Research Article

Formulation And Pharmacokinetic Study Of Mosapride-Loaded Mucoadhesive Microspheres

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Abstract

The present study aimed to develop and optimize gastroretentive mucoadhesive microspheres of Mosapride using sodium alginate and HPMC K15M to modify its plasma concentration–time profile. A Box–Behnken experimental design was employed to investigate the influence of three independent formulation variables, namely sodium alginate concentration (1.5–2.5% w/v), HPMC K15M concentration (0.50–1.00% w/v) and calcium chloride concentration (2.0–4.0% w/v), on entrapment efficiency and particle size. Thirteen experimental batches (F1–F13) were prepared and evaluated. Based on the experimental and predicted responses, formulation F3 was selected as the optimized formulation, containing 2.50% w/v sodium alginate, 0.75% w/v HPMC K15M and 2.00% w/v calcium chloride. The optimized formulation exhibited an experimental entrapment efficiency of 87.65% and particle size of 680.30 µm, which were close to the predicted values of 87.56% and 678.99 µm, respectively. The pharmacokinetic evaluation was performed in rabbits, and plasma concentrations of Mosapride were determined using HPLC. The standard formulation showed a maximum plasma concentration (Cmax) of 3.44 ± 0.34 µg/mL at 0.5 h, whereas the optimized F3 microspheres exhibited a Cmax of 0.72 ± 0.07 µg/mL at 6 h. The AUC_{0-12} values were 5.89 and 5.67 µg·h/mL for the standard and optimized formulations, respectively. The apparent half-life increased from 0.61 h for the standard formulation to 2.38 h for F3. These findings indicate that the optimized gastroretentive microspheres modified the plasma concentration–time profile of Mosapride, producing delayed peak plasma concentration and prolonged drug exposure. Further investigations are required to confirm gastroretention and sustained-release performance.

Keywords: Mosapride, Gastroretentive microspheres, Box–Behnken design, Optimization, Pharmacokinetic evaluation, HPLC.

1. Introduction

Oral drug delivery is the most widely preferred route of drug administration because of its convenience, patient compliance, ease of administration and cost-effectiveness (Alqahtani et al., 2021). However, conventional oral dosage forms may exhibit certain limitations, including rapid gastric emptying, variable gastrointestinal transit time, incomplete drug absorption and fluctuations in plasma drug concentrations (Hua, 2020). These limitations can affect therapeutic efficacy, particularly for drugs having a narrow absorption window or requiring prolonged residence in the stomach for improved drug delivery (Nayak et al., 2010). To overcome these challenges, gastroretentive drug delivery systems have been developed to prolong the residence time of dosage forms in the stomach and facilitate controlled drug release (Streubel et al., 2006).

Gastroretentive drug delivery systems are designed to remain in the gastric region for an extended period and release the incorporated drug gradually. These systems may improve drug availability, prolong therapeutic action and reduce fluctuations in plasma drug concentrations (Das et al., 2021). Various approaches have been investigated for gastric retention, including floating systems, swelling and expandable systems, high-density systems, bioadhesive systems and magnetic systems. Among these approaches, mucoadhesive drug delivery systems have attracted considerable attention because of their ability to adhere to the gastric mucosal surface and potentially prolong the residence time of the formulation (Pawar et al., 2011).

Mucoadhesive microspheres are multiparticulate drug-delivery systems designed to adhere to the mucosal surface through interactions between the polymeric carrier and mucus layer (Vasir et al., 2003). Their small particle size and large surface area may provide better distribution over the gastric mucosa compared with conventional single-unit

dosage forms. Polymers such as sodium alginate and hydroxypropyl methylcellulose (HPMC) are frequently investigated for developing controlled-release and mucoadhesive formulations (Pawar et al., 2011).

