture scavenger [34]; talc was used in some studies [33]. For ease of ejection from the die, magnesium stearate [2,3,8,9,19,33,38] or calcium stearate [34] was employed.

3.2. Melting Method

In manufacturing by the melting method, the solid chewing gum base is heated to its softening or melting temperature, typically 50–90 °C, after which the API and excipients are incorporated. Product formation occurs during cooling of the melt in molds or during subsequent calibration [1,12,13,21]. As a result, a homogeneous nonporous elastomeric network is formed, in which the API is distributed molecularly or as finely dispersed inclusions. Release from such a structure is controlled by diffusion through the polymer matrix and erosion of the surface layers, resulting in a more gradual release of the active

substance than is observed for a compressed matrix. A key process parameter is the cooling rate, which determines crystallite size and, consequently, the mechanical properties of the gum.

Within this approach, mixtures of commercial gum bases are most commonly used, and varying their ratios enables adjustment of yield stress and Young's modulus over a wide range [1,12,13]. Aslani et al. demonstrated that increasing the fraction of hard bases from 50 to 70% raised the yield stress from 0.76 to 1.28 MPa and Young's modulus from 0.7 to 2.06 MPa [12]. In a study on ginger extract, compositional variation made it possible to obtain MCGs with yield stress from 0.4 to 1.03 MPa; at the same time, an increase in Young's modulus from 0.8 to 2.06 MPa led to a decrease in extract release from 94% to 71% over 30 min [13]. This pattern corroborates a direct relationship between mechanical properties and biopharmaceutical characteristics.

3.3. Direct Compression Method

The direct compression method employs powdered chewing gum bases obtained by cryogenic grinding or granulation and does not require heating. The component mixture is compressed on standard tableting equipment at a compression force of 5 to 15 kN [15], resulting in the formation of a porous matrix of compacted particles. The API in such a structure resides primarily on the particle surfaces or within interparticle voids. Release occurs upon contact with saliva, which dissolves surface layers, as well as through mechanical deformation during chewing that exposes fresh portions of the substance. Compression force is a critical parameter determining porosity, hardness, and release kinetics.

Among the most extensively studied bases for direct compression are Health in Gum® (HiG®)—a mixture of polyols and elastomers characterized by excellent flowability (angle of repose 26°, flow time 7.45 s/100 g, Hausner ratio 1.05–1.08) [2,9,17,33,35]—as well as Pharmagum® S and M, sorbitol- and elastomer-based, with an angle of repose of 27.5–29.75° and a Hausner ratio of 1.096–1.114 [3,14,15]. Polymeric bases, such as polyvinylpyrrolidone (PVP) and poly(vinyl acetate), are used less frequently, primarily for research purposes [17–20,27,29,32]. Modified chicle exhibits the poorest flowability (Carr index 21.88–23.52%) and requires the additional incorporation of glidants [32].

It is important to note that the addition of excipients substantially alters preformulation parameters: incorporation of 1.5% colloidal silicon dioxide reduces the angle of repose of HiG to 26° [34], whereas the taste-masking polymer Kyron T-114 (40%) in the same study increases it to 34.6° even in the presence of a glidant [35]. The importance of component ratios was demonstrated in the study by Akbal et al. [2], where systematic variation in base, glidant, and lubricant contents revealed a nonlinear influence of these components on the release profile. Contrary to expectations, the formulation with 93% base and 1.5% Aerosil exhibited retarded release, whereas that with 97% base and 0.5% Aerosil released 65% of the drug within the first 5 min. The optimal composition—97% base, 1% Aerosil, and 0.5% magnesium stearate—provided gradual and controlled release: 15% at 5 min and 93% at 20 min. The release retardation with excess Aerosil is likely attributable to the formation of a denser, less water-permeable matrix structure.

3.4. Influence of API Nature on the Choice of Manufacturing Method

The nature of the API is one of the key factors determining the choice of technological strategy. Based on an analysis of the literature, several groups of APIs can be distinguished that exhibit characteristic patterns.

Salts of weak bases constitute the most numerous group in the analyzed set. These include ambroxol hydrochloride [29], benzydamine hydrochloride [2], granisetron hydrochloride [18], levocetirizine dihydrochloride [33], ondansetron hydrochloride [27,28],

chlorpheniramine sulfate [31], cetirizine dihydrochloride [35], dolasetron [39], dextromethorphan hydrobromide [17], and venlafaxine (salt) [40]. These compounds are characterized by good solubility and wettability; when using direct compression, release reaches 90–99% within 20–30 min. The highest values were recorded for ambroxol hydrochloride (98.74% in 30 min [29]), chlorpheniramine maleate (88.98% in 30 min [38]), and meclizine hydrochloride (97.88% in 30 min [14]). Despite their high solubility, release from salts is strongly dependent on the hydrophobicity of excipients, especially glidants and lubricants [2].

Cationic peptides and proteins (KSL [5], KSL-W [4], lysozyme [9], papain [34]) are characterized by high molecular weight, polycationic nature, and the ability to adsorb onto hydroxyapatite and mucosal surfaces. Their release is moderate—71–82% in 30 min for KSL [5] and about 91% in 40 min for KSL in combination with CPC [4]. Na et al. [5] showed that about 20% of KSL is adsorbed onto hydroxyapatite within 5 min, which decreases its concentration in saliva but may enhance local antimicrobial action. Evaluation of peptide release requires specific analytical methods and consideration of proteolytic degradation in saliva [4].

Compounds of limited aqueous solubility and low to moderate polarity—curcumin, simvastatin, clotrimazole, fluconazole, and epigallocatechin-3-gallate [22]—share a common technological difficulty, although their lipophilicity varies widely: reported log P values range from about 0.5 (fluconazole [41]) through approximately 1 (epigallocatechin-3-gallate [22], calculated values only) to above 3 (curcumin [10], simvastatin [32], clotrimazole [36]). They exhibit slower and incomplete release unless solubilizers or complexing agents are employed. For curcumin without cyclodextrin, release was virtually absent, whereas a complex with sulfobutyl-β-cyclodextrins provided about 75% in 60 min [10]. For clotrimazole [36] and fluconazole [41], release reached 83–89% in 30 min. For this group, the melting method is often preferable because it ensures homogeneous distribution of the lipophilic active substance within the elastomeric matrix. Nicotine merits separate mention: although it is a weak base (pKa ≈ 8.1) with a modest log P of about 1.2 and high aqueous solubility, and therefore does not belong to the poorly soluble group above, it presents a comparable formulation challenge owing to its volatility and its ionization behavior in saliva; in the study reviewed here, it was formulated by the melting method [7].

