*Scientia Pharmaceutica*

ÖSTERREICHISCHE PHARMAZEUTISCHE GESELLSCHAFT

MDPI

*Article*

# Formulation Optimization of Felodipine Push–Pull Osmotic Pump Capsules Using Quality by Design Approach

**Chaowalit Monton [1,2,3,*] and Poj Kulvanich [4]**

[1] Drug and Herbal Product Research and Development Center, College of Pharmacy, Rangsit University, Pathum Thani 12000, Thailand
[2] Department of Pharmacognosy, College of Pharmacy, Rangsit University, Pathum Thani 12000, Thailand
[3] Medicinal Cannabis Research Institute, College of Pharmacy, Rangsit University, Pathum Thani 12000, Thailand
[4] Industrial Pharmacy Program, College of Pharmacy, Rangsit University, Pathum Thani 12000, Thailand; pojkul@gmail.com
* Correspondence: chaowalit@rsu.ac.th; Tel.: +66-29972222 (ext. 4911)

## Abstract

Recently, the Quality by Design (QbD) principle has been implemented in the pharmaceutical industry to enhance product and process understanding through a science- and risk-based approach. This study aimed to apply QbD principles to the formulation development of felodipine push–pull osmotic pump (PPOP) capsules. The quality target product profile (QTPP) and critical quality attributes (CQAs) were established. A Box–Behnken experimental design was employed to optimize the formulation variables, including the amounts of Polyox WSR N80, Polyox WSR Coagulant, and sodium chloride, selected based on the initial risk assessment. Four responses were monitored: lag time, release rate and $R^2$ based on zero-order release kinetics, and drug release at 24 h. Results indicated that the optimal formulation consisted of 125 mg Polyox WSR N80, 26 mg Polyox WSR Coagulant, and 30 mg sodium chloride. This formulation met the predefined criteria for lag time ($\leq$6 h) and release kinetics ($R^2 \geq 0.95$), while drug release at 24 h remained below the target value ($\geq$80%). Because most fitted response surface models were not statistically significant, the generated regression equations and response surfaces were interpreted qualitatively to identify formulation trends rather than as predictive models. Experimental verification showed reasonable consistency in overall response trends, although substantial deviations between predicted and observed values were observed for some responses, particularly drug release at 24 h. Therefore, the present work should be considered a formulation-development and QbD feasibility study rather than a definitive optimization study. These findings demonstrate that the QbD-based approach enabled systematic, multivariate optimization and design space establishment, providing a more structured framework for formulation refinement compared with prior exploratory development and supporting controlled drug release characteristics of felodipine PPOP capsules.

**Keywords:** design of experiments; design space; osmotic drug delivery; response surface methodology; sustained release



Academic Editor: Claudio J. Salomón

Received: 4 May 2026
Revised: 16 June 2026
Accepted: 23 June 2026
Published: 25 June 2026



## 1. Introduction

Hypertension is a chronic noncommunicable disease and a leading cause of premature mortality worldwide [1–4]. Several classes of antihypertensive drugs are available for treatment. Felodipine, a poorly water-soluble calcium channel blocker, is one such agent.

Extended-release formulations of felodipine are commercially available as tablets containing 2.5, 5, or 10 mg of the drug. Although felodipine is completely absorbed following oral administration, it undergoes extensive first-pass metabolism, leading to a low bioavailability of approximately 20%. Felodipine is primarily absorbed in the small intestine, and its absorption is dependent on its dissolution behavior. Moreover, its absorption can be influenced by food intake [5].

An osmotic pump is a controlled drug delivery system that relies on osmotic pressure to regulate the release of active pharmaceutical ingredients (APIs). Water permeates through a semipermeable membrane, generating internal pressure that drives sustained drug release [6–10]. Compared with conventional oral dosage forms, osmotic pumps provide a nearly zero-order release profile, maintaining steady therapeutic levels and showing strong in vitro–in vivo correlation [11–18]. This system prolongs drug action, reduces dosing frequency, enhances compliance, and minimizes plasma fluctuations [19,20]. Moreover, osmotic pumps operate independently of drug properties, physiological conditions, and food intake, ensuring consistent and predictable performance [13,19,21].

Although osmotic pump tablets containing felodipine alone [22] or in combination with other antihypertensive agents [23] have been developed, the capsule dosage form was selected in this study due to its distinct advantages over tablets. Capsules offer easier formulation and preparation and require fewer manufacturing steps as granulation and compression are unnecessary. In addition, capsules may provide improved patient acceptability in certain cases due to their smooth surface and ease of swallowing, although tablets are generally associated with a lower risk of swallowing difficulties [24]. Furthermore, the developed system employs an insoluble polymer coating (cellulose acetate), and the use of crosslinked hard gelatin capsules (HGCs) may further reduce adhesion to the oral cavity, potentially enhancing ease of administration.

Recently, Quality by Design (QbD), "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management", was applied in the pharmaceutical industry [25]. The key elements of QbD include: (1) a Quality Target Product Profile (QTPP) that defines the drug product's critical quality attributes (CQAs); (2) product design and understanding, which involves identifying critical material attributes (CMAs); (3) process design and understanding, focusing on the identification of critical process parameters (CPPs) and CMAs, and their relationship to CQAs; (4) a control strategy that outlines specifications for drug substances, excipients, and the drug product, along with controls at each stage of manufacturing; and (5) process capability and continuous improvement. QbD tools and methods include prior knowledge, risk assessment, mechanistic models, design of experiments (DoE), data analysis, and process analytical technology (PAT) [26,27]. QbD facilitates an efficient reduction in development time and costs, aligns with Food and Drug Administration (FDA) submission guidelines and expectations, and may shorten approval times. In contrast, in a non-QbD approach, sources of variability are investigated but often in a less systematic and less comprehensive manner, which may increase the risk of failing to identify potential interactions among formulation and process variables during development and only become evident during commercial production, where detection and control are more challenging. This may result in manufacturing interruptions and potential drug shortages, thereby necessitating subsequent root cause analysis [26].

In a previous study, the feasibility of a felodipine PPOP capsule was established through a comprehensive characterization of the drug substance, crosslinked HGCs, and key formulation and processing variables influencing drug-release behavior. That study employed a one-factor-at-a-time (OFAT) approach, primarily for factor screening and

feasibility assessment. It enabled the preliminary identification of formulation variables, such as polymers in push and pull layers and an osmotic-inducing agent, that significantly influenced drug release profiles [28]. However, the OFAT approach is inherently limited in its ability to evaluate interactions among multiple variables and does not support systematic optimization or definition of a formulation design space.

Building on these findings, the present study extends the previous work by applying the QbD framework to enable a more systematic and science-based formulation development. Specifically, a QTPP and CQAs were defined to guide formulation targets, and a risk-based approach was employed to identify critical formulation variables. These variables were subsequently investigated using DoE and response surface methodology to allow for simultaneous evaluation of multiple factors and their combined effects on drug-release behavior. This multivariate approach provides a more structured understanding of factor–response relationships compared with the preliminary OFAT-based screening.

Furthermore, the application of QbD in this study facilitates the establishment of an empirical design space, within which formulation variables can be adjusted while maintaining desired product performance. This represents a progression from exploratory experimentation toward a more systematic and quantitative optimization strategy. Importantly, the establishment of such a scientifically justified design space and enhanced process understanding is beneficial for regulatory submission and supports future product registration. Therefore, the objective of this study was to apply a QbD-based approach in combination with DOE to systematically evaluate and optimize critical formulation variables and to establish a design space for felodipine PPOP capsules with controlled drug release characteristics. Importantly, the primary objective of this work was methodological, specifically to demonstrate the application of a QbD-based framework for formulation development and optimization rather than to establish a clinically finalized product.

## 2. Materials and Methods

### *2.1. Materials*

Felodipine European Pharmacopoeia (EP) reference standard was purchased from Sigma-Aldrich Pte Ltd., Ascent, Singapore. Felodipine drug substances were obtained from Berlin Pharmaceutical Industry Co., Ltd., Bangkok, Thailand. Clear hard gelatin capsule (HGC) No. 2 was obtained from Lonza (Bangkok, Thailand) Co., Ltd., Bangkok, Thailand. Cellulose acetate with 10% polyethylene glycol (Corelease® CA 500F190004), polyethylene oxide (PEO, molar mass 200K, Polyox™ WSR N80 LEO NF; and PEO, molar mass 5000K, Polyox™ WSR Coagulant LEO NF) were obtained as samples from Colorcon Asia Pvt. Ltd., (Verna, India). Hereafter, the term molar mass, as recommended by IUPAC, is referred to as molecular weight (MW), as it is more commonly used in pharmaceutical and industrial contexts. FD&C Blue No. 2 Lake (indigo carmine) was purchased from Chanjao Longevity Co., Ltd., Bangkok, Thailand. Hypromellose (E5) was obtained as a sample from DKSH (Thailand) Ltd., Bangkok, Thailand. Polyethylene glycol (PEG) 4000 was obtained as a sample from Onimax Co., Ltd., Bangkok, Thailand. Sodium chloride (NaCl) was purchased from Honeywell(Charlotte, NC, USA), Detroit, USA. Spray-dried lactose (SuperTab® 11SD) was purchased from Maxway Co., Ltd., Bangkok, Thailand. Sodium lauryl sulfate (SLS) and formaldehyde (40% *v*/*v*) were purchased from Kemaus, Elago Enterprises Pty Ltd., Cherrybrook, Australia.

### *2.2. QbD Approach for the Development of Felodipine PPOP Capsules*

#### 2.2.1. Establishment of QTPPs

QTPP elements, including dosage form, dosage design, route of administration, dosage strength, pharmacokinetics, stability, drug product quality attributes (i.e., physical at-

tributes, identification, assay, uniformity of dosage unit, drug release, degradation products, microbial limits, heavy metals, and residual solvents), and container closure system, were established with their targets and justifications [29].