Sodium alginate is a natural, biocompatible and biodegradable polymer that forms a gel in the presence of divalent cations such as calcium ions. This property makes it suitable for preparing microspheres through the ionotropic gelation technique (Sachan et al., 2009). Calcium chloride acts as a cross-linking agent, facilitating the formation of a three-dimensional polymeric network. HPMC K15M can be incorporated to modify matrix characteristics and influence drug-release behaviour. Recent investigations have also highlighted the potential of sodium alginate-based systems in pharmaceutical drug delivery applications (Kumari et al., 2026).

Mosapride citrate is a gastroprokinetic drug belonging to the class of selective serotonin 5-hydroxytryptamine-4 (5-HT_4) receptor agonists. It enhances gastrointestinal motility by stimulating 5-HT_4 receptors in the enteric nervous system, thereby promoting acetylcholine release and improving gastric emptying. It is used in the management of gastrointestinal motility disorders and symptoms associated with functional dyspepsia. Clinical investigations have evaluated the efficacy of Mosapride in improving gastrointestinal motility and postoperative intestinal recovery (Thampongsa et al., 2025).

The relatively rapid attainment of peak plasma concentration and short apparent half-life provide a rationale for investigating modified-release formulations that can alter the rate of drug availability (Leucuta, 2012). Gastroretentive mucoadhesive microspheres may offer an approach to modifying the plasma concentration–time profile by controlling drug release and potentially prolonging contact with the gastric mucosa (Dhaliwal et al., 2008). However, the actual gastroretention and sustained-release performance of such formulations need to be established through appropriate in-vitro and in-vivo investigations.

The formulation and process variables play an important role in determining the physicochemical characteristics and performance of microspheres. Sodium alginate concentration may influence polymeric solution viscosity, particle formation and entrapment efficiency (Frent et al., 2022). HPMC K15M concentration may affect matrix structure and drug diffusion, whereas calcium chloride concentration may influence the degree of polymer cross-linking and microsphere characteristics (Patel et al., 2016). Therefore, systematic optimization of these variables is essential to obtain a formulation with desirable particle size and drug entrapment efficiency.

Quality by Design (QbD) and Design of Experiments (DoE) approaches provide systematic methods for understanding the influence of formulation variables and their interactions on product characteristics. The Box–Behnken design is a response-surface methodology that evaluates the effects of independent variables at different levels using a limited number of experimental batches. It helps establish mathematical relationships between formulation variables and responses and assists in identifying an optimized formulation (Huang et al., 2009).

Considering these aspects, the present study was designed to formulate and optimize Mosapride-loaded gastroretentive mucoadhesive microspheres using sodium alginate, HPMC K15M and calcium chloride. A three-factor, three-level Box–Behnken experimental design was employed to investigate the influence of formulation variables on entrapment efficiency and particle size. The optimized formulation was selected based on experimental and predicted responses and subsequently subjected to pharmacokinetic evaluation in rabbits using HPLC analysis. The plasma concentration–time profile and pharmacokinetic parameters, including maximum plasma concentration (Cmax), time to reach maximum plasma concentration (Tmax), area under the curve (AUC) and apparent elimination half-life ($t_1/_2$), were compared with those of the standard formulation to investigate the potential of the developed microspheres for modifying Mosapride release and systemic exposure.

2. Material and Methods

2.1 Material

Mosapride citrate was used as the active pharmaceutical ingredient for the preparation of gastroretentive mucoadhesive microspheres. Sodium alginate, HPMC K15M and calcium chloride were used as formulation polymers and cross-linking agents. Other materials, including distilled water, analytical-grade solvents and reagents, were used during formulation development and evaluation. The chemicals and reagents may be sourced from Merck Life Science

Pvt. Ltd., Mumbai, India; Loba Chemie Pvt. Ltd., Mumbai, India; and HiMedia Laboratories Pvt. Ltd., Mumbai, India. All chemicals were of analytical grade.

