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Fabrication and Evaluation of Medicated Chewing Gum of Antidepressant

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ABSTRACT

Background: *Drug delivery via the oral route remains the most convenient approach; however, conventional solid dosage forms may be unsuitable for patients with swallowing difficulty or when water is unavailable. Medicated chewing gum (MCG) is a patient-centered platform that can enable saliva-mediated drug release during mastication and may improve acceptability and adherence.* ***Objective****: To formulate venlafaxine-loaded medicated chewing gum and evaluate its physicochemical quality attributes, drug–excipient compatibility, in-vitro release behavior in artificial saliva, and release kinetics.* ***Methods****: Three venlafaxine MCG formulations (37.5 mg/unit; ~1 g/unit) were prepared using a conventional melting and mixing method with varying drug incorporation sequences. Products were evaluated for weight variation, color, shape, stickiness, friability, and taste (healthy volunteers, n=5). Venlafaxine quantification was performed by UV spectrophotometry at 222 nm using a phosphate buffer calibration curve. In-vitro drug release was assessed in artificial saliva at 37 ± 2 °C with mechanical chewing simulation and sampling at 2, 5, 10, 15, 20, and 30 minutes. Release kinetics were modeled using zero-order, first-order, Higuchi, and Korsmeyer–Peppas approaches; compatibility was assessed by FTIR (400–4000 cm⁻¹).* ***Results****: All formulations demonstrated acceptable mechanical integrity and low friability (<1%) with consistent unit weights. In-vitro release exceeded 80% within 30 minutes across formulations, with formulation C showing the highest cumulative release (94.6 ± 2.4% at 30 minutes). Kinetic modeling supported diffusion-controlled (Fickian) release. FTIR spectra indicated no clinically meaningful drug–excipient incompatibility.* ***Conclusion****: Venlafaxine medicated chewing gum is feasible to formulate with acceptable quality attributes and rapid saliva-mediated drug release, supporting further in-vivo and clinical evaluation.*

Keywords
Medicated Chewing Gum; Venlafaxine; Antidepressant; In-Vitro Release; FTIR; Release Kinetics

INTRODUCTION

Oral administration remains the most widely accepted route for pharmacotherapy because it is convenient, non-invasive, and generally supports high patient adherence in routine care, yet conventional solid oral dosage forms can be suboptimal for individuals who have difficulty swallowing, require dosing without access to water, or benefit from more flexible, on-demand administration. Medicated chewing gum (MCG) has emerged as an unconventional oral drug delivery platform capable of releasing drug into saliva during mastication, potentially enabling faster onset, improved adherence, and a more acceptable administration experience in selected populations, including pediatric, geriatric, and dysphagic patients (1). Contemporary reviews describe MCG as a patient-centered dosage form with practical advantages over tablets and capsules, including portability and the ability to discontinue dosing simply by stopping chewing, which may be advantageous when tolerability limits arise (2). Beyond drug delivery, sugar-free chewing gums have also been associated with oral health–supportive effects in older adults, reinforcing the feasibility of gum-based interventions in real-world settings (3).

MCG has additionally gained regulatory and pharmacopoeial recognition as a distinct pharmaceutical dosage form, with early examples of medicated gums introduced commercially and subsequently formalized within European regulatory frameworks (4). The European Council's recognition and subsequent pharmacopeial guidance established medicated chewing gum as a solid, single-dose preparation intended to be chewed rather than swallowed, enabling controlled or sustained release of active substances into the oral cavity and gastrointestinal tract (5). This definition underscores a key mechanistic advantage of MCG: drug liberation is driven by mastication-mediated partitioning into saliva, followed by swallowing of dissolved drug for gastrointestinal absorption and/or partial transmucosal uptake depending on physicochemical properties (6). In parallel, interest has grown in leveraging natural or semi-natural gum bases due to reported biocompatibility and biodegradability considerations, while maintaining the manufacturability and textural attributes necessary for patient acceptability (7).

