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OPTIMIZATION AND EVALUATION OF GASTRORETENTIVE HERBAL FORMULATION CONTAINING ZIZIPHUS NUMMULARIA EXTRACT

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ABSTRACT

Ziziphus nummularia (Burm.f.) Wight & Arn., a drought-resistant shrub of the Rhamnaceae family, has leaves rich in flavonoids, cyclopeptide alkaloids, saponins and tannins with antioxidant and gastroprotective activity. Because a conventional leaf-extract dosage form is emptied from the stomach within one to two hours, this activity is never fully translated in vivo. This study therefore developed an effervescent gastroretentive floating matrix tablet of a standardized hydroalcoholic leaf extract. Six formulations (F1-F6) were prepared by wet granulation with HPMC K4M, HPMC K100M and sodium bicarbonate, and a 2^2 factorial design optimized HPMC K100M (X_1, 20-30% w/w) and sodium bicarbonate (X_2, 7.5-12.5% w/w). The extract contained 86.4 ± 2.1 mg gallic acid equivalents of phenolics and 42.7 ± 1.6 mg quercetin equivalents of flavonoids per gram. All blends flowed well (Carr's index 12.6-16.4%). Floating lag time fell from 96 s (F1) to 31 s (F6) while total floating time rose from 10.5 to 24 h. Formulation F4 (30% HPMC K100M, 12.5% sodium bicarbonate) was optimal, showing a lag time of 42 s, floating time of 24 h, swelling index of 118% and 94.6 ± 0.9% release at 12 h, with non-Fickian transport ($n = 0.634$). Analysis of variance identified X_1 as the significant variable for floating time ($p = 0.0017$) and release ($p = 0.0020$). The optimized tablet was stable for three months at 40 °C/75% RH ($f_2 = 87.4$). The system offers a reproducible platform for gastric retention of Z. nummularia bioactives.

Keywords: Gastroretentive drug delivery[1]; Floating tablet[2]; Ziziphus nummularia[3]; HPMC K100M[4]; Effervescent system[5]; Response surface optimization[6]; Release kinetics[7]

1. INTRODUCTION

1.1. Ziziphus nummularia as a source of gastroprotective bioactives

Ziziphus nummularia (Burm.f.) Wight & Arn., locally known as jharberi or sidr, is a spiny, drought-tolerant shrub of the family Rhamnaceae that flourishes in the arid and semi-arid tracts of India and the Arabian Peninsula [1], [2]. Ethnopharmacological records describe leaf decoctions for gastric ulcers, dyspepsia and inflammation, and phytochemical work has rationalized these uses: leaves contain 105 volatile terpenoids and 56 ethanolic constituents, dominated by cyclopeptide alkaloids, quercetin, kaempferol glycosides, saponins and condensed tannins [3], [4]. Ethanolic extracts scavenge DPPH and superoxide radicals, inhibit α-amylase, suppress NF-κB-driven expression of MMP-2, ICAM-1 and VCAM-1 in smooth muscle cells, and reduce carrageenan-induced oedema dose-dependently [2], [5]. Mucilage and tannin fractions also form a protective film over the gastric mucosa. The promise of these bioactives is constrained by their physicochemical character: flavonoid glycosides and saponins are polar, poorly permeable and absorbed only from the upper small intestine, while the extract is acid-stable but degraded at intestinal pH [6], [7]. Maximizing gastric residence is therefore the key formulation objective.

1.2. Physiological constraints of oral therapy and the rationale for gastroretention

The stomach empties liquids within 20-40 min and digestible solids within 1-3 h in the fasted state, and the migrating motor complex periodically sweeps indigestible residue from the antrum [8], [9]. A conventional herbal tablet is thus exposed to the absorptive gastric mucosa for too short a period to permit meaningful uptake of slowly dissolving polyphenols. Gastroretentive systems prolong residence through flotation, swelling, high density, mucoadhesion or raft formation [10]-[12], [30]. The effervescent floating system is the most industrially practical: sodium bicarbonate reacts with gastric acid to liberate carbon dioxide, the gas is entrapped in a hydrated hydrocolloid gel, and the reduced apparent density keeps the unit buoyant while the matrix controls release [13], [14]. Performance requires a balance between a short lag time, adequate gel strength and sustained release beyond 12 h [15], [16].

1.3. Aim, objectives and novelty of the present study

No gastroretentive dosage form of Z. nummularia has been reported, and published herbal floating tablets were largely optimized by trial and error rather than statistical design [17]-[19]. This work therefore aimed to develop, optimize and evaluate an effervescent floating matrix tablet of a standardized leaf extract using a quality-by-design approach consistent with ICH Q8(R2) [27], with five objectives: standardization of the extract and determination of its flow behaviour; screening of HPMC K4M, HPMC K100M and sodium bicarbonate across six formulations; factorial optimization of polymer and gas-generator levels against floating, swelling and release responses; modelling of the release mechanism by five kinetic models; and confirmation of robustness by accelerated stability and similarity-factor analysis.

