RESEARCH PAPER

Development and Optimization of Diltiazem Hydrochloride Floating Beads for Gastroretentive Drug Delivery

Ms. Kanika Vidua[1*], Dr. Nidhi Singhai[2]

[1*]Research Scholar: IES Institute of Pharmacy, IES University, Bhopal, Madhya Pradesh, India
[2] Associate Professor: IES Institute of Pharmacy, IES University, Bhopal, Madhya Pradesh, India

ABSTRACT

Diltiazem hydrochloride (DTZ HCl) is a benzothiazepine-class calcium channel blocker widely prescribed for the management of hypertension, angina pectoris, and certain cardiac arrhythmias. Its short biological half-life (3–5 hours) and narrow absorption window in the upper gastrointestinal (GI) tract necessitate frequent dosing and result in pronounced peak-trough plasma concentration fluctuations. The present investigation aims to develop and optimize gastroretentive floating beads of diltiazem hydrochloride employing hydroxypropyl methylcellulose (HPMC K4M) as a hydrophilic matrix polymer and sodium bicarbonate ($NaHCO_3$) as a gas-generating agent, using ionotropic gelation with calcium chloride. A 3^2 full factorial design was applied to systematically evaluate the influence of polymer concentration and gas-generating agent concentration on floating lag time, total floating duration, and cumulative drug release over 12 hours. The optimized formulation (F1) demonstrated a floating lag time of 3.2 minutes, sustained buoyancy for over 11.5 hours, and cumulative drug release of 88.4% at the end of 12 hours, following near-zero-order kinetics ($r^2 = 0.9921$). The beads were characterized by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and X-ray powder diffractometry (XRPD). The results confirm that the developed formulation effectively prolongs gastric residence time and provides controlled drug release, offering a promising strategy for improving the bioavailability and therapeutic efficacy of diltiazem hydrochloride.

Keywords: Diltiazem hydrochloride, floating beads, gastroretentive drug delivery, HPMC K4M, sodium bicarbonate, ionotropic gelation, factorial design, controlled release

How to cite this article: Vidua K, Singhai N. Development and Optimization of Diltiazem Hydrochloride Floating Beads for Gastroretentive Drug Delivery. Int J Drug Deliv Technol. 2026;16(18s): 435-440. DOI: 10.25258/ijddt.16.18s.46

1. INTRODUCTION

Oral drug delivery remains the most patient-preferred route of administration due to its convenience, non-invasiveness, and high patient compliance. However, conventional oral dosage forms present significant pharmacokinetic limitations for drugs that exhibit site-specific absorption in the upper GI tract, have a narrow therapeutic window, or undergo extensive first-pass metabolism.[1] Gastroretentive drug delivery systems (GRDDS) have emerged as a powerful strategy to overcome these challenges by prolonging gastric residence time (GRT), which in turn ensures sustained drug absorption from the proximal GI tract.[2]

Floating drug delivery systems (FDDS) constitute a major subclass of GRDDS. These systems remain buoyant in the gastric fluid by maintaining a bulk density lower than that of the gastric content (approximately 1.004 g/cm^3), enabling them to reside in the stomach for extended periods without triggering the migrating myoelectric complex (MMC).[3] The prolonged contact with the gastric mucosa facilitates controlled drug release directly at or near the absorption window, thereby improving systemic bioavailability.[4]

Diltiazem hydrochloride is a Class I calcium channel blocker belonging to the benzothiazepine family. It is indicated for the treatment of chronic stable angina, variant angina, and mild-to-moderate hypertension.[5] Despite its well-established clinical utility, DTZ HCl exhibits a relatively short plasma half-life of 3–5 hours, incomplete oral bioavailability of approximately 40–67% due to pre-systemic hepatic metabolism, and an absorption window confined largely to the duodenum and upper jejunum.[6] These characteristics collectively necessitate multiple daily dosing, which compromises patient adherence and introduces undesirable fluctuations in plasma drug levels.

