DEVELOPMENT AND OPTIMIZATION OF FOSINOPRIL SODIUM SUSTAINED-RELEASE MATRIX TABLETS USING A 3^2 FULL FACTORIAL DESIGN

Hanuman Shrikishan Kolse[1]*, Dr. Shikha Jaiswal[2]
[1]*Research Scholar, Faculty of Pharmacy, Oriental University, Indore, Madhya Pradesh, 453555, India
[2] Supervisor, Faculty of Pharmacy, Oriental University, Indore, Madhya Pradesh, 453555, India
***Corresponding author,**
Mr. Hanuman Shrikishan Kolse,
Research Scholar, Faculty of Pharmacy,
Oriental University, Indore, Madhya Pradesh, 453555, India
Email: hanumankolse@gmail.com

ABSTRACT:
Background: Hydrophilic polymeric matrices provide a practical approach for achieving sustained drug release, although optimization of polymer composition is required to obtain the desired dissolution profile. **Objective:** This study aimed to develop and optimize Fosinopril Sodium sustained-release matrix tablets using HPMC K4M and sodium carboxymethyl cellulose (SCMC) and to evaluate the applicability of a 3^2 full factorial design for formulation optimization. **Methods:** HPMC K4M and SCMC were investigated as two independent formulation variables at three concentration levels, generating nine experimental formulations (F1–F9). The prepared tablets were evaluated for pre-compression and post-compression characteristics and subjected to in-vitro dissolution testing for 12 h. The dissolution-time responses t_{10}%, t_{50}%, t_{75}%, and t_{90}% were analyzed using second-order polynomial regression and response-surface methodology. Checkpoint formulations were used to compare predicted and experimentally observed responses. **Results:** The factorial formulations showed distinct dissolution behaviors across the investigated formulation space. F4, containing 30 mg HPMC K4M and 40 mg SCMC, was identified as the optimized formulation and exhibited t_{10}%, t_{50}%, t_{75}%, and t_{90}% values of 0.350, 2.268, 4.537, and 7.530 h, respectively. Checkpoint validation demonstrated prediction errors below 2% for all evaluated dissolution responses, supporting the predictive performance of the developed models. The dissolution profile of F4 was comparable to that of the marketed formulation, with a difference factor (f_1) of 1.543 and a similarity factor (f_2) of 89.561. **Conclusion:** The 3^2 factorial design provided a systematic basis for evaluating the combined effects of HPMC K4M and SCMC and identifying an optimized Fosinopril Sodium matrix formulation with sustained in-vitro drug release over 12 h. Further stability and in-vivo studies are warranted to establish its long-term and pharmacokinetic performance.
Keywords: Fosinopril Sodium; Sustained-release matrix tablet; HPMC K4M; Factorial design; Formulation optimization; Drug release; Response surface analysis
How to cite this article: Kolse HS, Jaiswal S. Development and Optimization of Fosinopril Sodium Sustained-Release Matrix Tablets Using a 3^2 Full Factorial Design. Int J Drug Deliv Technol. 2026;16(76s): 1222-1236. DOI: 10.25258/ijddt.16.76s.110

1. Introduction

1.1 Sustained-release oral drug delivery

Sustained-release oral dosage forms are designed to regulate drug release over an extended period and thereby provide more prolonged therapeutic exposure than conventional immediate-release formulations[1], [2]. Such systems can help reduce the frequency of administration and may improve dosing convenience and patient adherence[3]. Matrix-based delivery systems are particularly attractive because they can be prepared using relatively simple manufacturing approaches while providing predictable control of drug release through appropriate selection and concentration of matrix-forming polymers[4], [5].

1.2 Fosinopril Sodium as a formulation candidate

Fosinopril Sodium is an orally administered angiotensin-converting enzyme inhibitor used in the management of hypertension and related cardiovascular conditions[6], [7], [8]. The development of a sustained-release matrix formulation provides an opportunity to investigate controlled drug release from a hydrophilic polymeric system[9], [10]. The physicochemical characteristics of Fosinopril Sodium, including its solubility and partition behavior, are relevant to the design of an oral modified-release dosage form[11], [12]. Therefore, systematic selection of suitable matrix-forming polymers is important for obtaining the desired release characteristics[13], [14].

1.3 Hydrophilic matrix systems

Hydrophilic polymers are widely used to develop sustained-release matrix tablets because they form a hydrated polymeric barrier following contact with the dissolution medium[10], [15], [16]. HPMC K4M and sodium carboxymethyl cellulose (SCMC) are hydrophilic polymers capable of absorbing aqueous media, swelling, and contributing to gel-layer formation[17]. The resulting hydrated matrix can regulate drug movement by increasing diffusional resistance and through gradual matrix erosion[18], [19]. In the present study, these properties were utilized to investigate the ability of HPMC K4M and SCMC to modulate the release of Fosinopril Sodium.

1.4 Need for systematic formulation optimization

Conventional formulation development based primarily on trial-and-error approaches may require numerous experimental batches and may not adequately reveal the individual and combined effects of formulation variables[20], [21]. Design of Experiments (DoE) provides a systematic approach for evaluating formulation variables and their interactions[20], [22]. A factorial design is particularly useful because multiple variables can be investigated simultaneously using a defined set of experimental combinations[23], [24].

1.5 Rationale for the Present Study

A systematic investigation of the combined influence of HPMC K4M and SCMC concentrations on the dissolution characteristics of Fosinopril Sodium matrix tablets was undertaken using a 3^2 full factorial design. The factorial approach enabled simultaneous evaluation of the two polymer variables at three concentration levels and assessment of their individual and interactive effects on the dissolution-time responses.

It was hypothesized that systematic variation of HPMC K4M and SCMC concentrations would produce measurable changes in the dissolution-time responses and that their combined effects could be described using a 3^2 factorial model.

1.6 Study objective

The objective of the present study was to develop and optimize Fosinopril Sodium sustained-release matrix tablets using HPMC K4M and SCMC as formulation variables through a 3^2 full factorial experimental design, with dissolution parameters used as the principal responses.

2. Materials and Methods

2.1 Materials

2.1.1 Active pharmaceutical ingredient

Fosinopril Sodium was obtained as a gift sample from Simson Pharma Limited, Mumbai, India.

2.1.2 Excipients and chemicals

Hydroxypropyl methylcellulose K4M (HPMC K4M), sodium carboxymethyl cellulose (SCMC), lactose monohydrate, and magnesium stearate were procured from Sigma-Aldrich, St. Louis, MO, USA. Analytical-grade acetone and hydrochloric acid (HCl) were purchased from Merck KGaA, Darmstadt, Germany, while methanol of HPLC/analytical grade was obtained from Sigma-Aldrich, USA. All chemicals and reagents were used as received without further purification.

2.2 Preformulation Studies

Preformulation studies were performed to characterize Fosinopril Sodium and to assess its suitability for incorporation into the sustained-release matrix system. The studies included organoleptic evaluation, melting point determination, solubility assessment, partition coefficient determination, Fourier-transform infrared spectroscopy (FTIR), drug–excipient compatibility assessment, and UV–visible spectrophotometric characterization. In the present formulation-focused study, the preformulation investigations were primarily used to confirm the identity and compatibility of the drug with the selected excipients and to establish an analytical procedure for quantitative determination of Fosinopril Sodium during dissolution testing.

2.2.1 FTIR Characterization and Drug–Excipient Compatibility

FTIR spectroscopy was performed to characterize Fosinopril Sodium and assess its compatibility with the selected matrix-forming polymers, HPMC K4M and SCMC. The FTIR spectrum of Fosinopril Sodium was recorded over the range of 4000–500 cm^{-1} and showed characteristic absorption bands corresponding to its principal functional groups[25], [26]. A prominent absorption band in the 1725–1705 cm^{-1} region was attributed to carbonyl (C=O) stretching, consistent with the characteristic spectral features of Fosinopril Sodium[27].

The physical mixtures of Fosinopril Sodium with HPMC K4M and SCMC retained the characteristic absorption bands of the drug and respective polymers. The SCMC-containing mixture showed characteristic bands in the 3400–3200 cm^{-1}, 2950–2850 cm^{-1}, 1730–1700 cm^{-1}, 1600–1500 cm^{-1}, and 1300–1000 cm^{-1} regions, corresponding to the principal functional groups of the formulation components.