Small hydrophilic molecules, such as caffeine [6], metformin [42], ascorbic acid [15], and L-cysteine [16], display the fastest release—ascorbic acid released 100% in 30 min regardless of compression force [15], caffeine 88–89% in 30 min [6], and metformin approximately 86% in 20 min [42]. This creates challenges for taste masking, especially for metformin, for which a combination of sweeteners and the freeze-drying method was required [42].

Botanical extracts (*Lepidium sativum* [21], *Aloe vera* [1], green tea [12,22], ginger [13], licorice with xylitol [23], sumac [43]) are characterized by a wide spread of release values owing to the diverse chemical nature of their actives and markers. For *Lepidium sativum* (total phenolics), release reached 100% in 20 min [21]; for ginger, 94% in 30 min [13]; for EGCG, 77% in 15 min [22]; and for *Aloe vera* (carbohydrates), over 90% in 30 min [1]. A fundamental problem is the selection of a marker for quantitative determination, which often is not solely responsible for therapeutic activity and thus provides a distorted picture of the biopharmaceutical properties of the entire extract.

Biological agents (*Lactobacillus sporogenes* [3]) require special attention, as their viability is sensitive to temperature, humidity, pressure, oxygen, and storage time, which makes direct compression without heating the preferred method.

Thus, the choice of a manufacturing method for medicated chewing gums is generally guided by the physicochemical properties of the API: across the studies reviewed,

direct compression tended to be selected for thermolabile compounds, melting for lipophilic ones, and compression only for biological agents. This requirement necessitates the development of a systematic preformulation approach that enables early assessment of a formulation's suitability for the selected method.

3.5. Comparative Analysis of Methods and Control Parameters

The critical distinction between the two approaches is that, with melting, the API is distributed within a polymeric network and is released relatively slowly, whereas with compression, it resides on particle surfaces and is available for dissolution almost immediately. This is why direct compression is preferred for hydrophilic thermolabile compounds requiring a rapid onset of action, while the melting method is more appropriate for lipophilic substances for which controlled kinetics are desirable. An additional advantage of direct compression is the ability to use standard tableting equipment, simplifying scale-up, whereas the melting method requires specialized heated mixers and more complex temperature control.

These differences are reflected in the set of control parameters applied to each method. For medicated chewing gums produced by the melting method, texture profile analysis becomes critical, enabling assessment of hardness, cohesiveness, elasticity, and chewiness—parameters that directly determine organoleptic properties and ease of use [10,22,30,40]. Uniaxial tensile testing enables evaluation of Young's modulus, yield point, and tensile strength [12,13,30,40]. For compressed medicated chewing gums, by contrast, the most important are preformulation attributes describing flowability, compressibility, and dosability of the powder blend, which are most systematically evaluated within the SeDeM diagram framework [9,16]. However, the classical SeDeM does not account for a number of critical attributes specific to medicated chewing gums, necessitating its extension.

4. The Dissolution Test: Challenges and Limitations

The Dissolution test, regulated by the European Pharmacopoeia (Ph. Eur. 2.9.25), is the only pharmacopoeial method that models the release of the API from medicated chewing gums during mastication [25]. However, its design and operating conditions reflect an engineering rather than a physiological approach to simulating processes occurring in the oral cavity. This substantially limits the test's predictive power and its applicability for forecasting in vivo product performance.

According to the pharmacopoeial chapter, the test may be performed with one of two devices—Apparatus A or Apparatus B—which differ in chamber design and the mechanism of mimicking chewing movements. Apparatus A consists of a central chamber, two horizontal pistons with a 25 mm stroke, the distance between which may vary from 0.1 to 1.0 to 50 mm, and a single vertical piston with a 22 mm stroke that presses the gum and holds it in place. Apparatus B includes a cell, a vertical rod with an upper chewing surface, a base chamber with a lower chewing surface, and a rotor set at a 20° angle; the distance between the surfaces does not exceed 5 mm, and disintegration of the gum is prevented by nylon meshes with 1.4 mm openings [25]. In both cases, 20 mL of phosphate buffer (pH 6.0) at 37 ± 0.5 °C is used, the chewing rate is 60 strokes/min, and the amount of API released is determined either in the dissolution medium or in the gum residue.

The body of data obtained from analysis of original studies reveals systemic limitations of this test. First, real chewing involves not only compression but also shear forces, rotation, and changes in jaw movement trajectory, whereas the pharmacopoeial apparatuses reduce this complex process to linear oscillations. The standard frequency of 60 strokes/min does not reflect individual variability, which, according to the literature, can range from 40 to 80 strokes/min depending on age, muscle tone, and dental status. In the

study by Mehta and Trivedi, increasing the chewing frequency from 60 to 120 strokes/min shortened the release time of dimenhydrinate from 40 to 25 min [11], indicating high sensitivity of the process to mechanical factors and calling into question the representativeness of a single standard regimen.

Equally significant is the mismatch between the closed system used in the test and the dynamic nature of salivary flow under real-use conditions. In the oral cavity, saliva is continuously renewed at 0.5–2 mL/min at rest and up to 5–7 mL/min during chewing, whereas the standard 20 mL volume exceeds the physiological level by a factor of 3–10. This creates an "infinite sink" effect, maintaining a high concentration gradient and artificially accelerating release. Daharwal et al. demonstrated that the standard 20 mL volume led to rapid saturation of the medium with ambroxol hydrochloride, distorting the release kinetics [29].

Furthermore, the phosphate buffer used as the dissolution medium lacks salivary enzymes—amylase, lysozyme, and mucin—that can substantially affect release, particularly when natural polymers are used as the base. Studies by Mishra et al. and Ostadrahimi et al. showed that release of actives from medicated chewing gums based on zein and xanthan gum in vitro was markedly higher than in vivo, which the authors attributed to enzymatic degradation of the polymer base and changes in medium viscosity [31,43]. Similar patterns were noted in studies on *Aloe vera* extract [1] and licorice with xylitol [23].

