



Development and Evaluation of Bentonite-Treated *Carica papaya* Leaf Extract Lozenges for Management of Dengue-Associated Thrombocytopenia

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ABSTRACT

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Dengue fever remains an important public health problem and is frequently accompanied by thrombocytopenia, a marked fall in circulating platelet count. *Carica papaya* leaves have long been used for their reported platelet-boosting and anti-dengue properties, but their pronounced bitterness limits patient acceptability. This study examined whether bentonite treatment could reduce the bitterness of *Carica papaya* leaf extract without substantially altering its phytochemical content, and whether the treated extract could be formulated into an orally acceptable lozenge. Dried papaya leaves were treated with bentonite at three leaf-to-adsorbent ratios (1:10, 1:15, 1:20) by boiling or submersion, and the treated leaves were assessed for bitterness intensity by a trained sensory panel and for phytochemical content by qualitative screening, thin-layer chromatography and FTIR spectroscopy. Boiling with bentonite at a 1:15 ratio gave the greatest reduction in bitterness while retaining most of the major phytochemical constituents; only tannins and saponins were lost on treatment. The bentonite-treated extract was then formulated into lozenges by the heating-and-congealing method using polyethylene glycol (PEG), polyvinylpyrrolidone (PVP) and gelatin as base-forming agents, across five formulations (F1–F5) that varied the PEG:PVP ratio. The formulations showed acceptable average weight (2.16–3.08 g), friability (0.4–0.8%), hardness (10.1–12.2 kg/cm²), drug content (89.2–97.3%), moisture content (0.5–0.8%) and mouth-dissolving time (9.9–14.8 min). Formulation F4 gave the fastest and most complete in vitro drug release, reaching 98.91% within 45 min, and retained its physicochemical characteristics on short-term accelerated stability testing. These findings indicate that bentonite pretreatment can effectively mask the bitterness of *Carica papaya* leaf extract while preserving key bioactive constituents, and that the treated extract can be formulated into a stable, palatable lozenge with potential application in the supportive management of dengue-associated thrombocytopenia.

Introduction

Dengue fever, caused by the dengue virus and transmitted principally by *Aedes aegypti*, remains a major public health problem in tropical and subtropical regions [1,2]. Thrombocytopenia, a marked reduction in circulating platelets, is one of the hallmark laboratory findings in dengue fever and dengue haemorrhagic fever, and monitoring of platelet and haematocrit levels forms an important part of patient management [2,3]. No specific antiviral treatment is currently available for dengue, and management remains largely supportive.

Carica papaya leaves have traditionally been used for their reported anti-dengue and platelet-boosting properties, and several clinical and experimental studies have linked papaya leaf extract with an accelerated rise in platelet count in dengue patients [13–15]. However, the pronounced bitterness of papaya leaf extract, attributed largely to its saponin and tannin content, limits its acceptability as an oral remedy. Adsorbent clays such as

bentonite have previously been used to reduce bitterness and remove unwanted solutes from plant-derived extracts and beverages by selectively binding the offending compounds [24,34].

Lozenges are solid, slowly dissolving oral dosage forms that prolong the residence time of an active ingredient in the oral cavity and are well accepted across age groups, making them a suitable format for delivering a bitter herbal extract once its taste has been masked [10,11]. Building on this rationale, the present study investigated bentonite treatment as a means of reducing the bitterness of *Carica papaya* leaf extract while retaining its phytochemical profile, and evaluated the incorporation of the treated extract into a lozenge formulation intended for the supportive management of dengue-associated thrombocytopenia.

The aim of this study was to reduce the bitterness of *Carica papaya* leaf extract using an adsorbent treatment and to formulate and evaluate the treated extract as a

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lozenge dosage form for potential use in dengue-associated thrombocytopenia. The specific objectives were to treat papaya leaves with bentonite at different leaf-to-adsorbent ratios and application methods; to assess the resulting change in bitterness intensity by sensory panel evaluation; to compare the phytochemical profile of treated and untreated extracts by qualitative screening, TLC and FTIR; to evaluate the antibacterial activity of the extracts; to characterize the extract by preformulation studies; to formulate lozenges containing the treated extract by the heating-and-congealing method; and to evaluate the physicochemical properties, in vitro drug release and short-term stability of the resulting formulations.

