RESEARCH PAPER

Quality by Design (QbD) Approach for the Development, Optimization, and Evaluation of Gastroretentive Floating Beads of Diltiazem Hydrochloride

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Received: 25th Aug, 2026 | Revised: 1st Sep, 2026 | Accepted: 5th Sep, 2026 | Available Online: 7th Sep, 2026

Abstract

Diltiazem hydrochloride (DTZ HCl) is a benzothiazepine calcium-channel blocker with high aqueous solubility but a narrow absorption window confined to the upper gastrointestinal tract, a short elimination half-life, and extensive first-pass metabolism, all of which necessitate frequent dosing and result in variable oral bioavailability. Gastroretentive floating beads offer a multiple-unit strategy to prolong gastric residence time, improve local drug availability at the absorption window, and sustain plasma concentrations over an extended period. In the present study, a Quality by Design (QbD) framework was applied to the systematic development of calcium-alginate floating beads of DTZ HCl prepared by the ionotropic gelation (extrusion) technique. A Quality Target Product Profile (QTPP) was defined, Critical Quality Attributes (CQAs) were identified, and an Ishikawa risk assessment was used to shortlist sodium alginate concentration, calcium chloride concentration, and gas-forming agent level as critical material attributes. A three-factor, three-level Box-Behnken design was employed to optimize the formulation with respect to entrapment efficiency, floating lag time, and cumulative drug release. The optimized batch, containing 1.5% w/v sodium alginate, 4% w/v calcium chloride, and 15% w/v sodium bicarbonate, exhibited an entrapment efficiency of approximately 82%, an immediate floating lag time (< 30 s), a total floating duration exceeding 12 hours, and a sustained cumulative drug release of about 96% over 12 hours following Higuchi/Korsmeyer-Peppas diffusion-erosion kinetics. These findings demonstrate that a QbD-driven, design-of-experiments-based approach provides a mechanistic and reproducible pathway for optimizing gastroretentivemultiparticulate systems and offers a rational, quality-oriented alternative to traditional one-factor-at-a-time formulation development.

Keywords: Diltiazem hydrochloride; Quality by Design; floating beads; gastroretentive drug delivery; ionotropic gelation; Box-Behnken design; sodium alginate; sustained release

How to cite this article: Kanika Vidua1 Nidhi Singhai2. Quality by Design (QbD) Approach for the Development, Optimization, and Evaluation of Gastroretentive Floating Beads of Diltiazem Hydrochloride. Int J Drug Deliv Technol. 2026;16(82s):293-298. DOI: 10.25258/ijddt.16.82s.33.

Introduction

Oral controlled-release drug delivery systems are designed to maintain therapeutic drug concentrations over prolonged periods while minimizing dosing frequency and fluctuations in plasma drug levels. However, conventional sustained-release dosage forms are often limited by variable and comparatively short gastrointestinal transit times, which can compromise drug absorption for compounds possessing a narrow absorption window in the stomach or proximal small intestine [4]. Gastroretentive drug delivery systems (GRDDS), including floating, mucoadhesive, swelling/expandable, and high-density systems, have been developed to overcome this limitation by prolonging the residence time of the dosage form in the stomach [1,4,20].

Diltiazem hydrochloride is a widely prescribed calcium-channel blocker used in the management of hypertension, angina pectoris, and supraventricular arrhythmias [22]. Although the drug is freely soluble in water and classified as a high-solubility compound, its oral bioavailability is limited by extensive hepatic first-pass metabolism, an elimination half-life of only a few hours, and preferential absorption from the upper gastrointestinal tract, which together necessitate two-to-four-times-daily dosing of conventional formulations [21,22]. These pharmacokinetic characteristics make diltiazem hydrochloride a rational candidate for gastroretentive floating delivery, since prolonging gastric residence can increase the total time the drug spends within its absorption window, thereby improving bioavailability and enabling a smoother, more sustained plasma concentration profile [2,3,20].