Of particular note is the fact that the pharmacopoeial test does not account for adsorption of the released substance onto the oral mucosa and dental plaque. Cationic substances such as chlorhexidine, benzydamine, and granisetron have affinity for negatively charged mucins and can bind to them, reducing the amount that reaches the systemic circulation [2,8,19]. The pharmacopoeial test quantifies only the substance in the medium or in the gum residue, without considering the bound fraction, which leads to systematic overestimation of in vitro release compared with in vivo. Ankit and CK showed that for granisetron, in vitro release exceeded 55% in 15 min, whereas in vivo in saliva after 14 min it was only over 40% [18]. The authors attributed the 15% discrepancy specifically to adsorption and swallowing of a portion of the substance.

Finally, the pharmacopoeia permits two quantification approaches—assay in the dissolution medium or in the gum residue—but does not specify a preferred method, which reduces interlaboratory reproducibility. As shown by Aslani et al., assay in the gum residue often yields lower variability (RSD < 5%), whereas assay in the medium is prone to errors due to adsorption on the chamber walls and the need for volume-replacement correction [12,13].

Variability of Testing Methodologies as an Additional Challenge

A literature analysis reveals another significant problem—the lack of a unified standard for evaluating release from medicated chewing gums. More than half of the studies reviewed (19 of 34) used homemade apparatus or magnetic stirrers, which markedly limits its comparability across studies (Table 1). Only 10 studies employed commercial devices compliant with the European Pharmacopoeia, yet even in these cases the testing conditions differed in medium composition and in the frequency of chewing strokes, which ranged from 28 to 120 strokes/min. In two studies, a magnetic stirrer was used instead of simulating chewing, which cannot be considered an adequate model.

Table 1. Dissolution test conditions in the studies analyzed.

API/Marker	Apparatus/Method	Test Conditions	Reference
Aqueous extract of *Lepidium sativum* (total phenolics)	Not specified	Phosphate buffer pH 6.8, 37 °C	[21]
Aloe vera (total carbohydrates)	Commercial apparatus, model not specified	Phosphate buffer pH 6.8, 37 °C	[1]
Ambroxol hydrochloride	Erweka DRT-6	Phosphate buffer pH 6.8, 60 strokes/min, 37 °C	[29]
Cationic peptide KSL	AB FIA (Lund, Sweden)	Artificial saliva, 37 °C, 50 strokes/min	[5]
Benzydamine hydrochloride	Homemade apparatus	Artificial saliva pH 6.75, 50 strokes/min, 37 °C	[2]
Venlafaxine	Not specified	Artificial saliva, 37 °C	[40]
Granisetron hydrochloride	Homemade apparatus	Medium not specified, 60 and 120 strokes/min	[18]
Dimenhydrinate hydrochloride	Homemade apparatus	Artificial saliva, 60 and 120 strokes/min	[11]
Dolasetron	Homemade apparatus	Artificial saliva pH 6.4, 50 strokes/min, 37 °C	[39]
Domperidone maleate	Homemade apparatus	Phosphate buffer pH 6.4, 28–32 strokes/min	[44]
Green tea extract (caffeine)	Not specified	Phosphate buffer pH 6.8, 37 °C	[12]
Ginger extract (total phenolics)	Homemade apparatus	Phosphate buffer pH 6.8, 60 strokes/min, 37 °C	[13]
Diphenhydramine	Unnamed apparatus compliant with Ph. Eur.	Phosphate buffer pH 6.0, 37 °C	[30]
Caffeine	Homemade apparatus	Phosphate buffer pH 6.8, 60 strokes/min, 37 °C	[6]
Levocetirizine dihydrochloride	Homemade apparatus	Phosphate buffer pH 6.8	[33]
Meclizine hydrochloride	Erweka DRT-6	Artificial saliva pH 6.6, 56 strokes/min, 37 °C, 50 mL	[14]
Metformin	Homemade apparatus	Phosphate buffer pH 6.8, 50 strokes/min, 37 °C, 40 mL	[42]
Nicotine	Homemade apparatus	Phosphate buffer pH 6.8	[7]
Ondansetron	Magnetic stirrer	Phosphate buffer pH 6.8	[27]
Ondansetron hydrochloride	Commercial USP-compliant apparatus	Artificial saliva, 100 strokes/min, 37 °C	[28]
Lactobacillus sporogenes	Homemade apparatus	Artificial saliva, 37 °C	[3]
Simvastatin	Homemade apparatus	Artificial saliva, 60 strokes/min	[32]
Terbutaline sulfate	Magnetic stirrer	Phosphate buffer pH 6.8	[31]
Fluconazole	Not specified	Artificial saliva, 56 strokes/min	[41]

Chlorhexidine + chitosan	Homemade apparatus	Phosphate buffer pH 6.8, 40 strokes/min	[8]
Chlorhexidine (comparison of methods)	Homemade apparatus	Phosphate buffer pH 6.8, 500 mL	[19]
Chlorhexidine (with glycerol)	Homemade apparatus	Artificial saliva pH 6.4	[20]
KSL-W + CPC	AB FIA (Lund, Sweden)	Artificial saliva, 50 strokes/min, 37 °C	[4]
Chlorpheniramine maleate	Homemade apparatus	Phosphate buffer pH 6.4	[38]
Epigallocatechin-3-gallate	Homemade apparatus	Artificial saliva pH 6.8, 60 strokes/min, UV 278 nm	[22]
Ascorbic acid	Erweka, model not specified	Distilled water, 37 °C	[15]
Lysozyme	Unnamed apparatus compliant with Ph. Eur.	Phosphate buffer pH 6.0, 30 strokes/min, 37 °C, 40 mL	[9]
Clotrimazole	Not specified	Phosphate buffer pH 6.8, 60 strokes/min, 37 °C, 50 mL	[36]
Curcumin	Erweka DRT-1	Artificial saliva, 40 strokes/min, 37 °C, 40 mL	[10]

Most often, a phosphate buffer with pH 6.8 or similar values was used as the medium for the Dissolution test. Less frequently—in 14 studies—the test was performed in artificial saliva of varying composition. Kasa et al. [15] used distilled water. Such large methodological differences not only hamper comparison of results but are also one of the main reasons for the lack of a reliable in vitro–in vivo correlation.