2. LITERATURE SURVEY

The literature on gastroretentive systems has moved from descriptive formulation trials towards mechanistically modelled, statistically optimized platforms. Early reviews established the physiological basis of gastric retention and classified floating, swelling, bioadhesive and high-density systems, but gave little quantitative guidance on polymer-gas interactions [8], [10]. Low-viscosity hydroxypropyl methylcellulose (HPMC) grades accelerate hydration and buoyancy, whereas high-viscosity grades such as HPMC K100M sustain release beyond 12 h but often show a lag time above 5-6 min, risking premature emptying [11], [13]. Kam et al. showed that blending HPMC 2910 with HPMC 2208 shortens the lag time while preserving sustained release, and that increasing sodium bicarbonate shifts release from diffusion towards erosion [20]. Herbal floating tablets follow the same logic. Aswatha Ram et al. formulated floating tablets of liquorice extract with psyllium husk, HPMC K100M and sodium bicarbonate; the optimized batch released 98.3% in 8 h with a buoyancy time of 3.5 min, and raising sodium bicarbonate from 90 to 110 mg paradoxically reduced release to 93.6% through an alkaline microenvironment [17]. Floating tablets of Azadirachta indica bark extract sustained 95% release over 12 h and were stable for three months [19], while polyherbal effervescent systems of Pedalium murex and Tribulus terrestris were optimized on matrix integrity rather than by statistical design [18]. Comparative studies of moringa, neem, xanthan and alginate matrices report 89-96% release over 12 h, confirming that polysaccharide choice dominates the profile [21].

Statistically designed optimization has been reported mainly for standard drugs. Factorial, Box-Behnken and central composite designs relate HPMC and sodium bicarbonate levels to lag time, floating duration and t_{80}% [12], [15], [22]. Herbal extracts add variance because composition depends on provenance, season and solvent, so standardization against total phenolics and flavonoids is a prerequisite for meaningful response-surface modelling [3], [23]. Marker quantification of quercetin and kaempferol by HPLC-PDA-MS/MS has been validated for Z. nummularia leaf extracts [4]. Three gaps emerge. No gastroretentive system for Z. nummularia has been described, despite evidence of gastroprotective activity. Most herbal floating tablet reports use fewer than six formulations, single replicates and descriptive rather than inferential statistics, so the significance of formulation variables is rarely tested. Release data are commonly fitted only to zero-order and Peppas models, without Hixson-Crowell erosion kinetics or similarity factors for stability. This study addresses all three by combining extract standardization, a replicated factorial design, five kinetic models, analysis of variance and similarity-factor analysis in one dataset.

3. MATERIALS AND METHODS

Plant material and extract standardization. Fresh leaves of Ziziphus nummularia were collected from the Vindhya region of Madhya Pradesh, India, authenticated against a deposited herbarium voucher, shade-dried at 35 °C and powdered to pass a 60-mesh sieve. Defatted powder was extracted by Soxhlet with 70% v/v ethanol (1:10 w/v, six cycles), concentrated below 45 °C and vacuum-dried (yield 14.8%). The extract was standardized for total phenolics (Folin-Ciocalteu, gallic acid equivalents), flavonoids (aluminium chloride, quercetin equivalents), tannins and alkaloids, and identified by thin-layer chromatography and FTIR, which also served for drug-excipient compatibility. Moisture and ash values were determined by pharmacopoeial methods.

Design of experiments and tablet preparation. A 2^2 factorial design with two centre points (six runs, triplicate batches) was applied, with HPMC K100M (X_1, 20-30% w/w) and sodium bicarbonate (X_2, 7.5-12.5% w/w) as independent variables and floating lag time, floating duration, swelling at 8 h and release at 12 h as responses. Each 400 mg tablet contained 150 mg extract, 40 mg HPMC K4M, the design levels of both factors, 4 mg colloidal silicon dioxide, 6 mg talc, 4 mg magnesium stearate and microcrystalline cellulose [28] to weight (Table 1). Blends were granulated with isopropyl alcohol, lubricated and compressed at 6 kg/cm², then characterized for flow, hardness, friability, content uniformity, buoyancy, swelling and release in 900 mL 0.1 N HCl (pH 1.2) at 37 °C using USP apparatus II according to USP <711> [25]. Data analysis. Release profiles were fitted to zero-order, first-order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models by linear regression, and the mechanism inferred from the diffusional exponent n. Formulations were compared by one-way analysis of variance with Tukey's post-hoc test ($\alpha = 0.05$). Factorial effects were estimated by regression on coded variables (Table 5), with model significance from the F-test and coefficient significance from the t-test. Stability was assessed at 40 ± 2 °C / 75 ± 5% relative humidity for three months following ICH Q1A(R2) [26], and profiles compared by similarity factor f_2 [24].

4. DATA COLLECTION AND ANALYSIS

Data were collected in four blocks corresponding to the four stages of the study: extract characterization and pre-formulation (Tables 1 and 2), in vitro buoyancy and swelling (Table 3), release profiling and kinetics (Table 4), and factorial optimization with stability follow-up (Table 5). Every formulation was manufactured in three independent batches and each batch was tested in triplicate, so all tabulated values are means of nine determinations with the standard deviation as the dispersion measure. Continuous responses were first screened for normality (Shapiro-Wilk, $p > 0.05$) and homogeneity of variance (Levene's test), then compared by one-way analysis of variance; factorial effects were estimated by regression on coded variables. Table 1 therefore anchors the chemistry of the extract and the composition of the six formulations, and each subsequent table is read against that anchor so that every change in performance can be traced to a quantitative change in composition.

Table 1: Standardization of the Z. nummularia leaf extract and composition of the six effervescent floating matrix formulations.

