

Formulation and Evaluation of Gastroretentive Floating Matrix Tablets of Clarithromycin Using HPMC and Xanthan Gum: *In-Vitro* Characterization and *In-vivo* γ - Scintigraphic Assessment

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Abstract

Background: Clarithromycin is a macrolide antibiotic central to *Helicobacter pylori* eradication regimens, yet its short half-life necessitates multiple daily doses and conventional sustained-release forms leave the stomach before achieving effective local concentrations at the gastric mucosa. A gastroretentive floating system could prolong gastric residence and sustain release at the site of infection.

Objective: To develop and evaluate effervescent, hydrodynamically balanced floating matrix tablets of clarithromycin (500 mg) using hydroxypropyl methylcellulose (HPMC K4M and K15M) and xanthan gum, and to confirm gastric retention in human volunteers.

Methods: Fifteen batches (F1–F15) were prepared by wet granulation with isopropyl alcohol, using sodium bicarbonate as the gas-generating agent and microcrystalline cellulose as diluent. Granules were assessed for angle of repose, bulk and tapped density and compressibility index. Tablets were evaluated for hardness, friability, weight variation, drug content, dimensions, in vitro release (USP apparatus II, 0.1 N HCl, 50 rpm), release kinetics, floating lag time, total floating time and swelling. Drug–excipient compatibility was examined by FTIR and DSC. The optimized batch (F13) was compared with a marketed product, subjected to three-month accelerated stability testing (40 °C/75% RH), and studied by γ -scintigraphy using ^{99m}Tc -labelled tablets in six healthy volunteers under fasted and fed conditions.

Results: Granules showed good flow (angle of repose 24.2–30.3°; compressibility index 14.0–20.4%). Tablets met quality limits (hardness 4.4–6.0 kg/cm²; friability below 0.75%; drug content 94.1–104.8%). All batches floated within 2 minutes and remained buoyant for 10 hours or longer. Release rate was governed by polymer type and ratio: batches containing xanthan gum with HPMC K15M gave more controlled release than those with K4M, and increasing the xanthan fraction generally slowed release. Batch F13 (HPMC K15M 8%, xanthan gum 8%) released 99.0% of drug in 12 hours with a floating lag time of 112 s, followed the Korsmeyer–Peppas model ($n = 0.667$; anomalous transport), and was stable for three months. No drug–polymer interaction was detected. γ -Scintigraphy showed a mean maximum gastric residence time of about 160 minutes in fasted and about 320 minutes in fed volunteers.

Conclusion: The xanthan gum–HPMC floating matrix is a promising gastroretentive platform for clarithromycin, offering rapid buoyancy, sustained release and prolonged gastric retention, particularly in the fed state. Larger pharmacokinetic and clinical studies are warranted.

Keywords: Clarithromycin; gastroretentive drug delivery; floating matrix tablets; HPMC; xanthan gum; *Helicobacter pylori*; γ -scintigraphy

1. Introduction

Oral administration remains the most convenient and widely accepted route of drug delivery, and controlled-release (CR) dosage forms have been developed to maintain therapeutic plasma levels over extended periods while reducing dosing frequency and concentration-related adverse effects. Their performance, however, is constrained by physiology. A conventional CR dosage form traverses the stomach and small intestine within a few hours, so only the drug released before or near the absorption site is useful. For drugs with a narrow absorption window in the upper gastrointestinal tract, or for drugs intended to act locally in the stomach, the short and highly variable gastric residence time (GRT) is therefore the principal limitation [1–3], a point reiterated in recent reviews of gastroretentive technologies. Variability in gastric emptying, which is strongly influenced by the interdigestive migrating myoelectric complex (MMC) in the fasted state and by meal composition in the fed state, further produces unpredictable bioavailability [4].

Gastroretentive drug delivery systems (GRDDS) were conceived to overcome this limitation. Approaches include low-density floating systems, high-density sedimenting systems, mucoadhesive systems, expandable or unfoldable systems and magnetic or other miscellaneous devices [5–7]. Additive manufacturing (3D printing) has recently been explored as a route to floating and other gastroretentive devices whose geometry and density can be tailored [8,9]. Among them, floating systems have been the most extensively investigated because they are technologically simple, use well-accepted excipients and do not interfere with normal gastric motility. Floating systems are broadly classified as effervescent (gas-generating) or non-effervescent. In the hydrodynamically balanced system (HBS), first described for sustained-release capsules and tablets, a high level of gel-forming hydrocolloid hydrates on contact with gastric fluid to form a gelatinous barrier that entraps air, keeps the bulk density below unity and controls drug diffusion [10]. Effervescent systems add a carbonate or bicarbonate that liberates carbon dioxide in acidic medium, which is entrapped in the gel layer and shortens the time to buoyancy [11].

The success of any floating system depends on physiological and formulation variables. Food intake, the nature and frequency of meals, body posture, age, gender and the size and density of the dosage form all modify GRT [12,13]. In particular, floating dosage forms show clearly prolonged retention in the fed state, whereas in fasted subjects the housekeeper wave of the MMC can sweep even buoyant units into the intestine [14]. A realistic evaluation of any new floating formulation therefore requires *in vivo* imaging under both feeding conditions.

Clarithromycin is a 14-membered macrolide that inhibits bacterial protein synthesis by binding the 50S ribosomal subunit. It is widely prescribed for respiratory tract infections and, in combination with a proton pump inhibitor and amoxicillin or metronidazole, as a cornerstone of first-line *H. pylori* eradication therapy. The drug is well absorbed but undergoes first-pass metabolism to the active 14-hydroxy metabolite, giving an oral bioavailability of about 50–55%, and its elimination half-life of roughly 3–7 hours requires twice- or thrice-daily dosing with conventional tablets [15,16]. Consensus guidelines, including the recent Maastricht VI/Florence report, continue to include clarithromycin in *H. pylori* regimens only where local resistance is low [17,18], while surveillance documents a steady global rise in clarithromycin resistance [19]. A recent meta-analysis of 248 articles gave a pooled clarithromycin resistance prevalence of 27.5% [20], and a 2024 analysis of 178 reports found a pooled prevalence of 33.3%, rising from 29.1% in 2015–2019 to 36.5% in 2020–2023 [21]. Because *H. pylori* resides in and beneath the gastric mucus layer, effective eradication depends on achieving high and sustained drug concentrations at the gastric mucosa, something that systemic administration and conventional sustained-release tablets achieve poorly [22]. Maintaining concentrations above the minimum inhibitory concentration at the site of infection may also reduce the selective pressure that drives resistance.

