INFLUENCE OF HPMC K4M AND SODIUM CARBOXYMETHYL CELLULOSE ON SWELLING BEHAVIOR AND DRUG RELEASE OF FOSINOPRIL SODIUM SUSTAINED-RELEASE MATRIX TABLETS: A 3^2 FACTORIAL DESIGN APPROACH

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ABSTRACT:
Fosinopril Sodium is an angiotensin-converting enzyme inhibitor that may benefit from sustained-release delivery to maintain drug release over an extended period. The present study investigated the influence of HPMC K4M and sodium carboxymethyl cellulose (SCMC) on the swelling behavior and drug-release characteristics of Fosinopril Sodium matrix tablets. A 3^2 full factorial design was employed to study the effects of three levels of HPMC K4M and SCMC, resulting in nine formulations (F1–F9). The prepared tablets were evaluated for pre-compression and post-compression properties, swelling behavior, and in-vitro drug release. Dissolution data were further analyzed using dissolution-time parameters and release kinetic models to understand the mechanism of drug release. The formulations showed differences in swelling and drug-release behavior with changes in polymer composition. The optimized formulation, F4, containing 30 mg of HPMC K4M and 40 mg of SCMC, showed t_{10}%, t_{50}%, t_{75}%, and t_{90}% values of 0.350, 2.268, 4.537, and 7.530 h, respectively, and released the drug completely within 12 h. The findings indicated that the combined use of HPMC K4M and SCMC provided effective control over matrix hydration and drug release. Comparison with the marketed formulation showed similar dissolution behavior, with an f_1 value of 1.543 and an f_2 value of 89.561. Overall, the study demonstrates that the relative concentrations of HPMC K4M and SCMC can be used to modify swelling and drug-release behavior in Fosinopril Sodium sustained-release matrix tablets.

Keywords: Fosinopril Sodium; HPMC K4M; Sodium carboxymethyl cellulose; Matrix tablets; Swelling behavior; Drug release kinetics
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1. Introduction

1.1 Fosinopril Sodium and Rationale for Sustained Release

Fosinopril Sodium is an angiotensin-converting enzyme inhibitor used in the management of hypertension and related cardiovascular conditions[1], [2]. Conventional oral dosage forms may require repeated administration to maintain drug exposure over the dosing interval[3], [4]. Sustained-release dosage forms are designed to release the drug gradually over an extended period and may provide more consistent drug availability while reducing the frequency of administration[5], [6]. Matrix tablets are particularly useful for this purpose because their release characteristics can be adjusted by changing the type and concentration of the matrix-forming polymers[7], [8], [9].

1.2 Hydrophilic Matrix Systems

Hydrophilic matrix tablets are widely used for sustained drug delivery because of their relatively simple formulation and manufacturing process[10]. When the tablet comes into contact with an aqueous dissolution medium, the hydrophilic polymer absorbs water, swells, and forms a hydrated layer around the matrix[11], [12]. Drug release then occurs through a combination of diffusion through the hydrated polymer layer and gradual erosion of the matrix[13], [14]. The extent of hydration and the structure of the resulting gel layer depend, among other factors, on the type and amount of polymer used[15], [16].

1.3 Role of HPMC K4M

Hydroxypropyl methylcellulose K4M (HPMC K4M) is a commonly used hydrophilic matrix-forming polymer[17], [18]. Following hydration, it develops a swollen gel layer that can act as a barrier to drug transport[19], [20]. The thickness and strength of this hydrated layer are influenced by the amount of polymer present in the formulation and can consequently affect the rate of drug diffusion from the matrix[21], [22]. HPMC K4M was therefore selected as one of the formulation variables in the present study.

1.4 Role of Sodium Carboxymethyl Cellulose (SCMC)

Sodium carboxymethyl cellulose (SCMC) is another hydrophilic polymer capable of absorbing water and undergoing swelling[23]. Its hydration characteristics can contribute to formation and maintenance of the hydrated matrix during dissolution[21], [24]. The presence of SCMC can therefore influence water penetration, matrix swelling, and the subsequent movement of drug through the hydrated structure[25], [26]. In combination with HPMC K4M, SCMC provides an opportunity to modify the overall release characteristics of the matrix system[27].