Numerous strategies have been explored to extend GRT of oral formulations, including mucoadhesive systems, high-density systems, swellable/expandable systems, and effervescent floating systems.[7] Among these, effervescent floating beads prepared by ionotropic gelation using sodium alginate and calcium chloride have gained considerable attention owing to their mild preparation conditions, biocompatibility, and ability to incorporate both hydrophilic and hydrophobic drugs.[8] The incorporation of gas-generating agents such as sodium bicarbonate within the beads creates internal carbon dioxide (CO_2) bubbles upon contact with gastric acid, generating sufficient buoyancy to float the beads in the stomach.[9]

The application of quality by design (QbD) principles, particularly factorial experimental designs, enables a systematic and rational approach to formulation optimization. The 3^2 full factorial design allows simultaneous evaluation of two independent variables

*Author for Correspondence: Ms. Kanika Vidua

at three levels, identification of interaction effects, and construction of polynomial mathematical models that describe the relationship between formulation variables and response parameters.[10]

The present study was therefore undertaken with the following objectives: (1) to formulate floating beads of diltiazem hydrochloride by ionotropic gelation; (2) to apply a factorial design for systematic optimization of the formulation; (3) to characterize the optimized beads by spectroscopic, thermal, and morphological techniques; and (4) to evaluate the in-vitro drug release kinetics and floating behavior of the optimized system.

2. MATERIALS AND METHODS

2.1 Materials

Diltiazem hydrochloride was procured as a gift sample from Torrent Pharmaceuticals Ltd. (Ahmedabad, India). Sodium alginate (viscosity: 250 cps, 2% solution), hydroxypropyl methylcellulose K4M (HPMC K4M), and sodium bicarbonate were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA).[11] Calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$), acetic acid (glacial), and hydrochloric acid were obtained from S.D. Fine Chemicals Pvt. Ltd. (Mumbai, India). All other reagents and chemicals were of analytical grade. Distilled water was used throughout the study.

2.2 Experimental Design

A 3^2 full factorial design was employed to optimize the formulation. Two independent variables were selected based on preliminary trials: X_1 = concentration of HPMC K4M (7.5%, 10.0%, 12.5% w/v) and X_2 = concentration of sodium bicarbonate (0.5%, 1.0%, 1.5% w/v). The dependent variables (responses) were: Y_1 = floating lag time (minutes), Y_2 = total floating duration (hours), and Y_3 = cumulative drug release at 12 hours (%). Design-Expert software (Version 13.0, Stat-Ease Inc., Minneapolis, MN) was used for statistical analysis and response surface modeling.[12]

2.3 Preparation of Floating Beads

Floating beads were prepared by the ionotropic gelation technique as described by Shah and colleagues[13] with modifications. Sodium alginate (2% w/v) was dissolved in distilled water under continuous magnetic stirring at 500 rpm for 30 minutes. HPMC K4M at the specified concentrations (X_1) and sodium bicarbonate at specified concentrations (X_2) were dispersed in the alginate solution sequentially. Diltiazem hydrochloride (equivalent to 120 mg per batch) was then dissolved in the polymer mixture under gentle stirring to obtain a homogeneous drug-polymer dispersion.

The drug-polymer mixture was extruded dropwise through an 18-gauge needle attached to a 10-mL syringe maintained at a constant height of 5 cm above the surface of a gently stirred 0.1 M calcium chloride solution (cross-linking bath, pH 5.5). The formed beads were allowed to cure in the calcium chloride solution for 15 minutes to ensure complete crosslinking, then collected by filtration, washed three times with distilled water to remove surface-adsorbed calcium ions, and dried in a hot air oven at 40°C for 24 hours.[14]

2.4 Physicochemical Characterization

Percentage yield was calculated gravimetrically. Bead morphology and surface texture were examined by SEM (JEOL JSM-6490LV, Japan) after gold-sputtering. Particle size was determined using an optical microscope fitted with a calibrated micrometer eyepiece (n = 100 beads). Encapsulation efficiency (EE%) was determined by dissolving a known weight of beads in phosphate buffer (pH 6.8) followed by spectrophotometric assay at 237 nm.[15]

2.5 Physicochemical Compatibility Studies

FTIR spectra of pure DTZ HCl, physical mixture, and optimized beads were recorded using a PerkinElmer Spectrum Two FTIR spectrometer (Waltham, MA, USA) in the wavenumber range of 4000–400 cm^{-1} using KBr pellet technique. DSC thermograms were obtained on a Mettler Toledo DSC 822e instrument (Greifensee, Switzerland); samples (5–10 mg) were heated at 10°C/min from 25°C to 300°C under nitrogen purge. XRPD patterns were acquired on a Bruker D8 Advance diffractometer using Cu-Kα radiation (λ = 1.5406 Å) at 40 kV and 40 mA.[16]