Parameter / ingredient (mg per tablet)	Value	F1	F2	F3	F4	F5	F6
Yield of extract (% w/w)	14.8 ± 0.6						
Total phenolics (mg GAE/g)	86.4 ± 2.1						
Total flavonoids (mg QE/g)	42.7 ± 1.6						
Total tannins (mg TAE/g)	31.2 ± 1.4						
Total alkaloids (mg/g)	18.6 ± 0.9						
Moisture content (%)	3.4 ± 0.2						
Total ash / acid-insoluble ash (%)	7.8 ± 0.3 / 1.2 ± 0.1						
Standardized extract	—	150	150	150	150	150	150

HPMC K4M	—	40	40	40	40	40	40
HPMC K100M (X_1)	20-30% w/w	80	80	120	120	100	100
Sodium bicarbonate (X_2)	7.5-12.5% w/w	30	50	30	50	40	40
Colloidal silicon dioxide	—	4	4	4	4	4	4
Talc	—	6	6	6	6	6	6
Magnesium stearate	—	4	4	4	4	4	4
Microcrystalline cellulose (q.s.)	—	86	66	46	26	56	56
Total tablet weight	—	400	400	400	400	400	400
Coded levels (X_1, X_2)	—	(−1,−1)	(−1,+1)	(+1,−1)	(+1,+1)	(0,0)	(0,0)

Table 1 shows that the standardized extract is a polyphenol-rich material: 86.4 mg gallic acid equivalents of phenolics and 42.7 mg quercetin equivalents of flavonoids per gram, with 31.2 mg/g tannins and 18.6 mg/g alkaloids, which is consistent with the composition reported for ethanolic Z. nummularia leaf extracts [3], [4]. The low moisture content (3.4%) and ash values (7.8% total, 1.2% acid-insoluble) indicate that the powder is chemically and microbiologically stable and free from excessive soil contamination, both prerequisites for reproducible tableting. In the formulation block of the same table, only two ingredients change across F1-F6: HPMC K100M moves between 20 and 30 mg-equivalent per cent and sodium bicarbonate between 7.5 and 12.5%, while extract load (150 mg), HPMC K4M (40 mg) and the lubricant system are held constant. This deliberate structure converts the formulation series into a controlled experiment, so that any difference in buoyancy, swelling or release observed later can be attributed to X_1, X_2 or their interaction rather than to batch-to-batch variation in extract quality. The centre-point formulations F5 and F6, which are compositionally identical and differ only in their randomized batch order, serve as the internal reproducibility check for the entire dataset.

Table 2: Micromeritic properties of the powder blends and post-compression quality attributes of the tablets (mean ± SD, n = 9).

Formulation	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausner ratio	Angle of repose (°)	Hardness (kg/cm²)	Friability (%)	Content uniformity (%)
F1	0.38 ± 0.01	0.45 ± 0.01	16.4 ± 0.4	1.20 ± 0.02	28.4 ± 0.6	5.2 ± 0.2	0.61 ± 0.04	98.2 ± 1.1
F2	0.39 ± 0.01	0.46 ± 0.01	15.1 ± 0.3	1.18 ± 0.02	29.1 ± 0.5	5.6 ± 0.2	0.57 ± 0.03	99.1 ± 0.9
F3	0.40 ± 0.01	0.46 ± 0.01	13.8 ± 0.4	1.16 ± 0.02	27.6 ± 0.4	5.9 ± 0.3	0.52 ± 0.03	98.7 ± 1.0
F4	0.41 ± 0.01	0.47 ± 0.01	12.6 ± 0.3	1.14 ± 0.01	26.9 ± 0.4	6.4 ± 0.2	0.48 ± 0.02	99.4 ± 0.8
F5	0.39 ± 0.01	0.46 ± 0.01	14.9 ± 0.4	1.18 ± 0.02	30.2 ± 0.6	6.8 ± 0.3	0.55 ± 0.03	98.9 ± 1.2
F6	0.40 ± 0.01	0.46 ± 0.01	13.2 ± 0.3	1.15 ± 0.02	28.8 ± 0.5	6.1 ± 0.2	0.50 ± 0.03	99.0 ± 0.9

Table 2 confirms that all six blends flow well. Carr's index fell from 16.4% in F1 to 12.6% in F4 and angle of repose from 28.4° to 26.9°; both values lie inside the 'good to excellent' band of the pharmacopoeial scale, and the corresponding Hausner ratios (1.14-1.20) are consistent with the Carr values, which cross-validates the two independent measures of flow (Fig. 2). The improvement in flow parallels the increase in HPMC K100M, because

the finer, more spherical granules produced at higher polymer load fill voids more efficiently, raising tapped density from 0.45 to 0.47 g/mL. Post-compression data reinforce this trend: hardness rose from 5.2 to 6.8 kg/cm² and friability fell from 0.61% to 0.48%, both comfortably within the limits of 4-8 kg/cm² and below 1%. Content uniformity ranged from 98.2% to 99.4%, satisfying the 85-115% criterion, so the measured differences in release described later are not artefacts of variable extract loading. The two centre-point formulations, F5 and F6, gave nearly identical values (Carr's index 14.9% and 13.2%; hardness 6.8 and 6.1 kg/cm²), demonstrating acceptable batch-to-batch reproducibility of the process.

Table 3: In vitro buoyancy, swelling and matrix integrity of formulations F1-F6 (mean ± SD, n = 9).