1.5 Importance of Polymer Concentration and Polymer Combination

The concentration of a matrix-forming polymer is an important formulation variable because changes in polymer content can alter hydration, swelling, gel formation, and the resistance encountered by the drug during release[28], [29]. When two hydrophilic polymers are used together, their relative concentrations may also affect the overall behavior of the matrix[30]. Thus, evaluating HPMC K4M and SCMC separately may not fully describe the performance of their combination[31]. A systematic investigation of both polymers at different concentration levels is therefore useful for understanding their individual and combined effects on drug release[13], [32].

1.6 Swelling Behavior and Drug-Release Mechanisms

Swelling is an important feature of hydrophilic matrix systems and is closely associated with their ability to control drug release[33], [34]. After exposure to the dissolution medium, water penetrates the tablet and hydrates the polymer chains[35], [36]. Polymer swelling and gel-layer formation increase the distance through which dissolved drug must travel before reaching the surrounding medium[37], [38]. Drug release may subsequently occur through diffusion across the hydrated matrix, together with gradual erosion of the polymeric structure[39], [40]. The balance among these processes can influence the overall release profile of the formulation[41], [42].

1.7 Research Gap and Rationale

Although hydrophilic polymers such as HPMC K4M and sodium carboxymethyl cellulose (SCMC) are widely used in matrix-based drug delivery systems, their combined concentration-dependent effects may vary with the drug, polymer ratio, and formulation composition. In particular, systematic evaluation of the combined influence of HPMC K4M and SCMC on the swelling behavior and dissolution-time characteristics of Fosinopril Sodium matrix tablets remains limited. A formulation approach that considers the two polymers simultaneously may provide better insight into their individual and combined effects than changing one polymer at a time.

Therefore, the present study was designed to systematically investigate the influence of HPMC K4M and SCMC concentrations on the swelling behavior and drug-release characteristics of Fosinopril Sodium sustained-release matrix tablets. A 3^2 full factorial experimental design was employed to evaluate the effects of the two formulation variables at three concentration levels and to examine their combined influence on the dissolution-time responses.

1.8 Study Objective and Hypothesis

The objective of the present study was to investigate the influence of HPMC K4M and SCMC concentrations on the swelling behavior and drug-release characteristics of Fosinopril Sodium sustained-release matrix tablets using a 3^2 full factorial experimental design. The study further aimed to characterize the resulting dissolution behavior, establish mathematical relationships between polymer composition and dissolution-time responses, and identify an experimentally suitable formulation within the investigated design space.

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

2. Materials and Methods

2.1 Materials

Fosinopril Sodium was used as the model drug for preparation of sustained-release matrix tablets. HPMC K4M and sodium carboxymethyl cellulose (SCMC) were selected as hydrophilic matrix-forming polymers. Lactose monohydrate was used as a diluent, and magnesium stearate was used as a lubricant. All other reagents and materials used in the study were of appropriate pharmaceutical or analytical grade.

2.2 Preformulation and Drug–Excipient Compatibility

Preformulation investigations were performed to support the incorporation of Fosinopril Sodium into the hydrophilic matrix system. Fourier-transform infrared (FTIR) spectroscopy was used to assess the compatibility of Fosinopril Sodium with HPMC K4M and sodium carboxymethyl cellulose (SCMC). FTIR analysis indicated retention of the characteristic absorption bands of Fosinopril Sodium in the physical mixtures with HPMC K4M and SCMC, with no major spectral changes or newly appearing characteristic bands. These findings did not indicate detectable chemical incompatibility between the drug and the selected polymers under the conditions investigated.

2.3 Experimental Design and Formulation Composition

A three-level, two-factor full factorial design (3^2) was employed to investigate the effects of HPMC K4M (X_1) and SCMC (X_2) concentrations on the swelling behavior and drug-release characteristics of Fosinopril Sodium sustained-release matrix tablets. Each polymer was investigated at three concentration levels represented by coded values of −1, 0, and +1, generating nine experimental formulations (F1–F9).

The concentrations of HPMC K4M and SCMC were varied systematically, while the amount of Fosinopril Sodium and the total tablet weight were maintained at 20 and 200 mg per tablet, respectively. The experimental design and formulation composition are presented in Table 1.

