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Formulation and Evaluation of a Raft-Forming In-Situ Gel of Itopride Hydrochloride for Targeted Gastric Delivery

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ABSTRACT

Objective: The present study aimed to develop and optimize a raft-forming in-situ gel formulation of Itopride Hydrochloride for targeted gastric delivery to enhance gastric residence time and achieve sustained drug release. **Methods:** A 3^2 full factorial design was employed to investigate the influence of two independent variables sodium alginate (X_1) and HPMC K100M (X_2) on dependent responses: floating lag time (Y_1), viscosity (Y_2), and drug release at 6 hours (Y_3). Nine formulations (F1–F9) were prepared using the ionotropic gelation method and evaluated for physicochemical properties, in vitro buoyancy, gelation capacity, drug content, and release behavior in 0.1 N HCl (pH 1.2). Statistical optimization and model validation were performed using Design Expert® software (Version 13). **Results:** Among the formulations, batch F9 was identified as the optimized formulation, exhibiting a floating lag time of 30 seconds, viscosity of 153 cP, gelation time of 22 seconds, and drug release of 76.7% at 6 hours and 94.9% at 12 hours. All batches demonstrated total floating durations of over 12 hours and drug content within Pharmacopeial limits (98.59–99.31%). The optimized formulation showed no significant changes after 30 days of accelerated stability testing at $40 \pm 2^\circ\text{C}$ / 75% RH. **Conclusion:** The optimized raft-forming in-situ gel of Itopride Hydrochloride offers a promising gastroretentive drug delivery system, providing controlled drug release, enhanced gastric retention, and improved patient compliance. This formulation compared to previously reported formulations, the optimized batch (F9) exhibited improved gelation behaviour, sustained drug release, and enhanced gastric retention performance.

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INTRODUCTION:

Oral drug delivery remains the most preferred route of administration due to its simplicity, cost-effectiveness, patient compliance, and flexible dosage regimen. However, certain drugs suffer from limited oral bioavailability owing to their narrow absorption window, instability in the alkaline pH of the intestine, or rapid gastric emptying. One such

drug is Itopride Hydrochloride, a gastroprokinetic agent used in the treatment of functional dyspepsia and gastrointestinal motility disorders¹. Itopride is rapidly absorbed in the upper part of the gastrointestinal tract but has a relatively short biological half-life (6 hours), necessitating frequent dosing to maintain therapeutic plasma concentrations. This poses challenges for sustained therapeutic efficacy and patient adherence. To overcome such limitations, gastroretentive drug delivery systems (GRDDS) have gained considerable attention. These systems are designed to prolong the gastric residence time of dosage forms, thereby enhancing the absorption of drugs that are preferentially absorbed in the stomach or upper part of the small intestine². Among various GRDDS approaches such as floating systems, mucoadhesive systems, high-density systems, and swelling systems raft-forming in-situ gels offer

unique advantages. These systems remain in solution form prior to administration but undergo sol-to-gel transition in the stomach due to the acidic pH and interaction with physiological ions, forming a cohesive, floating gel (or raft). This raft floats on the gastric contents and acts as a reservoir for sustained drug release³.

Raft-forming systems typically consist of a gel-forming polymer (such as sodium alginate), a crosslinking ion source (e.g., calcium carbonate), and a gas-forming agent (e.g., sodium bicarbonate). Upon contact with gastric fluid, carbon dioxide is released, which gets entrapped in the gel matrix, reducing its density and allowing the system to float. The gel formation is also facilitated by the calcium ions, which crosslink the alginate chains. The resulting raft not only floats but also retains the drug in the gastric region, ensuring a controlled and site-specific drug release⁴. Several studies have explored in-situ gel formulations for gastroretentive delivery of drugs such as ranitidine, metoclopramide, and cisapride. However, the application of a raft-forming in-situ gel system for Itopride Hydrochloride remains relatively unexplored. Most available formulations of Itopride are in tablet or capsule form, which do not adequately address the challenges associated with its pharmacokinetics⁵. Given this background, the present study was undertaken to formulate and evaluate a raft-forming in-situ gel of Itopride Hydrochloride using sodium alginate and HPMC K100M as gelling polymers, with calcium carbonate and sodium bicarbonate as the crosslinking and floating agents, respectively. The formulation was assessed for physicochemical properties, floating behaviour, gelling capacity, in-vitro drug release, and drug release kinetics. This novel delivery approach aims to enhance the gastric residence time and sustain the release of Itopride, thereby improving its therapeutic efficacy and reducing dosing frequency⁶.

