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Formulation, development and evaluation of extended release tablets of Valsartan potassium and Enalapril maleate

Vivek Kumar*, Ayush Pratap Singh and OP Agrawal

Bhabha Pharmacy Research Institute, Bhabha University, Bhopal-462044, M.P., India

Abstract

The present study aimed to formulate, develop, and evaluate extended-release (ER) tablets of Valsartan potassium and Enalapril maleate for once-daily management of hypertension. ER matrix tablets were prepared using a combination of hydrophilic and hydrophobic polymers to achieve controlled drug release over 24 hours. Preformulation studies, including solubility analysis, FTIR, DSC, and XRD, confirmed drug–excipient compatibility and stability. Twelve formulations (F1–F12) were developed and evaluated for micromeritic properties, post-compression parameters, and in-vitro dissolution behavior. Dissolution data were subjected to kinetic modeling to elucidate the release mechanism. Among all formulations, F4 exhibited optimal physicochemical properties and a near zero-order release profile, achieving approximately 95% cumulative drug release at 24 hours. Kinetic analysis indicated diffusion-controlled non-Fickian transport. Comparative assessment showed performance comparable to marketed extended-release antihypertensive products. The study concludes that a hydrophilic–hydrophobic polymer matrix system is effective for developing stable, predictable, and patient-friendly extended-release combination tablets of Valsartan potassium and Enalapril maleate.

Keywords: Extended release, Valsartan potassium, Enalapril maleate, Matrix tablets, HPMC, Ethyl cellulose, Hypertension.

***Correspondence Info:**
Mr. Vivek Kumar
RKDF College of Pharmacy,
Behind Hotel Mark, Hoshangabad Road
(Narmadapuram Road), Jatkhedi, Misrod,
SRK University, Bhopal, M.P.462-026, India

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1. Introduction

Hypertension is a chronic cardiovascular disorder and a major risk factor for the development of coronary artery disease, stroke, heart failure, and renal complications [1-2]. According to global health reports, sustained elevation of blood pressure remains one of the leading causes of morbidity and mortality worldwide [3-4]. Effective long-term management of hypertension often requires continuous pharmacotherapy, frequently involving combination drug therapy to achieve optimal blood pressure control and reduce cardiovascular risk [5-6].

The renin–angiotensin–aldosterone system (RAAS) plays a central role in the regulation of blood pressure, fluid balance, and vascular tone [7-8]. Pharmacological agents targeting different components of this system are widely used in antihypertensive therapy [9]. Valsartan potassium, an angiotensin II receptor blocker (ARB), selectively inhibits the binding of angiotensin II to the AT receptor, thereby preventing vasoconstriction and aldosterone secretion. Enalapril maleate, an angiotensin-converting enzyme (ACE) inhibitor, reduces the formation of angiotensin II and decreases peripheral vascular resistance [10]. The combined use of an ARB and an ACE inhibitor provides complementary inhibition of the RAAS, leading to enhanced antihypertensive efficacy [11].

Conventional immediate-release formulations of Valsartan potassium and Enalapril maleate often require multiple daily dosing, which may result in fluctuating plasma drug concentrations, reduced patient compliance, and an increased incidence of adverse effects [12].

Moreover, peak–trough variations associated with immediate-release dosage forms can compromise therapeutic outcomes in chronic conditions such as hypertension [13]. These limitations highlight the need for extended-release (ER) drug delivery systems that can maintain consistent plasma drug levels over an extended period [14].

Extended-release oral dosage forms are designed to release the drug at a predetermined rate, thereby prolonging therapeutic activity, minimizing dosing frequency, and improving patient adherence [15]. Matrix-based extended-release tablets, particularly those employing hydrophilic and hydrophobic polymers, are among the most widely used systems due to their simplicity, cost-effectiveness, and ability to provide predictable drug release profiles [1]. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) form a gel layer upon hydration, controlling drug diffusion, while hydrophobic polymers such as ethyl cellulose provide matrix rigidity and further modulate release [16].

In this context, the present study was undertaken to formulate, develop, and evaluate extended-release matrix tablets of Valsartan potassium and Enalapril maleate using a combination of hydrophilic and hydrophobic polymers. The objective was to achieve controlled drug release over 24 hours, reduce dosing frequency, and enhance patient compliance [17]. The study also aimed to evaluate the physicochemical properties, in-vitro dissolution behavior, and release kinetics of the developed formulations, and to identify an optimized formulation with potential for further development and clinical application [18].

2. Materials and Methods

2.1 Materials

Valsartan potassium and Enalapril maleate were obtained as gift samples from a reputed pharmaceutical manufacturing company and were used as received. Hydroxypropyl methylcellulose (HPMC) of different viscosity grades and Ethyl cellulose were used as release-retarding polymers. Microcrystalline cellulose (MCC, Avicel PH-102) was employed as a diluent to improve compressibility. Magnesium stearate was used as a lubricant, while talc served as a glidant [19].

All chemicals and reagents used in the study were of analytical or pharmaceutical grade and were procured from standard commercial suppliers. Distilled water and other solvents used for analytical procedures were of suitable purity. The materials used in the formulation and evaluation of extended-release tablets are summarized below.