2.2 Formulation and characterization of Mucoadhesive Microspheres of Mosapride

Mosapride-loaded mucoadhesive microspheres were prepared using the ionotropic gelation method. Sodium alginate and HPMC K15M were accurately weighed according to the experimental design and dispersed separately in an appropriate quantity of purified water. The polymeric dispersions were allowed to hydrate adequately and then mixed to obtain a homogeneous polymer solution. A predetermined quantity of Mosapride was incorporated into the polymeric dispersion with continuous stirring to obtain a uniform drug–polymer mixture.

The prepared drug–polymer dispersion was subsequently added dropwise into an aqueous calcium chloride solution of the concentration specified by the experimental design, under continuous stirring. Calcium ions interacted with the carboxylate groups of sodium alginate, resulting in ionic cross-linking and formation of microspheres. The formed microspheres were allowed to remain in the calcium chloride solution for sufficient curing, followed by separation by filtration. The microspheres were washed with purified water to remove adhering calcium chloride and dried under suitable conditions until a constant weight was obtained. The dried microspheres were collected and stored in a suitable container until further evaluation (Gaur et al., 2014).

The prepared formulations (F1–F13) were evaluated for entrapment efficiency and particle size, and the obtained responses were analyzed statistically using the Box–Behnken Design. The formulation satisfying the predefined optimization criteria was selected as the optimized formulation and subjected to further characterization.

2.3 Selection of Factors and Responses for DOE

The preliminary studies revealed that the concentrations of sodium alginate, HPMC K15M and calcium chloride had a significant influence on microsphere formation, particle size, drug entrapment, and drug release. Therefore, these formulation variables were selected as independent factors for optimization.

2.4 Independent Variables (Factors)

Table 1: Independent Variables (Factors)

Factor	Independent Variable	Low Level (-1)	Medium Level (0)	High Level (+1)
A	Sodium Alginate (% w/v)	1.5	2.0	2.5
B	HPMC K15M (% w/v)	0.50	0.75	1.00
C	Calcium Chloride (% w/v)	2.0	3.0	4.0

Box–Behnken Experimental Design Matrix for Optimization of Mosapride Gastroretentive Microspheres

Table 2: Box–Behnken Experimental Design Matrix for Optimization of Mosapride Gastroretentive Microspheres

F. Code	Sodium Alginate (% w/v)	HPMC K15M (% w/v)	Calcium Chloride (% w/v)
F1	2.0	0.75	3.0
F2	1.5	0.75	4.0
F3	2.5	0.75	2.0
F4	2.5	1.00	3.0
F5	2.5	0.75	4.0
F6	2.0	0.50	4.0
F7	2.0	1.00	4.0
F8	2.0	0.50	2.0
F9	1.5	0.75	2.0
F10	1.5	1.00	3.0
F11	2.5	0.50	3.0

F12	1.5	0.50	3.0
F13	2.0	1.00	2.0

2.5 Determination of Entrapment Efficiency (%EE)

Accurately weighed microspheres equivalent to 50mg of Mosapride were crushed and transferred into a 100 mL volumetric flask containing 0.1 N HCl (pH 1.2)**.** The dispersion was stirred for 2 hours to ensure complete extraction of the drug from the polymeric matrix. The solution was filtered through a 0.45 µm membrane filter, suitably diluted, and analyzed using a UV–Visible spectrophotometer. The amount of drug entrapped in the microspheres was calculated from the calibration curve (Elkady et al., 2019).

2.6 Particle Size Analysis

The particle size of the microspheres was determined using a Malvern laser diffraction particle size analyzer. A suitable quantity of microspheres was dispersed in an appropriate dispersing medium and sonicated gently to obtain a uniform dispersion. The sample was introduced into the instrument, and particle size was measured by laser diffraction. The mean particle size and particle-size distribution were recorded for each formulation (Sriram and Katakam; 2016).

2.7 Pharmacokinetic Bioanalytical Study of Optimized Mucoadhesive Microspheres of Mosapride (F3)

The pharmacokinetic study was performed to evaluate the systemic drug exposure and release characteristics of Mosapride from the optimized mucoadhesive microspheres (F3). Suitable experimental rabbits were used for the study and were fasted for an appropriate period before drug administration, with free access to water. The optimized F3 microspheres were administered at a Mosapride dose equivalent to 5 mg.