Materials and Methods

Materials and Equipment

Carica papaya leaves, bentonite and the excipients used for lozenge preparation were procured from the sources listed in Table 1. The principal equipment used is listed in Table 2.

Table 1. Materials used in the study.

S.No	Material	Source
1	Bentonite (montmorillonite)	Vidhya Enterprises
2	Polyethylene glycol	Loba Chemie Pvt. Ltd.
3	Polyvinylpyrrolidone	Loba Chemie Pvt. Ltd.
4	Gelatin	S.D. Fine-Chem Ltd.
5	Ethanol	Arrow Enterprises
6	Alpha naphthol	Abhinandan Chemicals
7	Sulfuric acid	Alpha Scientific
8	Fehling's solution	Fisher Scientific
9	Dragendorff's and Mayer's reagents	Fisher Scientific / Kesari Scientific
10	Ferric chloride	Drops Chemicals
11	Biuret reagent	Modern Science Labs Pvt. Ltd.
12	Sucrose and corn syrup	Local market
13	Buffer salts (phosphate, sodium, potassium, calcium and magnesium salts)	Loba Chemie / Avantor / Universal Laboratories

Table 2. Equipment used in the study.

S.No	Equipment	Source
1	Electronic weighing balance	Shimadzu, India
2	UV spectrophotometer	Shimadzu UV1061, Japan
3	FT-IR spectrophotometer	Jasco FT/IR-4600, Japan
4	Digital pH meter	Elico India
5	Hot air oven	Parekh Scientific, India
6	Magnetic stirrer	Remi Motors, Germany
7	Stability chamber	Remi Motors, Germany
8	Dissolution apparatus (USP II)	Lab India DS 8000, India
9	Silicone mould	Meenakshi Labtech, India
10	Vernier calipers	Mitutoyo, Japan
11	Friability apparatus	Roche, India
12	Monsanto hardness tester	Veego Scientific
13	Incubator	Thermolab

Plant Collection and Bitterness Reduction

Carica papaya leaves were collected, shade-dried at room temperature for 10 days, and reduced to a coarse powder using sieve no. 16. Freshly dried leaves were combined with bentonite at leaf-to-adsorbent ratios of 1:10, 1:15 and 1:20, applied either by boiling or by submersion, giving six treatment combinations [33]. Treated leaves were divided for sensory evaluation and for subsequent extraction.

A sensory panel was trained to recognize and rank bitterness intensity using a caffeine reference solution; after screening interviews, triangle tests and a ranking task, two panelists were selected as trained assessors. Bitterness was scored on a scalar scale of 0 (undetectable) to 15 (strongly detectable) under standard sensory-booth conditions.

Extraction of *Carica papaya* leaves

The leaf powder (40 g) was extracted with 250 mL water by intermittent Soxhlet extraction for 16 h. The resulting extract was concentrated on a rotary evaporator to give a gummy, semi-solid crude extract, which was used for all subsequent phytochemical and formulation work [38].



Figure 1. Extraction of *Carica papaya* Leaves Soxhlet Apparatus

Phytochemical Screening

Treated and untreated aqueous leaf extracts were subjected to standard qualitative tests for carbohydrates (Molisch's and Fehling's tests), glycosides (Fehling's test after acid hydrolysis), alkaloids (Dragendorff's and Mayer's tests), phytosterols (Salkowski's test), proteins (Biuret test), phenols (ferric chloride test), tannins (gelatin test) and saponins (foam test), following established procedures [39].

Thin-Layer Chromatography

TLC was performed on silica-gel-coated glass plates activated at 110°C for 30 min, using a chloroform:methanol (6:4) mobile phase and a 1.5 h run time. Spots were visualized under UV light at 238 nm, and the retardation factor (R_f) was calculated as the ratio of the distance travelled by the solute to that travelled by the solvent front [40].

Antibacterial Screening

Antibacterial activity of the treated and untreated extracts was assessed by the agar well diffusion method against a Gram-positive (*Bacillus subtilis*) and a Gram-negative (*Escherichia coli*) organism, using standard nutrient agar plates seeded with a 24 h bacterial suspension. Wells were loaded with the extract solutions and plates were incubated at 37°C for 24 h before the zone of inhibition was measured [41].