Similarly, the characteristic absorption bands associated with HPMC K4M were retained in the Fosinopril Sodium–HPMC K4M physical mixture, with no significant disappearance or alteration of the principal bands reported. Overall, no significant shifts, disappearance of characteristic bands, or appearance of new bands were observed in the drug–polymer physical mixtures, suggesting the absence of detectable chemical interactions between Fosinopril

Sodium and HPMC K4M or SCMC under the conditions investigated.

2.2.2 UV–Visible Spectrophotometric Method

UV–visible spectrophotometry was used for quantitative determination of Fosinopril Sodium in the dissolution samples. A calibration curve was prepared using standard Fosinopril Sodium solutions over the concentration range established in the thesis, and the resulting relationship was used to calculate drug concentration in the dissolution samples. The analytical procedure was used as a supporting method for quantification of drug release rather than as an independent objective of the present formulation study.

The organoleptic characteristics, melting point, solubility, and partition coefficient of Fosinopril Sodium were evaluated during preformulation; however, these preliminary investigations are not discussed separately because they did not constitute independent formulation variables or study objectives in the present factorial optimization study.

2.3 Statistical Analysis

The experimental data obtained from the nine factorial formulations were analyzed using a 3^2 full factorial design to evaluate the effects of HPMC K4M (X_1) and SCMC (X_2) concentrations on the dissolution-time responses, namely t_{10}%, t_{50}%, t_{75}%, and t_{90}%. Second-order polynomial regression models incorporating linear, interaction (X_1X_2), and quadratic (X_1^2 and X_2^2) terms were used to describe the relationship between the formulation variables and the measured responses[28]. Analysis of variance (ANOVA) was used to assess the statistical significance of the fitted regression models, with $p < 0.05$ considered statistically significant. Response-surface methodology was used to visualize the combined influence of the two polymer variables on the dissolution responses and to support formulation optimization[29], [30].

The predictive performance of the developed regression models was further assessed using the checkpoint formulations C1 and C2 by comparing the predicted and experimentally observed dissolution responses and calculating the percentage prediction error. The optimized formulation was selected based on the experimentally defined dissolution-performance criteria and comparison of the responses within the investigated formulation space. Where applicable, model-generated predictions were compared with experimental observations to assess the adequacy of the optimization approach.

For comparison of the optimized formulation with the marketed formulation, the dissolution profiles were evaluated using the model-independent difference factor (f_1) and similarity factor (f_2)[31], [32], [33]. The factors were calculated from the corresponding dissolution data using the standard equations, with the comparison based on the specified common sampling time points. A low f_1 value and a high f_2 value were interpreted as indicating greater similarity between the dissolution profiles. All experimental measurements were reported as mean ± standard deviation where applicable.

3. Experimental Design

3.1 Selection of Formulation Variables

A statistical experimental design was employed to systematically investigate the influence of polymer concentration on the sustained-release performance of Fosinopril Sodium matrix tablets. HPMC K4M and sodium carboxymethyl cellulose (SCMC) were selected as the independent formulation variables because of their established roles in hydrophilic matrix formation and modulation of drug release. Upon hydration, hydrophilic polymers can form a gel layer that influences drug transport through a combination of diffusion, swelling, and matrix erosion mechanisms[34].

HPMC K4M was designated as X_1, while SCMC was designated as X_2. Each polymer was investigated at three concentration levels, represented by the coded values −1, 0, and +1. For HPMC K4M, the selected concentrations were 10%, 15%, and 20% w/w of the total tablet weight. The same concentration levels were used for SCMC.

Table 1 (a): Independent formulation variables and their coded levels

Variable	−1	0	1
X_1: HPMC K4M (% w/w)	10	15	20
X_2: SCMC (% w/w)	10	15	20

3.2 3^2 Full Factorial Design

A three-level, two-factor (**3^2**) full factorial design was employed to systematically investigate the effects of HPMC K4M and SCMC concentrations on the sustained-release characteristics of Fosinopril Sodium matrix tablets. HPMC K4M (X_1) and SCMC (X_2) were selected as the two independent formulation variables. Each variable was investigated at three concentration levels, corresponding to code values of −1, 0, and +1 for the low, intermediate, and high levels, respectively. The combination of the three levels of each factor generated nine experimental formulations (F1–F9). Full factorial designs permit simultaneous evaluation of the main effects of formulation variables as well as their interaction effects and are commonly used in pharmaceutical formulation optimization[35], [36].

The factorial design enabled simultaneous evaluation of the individual effects of HPMC K4M and SCMC and their combined influence on the dissolution behavior of the matrix tablets. The experimental

responses obtained from the nine formulations were subsequently used for regression analysis, response-surface analysis, and formulation optimization[37].

Table 1 (b): Experimental design matrix for the 3² full factorial design

Formulation	X_1: HPMC K4M	X_2: SCMC
F1	1	1
F2	1	0
F3	1	−1
F4	0	1
F5	0	0
F6	0	−1
F7	−1	1
F8	−1	0
F9	−1	−1

Table 1 a & b Experimental design matrix for the 3² full factorial design used for formulation development. X_1 represents HPMC K4M concentration and X_2 represents SCMC concentration. The coded levels −1, 0, and +1 correspond to the low (10%), intermediate (15%), and high (20%) polymer concentration levels, respectively.

The corresponding actual quantities of HPMC K4M and SCMC used in the nine formulations were 20, 30, and 40 mg per tablet, corresponding to 10%, 15%, and 20% w/w, respectively. The two polymers were varied according to the factorial combinations shown in Table 1, while the total tablet weight was maintained at 200 mg by adjustment of lactose monohydrate.

Drug–Excipient Compatibility was assessed by Fourier-transform infrared (FTIR) spectroscopy to evaluate the potential compatibility of Fosinopril Sodium with the selected matrix-forming polymers. The FTIR assessment did not indicate any major incompatibility between the drug and the formulation components under the conditions investigated. As the present study primarily focused on factorial formulation optimization and dissolution behavior, the FTIR findings were used only as a preliminary compatibility assessment and were not considered as independent evidence of formulation performance.

4. Formulation Development

4.1 Preparation of Matrix Tablets

Fosinopril Sodium sustained-release matrix tablets were prepared by the direct-compression technique. Each formulation contained 20 mg of Fosinopril Sodium. HPMC K4M and sodium carboxymethyl cellulose (SCMC) were selected as the matrix-forming polymers, lactose monohydrate was used as the diluent, and magnesium stearate was incorporated as the lubricant. The concentrations of HPMC K4M and SCMC were varied according to the 3² full factorial design, while the drug dose and total tablet weight were maintained constant.

For each formulation, Fosinopril Sodium, HPMC K4M, SCMC, and lactose monohydrate were accurately weighed and passed through an appropriate sieve to obtain a uniform powder mixture. The components were subsequently blended to achieve homogeneous distribution of the drug and matrix-forming polymers. Magnesium stearate was then incorporated during the final blending stage to facilitate powder flow and reduce friction during compression. The resulting powder blend was compressed using a suitable tablet compression machine to obtain tablets with a target weight of 200 mg.

The prepared tablets were collected and evaluated for their physical and pharmaceutical quality attributes, including appearance, weight variation, thickness, hardness, friability, and drug-content uniformity. The tablets were subsequently subjected to in-vitro dissolution testing to investigate the influence of polymer concentration on the sustained-release behavior of Fosinopril Sodium.

4.2 Composition of Fosinopril Sodium Sustained-Release Matrix Tablets

Nine formulations (F1–F9) were prepared according to the 3² full factorial design. HPMC K4M and SCMC were incorporated at 10%, 15%, and 20% levels, corresponding to the coded levels −1, 0, and +1, respectively. The amount of lactose monohydrate was adjusted to maintain a constant tablet weight of 200 mg, while magnesium stearate was maintained at 4 mg per tablet. The formulation composition is presented in Table 2.

Table 2: Composition of Fosinopril Sodium sustained-release matrix tablets

Ingredient (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Fosinopril Sodium	20	20	20	20	20	20	20	20	20
HPMC K4M	40	40	40	30	30	30	20	20	20
SCMC	40	30	20	40	30	20	40	30	20
Lactose monohydrate	96	106	116	106	116	126	116	126	136

Magnesium stearate	4	4	4	4	4	4	4	4	4
Total	200	200	200	200	200	200	200	200	200

Table 2 Composition of Fosinopril Sodium sustained-release matrix tablets prepared according to the 3^2 full factorial designs. Fosinopril Sodium and magnesium stearate were maintained at 20 and 4 mg per tablet, respectively, while HPMC K4M and SCMC concentrations were varied systematically. Lactose monohydrate was adjusted accordingly to maintain a total tablet weight of 200 mg.