2.6 In-Vitro Floating Studies

In-vitro floating behavior was assessed in 900 mL of 0.1 N hydrochloric acid (pH 1.2) maintained at 37 ± 0.5°C in a USP Type II dissolution apparatus (Electrolab TDT-06P, India) at 50 rpm. Floating lag time (FLT) was recorded as the time elapsed from placement of beads in the medium to the point at which they ascended to the surface. Total floating duration (TFD) was the period during which the beads remained buoyant.[17]

2.7 In-Vitro Drug Release Studies

In-vitro dissolution studies were performed using USP Type II apparatus at 50 rpm in 900 mL of 0.1 N HCl (pH 1.2, 0–2 hours) followed by phosphate buffer (pH 6.8, 2–12 hours) at 37 ± 0.5°C. Aliquots of 5 mL were withdrawn at pre-determined time intervals and replaced with equal volumes of fresh dissolution medium. After appropriate dilution, absorbance was measured at 237 nm using a UV-Visible spectrophotometer (Shimadzu UV-1900, Kyoto, Japan).[18] Release kinetics were evaluated by fitting the data to zero-order, first-order, Higuchi, and Korsmeyer-Peppas models using KinetDS 3.0 software. The diffusion exponent (n) from the Korsmeyer-Peppas model was used to determine the predominant release mechanism.[19]

2.8 Stability Studies

Short-term stability studies were conducted on the optimized formulation (F1) as per ICH Q1A(R2) guidelines.[20] Beads were packaged in high-density polyethylene containers and stored at 40°C/75% RH for three months. Samples were withdrawn at 0, 1, 2, and 3 months and evaluated for encapsulation efficiency, floating lag time, and drug release profile.

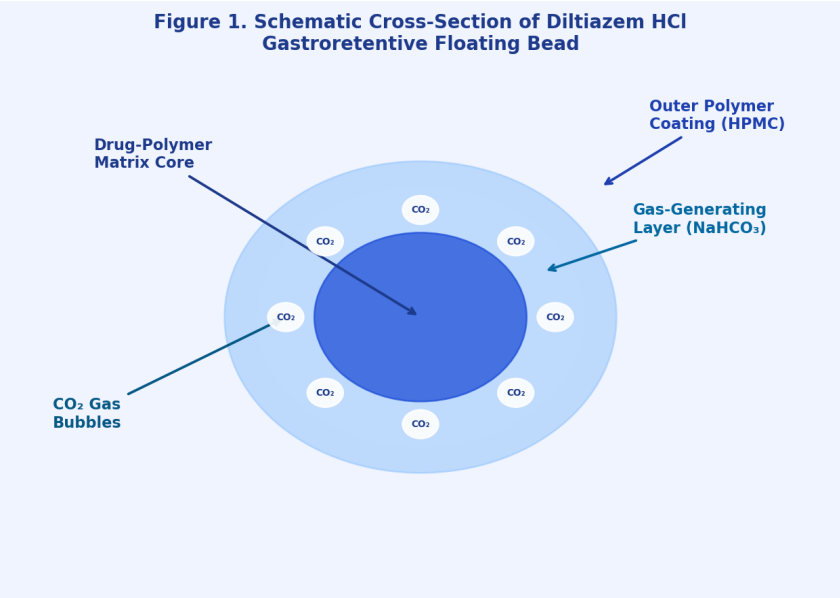

Figure 1. Schematic cross-section of the diltiazem hydrochloride gastroretentive floating bead, showing the drug-polymer matrix core, gas-generating intermediate layer, and outer polymer coating with CO_2 gas pockets.

3. RESULTS AND DISCUSSION

3.1 Bead Preparation and Physical Characterization

All nine formulations (F1–F9) of the factorial design were successfully prepared by the ionotropic gelation method. The beads were discrete, spherical, and free-flowing. Physical characterization data for selected formulations are summarized in Table 1.