Blood samples were collected from the marginal ear vein at predetermined time intervals of 0.5, 1, 2, 4, 6, 8, and 12 h following administration. The collected blood samples were transferred into appropriately labeled tubes and processed by centrifugation to separate plasma. The plasma samples were suitably prepared and analyzed using a validated HPLC bioanalytical method for quantitative estimation of Mosapride.

The obtained plasma concentration–time data were used to determine pharmacokinetic parameters including Cmax, Tmax, AUC, elimination half-life (t½), and elimination rate constant (Ke). These parameters were used to evaluate the absorption, systemic exposure, and sustained-release characteristics of the optimized Mosapride mucoadhesive microspheres (F3).

2.8 Dose validation

The dose of Mosapride was selected as 5 mg/kg for administration in the pharmacokinetic study. The optimized mucoadhesive microspheres (F3) were administered through the oral route by gavage**.** The selected dose was based on the intended experimental pharmacokinetic evaluation and the drug loading of the optimized microsphere formulation. Blood samples were collected at predetermined time intervals of 0.5, 1, 2, 4, 6, 8, and 12 h following administration.

The selected dose was maintained within an appropriate experimental range to facilitate measurement of Mosapride concentrations in plasma while evaluating the absorption, systemic exposure, and sustained-release characteristics of the optimized F3 formulation. The resulting plasma concentration–time profile was used for calculation of pharmacokinetic parameters such as Cmax, Tmax, AUC, t½ and Ke (Jha et al., 2011)**.**

2.9 Procedure

Each group consisted of six healthy male White rabbits weighing approximately 2.0–2.5 kg. The animals were maintained under controlled laboratory conditions with a 12-h light/dark cycle, temperature of 22 ± 2°C, and free access to water. The animals were obtained from a recognized breeding facility. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) and conducted in accordance with the applicable CPCSEA guidelines. Animals were acclimatized to the laboratory environment for one week prior to experimentation. Food was withdrawn overnight before drug administration, while water was provided ad libitum.

2.10 Experimental Groups

- **Standard group:** Received Mosapride oral suspension containing an equivalent dose of Mosapride.
- **Test group:** Received the optimized Mosapride mucoadhesive microspheres (F3) containing an equivalent dose of Mosapride.

2.11 Administration

- **Standard formulation:** The Mosapride standard formulation was administered orally by gavage at an appropriate dose volume.
- **Test formulation:** The optimized F3 mucoadhesive microspheres were administered orally by gavage at a dose equivalent to 5mg/kg of Mosapride. The microspheres were administered as a suitable aqueous suspension to ensure uniform dosing.

2.11 Blood Sampling

Approximately 0.5 ml of blood was collected from the marginal/outer ear vein at predetermined time intervals of 0, 0.5, 1, 2, 4, 6, 8, and 12 h following administration. Blood samples were collected into suitable anticoagulant-containing tubes and centrifuged at 3000 rpm for 10 min to separate plasma. The separated plasma samples were appropriately labelled and stored at −80 °C until bioanalysis.

2.12 Bioanalytical Method

A validated RP-HPLC-UV method was employed for the quantitative determination of Mosapride in rabbit plasma. Plasma samples were processed using a suitable sample-preparation procedure, followed by chromatographic analysis. A validated calibration curve covering the appropriate concentration range was used for quantification.

2.13 Pharmacokinetic Analysis

The plasma concentration–time data obtained for Mosapride were subjected to non-compartmental pharmacokinetic analysis using suitable pharmacokinetic software such as WinNonlin®. The principal pharmacokinetic parameters, including maximum plasma concentration (Cmax), time to reach maximum concentration (Tmax), area under the plasma concentration–time curve (AUC), elimination rate constant (Kel), and elimination half-life (t½), were determined. The pharmacokinetic profile of the optimized F3 microspheres was compared with that of the standard formulation to assess the effect of the mucoadhesive microsphere system on drug absorption, systemic exposure, and sustained-release characteristics.

