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# Formulation & Evaluation of Controlled Release Matrix Tablets of Fosinopril by Using Hydrophilic Polymer

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**ABSTRACT**

The pre-formulation characteristics of Fosinopril were thoroughly assessed, including sensory attributes, angle of repose, bulk density, tapped density, Hausner's ratio, Carr's index, and compressibility index, all of which conformed to the required pharmacopeial standards. FTIR spectroscopy confirmed the absence of any significant interaction between the drug and the polymers. Controlled-release matrix tablets containing Fosinopril were formulated using HPMC K100 M and Xanthan gum as the primary polymers. The tablets underwent a series of evaluations, such as hardness, weight variation, and friability testing, with the majority of batches meeting the established pharmacopeial criteria. The drug content across different batches varied from 93% to 100%. Dissolution tests were performed in both acidic (pH 1.2) and phosphate buffers (pH 6.8), showing that the formulations with Xanthan gum released the drug more rapidly than those with HPMC. Importantly, the formulation combining both HPMC and Xanthan gum (F9) exhibited a significantly prolonged release profile over 24 hours, achieving a cumulative release of 99.74%. Kinetic analysis of F9 indicated a zero-order release pattern (regression coefficient 0.993) and anomalous non-Fickian diffusion (n > 5), suggesting a controlled-release mechanism. Stability studies conducted under accelerated conditions for 3 months showed no significant degradation, indicating that formulation F9 is optimal for sustained drug delivery. Further in vivo studies are necessary to confirm these results.

***Keywords:*** *Fosinopril, controlled release, matrix tablets, HPMC K100 M, Xanthan gum,*

## 1. INTRODUCTION

The primary goal of any drug delivery system is to deliver an adequate amount of the drug to the targeted site in the body, ensuring the desired therapeutic effect is achieved. In recent times, there has been an increasing focus on improving drug delivery systems rather than developing new drug molecules. This shift in focus is due to the high costs associated with the development of new drugs and the potential to optimize existing, effective drugs by utilizing controlled release delivery methods. These systems offer the opportunity to enhance the therapeutic potential of already successful drugs[1].

### Controlled Drug Delivery

The primary aim of therapy for many drugs is to maintain a consistent therapeutic level of the drug in the blood or tissues, ensuring it remains effective without causing toxicity over an extended period. Controlled release dosage forms are developed to meet this objective. Various terms such as sustained release, prolonged action, controlled release, and extended action refer to drug delivery systems designed to provide a continuous release of the drug for a prolonged effect following a single dose. These systems can be broadly categorized into controlled release, which releases the drug at a set rate, and sustained

release, which simply prolongs the drug's release over time[2].

**Oral Controlled Drug Delivery System**

The oral route is the most commonly used and convenient method of drug administration, favoured due to its high patient acceptance. Compared to other routes like parenteral administration, oral drug delivery has fewer concerns related to sterility and potential harm at the site of administration. Controlled release preparations release the drug gradually in the gastrointestinal tract, allowing for systemic absorption. Given the flexibility and focus on designing oral dosage forms, this route has received considerable attention in drug delivery research[3].

**Dissolution-Controlled Release System**

Dissolution-controlled release systems slow down the drug's dissolution rate to control its release. This can be achieved by incorporating the drug into an insoluble polymer, or by coating the drug particles or granules with a polymeric material of varying thickness. Additionally, the drug may be incorporated into hydrophobic or hydrophilic matrices. The rate of drug release is controlled by the rate at which dissolution fluid penetrates the matrix, with factors such as the porosity of the structure influencing the release. In diffusion-controlled systems, the rate-limiting step is the diffusion of the drug through a polymeric membrane. These systems typically exhibit a non-zero order release rate due to increased diffusion resistance as the release process progresses[4].

**Water Penetration-Controlled Release System**

Water penetration-controlled release systems regulate the drug release by allowing water to enter the system. These systems can include several different mechanisms, one of which is osmotically controlled release[5].

**Osmotically Controlled Release System**

In an osmotically controlled system, the drug is released by solvent influx through a semi-permeable membrane, with the drug being expelled through a laser-drilled orifice. The movement of fluid into the system is driven by osmotic and hydrostatic pressure differences, with the rate of release being determined by the osmotic pressure of the formulation[6].

## 2. MATERIALS USED FOR MATRIX SYSTEMS

Matrix systems typically use hydrophilic or hydrophobic polymers. Common hydrophilic polymers include Hydroxypropyl methylcellulose (HPMC), Hydroxypropyl cellulose (HPC), xanthan gum, and others like sodium alginate and poly (ethylene oxide). These are often supplied in micronized forms, as small particles are essential for rapid formation of a gelatinous layer on the tablet surface. HPMC, a non-ionic water-soluble cellulose ether, comes in various grades (E, F, J, K series) based on the degree of substitution. Xanthan gum, a water-soluble polysaccharide, consists of a mix of sugars and is commonly used in such systems. Hydrophobic matrices include waxes (e.g., carnauba, beeswax) and water-insoluble polymers like Eudragit and ethyl cellulose, which control the release by forming a stable matrix[7].

**Hypertension**

Hypertension is characterized by an elevated blood pressure, typically higher than 140/90 mm Hg. It is a major risk factor for conditions like heart attack, stroke, congestive heart failure, kidney failure, and peripheral vascular disease. According to the World Health Organization, suboptimal blood pressure (SBP > 115 mm Hg) contributes significantly to cerebrovascular diseases and ischemic heart diseases, being a leading cause of death in Western countries[8].