Preformulation Studies

The bentonite-treated extract was characterized for organoleptic properties, density, viscosity, pH, moisture content, ash value and particle size distribution using standard pharmacopoeial procedures [42].

FTIR Spectroscopy

FTIR spectra of the untreated and bentonite-treated extracts were recorded on a Jasco FT/IR-4600 spectrophotometer fitted with an ATR accessory, scanning from 4000 to 400 cm⁻¹ at a resolution of 4 cm⁻¹ [43].

UV Spectrophotometric Analysis

The λ_{max} of the aqueous extract in phosphate buffer (pH 7.4) was determined by scanning over 200–800 nm and was found to be 238 nm. A standard calibration curve was constructed over the range 2–12 µg/mL at this wavelength (Table 3), giving a linear response (R² = 0.999).

Table 3. Calibration curve of *Carica papaya* extract in phosphate buffer, pH 7.4.

S.No	Concentration (µg/mL)	Absorbance at 238 nm
1	0	0
2	2	0.164
3	4	0.343
4	6	0.495
5	8	0.592
6	10	0.690
7	12	0.799

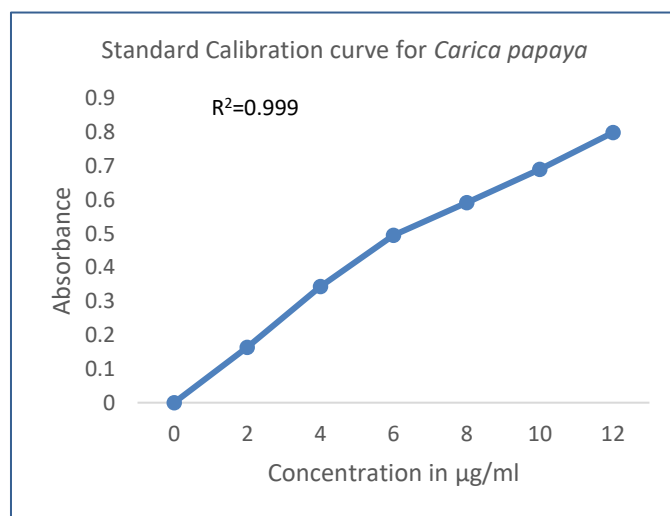


Figure 2. Standard Calibration Curve for *Carica papaya*

Formulation of Lozenges

Lozenges were prepared by the heating-and-congealing method. A syrupy base was formed by dissolving sucrose in water and heating to 105–110°C, after which the extract and other excipients (except the plasticizer) were incorporated with continued heating for 45 min. The plasticizer was then added, and the molten mass was poured into pre-cooled, pre-lubricated moulds and allowed to set before the lozenges were removed and air-dried. Five formulations (F1–F5) were prepared, varying

the PEG:PVP ratio while keeping the extract, gelatin, sucrose, citric acid and corn syrup content constant (Table 4) [45,47,48].

Table 4. Composition of *Carica papaya* leaf extract lozenges (F1–F5).

S.No	Constituent	F1	F2	F3	F4	F5
1	<i>Carica papaya</i> leaf extract	250 mg	250 mg	250 mg	250 mg	250 mg
2	Polyethylene glycol	150 mg	100 mg	75 mg	50 mg	0 mg
3	Polyvinylpyrrolidone	0	50	75	100	150
4	Gelatin	100 mg	100 mg	100 mg	50 mg	50 mg
5	Sucrose	200 mg	200 mg	200 mg	200 mg	200 mg
6	Citric acid	2 mg	2 mg	2 mg	2 mg	2 mg
7	Corn syrup	5 mL	5 mL	5 mL	5 mL	5 mL

Evaluation of Lozenges

The lozenges were evaluated for organoleptic characteristics; average weight (five lozenges per batch); friability (30 lozenges, Roche friabilator, 25 rpm, 4 min); hardness (Monsanto hardness tester, three lozenges); thickness (vernier calipers, three lozenges); drug content uniformity (spectrophotometric assay at 238 nm after dissolution in methanol and phosphate buffer, pH 6.8); moisture content (weight loss on desiccation over 24 h); and in vitro mouth-dissolving time using simulated salivary fluid (pH 5.7). In vitro drug release was studied using USP apparatus II (paddle, 100 rpm) in 900 mL phosphate buffer (pH 6.8) at $37 \pm 0.5^\circ\text{C}$, with samples withdrawn every 5 min up to 30 min and assayed spectrophotometrically [46,47,48,49]. Drug–excipient compatibility was additionally assessed by FTIR of the formulated lozenges.