#### 2.2.2. Identification of CQAs

CQAs were established based on the QTPP, with a focus on safety and efficacy. Targets and justifications were also provided for each topic [29].

#### 2.2.3. Initial Risk Assessment of Felodipine Drug Substance and Formulation Variables

Initial risk assessments of the felodipine drug substance were classified into three categories: Low (broadly acceptable risk, no further investigation needed), Medium (risk is acceptable, further investigation may be needed to reduce the risk), and High (risk is unacceptable, further investigation is needed to reduce the risk). Additionally, initial risk assessments for formulation variables were also evaluated. Justifications were also provided for each topic [29].

### *2.3. Design of Experiments*

The Box–Behnken design was selected due to its efficiency in evaluating quadratic response surfaces while requiring fewer experimental runs compared to other designs, such as central composite design, while producing comparable results. This step aimed to evaluate the effects of formulation variables on drug release and to optimize the felodipine PPOP formulation. It was hypothesized that variations in polymer content and osmotic agent concentration would influence the drug release behavior of the system. Three factors and their respective levels, determined from the screening step and the initial risk assessment in QbD, were included into the design: the amount of Polyox WSR N80 (100, 120, and 140 mg), the amount of Polyox WSR Coagulant (25, 30, and 35 mg), and the amount of NaCl (20, 25, and 30 mg). Four responses were evaluated: lag time, release rate, $R^2$, and drug release at 24 h. The $R^2$ value was obtained from linear regression analysis of the drug release profile to evaluate the release behavior. The calculation was performed using the entire release profile, starting from the onset of drug release. Factors and levels, and response and goal used in the Box−Behnken design for optimizing felodipine PPOP capsules are shown in Table 1. All experimental runs were performed in triplicate. Additionally, the experimental condition at the center point of the design was performed in three independent runs, each conducted in triplicate. For statistical analysis, the response value for each design point was calculated as the mean of triplicate measurements. Consequently, the DoE models were developed using the mean response of each formulation run, whereas replicate measurements were used to estimate experimental variability and pure error at the center points.

The 3D response surfaces were generated using Design-Expert version 11 (Stat-Ease Inc., Minneapolis, MN, USA). Coded and actual equations were provided. The design space was defined based on the following criteria: lag time not exceeding 6 h, $R^2$ of at least 0.95, and drug release at 24 h of at least 80%. A minimum lag time was not specified, as preliminary evaluation indicated that the lag time was unlikely to decrease substantially within the studied formulation range. Therefore, the optimization focused on limiting excessive lag time rather than constraining lower values. Although release rate was included as a response variable to describe the drug release behavior, no specific goal was assigned during optimization. This is because the release rate is dependent on other responses, particularly lag time and drug release at 24 h. Therefore, the optimization criteria were defined based on lag time, drug release at 24 h, and $R^2$, which more appropriately represent the desired release performance. The verification step was performed by selecting the optimal condition within the design space to prepare the optimal formulation and

re-evaluate it. The experimental values were compared with the predicted values to assess model performance. Agreement between experimental and predicted values within the 95% confidence interval (CI) was used as the criterion for accuracy and reliability of the model.

**Table 1.** Factors and levels, and response and goal used in the Box−Behnken design for optimizing felodipine PPOP capsules.

| Factors | Levels | | |
|---|---|---|---|
| | **−1** | **0** | **+1** |
| Amount of Polyox WSR N80 ($X_1$, mg) | 100 | 120 | 140 |
| Amount of Polyox WSR Coagulant ($X_2$, mg) | 25 | 30 | 35 |
| Amount of NaCl ($X_3$, mg) | 20 | 25 | 30 |
| **Responses** | **Goals** | | |
| Lag time ($Y_1$) | ≤6 h | | |
| Release rate ($Y_2$) | None | | |
| $R^2$ ($Y_3$) | ≥0.95 * | | |
| Drug release at 24 h ($Y_4$) | ≥80% | | |

* Based on zero-order release kinetics.

### *2.4. Preparation of Felodipine PPOP Capsules*

The felodipine PPOP capsule formulation consisted of two layers: a pull layer and a push layer. The pull layer contained 10 mg of felodipine as the API, 100–140 mg of Polyox WSR N80 as the entraining agent, and spray-dried lactose as a diluent to adjust the total weight to 150 mg per capsule. The push layer comprised 20–30 mg of NaCl as the osmogen, 25–35 mg of Polyox WSR Coagulant as the swelling agent, 0.2 mg of FD&C Blue No. 2 Lake as the coloring agent for side identification, and spray-dried lactose as a diluent to adjust the total weight to 75 mg per capsule.

According to the preparation procedure, all ingredients were first passed through a 60-mesh sieve, except FD&C Blue No. 2 Lake, which was passed through an 80-mesh sieve. Each layer was blended separately using a sequential mixing approach to ensure uniform distribution of the drug and excipients, prevent aggregation, and achieve consistent mechanical and swelling properties necessary for predictable PPOP performance. For the pull layer, felodipine was mixed with spray-dried lactose for 3 min, followed by the addition of Polyox WSR N80 and further mixing for another 3 min. For the push layer, FD&C Blue No. 2 Lake was blended with NaCl and spray-dried lactose for 3 min, after which Polyox WSR Coagulant was added and mixed for an additional 3 min. Each PPOP capsule was filled into a crosslinked HGC No. 2 capsule body, prepared by exposing the capsules to formaldehyde vapor for 12 h and drying them. The residual formaldehyde in capsules crosslinked under the specified conditions, reported in a previous study, was 0.50 ± 0.02 mg per capsule [28], which is lower than typical dietary intake from food (1.5–14 mg/day) and within safe limits for human exposure [30]. Nevertheless, residual formaldehyde remains a potential regulatory consideration during future product development. Therefore, tighter limits for residual formaldehyde, optimization of crosslinking conditions, or evaluation of alternative capsule modification strategies may be considered to further minimize residual formaldehyde exposure while maintaining capsule performance. The filling process involved layering 75 mg of the push layer first, followed by 150 mg of the pull layer, and sealing with a similarly crosslinked capsule cap.

The filled capsules were subcoated by dipping both the body and cap once into a subcoating solution containing 3% *w*/*w* hypromellose E5 and 2% *w*/*w* PEG 4000, dissolved in a

1:1 (*v*/*v*) mixture of 95% ethanol and water, and then dried with a hair dryer. Subsequently, the capsules underwent ten sequential coatings in a semipermeable membrane solution composed of 8% *w*/*w* Corelease CA with 10% PEG, dissolved in a 9:1 (*v*/*v*) mixture of acetone and water, with drying after each dip. A 0.6 mm delivery orifice was produced at the top of the capsule cap using a Nipro® hypodermic needle (Nipro Corporation, Osaka, Japan). Finally, the coated capsules were dried in a hot-air oven at 40 °C for 4 h.

### *2.5. Drug Release Study*

The drug release study was modified from the USP monograph for felodipine extended-release tablets (Dissolution Test 3) [31]. Dissolution testing was conducted using Apparatus 2 (paddle method) at 50 ± 1 rpm (Dissolution Tester Model 72-600-400, Hanson Research Corp., (Chatsworth, CA, USA). The dissolution medium comprised 500 mL of 1% SLS aqueous solution, maintained at 37 ± 0.5 °C. Felodipine PPOP capsules ($n$ = 3) were sunk at the vessel bottom with a capsule sinker. Samples of 5 mL were collected hourly from 1 to 12 h and at 24 h, with an equal volume of fresh medium added to maintain sink conditions. The samples were filtered and analyzed by HPLC, and the percentage of drug released was calculated using the felodipine calibration curve to construct the release profile.

### *2.6. HPLC Analysis of Felodipine*

The analysis was carried out using an Agilent 1260 Infinity II HPLC system equipped with a diode array detector and an autosampler. Chromatographic separation was achieved on an Infinity Poroshell 120 EC-C18 column (4.6 × 100 mm, 4 µm) protected by an Infinity Poroshell 120 EC-C18 guard column (4.6 × 5 mm, 4 µm). The column temperature was maintained at 25 °C. An isocratic mobile phase of water and acetonitrile (35:65, *v*/*v*) was employed at a flow rate of 1 mL/min, with an injection volume of 10 µL. Detection was performed at 360 nm using the photodiode array detector, and the felodipine content was quantified based on a calibration curve constructed from standard felodipine solutions.

## 3. Results and Discussion

### *3.1. Quality by Design*

ICH Q8(R2) defines QbD as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" [25]. Although QbD is typically used in the development of production processes to ensure the quality of final products, this study applies QbD principles exclusively during the product development phase. Consequently, only certain elements of QbD were utilized—excluding critical process parameters (CPPs) and control strategies—thereby emphasizing the focus on formulation development rather than the manufacturing process. Therefore, the present work should be considered a partial implementation of QbD. Full implementation would additionally require identification of CPPs, establishment of a control strategy, process validation, lifecycle management, and formal confirmation of the proposed design space.

The QTPP, the first QbD element, is defined as "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product" [25]. The QTPP encompasses various elements, including dosage form, dosage design, route of administration, dosage strength, pharmacokinetics, stability, drug product quality attributes (e.g., physical attributes, identification, assay, uniformity of dosage unit, drug release, degradation products, microbial limits, heavy metals, residual solvents), and the container closure

system [29]. These components were defined with specific target specifications of the felodipine PPOP capsule and justifications, as shown in Table 2.