The formulation design provided systematic variation of the two matrix-forming polymers while maintaining a constant Fosinopril Sodium dose and total tablet weight. HPMC K4M was investigated at 20, 30, and 40 mg per tablet, corresponding to 10%, 15%, and 20% w/w, respectively, while SCMC was varied at 20, 30, and 40 mg per tablet. This formulation arrangement enabled evaluation of the individual and combined effects of the two polymers on tablet characteristics and drug-release behavior within the factorial experimental design.

4.3 Manufacturing Controls

During preparation, particular attention was given to achieving uniform distribution of Fosinopril Sodium and the matrix-forming polymers before compression. Uniform blending is important because differences in component distribution can affect tablet weight uniformity, drug content, mechanical properties, and drug-release behavior.

Magnesium stearate was incorporated at the final blending stage to minimize its potential influence on powder bonding and tablet mechanical properties, particularly when excessive or prolonged lubrication is avoided.

The resulting tablets were visually inspected before further evaluation. All nine formulations were subsequently subjected to the specified physicochemical and mechanical evaluations, as described in the following sections.

5. Evaluation of Powder Blends

Prior to compression, the powder blends of formulations F1–F9 were evaluated for their micromeritic properties, including bulk density, tapped density, Carr's compressibility index, Hausner ratio, and angle of repose. All determinations were performed in triplicate, and the results were expressed as mean ± standard deviation where applicable. Bulk density was determined from the mass and untapped volume of the powder blend, whereas tapped density was determined after mechanical tapping to constant volume. Carr's compressibility index and Hausner ratio were calculated from the corresponding bulk and tapped density values. The bulk and tapped density values reported for F1–F9 ranged from 2.65 to 2.86 g/cm³ and 3.70 to 6.50 g/cm³, respectively. Carr's compressibility index ranged from 23.51% to 43.61%, while the Hausner ratio ranged from 1.30 to 1.77. The pre-compression properties of the nine formulations are summarized in Table 3.

5.1 Bulk Density

Bulk density was determined by measuring the volume occupied by a known mass of powder before mechanical tapping. It was calculated as the ratio of the powder mass to its initial untapped volume.

5.2 Tapped Density

Tapped density was determined after mechanical tapping of a known quantity of powder until a constant volume was obtained. It was calculated from the powder mass and final tapped volume.

5.3 Carr's Compressibility Index

Carr's compressibility index was calculated from the reported bulk and tapped density values using the standard relationship between these two parameters. The calculated values for formulations F1–F9 ranged from 23.51% to 43.61%. Because replicate-level bulk and tapped density measurements were not available for calculation of variability, Carr's index values are reported as calculated single values rather than as mean ± standard deviation.

5.4 Hausner Ratio

The Hausner ratio was calculated from the reported tapped and bulk density values and was used as an indicator of powder packing and cohesiveness. The calculated values for formulations F1–F9 ranged from 1.30 to 1.77. As replicate-level density data were not available, the Hausner ratio values are presented as calculated single values without standard deviation.

5.5 Angle of Repose

The angle of repose was determined using the fixed-funnel method by measuring the height and radius of the resulting powder cone. The determination was performed in triplicate. The angle of repose, together with bulk density, tapped density, Carr's compressibility index, and Hausner ratio, was used to characterize the flow and packing properties of the powder blends.

Table 3: Pre-compression properties of Fosinopril Sodium matrix tablet formulations

Formulation	Angle of repose (°)	Bulk density (g/cm³)	Tapped density (g/cm³)	Carr's index (%)	Hausner ratio

F1	25 ± 2	2.83 ± 0.05	3.70 ± 0.30	23.51	1.3
F2	27 ± 2	2.75 ± 0.04	4.50 ± 0.50	29.48	1.41
F3	29 ± 3	2.77 ± 0.05	5.10 ± 0.20	32.43	1.48
F4	30 ± 1	2.72 ± 0.03	4.50 ± 0.30	35.23	1.54
F5	28 ± 2	2.76 ± 0.02	4.10 ± 0.10	32.68	1.48
F6	29 ± 2	2.78 ± 0.05	4.10 ± 0.20	32.19	1.47
F7	30 ± 2	2.82 ± 0.03	5.50 ± 0.30	37.33	1.59
F8	28 ± 1	2.65 ± 0.02	4.70 ± 0.30	43.61	1.77
F9	27 ± 1	2.86 ± 0.05	6.50 ± 0.10	36.44	1.57

Values are presented as mean ± standard deviation where applicable. Carr's compressibility index and Hausner ratio were calculated from the reported bulk and tapped density values and are therefore presented as calculated values without standard deviation.

The powder blends showed angle-of-repose values ranging from 25° to 30°, while bulk density ranged from 2.65 to 2.86 g/cm³ and tapped density from 3.70 to 6.50 g/cm³. Carr's compressibility index ranged from 23.51% to 43.61%, whereas the Hausner ratio ranged from 1.30 to 1.77. F1 exhibited the lowest Carr's index and Hausner ratio, whereas F8 showed the highest values for both parameters.

The observed variation in packing and compressibility characteristics among the formulations may be related to differences in the proportions of the hydrophilic matrix-forming polymers. These differences were reflected in the measured bulk and tapped densities and the corresponding compressibility indices and Hausner ratios. Overall, the powder blends were processed using the reported direct-compression approach and subsequently used for preparation of the matrix tablets.

6. Evaluation of Prepared Matrix Tablets

The prepared Fosinopril Sodium sustained-release matrix tablets were evaluated for appearance, weight variation, thickness, hardness, friability, and drug-content uniformity. The results for formulations F1–F9 are summarized in Table 4.

6.1 Appearance

All prepared matrix tablets exhibited an intact and uniform appearance without visible cracks, capping, or other major physical defects.

6.2 Weight Variation

The mean tablet weight of formulations F1–F9 ranged from 199.22 ± 0.32 to 202.11 ± 0.15 mg, indicating relatively low variation among the prepared batches.

6.3 Thickness

Tablet thickness ranged from 2.46 ± 0.14 to 2.85 ± 0.13 mm across the nine formulations. The relatively narrow range indicated consistency in tablet dimensions among the formulations.

6.4 Hardness

The hardness values ranged from 3.50 ± 0.20 to 4.08 ± 0.30 kg/cm². The observed values indicated adequate mechanical strength of the prepared matrix tablets for subsequent handling and dissolution testing.

6.5 Friability

Friability values ranged from 0.21 ± 0.026% to 0.52 ± 0.043%. The relatively low friability values indicated adequate resistance of the tablets to mechanical abrasion during handling.

6.6 Drug-Content Uniformity

The drug content of the prepared formulations ranged from 98.46 ± 0.44% to 99.58 ± 0.32%. The close agreement of the measured drug content with the intended drug content demonstrated uniform distribution of Fosinopril Sodium within the prepared matrix tablets.

Overall, formulations F1–F9 exhibited consistent tablet weight, dimensions, mechanical strength, low friability, and drug-content values across the formulation batches. These characteristics supported the suitability of the prepared tablets for subsequent in-vitro dissolution and formulation-optimization studies.

Table 4: Post-compression characteristics of Fosinopril Sodium sustained-release matrix tablets

Formulation	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Tablet weight (mg)	Drug content (%)
F1	3.50 ± 0.20	2.75 ± 0.11	0.27 ± 0.021	200.21 ± 0.13	99.12 ± 0.48
F2	3.51 ± 0.40	2.85 ± 0.13	0.24 ± 0.023	199.71 ±	98.48 ±

				0.27	0.52
F3	4.02 ± 0.40	2.77 ± 0.11	0.42 ± 0.041	199.22 ± 0.32	98.52 ± 0.36
F4	3.79 ± 0.30	2.63 ± 0.15	0.37 ± 0.021	199.53 ± 0.44	99.47 ± 0.45
F5	4.05 ± 0.40	2.67 ± 0.13	0.36 ± 0.053	201.01 ± 0.18	99.41 ± 0.31
F6	3.81 ± 0.30	2.55 ± 0.15	0.21 ± 0.026	202.11 ± 0.15	98.65 ± 0.36
F7	3.52 ± 0.50	2.57 ± 0.13	0.52 ± 0.043	200.62 ± 0.16	99.24 ± 0.33
F8	4.08 ± 0.30	2.55 ± 0.15	0.49 ± 0.022	201.11 ± 0.18	99.58 ± 0.32
F9	3.82 ± 0.40	2.46 ± 0.14	0.24 ± 0.026	199.62 ± 0.29	98.46 ± 0.44

Table 4 Post-compression characteristics of Fosinopril Sodium sustained-release matrix tablets. Values are presented as mean ± standard deviation.