3. Results and Discussion

The present study was undertaken to develop and optimize Mosapride gastroretentive mucoadhesive microspheres using sodium alginate, HPMC K15M and calcium chloride as formulation variables. A Box–Behnken experimental design was employed to investigate the influence of these independent variables on the formulation characteristics, particularly entrapment efficiency and particle size. The optimized formulation was further evaluated for its pharmacokinetic performance in rabbits and compared with the standard formulation.

The independent variables and their respective levels used for formulation optimization are presented in Table 1**.** Sodium alginate was selected as the primary polymer responsible for microsphere formation, while HPMC K15M was incorporated to modify the polymeric matrix and influence drug release characteristics. Calcium chloride was used as a cross-linking agent to facilitate the formation of alginate microspheres. The concentrations of sodium alginate, HPMC K15M and calcium chloride were varied at three levels to evaluate their effects on the formulation responses.

The Box–Behnken experimental design matrix consisting of 13 experimental batches (F1–F13) is presented in Table 2**.** The design enabled systematic evaluation of the combined effects of the three formulation variables. Variations in polymer concentration and cross-linking agent concentration were considered important factors influencing microsphere formation, drug entrapment and particle size. Sodium alginate concentration may affect the viscosity of the polymeric solution and the formation of the microsphere matrix, whereas HPMC K15M may influence matrix characteristics and drug diffusion. Calcium chloride concentration may affect the degree of cross-linking and the resulting structural characteristics of the microspheres.

Based on the experimental and predicted responses, formulation F3 was selected as the optimized formulation, as shown in Table 3**.** The optimized formulation contained 2.50% w/v sodium alginate, 0.75% w/v HPMC K15M and 2.00% w/v calcium chloride. The experimental entrapment efficiency was 87.65%, compared with the predicted value of 87.56%, showing a residual difference of only 0.09. Similarly, the experimental particle size was 680.30 µm, while the predicted particle size was 678.99 µm, with a residual difference of 1.31 µm. The close agreement between experimental and predicted values indicates good predictive performance of the optimization model for these responses.

The chromatographic analysis of Mosapride in plasma samples was performed using HPLC. The representative HPLC chromatogram of the plasma sample is presented in Figure 1. The chromatographic analysis was used to determine the plasma concentration of Mosapride at different sampling intervals following administration of the standard formulation and optimized F3 microspheres.

The plasma concentration–time profile of Mosapride following administration of the standard formulation and optimized F3 microspheres is presented in Figure 2**,** while the corresponding plasma concentration data are summarized in Table 4**.** Following administration of the standard formulation, the maximum plasma concentration was observed at 0.5 h, with a concentration of 3.44 ± 0.34 µg/mL. In comparison, the optimized F3 microspheres showed a delayed increase in plasma concentration, reaching 0.53 ± 0.05µg/mL at 2 h and a maximum observed concentration of 0.72 ± 0.07 µg/mL at 6 h. This delayed peak suggests that the microsphere formulation modified the drug absorption profile and may provide a prolonged drug-release pattern compared with the standard formulation.

The comparative pharmacokinetic parameters are presented in Table 5. The standard formulation exhibited a Cmax of 3.44 ± 0.34µg/mL and Tmax of 0.5 h, whereas the optimized F3 microspheres showed a lower Cmax of 0.72 ± 0.07µg/mL and a delayed Tmax of 6 h. The delayed Tmax and reduced Cmax indicate slower appearance of Mosapride in systemic circulation following administration of the microspheres. Furthermore, the AUC_{0-12} values were 5.89 µg·h/mL for the standard formulation and 5.67 µg·h/mL for the optimized F3 formulation. The comparable AUC values suggest that the overall systemic exposure to Mosapride during the 12-hour observation period was broadly similar between the two formulations.