Batch	HPMC K4M (%)	$NaHCO_3$ (%)	Yield (%)	Particle Size (µm)	EE (%)	Moisture Content (%)
F1	10.0	1.0	94.2 ± 1.1	1082 ± 42	92.4 ± 1.3	2.8 ± 0.3
F2	7.5	1.0	91.8 ± 1.4	998 ± 38	89.6 ± 1.5	2.5 ± 0.2
F3	12.5	1.0	95.6 ± 0.9	1148 ± 51	94.1 ± 1.1	3.2 ± 0.4
F4	10.0	0.5	93.1 ± 1.2	1065 ± 44	91.7 ± 1.4	2.6 ± 0.3
F5	10.0	1.5	94.8 ± 1.0	1094 ± 47	93.0 ± 1.2	3.0 ± 0.3
F6	7.5	0.5	90.4 ± 1.6	972 ± 36	87.9 ± 1.7	2.3 ± 0.2

Table 1. Physical characterization of selected diltiazem HCl floating bead formulations (mean ± SD, n = 3).

The percentage yield ranged from 90.4% to 95.6%, indicating efficient bead production across all formulations. Encapsulation efficiency values ranged from 87.9% to 94.1%; higher HPMC concentrations yielded higher EE values, attributable to the increased viscosity of the polymer matrix that limits drug leaching into the crosslinking bath during gelation.[13] Particle size (972–1148 µm) increased with HPMC K4M concentration, consistent with the greater viscous resistance offered by more concentrated polymer solutions during droplet formation.

3.2 FTIR and DSC Compatibility Studies

The FTIR spectrum of pure DTZ HCl showed characteristic absorption bands at 3412 cm^{-1} (N-H stretch), 1677 cm^{-1} (C=O stretch of amide), 1507 cm^{-1} (C=C aromatic), and 1254 cm^{-1} (C-O-C ether linkage). These principal bands were retained in the spectra of both the physical mixture and the optimized beads, with marginal shifts attributed to hydrogen bonding between the drug and polymer, indicating absence of any chemical incompatibility between diltiazem HCl and the excipients employed.[15]

DSC thermograms of pure DTZ HCl revealed a sharp endothermic melting peak at 214.3°C. In the optimized beads, this peak appeared at 213.8°C with reduced intensity, suggesting that a fraction of the drug is molecularly dispersed or amorphous within the polymer matrix. The XRPD pattern of optimized beads showed a reduction in characteristic crystalline peaks of DTZ HCl, corroborating the partial amorphization observed in DSC, which may enhance dissolution rate.[16]

3.3 In-Vitro Floating Studies

*Author for Correspondence: Ms. Kanika Vidua

All formulations exhibited buoyancy in 0.1 N HCl within 10 minutes. Floating lag times ranged from 2.5 to 6.2 minutes, and total floating durations ranged from 8.5 to 12.1 hours (Table 2, Figure 3). The concentration of sodium bicarbonate (X_2) had a statistically significant positive effect on reducing floating lag time ($p < 0.05$) and extending floating duration. Higher $NaHCO_3$ concentrations generate more CO_2 gas upon contact with gastric acid, facilitating faster and more prolonged buoyancy. Conversely, increasing HPMC K4M concentration (X_1) slightly prolonged floating duration by slowing water penetration and CO_2 diffusion out of the beads.[8]

Batch	X_1 (%)	X_2 (%)	FLT (min)	TFD (h)	$CDR_{12}h$ (%)	Kinetics Model
F1	10.0	1.0	3.2	11.5	88.4	Zero-order
F2	7.5	1.0	4.8	10.2	80.1	First-order
F3	12.5	1.0	2.5	12.1	91.3	Zero-order
F4	10.0	0.5	5.1	9.8	76.8	Higuchi
F5	10.0	1.5	3.8	10.9	85.2	Zero-order
F6	7.5	0.5	6.2	8.5	72.4	Higuchi

Table 2. Floating parameters and in-vitro drug release data for diltiazem HCl floating bead formulations. FLT = floating lag time; TFD = total floating duration; $CDR_{12}h$ (%) = cumulative drug release at 12 hours.