The nine formulations exhibited relatively consistent physical and mechanical characteristics, as reflected by the measured tablet weight, thickness, hardness, and friability values. Drug content remained close to the intended value across all formulations. These findings indicated satisfactory reproducibility of the prepared matrix tablets and supported their subsequent evaluation in the in-vitro dissolution study and factorial-design optimization.

7. *In-Vitro* Drug Release Study

7.1 Dissolution Testing

The in-vitro drug-release behavior of Fosinopril Sodium sustained-release matrix tablets was evaluated using USP Dissolution Apparatus II (paddle method)[38]. A dissolution medium volume of 900 mL was used, and the dissolution medium was maintained at 37 ± 0.5°C throughout the study. One tablet was placed in each dissolution vessel, and dissolution testing was continued for 12 h. Samples were withdrawn at 1-h intervals from 1 to 12 h. After each withdrawal, an equivalent volume of fresh dissolution medium, pre-equilibrated to the test temperature, was added to maintain a constant dissolution volume.

The withdrawn samples were filtered, suitably diluted where required, and analyzed by UV–visible spectrophotometry using the established analytical procedure. The cumulative percentage of Fosinopril Sodium released was calculated from the calibration relationship and plotted against time. Dissolution experiments were performed in triplicate, and the results were expressed as mean values.

7.2 Cumulative Drug-Release Profiles

The cumulative drug-release profiles of formulations F1–F9 over 12 h are presented in Fig. 1. All formulations exhibited gradual drug release, with cumulative release ranging from 5–9% at 1 h and 87–100% at 12 h. F4 showed the highest cumulative release, reaching 100% at 12 h. The differences among formulations demonstrate the influence of HPMC K4M and SCMC concentrations on Fosinopril Sodium release behavior.

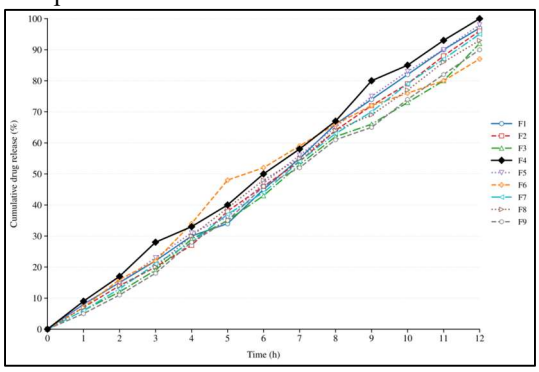

Figure 1: *In-vitro* cumulative drug-release profiles of Fosinopril Sodium sustained-release matrix tablets (F1–F9)

Figure 1 In-vitro cumulative drug-release profiles of Fosinopril Sodium sustained-release matrix tablets (F1–F9) over 12 h. Data represent mean values from triplicate dissolution experiments.

7.3 Dissolution Parameters

To quantitatively characterize and compare the release behavior of the nine factorial formulations, the time required to achieve 10%, 50%, 75%, and 90% drug release was determined and expressed as t_{10}%, t_{50}%, t_{75}%, and t_{90}%, respectively. These dissolution-time parameters provided a quantitative basis for evaluating differences in the release rate produced by the different combinations of HPMC K4M and SCMC.

Table 5: Dissolution parameters of Fosinopril Sodium sustained-release matrix tablets

Formulation	t_{10}% (h)	t_{50}% (h)	t_{75}% (h)	t_{90}% (h)
F1	0.43	2.84	5.67	9.43
F2	0.49	3.25	6.5	10.8
F3	0.65	4.22	8.44	14
F4	0.35	2.27	4.54	7.53
F5	0.46	3.02	6.04	10
F6	0.64	4.17	8.34	13.9

F7	0.51	3.36	6.72	11.1
F8	0.56	3.69	7.38	12.3
F9	0.56	3.73	7.47	12.46

Table 5 Dissolution-time parameters of Fosinopril Sodium sustained-release matrix tablets prepared according to the 3^2 full factorial design. t_{10}%, t_{50}%, t_{75}%, and t_{90}% represent the time required to achieve 10%, 50%, 75%, and 90% drug release, respectively.

The dissolution parameters showed clear differences among the nine formulations, demonstrating that the composition of the polymeric matrix influenced the rate of Fosinopril Sodium release. The t_{90}% values ranged from 7.53 h for F4 to 14.00 h for F3, while the corresponding t_{50}% and t_{75}% values ranged from 2.27 to 4.22 h and from 4.54 to 8.44 h, respectively. These differences demonstrate the ability of the formulation variables to modify the dissolution behavior of the matrix tablets.

Among the factorial formulations, F4 exhibited the shortest t_{50}%, t_{75}%, and t_{90}% values, at 2.27, 4.54, and 7.53 h, respectively. The thesis identifies F4 as the optimized formulation based on its overall dissolution characteristics and its suitability for controlled release over the investigated dissolution period.

The observed differences in dissolution behavior can be associated with the hydration and swelling characteristics of the hydrophilic polymers. Variation in HPMC K4M and SCMC concentrations altered the hydrated matrix environment and consequently the resistance encountered by the drug during release. Higher polymer concentrations generally produced longer dissolution times, consistent with greater matrix hydration and increased resistance to drug transport [34].

8. Factorial Design Analysis and Optimization

8.1 Effect of HPMC K4M and SCMC on Drug Release

The 3^2 full factorial design was used to investigate the individual and combined effects of HPMC K4M (X_1) and SCMC (X_2) concentrations on the dissolution behavior of Fosinopril Sodium matrix tablets. The dissolution responses selected for analysis were t_{10}%, t_{50}%, t_{75}%, and t_{90}%, representing the time required to achieve 10%, 50%, 75%, and 90% drug release, respectively.

The experimental results demonstrated considerable variation in dissolution times among F1–F9, confirming that polymer composition influenced the release behavior of the matrix tablets. Increasing the concentration of HPMC K4M generally increased the dissolution times. This effect can be attributed to greater hydration and formation of a thicker and more viscous gel layer, which increases diffusional resistance and consequently slows drug transport through the matrix[34].

SCMC also exerted a significant influence on the dissolution responses. Its hydrophilic character promotes water uptake, swelling, and gel formation within the matrix, thereby modifying the diffusion pathway available for Fosinopril Sodium. The thesis further indicates that the combined effects of HPMC K4M and SCMC were reflected in the interaction terms of the regression models.

Response-surface analysis demonstrated a progressive increase in t_{10}%, t_{50}%, t_{75}%, and t_{90}% with increasing concentrations of the polymers. Thus, higher polymer levels generally produced greater release-retarding effects. The results indicate that adjustment of the HPMC K4M–SCMC ratio provides a means of modifying matrix hydration, gel strength, diffusional resistance, and overall drug-release behavior.

8.2 Regression Analysis

Second-order polynomial regression models were developed to describe the relationship between the concentrations of HPMC K4M (X_1) and SCMC (X_2) and the dissolution responses t_{10}%, t_{50}%, t_{75}%, and t_{90}%. The models incorporated linear, interaction, and quadratic terms to evaluate the individual and combined effects of the formulation variables. The regression equations obtained from the factorial design were as follows.

Table 6: Regression models and statistical information for dissolution responses

Response	Polynomial regression equation	Statistics
Y_1: t_{10}%	$0.515 - 0.011X_1 - 0.095X_2 - 0.037X_1X_2 + 0.055X_1^2 + 0.0172X_2^2$	ANOVA significance assessed at $p < 0.05$
Y_2: t_{50}%	$3.395 - 0.077X_1 - 0.611X_2 - 0.251X_1X_2 + 0.362X_1^2 + 0.114X_2^2$	ANOVA significance assessed at $p < 0.05$
Y_3: t_{75}%	$6.789 - 0.156X_1 - 1.223X_2 - 0.505X_1X_2 + 0.721X_1^2 - 0.224X_2^2$	ANOVA significance assessed at $p < 0.05$
Y_4: t_{90}%	$11.280 - 0.259X_1 - 2.01X_2 - 0.840X_1X_2 + 1.21X_1^2 + 0.370X_2^2$	ANOVA significance assessed at $p < 0.05$

Table 6 Second-order polynomial regression models describing the effects of HPMC K4M (X_1) and SCMC (X_2) on the dissolution responses of Fosinopril Sodium sustained-release matrix tablets

Y_1, Y_2, Y_3, and Y_4 represent t_{10}%, t_{50}%, t_{75}%, and t_{90}%, respectively. The polynomial models incorporated linear, interaction (X_1X_2), and quadratic

(X_1^2 and X_2^2) terms to describe the effects of HPMC K4M and SCMC concentrations on the dissolution responses. Statistical significance of the regression models was assessed by analysis of variance (ANOVA) at $p < 0.05$. The regression coefficients indicate the contribution of the formulation variables to the dissolution responses, while the interaction and quadratic terms describe the combined and non-linear effects of polymer concentration. These models provided a mathematical basis for relating the concentrations of HPMC K4M and SCMC to the dissolution characteristics of the Fosinopril Sodium matrix tablets.