The elimination half-life was 0.61 h for the standard formulation and 2.38 h for the optimized F3 microspheres. The longer apparent half-life observed with F3 may indicate prolonged drug input or absorption-related changes in the plasma concentration profile. However, additional pharmacokinetic evaluation would be required to distinguish prolonged absorption from changes in the actual elimination process.

Overall, the findings indicate that the optimized F3 formulation successfully modified the plasma concentration–time profile of Mosapride, producing a delayed Tmax, lower Cmax and longer apparent half-life while maintaining a comparable AUC_{0-12} to the standard formulation. These results support the potential of sodium alginate and HPMC K15M-based gastroretentive microspheres as a drug-delivery approach for modifying Mosapride release and absorption. Further evaluation of gastroretention, in-vitro drug release, stability and pharmacokinetic performance over an extended sampling period is necessary to establish the formulation's suitability for sustained drug delivery.

Table 3: Optimized Formulation Selected Based on Experimental and Predicted Responses

Parameter	Optimized Formulation (F3)
Formulation Code	F3
Sodium Alginate (% w/v)	2.50
HPMC K15M (% w/v)	0.75
Calcium Chloride (% w/v)	2.00
Experimental Entrapment Efficiency (%)	87.65
Predicted Entrapment Efficiency (%)	87.56
Residual (EE)	0.09
Experimental Particle Size (µm)	680.30
Predicted Particle Size (µm)	678.99
Residual (Particle Size)	1.31

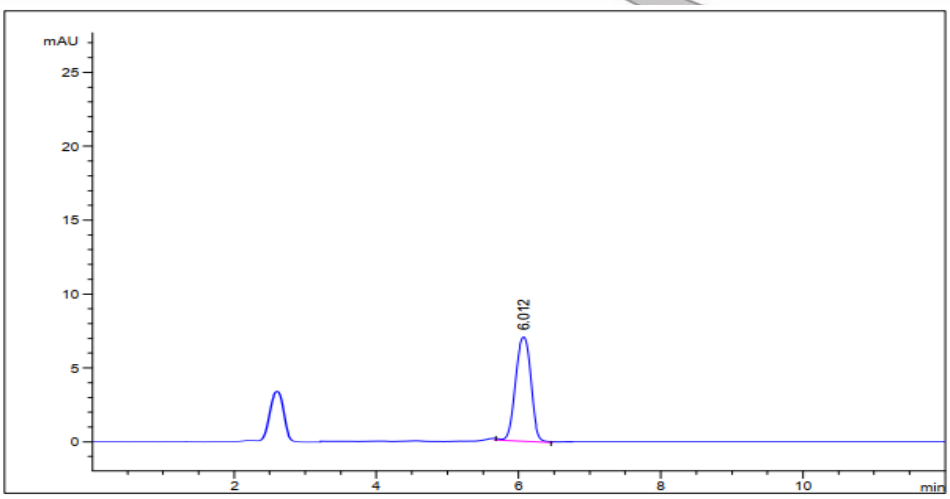

Figure 1: HPLC Chromatogram of plasma sample

Table 4: Results of Plasma Concentration–Time Profile of Mosapride

Time (h)	Standard (µg/ml)	Test F3 (µg/ml)
0	0.00 ± 0.00	0.00 ± 0.00
0.5	3.44 ± 0.34	0.00 ± 0.00
1	2.99 ± 0.30	0.00 ± 0.00
2	1.15 ± 0.12	0.53 ± 0.05
4	0.09 ± 0.01	0.61 ± 0.06
6	0.01 ± 0.00	0.72 ± 0.07
8	0.00 ± 0.00	0.61 ± 0.06
12	0.00 ± 0.00	0.19 ± 0.02