In addition to mechanical apparatus, Chaudhary and Shahiwala [35] employed the chew-out method, in which medicated chewing gums were provided to volunteers to chew at a comfortable pace, after which the concentration of the remaining active substance was determined in the gum residue. This method is physiological; however, owing to the limited sample, it is difficult to account for between-subject variability and individual differences in chewing rate and force, leading to high variability of results. Moreover, chew-out does not permit standardization of conditions, which hampers reproducibility, and this method cannot be used alone to perform the Dissolution test.

A separate issue is the use of UV spectrophotometry for quantification of active substances from plant extracts [1,12,13,21,22]. This method provides an integral signal of all chromophoric groups and does not allow discrimination between the target marker compound and accompanying constituents. For example, at a wavelength of 278 nm, not only epigallocatechin-3-gallate but also other catechins and their derivatives contribute to the signal [22]. Consequently, the reported release value can be substantially overestimated due to the detection of other polyphenols. A similar situation arises when using the Folin–Ciocalteu method to determine total phenolics [13,21]. Thus, when developing medicated chewing gums with a plant-derived active substance, the accuracy and selectivity of the analytical method must be taken into account.

Thus, in its current form, the “Dissolution” test is a quality control tool suitable for batch rejection but not a predictive tool for development. It answers whether the product meets its stated specifications but does not address its behavior in the patient’s body. Establishing a full in vitro–in vivo correlation for medicated chewing gums remains an unresolved challenge, necessitating the development of more physiologically relevant testing approaches, including the use of artificial saliva containing mucin and enzymes, as

well as modeling dynamic medium renewal and variability of chewing forces. It is precisely this gap—the absence of a standardized, reproducible, and predictive approach to evaluating release—that points to the need for a systematic preformulation tool; the SeDeM-MCG scheme proposed below is intended to serve this purpose, although its predictive value remains to be demonstrated, enabling prediction of medicated chewing gum behavior even before selecting a testing protocol.

5. Preformulation Screening: From Classical SeDeM to the Extended SeDeM-MCG System

Successful development of medicated chewing gums faces the challenges discussed in the preceding sections: an incomplete and fragmented regulatory framework; technological heterogeneity driven by fundamental differences between direct compression and the melting method; and the lack of reliable in vitro–in vivo correlation due to the limited predictive power of pharmacopeial tests and the fragmentation of methodologies. Collectively, these problems point to a critical gap at the preformulation stage: the developer lacks a tool that would allow, at early stages and before labor-intensive experimental studies, an assessment of whether a given composition will possess the necessary quality attributes—above all, dose uniformity and a reproducible release profile.

The classical SeDeM system (System Expert for Development of Medicines), well established for predicting the suitability of powder blends for direct compression of tablets, represents a step in the right direction [9,16,37]. This system comprises 12 parameters grouped into five factors: dimension, compressibility, flowability, lubricity/stability, and dosability. Numerical limits are set for each parameter, and when the Parameter Index exceeds 5.0, the blend is considered suitable for direct compression. For HiG and Pharmagum S bases, SeDeM shows excellent results: Carr's index is 5–10%, angle of repose 26–30°, and flow time 7–12 s/100 g [9,16].

However, as shown by a number of studies, even blends with an excellent SeDeM profile can yield medicated chewing gums with unsatisfactory dose uniformity and irreproducible release. In the work of Zieschang et al., a HiG blend with 1% Aerosil had a Parameter Index above 6.0; however, the introduction of 5% lysozyme hydrochloride reduced this value to 4.2 and, more importantly, led to segregation during mixing, which was not reflected in the SeDeM assessment [9]. In the study by Chaudhary and Shahiwala, a HiG blend with Kyron T-114 and Aerosil had acceptable flow properties; however, the finished medicated chewing gum showed high variability of API content (RSD > 6%), necessitating additional control at the compression stage [35]. Thus, classical SeDeM answers the question of whether the blend can be compressed, but not the questions of uniform distribution of the active ingredient in the finished product, stability of its mechanical properties during storage, and the rate of release upon contact with saliva.

Based on a literature analysis and physicochemical reasoning, the authors propose complementing classical SeDeM with three new parameters, each addressing a specific gap identified in the analysis of the literature and experimental data.

The first such parameter is the granulometric compatibility index (Δd), defined as the absolute difference between the median particle diameters of the base and the active ingredient: $\Delta d = |d50(\text{base}) - d50(\text{API})|$. The works of Akbal et al., Muthukumar et al., and Zieschang et al. demonstrate that a large particle size difference leads to segregation during mixing, transport, and die filling, causing dose nonuniformity [2,9,17]. In a study on lysozyme hydrochloride, the API particles had d50 = 0.09–0.25 mm, whereas the HiG base had d50 = 0.7–1.0 mm; Δd was 0.45–0.75 mm, which correlated with RSD > 5% for content in the finished medicated chewing gums [9]. In the work of Zieschang et al., when Δd > 0.4 mm, segregation became statistically significant [9]. This parameter is measured by

laser diffraction or sieve analysis followed by calculation of the difference in median diameters. The predictive value of Δd is that, within the proposed scheme, values below 0.2 mm would be expected to carry a minimal segregation risk; values of 0.2–0.4 mm would suggest an increase in mixing time or the introduction of surfactants; and at greater than 0.4 mm, either granulation of the API with a portion of the base or switching to the melting method is required.

The second proposed parameter is the elastic recovery index (ERI), defined as the relative change in tablet height 24 h after ejection: ERI = [(H_0 − H_{24}) / H_0] × 100%, where H_0 is the tablet height immediately after ejection and H_{24} is the height after 24 h of storage at 25 °C and 60% relative humidity. The rationale for this parameter is that gum bases containing elastomers undergo elastic deformation and partially recover their shape after the compression pressure is released. This phenomenon, well known in rubber technology [10], is not systematically evaluated in pharmaceutical practice for medicated chewing gums. However, the studies by Ankit and CK, Rajitha and Rao, and Pathan and Nitalikar show that high elastic recovery leads to reduced hardness, increased porosity, and, consequently, accelerated release [18–20]. In the study by Pathan and Nitalikar on chlorhexidine with a PVP-based formulation, ERI ranged from 1.5 to 4.2% and correlated with 30 min release with a coefficient of determination $R^2 = 0.87$ [20]. In the work of Al Hagbani et al., for polyisobutylene, the ERI reached 5.5%, which rendered the gum overly soft and unstable during storage [10]. ERI is measured by compressing tablets under standard conditions, followed by measuring height at 30 s and at 24 h in an environmental chamber. At ERI below 1.5%, the recovery is considered minimal and properties stable; at 1.5–3.0%, monitoring of hardness would appear prudent; and above 3.0%, a composition adjustment—introduction of plasticizers or an increase in compression force—would be indicated.