This reasoning has prompted gastroretentive approaches for clarithromycin, including floating tablets and floating *in situ* gelling systems [23,24]. A recent clarithromycin–pantoprazole floating bilayer tablet based on sodium alginate, chitosan and HPMC K15M released about 83% of the clarithromycin over 24 hours [25]. Nevertheless, systematic comparisons of polymer combinations with *in vivo* human confirmation of retention

remain limited. HPMC is the most widely used hydrophilic matrix former, available in several viscosity grades, and controls release by gel-layer formation, swelling and erosion [26,27]. Xanthan gum, an anionic microbial polysaccharide, hydrates rapidly to produce a strong, time-independent swelling matrix and has been used for sustained-release tablets [28]. Sodium bicarbonate not only produces buoyancy but also raises the pH of the matrix micro-environment, which influences gelation of the polymers [29]. Earlier work on floating matrix systems has shown that careful balancing of gel strength, gas generation and compression conditions determines both floating behavior and release [30–33].

The objective of the present study was therefore to design effervescent floating matrix tablets of clarithromycin (500 mg) using HPMC K4M, HPMC K15M and xanthan gum, to examine how polymer type and ratio influence buoyancy and release, to select an optimized batch, to examine its compatibility, stability and release relative to a marketed product, and to verify gastric retention by γ -scintigraphy in healthy human volunteers in the fasted and fed state.

2. Materials and Methods

2.1 Materials

Clarithromycin was obtained as a gift sample from a pharmaceutical manufacturer. HPMC K4M, HPMC K15M and HPMC K100M, crospovidone and microcrystalline cellulose (MCC) were procured from commercial suppliers, as were xanthan gum, sodium bicarbonate, magnesium stearate, talc, Folin–Ciocalteu's phenol reagent, isopropyl alcohol, sodium carbonate and hydrochloric acid. All other chemicals were of analytical grade. The functional roles of the excipients (hydrophilic matrix former, gas-generating agent, diluent, glidant and lubricant) follow standard pharmaceutical excipient references [34]. Equipment included an Electrolab dissolution tester, a Shimadzu UV-1601 spectrophotometer, a Monsanto hardness tester, a Roche friabilator, a differential scanning calorimeter, an FTIR spectrophotometer, a stability chamber and a dual-head gamma camera.

2.2 Characterization of the drug and calibration

The drug sample was characterized by physical appearance, organoleptic properties, melting point and solubility in various solvents. For quantification, a colorimetric method based on Folin–Ciocalteu reagent was used. A stock solution (1000 $\mu\text{g/mL}$) of clarithromycin in 0.1 N HCl was diluted to 200 $\mu\text{g/mL}$; aliquots of 0.5–3.0 mL were treated with 2 mL of dilute Folin–Ciocalteu reagent (1:2) and 2 mL of 20% sodium carbonate, made to 10 mL with 0.1 N HCl and allowed to react for 15 minutes. Absorbance was read at 760 nm against a reagent blank, and the calibration equation was generated using PCP Disso v3 software.

2.3 Preliminary studies and polymer selection

Preliminary trials evaluated HPMC K4M, K15M and K100M, hydroxypropyl cellulose (HPC HF, HXF), hydroxyethyl cellulose (HEC HHX, HX) and xanthan gum, alone and in combination, for tablet integrity, floating behavior and release control. On the basis of floating, integrity and swelling, binary blends of xanthan gum with HPMC K4M or K15M were selected for detailed study.

2.4 Preparation of floating matrix tablets

Fifteen batches (F1–F15) were prepared (Table 1). Drug, polymers, sodium bicarbonate and MCC were blended in a glass mortar and granulated with isopropyl alcohol. The wet mass was passed through a #16 sieve, dried at 60 °C in a hot-air oven and sized through #20/44 sieves. The granules were lubricated with magnesium stearate (0.5% w/w) and talc (1% w/w) for 4–5 minutes and compressed into capsule-shaped tablets with 16.4 × 8 mm punches, each containing 500 mg clarithromycin (drug loading 66.5%, tablet weight about 750 mg).

Table 1. Polymer composition (% w/w) of the floating matrix tablet batches

Batch	HPMC K4M	HPMC K15M	Xanthan gum	NaHCO ₃	MCC
F1	15	–	–	10	7
F2	–	15	–	10	7
F3	–	–	15	10	7
F4	10	–	5	10	7
F5	5	–	10	10	7
F6	7.5	–	7.5	10	7
F7	–	10	5	10	7
F8	–	5	10	10	7
F9	–	7.5	7.5	10	7
F10	8	–	8	10	10
F11	4	–	4	10	10
F12	6	–	6	10	10
F13	–	8	8	10	10
F14	–	4	4	10	10
F15	–	6	6	10	10

All batches contained 66.5% clarithromycin, 0.5% magnesium stearate and 1% talc.

2.5 Evaluation of granules

The angle of repose was determined by the fixed-funnel method using the relation $\tan \theta = h/r$. Loose bulk density (LBD) and tapped bulk density (TBD) were measured in a 100 mL cylinder tapped from a height of 2.5 cm until no further volume change occurred. Carr's compressibility index was calculated as $[(TBD - LBD)/TBD] \times 100$ and interpreted according to the classical flow scale [35].

2.6 Evaluation of tablets

Hardness ($n = 10$) was measured with a Monsanto tester. Friability was determined on six tablets in a Roche friabilator at 25 rpm for 100 revolutions. Weight variation was evaluated on twenty tablets, and length and thickness on ten tablets with vernier calipers. For drug content, ten tablets were powdered, a quantity equivalent to 500 mg of drug was dissolved in 250 mL of 0.1 N HCl, filtered and developed with Folin–Ciocalteu reagent as described for calibration.

In vitro dissolution was carried out in triplicate with USP apparatus II (paddle) in 900 mL of 0.1 N HCl at 37 ± 0.5 °C and 50 rpm. Samples (5 mL) were withdrawn at predetermined intervals, replaced with fresh medium, filtered, developed with the colorimetric reagent and read at 760 nm.

Release kinetics. Dissolution data were analyzed with PCP Disso v3 using zero-order, first-order [36], Hixson–Crowell [37], matrix (Higuchi-type) [38] and Korsmeyer–Peppas models [39]. In the Korsmeyer–Peppas equation ($Mt/M_\infty = kt^n$), the exponent n was interpreted as Fickian diffusion ($n = 0.5$), anomalous transport ($0.5 < n < 1.0$), case-II transport ($n = 1.0$) or super case-II transport ($n > 1.0$) [40,41]. Percent dissolution efficiency (DE) and mean dissolution time (MDT) were also derived [42].

Buoyancy. Floating lag time (time to rise to the surface) and total floating time were observed visually in the dissolution vessel (0.1 N HCl, 37 °C), in triplicate.

Swelling index. Tablets were weighed (W_1), immersed in 900 mL of medium at 37 °C, removed hourly, blotted and reweighed (W_2). Swelling index was calculated as $(W_2 - W_1)/W_1$.

2.7 Compatibility studies

FTIR spectra of pure drug and the physical mixture with the polymer blend of the optimized batch were recorded using the KBr method. DSC thermograms of the drug and the physical mixture were recorded to detect shifts, disappearance or broadening of endotherms indicating interaction or polymorphic change.

