Formulation and Optimization of Gastroretentive Effervescent Floating Matrix Tablets of Tofacitinib Citrate Using a 3^2 Full Factorial Design

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Abstract

Background: Tofacitinib citrate is a BCS Class 3 drug that is highly soluble in gastric fluid but far less soluble at intestinal pH, so prolonged gastric residence is a rational delivery strategy.

Objective: To develop and select an effervescent floating matrix tablet of tofacitinib citrate (17.77 mg, equivalent to 11 mg tofacitinib) using a 3^2 full factorial design.

Methods: Nine batches (F1–F9) were prepared by wet granulation with isopropyl alcohol. HPMC K100M (30, 40, 50 mg) and sodium bicarbonate (20, 30, 40 mg) were varied; xanthan gum, citric acid, PVP K30 and lubricants were constant. Compatibility was studied by FTIR. Granules and tablets were evaluated for flow, physical quality, floating, swelling, assay (HPLC) and release in 0.1 N HCl over 12 h. Floating lag time was analysed by two-way ANOVA and the other responses by regression on coded factors.

Results: FTIR showed no new bands suggesting a chemical interaction. All batches floated within 13.3–26.7 s and stayed buoyant for more than 12 h. Floating lag time depended on a significant HPMC × bicarbonate interaction ($p < 0.001$). Swelling at 12 h (146.7–226.4%) rose with both HPMC ($p < 0.001$) and bicarbonate ($p < 0.001$). Release at 6 h fell from 78–81% (30 mg HPMC) to 50–55% (50 mg HPMC) and was not significantly affected by bicarbonate. Assay was 98.15–100.14%. Batch F7 (50 mg HPMC K100M, 20 mg sodium bicarbonate) released 26% at 1 h and 97% at 12 h, with the most linear release profile of the nine batches (zero-order $R^2 = 0.983$) and a Korsmeyer–Peppas exponent of 0.43.

Conclusion: F7 gave controlled, diffusion-influenced release with sustained buoyancy and is a promising gastroretentive candidate. Its hardness was marginally above target, no check-point batch, stability or in vivo data were generated, and its suitability for once-daily dosing needs pharmacokinetic confirmation.

Keywords: tofacitinib citrate; gastroretentive; floating tablet; HPMC K100M; xanthan gum; 3^2 factorial design

1. Introduction

Tofacitinib is an oral Janus kinase inhibitor, active mainly against JAK1 and JAK3, and is used in rheumatoid arthritis and ulcerative colitis. Because treatment is long term, dosing convenience matters. The immediate-release tablet is taken twice daily, whereas the once-daily 11 mg extended-release product relies on osmotic-pump technology [1,2]. A model-informed bridging analysis found tofacitinib exposure from 11 mg extended-release once daily comparable to that from 5 mg

immediate-release twice daily [1]. A simpler matrix tablet that delivers the same 11 mg dose over a prolonged period would therefore be a practical alternative to a technology that is demanding to manufacture.

The biopharmaceutical profile supports a gastric approach. Tofacitinib citrate is classified as BCS Class 3 (high solubility, low permeability), with solubility above 28 mg/mL at pH 1.0 that falls to 0.20 mg/mL above pH 8 [3]. In our own measurements the citrate salt dissolved to 23.86 mg/mL in 0.1 N HCl (pH 1.2) but only 0.12 mg/mL at pH 6.8. The drug is absorbed rapidly, with peak plasma levels about 1 h after an oral dose [4]. A tablet that leaves the stomach within a couple of hours releases much of its drug where it is least soluble. Prolonging gastric residence should keep the drug in solution at the upper gastrointestinal tract for longer. We note that the relative absorption of tofacitinib from different gastrointestinal regions has not been established in the literature we reviewed, so gastric retention here is a rational hypothesis that in vivo work must test.

Gastric residence can be prolonged by mucoadhesion, swelling, high-density systems and flotation [5,6]. Effervescent floating matrices are among the easiest to make on conventional equipment. On contact with gastric fluid, sodium bicarbonate and an acid generate carbon dioxide that is trapped in the hydrating polymer gel and lowers the apparent density below that of gastric contents [7,8]. The gel layer then controls drug release. High-viscosity HPMC grades form strong gels, and xanthan gum can reinforce them [9,10]. Floating tablets of tofacitinib citrate have been reported with HPMC K4M and Carbopol 934 [11] and with xanthan gum in a 3^2 design [12]. To our knowledge, the combination of HPMC K100M with xanthan gum has not been reported for this drug.

Factorial designs have been used to study how polymer and gas-forming agent levels interact in floating tablets [13–15]. A three-level design can also reveal curvature that a two-level design would miss. We applied a 3^2 full factorial design to examine how HPMC K100M and sodium bicarbonate affect floating, swelling and release of a 200 mg tablet containing tofacitinib citrate equivalent to 11 mg tofacitinib, and selected a batch against pre-defined targets.