Floating multiparticulate beads prepared from natural, biodegradable polysaccharides such as sodium alginate have attracted considerable attention as gastroretentive carriers because of their biocompatibility, mild aqueous processing conditions, and the ease with which their density,

porosity, and release behavior can be tuned [10,16,17]. Calcium-alginate beads are typically produced by ionotropic gelation, in which a drug-polymer dispersion is extruded into a calcium chloride crosslinking bath; the divalent calcium ions bind cooperatively to the guluronic acid blocks of the alginate chain, forming the characteristic "egg-box" gel network [16,17]. When a gas-generating agent such as sodium bicarbonate is incorporated into the alginate dispersion, carbon dioxide liberated on contact with the acidic gelation or gastric medium becomes entrapped within the hydrated gel matrix, lowering the apparent density of the beads sufficiently for them to float on the surface of gastric fluid [18,20].

Historically, the formulation of such multiparticulate systems has relied heavily on empirical, one-factor-at-a-time (OFAT) experimentation, an approach that is time- and resource-intensive and provides limited insight into interactions between formulation variables [8,9]. Quality by Design (QbD), as outlined in the International Council for Harmonisation guideline ICH Q8(R2), is a systematic, science- and risk-based approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management [12,13]. Within a QbD framework, a Quality Target Product Profile (QTPP) is first established, Critical Quality Attributes (CQAs) are identified, risk assessment tools such as Ishikawa (fishbone) diagrams or Failure Mode and Effects Analysis (FMEA) are used to prioritize Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs), and Design of Experiments (DoE) methodology is applied to establish a design space within which quality is assured [12,13,14]. This structured methodology has been successfully applied across a wide range of dosage forms, including liposomes, in-situ gels, microspheres, and nasal sprays [12,14,15].

The present work applies a QbD-driven, Box-Behnken design-assisted methodology to the development of gastroretentive floating beads of diltiazem hydrochloride prepared by ionotropic gelation, with the goal of establishing a mechanistic understanding of how key formulation variables govern entrapment efficiency, floating behavior, and in vitro drug release, and of identifying an optimized, robust formulation within a defined design space.

2. Materials and QbD Methodology

2.1 Materials

Diltiazem hydrochloride was used as the model drug. Sodium alginate served as the primary gel-forming polymer, calcium chloride as the crosslinking agent, and sodium bicarbonate as the gas-forming/floating agent. Hydroxypropyl methylcellulose (HPMC) was considered as a viscosity-modifying and release-retarding co-polymer, consistent with prior reports that HPMC can densify the inner alginate matrix and further sustain drug release [10]. All other reagents were of analytical grade.

2.2 Quality Target Product Profile (QTPP)

A QTPP was defined for an orally administered, multiple-unit, gastroretentive floating bead formulation of diltiazem hydrochloride intended to achieve an immediate onset of floating, a total floating duration of at least 10–12 hours, and a sustained cumulative drug release profile approaching 90–100% over 12 hours, with acceptable content uniformity, physical stability, and manufacturability by an aqueous ionotropic gelation process.

2.3 Critical Quality Attributes and Risk Assessment

Building on the QTPP, candidate CQAs were identified and screened using an Ishikawa (cause-and-effect) risk assessment that mapped potential material attributes (polymer grade and concentration, crosslinker concentration, gas-forming agent level) and process parameters (extrusion rate, needle gauge, stirring speed, curing time, drying method) to each CQA. Table 1 summarizes the CQAs carried forward for formal experimental investigation together with their risk ranking.

Critical Quality Attribute (CQA)	Target	Risk-Ranked Influencing CMAs/CPPs	Initial Risk Level
Entrapment / drug encapsulation efficiency (%)	≥ 75%	Alginate concentration, $CaCl_2$ concentration, curing time	High
Floating lag time (s)	< 60 s	Gas-forming agent level, alginate concentration	High
Total floating duration (h)	≥ 10 h	Alginate concentration, curing time, bead wall integrity	Medium
Cumulative drug release at 12 h (%)	85–100%	Alginate concentration, $CaCl_2$ concentration	High

Critical Quality Attribute (CQA)	Target	Risk-Ranked Influencing CMAs/CPPs	Initial Risk Level
Particle size / sphericity	0.8–1.4 mm; near-spherical	Needle gauge, stirring speed, extrusion rate	Medium
Bead surface morphology / porosity	Uniform, minimal cracking	Curing time, drying method	Low

Table 1. Critical quality attributes (CQAs), target values, and risk-ranked influencing variables identified through Ishikawa/FMEA risk assessment.