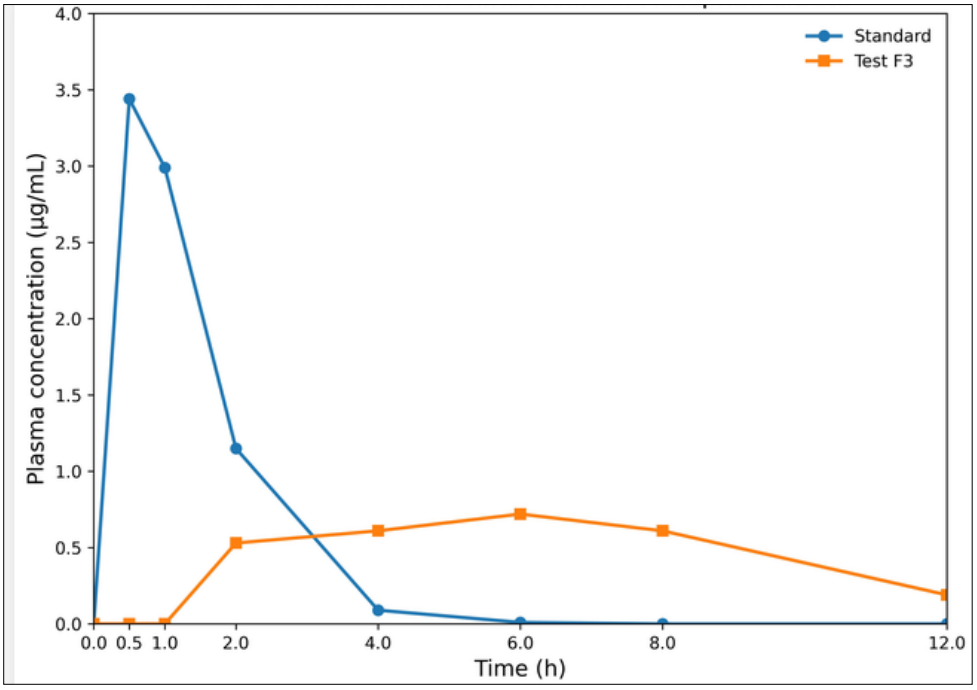

Figure 2: Plasma concentration–time profile of Mosapride following administration of standard formulation and optimized F3 mucoadhesive microspheres in rabbits.

Table 5: Comparative Pharmacokinetic Parameters of Mosapride Following Administration of Standard Formulation and Optimized F3 Mucoadhesive Microspheres in Rabbits

Parameter	Standard	Test F3
Cmax (µg/mL)	3.44 ± 0.34	0.72 ± 0.07
$AUC_{0–12}$ (µg·h/mL)	5.89	5.67
Tmax (h)	0.5	6
$t_{1/2}$ (h)	0.61	2.38

4. Conclusion

The present study successfully developed and optimized Mosapride-loaded gastroretentive mucoadhesive microspheres using sodium alginate, HPMC K15M and calcium chloride. The Box–Behnken experimental design facilitated the optimization of formulation variables, and formulation F3 was selected as the optimized batch, exhibiting an entrapment efficiency of 87.65% and a particle size of 680.30 µm. The pharmacokinetic evaluation in rabbits demonstrated a delayed Tmax (6 h), reduced Cmax (0.72 ± 0.07 µg/mL) and increased apparent half-life (2.38 h) compared with the standard formulation. The comparable $AUC_{0–12}$ values indicated broadly similar systemic exposure during the observation period. These findings suggest that the optimized microspheres can modify the plasma concentration–time profile of Mosapride and may offer potential for prolonged drug delivery. Further studies on in-vivo gastroretention, extended pharmacokinetic evaluation, stability and safety are required to establish their suitability as a gastroretentive drug-delivery system.