8.3 Response-Surface Analysis

Response-surface analysis was used to visualize the combined influence of HPMC K4M (X_1) and SCMC (X_2) concentrations on the dissolution-time responses. The generated three-dimensional surfaces provided a graphical representation of the relationship between the two formulation variables and the time required to achieve 10%, 50%, 75%, and 90% drug release. The response surfaces for t_{10}%, t_{50}%, t_{75}%, and t_{90}% are presented in Figs. 2–5, respectively.

The response surfaces demonstrated a concentration-dependent and interactive influence of HPMC K4M and SCMC on the dissolution-time responses. Changes in the concentration of either polymer altered the dissolution responses, while the magnitude and direction of the response depended partly on the concentration of the other polymer. This behavior was consistent with the inclusion of the X_1X_2 interaction terms in the regression models and indicated that the combined polymer composition contributed to the dissolution characteristics of the matrix tablets.

The response-surface analysis therefore provided a graphical representation of the combined and non-linear influence of HPMC K4M and SCMC on the dissolution-time parameters and supported the systematic optimization of polymer concentrations using the 3^2 full factorial design. The observed changes in dissolution behavior can be associated with polymer hydration, swelling, gel-layer formation, and the resulting resistance to drug transport within the hydrated matrix.

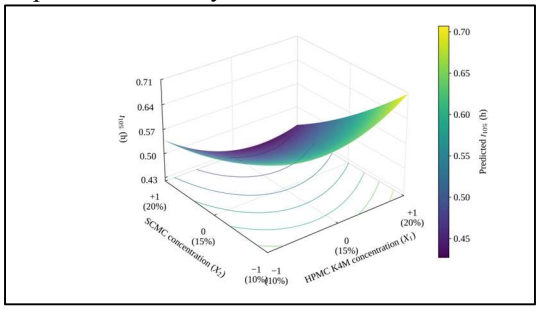

Figure 2: Response-surface plot showing the combined effect of HPMC K4M (X_1) and SCMC (X_2) concentrations on the time required for 10% drug release (t_{10}%) from Fosinopril Sodium sustained-release matrix tablets.

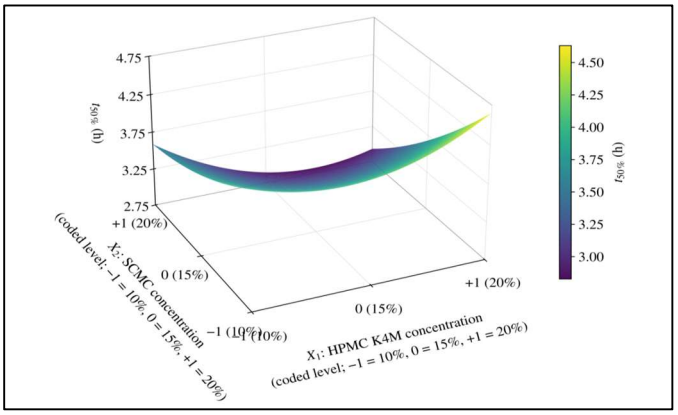

Figure 3: Response-surface plot showing the combined effect of HPMC K4M (X_1) and SCMC (X_2) concentrations on the time required for 50% drug release (t_{50}%) from Fosinopril Sodium sustained-release matrix tablets.

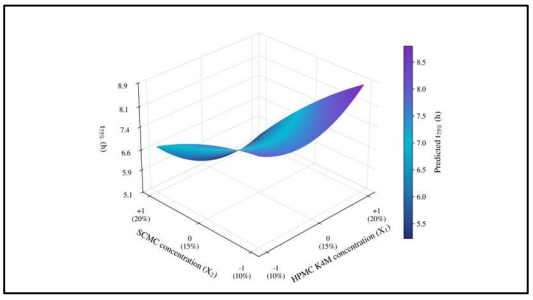

Figure 4: Response-surface plot showing the combined effect of HPMC K4M (X_1) and SCMC (X_2) concentrations on the time required for 75% drug release (t_{75}%) from Fosinopril Sodium sustained-release matrix tablets.

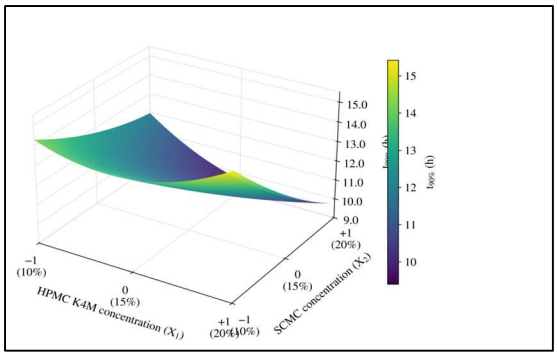

Figure 5: Response-surface plot showing the combined effect of HPMC K4M (X_1) and SCMC (X_2) concentrations on the time required for 90% drug release (t_{90}%) from Fosinopril Sodium sustained-release matrix tablets.

8.4 Validation of the Optimization Model

The predictive performance of the regression models was further examined using two checkpoint formulations, C1 and C2, prepared at intermediate levels of the formulation variables. The predicted dissolution responses showed close agreement with the experimentally observed values.

For C1, the predicted and observed values for t_{10}%, t_{50}%, t_{75}%, and t_{90}% were 0.578, 3.792, 7.588, and 12.605 h and 0.589, 3.789, 7.595, and 12.597 h, respectively. For C2, the corresponding predicted values were 0.474, 3.102, 6.210, and 10.315 h, while the observed values were 0.481, 3.117, 6.218, and 10.333 h.

The close agreement between predicted and observed responses supports the predictive capability of the developed mathematical models. The thesis therefore identifies the factorial design and response-surface approach as suitable for establishing the relationship between polymer concentration and dissolution behavior.

9. Selection of Optimized Formulation

9.1 Optimization Criteria

The optimization criterion was based on obtaining a controlled and sustained in-vitro dissolution profile appropriate for a 12-h release period. The dissolution-time responses t_{10}%, t_{50}%, t_{75}%, and t_{90}% were considered collectively to assess the release characteristics of the factorial formulations. Formulations providing progressive drug release throughout the dissolution period, without excessively rapid or excessively prolonged release, were considered preferable within the investigated formulation space. No separate numerical desirability value was available in the verified thesis material; therefore, F4 was selected on the basis of the experimentally defined dissolution characteristics reported for the factorial formulations rather than on a software-derived overall desirability score.

9.2 Selection of F4

Based on the dissolution-response profiles obtained for the nine factorial formulations, F4 was identified as the optimized formulation. F4 contained 30 mg of HPMC K4M and 40 mg of SCMC and exhibited t_{10}%, t_{50}%, t_{75}%, and t_{90}% values of 0.350, 2.268, 4.537, and 7.530 h, respectively. These responses demonstrated progressive drug release during the 12-h dissolution study and were considered appropriate according to the experimental formulation-selection criterion. F4 was therefore selected for further comparison with the marketed formulation.

9.3 Predicted Versus Experimental Response

The predictive capability of the factorial regression models was evaluated using checkpoint formulations prepared at intermediate levels of the independent variables. Two checkpoint formulations, C1 and C2, were used to compare the dissolution responses predicted by the developed mathematical models with the corresponding experimentally observed values. The close agreement between the predicted and experimental responses supported the predictive capability of the developed regression models.