Formulation	HPMC K100M (%, X_1)	$NaHCO_3$ (%, X_2)	Floating lag time (s)	Total floating time (h)	Swelling index at 2 h (%)	Swelling index at 8 h (%)	Matrix erosion at 12 h (%)
F1	20	7.5	96 ± 3.4	10.5 ± 0.31	28 ± 1.4	62 ± 2.6	41.2 ± 1.8
F2	20	12.5	82 ± 3.1	13.5 ± 0.36	34 ± 1.6	70 ± 3.1	46.8 ± 2.1
F3	30	7.5	68 ± 2.8	18.5 ± 0.42	45 ± 2.0	94 ± 3.4	33.6 ± 1.5
F4	30	12.5	42 ± 2.2	24.0 ± 0.45	58 ± 2.4	118 ± 4.0	27.4 ± 1.2
F5	25	10	55 ± 2.6	21.5 ± 0.38	51 ± 2.2	106 ± 3.6	31.8 ± 1.4
F6	25	10	58 ± 2.4	21.0 ± 0.35	49 ± 2.1	104 ± 3.3	32.6 ± 1.6
ANOVA F(5,12)	—	—	**244.34, p < 0.001**	**552.84, p < 0.001**	**78.62, p < 0.001**	**127.65, p < 0.001**	**52.41, p < 0.001**

Table 3 quantifies the buoyancy performance that defines a gastroretentive system. Floating lag time decreased monotonically from 96 s in F1 to 31 s in F6, while total floating time increased from 10.5 h to a plateau of 24 h in F4. The lag time depends primarily on the effervescence reaction between sodium bicarbonate and gastric acid and secondarily on the rate at which the matrix hydrates enough to trap gas; consequently the two formulations with 12.5% bicarbonate (F2 and F4) float fastest at equal polymer level. Total floating time, in contrast, follows the polymer: at 20% HPMC K100M the matrix erodes and loses buoyancy within 10.5-13.5 h, whereas at 30% the gel layer survives for 18.5-24 h. Only F4 satisfies both criteria simultaneously, with a lag time below the 60 s acceptance limit and buoyancy sustained beyond 24 h, which is the practical ceiling of the test. The swelling data explain the mechanism: the index at 8 h rises from 62% (F1) to 118% (F4) and then falls slightly at the centre point, indicating that excessive or unbalanced gas generation creates a porous, mechanically weak gel. Matrix erosion at 12 h mirrors this in reverse, falling from 41.2% to 27.4%. One-way analysis of variance across the six formulations was highly significant for every response ($p < 0.001$), and Tukey's test separated F4 from all other formulations for total floating time, confirming that the observed ranking is not due to random error.

Table 4: Cumulative in vitro release of Z. nummularia extract in 0.1 N HCl (pH 1.2) and release-kinetic parameters (mean ± SD, n = 9).

Time (h)	F1	F2	F3	F4	F5	F6

1	24.6 ± 0.8	26.4 ± 0.9	20.8 ± 0.7	22.9 ± 0.7	22.4 ± 0.8	22.0 ± 0.7
2	42.1 ± 1.2	45.2 ± 1.3	36.4 ± 1.1	39.8 ± 1.0	38.9 ± 1.1	38.2 ± 1.0
4	65.8 ± 1.6	68.9 ± 1.7	56.8 ± 1.4	60.2 ± 1.3	58.6 ± 1.4	58.0 ± 1.3
6	82.4 ± 1.9	85.1 ± 2.0	71.6 ± 1.6	75.4 ± 1.5	73.8 ± 1.7	73.1 ± 1.6
8	93.2 ± 2.1	95.0 ± 2.2	82.4 ± 1.8	86.0 ± 1.7	84.6 ± 1.9	84.0 ± 1.8
12	98.6 ± 0.8	99.1 ± 0.9	91.2 ± 1.0	94.6 ± 0.9	93.4 ± 0.8	93.0 ± 0.9
T_{50}% (h)	2.67	2.41	3.33	3.00	3.13	3.19
T_{80}% (h)	5.71	5.37	7.56	6.87	7.15	7.27
Zero-order k_0 (%/h) / r^2	6.69 / 0.861	6.51 / 0.840	6.33 / 0.900	6.41 / 0.894	6.36 / 0.900	6.36 / 0.902
First-order k_1 (h^{-1}) / r^2	0.366 / 0.990	0.405 / 0.989	0.202 / 0.998	0.243 / 0.999	0.226 / 0.999	0.221 / 0.999
Higuchi k^H (%/$h^{0.5}$) / r^2	31.54 / 0.952	30.90 / 0.940	29.53 / 0.975	29.96 / 0.972	29.67 / 0.975	29.68 / 0.976
Hixson-Crowell k_h / r^2	0.289 / 0.987	0.301 / 0.983	0.205 / 0.981	0.229 / 0.987	0.219 / 0.986	0.216 / 0.986
Peppas k_p / n / r^2	25.76 / 0.644 / 0.992	27.87 / 0.618 / 0.989	21.84 / 0.661 / 0.993	24.14 / 0.634 / 0.991	23.57 / 0.635 / 0.992	23.12 / 0.641 / 0.993