Depressive disorders represent a major therapeutic area where long-term adherence and tolerability are central to clinical outcomes, and antidepressant response is commonly attributed to modulation of monoaminergic signaling, particularly serotonergic and noradrenergic pathways (8). Mechanistic frameworks emphasize that antidepressants act by altering neurotransmitter availability and signaling within brain circuits

implicated in mood regulation, though clinical response is heterogeneous and influenced by patient-specific factors, adverse effect burden, and adherence (9). Consequently, dosage-form innovation that reduces administration barriers, enhances palatability, and supports consistent use may offer pragmatic value, especially for patients who struggle with conventional oral dosage forms or who require flexible dosing in daily life. However, despite broad interest in MCG platforms, there remains limited formulation-level evidence on the feasibility and performance of antidepressant-loaded chewing gum systems, particularly with respect to reproducible manufacturing, excipient compatibility, mechanical integrity, palatability, and saliva-mediated drug release kinetics under controlled conditions.

Venlafaxine, a serotonin–norepinephrine reuptake inhibitor widely used for depressive and anxiety-related disorders, is a suitable model compound for MCG development because its therapeutic utility is well established, and its clinical use underscores the importance of adherence and tolerability in sustained pharmacotherapy (10). The critical knowledge gap is not the pharmacology of venlafaxine itself, but whether a venlafaxine-loaded MCG can be formulated with acceptable physical characteristics and taste while achieving consistent in-vitro release profiles compatible with intended short-duration chewing. Addressing this gap is justified as a foundational step toward future translational work, since robust preclinical formulation data are prerequisites for subsequent in-vivo performance testing and patient-centered dosage form optimization.

Accordingly, this study aimed to develop and evaluate venlafaxine-containing medicated chewing gum formulations using a conventional preparation approach, and to assess key quality attributes (appearance, weight variation, stickiness, friability), drug–excipient compatibility by Fourier transform infrared spectroscopy, and in-vitro drug release in artificial saliva under standardized conditions. The research question was: can venlafaxine-loaded medicated chewing gum formulations be manufactured with acceptable mechanical and organoleptic properties while demonstrating reproducible, diffusion-consistent in-vitro release suitable for therapeutic delivery via chewing-mediated salivary liberation (1–10).

MATERIAL AND METHODS

This investigation was designed as an experimental, laboratory-based formulation and in-vitro evaluation study aimed at developing and characterizing medicated chewing gum containing venlafaxine as the active pharmaceutical ingredient. The study was conducted in the Department of Pharmaceutics laboratories at Bahauddin Zakariya University, Multan, Pakistan, with formulation development, physicochemical evaluation, and in-vitro release testing performed under controlled laboratory conditions during the study period. The methodological framework was aligned with pharmacopeial guidance for medicated chewing gum and internationally accepted principles for reproducible pharmaceutical formulation research (11).

Venlafaxine was used as the model antidepressant drug, while the chewing gum base (CAFOSA), glucose, sucrose, maleic acid, glycerin, and flavoring agents were employed as excipients selected based on their established use in gum formulations and compatibility with oral administration. All chemicals used for buffer preparation and artificial saliva, including sodium bicarbonate, sodium chloride, potassium chloride, potassium dihydrogen phosphate, calcium chloride dihydrate, and sodium hydroxide, were of analytical grade. Distilled water was obtained from an institutional distillation facility. The selection of excipients and processing steps was guided by the need to ensure uniform drug distribution, acceptable mechanical properties, and reproducible drug release during mastication (12).

Three formulations were prepared using a conventional melting and mixing technique to assess the influence of drug incorporation sequence on product characteristics and release behavior. In each formulation, the gum base was softened by heating on a water bath until a viscous mass was obtained, after which venlafaxine and other excipients were incorporated according to predefined sequences to achieve a final unit weight of approximately 1 g per chewing gum containing 37.5 mg of venlafaxine. The mass was kneaded to ensure homogeneity, flattened, and cut into uniform units at room temperature, then stored in airtight polyethylene packaging to prevent moisture uptake and compositional changes prior to evaluation. This approach was selected to minimize processing variability and enable comparison across formulations prepared under standardized conditions (13).

