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Research Article

Formulation and Optimization of Ramipril-Hydrochlorothiazide Bilayer Tablets for Sequential Release Using Factorial Design

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Abstract:
A bilayer tablet combining a rapid-release segment of ramipril (5 mg) with a sustained-release segment of hydrochlorothiazide (12.5 mg) was developed to improve hypertension management. A 3^2 full-factorial design was employed, varying the total polymer content (HPMC K4M + HPMC K100M) in the sustained-release layer (22.22–38.89 %) and the amount of croscarmellose sodium in the immediate-release layer (3.33–10 %). Pre-formulation studies confirmed the identity and purity of both drugs (FTIR peaks at 3420 cm^{-1} and 1740 cm^{-1} for ramipril; 3360 cm^{-1} and 1340 cm^{-1} for hydrochlorothiazide) and showed no significant interaction with the selected excipients. Powder blends exhibited acceptable flow properties (Carr's index 17–23 %, angle of repose 27–32°). All tablets met compendial specifications for weight (299–301 mg), hardness (6.2–7.2 $kg \cdot cm^{-2}$), friability (<1 %) and drug content (98–101 %). In vitro release demonstrated >85 % ramipril release within 30 min, with formulation F9 achieving 99.6 % in 20 min. Hydrochlorothiazide release extended over 12 h, ranging from >94 % at 10 h (F1–F3) to ~80 % at 12 h (F7–F9). Release kinetics best fitted the Korsmeyer-Peppas model ($R^2 > 0.99$, $n = 0.50–0.68$), indicating a combined diffusion-swelling mechanism. Formulation F5 (30.56 % polymer, 6.67 % disintegrant) was identified as optimal, showing a disintegration time of 9.4 min, swelling of 168 % at 8 h, and stability for three months under accelerated conditions (40 °C/75 % RH, $f_2 > 94$). The results demonstrate that increasing disintegrant levels accelerates ramipril release, while higher polymer concentrations sustain hydrochlorothiazide delivery, providing a convenient once-daily antihypertensive therapy.
Keywords: bilayer tablet, ramipril, hydrochlorothiazide, immediate release, sustained release, HPMC, croscarmellose sodium, factorial design, dissolution kinetics, stability.

Introduction

The oral route remains the most commonly used and convenient method for delivering medications. It is widely preferred in pharmaceutical practice because it allows greater flexibility in designing dosage forms compared with other routes. Nearly 90% of drugs intended for systemic action are administered orally. This route is still favoured due to multiple advantages, such as ease of use, avoidance of pain, versatility and, most importantly, better patient compliance. The most common oral dosage forms are tablets and

capsules; however, a frequent limitation is that some patients find them difficult to swallow [1]. Tablets are solid unit dosage forms, usually flat or biconvex in shape, produced by compressing a drug alone or with suitable excipients. They may be swallowed whole, chewed, or dissolved or dispersed in water before administration. Certain implants or pessaries may also be manufactured in tablet form. Tablet size and shape can vary extensively depending on the dose of medication and the intended route of administration.

Benefits of Layer Tablets:

- Physical and Chemical Separation: Incompatibility of active-active, excipient-excipient, and active-excipient components can be mitigated using physical separation methods. A well-known example of such an interaction is the Maillard reaction occurring during tablet compression.
- Numerous Release Profile: These drug delivery systems can facilitate various release kinetics for the same or different pharmaceuticals with identical or diverse physicochemical attributes through the use of numerous layers. Each monolith was designed to regulate the administration of medication doses through various release control techniques.
- Immediate Release (Disintegrating Monolith): Disintegrating monoliths provide the rapid release necessary to attain peak plasma concentration. The introduction of an initial loading dose in conventional dosage forms was overlooked due to the deployment of this strategy.
- Delayed Release (Erodible Monolith): Delayed release is accomplished through the use of an erodible monolith, which administers the second dose of active ingredients in the distal regions of the gastrointestinal tract (GIT).
- Controlled Release (Swelling Monolith): Swelling monoliths operate through both swelling and erosion mechanisms, facilitating the continuous release of the medicine throughout the gastrointestinal tract.
- To Facilitate Repeat Action: Multilayered tablets are ideally suited for repeat-action formulations, where one layer of the tablet or the outer layer of a compression-coated tablet delivers the initial dose, swiftly disintegrating in the stomach. The inner tablet comprises components that are insoluble in stomach conditions but release in the intestinal milieu.
- Enhanced Management of Release Profile: Implementing layering in the tablet formulation is a practical approach to achieving improved control over the release profile. It serves as a feasible substitute for traditional matrix tablets to avoid the early burst release and attain a zero-order release profile. [2]