2. Materials and Methods

2.1 Materials and equipment

Tofacitinib citrate was obtained as a gift sample from Aurore Lifesciences, and its identity and purity were confirmed against the supplier’s certificate of analysis. HPMC K100M (Colorcon), xanthan gum (Anmol Chemicals), sodium bicarbonate (Merck), anhydrous citric acid (Sisco Research Laboratories), PVP K30 (JRS Pharma), microcrystalline cellulose PH-101 (Chemfield Cellulose), magnesium stearate (Peter Greven) and talc (IMIFABI) were of pharmaceutical grade. Chromatographic solvents were HPLC grade. Equipment comprised a Sartorius balance, Cadmach tablet press, Mettler Toledo halogen moisture analyser, Lab India hardness tester (TH 1050 M), Electrolab tap density tester and friabilator (EF-2), Insize Vernier caliper, a Bruker FTIR

spectrometer, a Malvern laser-diffraction analyser, a Lab India UV spectrophotometer and USP dissolution apparatus, and a Waters HPLC system with Empower 3 software.

2.2 Preformulation studies

Colour, odour and appearance were recorded. The melting range was determined by the capillary method in triplicate. Equilibrium solubility was measured by the shake-flask method in water, 0.1 N HCl (pH 1.2), acetate buffer (pH 4.5) and phosphate buffer (pH 6.8) with continuous agitation, followed by filtration and dilution. Particle size (d10, d50, d90) was measured by wet-dispersion laser diffraction. For the UV method, standards of 2–30 µg/mL (and a blank) were prepared in 0.1 N HCl from a stock solution, absorbance was read at 287 nm, and the calibration line was fitted by linear regression.

2.3 Drug–excipient compatibility

FTIR spectra of the pure drug and of a physical mixture of the drug with all excipients in formulation proportions were recorded under identical conditions (approximately 4000–600 cm^{-1}). The spectra were compared for shifted, missing or additional bands.

2.4 Experimental design

A 3^2 full factorial design was used. The independent variables were HPMC K100M (X_1: 30, 40, 50 mg) and sodium bicarbonate (X_2: 20, 30, 40 mg), coded −1, 0 and +1. The responses were floating lag time (Y_1), total floating time (Y_2) and cumulative release at 12 h (Y_3) (Table 2). The nine combinations gave batches F1–F9 (Table 1). Each tablet contained 17.77 mg tofacitinib citrate (11 mg tofacitinib) and weighed 200 mg, with microcrystalline cellulose adjusted to keep the weight constant. After evaluation, the batch for further development was chosen against pre-defined targets for release, floating and tablet quality (Table 2). A minimum of 85% release at 12 h was the design criterion for Y_3, and a stricter 95% was applied when choosing among batches that met the other targets.

Table 1. Composition of formulations F1–F9 (mg per tablet).

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tofacitinib citrate	17.77	17.77	17.77	17.77	17.77	17.77	17.77	17.77	17.77
HPMC K100M (X_1)	30	30	30	40	40	40	50	50	50
Xanthan gum	10	10	10	10	10	10	10	10	10
Sodium bicarbonate (X_2)	20	30	40	20	30	40	20	30	40
Citric acid (anhydrous)	12	12	12	12	12	12	12	12	12
PVP K30	5	5	5	5	5	5	5	5	5
MCC PH-101 (q.s.)	99.23	89.23	79.23	89.23	79.23	69.23	79.23	69.23	59.23
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4
Total	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Table 2. Factorial design variables, responses and targets.

Item	Definition	Levels / target
X_1	HPMC K100M (mg)	30 / 40 / 50 (−1 / 0 / +1)
X_2	Sodium bicarbonate (mg)	20 / 30 / 40 (−1 / 0 / +1)
Y_1	Floating lag time	< 60 s
Y_2	Total floating time	> 12 h
Y_3	Cumulative release at 12 h	≥ 85% (design); ≥ 95% (batch selection)
Selection	Release profile	≤ 30% at 1 h; about 45–60% at 4–6 h
Selection	Tablet quality	Hardness 5.5–7.5 kg/cm²; friability < 1%; assay 95–105%

2.5 Preparation of tablets

All powders were passed through 40- and 60-mesh sieves. The drug, HPMC K100M, xanthan gum, sodium bicarbonate, citric acid and microcrystalline cellulose were mixed geometrically for 10 min. PVP K30 was dissolved in a minimum quantity of isopropyl alcohol, chosen as a non-aqueous fluid so that the effervescent pair would not react prematurely, and added dropwise to the blend with continuous mixing in a rapid mixer granulator until a coherent damp mass formed (end point checked by passing the mass through a 16-mesh sieve). The granules were dried in a hot-air oven at 50 °C for about 2 h until loss on drying fell below 2% w/w, sized through a 20-mesh sieve, and lubricated for 2 min with magnesium stearate and talc. Tablets were compressed on a single-punch machine with 7.5 mm round standard concave punches to a hardness of 5.5–7.5 kg/cm² and a target weight of 200 mg.

2.6 Evaluation of granules and tablets

Bulk and tapped volumes (500 taps) were used to calculate bulk and tapped density, Carr's index and Hausner's ratio, and the angle of repose was measured by the fixed-funnel method; flow was judged against standard scales [16]. Acceptance limits were Carr's index ≤ 25%, Hausner's ratio ≤ 1.25 and angle of repose ≤ 35°. Weight variation, hardness (Pfizer-type tester), friability (twenty tablets, 100 rpm for 4 min, Roche friabilator) and thickness (digital Vernier caliper) were determined. Weight, hardness and thickness are reported as mean ± SD of three tablets per batch. The IP weight-variation limit for tablets of 130–324 mg is ±7.5%.