2.8 Comparison with marketed product and stability studies

The release of the optimized batch F13 was compared with two marketed 500 mg clarithromycin tablets, a conventional film-coated tablet (Crixan FC) and an extended-release tablet (Crixan OD). Accelerated stability testing followed ICH recommendations [43]: F13 tablets were stored in closed HDPE bottles at 40 °C/75% RH for three months and examined at 0, 1, 2 and 3 months for hardness, friability, assay, floating lag time, buoyancy on disturbance and in vitro release.

2.9 In vivo γ -scintigraphic study

Gastric retention of F13 was assessed at a nuclear medicine institute after approval by the institutional ethics committee and written informed consent. Six healthy, non-smoking, non-alcoholic volunteers were enrolled in two groups of three. Group (a) fasted overnight (at least 12 hours) and for 6 hours post-dose; group (b) received a standardized breakfast of about 450 kcal. One hour after the meal (group b) or in the fasted state (group a), a ^{99m}Tc -labelled tablet was swallowed with 200 mL of water. Direct incorporation of the radionuclide into an excipient aliquot before tableting is the conventional labelling approach for simple dosage forms and uses a very small tracer quantity that does not compromise product performance [44]. Static images (3 min/image) were acquired with a dual-head gamma camera at intervals up to 24 hours, with volunteers kept ambulatory between acquisitions and allowed up to 1000 mL of water. GRT was taken as the time at which the tablet was last seen in the stomach. Body surface area of volunteers was calculated by the Mosteller formula [45].

3. Results and Discussion

3.1 Drug characterization and calibration

The drug sample was a white, odorless crystalline powder with a bitter taste, insoluble in water, soluble in acetone and slightly soluble in methanol, ethanol and acetonitrile. The observed melting range (225–227 °C) was close to the reported range for clarithromycin, confirming identity. The calibration line in 0.1 N HCl at 760 nm was linear ($Y = 0.0054X - 0.0037$; $r = 0.998$) and was used for all subsequent estimations.

3.2 Selection of the delivery system and polymers

Short half-life, frequent dosing, bioavailability limited by first-pass metabolism and the need for local gastric action make clarithromycin a logical candidate for a gastroretentive sustained-release system. An effervescent HBS was selected in preference to a non-effervescent system because non-effervescent matrices may swell too slowly and show longer lag times before buoyancy, whereas gas generation provides rapid flotation, an essential feature when dosage forms must avoid premature emptying [11,46]. Sodium bicarbonate also acts as a buffering agent in the acidic gastric medium (fasting gastric pH is around 1–2), producing CO_2 that is trapped in the hydrated gel layer [29].

During the preliminary screening, HPC and HEC grades did not provide adequate floating and eroded early. Xanthan gum alone produced the shortest floating lag time but the tablets lacked structural integrity, and increasing its proportion did not solve this. HPMC K4M and K15M gave good tablet integrity, gel formation and floating. The combination of xanthan gum with HPMC was therefore selected in order to merge the rapid, strong swelling of xanthan with the stable gel layer of HPMC, a strategy consistent with the known behaviour of hydrophilic matrices in which polymer mixtures give gel barriers of tailored consistency [27,28].

3.3 Granule properties

The angle of repose of the granules of all batches ranged from 24.2° to 30.3°, which indicates good to excellent flow (Table 2). Loose bulk density ranged from 0.394 to 0.525 g/mL and tapped density from 0.489 to 0.623 g/mL. Compressibility index values ranged between 14.0% and 20.4%, which fall in the good to fair flow range [35]. Batches F10–F15, which had a higher MCC content, showed somewhat higher bulk densities, consistent with the contribution of a densifying diluent. These granule properties were adequate for uniform die filling and the production of tablets with low weight variation. The angle of repose and Carr's index of each batch are compared with the accepted limits in Figure 1.

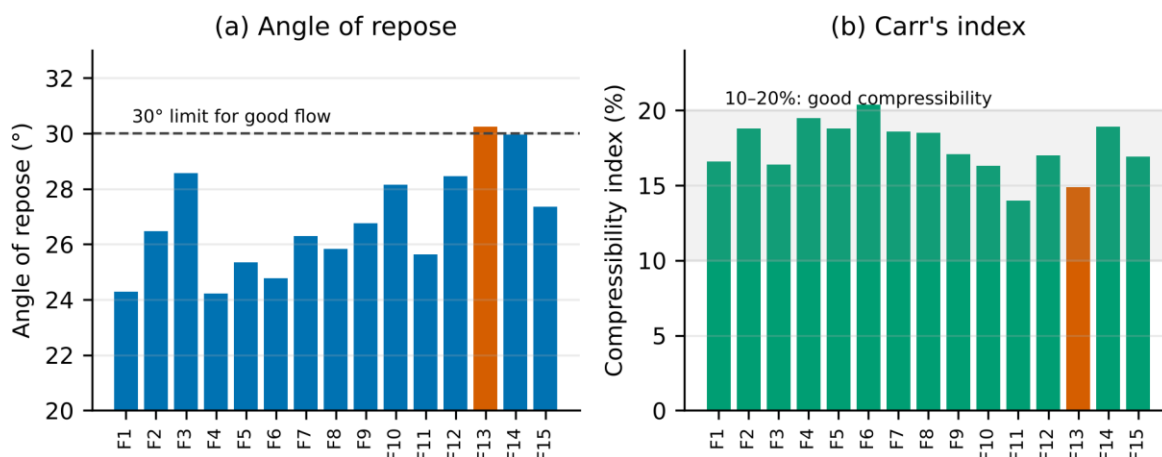


Figure 1. Granule flow properties of batches F1–F15: (a) angle of repose and (b) Carr's compressibility index. The optimized batch F13 is highlighted.

Table 2. Summary of granule and tablet quality attributes (F1–F15)

Parameter	Range observed
Angle of repose (°)	24.22–30.25
Loose bulk density (g/mL)	0.394–0.525
Tapped bulk density (g/mL)	0.489–0.623
Compressibility index (%)	14.0–20.4
Hardness (kg/cm ²)	4.4–6.0
Friability (%)	0.31–0.73
Weight (mg)	746.1–755.1
Drug content (%)	94.07–104.78
Length (mm)	16.37–16.41
Thickness (mm)	5.87–6.46

3.4 Physical characteristics of tablets

All tablets were of uniform size and weight (Table 2). The mean hardness lay between 4.4 and 6.0 kg/cm², sufficient for handling while avoiding excessively dense compacts that would delay hydration. Friability was below 1% for all batches (0.31–0.73%), weight variation was small (SD up to about 5 mg on a ~750 mg tablet) and the drug content of 94.1–104.8% showed acceptable content uniformity. The slightly higher assay of batch F8 (104.8%) remains within generally accepted limits for tablets. The tablets were therefore of satisfactory pharmaceutical quality, and differences in release between batches could be attributed to formulation composition rather than to physical variability.