**Table 2.** QTPP for felodipine PPOP capsules.

| QTPP Elements | | Target | Justification |
|---|---|---|---|
| Dosage form | | Push–pull osmotic pump capsules | Alternative form of felodipine ER dosage form. Osmotic pump design needed to meet label claims. Currently, there is no osmotic pump capsule of felodipine available in the market. |
| Dosage design | | Extended-release provides coverage for 24 h | The extended-release formulation is designed to reduce dosing frequency and enhance patient compliance. |
| Route of administration | | Oral | Same route of administration as felodipine ER tablets. |
| Dosage strength | | 10 mg | In Thailand, three dosage strengths are available—2.5 mg, 5 mg, and 10 mg—administered once daily. This study selected the highest strength (10 mg) for use in the development phase. |
| Pharmacokinetics | | Half-Life: 10–16 h<br>Onset: 2–5 h<br>Duration of action: 24 h<br>Peak plasma time: 2–5 h<br>Treatment range: 4–6 nmol/L<br>Toxic range: >30 nmol/L<br>Excretion: urine (37%) and feces (10%)<br>Bioavailability: 20%<br>Protein bound: 99%<br>Volume of distribution: 10 L/kg<br>Metabolism: hepatic P450 enzyme CYP3A4<br>Metabolites: pyridine analog (inactive)<br>Clearance: 823 mL/min<br>Dialyzable: hemodialysis: no | Refer to the Medscape database [32]. Bioequivalence to commercial felodipine ER tablets. |
| Stability | | At least 2 years at room temperature. | Equivalent to or longer than marketed felodipine ER tablets. |
| Drug product quality attributes | Physical attributes | A two-layer powder mixture composed of a push layer (blue) and a pull layer (white) was filled into a clear, crosslinked HGC (size No. 2) and coated with cellulose acetate. | |
| | Identification | Meet the USP monograph requirements for felodipine ER tablets: The retention time and UV spectrum of the major peak of the sample solution correspond to that of the standard solution, as obtained in the Assay [31]. | |
| | Assay | 90.0–110.0% of the labeled amount [31]. | |
| | Uniformity of dosage unit | Meet the USP requirement: Uniformity of Dosage Units <905> Content Uniformity. | |

**Table 2.** *Cont.*

| QTPP Elements | | Target | Justification |
|---|---|---|---|
| Drug product quality attributes | Drug release | According to the USP monograph Dissolution <711> Test 1 for felodipine ER tablets, the dissolution requirements are 10–30% at 2 h, 42–68% at 6 h, and NLT 75% at 10 h [31] or dissolution similar to commercial felodipine ER tablets (similarity factor, $f_2$ > 70%). However, the formulation under development is intended for the delivery of 10 mg of felodipine over 24 h, for which no official release requirement is currently available. Therefore, a drug release profile approaching 100% within 24 h, with a short lag time, is targeted. | |
| | Degradation products | Meet the USP monograph requirements for felodipine ER tablets: felodipine related compound A NMT 2.0%, any unspecified impurity NMT 0.2%, and total impurities NMT 3.0% [31]. | |
| | Microbial limits | Meet the USP requirements: Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests <61>, and Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms <62>. | |
| | Heavy metals | Meet the USP requirements: Elemental Impurities—Limits <232>. | |
| | Residual solvents | Meet the USP requirements: Residual Solvents <467>. | |
| Container closure system | | Store in tightly closed containers, protected from light, such as in Alu-Alu packaging. | It is necessary to ensure the target shelf-life and preserve tablet integrity during shipping. While ER tablets are packaged in bottles, osmotic pump capsules, which contain a delivery orifice, require individual packaging to maintain their integrity. |

The CQA, the second QbD element, is defined as "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality" [25]. CQAs were identified based on the QTPP, with a focus on safety and efficacy considerations [29]. Specific targets and justifications are shown in Table 3. The CQAs of this felodipine PPOP capsule were identification, assay, uniformity of dosage unit (content uniformity), drug release, degradation products, microbial limits, heavy metals, and residual solvents. In the case of identification, it was evaluated since the felodipine drug substance and finished goods were obtained. Identification was skipped in the initial risk assessment due to the same drug substance was used throughout the study. Additionally, it could be easily confirmed by comparing the retention time of the felodipine standard from the HPLC analysis and its corresponding UV spectrum. Although microbial limits, heavy metals, and residual solvents were not specified in the monographs, they still need to be tested in the finished product. However, as this work was conducted at the R&D stage and not at scale-up or manufacturing scale, these parameters were not investigated at this stage. Therefore, the initial risk assessment focused on the following CQAs: assay, uniformity of dosage unit (content uniformity), drug release, and degradation products, which are the most critical for guiding early-stage formulation development.

**Table 3.** CQAs for felodipine PPOP capsules.

| Quality Attributes of the Product | | Target | Is This a CQA? | Justification |
|---|---|---|---|---|
| Physical attributes | Appearance | A two-layer powder mixture is filled in a clear, crosslinked HGC (size No. 2) and coated with cellulose acetate. | No | Appearance do not affect safety or efficacy, but they can influence patient acceptability. This product is of a small size. |
| | Size | HGC (size No. 2) | No | Size does not affect safety or efficacy, but it can influence a patient's ability to swallow. This product was small in size, making it easy to swallow. |
| Identification | | Conform to the USP monograph requirements of felodipine ER tablets | Yes | Identification is critical for safety and efficacy. Identification must be monitored upon receipt of raw materials to ensure that the entire process uses the correct drug substance. |
| Assay | | 90.0–110.0% of felodipine | Yes | The assay is critical for safety and efficacy. |
| Uniformity of dosage unit (content uniformity) | | Conform to Uniformity of Dosage Units <905> Content Uniformity | Yes | Content uniformity is critical for both safety and efficacy, particularly for low-dose drug products. |
| Drug release | | Felodipine dissolution at 24 h approached 100%, with a short lag time. | Yes | Drug release affects bioavailability; therefore, it impacts safety and efficacy. |
| Degradation products | | Conform to the USP monograph requirements for felodipine ER tablets: felodipine related compound A NMT 2.0%, any unspecified impurity NMT 0.2%, and total impurities NMT 3.0% | Yes | Degradation products and impurities affect safety and efficacy. |
| Microbial limits | | Conform to the USP requirements: Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use <1111> | Yes | Microbial contamination is critical for safety. |
| Heavy metals | | Conform to USP requirements: Elemental Impurities—Limits <232>. | Yes | Heavy metals are critical for safety. |
| Residual solvents | | Conform to USP requirements: Residual Solvents <467>. | Yes | Residual solvents are critical for safety. |

During the R&D process, the focus was on identifying an optimal formulation. The initial risk assessment of felodipine drug substance attributes and formulation variables was focused on four CQAs: assay, uniformity of dosage unit (content uniformity), drug release, and degradation products. The risk assessment of the drug substance attributes was carried out to evaluate how each attribute could potentially affect the CQAs of the drug product [29,33]. The initial risk assessment of felodipine drug substance attributes, along with formulation variables, with the corresponding justifications, is presented in Tables 4–7, respectively. The felodipine drug substance attributes were excluded from the following steps because altering their characteristics was challenging. Consequently, only formulation variables were examined further.

**Table 4.** Initial risk assessment of felodipine drug substance attributes.

| Drug Product CQAs | Felodipine Drug Substance Attributes | | | | | | |
|---|---|---|---|---|---|---|---|
| | Particle Size Distribution | Flow Properties | Hygroscopicity | Moisture Content | Solubility | Residual Solvents | Chemical Stability |
| Assay | Medium | Medium | Low | Low | Low | Low | High |
| Uniformity of dosage units (content uniformity) | High | High | Low | Low | Low | Low | High |
| Drug release | High | Low | Low | Low | High | Low | Low |
| Degradation products | Low | Low | Low | Low | Low | Low | High |

**Table 5.** Justification for the initial risk assessment of felodipine drug substance attributes.

| Variables | Drug Product CQAs | Justification |
|---|---|---|
| Particle size distribution | Assay | The particle size and particle size distribution of the drug substance significantly influence the flowability of the powder mixture during the manufacturing process. Poor flowability is often associated with smaller particle sizes and a broad particle size distribution, which in extreme cases may lead to assay failure. The risk is medium. |
| | Uniformity of dosage units (content uniformity) | The particle size and particle size distribution directly affect flowability. Poor flowability is often associated with smaller particle sizes and a broad particle size distribution, which may lead to content uniformity failure. It is a microdose product. The risk is high. |
| | Drug release | Particle size and particle size distribution directly impact drug release. A smaller particle size results in a higher surface area for dissolution. Moreover, a narrow particle size distribution promotes a more uniform drug release rate. The risk is high. |
| | Degradation products | Particle size and particle size distribution are not related to degradation product formation. The risk is low. |
| Flow properties | Assay | Felodipine is a low-dose drug; therefore, it does not significantly affect the flow properties of the powder mixture. However, in extreme cases, it may impact the assay. The risk is medium. |
| | Uniformity of dosage units (content uniformity) | Flow properties directly affect content uniformity. Poor flow properties can result in content uniformity failures. The risk is high. |
| | Drug release | The flow properties of the drug substance are not related to drug release. Instead, drug solubility is the primary factor influencing drug release. The risk is low. |
| | Degradation products | Flow properties are not related to degradation product formation. The risk is low. |