**Clinical Classification of Hypertension**

Hypertension is categorized based on the severity of the elevated blood pressure, ranging from mild to malignant forms. This classification helps in determining appropriate treatment approaches it is in the table no 01.[9, 10]

**Table no: 01- Clinical classification of hypertension**

| Category | Systolic (mm Hg) | Diastolic (mm Hg) |
|---|---|---|
| Normal | >130 | <85 |
| High Normal | 130-139 | 85-89 |
| **Hypertension** | | |
| Mild stage(stage1) | 140-159 | 90-99 |
| Moderate(stage2) | 160-179 | 100-109 |
| Severe(stage3) | 180-209 | 110-119 |
| Very sever(stage4) | >210 | >120 |

| | | |
|---|---|---|
| Malignant hypertension | >200 | >140 |

**Sodium and Water Retention in Hypertension**

Sodium and water retention play a crucial role in regulating blood volume and cardiac output. The concentration of sodium in the blood is controlled through various mechanisms, including the release of aldosterone, a decrease in the glomerular filtration rate, and the secretion of atriopeptin from the heart's atria. The vasopressor effect of Angiotensin-II is counteracted by a reduction in the release of vasodepressor agents like prostaglandins. Endocrine-related hypertension can arise from conditions such as hyperfunction of the adrenal cortex or hyperparathyroidism. Constriction of the aorta leads to systolic hypertension, while diastolic hypertension may result from circulatory changes. Neurogenic hypertension is linked to conditions such as psychogenic factors or increased intracranial pressure[11, 12].

**Antihypertensive Agents**

Antihypertensive agents are medications used to reduce high blood pressure in individuals with hypertension.

**ACE Inhibitors**

Examples of ACE inhibitors include drugs such as Fosinopril, Captopril, Enalapril, Lisinopril, Trandolapril, and Benazepril.

**Fosinopril Overview**

Fosinopril has been shown to be effective in managing essential hypertension. A daily dose of 4 to 16 mg has been proven more effective than a placebo in treating mild-to-moderate hypertension. For most patients, doses higher than 8 mg do not provide additional benefits, although some individuals may experience improved therapeutic results with doses of 12 or 16 mg daily. The antihypertensive effects of Fosinopril are linear up to 8 mg, with 2 mg doses offering minimal effect. When combined with other drugs such as hydrochlorothiazide, indapamide, or nifedipine, Fosinopril enhances blood pressure control in patients who do not respond adequately to monotherapy. Long-term studies have demonstrated that Fosinopril, when initiated at 4 mg once daily and adjusted as needed to 8 mg, significantly reduces systolic and diastolic blood pressure over time. After one year, systolic and diastolic blood pressures were reduced by 29 mmHg and 19 mmHg, respectively, with Fosinopril alone normalizing blood pressure in 55% of patients and achieving blood pressure control in 78%. After three years, Fosinopril at doses of 4 or 8 mg maintained blood pressure control in 56% of patients[13, 14].

The effectiveness of Fosinopril has also been demonstrated in elderly patients with essential hypertension. In a double-blind study, doses of 2 to 8 mg daily led to reductions in both systolic and diastolic pressures, with 92.5% of patients achieving blood pressure control. A separate open study with 2,927 patients over 70 years old also showed substantial improvements in blood pressure control after 3 to 6 months of treatment, with diastolic blood pressure dropping by 28 mmHg and systolic by 16.6 mmHg. Fosinopril has proven effective in patients with comorbid conditions such as hyperlipidaemia, Type II diabetes, ischemic heart disease, cardiac arrhythmias, peripheral arterial disease, nephropathy with proteinuria, and chronic obstructive pulmonary disease[15, 16, and 17].

Importantly, Fosinopril efficacy was maintained in patients with concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) like indomethacin or diclofenac. It did not negatively impact lipid profiles, glucose control, or renal function, even in patients with diabetes. Studies have shown that Fosinopril does not interfere with lipid or carbohydrate metabolism and is safe for long-term use in hypertensive patients with diabetes, improving outcomes without negatively affecting metabolic health or kidney function.[18,19]

## 3. MATERIALS AND METHODS

**Formulation of controlled release matrix tablets of Fosinopril by direct compression method[20, 21, 22, 23, 24]**

The key ingredients included in the formulation are

Hydrophilic polymers : Xanthan gum and HPMC K100M

Filler : MCC

Anti-adherent : Talc

Lubricant : Magnesium Stearate

Binder : PVP

Accurate amounts of polymer and microcrystalline cellulose (MCC) were measured and combined in a mortar using a geometric mixing technique. To this mixture, the required quantity of Fosinopril was added and thoroughly blended using a pestle. The resulting powder blend was then lubricated with magnesium stearate and talc, mixing for approximately 3 minutes. The powder was then compressed into tablets using a rotary tablet compression machine, equipped with 6 mm round, flat-faced punches with plain surfaces. The average weight of each tablet was 100 mg. Prior to compression, the

powder blend was evaluated for various physical properties such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. After compression, the tablets were subjected to further evaluations, including drug release kinetics, and the formulation was tested across a range of conditions, from F1 to F9 were given in table no 02[20, 21, 22].

**Table no: 02- Formulation of Fosinopril controlled release matrix tablet**

| Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| **Fosinopril** | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| **HPMC K100M** | 30 | 35 | 40 | - | - | - | 15 | 20 | 20 |
| **Xanthan gum** | - | - | - | 30 | 35 | 40 | 20 | 15 | 20 |
| **PVP** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **MCC** | 59 | 54 | 49 | 59 | 54 | 49 | 54 | 54 | 49 |
| **Talc** | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Mg. stearate** | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Total wt. (mg)** | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

## 4. RESULTS AND DISCUSSION

## PRE-FORMULATION STUDIES

### Appearance

The sample of Fosinopril was white or almost white, odour less or almost odour less crystalline powder[23].

### Solubility

The Fosinopril was soluble in water, methanol, ethanol, acetic acid and ethyl acetate, very slightly soluble in ether, chloroform and benzene[24, 25]

### Melting point

The melting point was found to be 126□-128□C.