Mechanism of superdisintegrants by swelling

Swelling Process

Water penetrates the superdisintegrant particles, causing them to swell in multiple dimensions and generate internal pressure that overcomes interparticle bonds in the tablet matrix. This expansion pushes apart adjacent components, fracturing the tablet into smaller fragments for faster dissolution. Sodium starch glycolate exemplifies this by incorporating cross-links and carboxymethyl groups that enhance water uptake without gel formation, achieving over 20 times its weight in water absorption. [3]

Key Factors Influencing Swelling

Particle size, porosity, and chemical structure affect swelling efficiency; larger, porous particles like those in croscarmellose sodium facilitate quicker water ingress and two- or three-dimensional expansion. Swelling force correlates directly with water absorption capacity, with ionic strength and pH of the medium modulating performance—acidic conditions may reduce uptake for some agents. This mechanism dominates in non-soluble matrices but works alongside wicking in many formulations. [4]

Materials and Methods

The selection of appropriate materials is fundamental to the successful development of any pharmaceutical formulation. For the present investigation, all active pharmaceutical ingredients, excipients, chemicals, reagents, and equipment were carefully selected based on their pharmaceutical acceptability, compatibility, and compliance with pharmacopoeial standards. The materials used in this study were procured from reputed Indian manufacturers and suppliers to ensure quality, consistency, and reliability throughout the formulation development process. Ramipril and Hydrochlorothiazide were selected as the model drugs for this bilayer tablet formulation.

Both active pharmaceutical ingredients were obtained as gift samples from renowned Indian pharmaceutical companies and were used without further purification. The authenticity and purity of the drugs were confirmed through melting point determination, UV spectroscopic analysis, and FTIR spectroscopy before their use in formulation development.

Table 1: shows Active Pharmaceutical Ingredients

S. No.	Active Ingredient	Name of Manufacturer
1.	Ramipril	Aurobindo Pharma Ltd. Hyderabad, India
2.	Hydrochlorothiazide	Cipla Ltd. Mumbai, India

Table 2: shows Excipients

S. No.	Excipients	Grade	Name of Manufacturer	Functional Category
1.	Hydroxypropyl Methylcellulose	HPMC K4M	Colorcon Asia Pvt. Ltd., Goa, India	Sustained release polymer
2.	Hydroxypropyl Methylcellulose	HPMC K100M	Colorcon Asia Pvt. Ltd., Goa, India	Rate controlling polymer
3.	Povidone	PVP K30	Loba Chemie Pvt. Ltd., Mumbai, India	Binder
4.	Microcrystalline Cellulose	Avicel PH 102	Signet Chemical Corporation, Mumbai, India	Binder and diluent
5.	Lactose Anhydrous	Pharmatose DCL 15	Lactose India Limited, Maharashtra, India	Diluent
6.	Pregelatinized Starch	Starch 1500	Colorcon Asia Pvt. Ltd., Goa, India	Diluent and binder
7.	Croscarmellose Sodium	Ac-Di-Sol	JRS Pharma India Pvt. Ltd., Hyderabad, India	Superdisintegrant
8.	Sodium Starch Glycolate	Primogel	Roquette India Pvt. Ltd., Maharashtra, India	Disintegrant
9.	Sodium Bicarbonate	IP Grade	Solvay Chemicals India Pvt. Ltd., Pune, India	pH modifier and alkalizing agent
10.	Sodium Stearyl Fumarate	PRUV	JRS Pharma India Pvt. Ltd., Hyderabad, India	Lubricant
11.	Talc	IP Grade	Luzenac India Pvt. Ltd., Rajasthan, India	Glidant and lubricant
12.	Magnesium Stearate	IP Grade	Ferro Chem Industries, Mumbai, India	Lubricant