**Table 5.** *Cont.*

| Variables | Drug Product CQAs | Justification |
|---|---|---|
| Hygroscopicity | Assay | Felodipine is not hygroscopic. The risk is low. |
| | Uniformity of dosage units (content uniformity) | |
| | Drug release | |
| | Degradation products | |
| Moisture content | Assay | According to the certificate of analysis (COA), the felodipine drug substance used in this study exhibited a value of 0.18%, while analysis conducted in the laboratory yielded a value of 0.11% [28], both of which are considered very low. Therefore, it does not impact the assay, content uniformity, drug release, or degradation product formation. The risk is low. |
| | Uniformity of dosage units (content uniformity) | |
| | Drug release | |
| | Degradation products | |
| Solubility | Assay | Solubility does not affect the assay, as the assay procedure typically uses solvents and methods that readily dissolve the drug substance from the drug product. The risk is low. |
| | Uniformity of dosage units (content uniformity) | Solubility does not affect the content uniformity, as the content uniformity determination procedure typically uses solvents and methods that readily dissolve the drug substance from the drug product. The risk is low. |
| | Drug release | Felodipine is a BCS class II drug, i.e., low solubility and high permeability. Solubility directly affects the release of the drug substance. According to the COA, felodipine is freely soluble in acetone and in methanol; very slightly soluble in heptane, and insoluble in water. Felodipine is a poorly water-soluble drug. Low solubility can result in drug release failure. The risk is high. |
| | Degradation products | Solubility is not related to degradation product formation. The risk is low. |
| Residual solvents | Assay | According to the COA, residual solvent analysis by GC detected ethanol at 356 ppm, with isopropanol and methyl tert-butyl ether not detected. The residual solvent levels are low and, therefore, do not impact the assay, content uniformity, drug release, or degradation product formation. The risk is low. |
| | Uniformity of dosage units (content uniformity) | |
| | Drug release | |
| | Degradation products | |
| Chemical stability | Assay | Chemical stability directly affects both the assay and content uniformity. Low chemical stability, characterized by high levels of degradation products or impurities, can result in assay and content uniformity failures. The risk is high. |
| | Uniformity of dosage units (content uniformity) | |
| | Drug release | Drug solubility is the primary factor influencing drug release. Drug release is not related to chemical stability. The risk is low. |
| | Degradation products | In terms of impurities, according to the COA, the residue on ignition is 0.03%; ethyl 3-aminocrotonate is not detected; felodipine-related compound A is 0.03%; methyl benzylidene acetoacetate is not detected; the sum of dimethyl felodipine and diethyl felodipine is 0.07%; any unspecified impurity is 0.02%; and the total impurity is 0.12%.<br>Felodipine is a photosensitive drug. Two photoproducts are formed after UV irradiation: a pyridine derivative through oxidation and a felodipine dimer through dimerization. The powder form shows a higher amount of the pyridine derivative [34]. Under stress conditions, felodipine degraded by 15.6% through oxidation, 10.4% through thermolysis, 8.1% through basic hydrolysis, and 1.2% through acid hydrolysis [35]. Another study found that, over a longer test period, felodipine degraded by 100% through oxidation, 29.66% through basic hydrolysis, 10.19% through acid hydrolysis, 4.42% under sunlight, and 0.35–1.08% through thermolysis [36]. Additionally, a study identified two degradation products resulting from the basic degradation of felodipine [37].<br>Chemical stability directly affects degradation product formation. The risk is high. |

**Table 6.** Initial risk assessment of formulation variables.

| Drug Product CQAs | Formulation Variables | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Polyox WSR N80 | Spray-Dried Lactose | Polyox WSR Coagulant | NaCl | FD&C Blue No. 2 Lake | HPMC E5 | PEG 4000 | Corelease CA |
| Assay | Low | Low | Low | Low | Low | Low | Low | Low |
| Uniformity of dosage units (content uniformity) | Medium | Medium | Low | Low | Low | Low | Low | Low |
| Drug release | High | Low | High | High | Low | Low | Low | High |
| Degradation products | Low | Low | Low | Low | Low | Low | Low | Low |

**Table 7.** Justification for the initial risk assessment of the formulation variables.

| Variables | Drug Product CQAs | Justification |
|---|---|---|
| Polyox WSR N80 | Assay | Polyox WSR N80 does not affect the assay. The risk is low. |
| | Uniformity of dosage units (content uniformity) | Polyox WSR N80 is mixed into the pull layer, which contains the drug substance. In extreme cases, variations in particle size distribution within this layer can lead to segregation of the powder mixture, potentially affecting content uniformity. The risk is medium. |
| | Drug release | Polyox WSR N80 is an entraining agent that promotes homogeneous drug delivery from the osmotic pump. It directly affects drug release. The risk is high. |
| | Degradation products | No reports indicate that Polyox WSR N80 promotes the degradation of felodipine. Furthermore, PEO is used as an ingredient in the commercial formulation of nifedipine ER tablets [38], and since nifedipine belongs to the same class as felodipine, it can be considered compatible with felodipine. The risk is low. |
| Spray-dried lactose | Assay | Spray-dried lactose does not affect the assay. The risk is low. |
| | Uniformity of dosage units (content uniformity) | Spray-dried lactose is mixed into the pull layer, which contains the drug substance. In extreme cases, variations in particle size distribution within this layer can lead to segregation of the powder mixture, potentially affecting content uniformity. The risk is medium. |
| | Drug release | Spray-dried lactose is inherently a highly water-soluble ingredient. It does not affect drug release. The risk is low. |
| | Degradation products | Lactose is used as an ingredient in the commercial formulation of felodipine ER tablets [5]; therefore, it is considered compatible with felodipine. The risk is low. |
| Polyox WSR Coagulant | Assay | Polyox WSR Coagulant is not related to assay or content uniformity, as it is located in the push layer, which does not contain the drug substance. The risk is low. |
| | Uniformity of dosage units (content uniformity) | |
| | Drug release | Polyox WSR Coagulant acts as a swelling agent, pushing the drug from the internal compartment of the osmotic pump to the outside. It directly affects drug release. The risk is high. |
| | Degradation products | No reports indicate that Polyox WSR Coagulant promotes the degradation of felodipine. Furthermore, PEO is used as an ingredient in the commercial formulation of nifedipine ER tablets [38], and since nifedipine belongs to the same class as felodipine, it can be considered compatible with felodipine. The risk is low. |

**Table 7.** *Cont.*

| Variables | Drug Product CQAs | Justification |
|---|---|---|
| NaCl | Assay | NaCl is not related to assay or content uniformity, as it is located in the push layer, which does not contain the drug substance. The risk is low. |
| | Uniformity of dosage units (content uniformity) | |
| | Drug release | NaCl acts as an osmogen, generating osmotic pressure to facilitate the delivery of the drug from the internal compartment of the osmotic pump. It directly affects drug release. The risk is high. |
| | Degradation products | No reports indicate that NaCl promotes the degradation of felodipine. Furthermore, NaCl is used as an ingredient in the commercial formulation of nifedipine ER tablets [38], and since nifedipine belongs to the same class as felodipine, it can be considered compatible with felodipine. The risk is low. |
| FD&C Blue No. 2 Lake | Assay | FD&C Blue No. 2 Lake is added in a small amount to differentiate between the push and pull layers. It does not affect assay, content uniformity, or drug release. The risk is low. |
| | Uniformity of dosage units (content uniformity) | |
| | Drug release | |
| | Degradation products | FD&C Blue No. 2 Lake is used as an ingredient in the commercial formulation of felodipine ER tablets [5]; therefore, it is considered compatible with felodipine. The risk is low. |
| HPMC E5 | Assay | HPMC E5, a low viscosity grade, is used as a subcoating polymer to promote better adhesion of corelease CA to the crosslinked HGC shell. It does not affect assay, content uniformity, or drug release. Furthermore, it does not come into contact with the drug substance, nor does it interact to produce degradation products. The risk is low. |
| | Uniformity of dosage units (content uniformity) | |
| | Drug release | |
| | Degradation products | |
| PEG 4000 | Assay | PEG 4000 is added in small amounts as a plasticizer in the subcoating layer and does not come into direct contact with felodipine. It does not affect the assay, content uniformity, or drug release. The risk is low. |
| | Uniformity of dosage units (content uniformity) | |
| | Drug release | |
| | Degradation products | PEG is used as an ingredient in the commercial formulation of felodipine ER tablets [5] and is therefore considered compatible with felodipine. PEG 4000 is added in small amounts as a plasticizer in the subcoating layer and does not come into direct contact with felodipine. The risk is low. |
| Corelease CA | Assay | Corelease CA is not related to assay or content uniformity, as it is an outer layer located outside the crosslinked HGC assembly. The risk is low. |
| | Uniformity of dosage units (content uniformity) | |
| | Drug release | Corelease CA is the outer layer that controls water imbibition into the internal osmotic pump system, thereby directly affecting drug release. The risk is high. |
| | Degradation products | Corelease CA, as the outer layer, does not come into contact with the internal osmotic pump system that contains the drug substance; therefore, it does not affect the formation of degradation products. The risk is low. |

### *3.2. Modeling of the Release Characteristics of Felodipine PPOP Capsule*

The amounts of Polyox WSR N80 (100, 120, and 140 mg), Polyox WSR Coagulant (25, 30, and 35 mg), and NaCl (20, 25, and 30 mg) were varied according to the Box–Behnken experimental design. The coded and actual equations derived from the modeling are presented below. Coded equations were used to evaluate the degree of each factor's effect on the response by transforming all factors into the same range (−1 to +1). Conversely, actual equations were employed to predict responses using the actual values of each factor [39]. However, ANOVA results indicated that the fitted models were not statistically significant (Supplementary Material, Table S1). Therefore, the regression equations were not considered suitable for predictive purposes and were interpreted only to provide a qualitative

indication of factor–response relationships. Consequently, the associated response surface plots and design space should also be interpreted with caution. The identified design space is intended to provide preliminary guidance for formulation optimization and factor understanding rather than a statistically confirmed design space in the strict ICH Q8 sense. Based on the observed trends, the amount of Polyox WSR N80 appeared to have the greatest influence on each response, while the amount of Polyox WSR Coagulant had a greater effect on lag time, $R^2$, and release at 24 h than the amount of NaCl, except for the release rate.