3.5 Buoyancy behavior

All batches began to float in less than two minutes (59.6–114.3 s) and remained buoyant for at least 10 hours, and most for more than 12 hours (Table 3). Effervescence was visible on the tablet surface from the moment of immersion. The shortest lag time (59.6 s) was found for the xanthan-only batch F3, reflecting the very rapid hydration of xanthan gum, but as noted these tablets had poor integrity. For the blends, lag times of 93–114 s were recorded. Lag times and total floating times of all batches are compared in Figure 2.

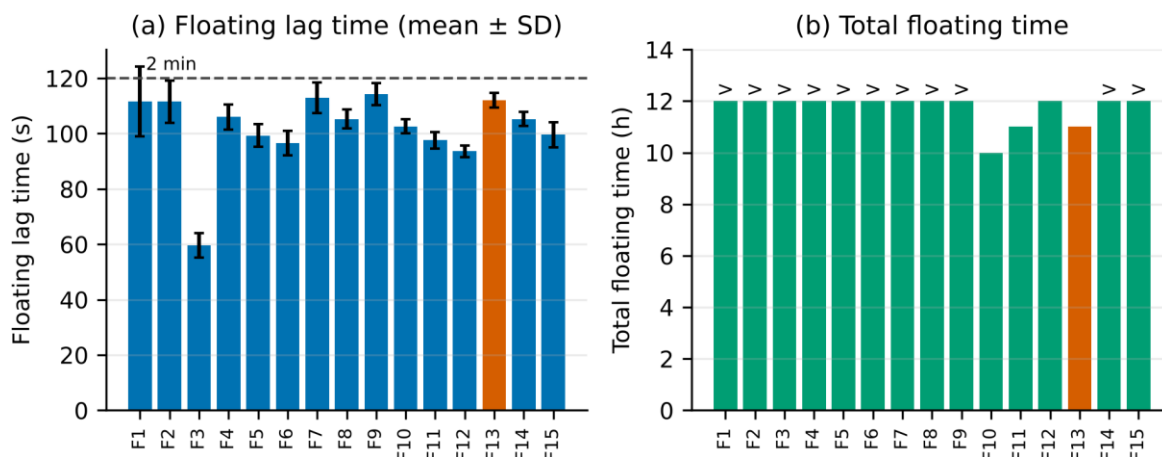


Figure 2. Buoyancy behavior of batches F1–F15: (a) floating lag time (mean ± SD, n = 3) and (b) total floating time ('>' indicates buoyancy beyond 12 h).

Table 3. Floating behavior and key release parameters of selected batches

Batch	Floating lag time (s)	Total floating time (h)	Release at 6 h (%)	Release at 12 h (%)	DE _{12h} (%)	MDT (h)
F1	111.6 ± 12.6	>12	59.2	87.2	56.8	4.19
F3	59.6 ± 4.5	>12	42.3	77.4	41.3	5.60
F4	106.0 ± 4.6	>12	40.9	80.2	42.6	5.63
F5	99.3 ± 4.0	>12	35.3	66.0	35.5	5.56
F9	114.3 ± 4.0	>12	31.3	64.6	35.2	5.46
F10	102.6 ± 2.5	10	72.1	99.3	66.6	3.96
F12	93.6 ± 2.1	12	60.7	92.8	58.6	4.43
F13	112.0 ± 2.6	11	63.6	99.0	62.0	4.49
F14	105.3 ± 2.5	>12	57.1	97.0	55.5	5.13
F15	99.6 ± 4.5	>12	61.8	91.2	57.3	4.46

Buoyancy arises from a combined effect: carbon dioxide is generated by reaction of bicarbonate with gastric acid and is entrapped in the swollen polymer, while the gel layer simultaneously expands the tablet volume. Both effects reduce apparent density below that of gastric fluid. This is consistent with the established principle that the resultant weight, the net vertical force obtained from the difference between buoyancy and gravity forces, must remain positive for the dosage form to float, and that matrix hydration and gas evolution continuously modify this force over time [47]. In a matrix tablet the balance between polymer hydration and gas entrapment is critical: too little gel strength allows gas to escape, whereas an overly dense matrix delays hydration and floating onset. The lag times below two minutes recorded here are advantageous, because delayed buoyancy exposes a dosage form to premature emptying in the fasted state [11,46]. The slightly shorter total floating time of F10 (10 h) and F13 (11 h) relative to other batches probably reflects faster erosion of the matrix in the 16% polymer combinations, which also showed the fastest release.

3.6 In vitro drug release

The release profiles of the 15 batches are summarized in Table 3 and clearly depended on polymer type and ratio. Figures 3 and 4 show the cumulative release profiles.

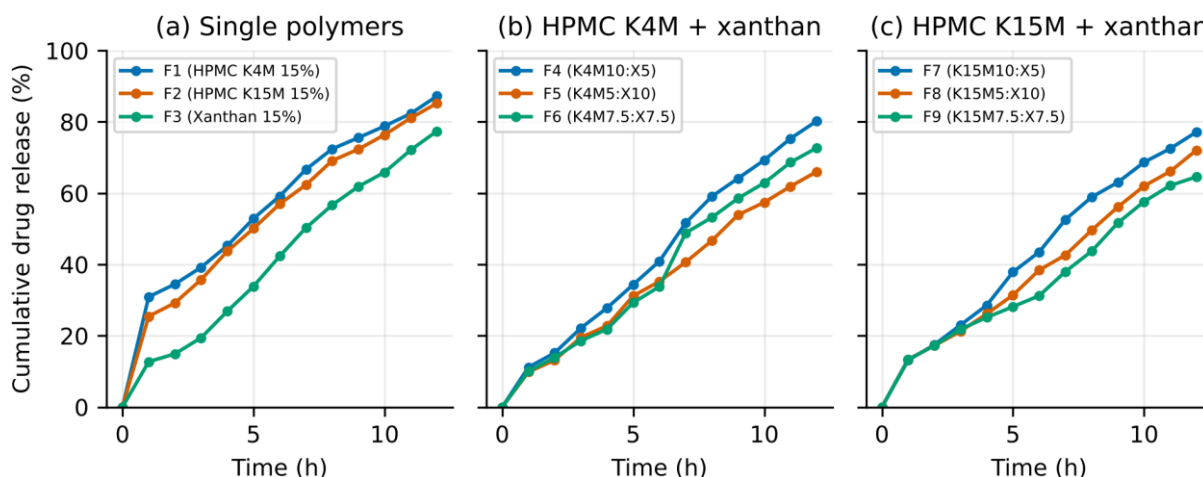


Figure 3. In vitro release profiles in 0.1 N HCl: (a) single polymers (F1–F3), (b) HPMC K4M–xanthan blends (F4–F6), (c) HPMC K15M–xanthan blends (F7–F9).

