

Formulation and Optimization of Sustained-Release Gastroretentive Microspheres of Vonoprazan Using Box–Behnken Design

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Abstract

Background: Vonoprazan is a novel potassium-competitive acid blocker (P-CAB) with potent acid-suppressive activity; however, its therapeutic efficacy may be limited by rapid gastric emptying. The present study aimed to formulate and optimize sustained-release gastroretentive microspheres of vonoprazan using the ionotropic gelation technique to prolong gastric residence time and achieve controlled drug release.

Methods: Gastroretentive microspheres were prepared using sodium alginate and HPMC K100M as matrix-forming polymers and calcium chloride as the cross-linking agent. A three-factor, three-level Box–Behnken design was employed to optimize sodium alginate concentration (1–3% w/v), HPMC K100M concentration (0.5–1.5% w/v), and calcium chloride concentration (2–6% w/v). The formulations were evaluated for encapsulation efficiency, particle size, percentage yield, drug loading, swelling index, floating behavior, and in vitro drug release. Numerical optimization was performed using the desirability function approach.

Results: The encapsulation efficiency ranged from 85.18% to 94.21%, particle size varied between 171 and 221 nm, and cumulative drug release after 12 h ranged from 66.7% to 79.8%. ANOVA confirmed that the developed models were statistically significant ($p < 0.05$), with sodium alginate concentration significantly affecting encapsulation efficiency, while sodium alginate and HPMC K100M significantly influenced particle size and drug release. The optimized formulation contained 3.0% w/v sodium alginate, 1.5% w/v HPMC K100M, and 4.123% w/v calcium chloride, with predicted values of 93.55% encapsulation efficiency, 172.83 nm particle size, and 79.80% drug release, achieving a desirability of 0.945. The optimized microspheres also demonstrated excellent floating ability, high swelling capacity, and satisfactory stability.

Conclusion: The optimized gastroretentive microspheres of vonoprazan successfully provided sustained drug release with high encapsulation efficiency and desirable physicochemical characteristics. The Box–Behnken design proved to be an effective optimization tool for developing a robust gastroretentive delivery system with potential to improve the therapeutic performance of vonoprazan.

Keywords: Vonoprazan; Gastroretentive Microspheres; Ionotropic Gelation; Box–Behnken Design; Sustained Drug Release; Response Surface Methodology.

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1. Introduction

Vonoprazan is a novel potassium-competitive acid blocker (P-CAB) that provides rapid, potent, and sustained inhibition of gastric acid secretion, making it an effective therapeutic agent for peptic ulcer disease and gastroesophageal reflux disease (GERD) (Zidan et al., 2024). Compared with conventional proton pump inhibitors, vonoprazan exhibits a faster onset of action, prolonged acid suppression, and improved therapeutic efficacy. However, rapid gastric emptying may limit its gastric residence time and reduce its overall therapeutic performance (Akintuyi, 2024). Gastroretentive drug delivery systems have been developed to prolong gastric residence time, enhance drug bioavailability, and provide sustained drug release. Among these systems, polymeric microspheres prepared by ionotropic gelation offer advantages such as high drug entrapment, controlled drug release, biocompatibility, and ease of preparation (Shams et al., 2024). Sodium alginate and HPMC K100M are widely used polymers for preparing sustained-release gastroretentive microspheres because they form a stable gel matrix and effectively regulate drug release (Rizvi et al., 2024). In the present study, sustained-release gastroretentive microspheres of vonoprazan were formulated using the ionotropic gelation technique and optimized using a three-factor, three-level Box–Behnken design. The effects of sodium alginate concentration, HPMC K100M concentration, and calcium chloride concentration on encapsulation efficiency, particle size, and in vitro drug release were systematically investigated to obtain an optimized formulation with desirable physicochemical characteristics and sustained-release performance.

2. Materials and Methods

2.1 Materials

Vonoprazan was obtained as a gift sample from a reputed pharmaceutical manufacturer. Sodium alginate and Hydroxypropyl methylcellulose (HPMC K100M) were used as matrix-forming polymers, while calcium chloride served as the cross-linking agent. Sodium bicarbonate was incorporated as a gas-generating agent to impart gastroretentive floating properties to the microspheres. All chemicals and reagents used were

of analytical grade and employed without further purification. Double-distilled water was used throughout the study.

