Formulation and Optimization of Gastroretentive Floating Matrix Tablets of Itopride Hydrochloride Using Box–Behnken Design

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ABSTRACT

The present study aimed to formulate and optimize gastroretentive floating matrix tablets of Itopride Hydrochloride to enhance gastric residence time and achieve sustained drug release [1]. Floating tablets were prepared using hydrophilic polymers, namely HPMC K100M and Carbopol 934P, along with sodium bicarbonate as a gas-generating agent [2]. A Box–Behnken Design was employed to evaluate the effect of formulation variables on floating lag time, total floating time, and cumulative drug release. Seventeen experimental formulations were developed and evaluated [3]. The floating lag time ranged from 42.7 to 68.3 seconds, while total floating time varied between 9.1 and 13.0 hours, indicating effective buoyancy and prolonged gastric retention. In vitro drug release studies demonstrated a sustained release profile, with cumulative drug release ranging from 78.2% to 85.0% at 12 hours. Statistical analysis revealed that all formulation variables significantly influenced the responses ($p < 0.05$), with a non-significant lack of fit confirming model adequacy. The optimized formulation, containing HPMC K100M (150 mg), sodium bicarbonate (60 mg), and Carbopol 934P (18.50 mg), exhibited a floating lag time of 42.7 seconds, total floating time of 13.19 hours, and 78.46% drug release at 12 hours, with a desirability value of 0.987. Experimental validation showed close agreement with predicted values, with percentage prediction error below 5%. The developed gastroretentive floating system of Itopride Hydrochloride offers a promising approach for sustained drug delivery, improved bioavailability, and enhanced patient compliance. Further in vivo studies are recommended to confirm its clinical performance.

Keywords: Gastroretentive Drug Delivery, Floating Tablets, Itopride Hydrochloride, Box–Behnken Design, Sustained Release, Optimization

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Introduction

Oral drug delivery remains the most widely used route of administration due to its convenience, cost-effectiveness, and high patient compliance [1]. However, conventional oral dosage forms often exhibit limitations such as rapid gastric emptying and incomplete drug absorption, particularly for drugs with a narrow absorption window [2-4]. Gastroretentive

drug delivery systems (GRDDS), especially floating drug delivery systems, have been developed to prolong gastric residence time and enhance drug bioavailability by maintaining the dosage form in the stomach for an extended period [5,6]. Itopride Hydrochloride is a gastroprokinetic agent used in the treatment of functional dyspepsia and related gastrointestinal disorders [7]. It possesses a relatively short half-life and requires multiple daily dosing, which may reduce patient compliance [8]. Since Itopride is primarily absorbed in the upper gastrointestinal tract, the development of a gastroretentive floating formulation is considered a promising strategy to improve its therapeutic performance [9]. Floating matrix tablets prepared using hydrophilic polymers such as HPMC and Carbopol can provide controlled drug release along with prolonged gastric retention [10]. In addition, gas-generating agents like sodium bicarbonate facilitate buoyancy by reducing tablet density. In this study, Box–Behnken Design was employed to optimize formulation variables and evaluate their effect on floating behavior and drug release, with the aim of developing an effective sustained-release gastroretentive system [11].

Materials and Methods

Materials

Itopride Hydrochloride was obtained as a gift sample from a reputed pharmaceutical manufacturer. Hydroxypropyl methylcellulose (HPMC K100M) and Carbopol 934P were procured from authorized suppliers. Sodium bicarbonate was used as a gas-generating agent to impart buoyancy. Microcrystalline cellulose (MCC) was used as a diluent, while magnesium stearate and talc were used as lubricant and glidant, respectively. All other chemicals and reagents used in the study were of analytical grade and utilized without further purification.