### Physical characteristics of drug

**Table no: 03- Physical characteristics of drug (Fosinopril)**

| S. No | Parameter | Specifications |
|---|---|---|
| 1 | Loss on Drying (%) | 0.40 |
| 2 | Bulk density (g/ml) | 0.415 |
| 3 | Tapped Density (g/ml) | 0.498 |
| 4 | Hausner's ratio | 1.26 |
| 4 | Compressibility index (%) | <15 |
| 5 | Angle of repose (□') | 24.11° |

All the powder characteristics were good and satisfied according to pharmacopeia.

### FTIR Studies[26, 27]

Chemical interactions between the drug and excipients can potentially alter the drug's therapeutic effectiveness. To explore any such interactions, the FTIR spectra of the pure drug and the optimized formulations were examined within the range of 400-4000 $cm^{-1}$. Compatibility studies were conducted using an FT-IR Spectrophotometer, where the FT-IR spectrum of pure Fosinopril was compared to that of the physical mixture containing Fosinopril, HPMC K100 M, Xanthan gum, MCC, PVP, Talc, and Magnesium stearate. This analysis helped assess the potential for any interactions between the drug and the

excipients. The spectra for all formulations are shown below figure no 4 to 9.

**Figure No 4: FTIR spectra of Fosinopril**

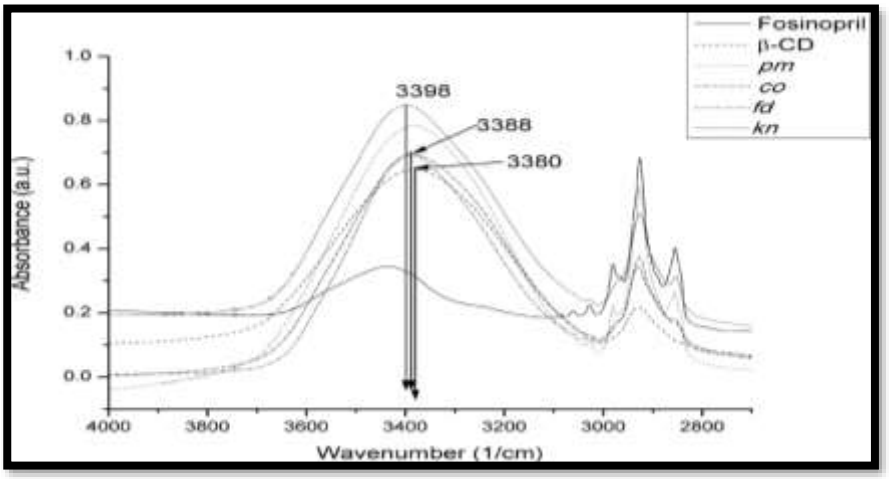



**Figure No 10: FTIR spectra of Drug with excipients**

**Table No 10: FT-IR Peaks of various compounds**

| **Wave number in $cm^{-1}$** | **Functional groups** | **Pure drug Fosinopril** | **Physical mixture** |
|---|---|---|---|
| 1210-1150 | C-N Stretching | 1151.2 $cm^{-1}$ | 1152.4 $cm^{-1}$ |
| 1360-1180 | C-$NH_2$ Stretching | 1306.1 $cm^{-1}$ | 1307.5 $cm^{-1}$ |
| 1900-1600 | C=O Stretching | 1800.8 $cm^{-1}$ | 1800.8 $cm^{-1}$ |
| 2990-2850 | C-$CH_3$ Stretching | 2984.9 $cm^{-1}$ | 2983.2 $cm^{-1}$ |
| 3490-3300 | N-H Stretching | 3305.9 $cm^{-1}$ | 3306.7 $cm^{-1}$ |

The FTIR spectrum analysis revealed no changes in the characteristic peaks of pure Fosinopril when compared to the physical mixture of the drug with the polymers and excipients. The expected peaks were present, confirming the authenticity of the materials used in the study. As shown in Table 10, the key peaks corresponding to stretching vibrations of C-N, C-NH2, C=O, C-CH3, and N-H were preserved in the optimized formulations. Additionally, new peaks were observed, corresponding to the excipients, indicating no interaction between the drug and the excipients.[28, 29]

**Evaluation of pre compression parameters**

| **Formulation code** | **Angle of repose (± SD)** | **BD (gm/ml) (± SD)** | **TD (gm/ml) (± SD)** | **Carr's Index (%) (± SD)** | **Hausner's ratio (± SD)** |
|---|---|---|---|---|---|
| **F1** | 23.03±0.04 | 0.412±0.02 | 0.477±0.02 | 14.92±0.05 | 1.18±0.05 |
| **F2** | 20.85±0.01 | 0.407±0.03 | 0.486±0.01 | 14.91±0.07 | 1.19±0.04 |
| **F3** | 20.85±0.04 | 0.410±0.06 | 0.481±0.01 | 13.93±0.04 | 1.21±0.02 |
| **F4** | 22.30±0.07 | 0.398±0.04 | 0.491±0.07 | 14.72±0.01 | 1.19±0.06 |
| **F5** | 19.98±0.09 | 0.396±0.03 | 0.480±0.03 | 13.12±0.03 | 1.16±0.03 |
| **F6** | 22.06±0.06 | 0.412±0.01 | 0.489±0.01 | 14.27±0.01 | 1.15±0.01 |
| **F7** | 23.19±0.03 | 0.409±0.04 | 0.472±0.02 | 13.56±0.04 | 1.16±0.03 |

| | | | | | |
|---|---|---|---|---|---|
| **F8** | 22.05±0.09 | 0.401±0.05 | 0.492±0.03 | 12.91±0.07 | 1.17±0.05 |
| **F9** | 24.11±0.03 | 0.415±0.01 | 0.498±0.04 | 15.00±0.06 | 1.26±0.04 |

**Table No 13: Powder characterization of formulations**

(n=3±S.D) (S. D=Standard deviation)