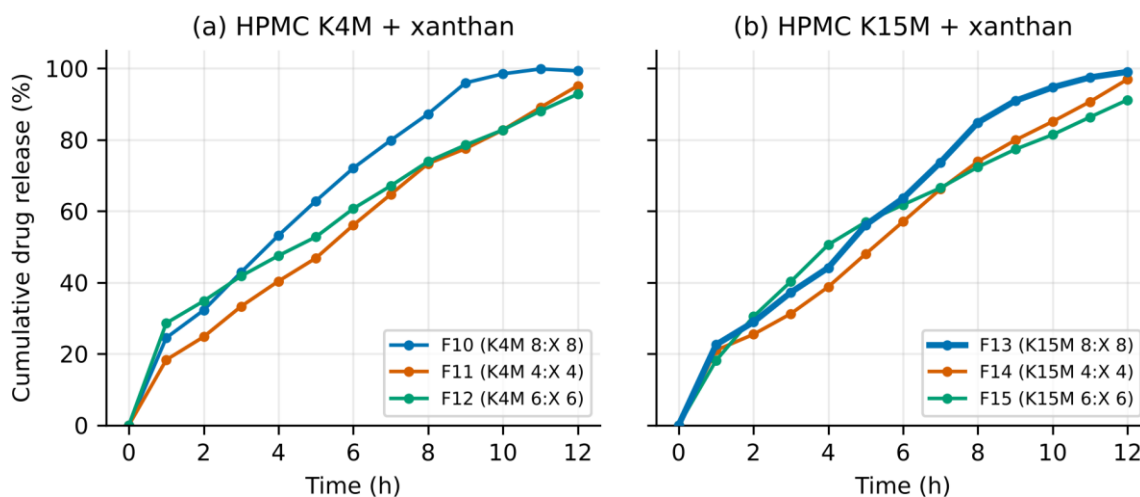


Figure 4. In vitro release profiles of batches F10–F15 containing 10% MCC: (a) HPMC K4M–xanthan blends, (b) HPMC K15M–xanthan blends. F13 is drawn with a heavier line.

Single polymers. The HPMC K4M batch (F1) released 30.9% of the drug within one hour and 87.2% in 12 hours, indicating a considerable early burst, as might be expected for a lower-viscosity grade that forms a gel layer more slowly. The xanthan-only batch (F3) released only 12.7% at one hour and 77.4% at 12 hours (DE 41.3%), showing the strongest early retardation. Xanthan gum thus retarded release more than the HPMC grades, because of its rapid and extensive hydration that forms a thick, viscous gel resistant to erosion. This agrees with reports that xanthan gum matrices provide time-independent swelling and drug diffusion control [28].

Effect of xanthan gum fraction. In the batches containing 15% total polymer and 7% MCC (F4–F9), release at 12 hours was 80.2% (F4, K4M 10: xanthan 5), 72.7% (F6, 7.5:7.5) and 66.0% (F5, 5:10) for the K4M series, and 77.2% (F7, K15M 10: xanthan 5), 64.6% (F9, 7.5:7.5) and 72.1% (F8, 5:10) for the K15M series. In general, increasing the proportion of xanthan gum decreased release, in line with the greater gel strength and swelling of xanthan, although the K15M series was not strictly monotonic (F9 released less than F8). Equal-ratio blends gave the most retarded profiles with K15M, suggesting a synergistic gel-network interaction between HPMC and xanthan gum, which has been described for polysaccharide–cellulose ether combinations

[27]. The inverse relation between polymer proportion and drug release is a recognized characteristic of hydrophilic matrices [26].

Effect of HPMC grade. At matched ratios, the K15M-based batches released more slowly than the K4M batches in the early phase, as the higher viscosity grade produces a more resistant gel barrier. Overall, the rate and extent of release were more controlled with xanthan–K15M blends than with xanthan–K4M blends, as found in the dissolution efficiency values.

Effect of diluent and total polymer level. The batches F10–F15, which contained 10% MCC rather than 7%, released 91–99% of drug within 12 hours, much more than the F4–F9 series at similar total polymer levels (64–80%). Several factors may contribute. First, a higher diluent content reduces the relative polymer fraction in the matrix and shortens diffusion pathways, an effect commonly observed when diluents are used in hydrophilic matrices [26]. Second, the 1:1 xanthan-to-HPMC ratio may form a more open gel at the polymer concentrations used. Because the study varied several factors simultaneously, the relative contribution of diluent level and polymer concentration cannot be separated from these data; a factorial design would be needed to quantify these effects. Dissolution efficiency and mean dissolution time for all batches are compared in Figure 5.

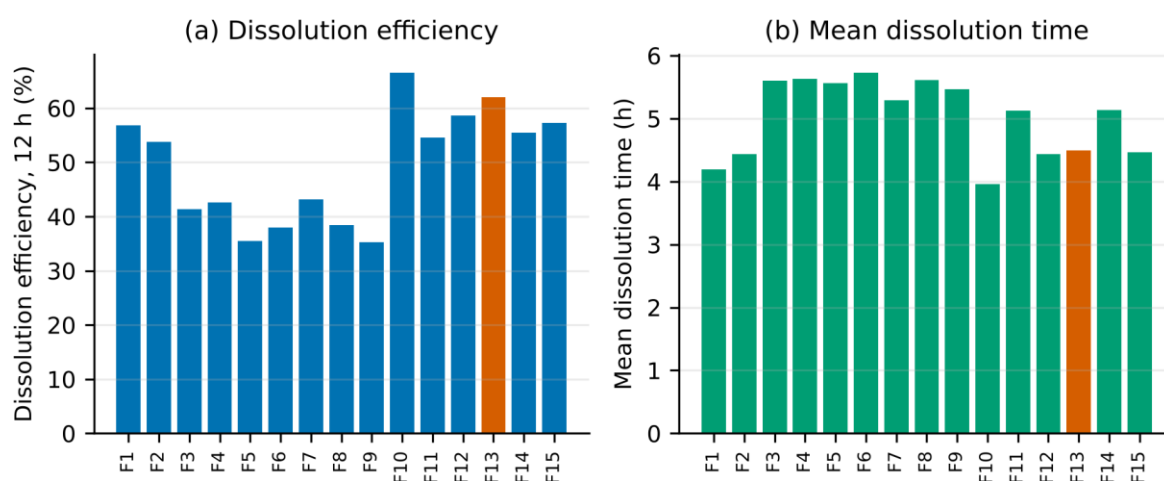


Figure 5. Release-rate descriptors of batches F1–F15: (a) percent dissolution efficiency at 12 h and (b) mean dissolution time.

Optimized batch. Within the F10–F15 series, F10 (K4M 8%: xanthan 8%) and F13 (K15M 8%: xanthan 8%) gave nearly complete release (99.3% and 99.0% at 12 h). F10 released drug faster (24.5% at 1 h, complete by 10–11 h; DE 66.6%; MDT 3.96 h) and showed the shortest floating duration (10 h), so that buoyancy barely covered the release period. F13 offered a lower initial release (22.5% at 1 h), a smoother profile through 8 hours (84.8% at 8 h), complete release at 12 hours, a floating lag time of 112 s and buoyancy for 11 hours (DE 62.0%; MDT 4.49 h). Because it combined a controlled early phase with complete release, adequate gel integrity and buoyancy that covers most of the release period, F13 was chosen as the optimized batch. F12 and F15 released more slowly (92.8% and 91.2%), and F11/F14 with only 8% polymer showed higher variability (e.g., SD up to 7% in F11). The release profile of F13 with its standard deviations is shown in Figure 6.