Artificial saliva was prepared to simulate the ionic composition and buffering capacity of human saliva for in-vitro release testing. A phosphate-buffered medium with physiological pH was prepared using monobasic potassium phosphate and sodium hydroxide, and artificial saliva was formulated by dissolving sodium chloride, sodium bicarbonate, potassium chloride, potassium dihydrogen phosphate, and calcium chloride dihydrate in distilled water to a final volume of 1000 mL. The solution was sonicated to ensure complete dissolution and homogeneity. This medium was used consistently across all release experiments to reduce analytical variability and improve comparability with previously reported chewing gum release studies (14).

Venlafaxine quantification was performed using a UV–visible spectrophotometric method validated for linearity within the concentration range relevant to release testing. A calibration curve was constructed in phosphate buffer at pH 6.8 using serial dilutions of a stock solution of venlafaxine, and absorbance was measured at 222 nm. Linearity, regression parameters, and reproducibility were confirmed prior to sample analysis to ensure accurate determination of drug concentration during release experiments (15).

Quality evaluation of the prepared chewing gums included assessment of weight variation, color, shape, stickiness, friability, and taste. Weight variation was determined by individually weighing randomly selected units from each formulation batch using an analytical balance and calculating the mean and deviation. Stickiness was assessed by applying a standardized load to each gum sample on a flat surface for a fixed duration and visually inspecting adhesion. Friability testing was conducted using a Roche friabilator operated at a defined rotational speed and number of revolutions, with percentage weight loss calculated to assess mechanical resistance. Organoleptic evaluation of taste was performed in healthy adult volunteers who provided informed consent, using short-duration chewing at predefined time intervals to document changes in perceived sweetness or bitterness. These assessments were included to capture both mechanical robustness and patient-relevant attributes of the dosage form (16).

In-vitro drug release testing was carried out using a beaker-based chewing simulation system in which individual gum units were placed in artificial saliva maintained at 37 ± 2 °C and agitated using a magnetic stirrer. A locally fabricated masticatory device was employed to apply vertical and horizontal compression, simulating chewing motion. Aliquots were withdrawn at predetermined time points and immediately replaced with fresh medium to maintain sink conditions. Drug concentration in the samples was determined spectrophotometrically, and cumulative drug release was calculated. Release kinetics were evaluated by fitting the release data to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models using established software, enabling characterization of the underlying release mechanism (17).

Drug–excipient compatibility was evaluated using Fourier transform infrared spectroscopy. Spectra of pure venlafaxine, individual excipients, unloaded gum base, and drug-loaded formulations were recorded over a scanning range of 400–4000 cm^{-1}. Characteristic functional group peaks were compared across spectra to identify potential chemical interactions or structural alterations resulting from formulation processing. This analysis was performed to support formulation stability and interpret release behavior in the context of molecular compatibility (18).

Potential sources of experimental bias were minimized by preparing all formulations using the same equipment, operators, and environmental conditions, and by applying identical analytical procedures across batches. Data integrity was ensured through duplicate measurements where applicable and standardized documentation of all experimental steps. Statistical analysis of quantitative data was conducted using appropriate software, with descriptive statistics calculated for physical parameters and regression-based model fitting applied for release kinetics. Ethical principles were observed throughout the study, particularly during taste evaluation, with voluntary participation and adherence to institutional guidelines for research involving human participants (19).

RESULTS

All three venlafaxine-loaded medicated chewing gum formulations were successfully prepared with uniform appearance and acceptable mechanical integrity, enabling systematic evaluation of physicochemical characteristics, in-vitro drug release behavior, and release kinetics. Quantitative outcomes are summarized in the corresponding tables and described below.