Experimental Design

A 3^2 full factorial design was employed to systematically study the effects of two independent variables on the performance characteristics of the bilayer tablets. The two independent variables selected were polymer concentration (X_1) representing the combined percentage of HPMC K4M and HPMC K100M in the sustained release layer, and disintegrant concentration (X_2) representing the percentage of croscarmellose sodium in the immediate release layer.

Each independent variable was evaluated at three levels: low (-1), medium (0), and high (+1), resulting in a total of nine formulation batches (F1 to F9). The factorial design matrix with coded levels is presented in Table in the below. [5]

Table 3: shows Factorial Design Matrix (3^2 Full Factorial Design)

Batch	Independent Variable X_1: Polymer Concentration (%)	Independent Variable X_2: Disintegrant Concentration (%)	Coded Level (X_1, X_2)
F1	22.22 (Low: -1)	3.33 (Low: -1)	-1, -1
F2	22.22 (Low: -1)	5.0 (Medium: 0)	-1, 0
F3	22.22 (Low: -1)	6.67 (High: +1)	-1, +1
F4	30.56 (Medium: 0)	5.0 (Low: -1)	0, -1
F5	30.56 (Medium: 0)	6.67 (Medium: 0)	0, 0
F6	30.56 (Medium: 0)	8.33 (High: +1)	0, +1
F7	38.89 (High: +1)	6.67 (Low: -1)	+1, -1
F8	38.89 (High: +1)	8.33 (Medium: 0)	+1, 0
F9	38.89 (High: +1)	10.0 (High: +1)	+1, +1

Note: X_1 = Total polymer concentration in sustained release layer (HPMC K4M + HPMC K100M); X_2 = Disintegrant concentration in immediate release layer (Croscarmellose sodium)

Method of Preparation of Bilayer Tablets

Bilayer tablets containing Ramipril (5 mg) in the immediate release layer and Hydrochlorothiazide (12.5 mg) in the sustained release layer were prepared using a combination of direct compression and wet granulation techniques.

Preparation of Immediate Release Layer (Ramipril Layer)

The immediate release layer was prepared by direct compression method to ensure rapid drug release.

The immediate release layer containing Ramipril was prepared by direct compression method to achieve rapid drug release after administration. The preparation process began with accurate weighing of all ingredients including Ramipril, lactose anhydrous, microcrystalline cellulose, and pregelatinized starch according to the quantities specified in Table (6.7) for each formulation batch.

Each ingredient was individually passed through a #20 mesh sieve to obtain uniform particle size and remove any lumps before mixing.

The sieved materials were then transferred into a clean, dry porcelain mortar for blending.

Uniform powder mixing was achieved using the geometric dilution technique, where the ingredients were thoroughly mixed for 10 minutes to ensure even distribution throughout the blend.

After initial mixing, croscarmellose sodium acting as a superdisintegrant was added to the powder mixture, and mixing was continued for another 5 minutes to ensure uniform distribution of this important disintegration agent. In the final mixing step, sodium stearyl fumarate and

talc, serving as lubricant and glidant respectively, were added to the blend and gently mixed for about 2-3 minutes using careful mixing to avoid over-lubrication that could negatively affect tablet hardness and disintegration characteristics. The final lubricated blend was evaluated for pre-compression parameters before being stored in airtight containers at room temperature until the compression stage. [6]

Formulation Batches of Bilayer Tablets of Ramipril and Hydrochlorothiazide (3^2 Factorial Design)