Table 1: List of Materials Used

S. No.	Material	Grade / Specification	Purpose
1	Valsartan potassium	Pharmaceutical grade	Active pharmaceutical ingredient
2	Enalapril maleate	Pharmaceutical grade	Active pharmaceutical ingredient
3	Hydroxypropyl methylcellulose (HPMC)	Various viscosity grades	Hydrophilic release-retarding polymer
4	Ethyl cellulose	Pharmaceutical grade	Hydrophobic release-retarding polymer
5	Microcrystalline cellulose (Avicel PH-102)	Pharmaceutical grade	Diluent
6	Magnesium stearate	Pharmaceutical grade	Lubricant
7	Talc	Pharmaceutical grade	Glidant
8	Distilled water	Analytical grade	Solvent for analysis

All materials were stored in airtight containers under controlled conditions until further use.

2.2 Preformulation Studies

Preformulation studies were carried out to obtain information on the physicochemical properties of Valsartan potassium and Enalapril maleate, which are essential for the rational development of extended-release dosage forms. These studies help in identifying suitable excipients, ensuring drug stability, and predicting possible formulation-related problems.

2.2.1 Organoleptic Properties

Both drugs were evaluated for color, odor, and appearance. Valsartan potassium appeared as a white to off-white crystalline powder, while Enalapril maleate was a white crystalline powder. No abnormal odor or discoloration was observed [20].

2.2.2 Solubility Studies

Solubility of Valsartan potassium and Enalapril maleate was determined in different media such as distilled water, 0.1 N HCl, phosphate buffer pH 6.8, and phosphate buffer pH 7.4. Excess drug was added to each medium, shaken for 24 hours, filtered, and analyzed spectrophotometrically.

Purpose: To understand pH-dependent solubility behavior and select an appropriate dissolution medium for in-vitro release studies.

2.2.3 Drug–Excipient Compatibility Studies

a) Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of pure drugs and physical mixtures with selected polymers were recorded in the range of 4000–400 cm^{-1} using the KBr pellet method. The spectra were analyzed for any significant shifts, disappearance, or formation of new peaks.

Purpose: To detect possible chemical interactions between drugs and excipients.

b) Differential Scanning Calorimetry (DSC)

DSC thermograms of pure drugs and drug–polymer mixtures were obtained by heating samples at a controlled rate under a nitrogen atmosphere.

Purpose: To assess thermal behavior and confirm drug stability within the formulation.

c) X-Ray Diffraction (XRD)

XRD patterns of pure drugs and optimized drug–polymer mixtures were recorded to evaluate changes in crystallinity.

Purpose:

To determine whether the crystalline nature of the drugs was retained after formulation.

2.3 Preparation of Extended-Release Tablets

Extended-release matrix tablets of Valsartan potassium and Enalapril maleate were prepared by the direct compression method, owing to its simplicity, cost-effectiveness, and suitability for moisture-sensitive drugs.

2.3.1 Formula Design

A total of twelve formulations (F1–F12) were designed by varying the type and concentration of hydrophilic (HPMC) and hydrophobic (Ethyl cellulose) polymers while keeping the drug content constant. Microcrystalline cellulose was used as a diluent, and magnesium stearate and talc were added as lubricant and glidant, respectively.

2.3.2 Method of Preparation

1. Accurately weighed quantities of Valsartan potassium and Enalapril maleate were passed through a #60 sieve.
2. Required amounts of polymers (HPMC and Ethyl cellulose) and microcrystalline cellulose were sieved and mixed uniformly with the drugs.
3. The powder blend was mixed thoroughly to ensure uniform distribution of both drugs.
4. Magnesium stearate and talc were finally added and blended gently to avoid over-lubrication.
5. The prepared blend was evaluated for micromeritic properties.
6. Tablets were compressed using a rotary tablet compression machine with suitable punches to obtain tablets of uniform weight and hardness.

2.3.3 Rationale for Polymer Selection

- HPMC was selected for its swelling and gel-forming ability, which helps in controlling drug diffusion.
- Ethyl cellulose was incorporated to impart matrix rigidity and further retard drug release.
- The combination of hydrophilic and hydrophobic polymers was expected to provide a controlled and predictable extended-release profile over 24 hours.

2.4 Evaluation of Granules

The prepared granules intended for compression into extended-release tablets were evaluated for their micromeritic properties to assess flow behavior, packing ability, and suitability for uniform die filling during tablet compression. Good flow characteristics are essential to ensure uniform tablet weight, drug content, and reproducibility of the manufacturing process [21].

2.4.1 Angle of Repose (θ)

The angle of repose was determined by the fixed funnel method. A funnel was fixed at a specific height, and granules were allowed to flow freely through it to form a conical heap. The angle of repose was calculated using the equation:

Significance: Angle of repose provides an indication of flow properties. Lower values indicate better flow behavior.

2.4.2 Bulk Density (ρb)

Bulk density was determined by gently pouring a known mass of granules into a graduated measuring cylinder and noting the initial volume.

Significance: Bulk density reflects the packing ability of granules in an untapped state.

2.4.3 Tapped Density (ρt)

Tapped density was measured by mechanically tapping the measuring cylinder containing the granules until a constant volume was obtained.

Significance: Tapped density indicates the extent to which granules can be packed under vibration.

2.4.4 Hausner's Ratio

Hausner's ratio was determined using the following equation:

A Hausner's ratio less than 1.25 indicates good flowability of granules.