References

1. Alqahtani MS, Kazi M, Alsenaidy MA, Ahmad MZ. Advances in oral drug delivery. Front Pharmacol. 2021;12:618411.
2. Hua S. Advances in oral drug delivery for regional targeting in the gastrointestinal tract—influence of physiological, pathophysiological and pharmaceutical factors. Front Pharmacol. 2020;11:524.
3. Nayak AK, Malakar J, Sen KK. Gastroretentive drug delivery technologies: current approaches and future potential. J Pharm Educ Res. 2010;1(2):1.
4. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery systems. Expert Opin Drug Deliv. 2006;3(2):217-33.
5. Das S, Kaur S, Rai VK. Gastro-retentive drug delivery systems: a recent update on clinical pertinence and drug delivery. Drug Deliv Transl Res. 2021;11(5):1849-77.
6. Pawar VK, Kansal S, Garg G, Awasthi R, Singodia D, Kulkarni GT. Gastroretentive dosage forms: a review with special emphasis on floating drug delivery systems. Drug Deliv. 2011;18(2):97-110.
7. Vasir JK, Tambwekar K, Garg S. Bioadhesive microspheres as a controlled drug delivery system. Int J Pharm. 2003;255(1-2):13-32.
8. Pawar VK, Kansal S, Garg G, Awasthi R, Singodia D, Kulkarni GT. Gastroretentive dosage forms: a review with special emphasis on floating drug delivery systems. Drug Deliv. 2011;18(2):97-110.
9. Sachan NK, Pushkar S, Jha A, Bhattcharya AJ. Sodium alginate: the wonder polymer for controlled drug delivery. J Pharm Res. 2009;2(8):1191-9.
10. Kumari A, Varunteja B, Mohanty S, Mishra A, Gupta N, Mukherjee T, et al. Advancement in sodium alginate-based drug delivery systems: applications and future prospects. AAPS PharmSciTech. 2026;27(4):196.
11. Thampongsa T, Saengsawang B, Supsamutchai C, Wilasrusmee C, Jirasiritham J, Punmeechao P, et al. The efficacy of mosapride on recovery of intestinal motility after elective colorectal cancer surgery: a randomized controlled trial. Ann Coloproctol. 2025;41(3):232.
12. Leucuta SE. Drug delivery systems with modified release for systemic and biophase bioavailability. Curr Clin Pharmacol. 2012;7(4):282-317.
13. Dhaliwal S, Jain S, Singh HP, Tiwary AK. Mucoadhesive microspheres for gastroretentive delivery of acyclovir: in vitro and in vivo evaluation. AAPS J. 2008;10(2):322-30.
14. Frent OD, Vicas LG, Duteanu N, Morgovan CM, Jurca T, Pallag A, et al. Sodium alginate—natural microencapsulation material of polymeric microparticles. Int J Mol Sci. 2022;23(20):12108.
15. Patel N, Lalwani D, Gollmer S, Injeti E, Sari Y, Nesamony J. Development and evaluation of a calcium alginate based oral ceftriaxone sodium formulation. Prog Biomater. 2016;5(2):117-33.
16. Huang J, Kaul G, Cai C, Chatlapalli R, Hernandez-Abad P, Ghosh K, et al. Quality by design case study: an integrated multivariate approach to drug product and process development. Int J Pharm. 2009;382(1-2):23-32.

17. Gaur PK, Mishra S, Kumar A, Panda BP. Development and optimization of gastroretentive mucoadhesive microspheres of gabapentin by Box–Behnken design. Artif Cells Nanomed Biotechnol. 2014;42(3):167-77.
18. Elkady OA, Tadros MI, El-Laithy HM. QbD approach for novel crosslinker-free ionotropic gelation of risedronate sodium–chitosan nebulizable microspheres: optimization and characterization. AAPS PharmSciTech. 2020;21(1):14.
19. Sriram N, Katakam P. Formulation and evaluation of mucoadhesive microspheres of pioglitazone hydrochloride prepared by ionotropic external gelation technique. J Encapsul Adsorpt Sci. 2016;6(1):22-34.
20. Jha RK, Tiwari S, Mishra B. Bioadhesive microspheres for bioavailability enhancement of raloxifene hydrochloride: formulation and pharmacokinetic evaluation. AAPS PharmSciTech. 2011;12(2):650-7.