Table 1: Experimental design and composition of Fosinopril Sodium sustained-release matrix tablets

Formulation	X_1: HPMC K4M	X_2: SCMC	Fosinopril Sodium (mg)	HPMC K4M (mg)	SCMC (mg)	Lactose monohydrate (mg)	Magnesium stearate (mg)	Total weight (mg)
F1	1	1	20	40	40	92	4	200
F2	1	0	20	40	30	102	4	200
F3	1	−1	20	40	20	112	4	200
F4	0	1	20	30	40	102	4	200
F5	0	0	20	30	30	112	4	200
F6	0	−1	20	30	20	122	4	200
F7	−1	1	20	20	40	112	4	200
F8	−1	0	20	20	30	122	4	200
F9	−1	−1	20	20	20	132	4	200

HPMC K4M, hydroxypropyl methylcellulose K4M; SCMC, sodium carboxymethyl cellulose.

2.4 Preparation of Matrix Tablets

The required quantities of Fosinopril Sodium, HPMC K4M, SCMC, and lactose monohydrate were accurately weighed and blended to obtain uniform powder mixtures. Magnesium stearate was subsequently added and mixed with the powder blend. The resulting blends were compressed using the reported direct-compression method to obtain tablets with a target weight of 200 mg. The same preparation procedure was followed for all nine formulations.

2.5 Pre-compression Evaluation

Before compression, the powder blends of formulations F1–F9 were evaluated for their micromeritic properties, including angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner ratio. Bulk density was determined by measuring the mass of a known quantity of powder and its initial untapped volume, whereas tapped density was determined after mechanical tapping until a constant volume was obtained. Carr's compressibility index and Hausner ratio were calculated from the corresponding bulk and tapped density values. Angle of repose was determined using the fixed-funnel method by measuring the height and radius of the resulting powder cone. Angle-of-repose determinations were performed in triplicate and expressed as mean ± standard deviation. The reported bulk and tapped density values were used for calculation of Carr's compressibility index and Hausner ratio.

Table 2: Pre-compression characteristics of Fosinopril Sodium sustained-release matrix tablet powder blends

Formulation	Angle of repose (°)	Bulk density (g/cm³)	Tapped density (g/cm³)	Carr's compressibility index (%)	Hausner ratio
F1	25 ± 2	2.83 ± 0.05	3.70 ± 0.30	23.51	1.3
F2	27 ± 2	2.75 ±	4.50 ±	29.48	1.41

		0.04	0.50		
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 for angle of repose, bulk density, and tapped density are presented as mean ± standard deviation where reported. 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.

2.6 Post-compression Evaluation

The prepared matrix tablets were evaluated for hardness, thickness, friability, weight variation, and drug content. The results of the post-compression evaluation are summarized in Table 3.

Table 3: 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 ± 0.27	98.48 ± 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

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.

2.7 Drug-Content Determination

Drug content was determined to assess the uniformity of Fosinopril Sodium in the prepared matrix tablets. Tablets were analyzed using the established analytical procedure, and the drug content was expressed as a percentage of the labeled amount.

2.8 Swelling Study

The swelling behavior of the matrix tablets was evaluated under conditions identical to those used for the in-vitro dissolution study. Before the experiment, the tablets were accurately weighed to determine their initial dry weight (W_0). Individual tablets were then immersed in the selected dissolution medium maintained at 37 ± 0.5°C. At predetermined time intervals of 1, 2, 4, 6, 8, and 12 h, the tablets were carefully removed from the medium and gently blotted with filter paper to remove excess surface medium without disturbing the hydrated matrix. The swollen tablets were immediately reweighed to determine their hydrated weight (W_t).

The swelling index (SI) was calculated from the change in tablet weight according to the following equation:

$$\textbf{SI (\%)} = \frac{W_t - W_0}{W_0} \times 100$$

where $\mathbf{W_0}$ is the initial dry weight of the tablet and $\mathbf{W_t}$ is the weight of the swollen tablet at the respective sampling time. The measurements were performed in triplicate, and the results were expressed as mean ± standard deviation.

The swelling profiles were evaluated to assess the hydration behavior of the HPMC K4M–SCMC matrix and to examine its relationship with the drug-release characteristics.