Experimental Design and Optimization

A Box–Behnken Design (BBD) was employed to evaluate the effect of formulation variables on the floating behavior and drug release characteristics of gastroretentive floating matrix tablets using Design-Expert® software. Three independent variables, namely HPMC K100M (A), sodium bicarbonate (B), and Carbopol 934P (C), were studied at three levels each. A total of 17 experimental runs, including replicated center points to estimate experimental error, were generated. The selected independent variables and their levels were chosen based on preliminary trials to achieve optimal floating characteristics and sustained drug release. The dependent variables (responses) included floating lag time (R1), total floating time (R2), and cumulative drug release at 12 hours (R3). Floating lag time was minimized, total floating time was maximized, and drug release was targeted in the range of 75–85% at 12 hours to ensure sustained release behavior [12,13]. The coded and actual levels of the independent variables are presented in Table 1, while the formulation composition and corresponding responses for all experimental runs are provided in Table 2.

Preparation of Gastroretentive Floating Tablets of Vonoprazan

Gastroretentive floating matrix tablets of Itopride Hydrochloride were prepared by the direct compression method. Accurately weighed quantities of the drug, HPMC K100M, Carbopol 934P, and sodium bicarbonate (as per Table 2) were passed through a #40 mesh sieve and blended uniformly using the geometric dilution technique to ensure homogeneity. Microcrystalline cellulose (MCC) was added as a diluent to adjust the tablet weight. Subsequently, talc and magnesium stearate were incorporated as glidant and lubricant, respectively, and mixed gently to avoid over-lubrication. The final powder blend was compressed into tablets using an 8 mm flat-faced punch on a rotary tablet compression machine. The prepared tablets were stored in airtight containers at room temperature for further evaluation [11-14].

Table 1. Independent Variables and Their Levels in Box–Behnken Design

Run	A: HPMC K100M (mg)	B: Sodium bicarbonate (mg)	C: Carbopol 934P (mg)
1	120	40	17.5
2	150	40	10
3	90	60	17.5
4	120	40	17.5
5	150	40	25
6	120	60	10
7	90	40	10
8	90	40	25
9	120	60	25
10	120	20	10
11	90	20	17.5
12	120	40	17.5
13	120	40	17.5
14	120	20	25
15	150	60	17.5
16	120	40	17.5
17	150	20	17.5

Table 2. Formulation Composition of Floating Tablets

Run	Itopride HCl (mg)	HPMC K100M (mg)	Carbopol 934P (mg)	Sodium bicarbonate (mg)	MCC (mg)	Talc (mg)	Mg stearate (mg)	Total (mg)
1	100	120	17.5	40	213.5	4	5	500
2	100	150	10	40	191	4	5	500
3	100	90	17.5	60	223.5	4	5	500
4	100	120	17.5	40	213.5	4	5	500
5	100	150	25	40	176	4	5	500
6	100	120	10	60	201	4	5	500
7	100	90	10	40	251	4	5	500
8	100	90	25	40	236	4	5	500
9	100	120	25	60	186	4	5	500
10	100	120	10	20	261	4	5	500
11	100	90	17.5	20	263.5	4	5	500
12	100	120	17.5	40	213.5	4	5	500
13	100	120	17.5	40	213.5	4	5	500
14	100	120	25	20	226	4	5	500
15	100	150	17.5	60	159.5	4	5	500
16	100	120	17.5	40	213.5	4	5	500
17	100	150	17.5	20	199.5	4	5	500

Characterization of Floating Tablets

Floating Lag Time (FLT)

Floating lag time was determined by placing each tablet in 500 mL of 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5°C using a USP Dissolution Apparatus II (paddle method). The time required for the tablet to rise to the surface of the medium and remain buoyant was recorded in seconds as floating lag time (FLT). The experiment was performed in triplicate and the mean values were reported [15,16].

Total Floating Time (TFT)

Total floating time was determined by continuously observing the tablets used in the FLT study in the same dissolution medium. The duration for which the tablet remained buoyant without disintegration or sinking was recorded as total floating time (TFT) in hours. Observations were continued for up to 12–14 hours depending on the integrity of the tablets [17].