Immediate Release Layer (Ramipril Layer) - 9 Batches

Table 4: shows Formulation Composition of Immediate Release Layer (Ramipril Layer)

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ramipril	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Lactose anhydrous	44.0	42.0	40.0	42.0	40.0	38.0	40.0	38.0	36.0
Microcrystalline cellulose	35.0	35.0	35.0	35.0	35.0	35.0	35.0	35.0	35.0
Pregelatinized starch	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Croscarmellose sodium	4.0	6.0	8.0	6.0	8.0	10.0	8.0	10.0	12.0
Sodium stearyl fumarate	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Talc	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Total IR layer weight	120	120	120	120	120	120	120	120	120
Disintegrant (%)	3.33	5.0	6.67	5.0	6.67	8.33	6.67	8.33	10.0

Preparation of Sustained Release Layer (Hydrochlorothiazide Layer)

The sustained release layer was prepared using wet granulation method to incorporate hydrophilic polymers for controlled drug release. The sustained release layer containing Hydrochlorothiazide was prepared using the wet granulation technique to incorporate hydrophilic polymers for achieving controlled drug release over an extended period. The preparation process started with accurate weighing of Hydrochlorothiazide, lactose anhydrous, microcrystalline cellulose, HPMC K4M, HPMC K100M, and sodium bicarbonate according to the quantities mentioned in Table 6.5 for each formulation batch. All powder ingredients were individually passed through a #20 mesh sieve to ensure uniform particle size. The sieved materials were then transferred to a clean, dry mortar and mixed thoroughly for 15 minutes using the geometric dilution method to achieve homogeneous blending. A binder solution was prepared by dissolving Povidone K30 at 5% w/v concentration in a hydro-alcoholic mixture containing water and ethanol in 1:1 ratio. This binder solution was added slowly to the powder blend with continuous mixing and trituration until a coherent, dampened mass of suitable consistency was formed. The wet mass was then passed through a #16 mesh sieve to produce uniform granules, which were spread evenly on stainless steel trays lined with butter paper. The granules were dried in a hot air oven (Universal, India) maintained at 50-55°C until the moisture content decreased below 2%, as determined by the loss on drying method. After drying, the granules were passed through a #20 mesh sieve to obtain uniform particle size distribution and were allowed to cool to room temperature. Finally, sodium stearyl fumarate and talc were added to the dried granules as lubricant and glidant respectively, followed by gentle mixing for 2-3 minutes to ensure uniform distribution while avoiding over-lubrication. The prepared granules were evaluated for various pre-compression parameters and stored in airtight containers under controlled conditions until bilayer tablet compression. [7]

Preparation of Sustained Release Layer (Hydrochlorothiazide Layer) – 9 Batches

Table 5: shows Formulation Composition of Sustained Release Layer (Hydrochlorothiazide Layer)

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hydrochlorothiazide	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
HPMC K4M	25.0	25.0	25.0	35.0	35.0	35.0	45.0	45.0	45.0
HPMC K100M	15.0	15.0	15.0	20.0	20.0	20.0	25.0	25.0	25.0
Lactose anhydrous	47.5	47.5	47.5	37.5	37.5	37.5	27.5	27.5	27.5
Microcrystalline cellulose	35.0	35.0	35.0	35.0	35.0	35.0	35.0	35.0	35.0
Sodium bicarbonate	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Povidone K30	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Sodium stearyl fumarate	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Talc	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
Total SR layer weight	180	180	180	180	180	180	180	180	180
Total polymer (%)	22.22	22.22	22.22	30.56	30.56	30.56	38.89	38.89	38.89

Compression of Bilayer Tablets

The bilayer tablets were prepared using a single punch tablet compression machine (Cadmach Machinery Co. Pvt. Ltd., Ahmedabad, India) equipped with a 10 mm diameter capsule-shaped punch and die set. Before compression, the die cavity and punches were thoroughly cleaned and dried to prevent any contamination. The compression parameters were carefully set and optimized, with pre-compression force maintained at 2-3 kN, final compression force at 8-10 kN, and machine speed adjusted to ensure uniform tablet production.