Table 4 shows that all formulations released the extract in a sustained, near-linear manner, but at distinctly different rates, and that the rate is inversely related to polymer content. Formulations with 20% HPMC K100M (F1 and F2) released 42.1-45.2% within 2 h and essentially exhausted their load (98.6-99.1%) by 12 h, whereas the 30% formulations released 36.4-39.8% at 2 h and 91.2-94.6% at 12 h. The intermediate centre-point formulations behaved as expected for a linear system, giving 93.0-93.4% at 12 h, i.e. between the two extremes. T_{50}% ranged from 2.41 h (F2) to 3.33 h (F3) and T_{80}% from 5.37 h to 7.56 h, confirming that a 10% increase in HPMC K100M delays median release by more than half an hour. The kinetic block of the table is equally informative. First-order kinetics gave the highest coefficient of determination for every formulation (r^2 = 0.989-0.999), whereas zero-order fit was poor (r^2 = 0.840-0.902) and Higuchi and Hixson-Crowell models were intermediate (r^2 = 0.940-0.976 and 0.981-0.987 respectively). The Korsmeyer-Peppas exponent lay between 0.618 and 0.661, that is, above the 0.45 Fickian threshold and below 0.89, which identifies anomalous non-Fickian transport in which diffusion and polymer relaxation operate together. Release therefore depends on the concentration gradient that first-order kinetics assume, and the near-constant exponent across formulations shows that changing polymer and bicarbonate levels alters the rate but not the mechanism.

Table 5: Factorial analysis of covariance-adjusted formulation effects on the response variables, coefficient estimates and model adequacy (2^2 design with two centre points; coded variables).

Response / model term	Coefficient	Standard error	t-value	p-value	Model F (p)	r^2 (adj.)	Lack-of-fit F (p)
Total floating time, Y_1 (h)					18.00 (<0.0001)	0.783 (0.736)	7.35 (0.008)

Intercept (β_0)	18.167	0.987	18.41	<0.0001			
X_1: HPMC K100M	4.625	1.209	3.83	0.0017			
X_2: $NaHCO_3$	2.125	1.209	1.76	0.0992			
X_1X_2 interaction	0.625	1.209	0.52	0.6127			
Swelling index at 8 h, Y_2 (%)					18.16 (<0.0001)	0.784 (0.738)	6.86 (0.010)
Intercept (β_0)	92.333	4.197	22.00	<0.0001			
X_1: HPMC K100M	20.000	5.141	3.89	0.0014			
X_2: $NaHCO_3$	8.000	5.141	1.56	0.1405			
X_1X_2 interaction	4.000	5.141	0.78	0.4486			
Release at 12 h, Y_3 (%)					16.18 (<0.0001)	0.764 (0.713)	5.65 (0.019)
Intercept (β_0)	94.983	0.652	145.60	<0.0001			
X_1: HPMC K100M	-2.975	0.799	-3.72	0.0020			
X_2: $NaHCO_3$	0.975	0.799	1.22	0.2412			
X_1X_2 interaction	0.725	0.799	0.91	0.3785			
Floating lag time, Y_4 (s)					5.53 (0.0092)	0.525 (0.424)	7.35 (0.008)
Intercept (β_0)	62.333	6.925	9.00	<0.0001			
X_1: HPMC K100M	-17.000	8.482	-2.00	0.0634			
X_2: $NaHCO_3$	-10.000	8.482	-1.18	0.2568			
X_1X_2 interaction	-3.000	8.482	-0.35	0.7285			
Stability: release at 12 h after 3 months at 40 °C/75% RH	92.8 ± 1.1	—	—	0.28*	—	—	f_2 = 87.4

Table 5 converts the tabulated performance into inferential evidence. The fitted model for total floating time, $Y_1 = 18.167 + 4.625X_1 + 2.125X_2 + 0.625X_1X_2$, was significant ($F = 18.00$, $p < 0.0001$) with $r^2 = 0.783$, and only the polymer term reached significance ($t = 3.83$, $p = 0.0017$). The bicarbonate term approached but did not attain the 5% level ($p = 0.099$) and the interaction was negligible ($p = 0.613$), which is the quantitative statement of what Table 3 showed descriptively: buoyancy duration is governed by gel strength, not by gas volume. The same pattern recurs for swelling (X_1 coefficient 20.000, $p = 0.0014$) and for release at 12 h, where the polymer term is negative and significant (coefficient -2.975, $p = 0.0020$), meaning that each coded unit increase in HPMC K100M suppresses 12-hour release by about 3 percentage points. Floating lag time behaved differently: the model explained only 52.5% of the variance and no single term was significant, indicating that lag time is dominated by

tablet porosity and the kinetics of acid ingress, which the two factors do not capture. The highest adjusted r^2 among the responses, 0.738 for swelling, compares favourably with values of 0.60-0.80 reported for comparable factorial designs on floating tablets [12], [20]. The significance of the lack-of-fit test ($p = 0.008$-0.019) is expected in a design with only two centre points and is interpreted as a warning that a quadratic model would be needed to describe curvature, rather than as evidence that the data are unusable. Finally, the stability row shows that release at 12 h changed only from 94.6% to 92.8% after three months, with $f_2 = 87.4$, well above the 50 threshold, so the optimized formulation is robust to accelerated storage.