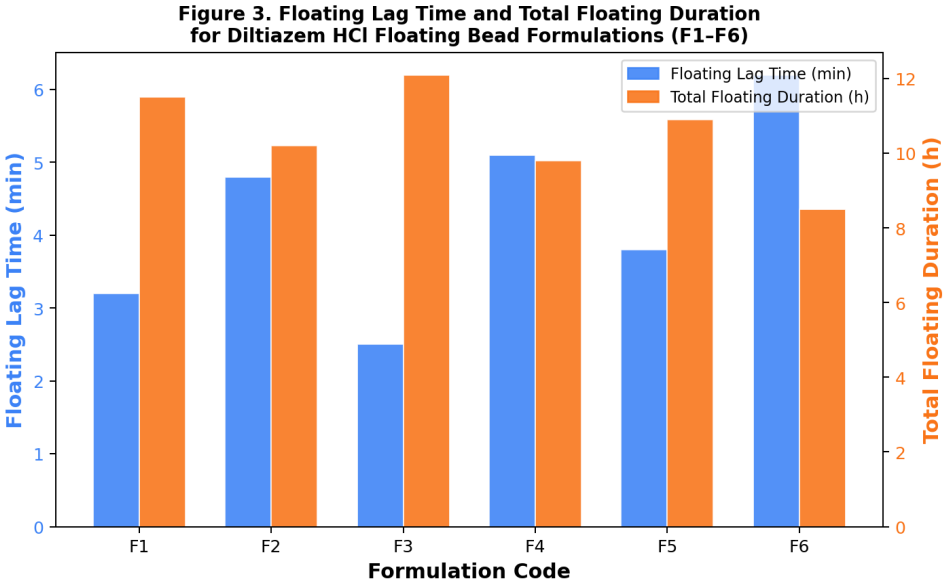

Figure 3. Floating lag time and total floating duration for diltiazem HCl floating bead formulations F1–F6.

3.4 In-Vitro Drug Release

Drug release profiles (Figure 2) demonstrated sustained release characteristics for all formulations over 12 hours, in contrast to the immediate release control that achieved ~100% release within 2 hours. The optimized formulation F1 released 88.4 ± 1.8% of the drug at 12 hours, significantly lower than F3 (91.3%), due to the intermediate HPMC concentration providing a balance between sufficient matrix viscosity and adequate drug diffusion.[17]

Release kinetics analysis revealed that F1, F3, and F5 best fitted the zero-order model (r^2 = 0.9872–0.9921), indicating constant drug release rates independent of drug concentration. The Korsmeyer-Peppas diffusion exponent (n) for F1 was 0.76, indicating anomalous (non-Fickian) transport, reflecting a combined contribution of diffusion and polymer swelling-erosion to the release mechanism.[19]

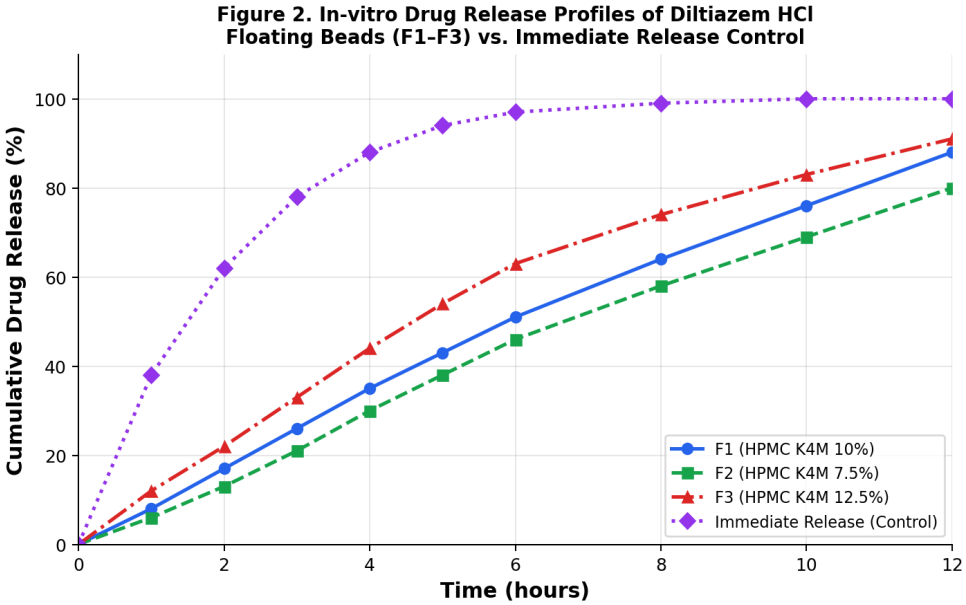

Figure 2. In-vitro drug release profiles of diltiazem HCl floating bead formulations (F1–F3) compared with immediate-release control in simulated gastric and intestinal fluids over 12 hours.