2.9 *In-vitro* Dissolution Study

The *in-vitro* drug-release behavior of Fosinopril Sodium sustained-release matrix tablets was evaluated using USP Dissolution Apparatus II (paddle method)[43]. 0.1 N hydrochloric acid (HCl) was used as the dissolution medium, based on the dissolution and analytical procedure reported in the original formulation study. A dissolution medium volume of 900 mL was used, and the 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 and suitably diluted where required before analysis by UV–visible spectrophotometry using the established Fosinopril Sodium calibration procedure. The calibration curve was prepared over the concentration range of 2–10 µg/mL, and the reported regression equation was $y = 0.095x + 0.018$.

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. The dissolution profiles of formulations F1–F9 were used to determine the time required to achieve 10%, 50%, 75%, and 90% drug release (t_{10}%, t_{50}%, t_{75}%, and t_{90}%, respectively).

2.10 Drug-release Kinetic Analysis

The dissolution data obtained for the Fosinopril Sodium sustained-release matrix tablets were analyzed using zero-order, first-order, Higuchi, and Korsmeyer–Peppas mathematical models to characterize the drug-release behavior. The coefficient of determination (R^2) was used to assess the linearity and comparative fit of the respective models. Among the models evaluated, the zero-order model showed the highest reported linearity, with R^2 values ranging from 0.993 to 0.999 across the investigated formulations.

The Korsmeyer–Peppas model was additionally considered for characterization of drug release from the polymeric matrix[44], [45]. The release exponent (n) was considered where available; however, formulation-specific n values. The kinetic analysis was used to provide a mathematical description of the dissolution profiles rather than to establish a definitive physical release mechanism.

2.11 Model-independent Comparison with Marketed Formulation

The dissolution profile of the optimized F4 formulation was compared with that of the marketed Fosinopril Sodium sustained-release formulation using the model-independent difference factor (f_1) and similarity factor (f_2).

The f_1 and f_2 values were calculated from the corresponding dissolution profiles using the reported sampling points. The resulting values were $f_1 = 1.543$ and $f_2 = 89.561$. The comparison was used to assess similarity between the dissolution profiles under the investigated conditions and was not interpreted as evidence of bioequivalence or therapeutic equivalence.

2.12 Statistical Analysis

The effects of HPMC K4M (X_1) and SCMC (X_2) concentrations on the dissolution-time responses were evaluated using a 3^2 full factorial experimental design. Second-order polynomial regression models incorporating linear terms (X_1 and X_2), an interaction term (X_1X_2), and quadratic terms (X_1^2 and X_2^2) were used to describe the relationships between the formulation variables and the dissolution responses (t_{10}%, t_{50}%, t_{75}%, and t_{90}%).

Analysis of variance (ANOVA) was used to assess the statistical significance of the fitted regression models, with $p < 0.05$ considered statistically significant[46]. Response-surface methodology was used to visualize the combined effects of HPMC K4M and SCMC concentrations on the dissolution-time responses[47]. The regression equations were also used to describe the relationship between the formulation variables and the experimentally observed dissolution behavior.

Where supported by the original statistical analysis, model F-value, model *p*-value, coefficient of determination (R^2), adjusted R^2, predicted R^2, lack-of-fit, standard error, adequate precision, and the statistical significance of individual model coefficients were considered in assessing model adequacy. These statistics were reported only when supported by the original Design-Expert/statistical output or validated experimental data and were not estimated or reconstructed from the regression equations.

The predictive performance of the developed models was further assessed using the available checkpoint formulations by comparing predicted and experimentally observed dissolution responses. The agreement between predicted and experimental values was considered as an additional assessment of the suitability of the factorial models for describing the formulation-dependent dissolution behavior.

3. Results

3.1 Powder-Flow Properties

The powder blends of formulations F1–F9 showed angle-of-repose values ranging from 25° to 30°. The reported bulk and tapped density values ranged from 2.65–2.86 and 3.70–6.50 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. F1 showed the lowest Carr's compressibility index and Hausner ratio, whereas F8 showed the highest values. These differences indicated variation in the packing and compressibility characteristics of the powder blends.

3.2 Tablet Characteristics

The prepared matrix tablets showed relatively consistent physical characteristics with respect to hardness, thickness, friability, and tablet weight **(**Table 2**).** Hardness ranged from 3.50 ± 0.20 to 4.08 ± 0.30 kg/cm², thickness ranged from 2.46 ± 0.14 to 2.85 ± 0.13 mm**,** and friability ranged from 0.21 ± 0.026% to 0.52 ± 0.043%. The measured tablet weights also showed limited variation among the formulations.