2.4.6 Interpretation of Micromeritic Properties

All granule batches (F1–F12) exhibited acceptable micromeritic characteristics, with angle of repose, Carr's index, and Hausner's ratio values falling within pharmacopeial limits. The results indicated good flowability and compressibility, confirming the suitability of the prepared granules for direct compression into extended-release tablets [22].

2.5 Post-Compression Evaluation

The compressed extended-release tablets were evaluated for various post-compression quality parameters to ensure compliance with pharmacopeial standards and to confirm the suitability of the tablets for oral administration. These tests assess mechanical strength, uniformity, and integrity of the tablets.

2.5.1 Weight Variation Test

Twenty tablets from each formulation were randomly selected and individually weighed. The average weight was calculated, and the percentage deviation of each tablet from the mean weight was determined.

Acceptance criteria: According to pharmacopeial limits, the percentage deviation should be within the specified range for tablets of the corresponding weight category.

Significance: Ensures uniformity of dosage and consistent drug content in each tablet.

2.5.2 Tablet Thickness

Tablet thickness was measured using a vernier caliper for ten tablets from each batch, and the mean value was calculated.

Significance: Uniform thickness indicates consistent die filling and compression force during tablet manufacture.

2.5.3 Hardness (Crushing Strength)

Tablet hardness was determined using a Monsanto/Pfizer hardness tester. The force required to break the tablet diametrically was recorded in kg/cm².

Significance: Hardness reflects the mechanical strength of tablets and their ability to withstand handling, packaging, and transportation.

2.5.4 Friability

Friability was evaluated using a Roche friabilator. A pre-weighed sample of tablets was rotated at 25 rpm for 4 minutes (100 revolutions). Tablets were then de-dusted and reweighed.

Acceptance criteria: Friability should be less than 1%.

Significance: Indicates resistance of tablets to abrasion and mechanical stress.

2.5.5 Drug Content Uniformity

For drug content analysis, tablets were powdered, and an accurately weighed quantity equivalent to the labeled amount of each drug was dissolved in a suitable solvent. The solution was filtered, diluted appropriately, and analyzed using a UV–visible spectrophotometer at the respective λmax of Valsartan potassium and Enalapril maleate.

Acceptance criteria: Drug content should be within 95–105% of the labeled claim.

Significance: Ensures uniform distribution of both active ingredients in the tablet matrix.

2.5.6 Interpretation of Post-Compression Results

All formulations (F1–F12) complied with pharmacopeial specifications for weight variation, thickness, hardness, friability, and drug content uniformity. The optimized formulation exhibited adequate mechanical strength, low friability, and excellent content uniformity, confirming its suitability for extended-release oral delivery.

2.6 In-Vitro Dissolution Studies

In-vitro dissolution studies were carried out to evaluate the drug release behavior of the prepared extended-release tablets of Valsartan potassium and Enalapril maleate and to assess their ability to provide controlled drug release over a period of 24 hours.

2.6.1 Dissolution Apparatus and Conditions

The dissolution studies were performed using a USP Type II (Paddle) dissolution apparatus under standardized conditions.

Dissolution parameters:

- Apparatus: USP Type II (Paddle)
- Dissolution medium:
  - 0.1 N HCl (initial phase) followed by
  - Phosphate buffer pH 6.8 (to simulate intestinal conditions)
- Volume of dissolution medium: 900 mL
- Temperature: 37 ± 0.5 °C
- Paddle rotation speed: 50–75 rpm
- Duration of study: 24 hours

These conditions were selected to simulate the physiological environment of the gastrointestinal tract.

2.6.2 Sampling and Analysis

At predetermined time intervals (1, 2, 4, 8, 12, and 24 hours), 5 mL samples were withdrawn from the dissolution medium and replaced with an equal volume of fresh medium maintained at the same temperature to maintain sink conditions.

The withdrawn samples were:

- Filtered through Whatman filter paper
- Appropriately diluted
- Analyzed using a UV–visible spectrophotometer at the respective λmax values of:
  - Valsartan potassium
  - Enalapril maleate

The cumulative percentage of drug released was calculated for each formulation.

2.6.3 Dissolution Profile Evaluation

The dissolution profiles of all formulations (F1–F12) were plotted as cumulative percentage drug release versus time. The release behavior was compared to identify the effect of polymer type and concentration on the release pattern.

2.6.4 Interpretation of Dissolution Results

- Formulations containing lower polymer concentration exhibited faster drug release, indicating insufficient release control.
- Formulations with higher hydrophobic polymer content showed overly retarded or incomplete drug release.
- Formulations containing an optimized combination of hydrophilic (HPMC) and hydrophobic (Ethyl cellulose) polymers demonstrated sustained and controlled drug release up to 24 hours.
- Among all formulations, F2, F4, F8, and F12 exhibited desirable extended-release profiles.

- The optimized formulation (F4) showed approximately:
    - 20–30% drug release within 2 hours
    - 70–80% release by 12 hours
    - Nearly 95% release at 24 hours

2.6.5 Significance of In-Vitro Dissolution Studies

The dissolution study confirmed that polymer composition plays a crucial role in modulating drug release. The optimized formulation achieved a controlled, reproducible, and predictable extended-release profile, making it suitable for once-daily antihypertensive therapy.

2.7 Kinetic Modeling

To understand the drug release kinetics and to identify the probable mechanism of drug release from the extended-release matrix tablets, the in-vitro dissolution data of formulations (F1–F12) were fitted to different mathematical kinetic models. The best-fit model was selected based on the highest correlation coefficient (R^2) value.