MATERIALS AND METHODS:

Materials:

Itopride Hydrochloride was obtained as a gift sample from Alkem Laboratories Ltd., Mumbai, India. Sodium alginate (viscosity grade) and calcium carbonate were procured from LobaChemie Pvt. Ltd., Mumbai, India. Hydroxypropyl methylcellulose K100M (HPMC K100M) was purchased from Central Drug House (P) Ltd., New Delhi, India. All other chemicals and reagents used were of analytical grade.

Experimental Design and Formulation of In-Situ Gels:

A 3² full factorial design was employed using Design Expert® software (Version 13, Stat-Ease Inc., USA) to systematically optimize the in-situ gel

formulation of Itopride Hydrochloride. In this design, two independent formulation variables were selected: X₁, the concentration of sodium alginate (% w/v), varied at three levels (1.5%, 2.0%, and 2.5%), and X₂, the concentration of HPMC K100M (% w/v), also varied at three levels (0.3%, 0.6%, and 0.9%). The dependent variables (responses) evaluated for optimization included Y₁: floating lag time (seconds), Y₂: viscosity (cP), and Y₃: percentage drug release at 6 hours. Based on the factorial design matrix, a total of nine formulations (F1–F9) were developed using the ion-induced gelation technique, wherein gel formation occurs through the interaction of calcium ions with sodium alginate in the acidic gastric environment, facilitating in-situ gelation upon administration⁷.

Method of Preparation (Ion-Induced Gelation Method):

Each formulation was prepared by dispersing a weighed amount of sodium alginate in deionized water under continuous stirring at 60 °C until a uniform solution was achieved. Subsequently, HPMC K100M was incorporated and allowed to hydrate with continued stirring to form a viscous polymeric solution. After the mixture was cooled to room temperature, Itopride Hydrochloride was added and dissolved thoroughly. Finally, calcium carbonate and sodium bicarbonate were added as gas-generating agents to facilitate buoyancy. The volume of each formulation was adjusted to 100 mL with distilled water, and the resulting in-situ gels were transferred into amber-coloured glass bottles and stored at room temperature for further evaluations⁸. The complete formulation composition is presented in Table 1.

Table 1. Composition of Raft-Forming In-Situ Gel Formulations (F1–F9)

Formulation Code	Sodium Alginate (% w/v)	HPMC K100M (% w/v)	Itopride HCl (mg/100 mL)	Calcium Carbonate (mg)	Sodium Bicarbonate (mg)
F1	1.5	0.3	100	500	1000
F2	2.0	0.3	100	500	1000
F3	2.5	0.3	100	500	1000
F4	1.5	0.6	100	500	1000
F5	2.0	0.6	100	500	1000
F6	2.5	0.6	100	500	1000
F7	1.5	0.9	100	500	1000
F8	2.0	0.9	100	500	1000
F9	2.5	0.9	100	500	1000

Evaluation of Formulated In-Situ Gels:

Physical Appearance and pH: Formulations were visually inspected for color, clarity, and phase separation. pH was measured using a calibrated digital pH meter (Eutech Instruments, Singapore) [9].

Viscosity Measurement: Viscosity was measured

using a Brookfield viscometer (Model: DV2T, Brookfield Engineering Labs, USA) with spindle no. 63 at 50 rpm and 25 ± 1 °C. All measurements were performed in triplicate⁹.

Gelation Study: 1 mL of each formulation was added to 50 mL of 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C to simulate gastric conditions. Gelation time and gel integrity were monitored visually for up to 8 hours¹⁰.

Floating Behaviour: 10 mL of each formulation was placed in 100 mL of 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C. Floating lag time and total floating duration were recorded. Tests were carried out in triplicate¹⁰.

Drug Content Uniformity: 1 mL of the formulation was diluted in 0.1 N HCl, filtered, and analyzed using a UV-Visible spectrophotometer (Shimadzu UV-1800, Japan) at 258 nm. Drug content was determined against a previously constructed calibration curve of Itopride Hydrochloride¹¹.

In-vitro Drug Release Study: Dissolution was performed using a USP Type II (paddle) apparatus (Electrolab TDT-08L, India). 900 mL of 0.1 N HCl (pH 1.2) was used as dissolution medium at 37 ± 0.5 °C and 50 rpm. Samples (5 mL) were withdrawn at specific intervals up to 12 hours, filtered, and analyzed at 258 nm. An equal volume of fresh medium was replaced to maintain sink conditions¹².