Table 7: Predicted and experimental dissolution responses of checkpoint formulations

Formulation	Response	Predicted (h)	Experimental (h)	Prediction Error (%)
C1	t_{10}%	0.578	0.589	1.87
C1	t_{50}%	3.792	3.789	0.08
C1	t_{75}%	7.588	7.595	0.09
C1	t_{90}%	12.605	12.597	0.06
C2	t_{10}%	0.474	0.481	1.46
C2	t_{50}%	3.102	3.117	0.48
C2	t_{75}%	6.21	6.218	0.13
C2	t_{90}%	10.315	10.333	0.17

The predicted and experimentally observed responses showed close agreement for both checkpoint formulations. For C1, the prediction errors ranged from 0.06% to 1.87%, whereas those for C2 ranged from 0.13% to 1.46%. The small differences between predicted and experimental values support the adequacy of the developed polynomial models for describing the dissolution responses within the investigated formulation space.

Table 7 Predicted and experimentally observed values of t_{10}%, t_{50}%, t_{75}%, and t_{90}% for checkpoint formulations C1 and C2. Prediction error (%) was calculated from the reported predicted and experimental values using the absolute percentage difference, $|\text{Experimental} - \text{Predicted}|/\text{Predicted} \times 100$. The checkpoint formulations were used to assess the predictive performance of the factorial regression models.

Importantly, the thesis does not separately report predicted values or prediction errors for the optimized F4 formulation. Therefore, no predicted values for F4 have been introduced into Table 7. The experimentally observed dissolution responses for F4 were 0.350 h for t_{10}%, 2.268 h for t_{50}%, 4.537 h for t_{75}%, and 7.530 h for t_{90}%.

10. Comparison with Marketed Product

10.1 Dissolution Profile Comparison

The in-vitro dissolution profile of the optimized F4 formulation was compared with that of the marketed Fosinopril Sodium sustained-release formulation

under the dissolution conditions described for the formulation study. The comparison was performed using the dissolution profiles obtained at the reported sampling intervals over the dissolution study period. The comparative dissolution profiles of F4 and the marketed formulation are presented in Fig. 6.

The same dissolution conditions were used for comparison of the optimized and marketed formulations to minimize the influence of experimental conditions on the observed dissolution profiles. The dissolution data were used for subsequent calculation of the model-independent difference factor (f_1) and similarity factor (f_2). The calculation was based on the corresponding dissolution percentages at the common sampling time points. In accordance with the procedure reported in the thesis, only one dissolution time point after the first occurrence of greater than 85% drug release was included in the f_1/f_2 comparison.

The comparative dissolution profiles of F4 and the marketed formulation are presented in **Fig. 6**.

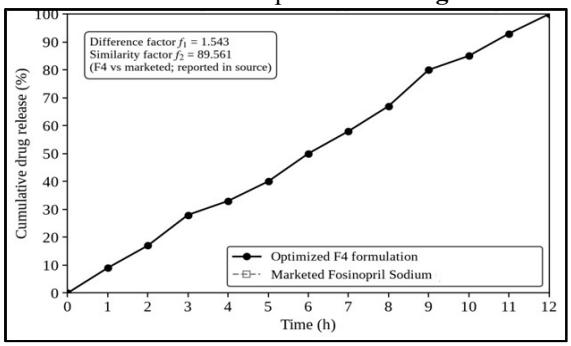

Figure 6: Comparative *in-vitro* dissolution profiles of optimized F4 formulation and the marketed Fosinopril Sodium sustained-release formulation.

Comparative in-vitro dissolution profiles of the optimized F4 formulation and the marketed Fosinopril Sodium sustained-release formulation. The profiles were compared using the model-independent difference factor (f_1) and similarity factor (f_2).

10.2 Similarity and Difference Factors

The dissolution profiles of the optimized F4 formulation and the marketed formulation were compared using the model-independent difference factor (f_1) and similarity factor (f_2). The calculated values were $f_1 = 1.543$ and $f_2 = 89.561$, indicating close similarity between the two dissolution profiles under the conditions investigated.

The high f_2 value and low f_1 value support the conclusion that the optimized F4 formulation exhibited a dissolution pattern comparable to that of the marketed formulation. However, dissolution-profile similarity should not be interpreted as evidence of bioequivalence or therapeutic equivalence, as such conclusions require appropriate in-vivo pharmacokinetic studies.

11. Discussion

11.1 Effect of Polymer Concentration

The factorial formulation study demonstrated that the concentrations of HPMC K4M and SCMC influenced the dissolution behavior of Fosinopril Sodium matrix tablets. The dissolution-time responses varied substantially across the nine formulations. In particular, t_{90}% ranged from 7.53 h for F4 to 14.0 h for F3, demonstrating a considerable difference in the time required to achieve 90% drug release across the experimental design space. Similarly, t_{50}% ranged from 2.27 h for F4 to 4.22 h for F3, while t_{75}% ranged from 4.54 to 8.44 h.

These differences indicate that polymer concentration and formulation composition were important determinants of drug-release behavior. HPMC K4M contributes to the formation of a hydrated polymeric matrix in which water penetration, polymer swelling, and drug diffusion are regulated. SCMC also contributes through its hydrophilic and swelling characteristics. However, the observed responses did not follow a simple monotonic relationship with the concentration of either polymer alone, indicating that the overall release behavior was dependent on the combination of HPMC K4M and SCMC concentrations.

11.2 Polymer Interaction

An important advantage of the 3^2 factorial design was its ability to evaluate the combined influence of HPMC K4M and SCMC. The X_1X_2 interaction term was incorporated into the second-order regression models for all four dissolution responses, demonstrating that the influence of one formulation variable was evaluated in relation to the level of the other variable.

The response-surface analysis further showed that changes in the concentrations of both polymers produced corresponding changes in the dissolution-time responses. Thus, the release characteristics were governed not simply by the concentration of an individual polymer but by the formulation combination. This behavior is relevant to hydrophilic matrix systems, in which the relative contribution of different polymers can influence hydration, swelling, gel development, diffusional resistance, and matrix erosion.

11.3 Matrix Hydration and Gel Formation

The sustained-release behavior can be associated with hydration and swelling of the hydrophilic polymers following exposure to the dissolution medium. The thesis reports progressive swelling of the formulations during the dissolution study, with F4 showing the highest reported swelling index at 12 h.

Upon hydration, HPMC K4M and SCMC form a swollen polymeric layer surrounding the tablet matrix. This hydrated layer can act as a barrier to

drug transport and increase the diffusional pathway through which dissolved drug passes. Continued hydration, swelling, diffusion, and gradual matrix erosion can therefore contribute to the overall release process.

The relationship between polymer composition, swelling behavior, and dissolution supports the proposed role of matrix hydration in regulating Fosinopril Sodium release. Nevertheless, gel-layer thickness and polymer erosion were not directly characterized in the present study. Therefore, these processes should be considered mechanistic interpretations supported by the dissolution and swelling observations rather than directly measured mechanisms.

11.4 Factorial Design as an Optimization Tool

The 3^2 full factorial design provided a systematic approach for evaluating the effects of HPMC K4M and SCMC on drug-release behavior. Unlike conventional trial-and-error formulation development, the factorial approach enabled simultaneous investigation of two formulation variables at three concentration levels and permitted evaluation of their combined influence.

In the present study, the two polymers generated nine experimental combinations. The resulting dissolution data were used to develop second-order polynomial models for t_{10}%, t_{50}%, t_{75}%, and t_{90}%. Response-surface analysis subsequently provided a graphical representation of the relationship between polymer composition and dissolution behavior.

A further strength of the experimental design was the evaluation of checkpoint formulations. For C1, the predicted and experimental values were 0.578 and 0.589 h for t_{10}%, 3.792 and 3.789 h for t_{50}%, 7.588 and 7.595 h for t_{75}%, and 12.605 and 12.597 h for t_{90}%, respectively. For C2, the corresponding predicted and experimental values were 0.474 and 0.481 h, 3.102 and 3.117 h, 6.210 and 6.218 h, and 10.315 and 10.333 h, respectively. The relatively small prediction errors reported for these checkpoint responses support the predictive usefulness of the developed mathematical models.

11.5 Optimized Formulation Performance

F4 was identified as the optimized formulation among the nine factorial batches. F4 contained 30 mg HPMC K4M and 40 mg SCMC and exhibited t_{10}%, t_{50}%, t_{75}%, and t_{90}% values of 0.350, 2.268, 4.537, and 7.530 h, respectively. The formulation achieved 100% drug release at 12 h under the conditions of the dissolution study.

The performance of F4 indicates a formulation balance between polymer-mediated matrix resistance and progressive drug transport. Its dissolution profile demonstrated controlled release throughout the 12-h study while permitting substantial drug release by the end of the test period. The combination of HPMC K4M and SCMC therefore provided a matrix composition capable of modifying Fosinopril Sodium release over the investigated period.