For the first layer compression containing the Ramipril immediate release formulation, the lower punch was positioned to provide the appropriate die cavity depth, and a pre-weighed quantity of 120 mg of the immediate release powder blend was manually introduced into the die cavity and distributed evenly across the surface. Light pre-compression was applied at low force (2-3 kN) to form a compact first layer, and any excess powder adhering to the die walls was carefully removed using a brush to prevent cross-contamination between layers. Subsequently, for the second layer addition, a pre-weighed quantity of 180 mg of the Hydrochlorothiazide sustained release granules was carefully placed over the pre-compressed first layer and distributed uniformly without disturbing the underlying layer. The final compression was then performed by compressing both layers together at the optimized final compression force of 8-10 kN, with adequate dwell time maintained to ensure strong interlayer bonding and prevent layer separation. The compression force was carefully adjusted to achieve the target tablet hardness while avoiding delamination or capping defects. After compression, the bilayer tablet was ejected from the die and visually inspected for any defects including capping, chipping, sticking, or layer separation. Tablets meeting the quality standards were collected and stored in airtight containers protected from light and moisture for further evaluation. Throughout the compression process, the total weight of each bilayer tablet was maintained at 300 mg (comprising 120 mg immediate release layer and 180 mg sustained release layer), and compression parameters were continuously monitored to ensure batch uniformity and consistency. [8]

Preformulation Studies

Preformulation assessments established the key physicochemical properties of Ramipril and Hydrochlorothiazide (HCTZ) while checking compatibility with excipients like HPMC K4M, HPMC K100M, microcrystalline cellulose, lactose, and others. API identity and purity were verified through infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and melting point tests. FTIR used KBr pellets scanned from 4000-400 cm^{-1} on a Bruker Alpha-II; DSC heated 3-5 mg samples at 10°C/min

under nitrogen on a Perkin Elmer 6000; melting points followed capillary method on Veego apparatus in triplicate.

Solubility was tested by shaking excess drug in water (pH 7), 0.1 N HCl (pH 1.2), acetate buffer (pH 4.5), and phosphate buffers (pH 6.8, 7.4) for 24 hours at 25°C, followed by UV analysis of filtrates. λmax values were set at 209-210 nm for Ramipril in 0.1 N HCl and 272 nm for HCTZ in pH 6.8 buffer via UV scanning (200-400 nm). Calibration curves (2-20 µg/mL) showed linearity ($R^2 > 0.99$) in respective media. [9]

Drug-Excipients Compatibility and Pre-Compression Parameters

FTIR compatibility tests mixed drugs with excipients (1:1 ratio), stored at 40°C/75% RH for 4 weeks, then scanned for peak shifts. No interactions appeared, confirming suitability. Pre-compression checks on blends included angle of repose (fixed funnel, $\theta = \tan^{-1}(h/r)$), bulk/tapped densities (100 mL cylinder, 1250 taps), Carr's index $[(\rho t-\rho b)/\rho t\times100][(\rho t-\rho b)/\rho t\times100]$, and laser diffraction for particle size (D10, D50, D90). [10]

Bilayer Tablet Evaluation

Tablets met IP limits: weight variation (±7.5% for >250 mg), hardness (5-8 kg/cm² via Monsanto tester), content uniformity (90-110% via UV at λmax post-sonication/extraction), friability (<1% after 100 rotations). Swelling index followed % weight gain in 0.1 N HCl over 8 hours; buoyancy measured lag time and duration in 200 mL HCl (37°C).