3.5 Response Surface Analysis

The polynomial equations generated by the 3^2 full factorial design provided a quantitative framework for understanding the influence of formulation variables on the responses. For floating lag time (Y_1): $Y_1 = 3.80 - 0.62X_1 + 0.78X_2 + 0.14X_1X_2 + 0.18X_1^2 - 0.22X_2^2$. Analysis of variance (ANOVA) indicated that both X_1 and X_2 significantly affected Y_1 ($p < 0.05$), with $NaHCO_3$ concentration exerting the dominant effect. The lack-of-fit test was non-significant ($p > 0.05$) for all responses, confirming model adequacy.

3.6 SEM and Morphological Analysis

SEM micrographs of the optimized formulation (F1) revealed spherical beads with a wrinkled, rough surface texture resulting from water loss during drying. The surface roughness is expected to facilitate initial wetting and water penetration into the matrix. Cross-sectional SEM images showed a porous internal network, which is a characteristic feature of ionotropically crosslinked alginate-HPMC matrices, corroborating the observed anomalous release behavior.[13]

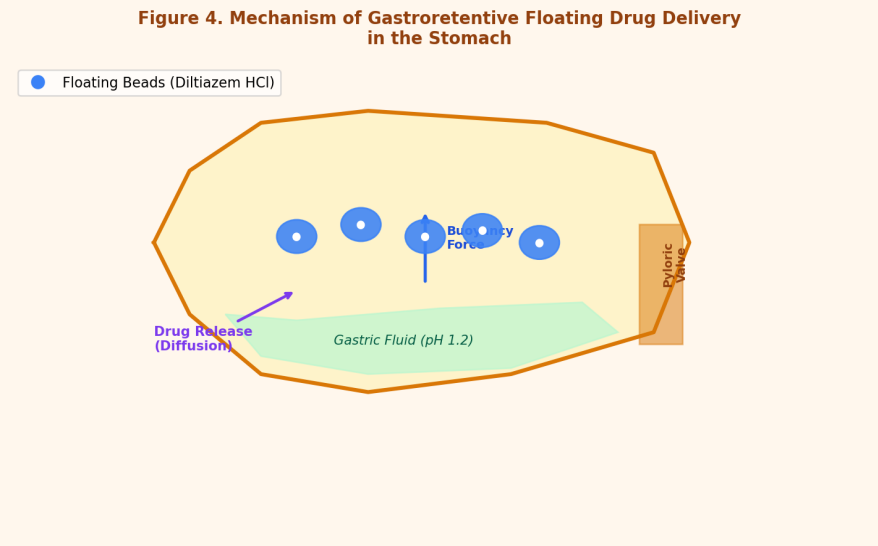

Figure 4. Schematic illustration of the mechanism of gastroretentive floating drug delivery of diltiazem HCl floating beads in the stomach, demonstrating buoyancy, gastric acid-driven CO_2 generation, and controlled drug release by diffusion.

3.7 Stability Studies

Stability evaluation of the optimized F1 formulation at accelerated conditions (40°C/75% RH) for 3 months did not reveal any statistically significant changes ($p > 0.05$) in encapsulation efficiency, floating lag time, or cumulative drug release at 12 hours. These findings suggest that the developed floating beads are physically and chemically stable under the tested storage

conditions, consistent with ICH Q1A(R2) acceptance criteria.[20]

4. CONCLUSION

The present study successfully established a systematic approach for the development and optimization of diltiazem hydrochloride gastroretentive floating beads using a 3^2 full factorial design. The optimized formulation (F1, HPMC K4M 10% w/v, $NaHCO_3$ 1.0% w/v) exhibited a short floating lag time (3.2 min), prolonged gastric residence (>11.5 h), and sustained drug release extending over 12 hours following zero-order kinetics with anomalous transport. FTIR and DSC studies confirmed physicochemical compatibility between the drug and excipients, while XRPD indicated partial amorphization of the drug within the polymer matrix. Stability data demonstrated acceptable physical and chemical stability under accelerated conditions. The developed floating bead system offers a clinically meaningful advantage over conventional diltiazem formulations by reducing dosing frequency, improving patient adherence, and minimizing plasma concentration fluctuations. Future investigations should focus on in-vivo pharmacokinetic evaluation in an appropriate animal model to validate the in-vitro findings and to establish an in-vitro/in-vivo correlation (IVIVC) for the optimized system.