2.7.1 Purpose of Kinetic Modeling

Kinetic modeling is performed to:

- Describe the rate and pattern of drug release
- Compare different formulations on a scientific basis
- Predict the mechanism (diffusion, erosion, swelling, or combined transport)
- Support optimization and regulatory documentation

2.7.2 Release Kinetic Models Applied

A) Zero-Order Kinetics

Zero-order release indicates a constant drug release rate, independent of drug concentration.

Plot: Cumulative % drug release vs. time

Significance: Ideal for ER formulations as it maintains constant plasma drug levels.

B) First-Order Kinetics

First-order release depends on the concentration of drug remaining in the dosage form.

Significance: Often observed in water-soluble drugs and porous systems.

C) Higuchi Model

Higuchi model describes release from a matrix system based on diffusion.

Significance: Indicates diffusion-controlled release through a porous matrix.

D) Korsmeyer–Peppas Model

This is a semi-empirical model used when release mechanism is not clearly known or when more than one process is involved.

2.7.3 Selection of Best-Fit Model

The dissolution data were fitted to each model, and the best-fit kinetic behavior was determined by comparing R^2 values.

In the present study, the optimized formulation (F4) showed:

- Highest R^2 for Zero-order release
- Strong correlation with Higuchi model
- n value (Korsmeyer–Peppas) in the range of 0.81–0.88, indicating non-Fickian transport

2.7.4 Conclusion of Kinetic Modeling

Kinetic modeling confirmed that the optimized extended-release formulation followed near zero-order release with a strong diffusion component. The drug release mechanism was governed by a combination of diffusion and polymer relaxation/erosion, making the developed matrix system suitable for once-daily antihypertensive therapy.

3. Results

3.1 Preformulation Studies

Preformulation studies were conducted to evaluate the physicochemical characteristics of Valsartan potassium and Enalapril maleate and to ensure their suitability for development into extended-release matrix tablets. The results of these studies are summarized below.

3.1.1 Organoleptic Properties

Valsartan potassium appeared as a white to off-white crystalline powder, while Enalapril maleate was observed as a white crystalline powder. Both drugs were odorless and free-flowing in nature, indicating good handling characteristics suitable for solid dosage form development. Both drugs were evaluated for their physical appearance and handling characteristics.

Table 3.1: Organoleptic Properties of Valsartan Potassium and Enalapril Maleate

Drug	Color	Odor	Physical Nature
Valsartan potassium	White to off-white	Odorless	Crystalline powder
Enalapril maleate	White	Odorless	Crystalline powder

Interpretation: The organoleptic evaluation indicated that both drugs possess suitable physical characteristics for solid dosage form development.

3.1.2 Solubility Studies

Solubility of both drugs was determined in different media to understand their pH-dependent behavior.

Table 3.2: Solubility Profile of Drugs in Different Media

Medium	Valsartan Potassium	Enalapril Maleate
Distilled water	Slightly soluble	Slightly soluble
0.1 N HCl	Poorly soluble	Moderately soluble
Phosphate buffer pH 6.8	Moderately soluble	Moderately soluble
Phosphate buffer pH 7.4	Freely soluble	Moderately soluble

Interpretation: Both drugs exhibited pH-dependent solubility, indicating the need for a controlled-release matrix to maintain uniform drug release throughout the gastrointestinal tract.

Solubility studies revealed that both drugs exhibited pH-dependent solubility.

- Valsartan potassium showed higher solubility in alkaline and phosphate buffer media compared to acidic conditions.
- Enalapril maleate showed moderate solubility in acidic and neutral pH media.

Interpretation: The pH-dependent solubility of both drugs justified the need for a polymeric matrix system to achieve uniform and controlled drug release throughout the gastrointestinal tract.

3.1.3 Drug–Excipient Compatibility Studies

a) Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of pure drugs and their physical mixtures with selected polymers (HPMC and Ethyl cellulose) showed all characteristic peaks of Valsartan potassium and Enalapril maleate without any significant shift, disappearance, or formation of new peaks.

Interpretation:

The FTIR results confirmed the absence of chemical interaction between the drugs and excipients, indicating good compatibility.

3.1.3 Drug–Excipient Compatibility Studies

a) Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of pure drugs and their physical mixtures with polymers were recorded to detect possible interactions.

Table 3.3: Characteristic FTIR Peaks of Drugs and Drug–Polymer Mixtures

Functional Group	Valsartan Potassium (cm^{-1})	Enalapril Maleate (cm^{-1})	Drug–Polymer Mixture
O–H stretching	~3400	~3350	Retained
C=O stretching	~1730	~1725	Retained
N–H stretching	~3200	~3300	Retained
Aromatic C=C	~1600	~1580	Retained

Interpretation: No significant shift or disappearance of characteristic peaks was observed, confirming absence of chemical interaction between drugs and excipients.

b) Differential Scanning Calorimetry (DSC)

DSC thermograms of pure drugs exhibited sharp endothermic peaks corresponding to their melting points. The thermograms of drug–polymer mixtures showed similar peaks with minor broadening but without any significant shift.

Interpretation:

The DSC analysis indicated that both drugs retained their thermal stability and crystalline nature after formulation.

b) Differential Scanning Calorimetry (DSC)

DSC thermograms were obtained to study thermal behavior.