2.2 Experimental Design

A three-factor, three-level Box–Behnken design (BBD) was employed using Design-Expert® software (Version 13) to optimize the formulation of sustained-release gastroretentive microspheres of vonoprazan (Sun et al., 2024). Three formulation variables were selected based on preliminary optimization studies, namely sodium alginate concentration (A, X_1), HPMC K100M concentration (B, X_2), and calcium chloride concentration (C, X_3). Each factor was evaluated at three coded levels (–1, 0, +1), corresponding to actual concentrations of 1–3% w/v for sodium alginate, 0.5–1.5% w/v for HPMC K100M, and 2–6% w/v for calcium chloride are given in Table 1 (Zhang et al., 2025). The Box–Behnken design generated 15 experimental runs, including replicated center points to estimate experimental error. The composition of all formulations is presented in Table 1. The dependent variables investigated were encapsulation efficiency (Y_1), particle size (Y_2), and cumulative in vitro drug release at 12 h (Y_3). The optimization criteria were established to maximize encapsulation efficiency and drug release while minimizing particle size (Rampal et al., 2024).

Table 1. Independent Variables Used in the Box–Behnken Design

Factor	Variable	Low (–1)	Medium (0)	High (+1)
A (X_1)	Sodium alginate concentration (% w/v)	1	2	3
B (X_2)	HPMC K100M concentration (% w/v)	0.5	1.0	1.5
C (X_3)	Calcium chloride concentration (% w/v)	2	4	6

2.3 Preparation of Sustained-Release Gastroretentive Microspheres of Vonoprazan

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Vonoprazan-loaded gastroretentive microspheres were prepared by the ionotropic gelation technique. Sodium alginate and HPMC K100M were accurately weighed according to the formulation composition (Table 2) and dispersed in double-distilled water under continuous magnetic stirring until a homogeneous polymeric solution was obtained. Vonoprazan was then dispersed uniformly into the polymer solution, followed by the addition of sodium bicarbonate as a gas-generating agent to improve buoyancy (Curran et al., 2024). The resulting dispersion was extruded dropwise through a 22-gauge needle into a gently stirred calcium chloride solution maintained at room temperature using a syringe fitted with a needle. Upon contact with the calcium chloride solution, the droplets instantaneously formed spherical microspheres due to ionic cross-linking between calcium ions and sodium alginate. The formed microspheres were allowed to cure in the cross-linking solution for 30 min, collected by filtration, washed thoroughly with distilled water to remove excess calcium ions, and dried at 40°C for 24 h before further characterization (Upadhyay et al., 2025).

Table 2. Composition of Vonoprazan Gastroretentive Microspheres According to the Box–Behnken Design

Ru n	A (X ₁): Sodium Alginate (% w/v)	B (X ₂): HPMC K100 M (% w/v)	C (X ₃): Calcium Chloride (% w/v)	Vonopraz an (mg)
1	2	0.5	2	20
2	3	0.5	4	20
3	2	1.5	6	20
4	2	1.0	4	20
5	3	1.0	6	20
6	2	1.0	4	20
7	2	1.0	4	20
8	1	1.5	4	20
9	3	1.5	4	20
10	1	0.5	4	20
11	1	1.0	2	20
12	2	1.5	2	20
13	3	1.0	2	20
14	1	1.0	6	20
15	2	0.5	6	20

2.4 RP-HPLC Method for Quantification of Vonoprazan

A reverse-phase high-performance liquid chromatography (RP-HPLC) method was employed for the quantitative estimation of vonoprazan during encapsulation efficiency, drug loading, and in vitro

drug release studies. Chromatographic analysis was performed using an HPLC system equipped with a quaternary pump, autosampler, column oven, and UV–Visible detector. Separation was achieved on a C18 reversed-phase column (250 × 4.6 mm, 5 µm particle size) maintained at 30 ± 2°C. The mobile phase consisted of acetonitrile and 0.02 M potassium dihydrogen phosphate buffer (pH adjusted to 3.0 with orthophosphoric acid) in the ratio of 60:40 (v/v). The mobile phase was filtered through a 0.45 µm membrane filter and degassed by ultrasonication before use. The flow rate was maintained at 1.0 mL/min, and the eluent was monitored at a wavelength of 230 nm. The injection volume was 20 µL, and the total run time was 10 min (Patel et al., 2025).