Statistical Analysis:

Effect of the independent variables on each response (Y_1 , Y_2 , Y_3) was evaluated using analysis of variance (ANOVA) in Design Expert® software. Model fitness was assessed using regression analysis and response surface plots. All measurements were conducted in triplicate, and data were expressed as mean $\pm$ standard deviation (SD)¹³.

RESULTS AND DISCUSSION:

Evaluation of Preformulation Parameters

Identity and purity of Itopride Hydrochloride were established through standard Preformulation studies. The drug was found to be a white crystalline powder with a bitter taste, and was freely soluble in water, consistent with compendia standards. The melting point was observed at 199 ± 0.5 °C, aligning closely with literature-reported values, thereby confirming its authenticity and purity. These physicochemical findings are summarized in Table 2.

Table 2. Preformulation Characteristics of Itopride Hydrochloride

Parameter	Observed Value
Appearance	White crystalline powder
Taste	Bitter

Solubility	Freely soluble in water
Melting Point (°C)	199 ± 0.5
pKa	9.4

Calibration Curve of Itopride Hydrochloride

A standard calibration curve of Itopride Hydrochloride was constructed in 0.1 N HCl to establish a reliable method for in vitro drug release studies. A stock solution of 100 µg/mL was prepared and serially diluted to obtain concentrations of 5, 10, 15, 20, and 25 µg/mL. The absorbance of each solution was measured at 224 nm (Figure 1) using a UV-Visible spectrophotometer against a blank of 0.1 N HCl. The results showed a linear relationship between absorbance and concentration over the tested range, conforming to Beer-Lambert's law. The linear regression equation was found to be $R^2 = 0.9986$ (Figure 2).

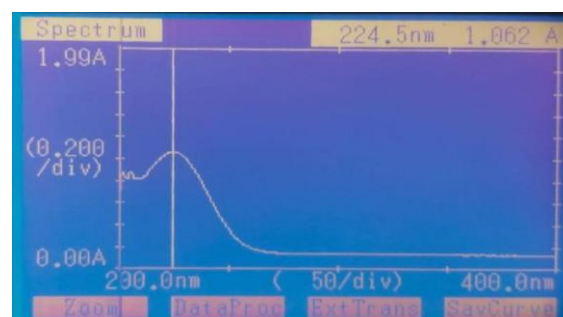


Figure 1. UV Spectra of Itopride Hydrochloride

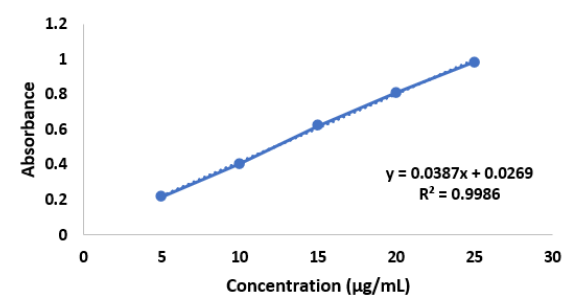


Figure 2. Standard Calibration Curve of Itopride Hydrochloride

Evaluation of Formulated Gels:

Physical Appearance and pH:

All the formulated in-situ gels (F1–F9) were visually inspected for physical appearance. The gels were found to be clear to slightly turbid, exhibiting good pharmaceutical elegance without any signs of phase separation or precipitation. Such clarity is indicative of uniform polymer dispersion and appropriate formulation compatibility. The pH values of the formulations were found to be in the range of 6.5 to 7.2, which falls within the acceptable physiological limits for oral administration. This near-neutral pH is beneficial for minimizing gastric irritation and ensuring the chemical stability of Itopride Hydrochloride, while also maintaining the integrity of gel-forming polymers such as sodium alginate.

Viscosity and Gelation Capacity:**Viscosity of Formulated Gels:**

Viscosity of all nine in-situ gel formulations was measured to assess their flowability and suitability for gastric retention. The values ranged from 123 to 175 cps, largely influenced by the concentration of sodium alginate and calcium chloride. The lowest viscosity was observed in Batch F2 (123 cps), while the highest was seen in Batch F8 (175 cps), attributed to its higher polymer content and stronger ionic crosslinking. Formulations F3 (162 cps), F5 (166 cps), and F7 (149 cps) also demonstrated elevated viscosities, indicative of enhanced gel-forming potential without compromising pourability (Table 3).