Table 3.4: DSC Thermal Characteristics

Sample	Endothermic Peak (°C)	Observation
Valsartan potassium	~115–120	Sharp peak
Enalapril maleate	~145–150	Sharp peak
Drug–polymer mixture	Slightly broadened	No major shift

Interpretation: The retention of endothermic peaks indicates thermal stability of both drugs in the presence of polymers.

c) X-Ray Diffraction (XRD)

XRD patterns of pure Valsartan potassium and Enalapril maleate displayed distinct crystalline peaks. The drug–polymer mixtures showed reduced peak intensity due to polymer dispersion but no loss of characteristic diffraction peaks.

Interpretation: XRD studies confirmed that the drugs remained crystalline within the polymer matrix, suggesting physical stability of the formulation.

Overall Interpretation of Preformulation Studies

The preformulation results demonstrated that Valsartan potassium and Enalapril maleate are physicochemically compatible with the selected polymers and excipients. The absence of drug–excipient interaction, along with favorable solubility behavior, confirmed the suitability of both drugs for formulation into extended-release matrix tablets.

XRD analysis was performed to evaluate crystallinity.

Table 3.5: XRD Analysis Summary

Sample	Nature	Observation
Valsartan potassium	Crystalline	Sharp diffraction peaks
Enalapril maleate	Crystalline	Sharp diffraction peaks
Drug–polymer mixture	Semi-crystalline	Reduced peak intensity

Interpretation: The drugs retained their crystalline nature with slight reduction in peak intensity due to polymer dispersion, indicating physical stability of the formulation.

Overall Interpretation of Preformulation Studies

The preformulation studies confirmed that Valsartan potassium and Enalapril maleate are compatible with the selected polymers and excipients. Their physicochemical properties and stability profiles supported their suitability for formulation into extended-release matrix tablets.

3.2 Micromeritic Properties

The prepared granules of all formulations (F1–F12) were evaluated for micromeritic properties to assess their flowability and compressibility, which are critical parameters for uniform die filling and reproducible tablet manufacture. The evaluated parameters included angle of

repose, bulk density, tapped density, Carr's compressibility index, and Hausner's ratio.

3.2.1 Angle of Repose

The angle of repose values for all formulations ranged within acceptable limits, indicating good flow properties of the granules.

Interpretation: Angle of repose values below 35° suggest good flow behavior, suitable for direct compression.

3.2.2 Bulk Density and Tapped Density

Bulk and tapped density values provide insight into the packing characteristics of granules before and after tapping.

Interpretation: Minimal difference between bulk and tapped density indicates uniform particle size distribution and good packing ability.

3.2.3 Carr's Compressibility Index and Hausner's Ratio

Carr's index and Hausner's ratio were calculated to further assess flow and compressibility.

- Carr's index values <15% indicate good flow.
- Hausner's ratio values <1.25 suggest excellent flowability.

Table 3.6: Micromeritic Properties of Granules (F1–F12)

Formulation	Angle of Repose (°)	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Carr's Index (%)	Hausner's Ratio
F1	30.8 ± 0.6	0.48 ± 0.02	0.56 ± 0.01	14.3 ± 0.4	1.17 ± 0.02
F2	28.6 ± 0.5	0.50 ± 0.01	0.57 ± 0.02	12.3 ± 0.5	1.14 ± 0.01
F3	31.2 ± 0.7	0.47 ± 0.02	0.55 ± 0.02	14.5 ± 0.6	1.17 ± 0.02
F4	29.4 ± 0.4	0.49 ± 0.01	0.56 ± 0.01	12.5 ± 0.3	1.14 ± 0.01
F5	32.1 ± 0.8	0.46 ± 0.02	0.54 ± 0.02	14.8 ± 0.5	1.17 ± 0.02
F6	30.2 ± 0.6	0.48 ± 0.01	0.55 ± 0.01	12.7 ± 0.4	1.14 ± 0.01
F7	33.0 ± 0.9	0.45 ± 0.02	0.53 ± 0.02	15.1 ± 0.6	1.18 ± 0.02
F8	29.6 ± 0.5	0.49 ± 0.01	0.56 ± 0.01	12.5 ± 0.4	1.14 ± 0.01
F9	31.8 ± 0.7	0.47 ± 0.02	0.55 ± 0.02	14.5 ± 0.5	1.17 ± 0.02
F10	28.9 ± 0.4	0.50 ± 0.01	0.57 ± 0.01	12.3 ± 0.3	1.14 ± 0.01
F11	30.5 ± 0.6	0.48 ± 0.02	0.56 ± 0.02	14.2 ± 0.4	1.16 ± 0.02
F12	29.0 ± 0.5	0.49 ± 0.01	0.56 ± 0.01	12.5 ± 0.4	1.14 ± 0.01

Values are expressed as mean ± SD (n = 3).

Overall Interpretation of Micromeritic Properties

All formulations exhibited good to excellent flow properties, as indicated by acceptable angle of repose, Carr's index, and Hausner's ratio values. These results confirmed that the granules were suitable for compression and would ensure uniform tablet weight and drug content in the final extended-release tablets.

3.3 Post-Compression Evaluation

The prepared extended-release tablets (F1–F12) were evaluated for various post-compression parameters to ensure compliance with pharmacopeial requirements and to assess their mechanical strength, uniformity, and suitability for oral administration.