2.7 Floating behaviour and swelling

Each tablet was placed in 900 mL of 0.1 N HCl at 37 ± 0.5 °C in a USP Type II apparatus at 50 rpm. Floating lag time was the interval until the tablet reached the surface (three tablets per batch), and total floating time was observed hourly up to 12 h. For swelling, tablets were removed at 1, 2, 4, 6, 8 and 12 h, blotted, and weighed, and swelling index was calculated as $[(W_t - W_0)/W_0] \times 100$.

2.8 Drug content

Drug content was determined by reversed-phase HPLC on a YMC Pack ODS-A column (150 × 4.6 mm, 5 µm) at 40 °C. The mobile phase was pH 5.5 phosphate buffer containing 1-octane sulphonic acid and acetonitrile (65:35, isocratic) at 1.0 mL/min, with detection at 287 nm, 10 µL injections and a 7 min run. A powder equivalent to 17.77 mg of tofacitinib citrate from twenty crushed tablets was

extracted with methanol, diluted with acetonitrile–water (50:50) and filtered (0.45 µm nylon) before injection. System suitability required a tailing factor of at most 2.0, a relative standard deviation of at most 2.0% for six standard injections and a similarity factor of 98.0–102.0%.

2.9 In vitro release and kinetics

Release was studied in 900 mL of 0.1 N HCl (pH 1.2) at 37.0 ± 0.5 °C using a USP Type II paddle at 50 rpm, with six tablets per batch. Samples (10 mL) were withdrawn at 1, 2, 3, 4, 6, 8, 10 and 12 h, replaced with fresh medium, filtered (0.45 µm), and read at 287 nm against a standard of 12 µg/mL; results were corrected for the volume withdrawn. Release data of all nine batches were fitted by linear regression (with intercept) to the zero-order and Higuchi models and, using points up to 60% release, to the Korsmeyer–Peppas model [17–20]. The Korsmeyer–Peppas model was fitted only where five or more points fell at or below 60%. Fit quality was compared by R^2. The similarity factor (f_2) [21] was computed on the mean profiles.

2.10 Statistical analysis

Floating lag time (three tablets per batch) was analysed by two-way ANOVA with replication (HPMC K100M × sodium bicarbonate, 18 error degrees of freedom). Swelling and release were measured once per batch and time point, so they were analysed by least-squares regression of the batch values on the coded factors. The linear model $Y = b_0 + b_1X_1 + b_2X_2$ is reported; the full quadratic model (with X_1X_2, X_1^2 and X_2^2 terms, three residual degrees of freedom) was also examined, and its additional terms were not significant ($p > 0.1$) for any of these responses. Because these regressions have few degrees of freedom, their p-values are exploratory. Significance was set at $p < 0.05$. Calculations used Python (NumPy, SciPy).

3. Results and Discussion

3.1 Drug characterization

The drug was a white to off-white, odourless crystalline powder that melted at 198–202 °C. Solubility fell steeply as pH rose (Table 3), in line with the published pH profile [3]. Because 11 mg of tofacitinib (17.77 mg citrate) dissolves in 250 mL at every pH tested, the low-dose strength is not solubility-limited; the concern is that drug released after leaving the stomach meets a medium in which it dissolves poorly. The particle size was fine (d10 1.87 µm, d50 6.72 µm, d90 17.90 µm), which favours content uniformity. The UV calibration line over 0–30 µg/mL was $y = 0.0757x + 0.0014$ with $R^2 = 0.9995$.

Table 3. Equilibrium solubility and particle size of tofacitinib citrate.

Medium	Solubility (mg/mL)	Particle size	Value (µm)
Water	2.90	d10	1.87
0.1 N HCl (pH 1.2)	23.86	d50	6.72
Acetate buffer (pH 4.5)	1.81	d90	17.90
Phosphate buffer (pH 6.8)	0.12		

3.2 Drug–excipient compatibility

The pure drug showed bands at 3374 cm^{-1} (O–H/N–H stretching), 3154 and 3136 cm^{-1} (aromatic C–H), 2978 and 2923 cm^{-1} (aliphatic C–H), 1732 cm^{-1} (carbonyl, mainly citrate), 1620 and 1528 cm^{-1} (heteroaromatic C=N/C=C and N–H), 1345 cm^{-1} (C–N), 1211, 1116 and 1055 cm^{-1} (C–O), and 844 and 704 cm^{-1} (aromatic C–H bending) (Table 4, Fig. 1). In the physical mixture the carbonyl band (1732 cm^{-1}), the heteroaromatic bands (1619 and 1528 cm^{-1}) and the C–N and C–O bands (1342 and 1210 cm^{-1}) were essentially unchanged. The O–H/N–H band moved to 3324 cm^{-1} and the aliphatic C–H bands to 2916 and 2850 cm^{-1}, the weak aromatic C–H bands near 3154 and 3136 cm^{-1} were no longer distinct, and a strong band appeared near 1016 cm^{-1} with a weak band at 1411 cm^{-1}. These changes are what one expects when the drug's modest peaks are overlapped by the broad hydroxyl, C–H and C–O absorptions of HPMC, xanthan gum and cellulose. No new band indicating a chemical reaction appeared and the characteristic drug peaks persisted, so the excipients were considered compatible. Thermal analysis would add confidence but was not performed.