In Vitro Release and Kinetics

Dissolution used USP II apparatus: 900 mL 0.1 N HCl (2 hours, 50 rpm Ramipril), then pH 6.8 buffer (75 rpm HCTZ, up to 12 hours). Samples analyzed via calibration curves; profiles matched commercial products (f_2 50-100, f_1 near 0). Kinetics fitted best to Korsmeyer-Peppas (highest R^2), with n values indicating diffusion/relaxation mechanisms. [11]

Stability Studies

Optimized tablets underwent ICH accelerated stability at 40°C ±2°C/75% ±5% RH for 6 months (sampling at 15, 30, 60, 90 days). No changes occurred in physical traits, buoyancy, or release (f_2 confirmed similarity). [12]

Result and Discussion

The present study was carried out to design, develop, and evaluate bilayer tablets containing Ramipril and Hydrochlorothiazide for effective management of hypertension.

The work was done step-by-step, beginning with preformulation studies to understand the physical and chemical properties of the drugs. This was followed by the development of bilayer tablet formulations using a factorial design to study the effect of different formulation variables.

The prepared tablets were then evaluated for various physical and chemical parameters.

Preformulation Study

FTIR spectra of Ramipril

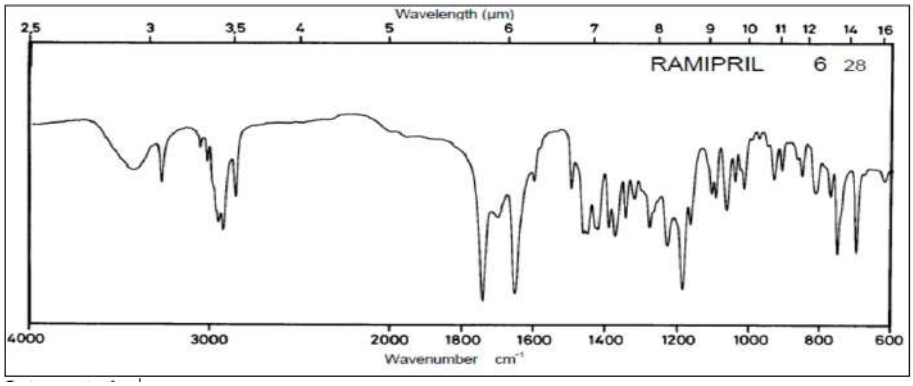

Fig 1: shows FTIR Spectra of Ramipril

Interpretation

The FTIR spectrum of Ramipril showed all its main peaks. A broad peak at 3420 cm^{-1} confirmed the N-H group. Sharp peaks at 2960 cm^{-1} and 2870 cm^{-1} were due to C-H stretching. A strong peak at 1740 cm^{-1} indicated the ester bond, and 1650 cm^{-1} showed the amide group. Other small peaks at 1450, 1380, 1240, and around 750–690 cm^{-1} matched C-H bending, CH_3 bending, C-O stretching, and aromatic ring, confirming Ramipril's structure.