The third parameter is the contact angle of the powder blend (Θ), measured by the sessile drop method on the surface of a compressed tablet. This parameter reflects the ability of the dissolution medium to penetrate the matrix pores and initiate API release. The works of Salih and Kadhim, Amaly et al., and Ostadrahimi et al. show that adding hydrophilic fillers such as sorbitol or xylitol reduces the contact angle from 65–70° to 35–40°, which correlates with an increase in release from 60 to 90% in 30 min [21,23,43]. In the study by Mansoori et al. for epigallocatechin gallate, the contact angle was 42°, providing 84% release in 30 min [22]. For lipophilic substances, by contrast, a high contact angle (>70°) can be advantageous, ensuring prolonged release, as shown by Al Hagbani et al. for curcumin [10]. Θ is measured by compressing flat tablets from the blend without lubricants, depositing a drop of distilled water, and measuring the angle at 10 s. At Θ < 40°, the wettability is considered excellent, which is recommended for hydrophilic APIs with rapid release; at 40–60°, it is moderate, acceptable for most compositions; and at Θ > 60°, the introduction of hydrophilic fillers is recommended.

The reliability factor, f, is calculated as the ratio of the area of a regular n-sided polygon to the area of its circumscribed circle:

$$f = \frac{n\sin(2\pi/n)}{2\pi},$$

where n is the number of parameters and the angle is expressed in radians. For 12 and 15 parameters, the resulting values are approximately 0.955 and 0.971, respectively. This increase follows solely from the geometry of the diagram and should not be interpreted as evidence of improved predictive accuracy or experimental validation of SeDeM-MCG (Figure 3).

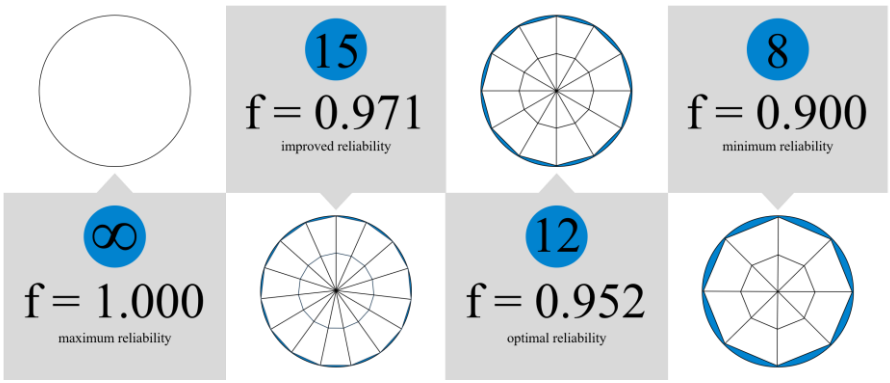

Figure 3. SeDeM-MCG reliability factors.

Integration of the proposed SeDeM-MCG system into the QbD concept enables, at the preformulation stage, assessment of risks not identified by classical SeDeM and shifts quality control from final testing to the design stage. Whereas classical SeDeM assesses only flowability and compactability, SeDeM-MCG uses Δd to predict dose uniformity, ERI to predict the stability of mechanical properties, and Θ to predict the release rate. This allows developers at early stages to decide on the need to adjust the composition or change the technological strategy, thereby reducing the number of unsuccessful experimental batches and shortening development time.

However, it should be emphasized that the proposed SeDeM-MCG system is hypothetical and is based on a retrospective analysis of a limited number of publications. Its predictive value and universality require mandatory experimental verification across a broad set of formulations with different APIs and gum bases. The threshold values proposed below (Table 2) are preliminary and serve only as guidance for planning experiments; the final limits must be established empirically for each specific combination of components.

Table 2. Preliminary threshold values of SeDeM-MCG parameters (require experimental validation).

Parameter	Designation/Unit	"Green Zone"	"Yellow Zone"	"Red Zone"	Rationale (Data from the Literature)	Status of Boundaries
Granulometric compatibility index (Δd)	Δd (mm)	<0.2	0.2–0.4	>0.4	[5,9,38]	upper: anchored (single studies); lower: proposed
Elastic recovery index (ERI)	ERI (%)	<1.5	1.5–3.0	>3.0	[32,39]	upper: anchored (single studies); lower: literature-informed, provisional
Wetting contact angle (Θ)	Θ (°)	<40	40–60	>60	[1,36,41,45]	both: interpolated/extrapolated—preliminary

Rationale for threshold values. For Δd, the boundary of 0.4 mm is based on the work by Zieschang et al. [9], where at Δd > 0.4 mm, segregation became statistically significant, as well as on studies [2,17] showing dose nonuniformity at Δd > 0.4 mm. The value of 0.2

mm was proposed as the lower limit of the "green zone," since in the cited studies no segregation was observed at $\Delta d < 0.2$ mm. For ERI, the boundary of 3.0% is based on data [10,20], where ERI > 3.0% led to decreased hardness and instability; 1.5% is taken from [20] as the level at which properties remain stable. For Θ, the boundaries of 40° and 60° are based on [21,23,40], where $\Theta < 40°$ correlated with high release (>85% in 30 min), and $\Theta > 60°$ with low (<70%). All the values indicated are preliminary and require confirmation in controlled experiments.

Based on the proposed system, the following stepwise algorithm can be suggested for a developer of medicated chewing gums. In the first stage, the Quality Target Product Profile (QTPP) is defined, including dose, release time, route of administration, and organoleptic requirements. In the second stage, the technological strategy is selected, as a general tendency—for thermolabile APIs, direct compression is preferred; for lipophilic ones (log P > 2), melting; for hydrophilic substances requiring rapid release, also direct compression; the final choice remains formulation-specific. In the third stage, a preformulation screening according to the SeDeM-MCG system is performed, including evaluation of the 12 classical parameters and three new ones (Δd, ERI, Θ). In the fourth stage, the results are interpreted and, if necessary, the composition is adjusted: at $\Delta d > 0.4$ mm, granulation or switching to melting would be indicated under the provisional scheme; at ERI > 3.0%, an increase in compression force or introduction of a plasticizer; at $\Theta > 60°$, the introduction of hydrophilic fillers (sorbitol, xylitol up to 20–30% *w*/*w*). In the fifth stage, pilot compression is carried out with assessment of hardness, friability, and uniformity, as well as the Dissolution test in a modified medium (artificial saliva). The sixth stage is validation and scale-up, provided that all indicators are in the "green zone" (noting that these zones require experimental refinement).