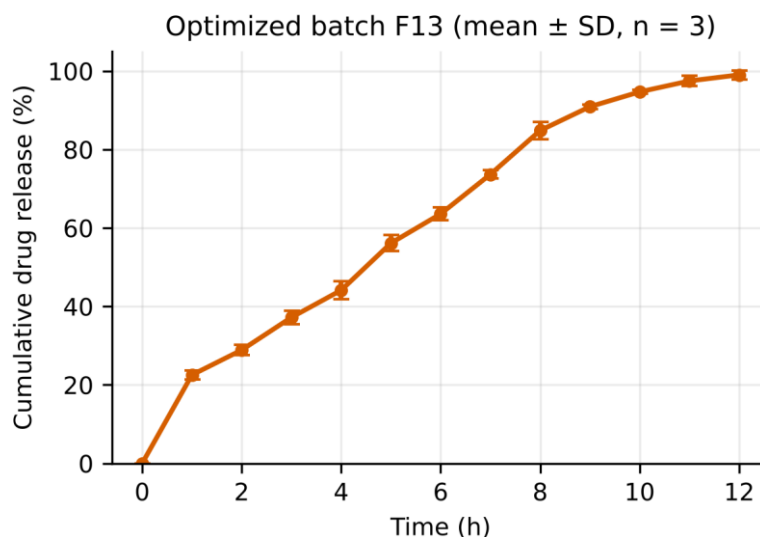


Figure 6. Release profile of the optimized batch F13 (mean $\pm$ SD, $n = 3$).

The wide standard deviations recorded for F12 at early time points (up to about $\pm 11\%$) underline that formulations with intermediate gel strength may be more sensitive to hydrodynamic differences between vessels. This observation supports choosing a batch such as F13, which shows low variability throughout (SD generally 0.5–2.3%).

3.7 Release kinetics and mechanism

Table 4 summarizes the best-fit model and the diffusion exponent for the optimized batch and for representative batches.

Table 4. Release kinetic parameters of selected batches

Batch	Zero order (R)	First order (R)	Matrix (R)	Peppas (R)	Hixson–Crowell (R)	n (Peppas)
F1	0.8762	0.9891	0.9934	0.9767	0.9791	0.463
F3	0.9941	0.9802	0.9411	0.9806	0.9919	0.818
F9	0.9840	0.9802	0.9477	0.9748	0.9866	0.671
F10	0.9302	0.8803	0.9866	0.9935	0.9783	0.625
F13	0.9625	0.8997	0.9749	0.9890	0.9799	0.667

The low-polymer HPMC K4M batch F1 ($n = 0.463$) followed matrix-type diffusion, consistent with Fickian release from a conventional hydrophilic matrix [38]. In batches rich in xanthan gum or in the equal-ratio K15M blends (F3–F9), the Hixson–Crowell or zero-order models gave very high correlation, indicating that polymer swelling and surface erosion with a changing surface area contribute significantly [37]. The diffusion exponents for these batches (about 0.67–0.87) were above 0.5. Most of the batches in the F10–F15 series, including F13, were best described by the Korsmeyer–Peppas model, with n between 0.52 and 0.70. For F13, $n = 0.667$ indicates anomalous (non-Fickian) transport, in which drug diffusion through the hydrated gel layer and polymer relaxation/erosion operate together [39,40]. The exponents of all batches are compared in Figure 7.

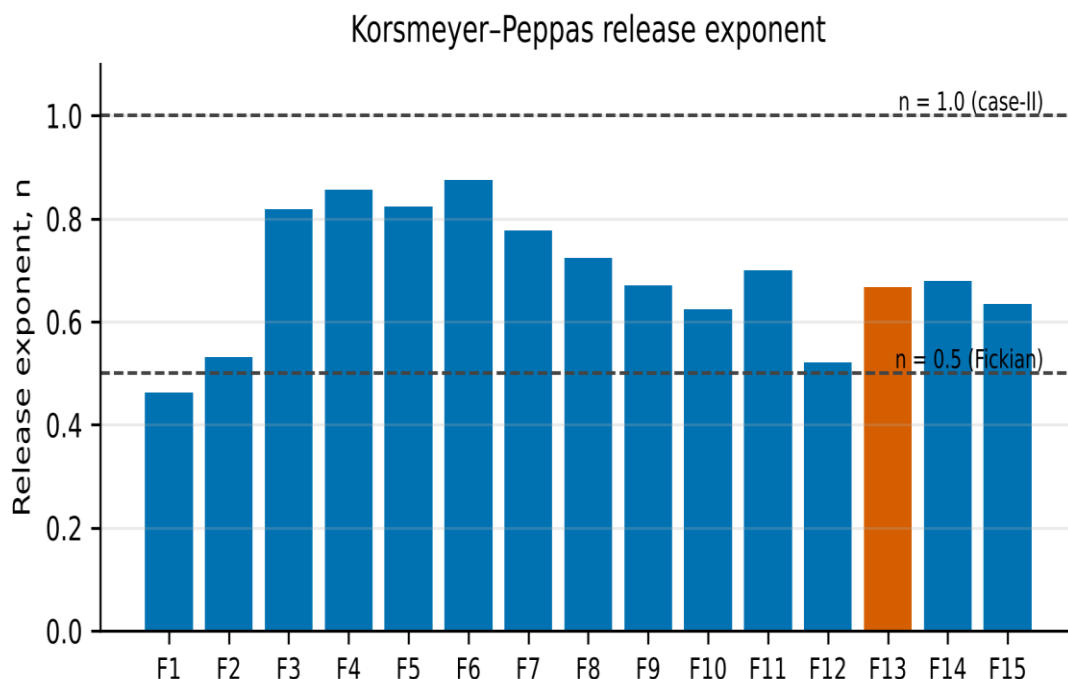


Figure 7. Korsmeyer–Peppas release exponent (n) of batches F1–F15. Values between 0.5 and 1.0 indicate anomalous (non-Fickian) transport.

It must be noted that the selection of a "best" model on correlation coefficients alone is of limited discriminatory power, since several models gave R values above 0.97 for the same batch. Model selection becomes more reliable when it is combined with mechanistic evidence such as swelling and erosion measurements [41]. In this study, the observed swelling profile of F13 (rapid increase over 3–4 hours, a plateau of 2–3 hours and a decline as erosion begins) supports a mechanism in which diffusion dominates in the early swollen phase while erosion contributes in the later phase. This combined behavior is typical of swellable matrices that comprise hydrophilic polymers and is consistent with the anomalous exponent [27,39].