Code equations:

$$Y_1 = 5.82 - 1.30X_1 + 0.19X_2 + 0.02X_3$$

$$Y_2 = 4.08 - 0.35X_1 - 0.11X_2 + 0.13X_3 + 0.04X_1X_2 - 0.08X_1X_3 - 0.75X_2X_3 - 0.52{X_1}^2 + 0.57{X_2}^2 - 0.35{X_3}^2$$

$$Y_3 = 0.98 - 0.0063X_1 + 0.0059X_2 - 0.003X_3$$

$$Y_4 = 72.70 - 2.36X_1 - 2.31X_2 + 1.37X_3 + 1.84X_1X_2 - 1.30X_1X_3 - 13.59X_2X_3 - 10.72{X_1}^2 + 8.88{X_2}^2 - 5.05{X_3}^2$$

Actual equations:

$$Y_1 = 12.40 - 0.06X_1 + 0.04X_2 + 0.004X_3$$

$$Y_2 = -24.49 + 0.31X_1 - 0.69X_2 + 1.73X_3 + 0.0004X_1X_2 - 0.0008X_1X_3 - 0.03X_2X_3 - 0.001{X_1}^2 + 0.02{X_2}^2 - 0.01{X_3}^2$$

$$Y_3 = 0.99 - 0.0003X_1 + 0.001X_2 - 0.0006X_3$$

$$Y_4 = -479.14 + 6.09X_1 - 10.39X_2 + 28.24X_3 + 0.02X_1X_2 - 0.01X_1X_3 - 0.54X_2X_3 - 0.03{X_1}^2 + 0.36{X_2}^2 - 0.20{X_3}^2$$

where $X_1$, $X_2$, and $X_3$ represent the amounts of Polyox WSR N80, Polyox WSR Coagulant, and NaCl, respectively, in coded or actual values, and $Y_1$, $Y_2$, $Y_3$, and $Y_4$ correspond to lag time, release rate, $R^2$, and release at 24 h, respectively.

The effects of formulation variables on the responses were further interpreted based on the coefficients of the fitted models. For lag time ($Y_1$), the model suggests that increasing polymer content may reduce lag time, although this effect was not statistically significant, while $X_2$ and $X_3$ showed minimal influence. For release rate ($Y_2$), both linear and interaction terms were observed, suggesting a more complex relationship among variables. Notably, the negative interaction between $X_2$ and $X_3$ indicates a combined effect that reduces the release rate. Quadratic terms further suggest non-linear behavior within the studied range. It should be noted that, due to the lack of statistical significance of the regression models, these observations represent qualitative trends and should not be interpreted as statistically confirmed effects.

For $R^2$ ($Y_3$), all coefficients were relatively small, indicating that the response was not highly sensitive to variations in formulation variables, supporting the robustness of the system. In contrast, drug release at 24 h ($Y_4$) was strongly influenced by the formulation variables, particularly the negative interaction between $X_2$ and $X_3$ and the significant quadratic terms, indicating that both interaction and curvature effects play important roles in controlling drug release. Overall, these results demonstrate that while certain responses are sensitive to formulation changes, others remain relatively stable, suggesting limited sensitivity of the responses to factor variation within the studied design space.

The 3D response surface plots are illustrated in Figure 1. The 3D response surfaces were used to visualize trends, suggesting that increasing Polyox WSR N80 may shorten the lag time and decreased $R^2$ while affecting the release rate and release at 24 h.

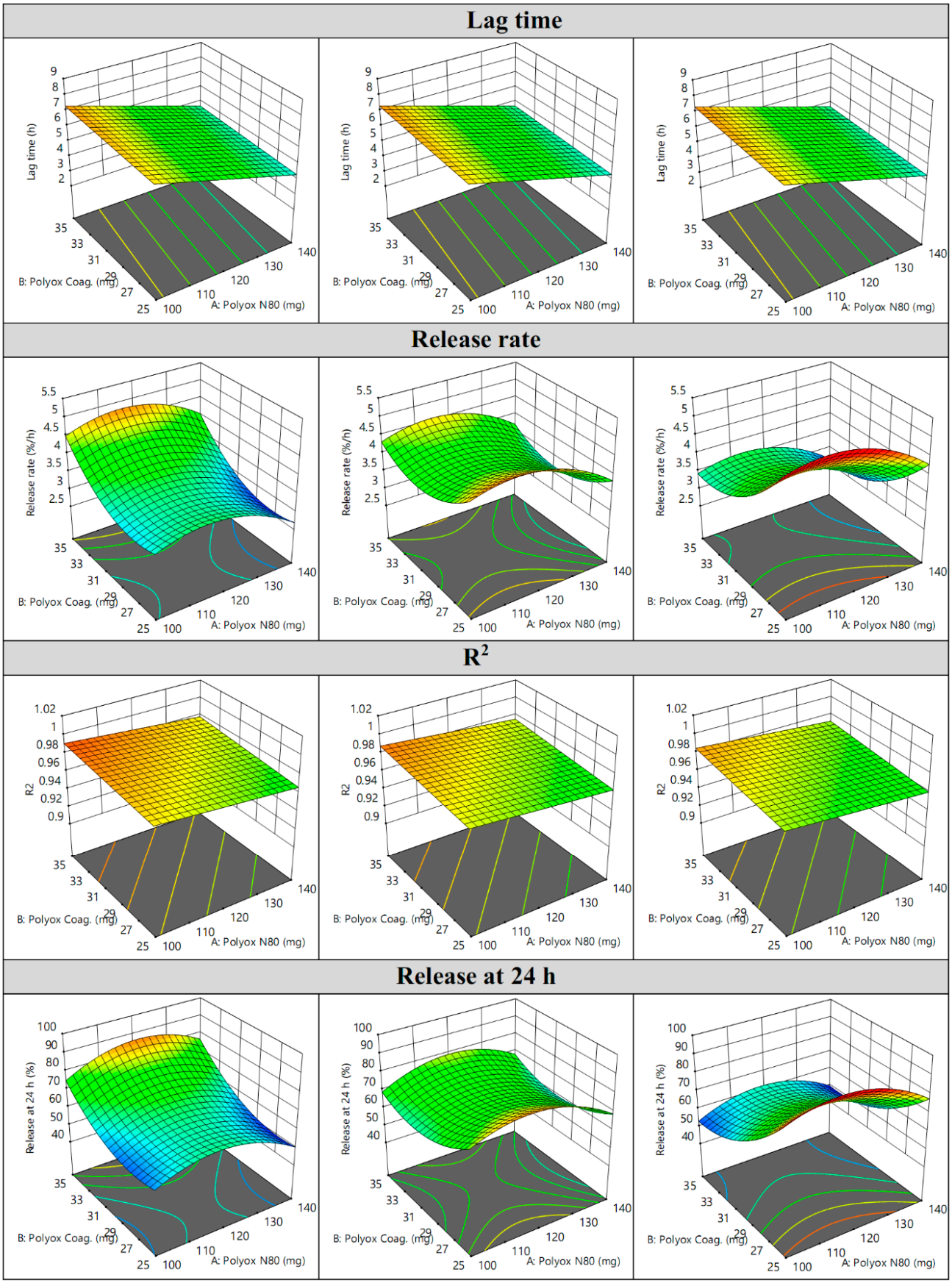


**Figure 1.** Response surfaces of lag time, release rate, $R^2$, and release at 24 h when the amount of NaCl was 20 mg (**left**), 25 mg (**middle**), and 30 mg (**right**).

In general, increasing the concentration of PEO in the pull layer enhances the viscosity of drug suspensions, thereby prolonging drug release. However, when PEO MW 100K was used at 200, 250, and 300 mg, the drug release profile remained comparable, with only a slight reduction in topiramate release observed at higher concentrations [40]. A similar trend was noted with PEO MW 200K, where varying the concentration produced comparable rivaroxaban release in terms of $f_2$, although a minor decrease in release was observed as the polymer amount increased [41]. These findings are consistent with several reports. For instance, increasing PEO MW 100K from 170 to 230 mg in ondansetron HCl PPOP tablets [42], from 150 mg to 250 mg in fenofibrate PPOP tablets [43], and from 60 mg to 120 mg in felodipine PPOP tablets [22] resulted in retarded drug release. By contrast, increasing PEO MW 200K (Polyox WSR N80) from 90 to 130 and 170 mg enhanced the release of diltiazem HCl, propranolol HCl, and paracetamol. In this case, the lowest drug release was obtained at 90 mg, while no significant difference was observed between 130 and 170 mg [44]. Taken together, these findings emphasize the importance of optimizing the Polyox concentration to identify the most appropriate range for achieving the desired drug release profile, which is consistent with the results of the present study.

In the case of Polyox WSR Coagulant (PEO MW 5000K), a swelling agent that facilitates drug release, its increase resulted in a slight increase in both lag time and $R^2$, while its effect on the release rate and drug release at 24 h varied depending on the NaCl level. At a low NaCl concentration, increasing the amount of Polyox WSR Coagulant led to a higher release rate and 24 h release values. At a medium NaCl concentration, these values initially decreased and then increased, whereas at a high NaCl concentration, increasing the amount of Polyox WSR Coagulant caused a reduction in both parameters.

Generally, increasing the amount of PEO led to a retardation of drug release, as observed for PEO MW 5000K [41]. These findings were consistent with other studies, in which increasing the amount of PEO MW 7000K from 100 mg to 160 mg in the push layer significantly slowed the release of topiramate [40]. Conversely, other studies reported the opposite effect. For instance, increasing PEO MW 7000K from 85 mg to 115 mg enhanced the release of ondansetron HCl [42]. Similarly, increasing PEO MW 6000K from 150 mg to 250 mg improved the release of fenofibrate [43], and increasing PEO MW 6000K from 30 mg to 90 mg also enhanced felodipine release [22]. However, the present study observed that Polyox WSR Coagulant could both enhance and retard drug release depending on the amount of NaCl in push layer, and it also promoted a better $R^2$ value.