Table 4. FTIR bands (cm^{-1}) of tofacitinib citrate and the physical mixture.

Drug	Mixture	Assignment	Observation
3374.31	3324.24	O–H / N–H stretching	Shifted (overlap with excipient O–H)
3154.39, 3135.84	–	Aromatic C–H stretching	Not distinct in mixture
2977.94	2916.02	Aliphatic C–H stretching	Shifted
2923.06	2849.88	Aliphatic C–H stretching	Shifted
1731.83	1731.89	C=O stretching (citrate)	Retained
1619.53	1619.19	C=N / C=C (heteroaromatic)	Retained
1527.60	1528.04	C=C / N–H	Retained
–	1410.91	C–H bending	Additional weak band (excipients)
1344.72	1342.13	C–N stretching	Retained
1210.56	1209.91	C–O stretching	Retained
1116.13	–	C–O stretching	Not distinct
1054.56	1015.80	C–O / C–C (polymeric)	Shifted (strong excipient band)
843.57	841.13	Aromatic C–H bending	Retained
704.13	659.14	Skeletal / C–H bending	Shifted

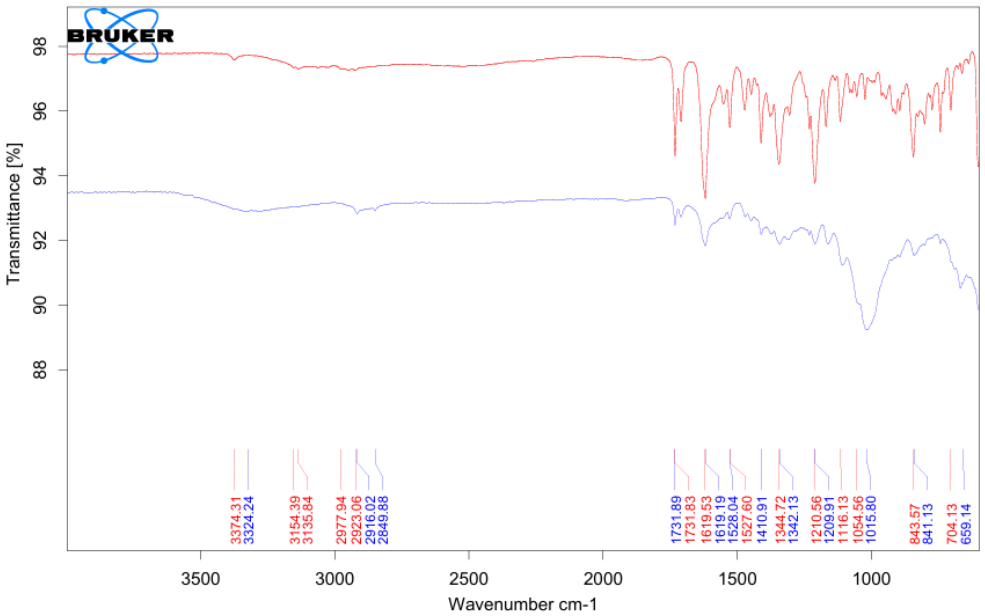

Fig. 1. FTIR spectra of tofacitinib citrate (upper trace) and the drug–excipient physical mixture (lower trace).

3.3 Granule properties

Bulk density ranged from 0.265 to 0.358 g/mL and tapped density from 0.321 to 0.425 g/mL (Table 5). Carr's index was 14.29–18.18% for F1–F8, giving good flow for F1, F2, F5 and F6 and fair flow for F3, F4, F7 and F8 on the USP scale, and 22.50% for F9 (passable). Hausner's ratios were 1.167–1.222 for F1–F8, but F9 reached 1.290, above the 1.25 limit. Angles of repose were 30.47–33.69° for F1, F2 and F4–F6 but 37.57–42.27° for F3 and F7–F9, exceeding the 35° limit. Flow therefore tended to worsen at the higher polymer level, in line with the cohesive, hydrophilic nature of HPMC K100M, although F3 (30 mg HPMC, 40 mg bicarbonate) shows that bicarbonate content also matters. Poor flow did not translate into poor tablets, since weight variation stayed small in every batch (Table 6), but F7 would benefit from a glidant or granule-size optimization at scale-up.

Table 5. Micromeritic properties of the granules (calculated from the measured weights, volumes and cone dimensions).