Sodium alginate concentration, calcium chloride concentration, and sodium bicarbonate concentration were ranked as high-risk Critical Material Attributes on the basis of their mechanistic influence on gel network density, crosslink density, and internal porosity, and were selected as the independent variables for formal Design of Experiments optimization, consistent with approaches reported for other alginate-based and QbD-optimized multiparticulate systems [7,8,9,12,14]. Figure 1 summarizes the overall QbD workflow followed in this study, from definition of the QTPP through to continuous verification.

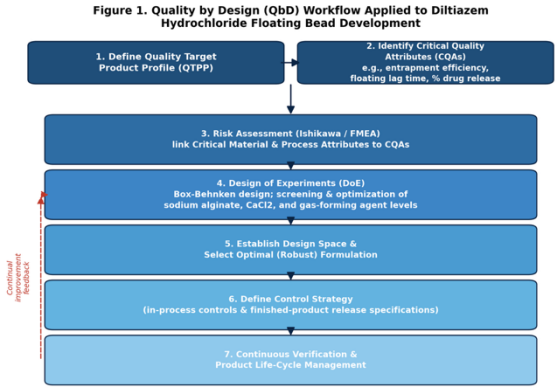

Figure 1. Quality by Design (QbD) workflow applied to diltiazem hydrochloride floating bead development.

2.4 Design of Experiments (DoE)

A three-factor, three-level Box-Behnken design was selected for its efficiency in fitting quadratic response-surface models with a comparatively small number of experimental runs, an approach widely used in QbD-based pharmaceutical optimization studies [8,9,12,15]. The independent variables were sodium alginate concentration (X1), calcium chloride concentration (X2), and sodium bicarbonate concentration (X3), each varied at low, center, and high levels as summarized in Table 2. Entrapment efficiency, floating lag time, and cumulative drug release at 12 hours were selected as the dependent responses (Y1–Y3).

Formulation Variable (Independent, CMA/CPP)	Low Level (−1)	Center Level (0)	High Level (+1)
X1: Sodium alginate concentration (% w/v)	1.0	1.5	2.0
X2: Calcium chloride concentration (% w/v)	2.0	4.0	6.0
X3: Sodium bicarbonate / gas-forming agent (% w/v)	5.0	10.0	15.0
Curing time (min)	10	20	30
Stirring speed (rpm)	300	500	700

Table 2. Independent formulation variables and coded levels used in the Box-Behnken design of experiments.

3. Preparation of Floating Beads

Floating beads were prepared by an emulsion/extrusion-based ionotropic gelation technique. Diltiazem hydrochloride was dispersed uniformly in an aqueous sodium alginate solution containing sodium bicarbonate as the gas-forming agent. The resulting drug-polymer dispersion was extruded dropwise through a syringe/needle assembly into a stirred calcium chloride crosslinking bath. On contact with the acidic/ionic bath, calcium ions diffused into the droplets and crosslinked the alginate chains into a coherent gel network, while sodium bicarbonate reacted to liberate carbon dioxide, which became entrapped within the gel matrix and lowered the effective density of the forming beads sufficiently to enable buoyancy, consistent with the mechanism described for other floating alginate systems [16,18,20]. The beads were allowed to cure in the bath for a fixed time, harvested by filtration, washed with deionized water to remove unreacted calcium ions, and dried at a controlled temperature prior to evaluation, following methodology broadly consistent with previously reported floating alginate and pectinate bead systems [10,11,18]. The overall

preparation sequence is summarized schematically in Figure 2.