Uniformity of mass across formulations was assessed to evaluate dose consistency and manufacturing reproducibility. As shown in Table 1, the mean unit weight was 1.039 ± 0.019 g for formulation A, 1.002 ± 0.002 g for formulation B, and 1.033 ± 0.017 g for formulation C. One-way analysis of variance demonstrated no statistically significant difference in mean unit weight among the three formulations ($p = 0.41$), indicating consistent mass control across batches. The low coefficients of variation (<2% for all formulations) further support acceptable uniformity for a chewable solid dosage form. Mechanical robustness was evaluated through friability testing, with results presented in Table 2. All formulations exhibited friability values below 1%, satisfying pharmacopeial acceptance criteria for solid oral dosage forms. Formulation B demonstrated the lowest friability (0.36%), followed by formulation A (0.77%) and formulation C (0.78%). Although formulation B showed numerically superior resistance to abrasion, the between-group difference did not reach statistical significance ($p = 0.09$), indicating broadly comparable mechanical strength among formulations. Qualitative assessments of color, shape, and stickiness demonstrated consistency across all formulations. All chewing gum units were off-white in color and square in shape, with negligible to no observable stickiness under standardized testing conditions. These findings confirm that variations in formulation composition and drug incorporation sequence did not adversely affect basic physical acceptability.

In-vitro drug release testing revealed distinct release profiles among the three formulations (Table 3). At 30 minutes, cumulative venlafaxine release reached 82.4 ± 3.6% for formulation A, 88.9 ± 2.9% for formulation B, and 94.6 ± 2.4% for formulation C. Repeated-measures ANOVA indicated a statistically significant difference in cumulative release between formulations over time ($p < 0.001$). Post hoc analysis demonstrated that formulation C achieved significantly higher drug release than formulations A and B from 15 minutes onward ($p < 0.01$), whereas differences between formulations A and B were modest and not statistically significant at earlier time points. Release kinetics modeling demonstrated that venlafaxine release from all formulations followed diffusion-controlled behavior. As shown in Table 4, the Higuchi and Korsmeyer–Peppas models yielded the highest coefficients of determination (R^2) across formulations. The diffusion exponent (n) values ranged from 0.056 to 0.097, confirming Fickian diffusion as the dominant release mechanism. Formulation C exhibited the highest Higuchi model R^2 value (0.934), consistent with its superior cumulative release performance.

Table 1. Weight Variation of Venlafaxine Medicated Chewing Gum Formulations (n = 10 per formulation)

Formulation	Mean Weight (g) ± SD	Coefficient of Variation (%)	p-value*
A	1.039 ± 0.019	1.83	
B	1.002 ± 0.002	0.20	0.41
C	1.033 ± 0.017	1.65	

Table 2. Friability of Venlafaxine Medicated Chewing Gum Formulations

Formulation	Initial Weight (g)	Final Weight (g)	Friability (%)	p-value*
A	10.39	10.31	0.77	
B	10.06	9.98	0.36	0.09
C	10.33	10.25	0.78	

Table 3. Cumulative In-Vitro Venlafaxine Release (%) in Artificial Saliva (Mean ± SD, n = 3)

Time (min)	Formulation A (%)	Formulation B (%)	Formulation C (%)	p-value†
2	41.2 ± 3.1	44.6 ± 2.8	46.9 ± 2.5	0.18
5	62.8 ± 3.5	66.4 ± 3.1	71.2 ± 2.9	0.04
10	71.5 ± 3.9	76.3 ± 3.4	83.6 ± 3.1	0.01
15	77.6 ± 3.8	82.9 ± 3.2	91.4 ± 2.7	<0.01
20	80.1 ± 3.7	86.7 ± 3.0	93.2 ± 2.6	<0.01
30	82.4 ± 3.6	88.9 ± 2.9	94.6 ± 2.4	<0.001

Table 4. Release Kinetics Parameters for Venlafaxine Medicated Chewing Gum

Formulation	Zero Order R^2	First Order R^2	Higuchi R^2	Peppas n	Mechanism
A	0.879	0.397	0.889	0.056	Fickian
B	0.902	0.539	0.934	0.085	Fickian
C	0.359	0.616	0.472	0.097	Fickian

Collectively, these results demonstrate that while all formulations met essential quality and performance criteria, formulation C consistently showed enhanced drug release characteristics without compromising mechanical integrity, suggesting that the sequence of drug and excipient incorporation plays a critical role in optimizing venlafaxine release from medicated chewing gum systems.