Gelation Time:

Gelation time is critical for raft formation in the acidic gastric environment. Across all formulations, gelation time ranged from 19 to 35 seconds. Batch F8 (19 sec) and F5 (21 sec) showed the fastest sol-to-gel transition, favourable for rapid in situ gelation. Batch F2, having a lower concentration of gelling agents, exhibited the longest gelation time of 35 seconds (Table 3).

Gel Strength:

Gel strength of the gel was recorded qualitatively as “++” (moderate) to “+++” (strong). Strong gel formation (+++) was observed in Formulations F3, F4, F5, F7, F8, and F9, suggesting good mechanical integrity upon contact with gastric fluid. This contributes significantly to prolonged gastric residence (Table 3).

Floating Lag Time and Total Floating Duration:

Floating lag time (FLT) varied between 25 and 40 seconds, influenced by polymer concentration and gelation kinetics. The shortest FLT was recorded in F8 (25 sec), whereas F6 showed the longest at 40 seconds. All batches floated for more than 12 hours, indicating effective gastric retention and the potential for sustained drug release (Table 3).

Drug Content Uniformity:

Drug content ranged from 98.59% (F4) to 99.31% (F9). This indicates excellent drug entrapment efficiency and uniform distribution across the formulations. The slight variation is within acceptable Pharmacopeial limits and reflects robust formulation reproducibility. The values are listed in Table 3.

Table 3. Evaluation Parameters of Formulated Batches of Itopride Hydrochloride Raft-Forming In-Situ Gels

Batch	pH	Viscosity (cps)	Gelation Time (sec)	Gel Strength	Floating Lag Time (sec)	Total Floating Time (h)	Drug Content (%)
F1	6.81	141	24	++	32	>12	98.97 ± 0.34
F2	6.88	123	35	++	38	>12	98.76 ± 0.28
F3	6.91	162	23	+++	29	>12	99.18 ± 0.30
F4	6.95	128	33	+++	36	>12	98.59 ± 0.41
F5	7.02	166	21	+++	27	>12	98.91 ± 0.39
F6	6.73	130	31	++	40	>12	99.14 ± 0.32
F7	6.99	149	26	+++	31	>12	98.83 ± 0.26
F8	6.76	175	19	+++	25	>12	98.64 ± 0.33
F9	6.79	153	22	+++	30	>12	99.31 ± 0.29

In-Vitro Drug Release Study:

The in vitro drug release of Itopride Hydrochloride from raft-forming in-situ gel formulations (F1–F9) was evaluated in 0.1 N HCl (pH 1.2) over 12 hours using USP Type II apparatus. The cumulative release varied significantly based on polymer composition and viscosity. Formulation F2 exhibited the fastest release (96.2% at 6 h; 99.3% at

12 h), while F1 showed the most sustained profile (97.1% at 12 h). Controlled release was also observed with F3 (93.4%) and F8 (94.2%). The results indicate that higher polymer concentrations and crosslinking delay drug diffusion by forming denser gels, release profiles are shown in Table 4, and the comparative release curves are illustrated in Figure 3.

Table 4. In Vitro Drug Release Profiles of Itopride Hydrochloride F1 to F9

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	28.7	33.4	19.3	27.1	22.8	29.6	24.2	18.1	20.6
2	48.5	53.1	38.4	45.6	42.9	51.0	43.7	36.8	39.3
4	71.2	78.6	58.6	70.2	64.1	75.4	66.5	55.9	61.4
6	85.9	96.2	72.7	87.5	79.8	91.3	80.6	70.1	76.7
8	91.8	98.4	84.3	93.9	88.2	96.1	89.7	81.2	86.5
10	95.2	99.0	90.8	97.1	92.5	98.0	94.1	89.4	91.3
12	97.1	99.3	93.4	98.4	95.9	99.1	96.8	94.2	94.9

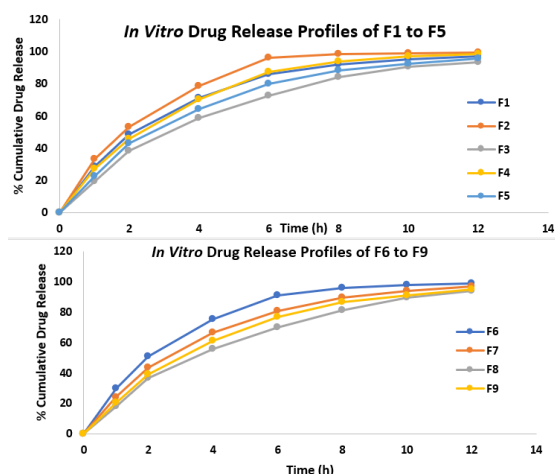


Figure 3. Comparative In Vitro Drug Release Profiles of F1 to F9

Statistical Analysis and Optimization:

A 3^2 full factorial design was applied to evaluate the effects of sodium alginate (X_1) and HPMC K100M (X_2) on floating lag time (Y_1), viscosity (Y_2), and drug release at 6 h (Y_3). The results were statistically analyzed using Design Expert® (Version 13). All models were found to be significant ($p < 0.05$) with $R^2 > 0.98$, indicating a good fit (Table 5). Based on desirability function criteria (minimize FLT, target viscosity, maximize drug release), Formulation F9 was identified as the optimized batch.

Table 5. Statistical Optimization Results

Response	Model Type	R^2	Effect of Polymers
Floating Lag Time (Y_1)	Quadratic	0.985	Decreases with $\uparrow X_1$ and $\uparrow X_2$
Viscosity (Y_2)	Quadratic	0.991	Increases with $\uparrow X_1$ and $\uparrow X_2$
Drug Release at 6 h (Y_3)	Quadratic	0.987	Decreases with $\uparrow X_1$ and $\uparrow X_2$

Stability Study:

The optimized formulation (F9) was subjected to an accelerated stability study as per ICH guidelines. The sample was stored at $40 \pm 2^\circ\text{C}$ / $75 \pm 5\%$ RH in a stability chamber for a period of 30 days. At the end of the storage period, the formulation was evaluated for appearance, pH, viscosity, floating behaviour, and drug content. No significant changes were observed in any of the parameters, and all values remained within acceptable limits, as compared to the initial measurements. The formulation retained its clarity, appropriate gelation properties, and sustained floating ability, with drug content above 98%, indicating good physical and chemical stability under accelerated conditions (Table 6).

Table 6. Stability Profile of Optimized Batch (F9) at $40 \pm 2^\circ\text{C}$ / 75% RH

Parameter	Initial Value	After 30 Days	% Change
Appearance	Clear, gel-forming	No change	—
pH	6.79	6.77	$< 0.3\%$
Viscosity (cP)	153	151	$< 1.5\%$
Floating Lag Time (sec)	30	31	$< 3.3\%$
Total Floating Time (h)	> 12	> 12	No change
Drug Content (%)	99.31 ± 0.29	98.97 ± 0.34	$< 0.5\%$

Comparison with Reported In-Situ Gel Systems:

The developed Itopride Hydrochloride-loaded raft-forming in-situ gel formulations were evaluated and optimized for key performance parameters including floating lag time, viscosity, gelation behaviour, drug release kinetics, and gastric retention. The optimized batch (F9) demonstrated excellent performance across these metrics, including a floating lag time of 30 seconds, sustained floating for more than 12 hours, and 94.9% cumulative drug release at 12 hours. When compared with previously reported in-situ gel systems, the results of this study show comparable or superior outcomes, Nayak et al. (2018)¹⁴ formulated a similar sodium alginate-based in-situ gel for Ranitidine hydrochloride with a floating lag time of approximately 45 seconds and sustained drug release up to 8 hours, whereas the present system extends the release duration to 12 hours with a shorter lag time. Likewise, Sasmal et al. (2017)¹⁵ reported an in-situ gel formulation of Metoclopramide hydrochloride using sodium alginate and calcium carbonate, where gel strength and floating behaviour were acceptable but drug release exceeded 90% within 6 hours. In contrast, our formulation (F9) exhibits more controlled release kinetics suitable for prolonged gastric retention.

CONCLUSION:

The present study successfully developed and evaluated a raft-forming in-situ gel formulation of Itopride Hydrochloride using ion-induced gelation, optimized via a 3^2 full factorial design. Among all batches, formulation F9 exhibited optimal physicochemical and functional characteristics, including appropriate pH, high viscosity, rapid gelation time, strong gel strength, prolonged buoyancy, uniform drug content, and sustained drug release up to 12 hours. The statistical analysis confirmed the significant influence of sodium alginate and HPMC K100M concentrations on key performance parameters. When compared to similar reported in-situ gel systems in the literature, the optimized formulation demonstrated comparable or superior control over drug release and floating behaviour, indicating its potential for enhanced gastric retention and improved therapeutic efficacy.

These findings suggest that F9 is a promising candidate for targeted gastric delivery of Itopride Hydrochloride.

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CONFLICT OF INTEREST:

No conflict of interest.

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