3.8 Swelling behavior

The swelling index of F13 rose steadily during the first 3–4 hours, remained nearly constant for another 2–3 hours and thereafter decreased as polymer erosion exceeded water uptake. Swelling is a prerequisite for floating of hydrophilic matrices, because the gel layer both entraps CO_2 and increases tablet volume, lowering density. In addition, swollen tablets with dimensions greater than the pyloric opening may resist gastric emptying even after the CO_2 is no longer sustaining flotation, an additional retention mechanism proposed for swellable gastroretentive systems [48]. Maintaining an appropriate balance between swelling and erosion is therefore a key design requirement; here, the xanthan–HPMC combination achieved sufficient integrity to remain floating for 11 hours while delivering complete release.

3.9 Drug–excipient compatibility

The FTIR spectrum of clarithromycin showed characteristic bands at 3468.5 cm^{-1} (O–H stretching), 2969.8 cm^{-1} (methyl C–H stretching), 1736.9 cm^{-1} (lactone/ester carbonyl), 1681.6 cm^{-1} (ketone C=O stretching), 1452.0 cm^{-1} (C–H bending) and 1170.1 and 1052.1 cm^{-1} (C–O stretching). In the spectrum of the physical mixture with HPMC and xanthan gum, these bands persisted without significant shifts, indicating the absence of chemical interaction. DSC showed a single sharp melting endotherm of the drug at $227.7\text{ }^\circ\text{C}$, which was retained in the physical mixture without shift or notable broadening. No polymorphic change or incompatibility was therefore evident, and the wet granulation, drying and compression processes did not alter the solid state of the drug.

3.10 Comparison with marketed products

The release profile of F13 was more regulated than that of the conventional marketed tablet (Crixan FC), which as an immediate-release product exhausts its drug load over a short period. Compared with the marketed extended-release tablet (Crixan OD), the overall release performance was similar, and F13 provided slightly better control. It should be noted that the marketed extended-release tablets are not gastroretentive; the advantage of the floating tablet lies in its prolonged presence in the stomach in addition to the sustained release profile. The in vitro comparison alone cannot demonstrate superiority in efficacy, since the influence of retention on local mucosal concentration can be established only through in vivo drug-level or clinical eradication studies. Gastroretentive carriers have been proposed for exactly this reason in *H. pylori* therapy, where local residence and mucosal penetration, rather than plasma profile, are the critical determinants of success [22,49].

3.11 Accelerated stability

After three months at 40 °C/75% RH in closed HDPE bottles, F13 tablets retained color and integrity and remained buoyant under disturbance at every time point (Table 5). Hardness stayed between 4.4 and 5.6 kg/cm², friability between 0.40% and 0.47%, assay between 97.6% and 100.0%, and 12-hour release between 98.5% and 99.8%. Floating lag time varied from 106 to 122 s, without any statistically meaningful trend. These results indicate that effervescent bicarbonate-containing tablets, which can be moisture-sensitive, remained stable when packaged in closed containers. Sodium bicarbonate is known to decompose slowly in the presence of moisture at elevated humidity [34], so protective packaging with a desiccant is advisable for commercial development. Although the stability data cover only the accelerated condition for three months, they support continuing with long-term studies. The trends in assay, release, floating lag time, hardness and friability are plotted in Figure 8.

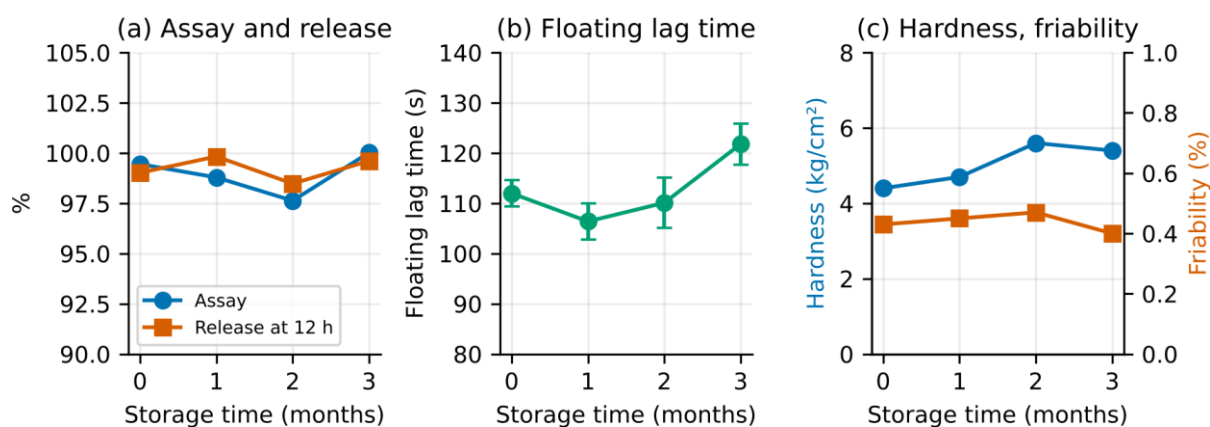


Figure 8. Accelerated stability of F13 at 40 °C/75% RH: (a) assay and 12-h release, (b) floating lag time (mean $\pm$ SD), (c) hardness and friability.

Table 5. Accelerated stability data for F13 (40 °C/75% RH)

Parameter	0 month	1 month	2 months	3 months
Hardness (kg/cm ²)	4.4	4.7	5.6	5.4
Friability (%)	0.43	0.45	0.47	0.40
Assay (%)	99.45	98.79	97.63	100.02
Floating lag time (s)	112.0 $\pm$ 2.6	106.4 $\pm$ 3.6	110.1 $\pm$ 5.1	121.8 $\pm$ 4.1
Buoyancy on disturbance	Float	Float	Float	Float

In vitro release at 12 h (%)	99.02	99.83	98.48	99.61
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3.12 In vivo γ -scintigraphic evaluation

The gastric residence of F13 was visualized by γ -scintigraphy, a non-invasive technique that tracks the labelled dosage form through the gastrointestinal tract under normal physiological conditions and allows correlation of transit with drug-release behavior [44]. The maximum GRT values are given in Table 6. In the fasted group the tablet remained in the stomach for 180, 180 and 120 minutes (mean 160 min), whereas in the fed group the GRT was 360, 300 and 300 minutes (mean 320 min), as plotted in Figure 9.