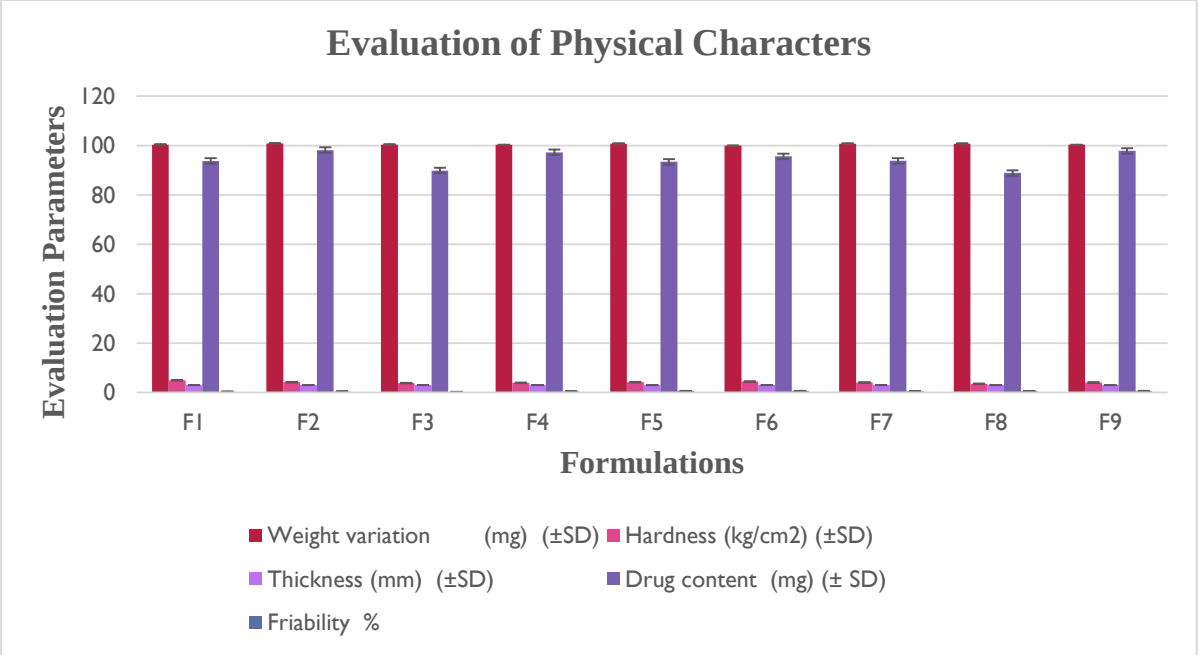
For the powder blend of all the formulated batches, the angle of repose was found to be in the range of 19° to 24°, thus indicating that the flow properties were excellent. Hausner's ratio was less than 1.20 for all the batches indicating good flow properties.

**Evaluation of Fosinopril tablets[30]**

**Table No 14: Evaluation of Physical Characteristics of controlled release matrix tablets of Fosinopril**

| **Formulation code** | **Weight variation (mg) (±SD)** | **Hardness (kg/cm$^2$) (±SD)** | **Thickness (mm) (± SD)** | **Drug content (mg) (± SD** | **Friability %** |
|---|---|---|---|---|---|
| F1 | 100.4±1.24 | 4.93±0.23 | 3.009±0.02 | 93.76±0.19 | 0.30 |
| F2 | 100.9±1.61 | 4.13±0.30 | 3.009±0.02 | 98.16±0.27 | 0.40 |
| F3 | 100.4±1.56 | 3.73±0.11 | 3.008±0.02 | 89.87±0.41 | 0.16 |
| F4 | 100.3±1.28 | 3.93±0.23 | 3.009±0.02 | 97.28±0.33 | 0.40 |
| F5 | 100.8±1.16 | 4.13±0.15 | 3.008±0.02 | 93.48±0.26 | 0.60 |
| F6 | 100.0±1.42 | 4.4±0.2 | 3.010±0.0 | 95.67±0.17 | 0.60 |
| F7 | 100.8±1.00 | 4.0±0.2 | 3.009±0.02 | 93.87±0.32 | 0.50 |
| F8 | 100.8±1.28 | 3.53±0.11 | 3.009±0.02 | 88.92±0.21 | 0.51 |
| F9 | 100.3±1.04 | 4.0±0.115 | 3.009±0.02 | 97.87±0.16 | 0.57 |

(n=3±S.D) (S. D=Standard deviation)



As discussed, the formulations F1 to F9 were evaluated for various parameters such as hardness, thickness, weight variation, friability, and drug content. The variations observed for all the formulations were within the pharmacopeial specifications.

The thickness of all formulations (F1 to F9) ranged from 3.008 to 3.010 mm. The hardness values for the formulations were between 3.53 and 4.13 kg/cm². The diameter of the tablets in all formulations ranged from 6.008 to 6.010 mm. Friability values for all formulations ranged from 0.16% to 0.60%. The drug content across all formulations (F1 to F9) ranged from 93% to 100%. These results confirm that all physical parameters, including hardness, thickness, weight variation, friability, and drug content, met the pharmacopeial standards, indicating the quality of the prepared formulations.