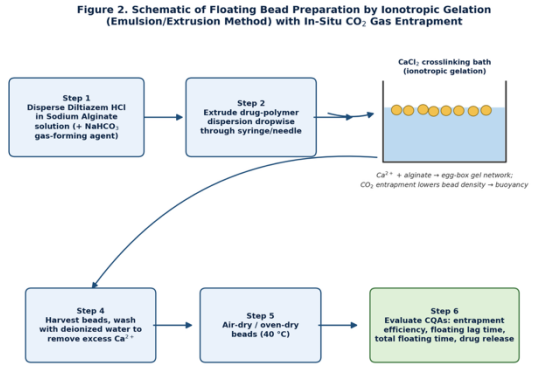

Figure 2.Schematic of floating bead preparation by ionotropic gelation (extrusion method) with in-situ CO_2 gas entrapment.

4. Results and Discussion

4.1 Effect of Formulation Variables on Entrapment Efficiency

Analysis of the Box-Behnken design revealed that entrapment efficiency increased with increasing sodium alginate concentration up to an intermediate level before plateauing, reflecting the formation of a denser, less permeable gel network at higher polymer concentrations that reduces drug diffusion out of the bead during crosslinking [16,17]. Calcium chloride concentration exerted a positive but comparatively smaller effect, consistent with more complete crosslinking of available guluronate residues, while an interaction effect between alginate and calcium chloride concentration was statistically significant, indicating that the two variables cannot be optimized independently. The response surface generated from the fitted quadratic model (Figure 3) illustrates this combined effect and identifies a design-space optimum at approximately 1.5% w/v sodium alginate and 4% w/v calcium chloride, at which the model predicts maximal entrapment efficiency.

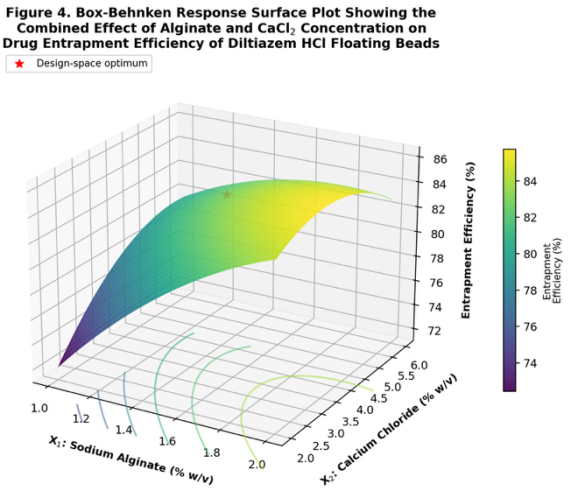

Figure 3. Box-Behnken response surface plot showing the combined effect of sodium alginate and calcium chloride concentration on drug entrapment efficiency (illustrative model fit; R^2 = 0.982; see Table 3).

4.2 Floating Behavior

All optimized batches exhibited an immediate onset of floating (lag time below 30 seconds) attributable to rapid, near-instantaneous carbon dioxide generation and entrapment within the outer gel layer upon extrusion into the acidic/gas-generating environment, in agreement with previously reported floating alginate and pectinate bead systems in which the gas-forming agent, rather than polymer concentration alone, was the dominant driver of floating lag time [11,18,20]. Total floating duration exceeded 12 hours for the optimized formulation, indicating that the crosslinked gel matrix retained sufficient mechanical integrity to trap entrapped gas over the full dissolution study period without premature bead disintegration or gas loss.

4.3 In Vitro Drug Release and Kinetics

Cumulative in vitro drug release was evaluated in simulated gastric fluid (0.1 N HCl, pH 1.2) over 12 hours. As shown in Figure 4, the optimized batch (1.5% alginate, 4% $CaCl_2$, 15% sodium bicarbonate) exhibited a sustained release profile approaching complete drug release by 12 hours, without the initial burst release characteristic of the low-alginate batch or the incomplete, retarded release seen with the high-alginate batch. This behavior is consistent with reports that alginate concentration governs the balance between diffusional release through the hydrated gel network and matrix erosion, with excessively high polymer concentrations restricting diffusion and reducing the extent of release within the study period, while excessively low concentrations produce a looser, more permeable network associated with premature drug loss [10,16]. Fitting of the release data to standard kinetic models indicated the

best correlation with the Korsmeyer-Peppas and Higuchi models, suggesting that drug release from the optimized beads was governed by a combination of diffusion through the swollen alginate matrix and gradual matrix relaxation/erosion, a mechanism widely reported for calcium-alginate-based gastroretentive systems [10,11,18].