2.5 Characterization of Microspheres

2.5.1 Encapsulation Efficiency (EE%)

Encapsulation efficiency was determined by the indirect method. Microspheres equivalent to 20 mg of vonoprazan were crushed and extracted using phosphate buffer (pH 6.8). The solution was filtered and analyzed using a UV–Visible spectrophotometer at the λ_{max} of vonoprazan (Ngugi et al., 2024). Encapsulation efficiency was calculated using the following equation:

$$EE\% = \frac{\text{Total drug} - \text{Free drug}}{\text{Total drug}} \times 100$$

2.5.2 Particle Size Analysis

The mean particle size of the microspheres was determined using a laser diffraction particle size analyzer. Dried microspheres were dispersed uniformly in distilled water prior to measurement, and the average particle size was recorded in nanometers (Lebrini & Gotor, 2024).

2.5.3 In Vitro Drug Release Study

The in vitro drug release study was performed using the USP type II (paddle) dissolution apparatus. Microspheres equivalent to 20 mg of vonoprazan were placed in 900 mL of 0.1 N hydrochloric acid (pH 1.2) maintained at 37 ± 0.5°C with a paddle rotation speed of 50 rpm. Aliquots (5 mL) were withdrawn at predetermined intervals up to 12 h and replaced with an equal volume of fresh dissolution medium. Samples were filtered, suitably diluted, and analyzed spectrophotometrically at the λ_{max} of vonoprazan (Patil et al., 2024).

2.6 Optimization of Formulation

Formulation and Optimization of Sustained-Release Gastroretentive Microspheres of Vonoprazan Using Box–Behnken Design

Numerical optimization was performed using Design-Expert® Version 13 employing the desirability function approach. The optimized formulation was selected based on maximum encapsulation efficiency and cumulative drug release with minimum particle size. The optimized formulation was subsequently prepared and experimentally validated to compare the predicted and observed responses (Singh et al., 2024).

2.7 Evaluation of Optimized Formulation F-16

2.7.1 Percentage Yield

The percentage yield of the prepared gastroretentive microspheres was determined by comparing the practical weight of the dried microspheres with the total theoretical weight of the drug and excipients used in the formulation (Coco et al., 2024). The percentage yield was calculated using the following equation:

$$\text{Percentage Yield (\%)} = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$$

2.7.2 Drug Loading

Drug loading was determined by accurately weighing microspheres equivalent to 20 mg of vonoprazan, dispersing them in the mobile phase, and sonicating until complete drug extraction. The resulting solution was filtered through a 0.45 µm membrane filter and analyzed using the RP-HPLC method (Yin et al., 2025). Drug loading was calculated using the following equation:

$$\text{Drug Loading (\%)} = \frac{\text{Amount of Drug Entrapped}}{\text{Weight of Microspheres}} \times 100$$

2.7.3 Swelling Index

The swelling behavior of the optimized microspheres was evaluated by immersing a known quantity of dried microspheres in 0.1 N hydrochloric acid (pH 1.2) maintained at $37 \pm 0.5^\circ\text{C}$. At predetermined time intervals, the swollen microspheres were removed, blotted gently to remove excess surface medium, and weighed (Miranda et al., 2025a). The swelling index was calculated using the following equation:

$$\text{Swelling Index (\%)} = \frac{W_t - W_0}{W_0} \times 100$$

Where, W_0 is the initial weight of the dried microspheres and W_t is the weight of the swollen microspheres at time t .

2.7.4 Floating Behaviour

The floating behavior of the optimized microspheres was evaluated in 900 mL of 0.1 N hydrochloric acid (pH 1.2) using a USP type II dissolution apparatus maintained at $37 \pm 0.5^\circ\text{C}$ and stirred at 50 rpm. Floating lag time and total floating duration were recorded (Miranda et al., 2025b). The percentage buoyancy was determined by separating the floating and settled microspheres after the study period and calculated using the following equation:

$$\text{Buoyancy (\%)} = \frac{\text{Weight of Floating Microspheres}}{\text{Total Weight of Microspheres}} \times 100$$

2.8 Statistical Analysis

All experiments were performed in triplicate, and the results are expressed as mean $\pm$ standard deviation (SD). Statistical analysis, regression modeling, analysis of variance (ANOVA), response surface plots, and numerical optimization were carried out using Design-Expert software (Version 13, Stat-Ease). A p-value < 0.05 was considered statistically significant (Mohammed, 2025).