3.3 Drug-Content Uniformity

The drug content of formulations F1–F9 ranged from 98.46 ± 0.44% to 99.58 ± 0.32% **(**Table 2**)**. The relatively narrow variation in drug content indicated uniform distribution of Fosinopril Sodium within the prepared matrix tablets.

3.4 Swelling Behavior

The swelling behavior of the matrix tablets varied with the concentrations and combinations of HPMC K4M and SCMC. Progressive hydration and swelling were observed during exposure to the dissolution medium. Among the investigated formulations, F4 showed the highest reported swelling index at 12 h**.**

The differences in swelling behavior were considered together with the dissolution results to assess the influence of polymer composition on water uptake, matrix hydration, and structural integrity.

3.5 Effect of HPMC K4M and SCMC on Dissolution

The cumulative in-vitro drug-release profiles of formulations F1–F9 were evaluated over 12 h. The dissolution profiles are presented in **Fig. 1**.

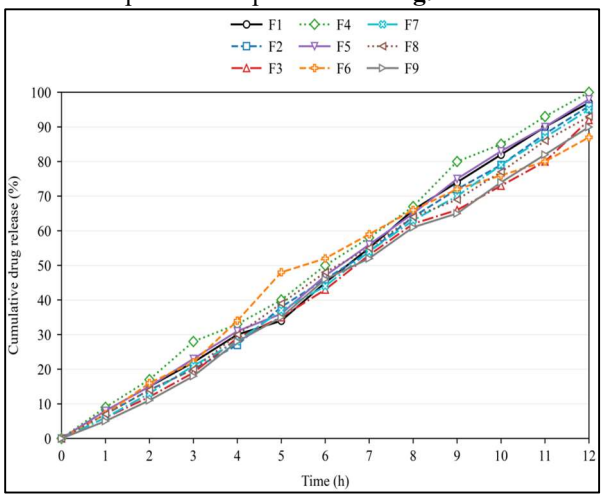

Figure 1: *In-vitro* cumulative drug-release profiles of Fosinopril Sodium sustained-release matrix tablets (F1–F9) over 12 h

Data represent mean values from triplicate dissolution experiments. All formulations demonstrated gradual drug release throughout the dissolution period. At 1 h, cumulative drug release ranged from 5% to 9%**,** whereas the cumulative release at 12 h ranged from 87% to 100%. Formulation F4 exhibited the highest cumulative drug release at the end of the study, reaching 100% at 12 h.

The differences among the formulations demonstrated that variation in HPMC K4M and SCMC concentrations influenced the dissolution behavior of Fosinopril Sodium matrix tablets.

3.6 Dissolution-Time Parameters

The time required to achieve 10%, 50%, 75%, and 90% drug release was determined as t_{10}%, t_{50}%, t_{75}%, and t_{90}%, respectively. The dissolution-time responses for the nine factorial formulations are presented in Table 4.

Table 4: Dissolution-time 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 4 Dissolution-time parameters of Fosinopril Sodium sustained-release matrix tablets prepared according to the 3² 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.

The dissolution-time responses varied across the nine formulations. The t_{90}% values ranged from 7.53 h for F4 to 14.00 h for F3, demonstrating substantial variation in the time required to achieve 90% drug release across the experimental design space. The t_{50}% and t_{75}% values ranged from 2.27 to 4.22 h and 4.54 to 8.44 h, respectively.

F4 exhibited the shortest t_{50}%, t_{75}%, and t_{90}% values among the experimental formulations, at 2.27, 4.54, and 7.53 h, respectively.

3.7 Drug-Release Kinetics

The dissolution data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. The coefficient of determination (R^2) was used to compare the fit of the respective models. The zero-order model showed the highest reported degree of linearity across the investigated formulations, with R^2 values ranging from 0.993 to 0.999.

The kinetic analysis provides a mathematical description of the observed dissolution profiles.

3.8 Statistical and Interaction Analysis

The 3^2 full factorial design was used to evaluate the individual and combined effects of HPMC K4M (X_1) and SCMC (X_2) on the dissolution-time responses. Second-order polynomial regression models containing linear, interaction (X_1X_2), and quadratic terms were developed for t_{10}%, t_{50}%, t_{75}%, and t_{90}%. The corresponding regression equations are presented in Table 5.