In the case of NaCl, an osmotic agent, it appeared not to have an effect on lag time, caused a slight decrease in $R^2$, and increased both the release rate and drug release at 24 h. The highest drug release was observed at the highest NaCl concentration.

Generally, the incorporation of NaCl in the push layer has been reported to significantly affect drug release. For example, increasing the NaCl content in the push layer of topiramate PPOP tablets from 20 mg to 35 mg and 50 mg markedly enhanced drug release and shortened lag time [40]. Similarly, varying the NaCl amount in the push layer of nimotidine PPOP tablets from 10 mg to 30 mg resulted in increased drug release [45]. In contrast, a study comparing different osmogens—glucose, NaCl, and lactose—found that glucose produced the highest drug release from fenofibrate PPOP tablets, followed by NaCl and lactose, with both NaCl and lactose exhibiting zero-order release kinetics [43]. Conversely, in felodipine PPOP tablets, NaCl promoted the highest release, followed by lactose and glucose [22]. Moreover, the distribution of NaCl within the tablet has been shown to affect release behavior. When NaCl was incorporated into either the pull layer alone or both the push and pull layers, glipizide release from PPOP tablets remained similar; however, inclusion of NaCl only in the push layer led to reduced release [46]. These findings

collectively highlight that the influence of NaCl on drug release is formulation-dependent, consistent with the present study.

### *3.3. Design Space and Optimal Formulation*

The 3D response surfaces were used to generate the design space based on the predefined criteria of lag time not exceeding 6 h, $R^2$ of at least 0.95, and drug release at 24 h of at least 80%—are shown in Figure 2. Evaluation of the Box–Behnken experimental runs showed that several individual formulations achieved or exceeded 80% release at 24 h. However, these conditions did not simultaneously satisfy all other performance requirements, particularly with respect to lag time control and zero-order release linearity, indicating inherent trade-offs among the studied responses. The design space was therefore defined as the region in which the predefined criteria were predicted to be satisfied simultaneously. However, experimental verification of the selected formulation showed that the observed drug release at 24 h remained below the predefined target of ≥80%. Therefore, although the selected formulation represented the most favorable balance among the investigated responses, the predefined drug release target was not fully achieved and additional optimization is required. Given that the regression models were not statistically significant, this design space should be interpreted as an empirical region derived from experimental observations rather than a statistically validated predictive design space. The selected optimal condition represents a formulation within this empirically defined region that provided balanced overall performance, although the corresponding 24 h release was slightly below 80%.

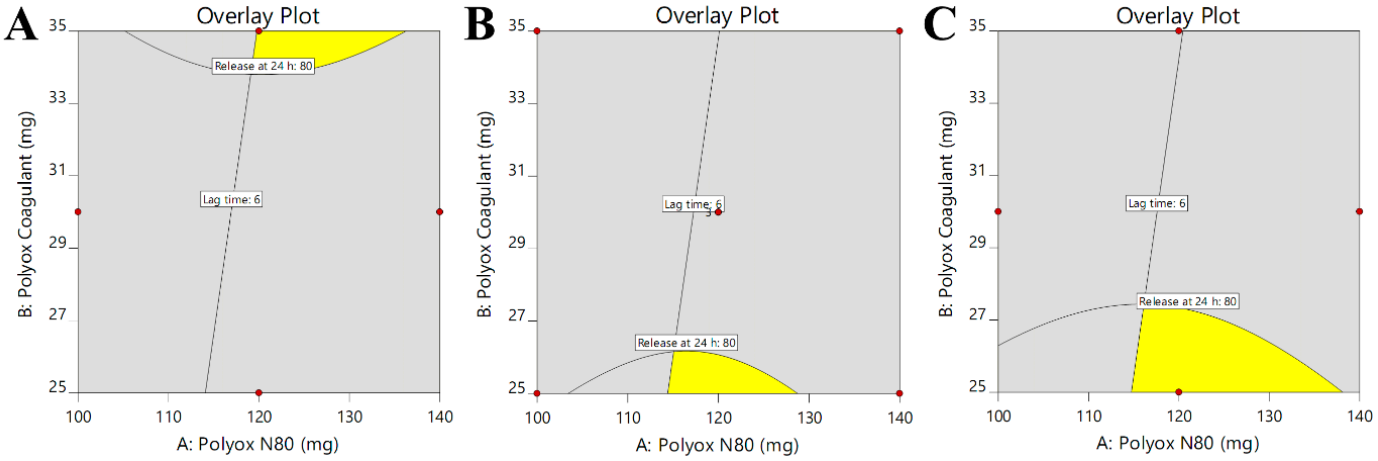


**Figure 2.** Design spaces defined based on the following criteria: lag time not exceeding 6 h, $R^2$ of at least 0.95, and drug release at 24 h of at least 80%, when the amount of NaCl was (**A**) 20 mg, (**B**) 25 mg, and (**C**) 30 mg.

Among the studied factors, a higher NaCl level (Figure 2C) generated the broadest design space compared with low or medium NaCl amounts, indicating a more favorable balance between osmotic driving force and release control. The optimal formulation located within this region was selected for verification to assess the predictive reliability of the model. This formulation comprised 125 mg Polyox WSR N80, 26 mg Polyox WSR Coagulant, and 30 mg NaCl. While the observed lag time of approximately 6 h may be longer than ideal for early-morning blood pressure control in antihypertensive therapy [47], this study primarily focused on establishing a QbD-based framework for PPOP formulation development, and lag time could be adjusted in future studies by modifying formulation or device parameters.

To ensure reproducibility between batches and uniformity within individual units, raw materials were accurately weighed and blended, and pull and push layers were filled using techniques that provided uniform volume per unit. Although coating was applied by dip method and orifices were created manually with a hypodermic needle, these procedures were standardized across batches. Verification showed that drug release profiles of the optimal formulations prepared for three lots (Figure 3) and the verification data (Table 8) were generally consistent with predicted values, with most data falling within the 95% CI. Despite some variability, the DoE results showed that the fitted model was not statistically significant (Supplementary Material, Table S1), indicating that the regression model lacks statistical validity for predictive purposes within the studied ranges. This does not necessarily imply formulation robustness but rather reflects limited model sensitivity and predictive precision. The observed drug release at 24 h was substantially lower than the corresponding model-predicted value, resulting in residual errors of approximately −12% to −19%. This discrepancy highlights the limited predictive capability of the fitted model for this response and is consistent with the lack of statistical significance observed in the ANOVA results. Therefore, the response surface models should be interpreted primarily as qualitative tools for understanding factor–response relationships rather than as reliable quantitative predictors of formulation performance. Therefore, the identified design space should be interpreted as an empirical operating region derived from experimental observations rather than a statistically validated predictive design space. Additional statistical metrics, such as robustness indices, could provide further insight into model reliability; however, given the non-significant ANOVA results, such analyses were not considered appropriate in this study and remain a potential direction for future work. It should be noted that the investigated factor levels were intentionally confined to relatively narrow ranges to preserve the structural integrity and functional reliability of the PPOP capsule. Although this restricted experimental domain may have limited the statistical detectability of factor effects, preliminary observations indicated that extending factor levels beyond the studied ranges could adversely affect drug release performance and increase the risk of capsule rupture or mechanical instability [28]. Therefore, the selected factor ranges were considered appropriate to ensure system robustness and manufacturability while enabling systematic evaluation within the QbD framework. This suggests that the system was relatively robust under the experimental conditions. The experimental verification confirmed that the optimized formulation exhibited consistent lag time and zero-order release behavior across batches. Although the verified 24 h drug release did not reach the predefined $\geq$80% target, it remained within the range observed in the experimental design. However, this indicates that the optimization process did not fully achieve the predefined target, likely due to trade-offs among multiple response criteria. Further investigation and refinement of formulation and/or process parameters may be required to achieve the desired performance. The discrepancy between the maximum observed release in individual experimental runs and the optimized condition reflects the trade-off inherent in multi-response optimization, where maximizing total release alone would compromise lag time or release kinetics.

Future studies may further refine lag time and release extent through modification of membrane characteristics or device parameters to enhance clinical applicability. Specifically, additional formulation and process parameters, including coating thickness, orifice size, and capsule crosslinking conditions, could be explored to further optimize release performance and better align with clinical requirements. To further enhance drug release beyond 80% at 24 h, additional formulation strategies may also be considered. In particular, the development of a more soluble felodipine system using solid dispersion techniques is proposed to improve the aqueous solubility of the drug substance. Such an approach

would enable the preparation of an elementary osmotic pump system, which is structurally simpler and delivers the drug in solution form rather than as a suspension, as in the PPOP system. This strategy is expected to reduce variability in drug release, particularly for poorly water-soluble drugs.