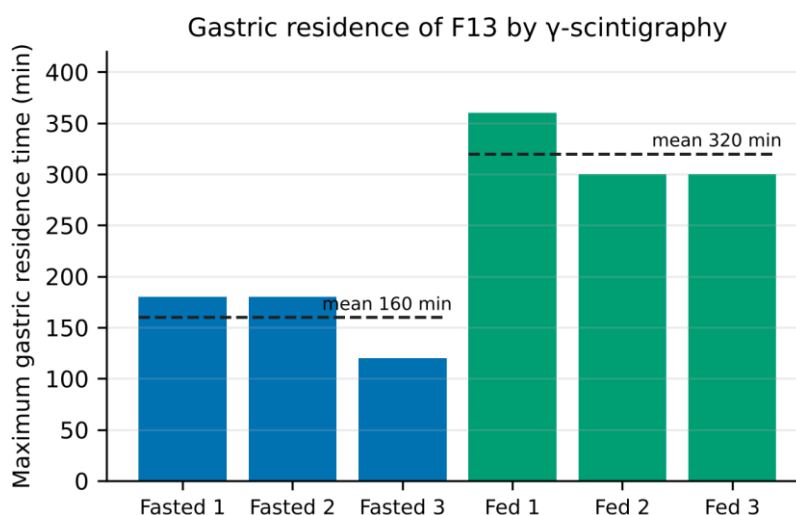


Figure 9. Maximum gastric residence time of F13 in fasted (n = 3) and fed (n = 3) volunteers by γ -scintigraphy; dashed lines show group means.

Table 6. Maximum gastric residence time (GRTmax) of F13

Group	Volunteer	GRTmax (min)	Group mean (min)
(a) Fasted	1	180	160
	2	180	
	3	120	
(b) Fed	4	360	320
	5	300	
	6	300	

The doubling of GRT after food reproduces a well-documented finding. After a meal the MMC is delayed, and the stomach is in a digestive motility pattern in which particles larger than a few millimeters are retained for the grinding phase, so a buoyant dosage form floats on the chyme and escapes emptying [12,14]. In the fasted state, the phase III contractions of the MMC recur approximately every two hours and sweep non-disintegrating units, including floating ones, into the small intestine; the fasted GRT of about 2–3 hours here is consistent with that cycle. Earlier in vivo studies of floating dosage forms similarly showed that the benefit of buoyancy is much greater after food than in the fasted state [13,14].

Three limitations of the in vivo study must be acknowledged. First, the sample size was small (three volunteers per group), so the results are descriptive and do not permit formal statistical comparison. Second, the groups were not crossover: the fasted group comprised male volunteers and the fed group female volunteers, so gender is confounded with feeding status. Because gastric emptying of indigestible solids has been reported to be slower in women than in men [12], part of the longer GRT in the fed group might be attributable to gender

rather than food alone. Third, retention was followed until the tablet left the stomach, but plasma concentration–time data and mucosal drug levels were not measured, so no pharmacokinetic conclusion can be drawn. A properly powered crossover design in a single sex or balanced groups, with simultaneous blood sampling, is recommended.

Despite these limitations, the findings are encouraging. Gastric retention of 5–6 hours after a light meal is longer than the typical fasted gastric residence of conventional tablets (generally under 2 hours) [13,14]. Since clarithromycin is administered in *H. pylori* regimens with food in many treatment protocols and twice-daily dosing, a formulation that shows its longest retention in the fed state is well matched to its clinical use. In the fasted state, the retention was shorter but still sufficient to deliver a considerable fraction of the dose in the stomach, given the release profile (about 44% released by 4 hours and 64% by 6 hours).

3.13 Discussion and formulation considerations

Several design principles emerge from this work. First, a balance of gas generation, gel strength and polymer swelling is needed: bicarbonate at 10% provided buoyancy in under two minutes without disrupting the matrix. Second, the combination of a swelling natural polysaccharide with a cellulose ether allows tuning of both the early and late phases of release; HPMC alone released too fast initially, while xanthan alone provided poor integrity. Third, release rate and floating duration must be matched. The faster batch F10 floated for only 10 hours, whereas F13 gave a slightly better compromise. Fourth, the practical effect of diluent level on release demonstrates that apparently minor changes in filler content can change the release profile substantially, an effect known for hydrophilic matrices and one that must be examined by a formal design of experiments in scale-up [26].

From a clinical perspective, the rationale for gastroretention of an antibiotic is both pharmacokinetic and pharmacodynamic. Prolonged presence of the antibiotic above the minimum inhibitory concentration in the gastric lumen, together with reduced exposure of colonic flora, can improve efficacy and may limit the emergence of resistance [50]. The risk of antibiotic resistance, particularly to clarithromycin in *H. pylori*, makes optimized local delivery a topic of continuing interest [17,19]. Floating beads, in situ gelling systems and mucoadhesive carriers have been pursued with antibiotics such as amoxicillin, metronidazole and clarithromycin for this reason [24,49,51]. Compared with the bilayer clarithromycin–pantoprazole floating tablet of Ullah et al. [25], which sustained clarithromycin release for 24 hours, the present single-layer system delivers its dose over about 12 hours, consistent with twice-daily dosing. Floating tablets have the advantage over those systems of conventional manufacturing technology (granulation and compression) that is readily scalable. Newer manufacturing routes such as 3D printing may in future allow density and geometry to be tuned independently of the formulation [8].

The Folin–Ciocalteu colorimetric assay is a non-specific reducing-substance method; although suitable for comparative screening in a drug–excipient system without interfering reducing agents, a stability-indicating HPLC assay would be preferred for regulatory submissions, particularly for stability samples, in which degradation products might contribute to the color reaction. Clarithromycin is also known to degrade at low pH; although the buoyancy mechanism generates a locally alkaline micro-environment within the gel layer that may protect the drug, the extent of acid degradation over 12 hours in 0.1 N HCl was not separately determined and should be examined. The dissolution medium (0.1 N HCl) represents a fasted-state stomach, and release should also be studied in media with higher pH and in fed-state simulated fluids. Finally, the 12-hour sustained release in a 500 mg unit would need to be reconciled with the clinical dosing schedule; the formulation is positioned as a twice-daily dosage form.

4. Conclusion

Effervescent floating matrix tablets of clarithromycin (500 mg) were successfully prepared by wet granulation using HPMC K4M, HPMC K15M and xanthan gum. All batches showed good granule flow, acceptable

physical quality, floating lag times under two minutes and buoyancy lasting 10 hours or more. Release rate was controlled primarily by polymer type and ratio, with xanthan gum-rich blends and K15M-based blends giving greater retardation, and with diluent content also influencing release. The optimized batch F13 (HPMC K15M 8%, xanthan gum 8%) released almost the entire dose over 12 hours by an anomalous (non-Fickian) mechanism, floated for 11 hours, was compatible with the polymers by FTIR and DSC, behaved comparably to a marketed extended-release tablet in vitro and was stable for three months under accelerated conditions. In human volunteers, γ -scintigraphy showed a mean gastric residence of about 160 minutes in the fasted state and about 320 minutes after a light meal. These findings support the xanthan gum–HPMC floating matrix as a viable gastroretentive platform for clarithromycin. Future work should include factorial optimization, a validated stability-indicating assay, long-term stability, a crossover pharmacokinetic study with adequate numbers and, ultimately, evaluation of gastric tissue concentration and *H. pylori* eradication.

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Conflict of interest

None declared.

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