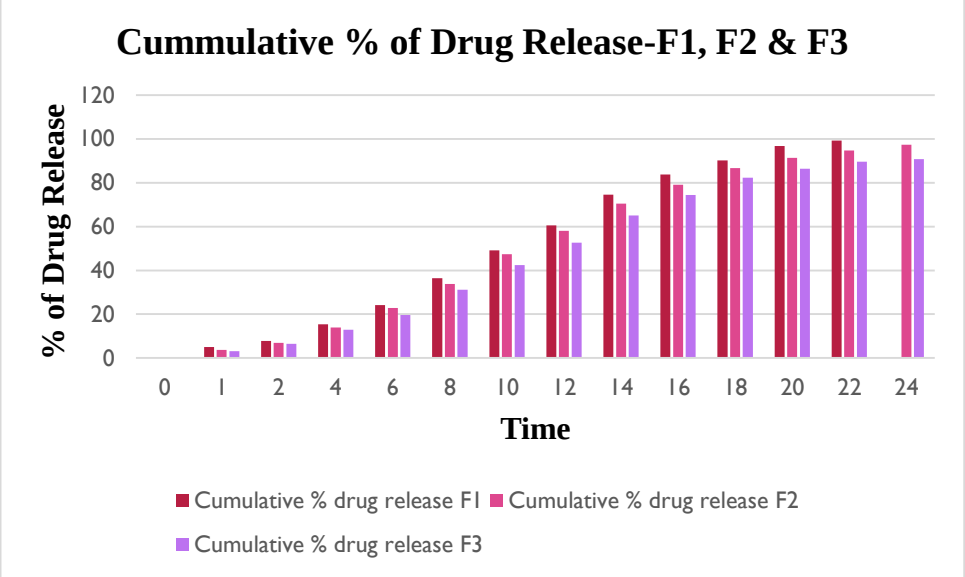
**In Vitro Drug Release Study**[31, 32]

Dissolution studies for formulations F1 to F9 were conducted using a USP dissolution apparatus (paddle method) with 900 mL of 0.1N HCl (pH 1.2) for the first 2 hours, followed by phosphate buffer (pH 6.8) for the remaining 22 hours as the dissolution medium. The results, as shown in Tables 15 to 17 and Figures 17 to 19, indicated that the dissolution profile was influenced by the concentration of the polymer in the formulation.

**Table No 15: Cumulative Percentage drug release of formulations with HPMC K100M ($F_1$-$F_3$)**

| Time (hr.) | Cumulative % drug release $F_1$ | Cumulative % drug release $F_2$ | Cumulative % drug release $F_3$ |
|---|---|---|---|
| **0** | 0 | 0 | 0 |
| **1** | 4.98 | 3.64 | 3.15 |
| **2** | 7.86 | 6.99 | 6.42 |
| **4** | 15.46 | 13.98 | 12.87 |
| **6** | 24.19 | 22.89 | 19.65 |
| **8** | 36.47 | 33.75 | 31.16 |
| **10** | 49.19 | 47.39 | 42.41 |
| **12** | 60.46 | 57.97 | 52.65 |
| **14** | 74.49 | 70.38 | 65.11 |
| **16** | 83.78 | 79.13 | 74.42 |
| **18** | 90.19 | 86.72 | 82.21 |
| **20** | 96.74 | 91.31 | 86.41 |
| **22** | 99.24 | 94.74 | 89.63 |
| **24** | - | 97.27 | 90.81 |

**Figure No 17: Cumulative percentage drug release of formulations containing HPMC K100 M**

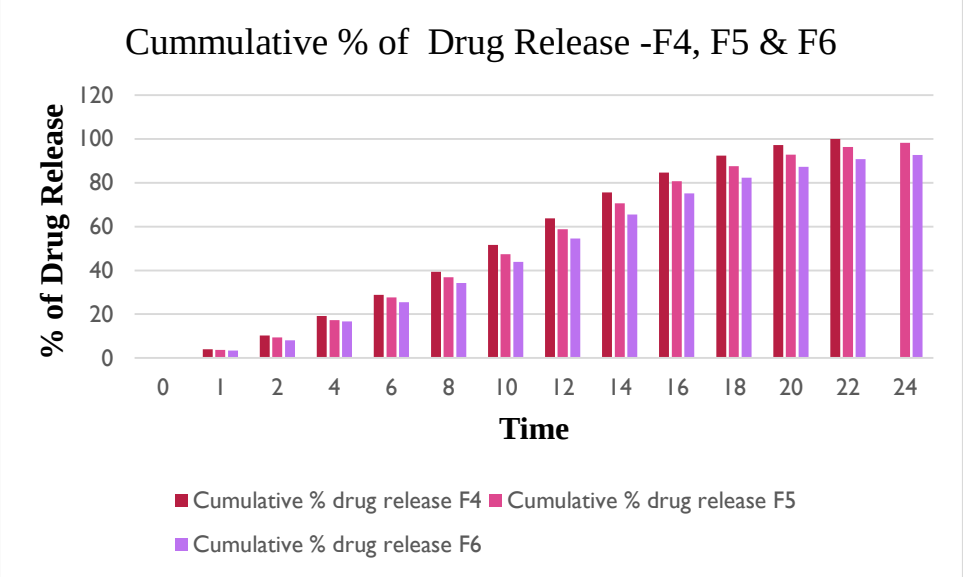



As seen in Figure 17, the polymer HPMC K100 M significantly influenced the drug release from the controlled-release matrix tablets. The drug release percentages for formulations F1, F2, and F3 were 99.24%, 97.27%, and 90.81%, respectively. The differences in the release profiles of these formulations were attributed to varying concentrations of the polymer. The cumulative percentage of drug release and the release coefficients for different models corresponding to each formulation are presented in Table 15.

**Table No 16: Cumulative Percentage drug release of formulations with Xanthan gum ($F_4$-$F_6$)**

| Time(hr.) | Cumulative % Drug release $F_4$ | Cumulative % Drug release $F_5$ | Cumulative % Drug release $F_6$ |
|---|---|---|---|
| **0** | 0 | 0 | 0 |
| **1** | 3.99 | 3.74 | 3.35 |
| **2** | 10.31 | 9.45 | 8.12 |
| **4** | 19.15 | 17.34 | 16.69 |
| **6** | 28.76 | 27.68 | 25.42 |
| **8** | 39.35 | 36.93 | 34.25 |
| **10** | 51.59 | 47.41 | 43.85 |
| **12** | 63.79 | 58.79 | 54.56 |
| **14** | 75.59 | 70.63 | 65.42 |
| **16** | 84.65 | 80.72 | 75.14 |
| **18** | 92.41 | 87.52 | 82.24 |
| **20** | 97.19 | 92.74 | 87.28 |
| **22** | 99.98 | 96.27 | 90.71 |
| **24** | - | 98.15 | 92.64 |