Batch	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausner's ratio	Angle of repose (°)	Flow (Carr, USP)
F1	0.325	0.382	15.00	1.176	30.47	Good
F2	0.333	0.389	14.29	1.167	33.69	Good
F3	0.305	0.366	16.67	1.200	37.57	Fair
F4	0.358	0.425	15.79	1.188	32.83	Fair
F5	0.300	0.351	14.58	1.171	32.01	Good
F6	0.324	0.378	14.29	1.167	33.69	Good
F7	0.265	0.321	17.39	1.211	37.57	Fair
F8	0.327	0.400	18.18	1.222	38.66	Fair
F9	0.305	0.394	22.50	1.290	42.27	Passable

3.4 Tablet quality and drug content

Average tablet weight lay between 198.8 and 200.9 mg, and no individual weight deviated from its batch mean by more than 2.0%, well inside the ±7.5% IP limit (Table 6). Friability was 0.05–0.13%, well below 1%, and thickness varied only from 4.42 to 4.53 mm. Hardness ranged from 5.97 ± 0.64 to 7.57 ± 0.21 kg/cm². Most batches fell inside the 5.5–7.5 kg/cm² target; F7 was marginally above it, although its friability of 0.07% shows that the extra strength did no harm. Hardness tended to be higher at 50 mg HPMC K100M. HPLC assay values lay between 98.15 ± 0.28% (F4) and 100.14 ± 0.22% (F6) of label claim, all within 95–105%, so the wet granulation process delivered the intended drug content in all nine batches.

Table 6. Physical properties of tablets and drug content (mean ± SD; weight, hardness and thickness n = 3; friability on twenty tablets).

Batch	Weight (mg)	Hardness (kg/cm²)	Friability (%)	Thickness (mm)	Drug content (% label claim)
F1	199.8 ± 1.8	6.27 ± 0.06	0.13	4.42 ± 0.02	98.79 ± 0.38
F2	200.6 ± 2.1	6.63 ± 0.15	0.10	4.44 ± 0.02	99.04 ± 0.35
F3	199.4 ± 1.8	7.00 ± 0.10	0.08	4.44 ± 0.01	100.02 ± 0.23
F4	200.9 ± 1.7	5.97 ± 0.64	0.12	4.47 ± 0.01	98.15 ± 0.28
F5	200.3 ± 2.5	6.00 ± 0.17	0.07	4.51 ± 0.01	99.88 ± 0.27
F6	199.1 ± 2.6	6.33 ± 0.21	0.05	4.53 ± 0.01	100.14 ± 0.22
F7	200.7 ± 2.6	7.57 ± 0.21	0.07	4.46 ± 0.02	99.24 ± 0.28
F8	199.5 ± 2.9	7.10 ± 0.26	0.08	4.50 ± 0.01	99.98 ± 0.27
F9	198.8 ± 3.9	6.63 ± 0.25	0.08	4.53 ± 0.01	100.09 ± 0.33

3.5 Floating behaviour and swelling

All tablets began to float within 30 s (Table 7, Fig. 2), inside the 60 s target, and all stayed afloat beyond 12 h, so Y_2 did not discriminate between batches. Two-way ANOVA of floating lag time showed significant effects of HPMC K100M ($F_{2,18}$ = 10.39, p = 0.001), sodium bicarbonate ($F_{2,18}$ = 12.98, p < 0.001) and, notably, their interaction ($F_{4,18}$ = 11.20, p < 0.001) (Table 8, Fig. 4a). At 30 and 40 mg HPMC K100M, raising sodium bicarbonate shortened the lag time (25.67, 21.67 and 14.33 s for F1–F3; 24.00, 17.33 and 13.33 s for F4–F6), as expected from faster gas generation. At 50 mg polymer this trend was lost (22.00, 21.67 and 26.67 s for F7–F9), which is the source of the interaction. A possible reason is that the denser gel formed at high polymer content delays hydration of the core and traps gas less readily, but this was not tested directly.

Swelling rose steadily with time and with polymer content: 146.7–158.9% at 30 mg, 172.5–189.8% at 40 mg and 209.3–226.4% at 50 mg HPMC K100M after 12 h (Table 7, Fig. 3). In the regression on coded factors, swelling at 12 h increased by 32.1 percentage points per HPMC level (p < 0.001) and by 7.8 points per bicarbonate level (p < 0.001) (R^2 = 0.994; Table 9, Fig. 4b). More gas generation may open the matrix and admit more fluid, although this was not examined. A thicker gel layer is the basis of both prolonged buoyancy and diffusional resistance, so these results fit the release behaviour described below.

Table 7. Floating lag time (FLT, mean ± SD, n = 3) and swelling index (%) of F1–F9; total floating time exceeded 12 h for every batch.

Batch	FLT (s)	1 h	2 h	4 h	6 h	8 h	12 h
F1	25.67 ± 2.08	41.8	69.4	94.2	117.5	134.1	146.7
F2	21.67 ± 2.52	46.3	71.8	103.6	126.2	137.9	151.4
F3	14.33 ± 1.53	49.1	78.2	106.9	129.8	147.3	158.9
F4	24.00 ± 1.73	52.7	80.6	118.4	140.3	159.7	172.5
F5	17.33 ± 2.52	53.9	87.1	121.5	151.6	164.8	185.2
F6	13.33 ± 1.15	58.4	89.7	130.2	154.9	175.6	189.8
F7	22.00 ± 3.61	61.2	99.5	136.8	171.4	185.9	209.3
F8	21.67 ± 3.21	66.7	101.8	147.3	174.2	197.5	213.6
F9	26.67 ± 2.52	68.5	110.4	149.7	185.1	201.8	226.4