Short-term accelerated stability of the optimized formulation was evaluated at $40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH for up to 90 days as per ICH guidelines, with physical appearance, drug content and hardness monitored at the end of the study [44].

Results and Discussion

Bitterness Intensity

Adsorbent treatment, application method and their interaction all had a significant effect ($p < 0.05$) on perceived bitterness. Most bentonite-treated samples showed reduced bitterness relative to the untreated extract, and boiling was more effective than submersion (Table 5) — an outcome attributed to the large specific

surface area of bentonite (approximately $800 \text{ m}^2/\text{g}$), which favours adsorption of bitter-tasting solutes.

Table 5. Bitterness intensity of bentonite-treated *Carica papaya* leaf extract.

Sample	Bitterness intensity (scalar score)
Bentonite, boiled (1:10)	0.5 ± 0.54
Bentonite, boiled (1:15)	0.3 ± 0.52
Bentonite, boiled (1:20)	1.2 ± 0.53
Bentonite, submerged (1:10)	3.8 ± 0.71
Bentonite, submerged (1:15)	3.2 ± 0.64
Bentonite, submerged (1:20)	2.8 ± 0.87

The boiled, 1:10 bentonite treatment gave the lowest overall bitterness score, and the 1:15 boiled treatment was selected for further phytochemical and formulation work as it gave comparably low bitterness (0.3, a mild rating) while using less adsorbent.

Phytochemical Screening

The bentonite-treated extract (1:15, boiled) was compared with the untreated extract for its qualitative phytochemical profile (Table 6). Carbohydrates, glycosides, alkaloids, phytosterols, proteins and phenols were detected in both extracts, whereas tannins and saponins, present in the untreated extract, were absent after bentonite treatment — consistent with adsorption of these bitter-tasting constituents by the clay.

Table 6. Phytochemical screening of untreated and bentonite-treated *Carica papaya* extract.

S.No	Constituent	Treated extract (bentonite, boiled)	Untreated extract
1	Carbohydrates	+	+
2	Glycosides	+	+
3	Alkaloids	+	+
4	Phytosterols	+	+
5	Proteins	+	+
6	Phenols	+	+
7	Tannins	–	+
8	Saponins	–	+

(+) indicates presence; (–) indicates absence of the constituent.

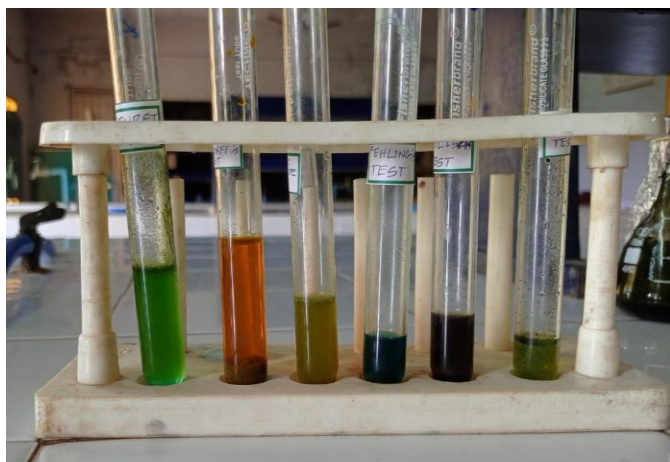


Figure 3. Phytochemical screening of untreated and bentonite-treated *Carica papaya* extract

Thin-Layer Chromatography

TLC of the extracts under UV light at 238 nm confirmed the presence of multiple phytochemical spots in both preparations. The untreated extract showed a higher R_f value (0.95) than the bentonite-treated extract (0.6), suggesting that the compounds retained after treatment were comparatively less polar than those present in the untreated extract; the results indicate that further isolation and characterization work would be needed to identify the individual constituents.