**Figure No 18: Cumulative percentage drug release of formulations containing Xanthan gum ($F_4$-$F_6$)**

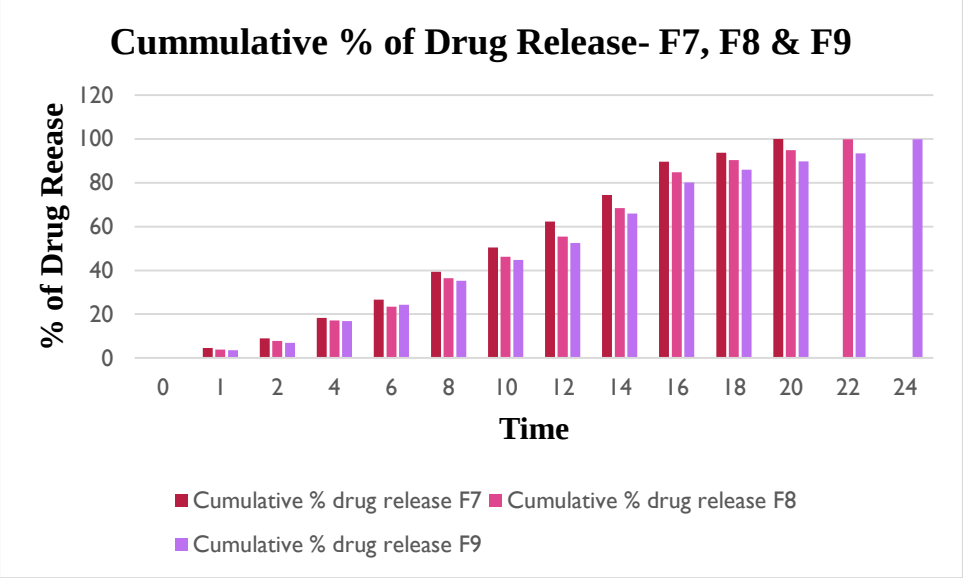



As shown in Figure 21, the polymer Xanthan gum had a significant impact on controlling the drug release from the controlled-release matrix tablets. The drug release percentages for formulations F4, F5, and F6 after 24 hours were 99.98%, 98.15%, and 92.64%, respectively. The variations in the drug release profiles of these formulations were due to the different concentrations of the polymer used. The cumulative percentage of drug release and the release coefficient values for the various models for each formulation are provided in Table 16.

**Table No 17: Cumulative Percentage drug release of formulations with combination of polymers ($F_7$-$F_9$)**

| Time (hr.) | Cumulative % drug release $F_7$ | Cumulative % drug release $F_8$ | Cumulative % drug release $F_9$ |
|---|---|---|---|
| **0** | 0 | 0 | 0 |
| **1** | 4.54 | 3.84 | 3.61 |
| **2** | 8.99 | 7.78 | 6.99 |
| **4** | 18.29 | 17.12 | 16.89 |
| **6** | 26.61 | 23.45 | 24.31 |
| **8** | 39.37 | 36.39 | 35.21 |
| **10** | 50.45 | 46.19 | 44.68 |
| **12** | 62.29 | 55.47 | 52.42 |
| **14** | 74.42 | 68.36 | 65.85 |
| **16** | 89.58 | 84.69 | 80.14 |
| **18** | 93.69 | 90.27 | 85.97 |
| **20** | 99.98 | 94.78 | 89.67 |
| **22** | - | 99.79 | 93.41 |
| **24** | - | - | 99.74 |

**Figure No 19: Cumulative percentage drug release of formulations containing Combination of polymers ($F_7$-$F_9$)**




As seen in Figure 22, the combination of HPMC K100 M and Xanthan gum effectively controlled the drug release from the matrix tablets. The drug release percentages for formulations F7, F8, and F9 after 24 hours were 99.98%, 99.79%, and 99.74%, respectively. These formulations were made using a blend of both polymers. The cumulative drug release percentages and the release coefficient values for different models of each formulation are shown in Table 17. The drug release from formulations F2, F3, F5, F6, and F9 was 97.27%, 90.81%, 98.15%, 92.64%, and 99.74% over 24 hours, respectively. On the other hand, formulations F1, F4, F7, and F8 released 90.45%, 92.41%, 93.61%, and 90.27%, respectively, and did not release the drug over the full 24-hour period. The formulation F9, which combined HPMC K100 M and Xanthan gum in a 1:1 ratio, achieved 99.74% drug release in 24 hours. Based on these results, formulation F9 was identified as the best formulation and was selected for further kinetic studies, as it provided the desired drug release over the 24-hour period.

**RELEASE KINETICS[33]**

**Table No 18: Release kinetics of the optimum formulation**

| Time (hr.) | √T | Log T | Cumulative % drug dissolved | Cumulative % drug un dissolved | Log Cumulative % drug dissolved | Log Cumulative % drug Un dissolved |
|---|---|---|---|---|---|---|
| **0** | 0 | 0 | 0 | 100 | 0 | 2 |
| **1** | 1 | 0 | 3.61 | 96.39 | 0.557 | 1.98 |
| **2** | 1.414 | 0.301 | 6.99 | 93.01 | 0.844 | 1.96 |
| **4** | 2.0 | 0.60 | 19.57 | 80.43 | 1.29 | 1.90 |
| **6** | 2.44 | 0.778 | 25.31 | 74.69 | 1.40 | 1.87 |
| **8** | 2.8 | 0.90 | 35.21 | 64.79 | 1.54 | 1.81 |
| **10** | 3.16 | 1.0 | 44.68 | 55.32 | 1.65 | 1.75 |
| **12** | 3.46 | 1.079 | 52.42 | 47.58 | 1.719 | 1.67 |
| **14** | 3.74 | 1.146 | 65.85 | 34.15 | 1.818 | 1.53 |
| **16** | 4.0 | 1.20 | 80.14 | 19.86 | 1.90 | 1.29 |
| **18** | 4.2 | 1.255 | 85.97 | 14.03 | 1.93 | 1.14 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **20** | 4.47 | 1.30 | 89.67 | 10.33 | 1.95 | 1.014 |
| **22** | 4.69 | 1.34 | 93.41 | 6.59 | 1.97 | 0.818 |
| **24** | 4.89 | 1.38 | 99.74 | 0.26 | 1.998 | -0.585 |