3. Results and Discussion

3.1 RP-HPLC Analysis of Vonoprazan

The RP-HPLC method was employed for the quantitative estimation of vonoprazan in the optimized gastroretentive microspheres. A sharp and well-resolved chromatographic peak was obtained with a retention time of 4.36 min, indicating efficient separation of the drug without interference from formulation excipients (Figure 1). The chromatographic analysis confirmed the suitability of the selected RP-HPLC method for the estimation of vonoprazan during encapsulation efficiency, drug loading, and in vitro drug release studies.

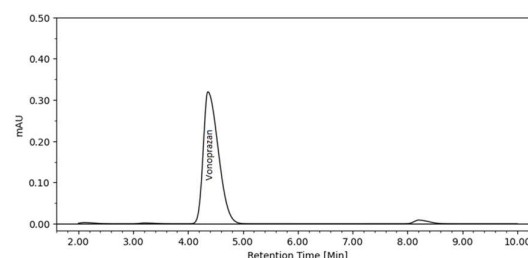


Figure 1. RP-HPLC chromatogram of vonoprazan

3.2 Evaluation of Vonoprazan Gastroretentive Microspheres

Vonoprazan-loaded sustained-release gastroretentive microspheres were successfully prepared by the ionotropic gelation technique according to the Box–Behnken experimental design. The prepared microspheres exhibited satisfactory encapsulation efficiency, appropriate particle size, and sustained drug release over 12 h. The observed responses for all experimental formulations are presented in Table 3.

Table 3. Experimental Responses of Vonoprazan Microspheres

Run	Response 1: Encapsulation Efficiency (%)	Response 2: Particle Size (nm)	Response 3: In Vitro Drug Release (% up to 12 h)
1	86.81	217	68.1
2	89.18	208	72.2
3	91.12	197	75.1
4	87.48	214	70.4
5	92.23	193	76.5
6	92.94	180	77.6
7	90.56	199	72.6
8	89.69	200	73.3
9	94.21	171	79.8
10	88.52	208	69.2
11	85.18	221	66.7
12	91.42	187	76.7
13	92.94	181	77.9
14	89.53	205	74.0
15	91.27	193	75.3

3.2.1 Effect of Independent Variables on Encapsulation Efficiency

The encapsulation efficiency of the prepared microspheres ranged from 85.18% to 94.21%, indicating efficient incorporation of vonoprazan within the polymeric matrix. The highest encapsulation efficiency (94.21%) was obtained in Run 9, whereas the lowest value (85.18%) was observed in Run 11. The results demonstrated that increasing the sodium alginate concentration significantly enhanced encapsulation efficiency owing to the formation of a denser polymeric network capable of entrapping a larger amount of drug. HPMC K100M further improved drug retention by increasing the viscosity of the polymer

solution and reducing drug diffusion into the cross-linking medium during microsphere formation. Calcium chloride concentration also influenced encapsulation efficiency by regulating the extent of ionic cross-linking. Moderate cross-linking produced compact microspheres with higher drug entrapment, whereas excessive cross-linking could reduce the internal free volume available for drug encapsulation.

3.2.2 Effect of Independent Variables on Particle Size

Particle size of the microspheres varied between 171 and 221 nm. The smallest particle size (171 nm) was observed in Run 9, while the largest particle size (221 nm) was obtained in Run 11. An increase in sodium alginate concentration generally increased the viscosity of the polymer solution, affecting droplet formation during ionotropic gelation. However, the optimized combination of sodium alginate, HPMC K100M, and calcium chloride produced uniformly cross-linked microspheres with reduced particle size. Higher calcium chloride concentrations promoted rapid gel formation, resulting in compact microspheres with smaller diameters. The addition of HPMC K100M contributed to improved structural integrity without causing excessive enlargement of the microspheres.