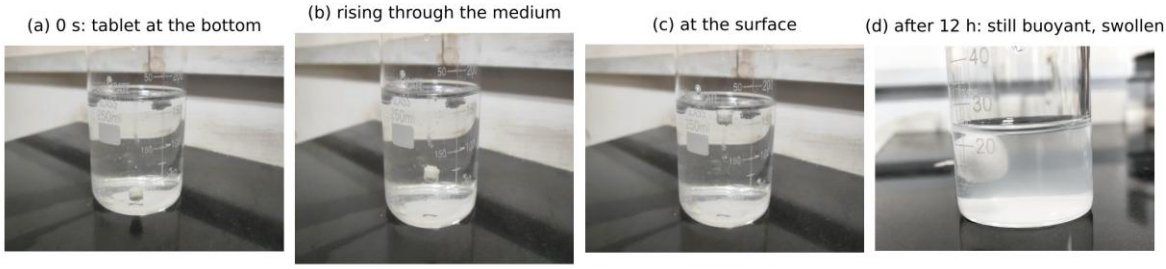

Fig. 2. Floating behaviour of a representative tablet in 0.1 N HCl: (a) at introduction, (b) rising, (c) at the surface, and (d) after 12 h, swollen and still buoyant.

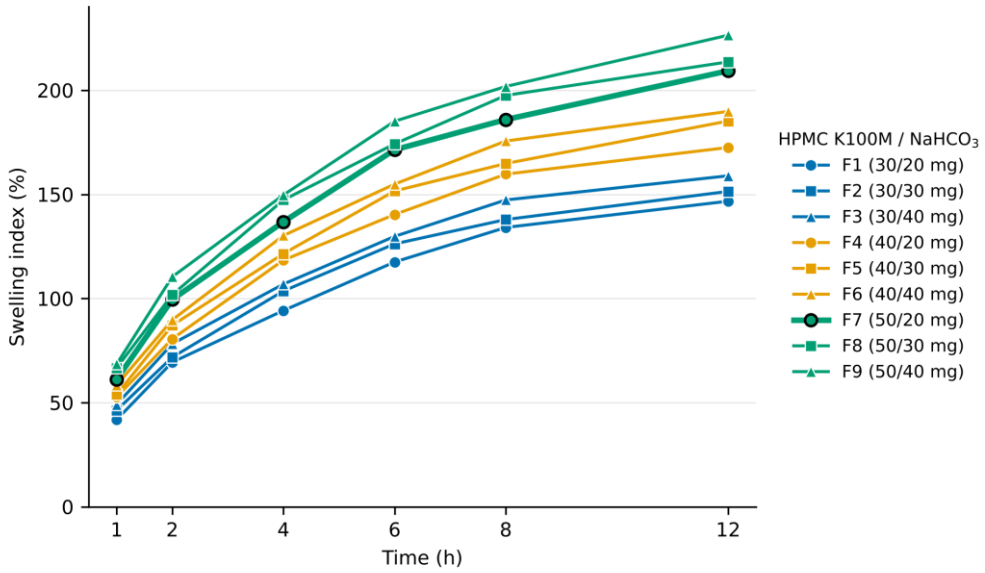

Fig. 3. Swelling index of F1–F9 in 0.1 N HCl over 12 h (colour = HPMC K100M level; marker = sodium bicarbonate level).

Table 8. Two-way ANOVA of floating lag time (n = 3 per batch).

Source	Sum of squares	df	Mean square	F	p
HPMC K100M	123.19	2	61.59	10.39	0.001
Sodium bicarbonate	153.85	2	76.93	12.98	< 0.001
HPMC × bicarbonate	265.48	4	66.37	11.20	< 0.001
Error	106.67	18	5.93		
Total	649.19	26			

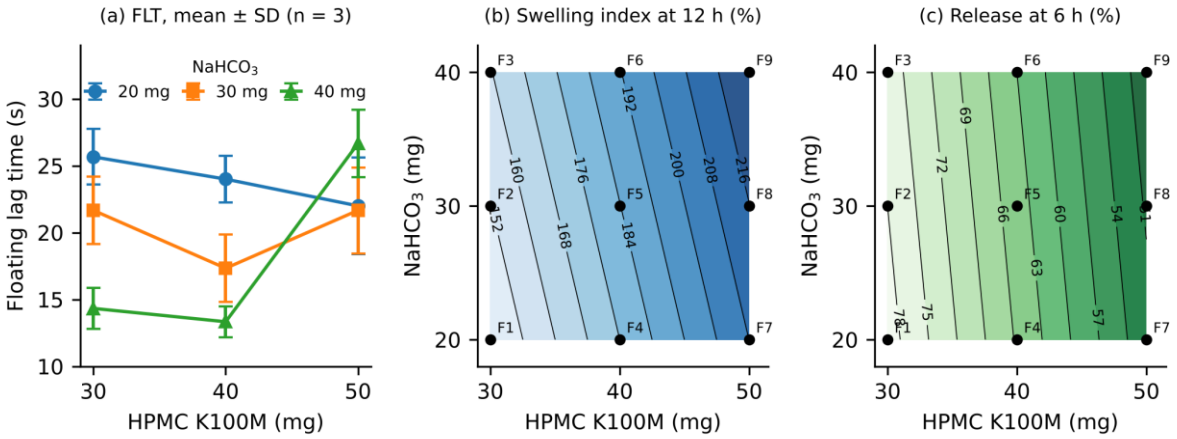

Fig. 4. (a) Floating lag time showing the HPMC K100M × sodium bicarbonate interaction (mean ± SD); (b) swelling index at 12 h and (c) release at 6 h predicted from the linear models in Table 9. Points mark the nine batches.