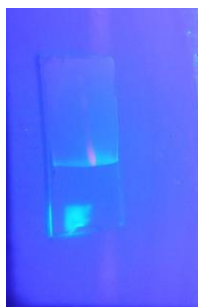


Figure 4. TLC profile of the untreated *Carica papaya* extract under UV light (238 nm).



Figure 5. TLC profile of the bentonite-treated *Carica papaya* extract under UV light (238 nm).

Antibacterial Activity

Both the treated and untreated extracts inhibited the growth of the Gram-positive and Gram-negative test organisms, although the bentonite-treated extract gave a smaller zone of inhibition than the untreated extract

against both organisms (Table 7), indicating that bentonite treatment reduced — without abolishing — the antibacterial activity of the extract.

Table 7. Zone of inhibition of untreated and bentonite-treated *Carica papaya* extract.

S.No	Extract	Gram-positive (<i>B. subtilis</i>)	Gram-negative (<i>E. coli</i>)
1	Untreated extract	14 mm	11 mm
2	Bentonite-treated extract	6 mm	5 mm
3	Standard	12 mm	10 mm

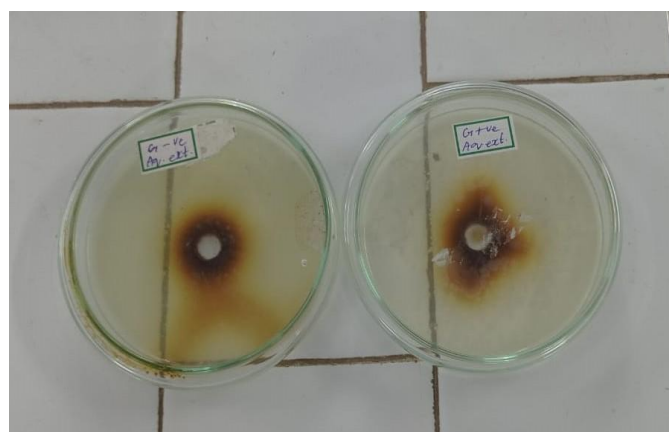


Figure 6. Zone of inhibition against *E. coli* and *B. subtilis* (untreated extract).

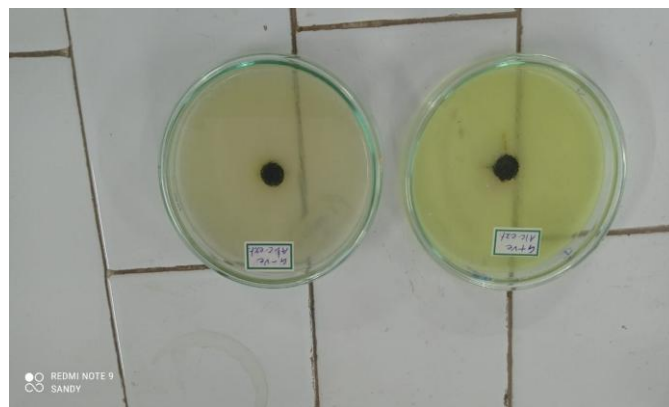


Figure 7. Zone of inhibition against *E. coli* and *B. subtilis* (bentonite-treated extract).

Preformulation Characteristics

The bentonite-treated extract was a pale green, characteristically bitter, semi-solid mass with a total yield of 16.3%. Its physicochemical characteristics are summarized in Table 8, and its particle size distribution in Table 9.

Table 8. Preformulation characteristics of the treated *Carica papaya* extract.

S.No	Parameter	Result
1	Colour	Pale green
2	Odour	Characteristic, bitter
3	Taste	Bitter
4	Total yield of extract	16.3%
5	Density	1.01 g/mL
6	Viscosity	0.09 poise
7	pH	7.2
8	Moisture content	40%
9	Ash value	17%

Table 9. Particle size analysis of the treated *Carica papaya* extract.