In Vitro Drug Release Study

In vitro drug release of Itopride Hydrochloride from floating tablets was evaluated using a USP Type II (paddle) dissolution apparatus operated at 50 rpm in 900 mL of 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5°C. Samples (5 mL) were withdrawn at predetermined time intervals up to 12 hours and replaced with fresh dissolution medium to maintain sink conditions [18]. The samples were filtered and analyzed using a UV–visible spectrophotometer at λmax ≈ 258 nm, and the cumulative percentage drug release was calculated [19].

Statistical Analysis

All experiments were carried out in triplicate and results were expressed as mean ± standard deviation (SD)**.** The data obtained were analyzed using Design-Expert® software by applying regression analysis, analysis of variance (ANOVA), and response surface methodology. The significance of the model and factors was evaluated at a confidence level of 95%, where $\mathbf{p < 0.05}$ was considered statistically significant [20].

Evaluation of Optimized Floating Tablets

The optimized formulation of Itopride Hydrochloride was evaluated for various physicochemical parameters.

Weight variation was determined using 20 tablets, while hardness was measured for six tablets using a Monsanto hardness tester. Thickness and diameter were measured using a digital Vernier caliper. Friability was assessed using a Roche friabilator operated at 25 rpm for 4 minutes. Drug content was determined by dissolving powdered tablets equivalent to 100 mg of drug in 0.1 N HCl, followed by spectrophotometric analysis. Floating behavior was evaluated in 0.1 N HCl (37 ± 0.5°C) by recording FLT and TFT. The swelling index was determined after 6 hours in acidic medium. In vitro drug release of the optimized formulation was evaluated using the USP Type II dissolution apparatus for 12 hours, and cumulative drug release was calculated.

Results and Discussion

Evaluation of Gastroretentive Floating Matrix Tablets

Gastroretentive floating matrix tablets of Itopride Hydrochloride were successfully formulated using hydrophilic polymers (HPMC K100M and Carbopol 934P) and a gas-generating agent (sodium bicarbonate). The effect of formulation variables on floating behavior and drug release was systematically investigated using Box–Behnken Design. The experimental design and observed responses for all 17 formulations are presented in Table 3.

Table 3. Experimental Design and Observed Responses of Gastroretentive Floating Tablets

Run	Floating Lag Time (sec)	Total Floating Time (h)	Drug Release at 12 h (%)
1	52.4	11.2	82.1
2	49.8	11.6	78.3
3	58.2	10.8	83.5
4	48.9	11.4	81.8
5	42.7	12.8	80.2
6	54.1	11.9	79.5
7	68.3	9.6	84.1
8	53.7	10.7	85.0
9	45.9	12.4	82.3
10	62.5	9.8	82.7
11	64.2	9.1	84.8
12	55.8	10.9	82.6
13	49.6	11.0	81.9
14	55.6	10.2	84.2
15	46.8	13.0	78.2
16	54.2	11.1	82.0
17	48.7	11.4	80.1

Floating Lag Time (FLT)

The floating lag time (FLT) of all formulations ranged from 42.7 to 68.3 seconds, indicating rapid buoyancy of the prepared tablets. The results demonstrated that sodium bicarbonate had a significant effect on FLT, where an increase in its concentration reduced the lag time due to rapid generation of carbon dioxide, which decreased the density of the tablet and enabled it to float quickly. HPMC K100M also contributed to floating behavior by forming a gel barrier upon hydration, which helped in trapping the generated gas within the matrix. In contrast, lower polymer concentration resulted in delayed floatation due to insufficient gel strength. The highest FLT was observed in Run 7 (68.3 sec), which contained lower polymer and gas-generating agent levels, whereas Run 5 (42.7 sec) showed the lowest FLT due to optimal composition of formulation variables.

Total Floating Time (TFT)

The total floating time (TFT) of the formulations ranged from 9.1 to 13.0 hours, demonstrating satisfactory buoyancy and prolonged gastric retention. Formulations containing higher concentrations of HPMC K100M and Carbopol 934P exhibited extended floating duration due to enhanced swelling and formation of a strong gel matrix that maintained tablet integrity. The maximum floating duration was observed in Run 15 (13.0 h), which contained higher levels of polymer and sodium bicarbonate, indicating improved matrix strength and gas entrapment. On the other hand, formulations with lower polymer content showed reduced floating duration due to weaker gel formation and faster erosion of the matrix.