3.2.3 Effect of Independent Variables on In Vitro Drug Release

The cumulative in vitro drug release after 12 h ranged from 66.7% to 79.8%, demonstrating the sustained-release characteristics of the gastroretentive microspheres. The highest drug release (79.8%) was achieved by Run 9, whereas the lowest release (66.7%) was observed in Run 11. Drug release was governed by the polymer concentration and the extent of ionic cross-linking. Increasing sodium alginate and HPMC K100M concentrations formed a stronger gel matrix, which prolonged drug diffusion and sustained release. Conversely, optimized polymer levels provided a balanced matrix that permitted controlled swelling and gradual drug diffusion over the study period. Calcium chloride concentration also influenced release behavior by controlling matrix density; excessive cross-linking slowed drug diffusion, whereas optimized cross-linking produced the desired sustained-release profile suitable for gastroretentive delivery.

3.3 Statistical Analysis and Model Fitting (ANOVA)

The significance of the developed models was evaluated by analysis of variance (ANOVA), and

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the results are summarized in Table 4. The models developed for encapsulation efficiency (Y_1), particle size (Y_2), and in vitro drug release at 12 h (Y_3) were statistically significant ($p < 0.05$), confirming the suitability of the selected Box–Behnken design for optimization. Sodium alginate concentration (A) significantly affected encapsulation efficiency, whereas both sodium alginate (A) and HPMC K100M concentration (B) significantly influenced particle size and drug release. Calcium chloride concentration (C) and the interaction terms were not statistically significant ($p > 0.05$). The lack-of-fit was non-significant for all responses ($p > 0.05$), indicating good agreement between the predicted and experimental values and confirming the adequacy of the developed models for optimization

center level. As shown in Figure 2A, encapsulation efficiency increased with increasing concentrations of sodium alginate and HPMC K100M, indicating improved drug entrapment due to the formation of a denser polymeric matrix. Figure 2B demonstrates that particle size decreased under the optimized polymer concentrations, resulting in smaller and more uniform microspheres. Similarly, Figure 2C shows that the cumulative drug release at 12 h increased with increasing sodium alginate and HPMC K100M concentrations, providing a sustained-release profile. The smooth contour patterns confirm the adequacy of the developed models and support the optimized formulation predicted by the Box–Behnken design.

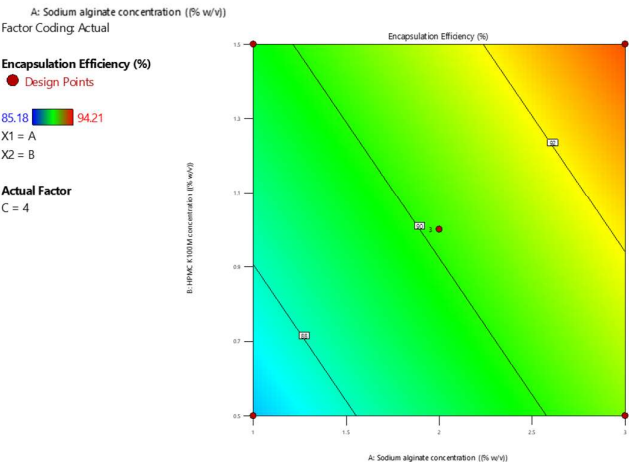
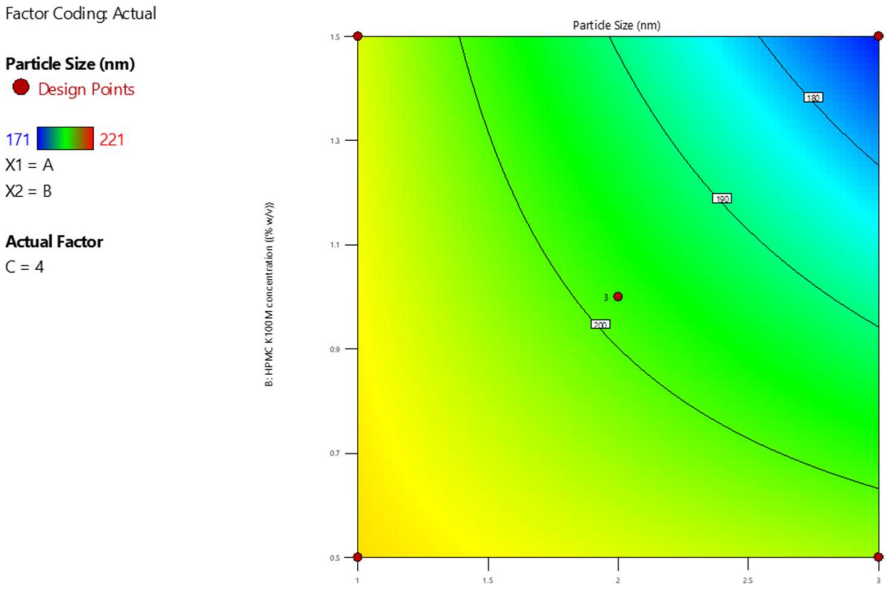
of sustained-release gastroretentive microspheres of vonoprazan.