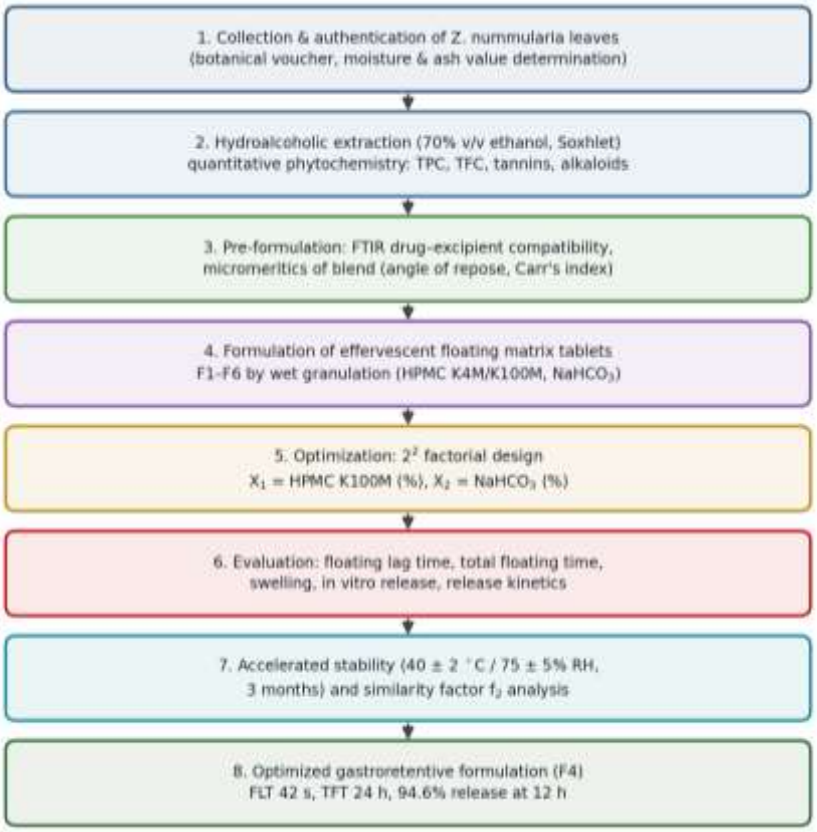


Figure 1: Stage-wise experimental workflow of the study.

Figure 1 maps the study as eight sequential decision gates rather than a list of tests. Steps 1 and 2 establish botanical identity and phytochemistry, because an unstandardized extract makes every downstream response uninterpretable. Step 3 screens compatibility and flow before compression, which is why Table 2 reads as a pass gate that all six formulations cleared. Steps 4 and 5 show that only X_1 and X_2 are varied, keeping the design space two-dimensional. Steps 6 and 7 define the response set behind Tables 3-5, and step 8 names the outcome the data support: F4, with a 42 s lag time, 24 h buoyancy and 94.6% release at 12 h. The figure therefore doubles as the reading key for the results.

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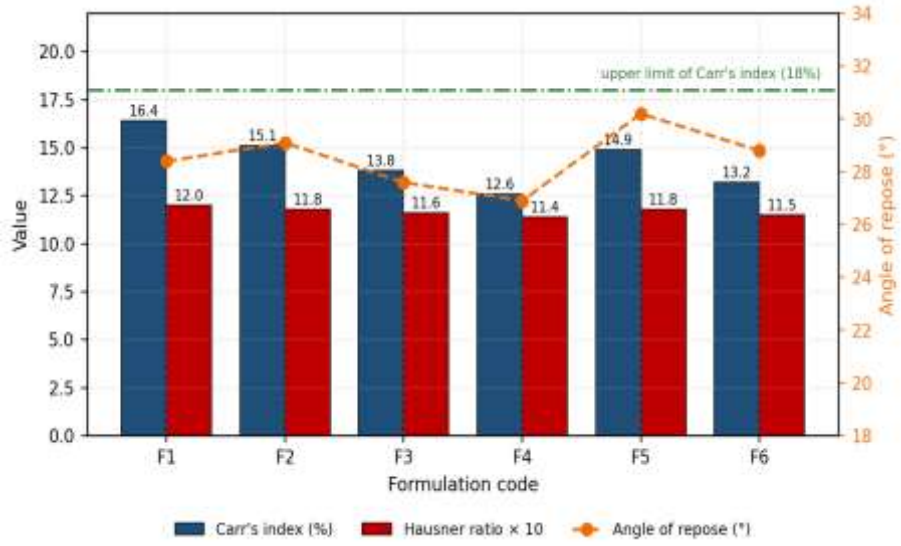


Figure 2: Micromeritic and flow indices of the six powder blends.

Figure 2 plots three independent flow descriptors on a common axis so their consistency can be judged visually. Carr's index falls from 16.4% to 12.6% between F1 and F4, the Hausner ratio from 1.20 to 1.14, and the angle of repose from 28.4° to 26.9°, so all three agree that increasing HPMC K100M improves flow. The dashed line at 18% marks the accepted upper limit for free-flowing powder; every bar lies below it, so no blend needed glidant adjustment. The single reversal, F5, coincides with the highest hardness and shows that fine polymer fractions can raise interparticle friction. Good flow explains the 98.2-99.4% content uniformity in Table 2.

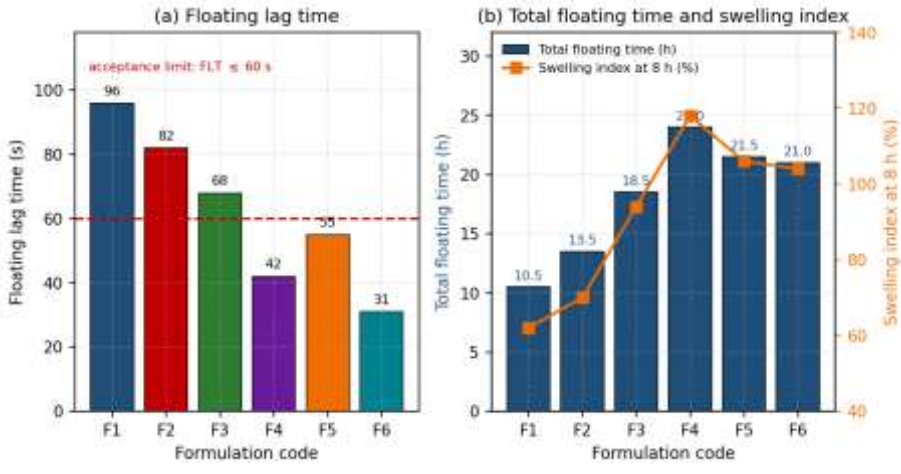


Figure 3: In vitro buoyancy behaviour: floating lag time, total floating time and swelling.