In Vitro Drug Release

The cumulative drug release at 12 hours ranged from 78.2% to 85.0%**,** indicating a sustained drug release profile suitable for gastroretentive delivery. Drug release was found to be inversely proportional to polymer concentration. Higher amounts of HPMC K100M and Carbopol 934P resulted in slower drug release due to increased viscosity and formation of a dense gel layer, which restricted drug diffusion. Conversely, increasing the concentration of sodium bicarbonate enhanced drug release by increasing matrix porosity, facilitating faster penetration of dissolution medium and diffusion of the drug. The highest drug release was observed in Run 8 (85.0%), whereas Run 15 (78.2%) exhibited the slowest release due to the formation of a highly viscous gel barrier.

Effect of Formulation Variables and ANOVA Analysis

The influence of formulation variables, namely HPMC K100M (A)**,** sodium bicarbonate (B), and Carbopol 934P (C), on the floating behavior and drug release characteristics of gastroretentive floating tablets of

Itopride Hydrochloride was evaluated using Design-Expert® software. The ANOVA results confirmed that the developed models for all responses, including floating lag time (R1), total floating time (R2), and cumulative drug release at 12 hours (R3), were statistically significant, with p-values < 0.05. The high F-values observed for all responses indicate a strong influence of formulation variables on the measured responses. For floating lag time (R1), the model F-value of 31.65 with a p-value of 3.04×10^{-6} confirmed model significance. Similarly, for total floating time (R2) and cumulative drug release (R3), the model F-values were 134.28 and 113.98, respectively, both with highly significant p-values (<0.0001), indicating robustness of the developed models. All three independent variables (A, B, and C) showed significant effects on each response ($p < 0.05$). HPMC K100M exhibited the highest influence on drug release (R3), while sodium bicarbonate significantly affected floating lag time due to its gas-generating ability. Carbopol 934P contributed to both floating duration and controlled drug release through gel formation and swelling behavior. Importantly, the lack of fit for all responses was found to be non-significant ($p > 0.05$), indicating a good agreement between the experimental and predicted values and confirming the adequacy of the model.

Table 4. ANOVA for Responses

Source	R1 F value	p-value	R2 F-value	p-value	R3 F-value	p-value
Model	31.65	<0.0001	134.28	<0.0001	113.98	<0.0001
A - HPMC K100M	57.95	<0.0001	209.88	<0.0001	266.90	<0.0001
B - Sodium bicarbonate	12.32	0.0038	163.91	<0.0001	43.33	<0.0001
C - Carbopol 934P	24.67	0.0003	29.06	0.0001	31.71	<0.0001
Lack of Fit	0.70	0.699	1.28	0.437	2.52	0.194
		(NS)		(NS)		(NS)
Significance	Significant	-	Significant	-	Significant	-

Response Surface Analysis

The interaction effects of formulation variables on different responses were further analyzed using contour plots generated by Design-Expert® software.

Floating Lag Time (R1)

The contour plot for floating lag time (Figure 1) demonstrates that increasing sodium bicarbonate concentration significantly reduced FLT due to rapid CO_2 generation, which decreased tablet density and enhanced buoyancy. Conversely, lower levels of polymer resulted in higher lag time due to insufficient gel formation.

Total Floating Time (R2)

The contour plot for total floating time (Figure 2) indicates that higher concentrations of HPMC K100M and Carbopol 934P increased the floating duration due to improved swelling and formation of a stable gel matrix. Lower polymer concentrations resulted in reduced buoyancy duration.