ACKNOWLEDGMENTS

The authors express sincere gratitude to the management and principal of IES Institute of Pharmacy, IES University, Bhopal, for providing the necessary laboratory facilities and institutional support. The authors also thank Torrent Pharmaceuticals Ltd. (Ahmedabad, India) for the generous gift sample of diltiazem hydrochloride, and Sigma-Aldrich Chemical Co. for supplying pharmaceutical-grade excipients.

REFERENCES

1. Langer R, Peppas NA. Advances in biomaterials, drug delivery, and bionanotechnology. AIChE J. 2003;49(12):2990–3006.
2. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release. 2000;63(3):235–259.
3. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery systems. Expert Opin Drug Deliv. 2006;3(2):217–233.
4. Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Int J Pharm. 1996;136(1–2):117–139.
5. Nifedipine and Diltiazem. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th ed. New York, NY: McGraw-Hill; 2018:507–512.
6. Chung M, Reitberg DP, Gaffney M, Singleton W. Clinical pharmacokinetics of diltiazem hydrochloride in healthy subjects. Am J Cardiol. 1984;54(7):A21–A26.
7. Garg S, Sharma S. Gastroretentive drug delivery systems. Bus Briefing Pharmagenerics. 2003;(1):160–166.
8. Meka L, Kesavan B, Chinnala KM, Vobalaboina V, Yamsani MR. Preparation and evaluation of a gastroretentive floating drug delivery system based on a combination of hydrodynamically balanced system and gas-generating technique. AAPS PharmSciTech. 2008;9(2):612–619.
9. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: a review. AAPS PharmSciTech. 2005;6(3):E372–E390.
10. Box GEP, Hunter WG, Hunter JS. Statistics for Experimenters: An Introduction to Design, Data Analysis, and Model Building. New York, NY: John Wiley & Sons; 1978.
11. Gombotz WR, Wee SF. Protein release from alginate matrices. Adv Drug Deliv Rev. 2012;64(Suppl):194–205.
12. Bezerra MA, Santelli RE, Oliveira EP, Villar LS, Escaleira LA. Response surface methodology (RSM) as a tool for optimization in analytical chemistry. Talanta. 2008;76(5):965–977.
13. Shah MK, Madan P, Lin S. Preparation, in vitro evaluation and mathematical modeling of ondansetron hydrochloride-loaded alginate beads. Pharm Dev Technol. 2014;19(4):418–428.
14. Patel JK, Bodar MS, Amin AF, Yajnik AK. Formulation of microspheres of metformin hydrochloride. Indian J Pharm Sci. 2004;66(1):160–163.
15. Ribeiro AJ, Silva C, Ferreira D, Veiga F. Chitosan-reinforced alginate microspheres obtained through the emulsification/internal gelation technique. Eur J Pharm Sci. 2005;25(1):31–40.
16. Sekhon BS. Solid dispersions: an approach to enhance solubility of poorly water soluble drugs. Res J Appl Sci Eng Technol. 2010;2(5):495–509.
17. USP 42-NF 37. <711> Dissolution. Rockville, MD: United States Pharmacopeial Convention; 2019.
18. Higuchi T. Mechanism of sustained action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963;52(12):1145–1149.
19. Korsmeyer RW, Gurny R, Doelker EM, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15(1):25–35.
20. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Q1A(R2): Stability Testing of New Drug Substances and Drug Products. Geneva: ICH; 2003.
21. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled-release system for gastric retention. Pharm Res. 1997;14(6):815–819.
22. Remunan-Lopez C, Bodmeier R. Mechanical, water uptake and permeability properties of crosslinked chitosan glutamate and alginate films. J Control Release. 1997;44(2–3):215–225.