FTIR Spectra of Hydrochlorothiazide

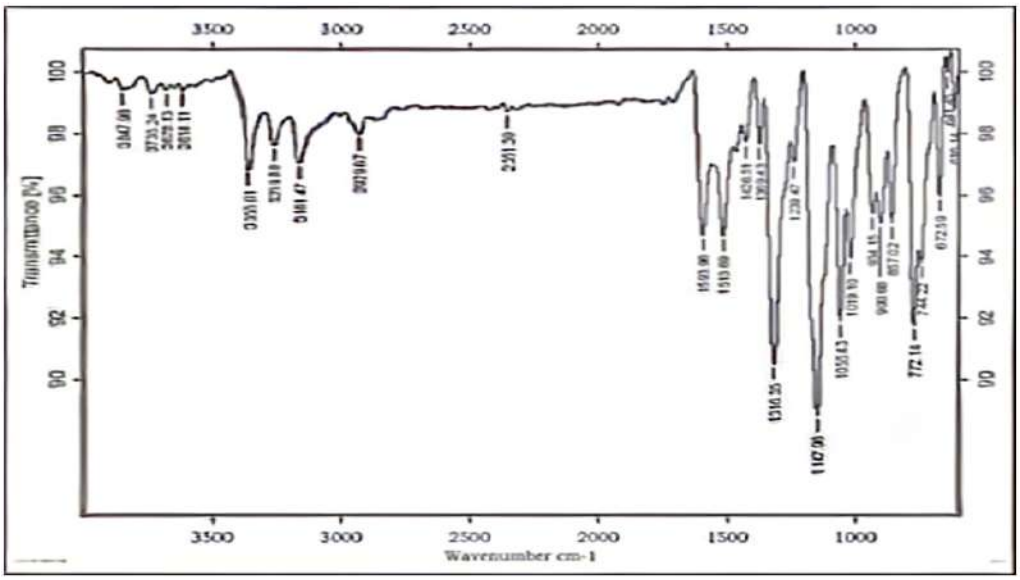

Fig 2: shows FTIR Spectra of Hydrochlorothiazide

Interpretation

The FTIR spectrum of Hydrochlorothiazide showed its main peaks. Peaks at 3360 cm^{-1} and 3260 cm^{-1} matched N-H stretching of sulfonamide groups. A peak at 3180 cm^{-1} was due to the N-H of the ring. Strong bands at 1340 cm^{-1} and 1160 cm^{-1} confirmed the sulfonyl (SO_2) groups. The peak at 1600 cm^{-1} showed aromatic C=C, and small peaks at 1450, 1090, and 820 cm^{-1} matched other key groups in the molecule. These results confirm the identity of Hydrochlorothiazide.

Melting Point Determination: The melting points of both drugs were determined in triplicate using the capillary tube method, and the results are presented in Table in the below.

Table 6: shows Melting Point Determination Results

Drug	Observed Melting Point (°C)	Standard Deviation	Pharmacopoeial Range (°C)	Observed Melting Point (°C)
Ramipril	110.5	± 1.2	105-112	110.5
Hydrochlorothiazide	273.8	± 0.8	273-275	273.8

Table 7: shows Solubility Profile of Ramipril and Hydrochlorothiazide in Different Solvents

Solvent System	pH	Ramipril Solubility (mg/mL)	USP Classification	Hydrochlorothiazide Solubility (mg/mL)	USP Classification

Distilled water	7.0	0.28 ± 0.02	Sparingly soluble	0.72 ± 0.04	Sparingly soluble
0.1 N HCl	1.2	2.45 ± 0.12	Soluble	0.85 ± 0.06	Sparingly soluble
Acetate buffer	4.5	1.82 ± 0.08	Soluble	1.24 ± 0.09	Soluble
Phosphate buffer	6.8	0.96 ± 0.05	Sparingly soluble	2.86 ± 0.14	Soluble

Values expressed as mean ± SD, n = 3

Table 8: Shows Wavelength of Maximum Absorption (λmax) for Ramipril

Drug	Medium	λmax (nm)	Molar Absorptivity (L mol^{-1} cm^{-1})
Ramipril	0.1 N HCl (pH 1.2)	210	12,450 ± 320
Ramipril	Phosphate buffer (pH 6.8)	209	11,890 ± 280