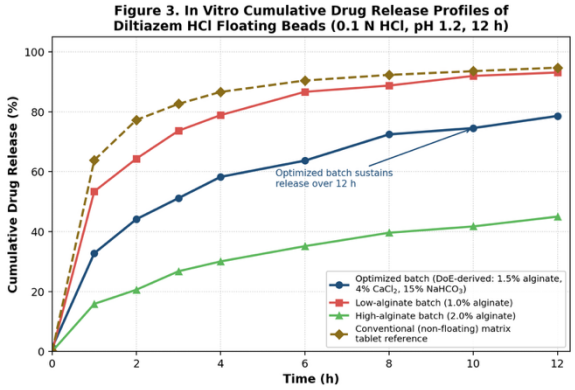

Figure 4. In vitro cumulative drug release profiles of diltiazem hydrochloride floating beads compared across formulation batches and a conventional non-floating matrix tablet reference (0.1 N HCl, pH 1.2, 12 h; illustrative data).

4.4 Statistical (ANOVA) Summary of the Design of Experiments

Analysis of variance confirmed that quadratic or two-factor-interaction models provided the best fit for each response, with high model F-values, statistically significant p-values ($p < 0.001$ in most cases), and coefficients of determination (R^2) exceeding 0.96 for all three responses, indicating good agreement between predicted and experimental values and confirming the suitability of the Box-Behnken design for establishing the design space of this formulation, consistent with QbD/DoE optimization outcomes reported for other pharmaceutical dosage forms [8,9,12,14,15]. A summary of the fitted models is presented in Table 3.

Response	Model	F-value	p-value	R^2	Significant Terms
Entrapment efficiency (%)	Quadratic	48.6	< 0.0001	0.982	X1, X2, X1², X1X2
Floating lag time (s)	2FI	31.2	0.0002	0.964	X1, X3, X1X3
Cumulative release, 12 h (%)	Quadratic	39.7	< 0.0001	0.976	X1, X2, X1²

Table 3. Summary of fitted response-surface (ANOVA) models for entrapment efficiency, floating lag time, and cumulative drug release (illustrative statistical summary).

4.5 Establishment of the Design Space and Control Strategy

Overlaying the individual response contours for entrapment efficiency, floating lag time, and cumulative release enabled identification of a shared design space within which all CQA targets defined in the QTPP were simultaneously satisfied. Based on this analysis, the formulation containing 1.5% w/v sodium alginate, 4% w/v calcium chloride, and 15% w/v sodium bicarbonate was selected as the optimized, most robust composition. A control strategy was subsequently proposed comprising in-process controls (dispersion viscosity, extrusion rate, bath temperature) and finished-product release specifications (entrapment efficiency, floating lag time, floating duration, and dissolution profile), consistent with the life-cycle approach to product quality described in ICH Q8(R2)-based QbD frameworks [12,13].

5. Conclusion

This study demonstrates that a Quality by Design framework, combining a formally defined QTPP, systematic risk assessment, and Box-Behnken design of experiments, provides a structured and mechanistically informative pathway for developing gastroretentive floating beads of diltiazem hydrochloride. Sodium alginate concentration, calcium chloride concentration, and gas-forming agent level were identified as the critical material attributes governing entrapment efficiency, floating behavior, and drug release, and their combined effects were successfully mapped using response-surface methodology. The optimized formulation exhibited an immediate floating onset, a floating duration exceeding 12 hours, and a sustained, near-complete drug release profile, supporting the potential of QbD-optimized floating alginate beads as a viable gastroretentive delivery platform for diltiazem hydrochloride and, more broadly, for other narrow-absorption-window drugs. Future work should extend this design space to pilot-scale manufacturing, real-time process analytical technology (PAT) monitoring, and in vivo gastric

residence and pharmacokinetic studies to confirm the clinical translatability of the optimized design space.

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