Table 4. ANOVA Summary

Response	F-value	p-value	Lack of Fit (p-value)
Encapsulation Efficiency (Y_1)	5.47	0.0151	0.9184
Particle Size (Y_2)	4.01	0.0374	0.9919
In Vitro Drug Release (Y_3)	7.56	0.0059	0.9982

3.4 Response Surface and Contour Plot Analysis

The contour plots (Figure 2) illustrate the effects of sodium alginate concentration (A) and HPMC K100M concentration (B) on the responses while maintaining calcium chloride concentration at its



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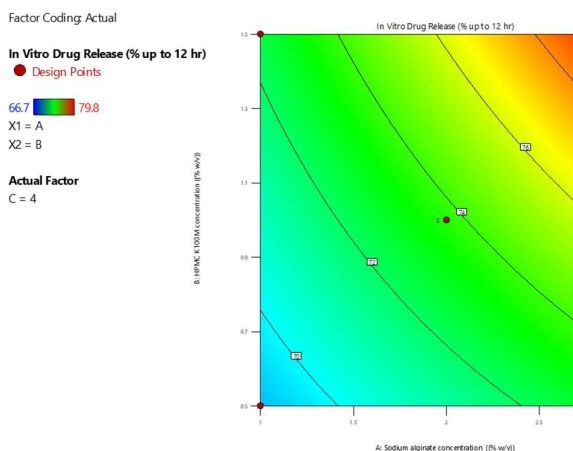


Figure 2. Contour plots showing the effects of sodium alginate concentration (A) and HPMC K100M concentration (B) on (A) Encapsulation Efficiency, (B) Particle Size, and (C) In Vitro Drug Release at 12 h of vonoprazan-loaded sustained-release gastroretentive microspheres.

3.5 Optimization Using Desirability Function

Numerical optimization was carried out using the desirability function approach to obtain an optimized formulation of sustained-release gastroretentive microspheres of vonoprazan. The independent variables, namely sodium alginate concentration (A), HPMC K100M concentration (B), and calcium chloride concentration (C), were maintained within the specified experimental ranges. The responses were optimized by maximizing encapsulation efficiency, minimizing particle size, and maintaining in vitro drug release within the desired range. The optimization criteria and constraints are presented in Table 5.

Table 5. Optimization Criteria and Constraints for Desirability Function

Parameter	Goal	Lower Limit	Upper Limit
Sodium alginate concentration (A, % w/v)	In range	1	3
HPMC K100M concentration (B, % w/v)	In range	0.5	1.5
Calcium chloride concentration (C, % w/v)	In range	2	6
Encapsulation Efficiency (%)	Maximize	85.18	94.21
Particle Size (nm)	Minimize	171	221

In Vitro Drug Release (%)	In range	66.7	79.8
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The optimized formulation selected by the Design-Expert® software exhibited a desirability value of 0.945, indicating excellent agreement between the selected formulation variables and the desired response criteria. The optimized formulation contained 3.0% w/v sodium alginate, 1.5% w/v HPMC K100M, and 4.123% w/v calcium chloride, with predicted responses of 93.553% encapsulation efficiency, 172.833 nm particle size, and 79.800% cumulative drug release at 12 h. The high desirability value confirms the suitability of the Box–Behnken design for optimizing the formulation of sustained-release gastroretentive microspheres of vonoprazan (Table 6).