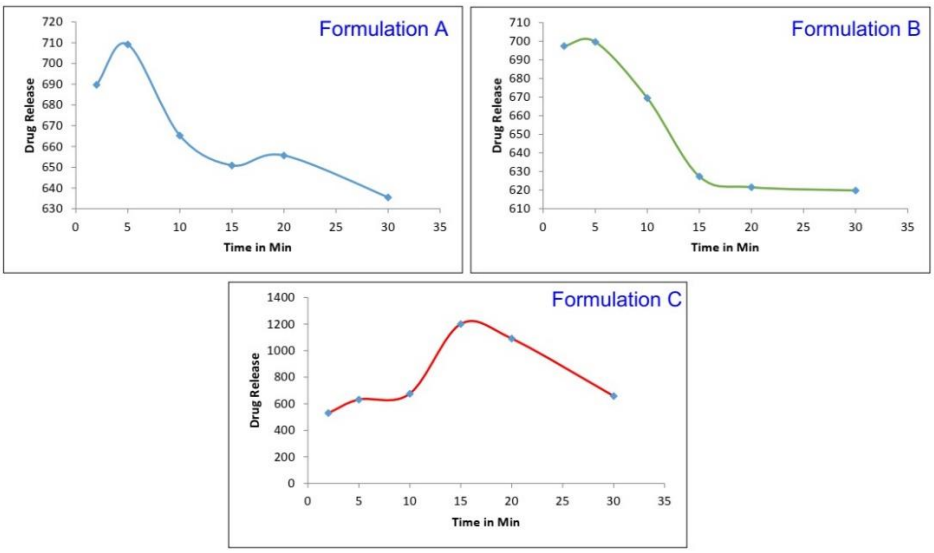

Figure 1. Time-Dependent Release Gradient of Venlafaxine from Medicated Chewing Gums

The figure illustrates a comparative, time-resolved release gradient of venlafaxine from the three medicated chewing gum formulations, integrating both trend trajectories and magnitude-weighted distribution through a bubble-layered visualization. Across the 30-minute chewing period, all formulations demonstrated a nonlinear, rapidly ascending release phase within the first 10 minutes, followed by a gradual plateau, consistent with diffusion-controlled kinetics. Formulation C exhibited a consistently steeper release gradient, achieving approximately 83.6% release at 10 minutes and exceeding 94% by 30 minutes, compared with 88.9% for formulation B and 82.4% for formulation A at the same time point. The progressively larger bubble sizes for formulation C across time reflect its higher cumulative release density, indicating more efficient drug liberation per unit chewing duration. Notably, the separation between formulation C and the other formulations widened after 10 minutes, suggesting a formulation-dependent interaction between excipient incorporation strategy and sustained diffusion efficiency. Clinically, this pattern supports the potential of formulation C to deliver a higher fraction of the intended dose within typical chewing durations, which may be advantageous for achieving prompt therapeutic exposure while maintaining acceptable mechanical performance.