Table 5: Second-order polynomial regression models describing the effects of HPMC K4M (X_1) and SCMC (X_2) on the dissolution-time responses of Fosinopril Sodium sustained-release matrix tablets

Response	Second-order polynomial equation
Y_1: t_{10}%	$Y_1 = 0.515 - 0.011X_1 - 0.095X_2 - 0.037X_1X_2 + 0.055X_1^2 + 0.0172X_2^2$
Y_2: t_{50}%	$Y_2 = 3.395 - 0.077X_1 - 0.611X_2 - 0.251X_1X_2 + 0.362X_1^2 + 0.114X_2^2$
Y_3: t_{75}%	$Y_3 = 6.789 - 0.156X_1 - 1.223X_2 - 0.505X_1X_2 + 0.721X_1^2 - 0.224X_2^2$
Y_4: t_{90}%	$Y_4 = 11.280 - 0.259X_1 - 2.01X_2 - 0.840X_1X_2 + 1.21X_1^2 + 0.370X_2^2$

Table 5 Second-order polynomial regression models for the dissolution-time responses. X_1 and X_2 represent the coded concentrations of HPMC K4M and SCMC, respectively; Y_1, Y_2, Y_3, and Y_4 represent t_{10}%, t_{50}%, t_{75}%, and t_{90}%, respectively.

The regression models showed that both polymer variables contributed to the observed variation in dissolution-time responses. The negative coefficients associated with the linear terms indicate the direction of the coded-factor effects within the fitted models, while the interaction and quadratic terms indicate that the influence of one polymer was dependent, in part, on the concentration of the other polymer. The magnitude of the response also increased substantially from t_{10}% to t_{90}%, reflecting the progressive effect of the polymer matrix on drug release over the dissolution period.

The experimental dissolution-time data further demonstrated clear differences among the nine formulations. The t_{90}% values ranged from 7.53 h for F4 to 14.0 h for F3, while t_{50}% ranged from 2.27 h to 4.22 h across the formulations. These differences indicate that changes in HPMC K4M and SCMC concentrations were associated with measurable changes in the rate of drug release.

The combined effects of the two polymers are relevant to the swelling and release behavior of the matrix system. Changes in polymer concentration can alter the extent of hydration and swelling of the matrix and, consequently, the diffusional pathway available for drug transport. The interaction terms in the fitted equations therefore provide a quantitative description of the combined influence of HPMC K4M and SCMC rather than treating their effects as entirely independent.

3.9 Model Validation and Optimization

The predictive performance of the factorial models was assessed using two checkpoint formulations, C1 and C2. The predicted and experimentally observed dissolution responses are presented in Table 6.

Table 6: Checkpoint validation of the factorial models

Checkpoint	Response	Predicted value (h)	Experimental value (h)
C1	t_{10}%	0.578	0.589
C1	t_{50}%	3.792	3.789
C1	t_{75}%	7.588	7.595
C1	t_{90}%	12.605	12.597
C2	t_{10}%	0.474	0.481
C2	t_{50}%	3.102	3.117
C2	t_{75}%	6.21	6.218
C2	t_{90}%	10.315	10.333

Table 6 Comparison of predicted and experimentally observed dissolution-time responses for the checkpoint formulations.

The predicted and experimental values showed close agreement across the evaluated responses, supporting the applicability of the developed models within the investigated formulation space.

F4 was selected as the optimized formulation according to the experimentally defined formulation-selection criterion. It 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% cumulative drug release at 12 h.

3.10 Optimization and Selection of F4

Among the nine factorial formulations, F4, containing 30 mg of HPMC K4M and 40 mg of

SCMC, was selected as the optimized formulation based on its experimentally observed dissolution behavior. F4 exhibited t_{10}%, t_{50}%, t_{75}%, and t_{90}% values of 0.350, 2.268, 4.537, and 7.530 h, respectively, indicating progressive drug release throughout the 12-h dissolution study. The selection of F4 was based on its observed dissolution profile and its suitability for achieving the intended sustained-release behavior within the investigated formulation range.