Cumulative Drug Release (R3)

The contour plot for cumulative drug release (Figure 3) shows that increasing polymer concentration decreased drug release due to the formation of a dense gel barrier, which restricted drug diffusion. In contrast, higher sodium bicarbonate levels increased drug release by enhancing matrix porosity

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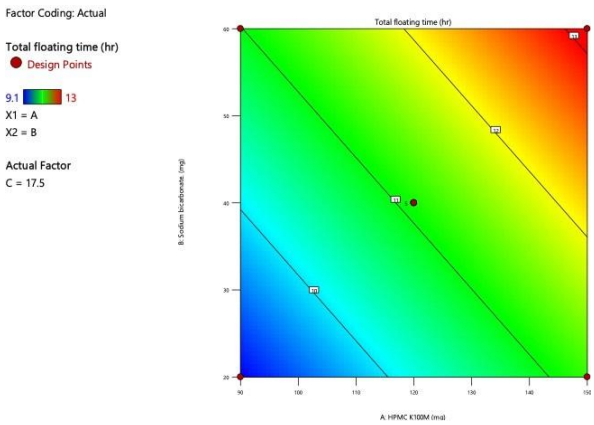

Figure 1. Contour plot showing the effect of HPMC K100M and sodium bicarbonate on floating lag time (R1)

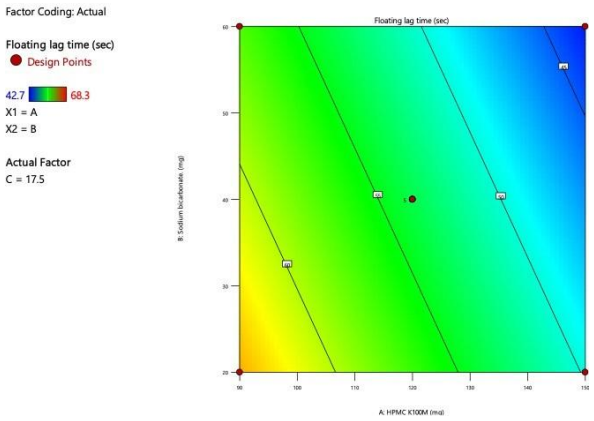

Figure 2. Contour plot showing the effect of HPMC K100M and Carbopol 934P on total floating time (R2)

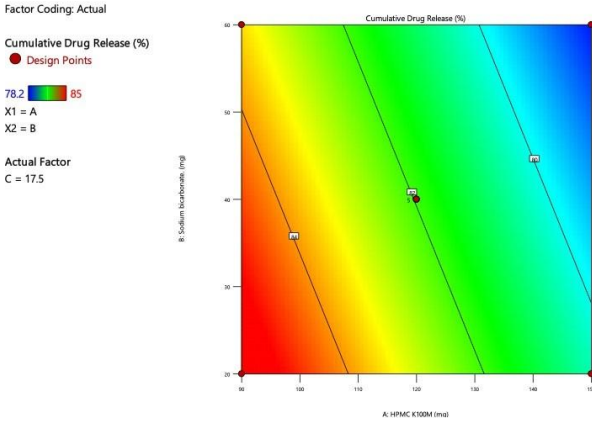

Figure 3. Contour plot showing the effect of HPMC K100M and sodium bicarbonate on cumulative drug release at 12 h (R3)

Optimized Formulation Batch (F-18)

The optimization of gastroretentive floating matrix tablets of Itopride Hydrochloride was carried out using the desirability function approach of Box–Behnken Design. The optimization criteria were set to minimize floating lag time (R1), maximize total floating time (R2), and achieve targeted drug release (R3) within the range of 75–85% at 12 hours. Based on these constraints, Solution No. 1 with a desirability value of 0.987 was selected as the optimized formulation. The optimized levels of formulation variables were HPMC K100M (150 mg), sodium bicarbonate (60 mg), and Carbopol 934P (18.50 mg). The composition of the optimized formulation is presented in Table 5, while the predicted and experimental response values are summarized in Table 6. The optimized formulation exhibited excellent gastroretentive performance with rapid buoyancy, prolonged floating duration, and controlled drug release. To validate the optimization model, the optimized formulation was prepared and evaluated experimentally. The observed values were found to be in close agreement with the predicted values, with percentage prediction error (%PE) less than 5%, indicating good reliability and predictive ability of the model.