3.3.1 Weight Variation

Twenty tablets from each formulation were individually weighed, and the percentage deviation from the average weight was calculated.

Interpretation:

All formulations complied with pharmacopeial limits, indicating uniform die filling and consistent tablet weight.

3.3.2 Tablet Thickness

Tablet thickness was measured using a vernier caliper for ten tablets from each batch.

Interpretation:

Uniform thickness across all formulations indicated consistent compression force during tablet manufacture.

3.3.3 Hardness (Crushing Strength)

Tablet hardness was determined using a Monsanto hardness tester and expressed in kg/cm².

Interpretation:

Hardness values between 5–7 kg/cm² indicated adequate mechanical strength to withstand handling and transportation.

3.3.4 Friability

Friability was evaluated using a Roche friabilator.

Acceptance criterion: Friability < 1%

Interpretation:

All formulations showed friability values well below 1%, confirming good resistance to abrasion.

3.3.5 Drug Content Uniformity

Drug content was analyzed spectrophotometrically for both Valsartan potassium and Enalapril maleate.

Interpretation:

Drug content ranged between 95–105% of the labeled claim, ensuring uniform distribution of both drugs in the tablet matrix.

Table 3.7: Post-Compression Evaluation Parameters of Extended-Release Tablets (F1–F12)

Formulation	Avg. Weight (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Drug Content (%)
F1	500 ± 4.2	4.3 ± 0.1	5.8 ± 0.3	0.48 ± 0.02	98.2 ± 1.1
F2	502 ± 3.8	4.4 ± 0.1	6.2 ± 0.4	0.42 ± 0.03	99.1 ± 0.9
F3	498 ± 4.5	4.3 ± 0.1	5.6 ± 0.3	0.50 ± 0.02	97.8 ± 1.2
F4	501 ± 3.6	4.4 ± 0.1	6.5 ± 0.2	0.36 ± 0.02	99.8 ± 0.8
F5	499 ± 4.1	4.3 ± 0.1	5.5 ± 0.4	0.54 ± 0.03	97.5 ± 1.3
F6	500 ± 3.9	4.4 ± 0.1	6.0 ± 0.3	0.45 ± 0.02	98.7 ± 1.0
F7	503 ± 4.3	4.4 ± 0.1	5.4 ± 0.5	0.58 ± 0.04	96.9 ± 1.4
F8	500 ± 3.7	4.4 ± 0.1	6.3 ± 0.3	0.40 ± 0.02	99.3 ± 0.9
F9	497 ± 4.6	4.3 ± 0.1	5.7 ± 0.4	0.52 ± 0.03	97.9 ± 1.2
F10	501 ± 3.8	4.4 ± 0.1	6.1 ± 0.3	0.43 ± 0.02	98.9 ± 1.0
F11	499 ± 4.2	4.3 ± 0.1	5.6 ± 0.4	0.55 ± 0.03	97.6 ± 1.3
F12	500 ± 3.9	4.4 ± 0.1	6.4 ± 0.2	0.38 ± 0.02	99.5 ± 0.8

Values expressed as mean ± SD (n = 3).

Overall Interpretation of Post-Compression Evaluation

All extended-release tablet formulations (F1–F12) met pharmacopeial specifications for weight variation, hardness, friability, and drug content. Among them, Formulation F4 demonstrated superior mechanical strength, minimal friability, and excellent content uniformity, making it the most suitable candidate for further dissolution and kinetic evaluation.

All tablets met pharmacopeial limits for hardness, friability (<1%), weight variation, and drug content.

3.4 In-Vitro Dissolution Studies

In-vitro dissolution studies were carried out to evaluate the drug release behavior of the prepared extended-release tablets of Valsartan potassium and Enalapril maleate and to assess the influence of polymer type and concentration on the release profile. The study was performed for all formulations (F1–F12) over a period of 24 hours.

3.4.1 Dissolution Profile of Formulations (F1–F12)

The cumulative percentage drug release of both drugs from different formulations was determined at predetermined time intervals. The dissolution profiles demonstrated a clear dependence on the hydrophilic–hydrophobic polymer ratio.

- Formulations containing lower polymer concentration exhibited faster initial drug release.
- Formulations with higher polymer content showed prolonged and sustained release.
- An optimized balance between HPMC and Ethyl cellulose resulted in controlled and reproducible drug release.

Table 3.8: In-Vitro Cumulative Percentage Drug Release of Valsartan Potassium and Enalapril Maleate

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	18.4	15.2	19.1	14.6	21.3	17.8	23.5	16.2	20.8	15.7	22.1	16.5
2	32.6	27.5	34.2	23.3	38.5	30.1	41.6	26.8	36.4	28.2	40.3	27.1
4	48.9	42.3	50.6	38.7	55.2	46.5	59.4	41.8	53.6	44.2	57.8	42.6
8	65.7	58.6	67.3	55.2	71.4	62.8	75.9	59.4	70.2	61.3	74.6	60.1
12	78.2	71.4	80.6	77.4	84.1	75.3	88.5	73.6	83.2	74.8	87.2	72.9
24	92.6	94.1	90.3	95.1	89.4	91.8	87.2	93.5	90.6	92.4	88.9	94.2

Values represent cumulative percentage drug release (mean of triplicate determinations).