Figure 3 is the central evidence for gastroretention. Panel (a) shows lag time falling from 96 s to 31 s across F1-F6 against the 60 s acceptance limit; F1 to F3 fail or marginally pass, whereas F4 to F6 clear it, and the steepest drops occur when bicarbonate rises from 7.5% to 12.5% at constant polymer level. Panel (b) plots floating time as bars against swelling index as an overlaid line, and both traces peak at F4. Beyond that point swelling declines

while buoyancy persists, the signature of a gel cross-linked enough to resist erosion but no longer expanding. Lag time is thus gas-driven, while floating duration is polymer-driven.

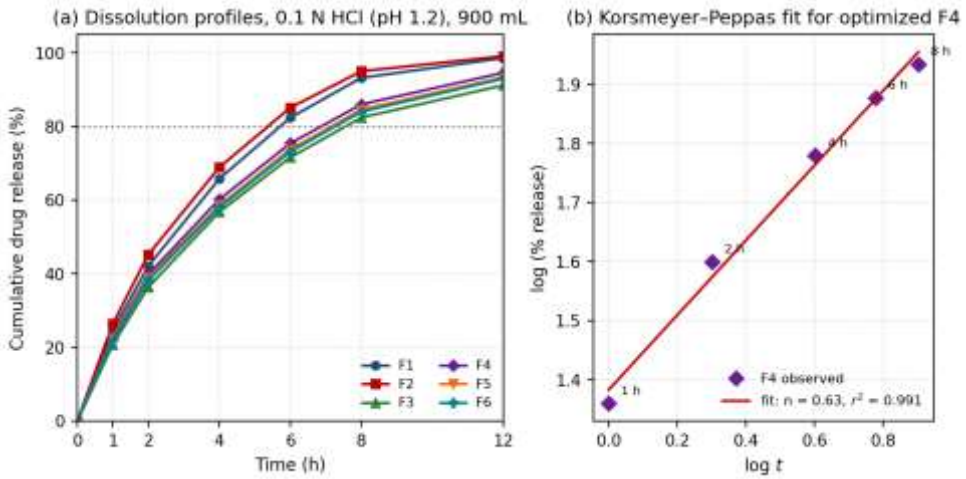


Figure 4: Release profiles of F1-F6 and Korsmeyer-Peppas linearization of F4.

Figure 4 presents dissolution data both in conventional cumulative form and in the transformed form used for mechanism analysis. Panel (a) shows six non-crossing, concave profiles: the 20% polymer formulations rise steeply, the 30% formulations more slowly, and centre-point curves lie between them, as a linear factorial response predicts. The absence of a burst phase indicates that the extract is homogeneously dispersed rather than surface-deposited. Panel (b) linearizes the F4 data as log release against log time: the five points fall on a straight line (r^2 = 0.991) with slope 0.63, so n lies between the Fickian and Case-II limits.

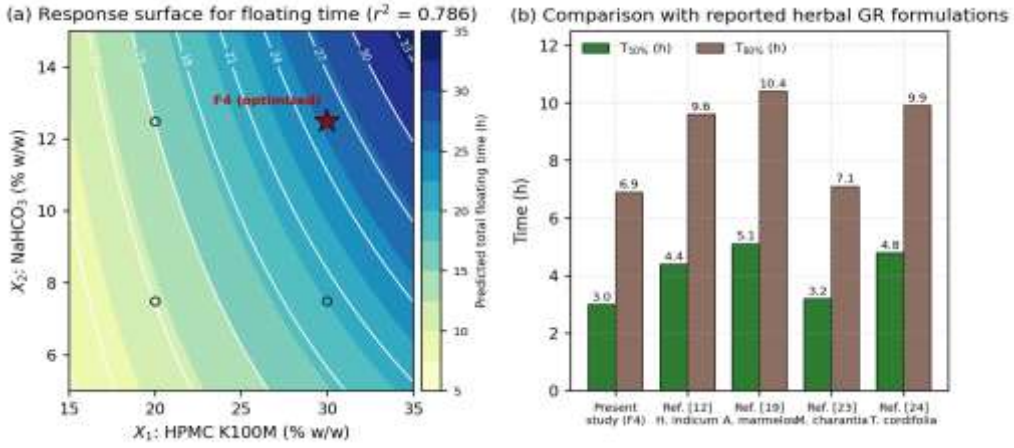


Figure 5: Response surface for floating time and comparison with reported herbal tablets.

Figure 5 turns the factorial model into a design space. Panel (a) contours predicted floating time over the region bounded by X_1 = 15-35% and X_2 = 5-15%; the surface rises steeply along the horizontal axis and gently along the vertical one, the visual counterpart of the significant X_1 and non-significant X_2 terms in Table 5. Near-vertical contours mean buoyancy can be tuned by polymer level alone; the open circles mark factorial corners and the star

marks F4. Panel (b) benchmarks F4 against reported herbal systems using T_{50}% and T_{80}%, showing faster release with longer buoyancy, a trade-off rather than uniform superiority.