Table 6. Predicted Optimized Formulation and Responses

Parameter	Predicted Value
Sodium alginate concentration (A, % w/v)	3.000
HPMC K100M concentration (B, % w/v)	1.500
Calcium chloride concentration (C, % w/v)	4.123
Encapsulation Efficiency (%)	93.553
Particle Size (nm)	172.833
In Vitro Drug Release at 12 h (%)	79.800
Desirability	0.945

3.6 Validation of Optimized Formulation

To validate the reliability of the optimization process, the optimized formulation predicted by the desirability function was prepared experimentally, and the observed responses were compared with the predicted values obtained from the model. The results are presented in Table 7. The observed values were in close agreement with the predicted values, with percentage prediction errors of less than 5% for all responses, confirming the reliability and predictive capability of the developed Box–Behnken model for optimizing sustained-release gastroretentive microspheres of vonoprazan.

Table 7. Predicted and Observed Responses of the Optimized Formulation

Response	Predicted	Observed	% Prediction Error
Encapsulation	93.553	93.2 ± 0.7	0.38

Efficiency (%)			
Particle Size (nm)	172.833	175.1 ± 3.4	1.31
In Vitro Drug Release at 12 h (%)	79.800	79.2 ± 0.8	0.75

3.6.1 Percentage Yield

The optimized formulation exhibited a percentage yield of $91.84 \pm 1.23\%$, indicating efficient microsphere formation with minimal material loss during the ionotropic gelation process. The high production yield demonstrated the reproducibility and suitability of the preparation method.

3.6.2 Drug Loading

The drug loading of the optimized gastroretentive microspheres was found to be $17.62 \pm 0.38\%$, confirming efficient incorporation of vonoprazan within the polymeric matrix.

3.6.3 Swelling Index

The optimized microspheres exhibited progressive swelling in simulated gastric fluid (0.1 N HCl, pH 1.2), which contributed to prolonged gastric residence and sustained drug release. The swelling index increased gradually with time, reaching $168.45 \pm 5.12\%$ after 8 h (Table 8).

Table 8. Swelling Index of the Optimized Formulation

Time (h)	Swelling Index (%)
1	38.41 ± 2.14
2	64.82 ± 3.06
4	108.37 ± 4.22
6	142.61 ± 4.76
8	168.45 ± 5.12

3.6.4 Floating Behaviour

The optimized gastroretentive microspheres demonstrated excellent floating characteristics in simulated gastric fluid. The floating lag time was 28 ± 3 s, and the microspheres remained buoyant for more than 12 h, confirming their gastroretentive potential. The percentage buoyancy was found to be $95.83 \pm 1.46\%$ (Table 9).

Table 9. Floating Characteristics of the Optimized Formulation

Parameter	Result
Floating Lag Time (s)	28 ± 3
Total Floating Time	>12 h
Buoyancy (%)	95.83 ± 1.46

3.7 Stability Study

The optimized formulation was subjected to accelerated stability studies at $40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH for 3 months in accordance with ICH guidelines (Table 10). No significant changes were observed in encapsulation efficiency, particle size, or in vitro drug release, indicating good physical stability of the optimized microspheres throughout the storage period.

Table 10. Stability Study of the Optimized Formulation

Parameter	Initial	After 3 Months
Encapsulation Efficiency (%)	93.20 ± 0.70	92.81 ± 0.81
Particle Size (nm)	175.10 ± 3.40	177.42 ± 3.96
In-Vitro Drug Release at 12 h (%)	79.20 ± 0.80	78.63 ± 0.94

4. Conclusion

The present study successfully formulated and optimized sustained-release gastroretentive microspheres of vonoprazan using the ionotropic gelation technique and a three-factor, three-level Box–Behnken design. The selected formulation variables significantly influenced encapsulation efficiency, particle size, and in vitro drug release, and the developed models demonstrated good statistical significance with non-significant lack of fit. The optimized formulation, comprising 3.0% w/v sodium alginate, 1.5% w/v HPMC K100M, and 4.123% w/v calcium chloride, exhibited 93.55% encapsulation efficiency, a particle size of 172.83 nm, and 79.80% cumulative drug release after 12 h, with a desirability value of 0.945. Furthermore, the optimized microspheres showed satisfactory percentage yield, drug loading, swelling behavior, buoyancy, and stability, confirming their suitability as a gastroretentive sustained-release drug delivery system. Overall, the findings demonstrate that Box–Behnken design is an efficient optimization tool for developing gastroretentive microspheres and that the optimized vonoprazan formulation has the potential to improve gastric residence time and provide sustained therapeutic drug release for the effective management of acid-related disorders.

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