Table 5. Composition of Optimized Floating Tablet (F-18)

Component	Quantity (mg/tablet)
Itopride Hydrochloride	100 mg
HPMC K100M	150 mg
Carbopol 934P	18.50 mg
Sodium bicarbonate	60 mg
MCC (q.s.)	158.50 mg
Talc	4 mg
Magnesium stearate	5 mg
Total Weight	**500 mg**

Table 6. Predicted vs Experimental Response Values of Optimized Formulation

Response Parameter	Predicted Value	Experimental Value	% Prediction Error
Floating Lag Time (sec)	42.70	43.90 ± 1.10	2.81
Total Floating Time (hr)	13.19	13.05 ± 0.25	1.06
Drug Release (12 h, %)	78.46	79.10 ± 0.40	0.82

**Mean ± SD (n = 3)*

Evaluation Results of Optimized Batch F-18

The optimized formulation (F-18) of Itopride Hydrochloride floating matrix tablets, comprising HPMC K100M (150 mg), Carbopol 934P (18.50 mg), and sodium bicarbonate (60 mg), was subjected to comprehensive physicochemical, mechanical, buoyancy, and in vitro release evaluations. The results demonstrated excellent tablet characteristics, including uniform weight, adequate hardness, low friability, and acceptable drug content, indicating good compressibility and mechanical strength. The optimized formulation exhibited rapid floating behavior, prolonged buoyancy, and a controlled drug release profile consistent with the desired gastroretentive system. All evaluation parameters were found to be within acceptable pharmacopeial limits. The detailed evaluation results of the optimized formulation are summarized in Table 6.

Table 6. Evaluation Parameters of Optimized Floating Tablet (F-18)

Parameter	Result

Weight variation (mg)	498.6 ± 2.1
Hardness (kg/cm²)	5.6 ± 0.3
Thickness (mm)	5.12 ± 0.08
Diameter (mm)	8.02 ± 0.03
Friability (%)	0.42
Drug Content (%)	99.28 ± 0.4
Floating Lag Time (sec)	43.9 ± 1.1
Total Floating Time (hr)	13.05 ± 0.25
Swelling Index (%) (after 6 h)	228.4 ± 2.5
Cumulative Drug Release (12 h, %)	79.10 ± 0.40

Conclusion

The present study successfully demonstrated the formulation and optimization of gastroretentive floating matrix tablets of Itopride Hydrochloride using a Box–Behnken Design approach. The prepared formulations exhibited desirable floating behavior, with floating lag time ranging from 42.7 to 68.3 seconds and total floating time between 9.1 and 13.0 hours, indicating effective buoyancy and prolonged gastric retention. The in vitro drug release study revealed a sustained release profile, with cumulative drug release ranging from 78.2% to 85.0% at 12 hours, demonstrating controlled drug delivery suitable for gastroretentive systems. Statistical analysis confirmed that formulation variables, particularly HPMC K100M and sodium bicarbonate, significantly influenced floating behavior and drug release ($p < 0.05$), while the non-significant lack of fit ($p > 0.05$) validated the adequacy of the developed models. The optimized formulation, obtained at HPMC K100M (150 mg), sodium bicarbonate (60 mg), and Carbopol 934P (18.50 mg), exhibited a floating lag time of 42.7 seconds, total floating time of 13.19 hours, and drug release of 78.46% at 12 hours, with a high desirability value of 0.987. The experimental values showed close agreement with predicted results, with percentage prediction error below 5%, confirming the reliability of the optimization process, the developed gastroretentive floating system of Itopride Hydrochloride provides an effective approach for enhancing gastric residence time and achieving sustained drug release. This formulation strategy has the potential to improve therapeutic efficacy and patient compliance. Further in vivo studies are recommended to establish in vitro–in vivo correlation and clinical applicability.

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