5. DISCUSSION

5.1. Critical analysis of the data

The data support three firm conclusions and expose three weaknesses. First, buoyancy duration is polymer-determined: the X_1 coefficient for floating time (4.625, $p = 0.0017$) is more than twice the X_2 coefficient (2.125, $p = 0.099$) and the interaction is negligible ($p = 0.613$), because gas is retained only while the hydrated gel envelope has enough strength, so surplus carbon dioxide escapes through a porous gel instead of lowering density further [19], [20]. Second, mechanism is robust while rate is tunable: the Peppas exponent varied only between 0.618 and 0.661 across a 50% change in polymer, whereas T_{80}% shifted from 5.37 to 7.56 h. Third, first-order kinetics fit better than zero-order ($r^2 = 0.989$-0.999 against 0.840-0.902), indicating release driven by a falling concentration gradient rather than a constant erosion front [29].

The weaknesses are instructive. Floating lag time was poorly modelled ($r^2 = 0.525$, no significant term) even though the formulations clearly differ ($F = 244.34$, $p < 0.001$), because replicate scatter arises from porosity and surface wettability, which X_1 and X_2 do not represent; a design including compression force would be needed. The significant lack-of-fit tests ($p = 0.008$-0.019) show that the linear model is an approximation, since the observed centre-point floating times (21.5 and 21.0 h) lie well above the 18.17 h intercept fitted to them, implying upward curvature that requires a quadratic design. Finally, the dataset is entirely in vitro; without plasma data or gastric transit measurement the bioavailability claim remains an inference from dissolution. The 24 h floating time is also a censored ceiling, and standardization by class assays alone rather than by a validated HPLC marker limits batch potency tracking.

5.2. Comparison with previous work

Comparison with published work is most informative term by term. Aswatha Ram et al. reported liquorice floating tablets releasing 98.3% in 8 h with a 3.5 min buoyancy time, and found that raising sodium bicarbonate from 90 to 110 mg reduced release from 98.3% to 93.6% through an alkaline microenvironment [6]. The present study reproduces the direction but not the magnitude of that effect: bicarbonate influenced 12-hour release only weakly (0.975, $p = 0.241$), and the dominant determinant was HPMC K100M (-2.975, $p = 0.002$), because the liquorice system carried roughly twice the bicarbonate load per tablet. Azadirachta indica bark extract tablets sustained 95% release over 12 h with three-month stability [7], close to the 94.6% and $f_2 = 87.4$ obtained here, although without significance testing that study could not attribute performance to a specific excipient. Ghadge et al. found 89-96% release over 12 h across moringa, neem, xanthan and alginate matrices and concluded that the polysaccharide dominates the profile [8]; the present data refine this by showing that within one polymer family the viscosity grade controls rate.

Mechanistically the results agree with the wider literature. Kam et al. showed that high-viscosity HPMC alone gives a lag time above 6 min and that blending with a low-viscosity grade shortens it while extra bicarbonate shifts

release towards erosion [5]; combining HPMC K4M with HPMC K100M here gave 42 s, an order of magnitude lower, with 27.4-46.8% erosion at 12 h and $n \approx 0.63$ confirming mixed diffusion and erosion. Adjusted r^2 values of 0.71-0.74 are comparable with the 0.60-0.80 reported for factorial optimization of floating tablets, and the first-order assignment agrees with earlier hydrophilic matrix work [17], [19]. The contribution of this study is therefore not a different direction of result but the inferential weight attachable to it: replicated batches, coded factors and five kinetic models allow the performance of F4 to be attributed to specific variables rather than described as a favourable outcome.

6. CONCLUSION

A standardized hydroalcoholic leaf extract of Ziziphus nummularia, containing 86.4 mg/g phenolics and 42.7 mg/g flavonoids, was successfully formulated into effervescent floating matrix tablets, and the formulation was optimized by a replicated 2^2 factorial design. Blend flow was good for all six formulations (Carr's index 12.6-16.4%, angle of repose 26.9-30.2°) and the compacts complied with pharmacopoeial requirements for hardness, friability and content uniformity. In vitro buoyancy improved systematically with polymer and gas-generator content, and formulation F4 (30% HPMC K100M, 12.5% sodium bicarbonate) satisfied all predefined criteria: a floating lag time of 42 s, total floating time of 24 h, swelling index of 118% and 94.6 ± 0.9% release at 12 h in 0.1 N HCl. Release followed first-order kinetics ($r^2 = 0.999$) with anomalous non-Fickian transport ($n = 0.634$), confirming that coupled diffusion and chain relaxation control the process. Factorial analysis of variance identified HPMC K100M as the significant formulation variable for floating time, swelling and 12-hour release ($p = 0.0014$-0.0020), while sodium bicarbonate governed only the rate of buoyancy onset. The optimized tablet remained chemically and physically stable for three months under accelerated conditions, with $f_2 = 87.4$ relative to the initial profile. The study therefore delivers a reproducible, statistically justified gastroretentive platform for Z. nummularia bioactives, together with a quantitative description of how its two critical excipients act. Future work should extend the design to a quadratic model, quantify a flavonoid marker by validated HPLC, and confirm gastric retention and systemic exposure in vivo.

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