3.6 In vitro drug release

Release profiles are given in Table 10 and Fig. 5. Polymer level had the dominant effect. At 6 h the 30 mg batches (F1–F3) had released 78–81%, against 50–55% for the 50 mg batches (F7–F9), consistent with a thicker, more viscous gel offering greater diffusional resistance [22]. In the regression, release at 4 h and 6 h fell by 10.8 and 13.7 percentage points per HPMC level ($p = 0.002$ and $p < 0.001$), whereas release at 12 h was not significantly affected by either factor ($R^2 = 0.44$; Table 9), reflecting near-complete release in all batches (90–99%). F1 showed the fastest early release (52% at 1 h), which indicates that 30 mg of polymer with 20 mg bicarbonate was not enough to form a protective gel quickly.

Sodium bicarbonate did not accelerate release. At 30 and 50 mg HPMC K100M, 6 h release fell slightly as bicarbonate increased (81, 80 and 78% for F1–F3; 55, 52 and 50% for F7–F9), and the 40 mg series was not monotonic (64, 55 and 64% for F4–F6). Only release at 1 h showed a significant bicarbonate effect, in the direction of slower early release (−8.2 points per level, $p = 0.039$). One possible explanation is that bicarbonate not neutralized by the fixed 12 mg of citric acid raised the pH inside the gel and lowered the drug's solubility there. We did not test this and offer it only as a hypothesis for follow-up work.

Table 9. Coded-factor models ($Y = b_0 + b_1X_1 + b_2X_2$); coefficients with p-values in parentheses (exploratory, see Section 2.10).

Response	b_0	b_1 (HPMC)	b_2 ($NaHCO_3$)	R^2	Adj. R^2
Swelling at 12 h (%)	183.8	+32.05 (< 0.001)	+7.77 (< 0.001)	0.994	0.992
Release at 1 h (%)	28.9	−6.00 (0.101)	−8.17 (0.039)	0.640	0.520
Release at 4 h (%)	57.3	−10.83 (0.002)	−2.83 (0.222)	0.829	0.771
Release at 6 h (%)	64.3	−13.67 (< 0.001)	−1.33 (0.476)	0.911	0.881
Release at 12 h (%)	95.0	−1.83 (0.129)	−1.33 (0.248)	0.440	0.254

Table 10. Cumulative drug release (%) in 0.1 N HCl.

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	52	30	28	40	17	19	26	26	22
2	61	47	34	50	23	25	37	35	30
3	69	57	45	57	34	33	44	44	37
4	73	71	66	61	46	54	50	48	47
6	81	80	78	64	55	64	55	52	50
8	87	94	84	70	76	71	67	61	66
10	93	96	89	85	91	84	85	77	72
12	97	99	97	95	95	90	97	91	94

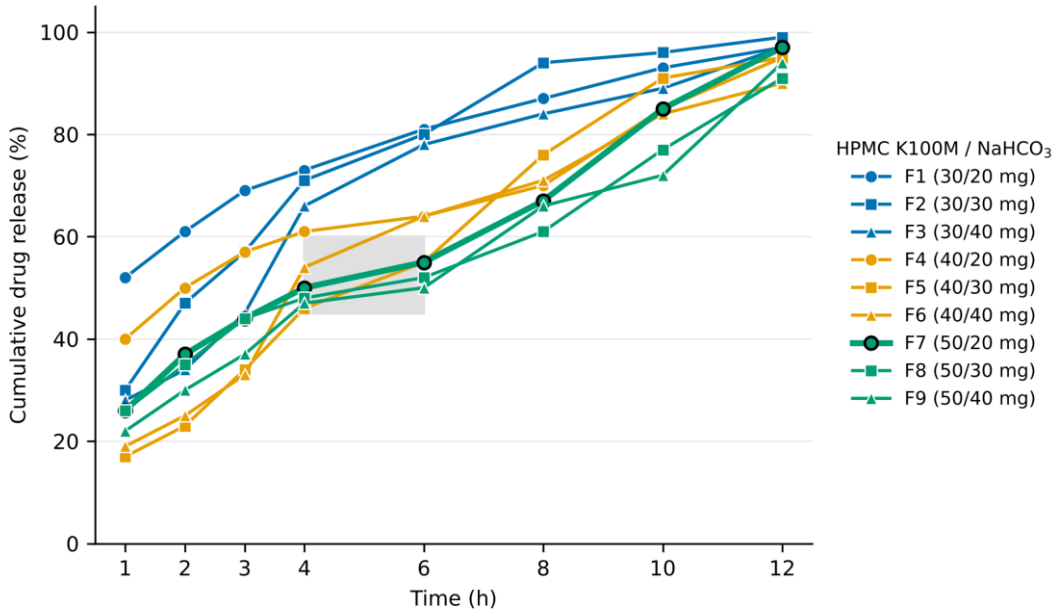

Fig. 5. In vitro release profiles of F1–F9 in 0.1 N HCl (pH 1.2), USP Type II, 50 rpm, 37 °C (colour = HPMC K100M level; marker = sodium bicarbonate level; F7 in bold). The grey box marks the target of about 45–60% release at 4–6 h.