Empirical, provisional equations are proposed below for incorporating the new parameters; they are not derived from first principles and will require calibration (Table 3).

Table 3. Equation to convert values to SeDeM-MCG radius values.

Parameter	Equation	Equation to Convert Values to SeDeM-MCG Radius Values
Granulometric compatibility index (Δd)	$\Delta d = \lvert d50(base) - d50(API) \rvert$	−21.4v + 12.28
Elastic recovery index (ERI)	$ERI = [(H_{24} - H_0)/H_0] \times 100\%$	−2.85v + 12.28
Wetting contact angle (Θ)	°, experimentally	−0.214v + 16.56

It is worth noting that the formulas proposed require experimental validation. They may be adjusted once a sufficient volume of experimental data has been accumulated.

The SeDeM-MCG scheme presented in this section is a hypothesis derived from a retrospective analysis of the literature. It is offered to structure future experimental work rather than as a validated instrument, and nothing in the following should be read as a claim of demonstrated predictive performance. The parameter definitions, the threshold zones and the conversion equations are provisional and remain unverified until confirmed in controlled experiments.

6. Conclusions

The systematic review of 42 original studies devoted to the design, technology, and standardization of medicated chewing gums makes it possible to formulate several key conclusions.

The regulatory framework for medicated chewing gums remains incomplete: only the European Pharmacopoeia provides detailed testing methodology, whereas the USP

and JP acknowledge the dosage form but do not offer dedicated instrumental solutions. This creates barriers to international registration and forces developers to rely on European standards.

The Dissolution test in its current form is a quality control tool for rejecting batches, but not a predictive means for development. Mechanical simulation of chewing in phosphate buffer does not account for the enzymatic activity of saliva, variability of chewing forces, adsorption onto the mucosa, and salivary flow dynamics, leading to systematic discrepancies between in vitro and in vivo. The literature analysis also revealed substantial variability in testing methodologies (apparatus, media, frequencies), which further complicates comparison of results and establishment of in vitro–in vivo correlation (IVIVC).

The technological choice between direct compression and melting is a fundamental biopharmaceutical decision determined by the physicochemical properties of the API. Direct compression forms a porous matrix and is preferable for hydrophilic thermolabile substances; melting creates a homogeneous elastomeric network and is better suited for lipophilic compounds.

The classical SeDeM system, effective for assessing the flowability of tablet blends, does not account for attributes critical to medicated chewing gums—segregation risk, elastic recovery, and wettability. To bridge this gap, a hypothetical extended SeDeM-MCG system is proposed with three new parameters: Δd (granulometric compatibility), ERI (elastic recovery), and Θ (contact angle of wettability). Their preliminary threshold values are justified by data from the literature but require mandatory experimental validation. Until such data are obtained, SeDeM-MCG should be regarded as a conceptual framework for planning preformulation studies, rather than as a ready-to-use standard.

7. Study Limitations

The following limitations should be considered when interpreting the results.

The decision rules proposed in the algorithm are qualitative and are intended as guidance; quantitative thresholds sometimes cited in practice—for example, a dose limit for direct compression—are not supported by systematic data and are therefore deliberately not included.

The proposed SeDeM-MCG system has not undergone experimental validation. The threshold values of the parameters are based on a limited set of data from the literature and should not be regarded as universal or definitive; they serve only as a working hypothesis for planning experiments and require obligatory empirical verification.

In addition, SeDeM-MCG was developed exclusively for the direct compression method. The parameters Δd and ERI are not applicable to melt-processed medicated chewing gums, where the critical quality attributes are determined by textural characteristics assessed by the texture profile analysis method. The development of a similar preformulation tool for the melting method remains a task for future studies.

The ERI and Θ parameters are sensitive to measurement conditions (compaction force, humidity, surface roughness, temperature). The absence of standardized measurement protocols in pharmaceutical practice may limit the reproducibility of results between laboratories.

Finally, the present review is limited to literature in English and Russian; studies in other languages could complement the conclusions. The rapid development of the medicated chewing gum market and the emergence of new gum bases may also require revision of certain provisions in the near future.

8. Perspectives

The results of this review open several promising avenues for further research.

The first priority is the experimental validation of the proposed SeDeM-MCG system. The following study design is proposed. At the first stage, select at least three gum bases (Health in Gum, Pharmagum S, and polyvinyl acetate) and at least three active substances from different classes (hydrophilic—for example, metformin or caffeine; lipophilic—curcumin or simvastatin; high-molecular-weight—lysozyme or the peptide KSL-W). For each composition, determine Δd (by laser diffraction), ERI (by measuring tablet height immediately after compression and after 24 h), and Θ (by the sessile drop method). Then, perform correlation analysis between these parameters and the critical quality attributes of the finished medicated chewing gums—dose uniformity (RSD, %), hardness (kg/cm^2), friability (%), and release profile (% at 30 min). Based on the obtained data, the threshold values of the parameters can be refined and standardized protocols for their measurement can be developed.

The second direction is the development of a similar preformulation system for the melting method based on texture profile analysis parameters and rheological measurements (melt viscosity, softening temperature, elastic modulus, yield stress).

The third direction is the refinement of the Dissolution test by implementing artificial saliva with mucin and amylase, a dynamic medium replacement regime, and testing at multiple chewing frequencies (40, 60, 80 strokes/min) to improve IVIVC.

The fourth direction is the development of mathematical models for predicting release based on SeDeM-MCG parameters using machine learning methods.

Finally, a promising avenue is the investigation of new biopolymeric bases (zein, prolamin, xanthan gum) to create biodegradable medicated chewing gums with adaptation of SeDeM-MCG for their evaluation.