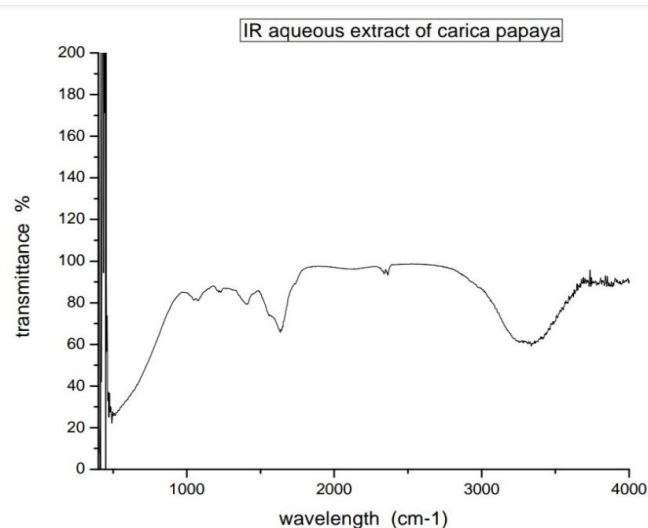
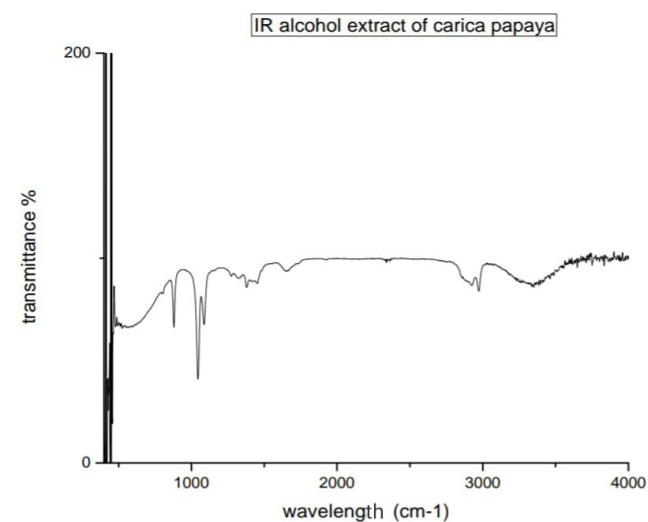
S.No	Mesh no.	Pore size (μm)	% Retained
1	#60	250	0
2	#80	180	12.4
3	#100	150	40.2
4	#140	106	53.4
5	#200	75	12

FTIR Compatibility

FTIR spectra of the untreated and bentonite-treated extracts (Figures 5 and 6) showed the expected absorption bands for the major functional groups present in the leaf extract, summarized in Table 10; no new bands or major shifts indicative of a chemical interaction with bentonite were observed.

Table 10. Principal FTIR absorption bands of untreated and bentonite-treated *Carica papaya* extract.

Extract	Frequency (cm^{-1})	Group assigned
Untreated	1000–1500	C–H bend
Untreated	1500–1750	N–H bend
Untreated	2000–2500	N=C=O stretch
Bentonite-treated	1000–1200	Aliphatic amine
Bentonite-treated	1500–1700	N–H bend
Bentonite-treated	2700–3000	C–H stretch

Figure 8. FTIR spectrum of the untreated *Carica papaya* leaf extract.Figure 9. FTIR spectrum of the bentonite-treated *Carica papaya* leaf extract.**Physicochemical Evaluation of Lozenges**

All five formulations were yellowish-green, smooth, non-gritty, square lozenges. Average weight ranged from 2.16 to 3.08 g, friability from 0.4% to 0.8%, hardness from 10.1 to 12.2 kg/cm², drug content from 89.2% to 97.3%, moisture content from 0.5% to 0.8%, and mouth-dissolving time from 9.9 to 14.8 min (Table 11), all within generally acceptable ranges for a moulded lozenge dosage form.

Table 11. Physicochemical evaluation of *Carica papaya* lozenge formulations (F1–F5).