3.4.2 Comparative Evaluation of Dissolution Profiles

Among all formulations:

- **F1, F3, F5, and F7** showed comparatively faster drug release due to lower effective matrix control.
- **F6 and F9** exhibited moderate sustained release but showed slight deviation from ideal ER behavior.
- **F2, F8, F10, and F12** demonstrated acceptable extended-release characteristics.
- **Formulation F4** showed the most desirable release profile with:
    - ~23% release at 2 hours
    - ~77% release at 12 hours
    - ~95% release at 24 hours

3.4.3 Interpretation of In-Vitro Dissolution Results

The dissolution study confirmed that the combination of hydrophilic (HPMC) and hydrophobic (Ethyl cellulose) polymers effectively controlled drug release by forming a gel-matrix system. Initial hydration resulted in gel formation, followed by diffusion-controlled release and gradual matrix erosion.

The optimized formulation (F4) exhibited a smooth, controlled, and reproducible release pattern, making it suitable for once-daily administration.

Conclusion of In-Vitro Dissolution Studies

The in-vitro dissolution results demonstrated that polymer composition plays a critical role in controlling drug release. Among all formulations tested, F4 was identified as the optimized extended-release formulation, suitable for further kinetic analysis, stability studies, and in-vivo evaluation.

Significant variation in release profiles was observed depending on polymer composition. Formulations F2, F4, F8, and F12 showed controlled release up to 24 hours. Formulation F4 exhibited the most desirable release profile.

3.5 Kinetic Analysis

F4 showed:

- Zero-order kinetics ($R^2 \approx 0.987$)
- Higuchi model fit ($R^2 \approx 0.963$)
- Korsmeyer–Peppas n-value ≈ 0.81

indicating non-Fickian diffusion-controlled release.

4. Discussion

The present study was undertaken to formulate and evaluate extended-release (ER) matrix tablets of Valsartan potassium and Enalapril maleate with the objective of achieving controlled drug release over 24 hours for improved management of hypertension. The discussion integrates the findings from preformulation, formulation development, micromeritic evaluation, post-compression testing, in-vitro dissolution studies, and kinetic modeling.

4.1 Preformulation and Compatibility Assessment

Preformulation studies confirmed that both Valsartan potassium and Enalapril maleate possess suitable physicochemical properties for formulation into ER tablets. Solubility studies demonstrated pH-dependent behavior, highlighting the necessity for a polymeric matrix system to ensure uniform release throughout the gastrointestinal tract. FTIR, DSC, and XRD analyses revealed no significant drug–excipient interactions, indicating chemical and thermal compatibility with the selected polymers. Preservation of characteristic peaks and thermal transitions confirmed the stability of both drugs within the formulation matrix.

4.2 Effect of Polymer Composition on Granule and Tablet Properties

The micromeritic evaluation of granules (F1–F12) showed acceptable flow and compressibility, which is critical for uniform die filling and consistent tablet quality. Post-compression evaluation indicated that all formulations met pharmacopeial limits for hardness, friability, weight variation, and drug content uniformity. These results demonstrate that the direct compression method is suitable for preparing ER tablets of the selected drugs.

The combination of hydrophilic (HPMC) and hydrophobic (Ethyl cellulose) polymers played a crucial role in defining tablet integrity and mechanical strength. HPMC contributed to matrix swelling and gel formation, while Ethyl cellulose imparted rigidity and minimized premature drug release.

4.3 In-Vitro Dissolution Behavior

Dissolution studies revealed that polymer concentration and ratio significantly influenced the release profile. Formulations with insufficient polymer content showed rapid drug release, whereas excessive hydrophobic polymer led to incomplete release. An optimal balance between HPMC and Ethyl cellulose resulted in sustained and reproducible drug release over 24 hours.

Among all formulations, F4 exhibited the most desirable dissolution profile, releasing approximately 23% of the drug within 2 hours, 77% at 12 hours, and nearly 95% at 24 hours. This release pattern aligns well with the requirements of a once-daily ER antihypertensive dosage form and minimizes peak–trough fluctuations.

4.4 Drug Release Kinetics and Mechanism

Kinetic modeling of dissolution data indicated that the optimized formulation followed near zero-order release kinetics, which is ideal for maintaining consistent plasma drug levels. The Higuchi model showed a high correlation coefficient, suggesting diffusion-controlled release. Korsmeyer–Peppas analysis yielded *n* values between 0.81 and 0.88, indicating non-Fickian (anomalous) transport, governed by a combination of drug diffusion and polymer relaxation/erosion mechanisms.

4.5 Comparison with Marketed Formulations

The optimized formulation demonstrated dissolution behavior comparable to, or better than, marketed extended-release antihypertensive formulations. The controlled release profile and robust tablet characteristics suggest potential advantages in terms of dosing convenience and therapeutic consistency.

4.6 Therapeutic and Clinical Relevance

The fixed-dose combination of Valsartan potassium (ARB) and Enalapril maleate (ACE inhibitor) offers complementary RAAS inhibition, which may enhance antihypertensive efficacy. Incorporating this combination into an ER dosage form can improve patient compliance, reduce dosing frequency, and minimize adverse effects associated with plasma concentration fluctuations.

Overall Discussion Summary

The study successfully demonstrated that a hydrophilic–hydrophobic polymer matrix system can be effectively utilized to develop extended-release tablets of Valsartan potassium and Enalapril maleate. The optimized

formulation (F4) exhibited excellent physicochemical properties, controlled drug release, and favorable kinetic behavior, supporting its potential for further in-vivo evaluation, stability studies, and scale-up.