3.7 Release kinetics

All nine batches were fitted to three models (Table 11). F7 had the highest zero-order R^2 of the nine batches (0.983; the next best was F5 at 0.981), meaning that its release rate was the most nearly constant. For F7, the Korsmeyer–Peppas exponent was 0.43, below the 0.45 limit for Fickian diffusion in cylindrical matrices, pointing to diffusion-controlled release through the hydrated gel; F8 (0.40) behaved similarly, while F9 (0.49) and F5 (0.70) fell in the anomalous-transport range. Differences in R^2 between the three models were small (for F7, 0.960–0.984), so the models cannot be

separated with confidence, and the exponent rests on only five points up to 60% release and should be read with caution. Higuchi fits were as good as or better than zero order for most of the faster-releasing batches (F1–F3, F6).

Table 11. Kinetic model fitting (R^2; linear regression with intercept).

Batch	Zero order	Higuchi	Korsmeyer–Peppas R^2	n
F1	0.949	0.994	–	–
F2	0.886	0.961	–	–
F3	0.903	0.957	–	–
F4	0.962	0.950	–	–
F5	0.981	0.982	0.972	0.70
F6	0.947	0.976	–	–
F7	0.983	0.960	0.984	0.43
F8	0.972	0.948	0.975	0.40
F9	0.976	0.954	0.977	0.49

Korsmeyer–Peppas was fitted only where five or more points were at or below 60% release (not available for F1–F4 and F6).

3.8 Selection of the batch for further development

F1–F4 were rejected because of burst or fast release (52% at 1 h for F1, 71% at 4 h for F2, 66% at 4 h for F3, 40% at 1 h for F4). F6, F8 and F9 released only 90%, 91% and 94% at 12 h and missed the 95% target. F5 and F7 met every release target. F7 was preferred for three reasons: its profile was the most uniform (no burst; 26% at 1 h, 50% at 4 h, 97% at 12 h), it formed a stronger gel (swelling 209.3% against 185.2% for F5), and F5 accelerated sharply between 6 and 8 h (55% to 76%) and had released 91% by 10 h. The mean profiles of F5 and F7 were nevertheless similar by the similarity factor (f_2 = 54.6; indicative only, since vessel-level variability was not used), so the choice between them rests on the profile shape rather than on a large difference in extent of release.

F7 has two weaknesses. Its hardness (7.57 ± 0.21 kg/cm²) slightly exceeded the 7.5 kg/cm² target, which can probably be corrected by lowering the compression force, and its granule flow was only fair (Carr's index 17.39%). F5, with hardness of 6.00 ± 0.17 kg/cm² and a Carr's index of 14.58%, is the closest alternative. Because the nine design points were evaluated directly and no additional check-point batch was prepared, the selection is a choice among tested batches, not a model-predicted optimum.

3.9 Limitations

The conclusions are limited by several factors. Swelling and release were measured once per batch and time point in the data analysed here, so the regression p-values are exploratory and vessel-to-vessel variability in release is not shown. Hardness, thickness and weight were measured on three tablets per batch. Release was studied in a single medium (0.1 N HCl), and no stability, in vivo buoyancy or pharmacokinetic data were generated. Xanthan gum was held constant, so its contribution relative to HPMC K100M alone was not separated. Release over 12 h was evaluated;

whether this supports once-daily dosing, and whether gastric retention improves absorption of this BCS Class 3 drug, must be established in vivo.

4. Conclusion

A 3^2 full factorial design allowed the effects of HPMC K100M and sodium bicarbonate on a tofacitinib citrate floating matrix tablet to be examined. HPMC K100M controlled swelling and early-to-mid release, while floating lag time depended on an interaction between the two variables. Batch F7 (17.77 mg tofacitinib citrate, 50 mg HPMC K100M, 10 mg xanthan gum, 20 mg sodium bicarbonate and 12 mg citric acid in a 200 mg tablet) floated in 22 s, stayed buoyant beyond 12 h, swelled to 209.3%, contained 99.24% of the label claim and released 97% of the drug over 12 h without an initial burst. These findings support F7 as a simple gastroretentive candidate and a possible alternative to osmotic technology. Compression-force adjustment, stability studies, radiological or scintigraphic retention studies and pharmacokinetic evaluation are the logical next steps.

Declarations

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Author contributions. Sathish K: investigation, formal analysis, writing – original draft. Mariyappan G: conceptualization, supervision, writing – review and editing. Karthi J: resources, project administration. All authors approved the final manuscript.

Ethics. Not applicable; no human participants or animals were used.

Data availability. The data supporting this study are included in the article and its Supplementary Material; further raw data are available from the corresponding author on reasonable request.

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