Importantly, the present findings establish in-vitro formulation performance only. They do not demonstrate in-vivo pharmacokinetic performance, bioequivalence, therapeutic efficacy, or clinical benefit. Such conclusions would require appropriate in-vivo investigations.

11.6 Comparison with Marketed Product

The optimized F4 formulation was further compared with the marketed formulation using model-independent dissolution-profile comparison. The calculated difference factor (f_1) was 1.543, whereas the similarity factor (f_2) was 89.561.

The low f_1 value and high f_2 value indicate close similarity between the dissolution profiles of F4 and the marketed formulation under the experimental conditions used. This comparison provides additional support for the dissolution performance of the optimized formulation because F4 was evaluated not only against the other factorial formulations but also against an established marketed product.

However, dissolution-profile similarity should not be interpreted as evidence of bioequivalence or therapeutic equivalence. Such conclusions require appropriately designed in-vivo pharmacokinetic and/or bioequivalence studies, which were beyond the scope of the present investigation.

11.7 Pharmaceutical Significance

The present study demonstrates the feasibility of developing Fosinopril Sodium sustained-release matrix tablets using HPMC K4M and SCMC as hydrophilic matrix-forming polymers. Systematic variation of the two polymers produced measurable differences in dissolution behavior, while the 3^2 factorial design provided a structured approach for investigating formulation effects and identifying an optimized composition.

Among the nine formulations, F4 exhibited the shortest t_{90}% value of 7.530 h and achieved complete drug release by 12 h under the investigated dissolution conditions. Its dissolution profile was also comparable to that of the marketed formulation, with an f_1 value of 1.543 and an f_2 value of 89.561.

Overall, the findings demonstrate the usefulness of factorial experimental design for systematic optimization of hydrophilic polymer combinations in sustained-release matrix tablets. Further studies, particularly stability evaluation and appropriate in-vivo pharmacokinetic and bioequivalence investigations, would be required to establish the long-term performance and clinical relevance of the optimized formulation.

12. Conclusion

Fosinopril Sodium sustained-release matrix tablets were successfully developed using HPMC K4M and SCMC and systematically optimized through a 3^2 full factorial design. Variation in polymer composition produced measurable differences in the dissolution-time responses, enabling identification of F4 as the optimized formulation. F4 provided sustained in-vitro drug release over 12 h and exhibited a dissolution profile comparable to that of the marketed formulation, with an f_1 value of 1.543 and an f_2 value of 89.561. The findings demonstrate the utility of factorial experimental design for the systematic optimization of hydrophilic matrix formulations. Further stability and in-vivo studies are required to establish the long-term stability and pharmacokinetic performance of the optimized formulation.

13. Abbreviations

API, Active Pharmaceutical Ingredient; ANOVA, Analysis of Variance; DoE, Design of Experiments; f_1, Difference Factor; f_2, Similarity Factor; FTIR, Fourier Transform Infrared Spectroscopy; HPMC, Hydroxypropyl Methylcellulose; HPMC K4M, Hydroxypropyl Methylcellulose K4M; IP, Indian Pharmacopoeia; QbD, Quality by Design; SCMC, Sodium Carboxymethyl Cellulose; SD, Standard Deviation; SR, Sustained Release; t_{10}%, Time required for 10% drug release; t_{50}%, Time required for 50% drug release; t_{75}%, Time required for 75% drug release; t_{90}%, Time required for 90% drug release; USP, United States Pharmacopeia; UV, Ultraviolet; X_1, HPMC K4M concentration; X_2, SCMC concentration; Y_1, t_{10}% dissolution response; Y_2, t_{50}% dissolution response; Y_3, t_{75}% dissolution response; Y_4, t_{90}% dissolution response; R^2, Coefficient of determination; C1 and C2, Checkpoint formulations; F1–F9, Factorial formulations 1–9.

14. Declarations

- **Ethics Approval:** Ethics approval was not required for this study because the work involved pharmaceutical formulation development and in-vitro evaluation of Fosinopril Sodium matrix tablets and did not involve human participants, human tissue, or experimental animals.
- **Consent for Publication:** Not applicable. This manuscript does not contain individual person's data or identifiable information.
- **Data Availability Statement:** The data generated and/or analyzed during the present study are available from the corresponding author upon reasonable request.
- **Conflict of Interest:** The authors declare that they have no competing interests or conflicts of interest that could have influenced the work reported in this manuscript.
- **Funding:** The authors received no specific funding for this study. The research was conducted without external financial support.
- **Author Contributions:** Hanuman Shrikishan Kolse: Conceptualization, Methodology, Investigation, Formulation development, Data curation, Formal analysis, Validation, Visualization, and Writing – original draft. Dr. Shikha Jaiswal: Conceptualization, Supervision, Methodology, Validation, Resources, Project administration, and Writing – review & editing. Both authors contributed to the interpretation of the results, critically reviewed the manuscript, and approved the final version for publication.

15. References

[1] P. Prajapat, D. Agrawal, and G. Bhaduka, "A brief overview of sustained released drug delivery system," *J. Appl. Pharm. Res.*, vol. 10, no. 3, pp. 05–11, 2022, doi: 10.18231/j.joapr.2022.10.3.5.11.

[2] P. Drapińska, K. Skulmowska-Polok, J. Chałupka, and A. Sikora, "Sustained-Release Oral Delivery of NSAIDs and Acetaminophen: Advances and Recent Formulation Strategies—A Systematic Review," *Pharmaceutics*, vol. 17, no. 10, 2025, doi: 10.3390/pharmaceutics17101264.

[3] T. H. Baryakova, B. H. Pogostin, R. Langer, and K. J. McHugh, "Overcoming barriers to patient adherence: the case for developing innovative drug delivery systems," *Nat. Rev. Drug Discov.*, vol. 22, no. 5, pp. 387–409, 2023, doi: 10.1038/s41573-023-00670-0.

[4] M. A. Waqar, N. Mubarak, A. M. Khan, R. Khan, F. Shaheen, and A. Shabbir, "Advanced polymers and recent advancements on gastroretentive drug delivery system; a comprehensive review," *J. Drug Target.*, vol. 32, no. 6, pp. 655–671, 2024, doi: 10.1080/1061186X.2024.2347366.

[5] N. Campos-Morales *et al.*, "PLGA-Based In Situ-Forming Implants, a Quality by Design Perspective," *Pharmaceutics*, vol. 18, no. 3, 2026, doi: 10.3390/pharmaceutics18030351.

[6] S. A. S. Farhadi and K. F. Dizaye, "Aliskiren, Fosinopril, and Their Outcome on Renin-Angiotensin-Aldosterone System (RAAS) in Rats with Thyroid Dysfunction," *Int. J. Endocrinol.*, vol. 2019, 2019, doi: 10.1155/2019/5960563.

[7] J. L. Izzo and M. R. Weir, "Angiotensin-converting enzyme inhibitors," *J. Clin. Hypertens.*, vol. 13, no. 9, pp. 667–675, 2011,

doi: 10.1111/j.1751-7176.2011.00508.x.

[8] H. Ahmad, H. Khan, S. Haque, S. Ahmad, N. Srivastava, and A. Khan, "Angiotensin-Converting Enzyme and Hypertension: A Systemic Analysis of Various ACE Inhibitors, Their Side Effects, and Bioactive Peptides as a Putative Therapy for Hypertension," *JRAAS - J. Renin-Angiotensin-Aldosterone Syst.*, vol. 2023, 2023, doi: 10.1155/2023/7890188.

[9] N. Kamaly, B. Yameen, J. Wu, and O. C. Farokhzad, "Degradable controlled-release polymers and polymeric nanoparticles: Mechanisms of controlling drug release," *Chem. Rev.*, vol. 116, no. 4, pp. 2602–2663, 2016, doi: 10.1021/acs.chemrev.5b00346.

[10] N. A. Khan *et al.*, "Preparation and Characterization of Hydrophilic Polymer Based Sustained-Release Matrix Tablets of a High Dose Hydrophobic Drug," *Polymers (Basel).*, vol. 14, no. 10, 2022, doi: 10.3390/polym14101985.

[11] K. Ménochet *et al.*, "Intestinal epithelium and drug transporters," *Oral Drug Deliv. Modif. Release Formul.*, pp. 39–64, 2021, doi: 10.1002/9781119772729.ch3.

[12] H. M. Hnin, E. Stefánsson, T. Loftsson, R. Asasutjarit, D. Charnvanich, and P. Jansook, "Physicochemical and Stability Evaluation of Topical Niosomal Encapsulating Fosinopril/γ-Cyclodextrin Complex for Ocular Delivery," *Pharmaceutics*, vol. 14, no. 6, 2022, doi: 10.3390/pharmaceutics14061147.