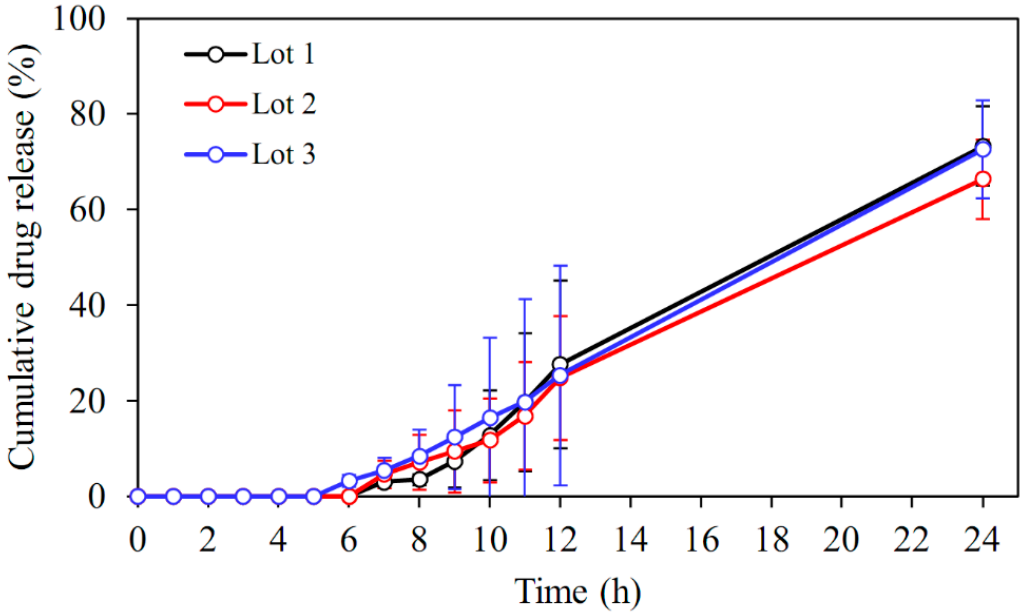


**Figure 3.** Drug release profiles of felodipine PPOP capsules formulated using the optimal formulation from different lots.

**Table 8.** Verification data, including predicted values, experimental values from different lots, and the 95% CI.

| Response | Predicted Value | Lot 1 | | Lot 2 | | Lot 3 | | 95% CI | |
|---|---|---|---|---|---|---|---|---|---|
| | | Experimental Value | Residual | Experimental Value | Residual | Experimental Value | Residual | Lower | Upper |
| Lag time (h) | 5.37 | 6.66 | 1.29 | 6.13 | 0.76 | 5.54 | 0.17 | 3.98 | 6.76 |
| Release rate (%/h) | 4.76 | 4.28 | −0.48 | 3.71 | −1.05 | 3.88 | −0.88 | 3.37 | 6.15 |
| $R^2$ | 0.9665 | 0.9887 | 0.0222 | 0.9932 | 0.0267 | 0.9967 | 0.0302 | 0.9340 | 0.9990 |
| Drug release at 24 h (%) | 85.48 | 73.30 | −12.18 | 66.38 | −19.10 | 72.64 | −12.84 | 63.36 | 107.60 |

Although a lag time of approximately 6 h was considered acceptable within the predefined optimization criteria, such a lag time may not be ideal for all clinical situations, particularly when antihypertensive activity is desired during the early morning period. Therefore, the present target was selected primarily from a formulation-development perspective to evaluate the performance of the PPOP system within the studied formulation range. Additional optimization will be required to further refine the lag time and release profile according to specific clinical objectives.

## 4. Conclusions

This study successfully established the QbD-based framework for the systematic development of PPOP capsules. The Box–Behnken experimental design enabled evaluation of the effects of Polyox WSR N80, Polyox WSR Coagulant, and NaCl levels on lag time, release

kinetics, and cumulative drug release at 24 h. Response surface analysis facilitated construction of a preliminary design space based on the predefined criteria of lag time ($\leq$6 h), release based on zero-order kinetic ($R^2 \geq 0.95$), and a target of $\geq$80% drug release at 24 h. However, because the fitted regression models demonstrated limited statistical significance and predictive capability, the proposed design space should be regarded as preliminary and requires further confirmation through additional experimentation. Although certain experimental formulations achieved or exceeded 80% release, simultaneous satisfaction of all predefined criteria revealed intrinsic trade-offs among responses. The selected formulation, identified within the empirically defined operating region, demonstrated controlled lag time and near zero-order release behavior during verification. However, experimental verification showed that the predefined QTPP/CQA target of $\geq$80% drug release at 24 h was not achieved. Therefore, the selected formulation should not be considered as satisfying all predefined optimization criteria, and further optimization is required to achieve the desired release performance. This outcome underscores the importance of defining an optimal operating region based on balanced multi-parameter performance rather than single-response maximization. Although regression models were generated, they were not statistically significant and were therefore used only for qualitative interpretation of trends, while conclusions were primarily based on experimental observations and verification results. Further optimization may be required to fully achieve the predefined drug release target, particularly through expansion of formulation or process parameter ranges. Therefore, the present work should be regarded as a formulation-development and QbD feasibility study intended to demonstrate systematic application of the QbD framework rather than to establish a clinically optimized final product. Overall, the findings provide mechanistic insight into factor–response interactions in pulsatile osmotic systems and confirm the utility of the QbD-driven approach for rational formulation optimization.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/scipharm94030052/s1, Table S1: ANOVA for responses of felodipine PPOP capsule (lag time, release rate, $R^2$, and drug release at 24 h).

**Author Contributions:** Conceptualization, C.M. and P.K.; methodology, C.M. and P.K.; software, C.M.; validation, C.M. and P.K.; formal analysis, C.M. and P.K.; investigation, C.M.; resources, P.K.; data curation, C.M.; writing—original draft preparation, C.M. and P.K.; writing—review and editing, C.M. and P.K.; visualization, C.M. and P.K.; supervision, C.M. and P.K.; project administration, C.M. and P.K.; funding acquisition, C.M. and P.K. All authors have read and agreed to the published version of the manuscript.

**Funding:** This work was supported by the National Research Council of Thailand (NRCT) under Grant no. N42A671016.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** The data supporting the results in this study are available within the paper and its Supplementary Materials.

**Acknowledgments:** We would like to thank Natawat Chankana, Worawan Saingam, Thaniya Wunnakup, Nalina Saniwee, and Siramanee Kumsaward for their support throughout the experiments. I would also like to acknowledge Berlin Pharmaceutical Industry Co., Ltd. (Bangkok, Thailand), Biolab Co., Ltd. (Samut Prakan, Thailand), Colorcon Asia Pvt. Ltd. (Bangkok, Thailand), New Charoen Pharmaceutical Co., Ltd. (Pathum Thani, Thailand), Kaewmungkornphaesaj Co., Ltd. (Ratchaburi, Thailand), Lonza (Bangkok, Thailand) Co., Ltd., Capsule Products Co., Ltd. (Bangkok, Thailand), and DKSH (Bangkok, Thailand) Ltd., for their provision of drug substances, pharmaceutical excipients, and hard gelatin capsules used in this work. During the preparation of this work the authors

used ChatGPT 3.5 in order to proofread and correct grammatical errors. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

**Conflicts of Interest:** The authors declare no conflicts of interest.

## References


1. World Health Organization. Hypertension. Available online: https://www.who.int/news-room/fact-sheets/detail/hypertension# (accessed on 14 October 2025).
2. Mills, K.T.; Stefanescu, A.; He, J. The global epidemiology of hypertension. *Nat. Rev. Nephrol.* **2020**, *16*, 223–237. [CrossRef] [PubMed]
3. Inoue, T. Unawareness and untreated hypertension: A public health problem needs to be solved. *Hypertens. Res.* **2025**, *48*, 1639–1642. [CrossRef] [PubMed]
4. Goorani, S.; Zangene, S.; Imig, J.D. Hypertension: A continuing public healthcare issue. *Int. J. Mol. Sci.* **2025**, *26*, 123. [CrossRef] [PubMed]
5. U.S. Food and Drug Administration. Plendil® (Felodipine) Extended-Release Tablets. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019834s025lbl.pdf (accessed on 21 September 2024).
6. Gerk, P.M.; Yu, A.B.C.; Shargel, L. Chapter 14—Physiologic factors related to drug absorption. In *Applied Biopharmaceutics & Pharmacokinetics*, 7th ed.; Shargel, L., Yu, A.B.C., Eds.; McGraw-Hill Education: New York, NY, USA, 2016.
7. Malaterre, V.; Ogorka, J.; Loggia, N.; Gurny, R. Oral osmotically driven systems: 30 years of development and clinical use. *Eur. J. Pharm. Biopharm.* **2009**, *73*, 311–323. [CrossRef] [PubMed]
8. Sun, Y.; Zhu, S.; Lu, W.; Chen, J.; Sun, C.; Guo, Y.; Wang, B.; Gao, S.; Fang, W.; Hu, R. A novel enteric positioning osmotic pump capsule-based controlled release system of sinomenine hydrochloride: In vitro and in vivo evaluation. *J. Drug Deliv. Sci. Technol.* **2019**, *49*, 188–194. [CrossRef]
9. Danielak, D.; Paszkowska, J.; Martin, L.; Gimbel, J.; Ferrizzi, D.; Dobosz, J.; Romański, M.; Baran, E.; Kulinowski, P.; Winiarski, M.; et al. Comprehensive evaluation of push-pull osmotic pump tablets using biopredictive dissolution tests in advanced modular platform, MRI visualizations, and pharmacokinetic simulations. *Mol. Pharm.* **2025**, *22*, 5576–5591. [CrossRef] [PubMed]
10. Navarro-Tumar, D.; García-Merino, B.; González-Fernández, C.; Ortiz, I.; San-Román, M.-F.; Bringas, E. Novel applications in controlled drug delivery systems by integrating osmotic pumps and magnetic nanoparticles. *Sensors* **2024**, *24*, 7042. [CrossRef] [PubMed]
11. Gundu, R.; Pekamwar, S.; Shelke, S.; Kulkarni, D.; Shep, S. Development, optimization and pharmacokinetic evaluation of biphasic extended-release osmotic drug delivery system of trospium chloride for promising application in treatment of overactive bladder. *Futur. J. Pharm. Sci.* **2021**, *7*, 160. [CrossRef]
12. Li, Y.; Pan, H.; Duan, H.; Chen, J.; Zhu, Z.; Fan, J.; Li, P.; Yang, X.; Pan, W. Double-layered osmotic pump controlled release tablets of actarit: In vitro and in vivo evaluation. *Asian J. Pharm. Sci.* **2019**, *14*, 340–348. [CrossRef] [PubMed]
13. Siew, A. Controlling drug release through osmotic systems. *Pharm. Technol.* **2013**, *37*. Available online: https://www.pharmtech.com/view/controlling-drug-release-through-osmotic-systems (accessed on 14 October 2025).
14. Li, M.; Shen, Q.; Lu, W.; Chen, J.; Yu, L.; Liu, S.; Nie, X.; Shao, L.; Liu, Y.; Gao, S.; et al. Development and evaluation of controlled release of metformin hydrochloride for improving the oral bioavailability based on a novel enteric osmotic pump capsule. *J. Drug Deliv. Sci. Technol.* **2020**, *60*, 102054. [CrossRef]
15. Hill, A.; Geißler, S.; Weigandt, M.; Mäder, K. Controlled delivery of nanosuspensions from osmotic pumps: Zero order and non-zero order kinetics. *J. Control. Release* **2012**, *158*, 403–412. [CrossRef] [PubMed]
16. Yang, Y.; Zhao, Z.; Wang, Y.; Yang, L.; Liu, D.; Yang, X.; Pan, W. A novel asymmetric membrane osmotic pump capsule with in situ formed delivery orifices for controlled release of gliclazide solid dispersion system. *Int. J. Pharm.* **2016**, *506*, 340–350. [CrossRef] [PubMed]
17. Nokhodchi, A.; Momin, M.N.; Shokri, J.; Shahsavari, M.; Rashidi, P.A. Factors affecting the release of nifedipine from a swellable elementary osmotic pump. *Drug Deliv.* **2008**, *15*, 43–48. [CrossRef] [PubMed]
18. Arjun, N.; Narendar, D.; Sunitha, K.; Harika, K.; Nagaraj, B. Development, evaluation, and influence of formulation and process variables on in vitro performance of oral elementary osmotic device of atenolol. *Int. J. Pharm. Investig.* **2016**, *6*, 238–246. [CrossRef] [PubMed]
19. Almoshari, Y. Osmotic pump drug delivery systems—A comprehensive review. *Pharmaceuticals* **2022**, *15*, 1430. [CrossRef] [PubMed]
20. Mahari, S.; Najafi, S.H.; Masoomzadeh, S.; Kumar, S.; Gholikhani, T. A review of osmotic pump applications as a reliable drug delivery system in pharmaceutical sciences. *Biomed. Res. Bull.* **2024**, *2*, 29–36. [CrossRef]