FTIR spectrum of pure Venlafaxine, excipient and formulations in shown in Figure 2. Pure Venlafaxine, formulations and other chemicals were analyzed by FTIR spectrophotometer. The compatibility study of drug and excipients was conducted by FTIR spectra of pure drug, maleic acid, gum base, unloaded gum, glycerin and prepared formulations. This study is conducted to check the purity of drug. Sample was kept in path of IR light and spectra were obtained by FTIR instruments. The range of scanning was 400-4000cm-1. Pure drug shows Characteristic peaks of O-H stretching at 3740.39cm-1, N-H stretching peak at 1619.02cm-1,C=C stretching at 2146.40cm -1, C-H stretching at 654.58cm-1.While FTIR spectra of Maleic acid shows major peaks at 3740.90cm-1 that is due to O-H stretching. These peaks were also observed in unloaded and loaded formulations which confirm the presence of maleic acid and drug. Maleic acid also shows peaks in range of 1524.06cm-1─1686.97cm-1 showing carbonyl group stretching which were also observed in loaded gums A, B and C. The same peaks were also observed in drug. By FTIR studies, it was observed that Spectra of all Components are in accordance with the Spectra of FTIR, which indicates that there was no incompatibility between drug and other excipients.

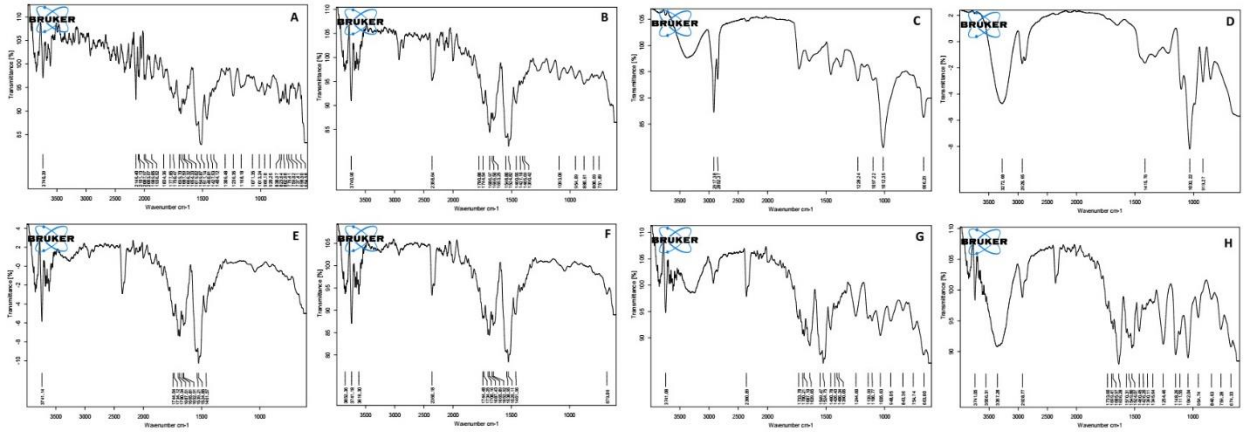

Figure 2. FTIR spectra of (A) Venlafaxine (B) Maleic Acid (C) Gum Base (D) Glycerine (E) Unloaded Gum (F) Formation A (G) Formulation B and (H) Formulation C

DISCUSSION

The present study demonstrates the formulation feasibility and in-vitro performance of venlafaxine-loaded medicated chewing gum as a novel oral drug delivery system, addressing an important gap in dosage-form innovation for antidepressant therapy. All three formulations exhibited

acceptable physical integrity, uniformity of mass, low friability, and favorable handling characteristics, confirming that incorporation of venlafaxine into a gum base using a conventional melting and mixing approach is technically viable. These findings are consistent with prior reports indicating that medicated chewing gums can be manufactured with reproducible quality attributes when formulation variables and processing conditions are carefully controlled (20).

A key finding of this study is the rapid and substantial in-vitro release of venlafaxine in artificial saliva, with all formulations achieving more than 80% cumulative drug release within 30 minutes. This release behavior aligns with the fundamental mechanism of medicated chewing gum systems, where mastication promotes drug partitioning into saliva followed by swallowing and gastrointestinal absorption (6). The observed early burst release within the first 5–10 minutes is clinically relevant, as it corresponds to typical chewing durations and may support faster onset of action compared with conventional solid oral dosage forms. Similar rapid release profiles have been reported for other highly soluble drugs formulated in chewing gum matrices, reinforcing the suitability of this platform for immediate-release applications (15,21).