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Abbreviations

The following abbreviations are used in this manuscript:

MCG	Medicated chewing gum
SeDeM	System Expert for Development of Medicines
QbD	Quality by Design
QTPP	Quality Target Product Profile
IVIVC	In vitro–in vivo correlation
ICH	International Council for Harmonization

Ph. Eur.	European Pharmacopoeia
USP	United States Pharmacopoeia
JP	Japanese Pharmacopoeia
Ph.RF	State Pharmacopoeia of the Russian Federation
EEUPh	Pharmacopoeia of the Eurasian Economic Union
API	Active pharmaceutical ingredient
PVP	Polyvinylpyrrolidone
CPC	Cetylpyridinium chloride
RSD	Relative standard deviation
UV	Ultraviolet

References

1. Aslani, A.; Ghannadi, A.; Raddanipour, R. Design, formulation and evaluation of *Aloe vera* chewing gum. *Adv. Biomed. Res.* **2015**, *4*, 175.
2. Akbal, Ö.; Cevher, E.; Araman, A.O. The development and in vitro evaluation of benzydamine hydrochloride medicated chewing gum formulations. *Istanb. J. Pharm.* **2017**, *47*, 45–51.
3. Poorna Theja, K.; Ramesh, Y.; Gnanaprakash, K.; Gobinath, M.; Sarvanan, D.; Kumar, B. Development and Evaluation of Medicated Chewing Gum of *Lactobacillus sporogenes*. *Int. J. Pharm. Sci. Rev. Res.* **2011**, *6*, 25–30.
4. Al-Ghananeem, A.M.; Leung, K.P.; Faraj, J.; DeLuca, P.P. Development of a sustained antiplaque and antimicrobial chewing gum of a decapeptide. *AAPS PharmSciTech* **2017**, *18*, 2240–2247.
5. Na, D.H.; Faraj, J.; Capan, Y.; Leung, K.P.; DeLuca, P.P. Chewing gum of antimicrobial decapeptide (KSL) as a sustained antiplaque agent: Preformulation study. *J. Control. Release* **2005**, *107*, 122–130.
6. Aslani, A.; Jalilian, F. Design, formulation and evaluation of caffeine chewing gum. *Adv. Biomed. Res.* **2013**, *2*, 72.
7. Aslani, A.; Rafiei, S. Design, formulation and evaluation of nicotine chewing gum. *Adv. Biomed. Res.* **2012**, *1*, 57.
8. Vasudha, L.S.; Yadav, H.K.S.; Mahesh, K.P.; Uniyal, S.; Ayaz, A.; Nagavarma, B.V.N. Formulation and evaluation of medicated chewing gum as an antiplaque and antibacterial agent. *J. Young Pharm.* **2014**, *6*, 3–10.
9. Zieschang, L.; Klein, M.; Jung, N.; Krämer, J.; Windbergs, M. Formulation development of medicated chewing gum tablets by direct compression using the SeDeM-Diagram-Expert-System. *Eur. J. Pharm. Biopharm.* **2019**, *144*, 68–78.
10. Al Hagbani, T.; Altomare, C.; Salawi, A.; Nazzal, S. D-optimal mixture design: Formulation development, mechanical characterization, and optimization of curcumin chewing gums using oppanol® B 12 elastomer as a gum-base. *Int. J. Pharm.* **2018**, *553*, 210–219.
11. Mehta, F.; Trivedi, P. Formulation and texture characterization of medicated chewing gum delivery of Dimenhydrinate Hydrochloride. *Pharm. Lett.* **2011**, *3*, 129–140.
12. Aslani, A.; Ghannadi, A.; Khalafi, Z. Design, formulation and evaluation of green tea chewing gum. *Adv. Biomed. Res.* **2014**, *3*, 142.
13. Aslani, A.; Ghannadi, A.; Rostami, F. Design, formulation, and evaluation of ginger medicated chewing gum. *Adv. Biomed. Res.* **2016**, *5*, 130.
14. Vegada, R.; Seth, A.K.; Sachin, C.; Parikh, P.; Chainesh, S.; Vinod, R. Formulation and evaluation of novel gum based drug delivery system of an antiemetic drug. *Int. J. Pharm. Res. Technol.* **2012**, *2*, 16–20.
15. Kása, P.; Jójárt, I.; Kelemen, A.; Pintye-Hódi, K. Formulation study of directly compressible chewable polymers containing ascorbic acid. *Pharm. Dev. Technol.* **2013**, *18*, 384–389.
16. Kartal, A.; Björkqvist, M.; Lehto, V.P.; Juppo, A.M.; Marvola, M.; Sivén, M. Compatibility of chewing gum excipients with the amino acid L-cysteine and stability of the active substance in directly compressed chewing gum formulation. *J. Pharm. Pharmacol.* **2008**, *60*, 1131–1138.
17. Muthukumar, S.; Nijanthan, S.; Vinesha, R.; Sundarajan, R.; Sridevi, M.; Salabha, A. Formulation and evaluation of medicated chewing gum consisting of dextromethorphan and guaifenesin for the treatment of cough. *Res. J. Pharm. Technol.* **2021**, *14*, 2445–2451.
18. Ankit, A.; Sudhakar, C.K. Design, Development, Characterization and in-vitro Evaluation of Medicated Chewing Gum: Granisetron Hydrochloride. *J. Drug Deliv. Ther.* **2018**, *8*, 43.
19. Rajitha, K.; Rao, Y.M. Formulation and evaluation of chlorhexidine medicated chewing gums by different methods. *Asian J. Pharm.* **2016**, *10*, 193–199.