3.11 Comparison with Marketed Formulation

The dissolution profile of the optimized F4 formulation was compared with that of the marketed Fosinopril Sodium sustained-release formulation. The comparison was performed using the model-independent difference factor (f_1) and similarity factor (f_2). The calculated f_1 and f_2 values were 1.543 and 89.561, respectively. The low f_1 value and high f_2 value indicated close similarity between the dissolution profiles under the investigated conditions. This comparison was limited to in-vitro dissolution-profile similarity and was not interpreted as evidence of bioequivalence, pharmacokinetic equivalence, or therapeutic equivalence.

4. Discussion

4.1 Influence of Polymer Concentration

The dissolution results demonstrated substantial variation in the release behavior of the nine factorial formulations. The t_{90}% values ranged from 7.530 h for F4 to approximately 14.0 h for F3, showing that relatively small changes in the proportions of HPMC K4M and SCMC produced marked differences in the time required to achieve 90% drug release. Similar differences were observed for t_{10}%, t_{50}%, and t_{75}%, indicating that polymer composition influenced drug release throughout the dissolution period rather than at a single stage of release.

HPMC K4M contributes to the formation of a hydrated polymeric matrix following contact with the dissolution medium. Hydration and swelling of the polymer can increase the diffusional resistance surrounding the drug and thereby modify the rate of drug transport from the matrix. SCMC also possesses hydrophilic and swelling characteristics and can contribute to the hydration and structural behavior of the matrix. The observed differences among F1–F9 therefore indicate that the relative amounts of the two polymers were important in determining the release characteristics of the formulations.

4.2 Influence of SCMC

The effect of SCMC was evident from the differences in dissolution responses obtained at different SCMC concentrations. Changes in SCMC concentration altered the time required to reach the specified drug-release levels, although the magnitude of the effect varied with the concentration of HPMC K4M. This indicates that SCMC did not act independently of the other formulation variable.

The swelling behavior provides additional support for the contribution of SCMC to matrix hydration. Greater hydration of the polymeric matrix can modify water penetration and the subsequent movement of dissolved drug through the hydrated region. However, the present study did not directly measure polymer erosion or gel-layer thickness; therefore, these processes should be regarded as mechanistic interpretations rather than directly measured observations.

4.3 Combined Polymer Effects

The factorial formulation design demonstrated that the combined concentrations of HPMC K4M and SCMC influenced the dissolution-time responses of the matrix tablets. Increasing or decreasing either polymer did not produce a simple linear change in release behavior across all formulations, indicating that the effect of one polymer was influenced by the concentration of the other. This interaction was reflected in the response-surface analysis and the corresponding second-order regression models.

F4, containing 30 mg HPMC K4M and 40 mg SCMC, was selected as the optimized formulation in the original formulation-development study. Its t_{10}%, t_{50}%, t_{75}%, and t_{90}% values were 0.350, 2.268, 4.537, and 7.530 h, respectively. However, F4 did not provide the longest dissolution time among the formulations; for example, F3 showed a t_{90}% value of 14.00 h. Therefore, the selection of F4 should be understood as a formulation-development choice based on its overall observed dissolution behavior within the investigated design space rather than simply as selection of the formulation with the slowest drug release.

4.4 Swelling–Drug-Release Relationship

The swelling results indicated that hydration of the polymer matrix was associated with changes in drug-release behavior. Upon exposure to the dissolution medium, the hydrophilic polymers absorbed water and underwent swelling, producing a hydrated matrix through which the drug could diffuse.

The relationship between swelling and dissolution is consistent with the expected behavior of hydrophilic matrix systems. Increased hydration can alter the diffusional pathway and resistance to drug transport, while progressive hydration and possible matrix erosion may contribute to release at later stages. Since gel-layer thickness and polymer erosion were not directly characterized in the present study, these mechanisms should not be interpreted as direct experimental measurements.

4.5 Drug-Release Mechanism and Kinetic Models

The dissolution data were evaluated using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models.

Among the models examined, the zero-order model showed the highest reported linearity, with R^2 values ranging from 0.993 to 0.999 across the investigated formulations. This indicates that the dissolution profiles were well described mathematically by the zero-order relationship under the experimental conditions used. The kinetic analysis should, however, be interpreted cautiously. The absence of verified formulation-specific Korsmeyer–Peppas n values and the corresponding fitting interval prevents quantitative interpretation of the release exponent. More importantly, kinetic model fitting alone cannot establish a definitive physical release mechanism. The observed release behavior may involve the combined effects of polymer hydration, swelling, drug diffusion, and progressive changes in the hydrated matrix during dissolution.