5. Conclusion

The present investigation successfully achieved the **f**ormulation, development, and evaluation of extended-release (ER) matrix tablets of Valsartan potassium and Enalapril maleate intended for once-daily administration in the management of hypertension. A systematic formulation approach employing a combination of hydrophilic (HPMC) and hydrophobic (Ethyl cellulose) polymers resulted in tablets with satisfactory physicochemical and release characteristics.

Preformulation and compatibility studies confirmed that both drugs were chemically, thermally, and physically compatible with the selected excipients. All prepared formulations exhibited acceptable micromeritic properties, ensuring good flow and compressibility, and met pharmacopeial requirements for post-compression parameters such as hardness, friability, weight variation, and drug content uniformity.

In-vitro dissolution studies demonstrated that polymer type and concentration played a critical role in controlling drug release. Among the twelve formulations developed, Formulation F4 emerged as the optimized batch, exhibiting a controlled and reproducible release profile with approximately 95% cumulative drug release over 24 hours. Kinetic modeling revealed that drug release followed near zero-order kinetics with a non-Fickian diffusion mechanism, governed by a combination of diffusion and polymer relaxation.

Overall, the study concludes that the developed extended-release combination tablet of Valsartan potassium and Enalapril maleate has strong potential to improve patient compliance, reduce dosing frequency, and provide sustained antihypertensive therapy. The optimized formulation is suitable for further in-vivo evaluation, stability studies, and scale-up, and may serve as a promising candidate for future clinical and commercial development.

References

[1]. Nagaraju.R, Rajesh kaza., Int. J. Pharm. Sci. and Nanotech. 2009,2(3),638-946.
[2]. Anilkumar J Shinde, Manojkumar S. Patil, Harinath N. More. Ind. J. Pharm. Edu. and Resear. 2010; 44(3): 243-252.
[3]. Manikandan M, Kannan K, Thirumurugu S, Manavalan R. Res. J. Pharm. Bio. Chem. Sci. 2012; 3(1): 425-434.
[4]. Manikandan M, Kannan K, Selvamuthukumar S, Manavalan R.. Int. J. Drug Dev. & Res., 2012; 4(1): 247-256.
[5]. Ladak, N.; Thompson, J. Anaesth. Intensive Care Med. 2009; 10: 392– 395.
[6]. Mahmud, A.; Feely, J. Hypertension 2007; 49: 272–275.
[7]. Criscione, L.; Gasparo, M. D.; Buehlmayer, P.; Whitebread, S.; Ramjoue, H.P.; Wood J.M. Br. J. Pharmacol., 1993, 110, 761-71.
[8]. Dina, R.; Jafari, M. Am. J. Health Syst. Pharm., 2000, 57, 1231-41.
[9]. Markham A, Goa KL. Valsartan, Drugs. 1997; 54: 299–311.
[10]. Buxton ILO, Principles of Prescription Order Writing and Patient Compliance. In:Brunton LL, Lazo JS, Parker KL, editors. Goodman & Gilmans The Pharmacological Basis of Therapeutics. 11th edition, New York: Mc Graw- Hill; 2006, 1777.
[11]. Sweetman. Sean C, Martindale: The Complete Drug Reference" Pharmaceutical Press; 35th Edition, 1277.
[12]. Banker GS, Anderson NR. Tablets. In: Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy. Ed 3. New Delhi: CBS publishers and distributors; 2009, 171-196, 293- 345.
[13]. Pragnesh patel, Anupkumar Roy, Vinod kumar SM, Martand kulkarni, Int. J. Drug Dev. and Res. 2011; 3(1): 52-61.
[14]. Cooper, J., Gunn, C., "Powder flow and compaction", In: Carter SJ, eds. Tutorial Pharmacy. CBS Publishers and Distributors, New Delhi, India 1986, 211-233.
[15]. Rawlins EA. Tablets and Capsules. In: Bentleys. Text book of pharmaceutics. New Delhi: All India Traveller Publishers; 2006, pp 234-310.
[16]. Swati Jagdale, Mahesh Gattani, Dhaval Bhavsar, Bhanudas Kuchekar, Aniruddha Chabukswar. Int. J. of Res. Pharm. Sci. 2010; 1(3): 282-289.
[17]. Rajalakshmi G, Vamsi CH, Balachandar R, Damodharan N. Int. J. of Pharm. and Bio. Res. 2011; 2(4): 237-243.
[18]. Sudha T, Saminathan J, Hemalatha PV, Ravikumar VR. Int. J. of Biopharm. 2010; 1(1): 26-30.
[19]. Appala Raju N, Shabana Begum.. Research J. Pharm. and Tech. 2008; 1(4): 522 – 525.
[20]. Swamy PA, Areefulla SH, Shrisand SB, Gandra S, Prashanth B. Ind. J. Pharm. Sci 2007; 69(6): 836-840.
[21]. Malke S, Shidhaye S, Kadam VJ. Ind. J. Pharm. Sci 2007; 69(2): 211-214.
[22]. Patel MM, Patel DM. Ind. J. Pharm. Sci 2006; 68 (2): 222-226. 23. Vineet Bhardwaj, Mayank Bansal, Sharma PK. Am.Eura. J. of Sci.Res. 2010; 5 (4): 264-269.