**Figure No 20: Zero order plot of $F_9$ Formulation**

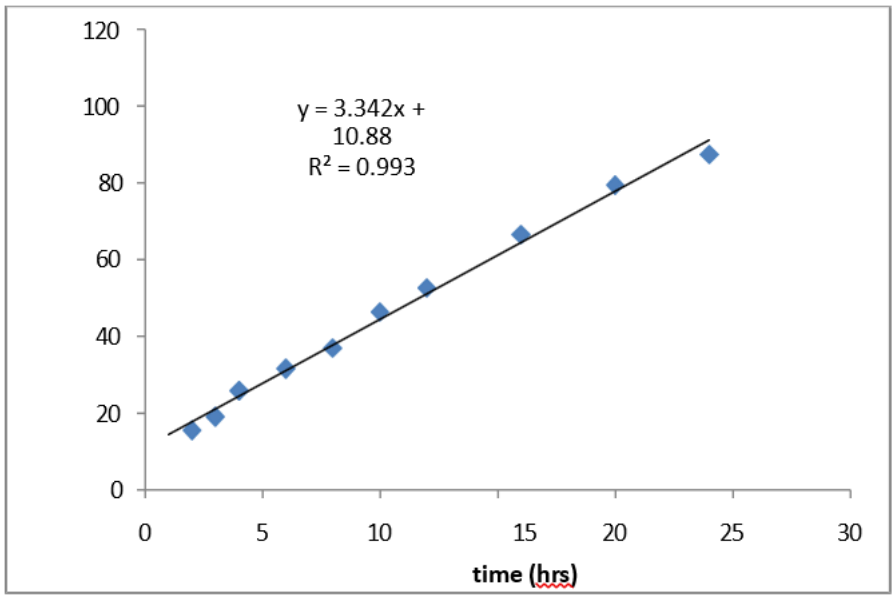
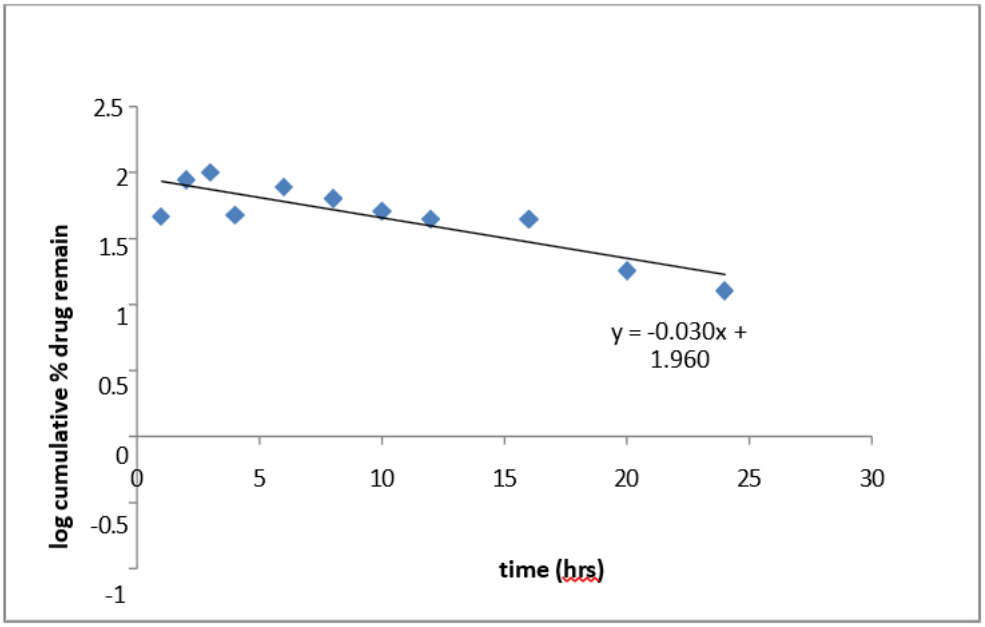
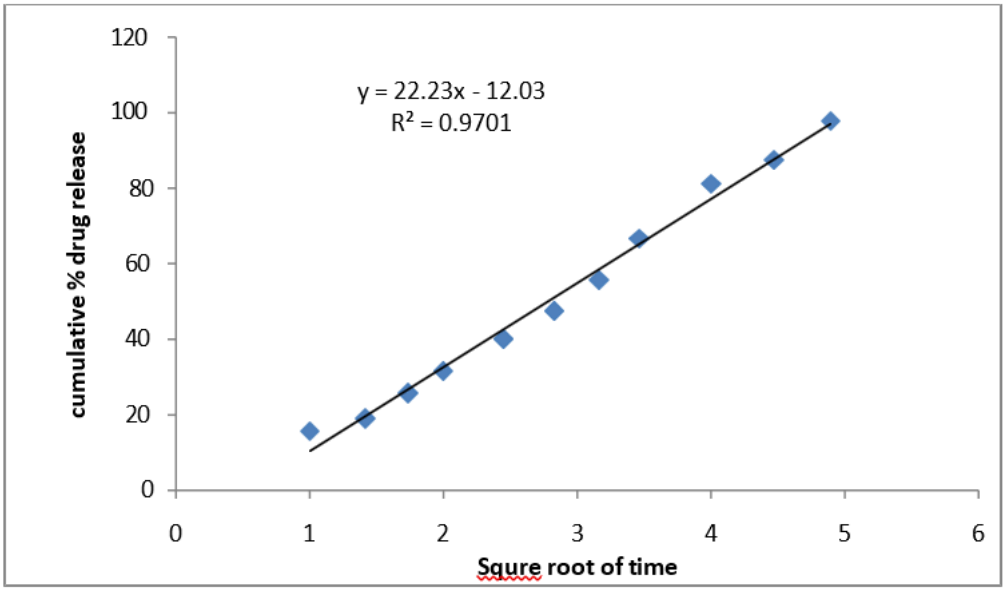