4.6 Relationship between Polymer Composition and Release Rate

The dissolution-time responses demonstrate that polymer composition could be used to modify the release characteristics of Fosinopril Sodium matrix tablets. The range in t_{90}% from 7.530 h to approximately 14.0 h illustrates the extent of variation obtained within the investigated formulation space.

Importantly, the response-surface analysis did not indicate that the effect of polymer concentration could be described simply as a uniform increasing or decreasing trend. Rather, the dissolution responses reflected a concentration-dependent and interactive influence of HPMC K4M and SCMC. This finding highlights the importance of evaluating polymer combinations when developing sustained-release matrix formulations.

4.7 Comparison with Marketed Formulation

The optimized F4 formulation showed close dissolution-profile similarity to the marketed formulation, with an f_1 value of 1.543 and an f_2 value of 89.561. These values support similarity between the dissolution profiles under the conditions investigated.

This comparison provides an additional in-vitro perspective on the performance of F4 beyond comparison among the experimental formulations. However, dissolution-profile similarity should not be interpreted as evidence of bioequivalence, pharmacokinetic equivalence, or therapeutic equivalence. Such conclusions require appropriate in-vivo studies.

4.8 Pharmaceutical Significance

The findings demonstrate that variation in HPMC K4M and SCMC concentrations can substantially modify the dissolution behavior of Fosinopril Sodium matrix tablets. The combination of swelling evaluation, dissolution-time responses, kinetic analysis, and factorial modeling provided complementary information on the performance of the investigated formulations.

The study therefore supports the use of HPMC K4M and SCMC as hydrophilic matrix-forming polymers for developing Fosinopril Sodium sustained-release tablets. Further work involving stability assessment and appropriate in-vivo pharmacokinetic studies would be required to establish the long-term and in-vivo performance of the formulation.

5. Conclusion

Fosinopril Sodium sustained-release matrix tablets were successfully developed using HPMC K4M and SCMC as hydrophilic matrix-forming polymers. Systematic variation of the two polymers produced measurable differences in swelling behavior and dissolution-time responses, while the 3^2 full factorial designs provided a structured approach for evaluating their combined effects.

Among the nine experimental formulations, F4, containing 30 mg HPMC K4M and 40 mg SCMC, was selected as the optimized formulation based on the formulation-selection approach used in the original study. F4 showed t_{10}%, t_{50}%, t_{75}%, and t_{90}% values of 0.350, 2.268, 4.537, and 7.530 h, respectively, with complete drug release at 12 h. Overall, the findings support the use of HPMC K4M and SCMC as a combined hydrophilic matrix system for controlling the in-vitro release of Fosinopril Sodium. Further stability and in-vivo studies are required to establish the long-term and pharmacokinetic performance of the optimized formulation.

6. Abbreviations

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; K–P, Korsmeyer–Peppas; R^2, coefficient of determination; SCMC, sodium carboxymethyl cellulose; 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–Vis, ultraviolet–visible spectrophotometry; X_1, coded concentration of HPMC K4M; X_2, coded concentration of SCMC; Y_1, t_{10}% response; Y_2, t_{50}% response; Y_3, t_{75}% response; Y_4, t_{90}% response.

7. Declarations

- **Ethics Approval and Consent to Participate:** Not applicable. This study did not involve human participants, human-derived samples, or animal experiments.
- **Consent for Publication:** Not applicable.

- **Competing Interests:** The authors declare that they have no competing interests.
- **Funding:** No external funding was received for this study.
- **Authors' Contributions:** Mr. Hanuman Shrikishan Kolse: Conceptualization, methodology, formulation development, investigation, data curation, formal analysis, and writing—original draft. Dr. Shikha Jaiswal: Supervision, validation, interpretation of results, and writing—review and editing.
    - Both authors contributed to the final review and approval of the manuscript.
- **Availability of Data and Materials:** The data generated and/or analyzed during the present study are included in this manuscript. Additional information may be made available from the corresponding author upon reasonable request.

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