[13] N. B. Demina, "Current Trends in the Development of Technologies for Matrix Formulations with Modified Release (Review)," *Pharm. Chem. J.*, vol. 50, no. 7, pp. 475–480, 2016, doi: 10.1007/s11094-016-1472-4.

[14] D. G. Dastidar, A. Biswas, A. Das, S. Naskar, and R. Mahish, "Development and Optimization of Sustained-Release Matrix Tablets of Diclofenac Sodium Using Carboxymethylated Chitosan Through Systematic Application of Design of Experiments," *Drug Metab. Bioanal. Lett.*, vol. 17, no. 3, pp. 121–136, 2025, doi: 10.2174/0118723128351869250213102431.

[15] A. Alhalmi, M. Altowairi, O. Saeed, N. Alzubaidi, M. Almoiliqy, and W. Abdulmalik, "Sustained Release Matrix System: An Overview," *World J. Pharm. Pharm. Sci.*, vol. 7, no. 6, pp. 1470–1486, 2018, doi: 10.20959/wjpps20186-11835.

[16] P. Timmins, D. Desai, W. Chen, P. Wray, J. Brown, and S. Hanley, "Advances in mechanistic understanding of release rate control mechanisms of extended-release hydrophilic matrix tablets," *Ther. Deliv.*, vol. 7, no. 8, pp. 553–572, 2016, doi: 10.4155/tde-2016-0026.

[17] A. Amanzholkyzy *et al.*, "Hydrogel Delivery Systems for Biological Active Substances: Properties and the Role of HPMC as a Carrier," *Molecules*, vol. 30, no. 6, 2025, doi: 10.3390/molecules30061354.

[18] L. Lamoudi, J. C. Chaumeil, and K. Daoud, "Swelling, erosion and drug release characteristics of Sodium Diclofenac from heterogeneous matrix tablets," *J. Drug Deliv. Sci. Technol.*, vol. 31, pp. 93–100, 2016, doi: 10.1016/j.jddst.2015.12.005.

[19] S. Bagde and B. D. Rohera, "Modification of the swelling behavior of a hydrophilic polymer as an approach to maintaining a constant gel layer thickness," *J. Drug Deliv. Sci. Technol.*, vol. 92, 2024, doi: 10.1016/j.jddst.2023.105294.

[20] A. Türkdoğan, T. Alloush, and B. Demiralp, "Experimental Design in Pharmaceutical Formulation Development: Achievements, Limitations and the Transition Toward Intelligent Optimization," *Sci. Pharm.*, vol. 94, no. 2, 2026, doi: 10.3390/scipharm94020038.

[21] I. Lucas, J. Sousa, and C. Vitorino, "Integrating artificial intelligence into drug delivery systems: Formulation development and current challenges," *Eur. J. Pharm. Biopharm.*, vol. 226, 2026, doi: 10.1016/j.ejpb.2026.115133.

[22] S. Beg, S. Swain, M. Rahman, M. S. Hasnain, and S. S. Imam, "Application of Design of Experiments (DoE) in Pharmaceutical Product and Process Optimization," *Pharm. Qual. by Des. Princ. Appl.*, pp. 43–64, 2019, doi: 10.1016/B978-0-12-815799-2.00003-4.

[23] E. M. Anderson, J. R. Niska, and E. E. Niska, "Factorial design," *Transl. Radiat. Oncol.*, pp. 327–330, 2023, doi: 10.1016/B978-0-323-88423-5.00110-2.

[24] A. Jankovic, G. Chaudhary, and F. Goia, "Designing the design of experiments (DOE) – An investigation on the influence of different factorial designs on the characterization of complex systems," *Energy Build.*, vol. 250, 2021, doi: 10.1016/j.enbuild.2021.111298.

[25] L. Sbârcea, I. Ledeți, L. Drəgan, L. Kurunczi, A. Fuliaş, and L. Udrescu, "Fosinopril

sodium-hydroxypropyl-β-cyclodextrin inclusion complex: Thermal decomposition kinetics and compatibility studies," *J. Therm. Anal. Calorim.*, vol. 120, no. 1, pp. 981–990, 2015, doi: 10.1007/s10973-015-4450-2.

[26] L. Udrescu *et al.*, "Physicochemical Analysis and Molecular Modeling of the Fosinopril β -Cyclodextrin Inclusion Complex," *J. Spectrosc.*, vol. 2014, 2014, doi: 10.1155/2014/748468.

[27] H. G. Brittain, K. R. Morris, D. E. Bugay, A. B. Thakur, and A. T. M. Serajuddin, "Solid-state NMR and IR for the analysis of pharmaceutical solids: Polymorphs of fosinopril sodium," *J. Pharm. Biomed. Anal.*, vol. 11, no. 11–12, pp. 1063–1069, 1993, doi: 10.1016/0731-7085(93)80083-D.

[28] P. Tang *et al.*, "Machine learning-guided optimization of probiotic chickpea milk fermentation enhances antioxidant capacity, volatile aroma profile, and sensory quality," *Futur. Foods*, vol. 13, 2026, doi: 10.1016/j.fufo.2026.101032.

[29] M. Akhtar *et al.*, "Response Surface Methodology (RSM) approach to formulate and optimize the bilayer combination tablet of Tamsulosin and Finasteride," *Saudi Pharm. J.*, vol. 32, no. 3, 2024, doi: 10.1016/j.jsps.2024.101957.

[30] M. A. Mujtaba *et al.*, "Design of Experiments Assisted Formulation Optimization and Evaluation of Efavirenz Solid Dispersion Adsorbate for Improvement in Dissolution and Flow Properties," *Drug Des. Devel. Ther.*, vol. 19, pp. 3715–3734, 2025, doi: 10.2147/DDDT.S517021.

[31] Y. T. Mekasha, A. Wondie Mekonen, S. Nigussie, R. E. Usure, and M. G. Feleke, "Modeling and comparison of dissolution profiles for different brands of albendazole boluses," *BMC Pharmacol. Toxicol.*, vol. 25, no. 1, 2024, doi: 10.1186/s40360-024-00774-2.

[32] S. A. Fouad, F. A. Malaak, M. A. El-Nabarawi, and K. A. Zeid, "Development of orally disintegrating tablets containing solid dispersion of a poorly soluble drug for enhanced dissolution: In-vitro optimization/in-vivo evaluation," *PLoS One*, vol. 15, no. 12 12, 2020, doi: 10.1371/journal.pone.0244646.

[33] A. Shahiwala and A. Zarar, "Pharmaceutical Product Lead Optimization for Better In Vivo Bioequivalence Performance: A case study of Diclofenac Sodium Extended Release Matrix Tablets," *Curr. Drug Deliv.*, vol. 14, 2017, doi: 10.2174/1567201814666171120124551.

[34] J. Siepmann and N. A. Peppas, "Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC)," *Adv. Drug Deliv. Rev.*, vol. 64, no. SUPPL., pp. 163–174, 2012, doi: 10.1016/j.addr.2012.09.028.

[35] J. Djuris, D. Vasiljevic, and S. Ibric, "Experimental design application and interpretation in pharmaceutical technology," *Comput. Appl. Pharm. Technol. Deliv. Syst. Dos. Forms, Pharm. Unit Oper.*, pp. 61–85, 2023, doi: 10.1016/B978-0-443-18655-4.00002-9.

[36] A. A. M. Shimojo, A. R. V. Fernandes, N. R. E. Ferreira, E. Sanchez-Lopez, M. H. A. Santana, and E. B. Souto, "Evaluation of the influence of process parameters on the properties of resveratrol-loaded NLC using 22 full factorial design," *Antioxidants*, vol. 8, no. 8, 2019, doi: 10.3390/antiox8080272.

[37] X. Zhang *et al.*, "Formulation optimization of dihydroartemisinin nanostructured lipid carrier using response surface methodology," *Powder Technol.*, vol. 197, no. 1–2, pp. 120–128, 2010, doi: 10.1016/j.powtec.2009.09.004.

[38] A. Mohammad, S. Singh, S. Swain, and D. Ghose, "Quality by Design Enabled β-Cyclodextrin Complexes of Lisinopril by Kneading Method: Improved Solubility and Bioavailability," *Curr. Mater. Sci.*, vol. 17, no. 2, pp. 135–147, 2023, doi: 10.2174/2666145416666230407100318.