20. Pathan, J.A.; Nitalikar, M.M. Formulation and evaluation of medicated chewing gum containing an antibacterial agent. *J. Curr. Pharm. Res.* **2014**, *4*, 1291–1296.
21. Salih, N.M.; Kadhim, R.J. Manufacturing of Medicate Chewing Gum Against Oral Pathogens by the Extract of Seeds of *Lepidium sativum* L. *Adv. Environ. Biol.* **2019**, *13*, 1–6.
22. Mansoori, R.; Jain, D.; Bishnoi, R.S. Formulation and evaluation of medicated chewing gum of EGCG (epigallocatechin gallate)-enriched extract of *Camellia sinensis* (green tea) for periodontal disease. *J. Adv. Sci. Res.* **2022**, *13*, 79–86.
23. Amaly, J.; Ramadoss, R.; Nitya, K.; Sandhya, S.; Selvam, S.P.; Shree, K.H.; Radha, G. Anti-cariogenic potential and pharmacokinetics of Licorice and Xylitol infused chewing gum. *J. Oral Biol. Craniofacial Res.* **2025**, *15*, 605–611.
24. Alekseev, K.V.; Blynskaya, E.V.; Tishkov, S.V.; Bueva, V.V.; Ivanov, A.A. Excipients for Use in the Technology of Medicated Chewing Gums. *Probl. Biol. Med. Pharm. Chem.* **2020**, *6*, 3–9.
25. Jain, J.; Das, S.; Khatiwara, D.; Bagchi, A.; Das, S.; Bahadur, S. Medicated chewing gum: As a new generation drug carrier/dosage form. *Univers. J. Pharm. Sci. Res.* **2022**, *8*, 13–18. https://doi.org/10.61114/UJPSR.8.2.2022.13-18.
26. Honale, V.S.; Muneshwar, S.D.; Thipe, S.S.; Sawale, A.V. Formulation and Evaluation of Herbal Anticancer Chewing Gum. *Asian J. Pharm. Anal.* **2023**, *13*, 278–284.
27. Dipesh, L.; Pranay, S.; Shruti, R. Formulation and evaluation of new medicated chewing gum for the treatment of nausea and vomiting induced by chemotherapy, radiation therapy and post operative conditions in cancer. *Asian J. Pharm. Clin. Res.* **2020**, *13*, 157–160.
28. Nagaich, U.; Chaudhary, V.; Karki, R.; Yadav, A.; Sharma, P. Formulation of medicated chewing gum of ondansetron hydrochloride and its pharmacokinetic evaluations. *Int. J. Pharm. Sci. Res.* **2010**, *1*, 32–40.
29. Daharwal, S.J.; Thakur, V.D.; Shrivastava, S.; Sahu, B.P. Designing and Optimization of Modified Dissolution Apparatus for Evaluation of Medicated Chewing Gum of Ambroxol HCl. *Asian J. Pharm. Res.* **2013**, *3*, 141–143.
30. Shete, R.B.; Muniswamy, V.J.; Pandit, A.P.; Khandelwal, K.R. Formulation of eco-friendly medicated chewing gum to prevent motion sickness. *AAPS PharmSciTech* **2015**, *16*, 1041–1050.
31. Mishra, S.; Shah, S.K.; Dubey, B.K. Formulation and evaluation of terbutaline sulfate medicated chewing gum for asthma management. *Asian J. Pharm. Clin. Res.* **2024**, *17*, 52–55.
32. Tarade, V.D.; Chemate, S.Z.; Tushar, J.V.; Kalyani, J.A. A study on the formulation and evaluation of simvastatin medicated chewing gum. *Int. J. Adv. Res. Ideas Innov. Technol.* **2016**, *4*, 484–494.
33. Marzouk, M.A.; Darwish, M.K.; Abd El-Fattah, M.A. Development of medicated chewing gum of taste masked levocetirizine dihydrochloride using different gum bases: In vitro and in vivo evaluation. *Drug Dev. Ind. Pharm.* **2020**, *46*, 395–402.
34. Yakovenko, O.; Masliy, J. The development of a dental drug in the form of medicated chewing gum. *Česk. Slov. Farm.* **2014**, *63*, 303–304.
35. Chaudhary, S.A.; Shahiwala, A.F. Directly compressible medicated chewing gum formulation for quick relief from the common cold. *Int. J. Pharm. Investig.* **2012**, *2*, 123–133.
36. Aslani, A.; Esfahani, S.K. Design, Formulation and Physicochemical Evaluation of Clotrimazole Chewing Gum. *Galen. Med. J.* **2021**, *10*, e1084.
37. Suñe Negre, J.M.; Roig Carreras, M.; Fuster García, R.; Hernández Pérez, C.; Ruhí Roura, R.; García Montoya, E.; Miñarro Carmona, M.; Pérez Lozano, P.; Ticó Grau, J.R. Nueva metodología de preformulación galénica para la caracterización de sustancias en relación a su viabilidad para la compresión: Diagrama SeDeM. *Cienc. Tecnol. Pharm.* **2005**, *15*, 125–136.
38. Bhoi, G.S.; Aloorkar, N.H.; Shinde, N.G.; Osmani, R.M. Formulation and evaluation of medicated chewing gum containing chlorpheniramine maleate. *Indo Am. J. Pharm. Res.* **2014**, *4*, 1309–1319.
39. Shaikh, A.; Agrawal, A.; Jain, N.K.; Gupta, M.K. Formulation and evaluation of medicated chewing gum of dolasetron as an antiemetic agent. *J. Drug Deliv. Ther.* **2017**, *7*, 125–128.
40. Bibi, A.; Ahmad, A.; Mustafa, S.A.N.; Aqsa, M.; Yousaf, S.; Mustafa, S.A.N.; Bukhari, S.R.N.; Munir, M.; Shah, S.N.H.;; Nasir, B.; et al. Fabrication and Evaluation of Medicated Chewing Gum of Antidepressant. *J. Health Wellness Commun. Res.* **2025**, *3*, e1022.
41. Chowdary, K.S.; Ahmed, M.G.; Charyulu, R.N. Development and evaluation of fluconazole medicated chewing gums for the treatment of oral candidiasis. *Int. J. Pharm. Drug Anal.* **2014**, *2*, 413–416.
42. Mostafavi, S.A.; Varshosaz, J.; Arabian, S. Formulation development and evaluation of metformin chewing gum with bitter taste masking. *Adv. Biomed. Res.* **2014**, *3*, 92.
43. Ostadrahimi, A.; Ezzati, S.; Bahadori, M.B.; Molani-Gol, R.; Ebrahimzadeh, A.V.; Moghaddas, K.E. Delivery of Sumac (*Rhus coriaria* L.) Extract in a Chewing Gum System and Its Functional, Textural, and Sensory Characterization. *Food Sci. Nutr.* **2025**, *13*, e70063.

44. Vig, V.R.; Tekade, B.W.; Jadhao, U.T.; Patil, V.R.; Chetan, S. Formulation Development and Evaluation of Medicated Chewing Gum of Domperidone maleate. *World, J. Pharm. Res.* **2017**, *6*, 646–655.
45. Sahu, J.K.; Prasad, S. Development and Characterization of Domperidone Containing Medicated Chewing Gum Formulations. *Int. J. Med. Pharm. Sci.* **2023**, *13*, 7–13.

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