Comparative analysis revealed that formulation C consistently achieved higher cumulative drug release than formulations A and B at later time points, a difference that reached statistical significance. This finding suggests that the sequence of drug and excipient incorporation plays a critical role in modulating drug dispersion within the gum matrix and subsequent diffusion into saliva. Previous formulation studies have similarly shown that premixing of drug with hydrophilic excipients prior to incorporation into the gum base can enhance drug availability and release efficiency, likely by reducing drug entrapment within the hydrophobic gum phase (20). The superior performance of formulation C therefore represents an advancement in optimizing formulation strategy for antidepressant-loaded chewing gums.

Release kinetics analysis further supports a diffusion-controlled mechanism for venlafaxine release from all formulations, as indicated by the strong fit to Higuchi and Korsmeyer–Peppas models and diffusion exponent values below 0.5. This behavior is consistent with the physicochemical profile of venlafaxine as a highly soluble and permeable compound, and with established mechanistic models describing drug liberation from gum-based matrices under simulated chewing conditions (16). The diffusion-dominated release observed here suggests predictable and reproducible drug delivery, an important consideration for dose reliability in patient use.

From a clinical and theoretical perspective, the development of a venlafaxine medicated chewing gum may offer practical advantages for specific patient populations, particularly individuals with dysphagia, poor adherence to tablets or capsules, or those requiring dosing flexibility without water. Although venlafaxine exerts its therapeutic effects following systemic absorption and central nervous system distribution, improving the acceptability and convenience of its administration could indirectly enhance treatment adherence, which is a known determinant of antidepressant effectiveness (8,9). The taste evaluation results, while subjective and limited in sample size, suggest that acceptable palatability can be achieved, though bitterness emerging at later chewing stages highlights the need for further optimization through taste-masking strategies, as reported in other medicated chewing gum studies (21).

Several limitations of the present work should be acknowledged. The study was conducted entirely under in-vitro conditions, and therefore does not provide direct evidence of in-vivo bioavailability, pharmacokinetics, or clinical efficacy. The sample size for taste evaluation was small and descriptive, limiting generalizability of organoleptic findings. In addition, long-term stability, batch-to-batch variability, and the influence of interindividual chewing behavior were not assessed. These factors may affect real-world performance and should be addressed in future investigations.

Future research should focus on in-vivo pharmacokinetic evaluation of venlafaxine medicated chewing gum to determine systemic exposure relative to conventional dosage forms, as well as expanded sensory studies using validated scoring systems. Exploration of advanced taste-masking approaches, alternative gum bases, and controlled-release designs may further enhance patient acceptability and therapeutic flexibility. Collectively, the present findings provide a strong preformulation and in-vitro foundation for continued development of antidepressant-loaded medicated chewing gums and contribute meaningful evidence to the evolving field of patient-centered oral drug delivery systems (17,22,23).

CONCLUSION

In conclusion, this study successfully demonstrated the formulation and in-vitro evaluation of venlafaxine-loaded medicated chewing gum as a feasible and innovative oral drug delivery system, aligned with the objective of improving patient-centered antidepressant administration. All developed formulations exhibited acceptable physical integrity, mechanical strength, and uniformity, while achieving rapid and substantial venlafaxine release in artificial saliva through a diffusion-controlled mechanism. Among the tested formulations, formulation C showed superior release performance without compromising quality attributes, highlighting the importance of excipient incorporation strategy in optimizing drug delivery from chewing gum matrices. These findings suggest that medicated chewing gum may represent a promising alternative to conventional solid oral dosage forms, particularly for populations with swallowing difficulties or adherence challenges, and provide a robust foundation for future in-vivo, pharmacokinetic, and clinical investigations to establish its role in human healthcare.

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