21. Mohapatra, S.K.; Dash, A.K. Chapter 13—Special dosage forms and drug delivery systems. In *Pharmaceutics*, 2nd ed.; Dash, A.K., Singh, S., Eds.; Academic Press: Cambridge, MA, USA, 2024; pp. 393–436.
22. Wu, C.; Zhao, Z.; Zhao, Y.; Hao, Y.; Liu, Y.; Liu, C. Preparation of a push-pull osmotic pump of felodipine solubilized by mesoporous silica nanoparticles with a core-shell structure. *Int. J. Pharm.* **2014**, *475*, 298–305. [CrossRef] [PubMed]
23. Zhao, S.; Yu, F.; Liu, N.; Di, Z.; Yan, K.; Liu, Y.; Li, Y.; Zhang, H.; Yang, Y.; Yang, Z.; et al. Synchronous delivery of felodipine and metoprolol tartrate using monolithic osmotic pump technology. *Drug Dev. Ind. Pharm.* **2016**, *42*, 1723–1731. [CrossRef] [PubMed]
24. von Orelli, J.; Leuenberger, H. Search for technological reasons to develop a capsule or a tablet formulation with respect to wettability and dissolution. *Int. J. Pharm.* **2004**, *287*, 135–145. [CrossRef] [PubMed]
25. ICH Expert Working Group. ICH Q8 (R2) Pharmaceutical Development. Available online: https://database.ich.org/sites/default/files/Q8_R2_Guideline.pdf (accessed on 25 August 2025).
26. Yu, L.X.; Amidon, G.; Khan, M.A.; Hoag, S.W.; Polli, J.; Raju, G.K.; Woodcock, J. Understanding pharmaceutical quality by design. *AAPS J.* **2014**, *16*, 771–783. [CrossRef] [PubMed]
27. Savitha, S.; Devi, K. Quality by Design: A review. *J. Drug Deliv. Ther.* **2022**, *12*, 234–239. [CrossRef]
28. Monton, C.; Kulvanich, P. Fabrication and evaluation of felodipine push-pull osmotic pump capsule. *Pharm. Dev. Technol.* **2026**, *31*, 183–198. [CrossRef] [PubMed]
29. Monton, C.; Kulvanich, P.; Chankana, N.; Rangsimawong, W.; Suksaeree, J.; Charoenchai, L.; Theanphong, O. Cluster analysis of fingerroot cultivated in different regions across Thailand and implementation of Quality by Design approach for R & D of fingerroot extract tablet. *Food Res. Int.* **2025**, *202*, 115728. [CrossRef] [PubMed]
30. World Health Organization. Formaldehyde. Available online: https://iris.who.int/bitstream/handle/10665/38645/9241542896-eng.pdf (accessed on 19 November 2024).
31. The United States Pharmacopeial Convention. *USPNF 2023-Felodipine Extended-Release Tablets*; The United States Pharmacopeial Convention: Rockville, MD, USA, 2022. [CrossRef]
32. WebMD LLC. Felodipine (Rx). Available online: https://reference.medscape.com/drug/cabren-cardioplen-xl-felodipine-342375#0 (accessed on 14 October 2025).
33. U.S. Food and Drug Administration. Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms. Available online: https://www.pharmaexcipients.com/wp-content/uploads/2023/03/Quality-by-Design-for-ANDAs.pdf (accessed on 14 October 2025).
34. Kawabata, K.; Kohashi, M.; Akimoto, S.; Nishi, H. Structure determination of felodipine photoproducts in UV-irradiated medicines using ESI-LC/MS/MS. *Pharmaceutics* **2023**, *15*, 697. [CrossRef] [PubMed]
35. Afonso Urich, J.A.; Marko, V.; Boehm, K.; Lara Garcia, R.A.; Fedorko, A.; Salar-Behzadi, S.; Jeremic, D. Stability-indicating UPLC-PDA-QDa methodology for carvedilol and felodipine in fixed-dose combinations using AQbD principles. *Sci. Pharm.* **2024**, *92*, 22. [CrossRef]
36. Cardoza, R.M.; Amin, P.D. A stability indicating LC method for felodipine. *J. Pharm. Biomed. Anal.* **2002**, *27*, 711–718. [CrossRef] [PubMed]
37. Babu, M.A.; Kumar, J.V.S.; Naresh, N.; Mankumare, S.D. Sensitive and validated UPLC-MS/MS method for the identification and characterization of forced degradation products for felodipine. *Acta Chromatogr.* **2024**, *36*, 114–124. [CrossRef]
38. Bayer Inc. ADALAT XL Product Monograph. Available online: https://www.bayer.com/sites/default/files/2020-11/adalat-xl-pm-eng_0.pdf (accessed on 14 October 2025).
39. Alam, M.A.; Ya, H.H.; Yusuf, M.; Sivraj, R.; Mamat, O.B.; Sapuan, S.M.; Masood, F.; Parveez, B.; Sattar, M. Modeling, optimization and performance evaluation of TiC/graphite reinforced Al 7075 hybrid composites using response surface methodology. *Materials* **2021**, *14*, 4703. [CrossRef] [PubMed]
40. Lin, W.; Li, Y.; Shi, Q.; Liao, X.; Zeng, Y.; Tian, W.; Xie, X.; Liu, H. Preparation and evaluation of bilayer-core osmotic pump tablets contained topiramate. *PLoS ONE* **2022**, *17*, e0264457. [CrossRef] [PubMed]
41. Saleem, M.T.; Shoaib, M.H.; Yousuf, R.I.; Siddiqui, F. RSM and AI based machine learning for quality by design development of rivaroxaban push-pull osmotic tablets and its PBPK modeling. *Sci. Rep.* **2025**, *15*, 7922. [CrossRef] [PubMed]
42. Gundu, R.; Pekamwar, S.; Shelke, S.; Shep, S.; Kulkarni, D. Sustained release formulation of ondansetron HCl using osmotic drug delivery approach. *Drug Dev. Ind. Pharm.* **2020**, *46*, 343–355. [CrossRef] [PubMed]
43. Zhao, Z.; Wu, C.; Zhao, Y.; Hao, Y.; Liu, Y.; Zhao, W. Development of an oral push-pull osmotic pump of fenofibrate-loaded mesoporous silica nanoparticles. *Int. J. Nanomed.* **2015**, *10*, 1691–1701. [CrossRef] [PubMed]
44. Monton, C.; Kulvanich, P. Push-pull osmotic pumps using crosslinked hard gelatin capsule as a structural assembly for delivery of drugs with different water solubilities. *J. Pharm. Innov.* **2022**, *17*, 791–805. [CrossRef]
45. Liu, X.; Wang, S.; Chai, L.; Zhang, D.; Sun, Y.; Xu, L.; Sun, J. A two-step strategy to design high bioavailable controlled-release nimodipine tablets: The push–pull osmotic pump in combination with the micronization/solid dispersion techniques. *Int. J. Pharm.* **2014**, *461*, 529–539. [CrossRef] [PubMed]

46. Missaghi, S.; Patel, P.; Farrell, T.P.; Huatan, H.; Rajabi-Siahboomi, A.R. Investigation of critical core formulation and process parameters for osmotic pump oral drug delivery. *AAPS PharmSciTech* **2014**, *15*, 149–160. [CrossRef] [PubMed]
47. White, W.B. The risk of waking-up. *Hypertension* **2010**, *55*, 835–837. [CrossRef] [PubMed]