**Figure No 21: First order plot of $F_9$ Formulation**



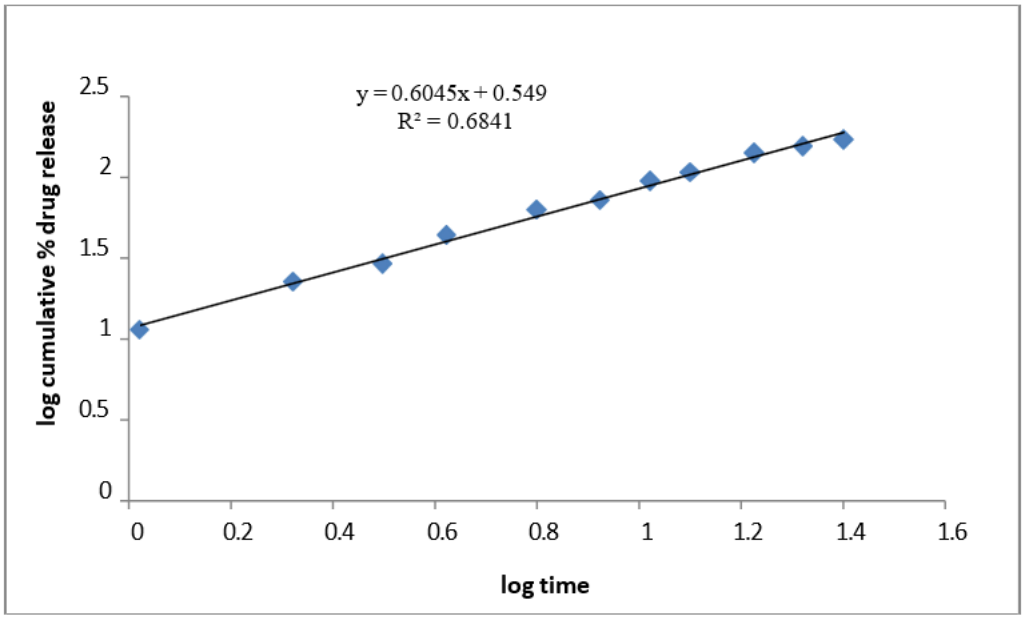

**HIGUCHI MODEL**

**Figure No 22: Higuchi Plot for $F_9$ Formulation**




**KORSEMEYER PEPPAS MODEL**

**Figure No 23: Korsemeyer Peppas Model For$F_9$ Formulation**




To determine the mechanism of drug release from the formulations, the release data were analyzed using various models: zero-order (cumulative amount of drug released versus time), first-order (log cumulative percentage of drug remaining versus time), Higuchi's model (cumulative percentage of drug released versus square root of time), and Korsmeyer-Peppas model (log cumulative percentage of drug released versus log time).

**Table No 19: Release Kinetics of Fosinopril**

| Formulation | Zero – Order R2 | First- Order R2 | Higuchi R2 | Korsmeyer and peppas | |
|---|---|---|---|---|---|
| | | | | R2 | N |

| | | | | | |
|---|---|---|---|---|---|
| **$F_9$** | 0.993 | 0.738 | 0.9701 | 0.6841 | 0.6045 |

The in vitro release data were analysed using the Korsmeyer-Peppas model, with the release exponent (n) value providing insights into the release mechanism from the dosage form. The value of n obtained was 0.6045, suggesting that the drug release was primarily diffusion-controlled, as evidenced by the linearity of the Higuchi model. The F9 formulation exhibited an anomalous (non-Fickian) diffusion mechanism, with the highest $R^2$ values for zero-order kinetics, indicating that the drug release from the matrix system was governed by both diffusion and erosion processes.

**Selection of Optimized Batch**

Formulation F9 of the controlled-release matrix tablet was selected as the optimized formulation, as it demonstrated the best linearity between cumulative Fosinopril release and time, as indicated by the highest correlation coefficient in all models. F9 fitted well to both the Korsmeyer-Peppas (0.6841) and zero-order (0.993) models.

## 5. SUMMARY AND CONCLUSION

The pre-formulation parameters, such as organoleptic properties, angle of repose, bulk density, tapped density, Hausner's ratio, Carr's index, and compressibility index, were evaluated for the pure drug and met the pharmacopeial specifications. FTIR studies confirmed no interactions between the drug and the polymer. Controlled-release matrix tablets of Fosinopril were formulated using HPMC K100 M and Xanthan gum. The formulated batches were evaluated for various physicochemical properties and dissolution profiles. The physical properties, including hardness, weight variation, and friability, were in accordance with pharmacopeial standards, and the drug content of all tablets ranged from 93% to 100%.

In vitro dissolution studies were conducted in both an acid buffer (pH 1.2) and phosphate buffer (pH 6.8). The release rate was faster with Xanthan gum compared to HPMC. Notably, the combination of polymers in formulation F9 significantly slowed the drug release over 24 hours, with a cumulative drug release of 99.74%. Kinetic analysis of F9 revealed zero-order kinetics (regression coefficient of 0.993) and anomalous (non-Fickian) diffusion ($n > 5$), confirming effective control of drug release. Based on these results, F9 was selected as the optimized formulation.

The accelerated stability studies for F9 conducted over three months showed no significant changes, indicating that the formulation remained stable. In conclusion, F9 proved to be the most effective formulation, exhibiting sustained drug release over 24 hours. Further in vivo studies are recommended to validate these findings.

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