S.No	Batch	Avg. weight (g)	Friability (%)	Hardness (kg/cm ²)	Thickness (mm)	Drug content (%)	Moisture (%)	Mouth-dissolving time (min)
1	F1	3.06	0.5	10.1	6.8	89.2	0.5	10.5
2	F2	3.05	0.6	12.2	6.9	90.3	0.7	11.3
3	F3	2.16	0.4	11.1	6.6	95.3	0.6	12.9
4	F4	3.08	0.5	10.2	6.5	97.3	0.5	9.9
5	F5	3.03	0.8	12.24	6.6	90.6	0.8	14.8

In vitro drug release

The in vitro release profile of *Carica papaya* extract from the lozenges is shown in Table 12. Across formulations, approximately 50% of the extract was released within 15–20 min, and F4 gave the fastest and most complete release, reaching 98.91% cumulative release at 45 min and was accordingly identified as the optimized formulation.

Table 12. In vitro cumulative drug release (%) of *Carica papaya* lozenge formulations (F1–F5).

Time (min)	F1	F2	F3	F4	F5
0	0	0	0	0	0
10	35.48	19.47	17.47	38.71	21.82
20	49.97	34.81	34.25	54.53	39.43
30	58.66	45.65	49.66	62.38	46.24
40	67.15	60.45	64.55	78.95	57.95
50	80.24	75.34	74.41	89.59	61.86
60	85.63	80.97	80.33	90.11	79.47

Stability Studies

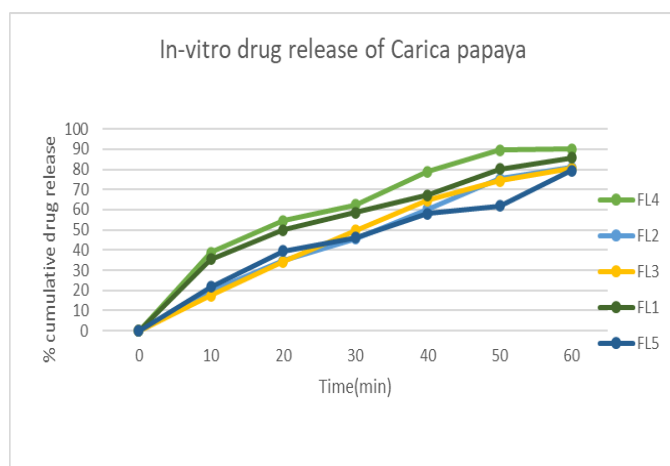
Formulation F4 was subjected to accelerated stability testing at 40±2°C/75±5% RH. No significant changes in physical appearance, drug content or hardness were observed after the study period (Table 13), and the in vitro release profile was likewise unchanged, indicating that the formulation retained its physicochemical and drug-release characteristics under accelerated storage conditions.

Table 13. Stability data for formulation F4 (40±2°C/75±5% RH).

Parameter	Initial	Final
Physical appearance	Yellowish-green lozenges	Yellowish-green lozenges
Drug content (%)	90.11 ± 0.15	90.08 ± 0.61
Hardness (kg/cm ²)	10.2 ± 0.21	9.9 ± 0.71

Conclusion

This study demonstrated that adsorbent treatment with bentonite can substantially reduce the bitterness of *Carica papaya* leaf extract, with boiling at a leaf-to-bentonite ratio of 1:15 giving a low bitterness score while largely preserving the extract's phytochemical profile; only tannins and saponins, both known bitter-tasting constituents, were lost on treatment. The treated extract was successfully incorporated into lozenges prepared by the heating-and-congealing method, and among the formulations evaluated, F4 (PEG:PVP 50:100 mg) gave the best combination of physicochemical properties, drug content and in vitro release, reaching 98.91% cumulative release within 45 min, with no significant change in its characteristics on short-term accelerated stability testing. These findings support the feasibility of combining an adsorbent-based bitterness-masking step with a lozenge dosage form to deliver *Carica papaya* leaf extract in a more palatable and stable format, and warrant further pharmacological evaluation of its platelet-supportive effects in the management of dengue-associated thrombocytopenia.

**Figure 10. Comparative in vitro drug release profiles of *Carica papaya* lozenge formulations (F1–F5).**

The standard curve of *Carica papaya* extract showed maximum absorption at 238 nm and obeyed the Beer-Lambert law over 2–10 µg/mL at this wavelength, consistent with the calibration data in Table 3.

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