Values expressed as mean ± SD, n = 3

Ramipril UV Characteristics

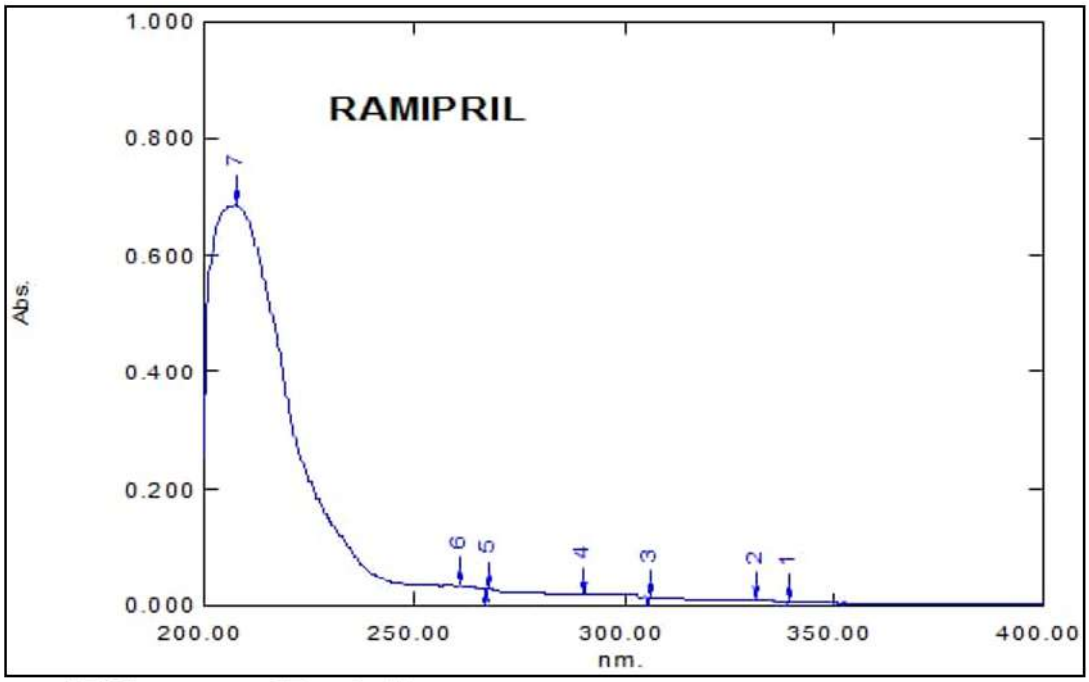

Fig 3: shows UV Spectrum of Ramipril

Table 9: shows Wavelength of Maximum Absorption (λmax) for Hydrochlorothiazide

Drug	Medium	λmax (nm)	Molar Absorptivity (L mol^{-1} cm^{-1})
Hydrochlorothiazide	0.1 N HCl (pH 1.2)	271	8,620 ± 240
Hydrochlorothiazide	Phosphate buffer (pH 6.8)	272	9,340 ± 290

Values expressed as mean ± SD, n = 3

Hydrochlorothiazide UV Characteristics

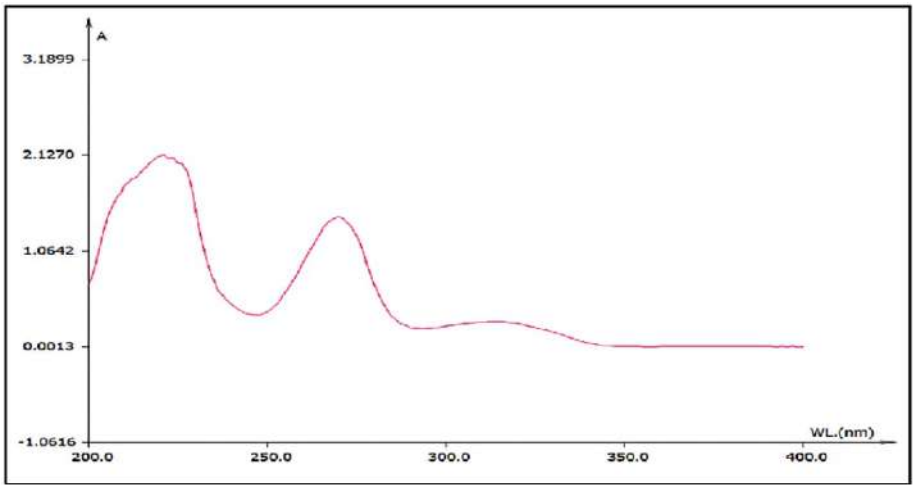

Fig 4: shows UV Spectrum of Hydrochlorothiazide

Standard Calibration Curves

Standard calibration curves were constructed for both drugs in relevant pH media to establish linear relationships between concentration and absorbance, validating Beer-Lambert's law compliance and ensuring accurate quantitative analysis.

Calibration Curve of Ramipril in 0.1 N HCl (pH 1.2)

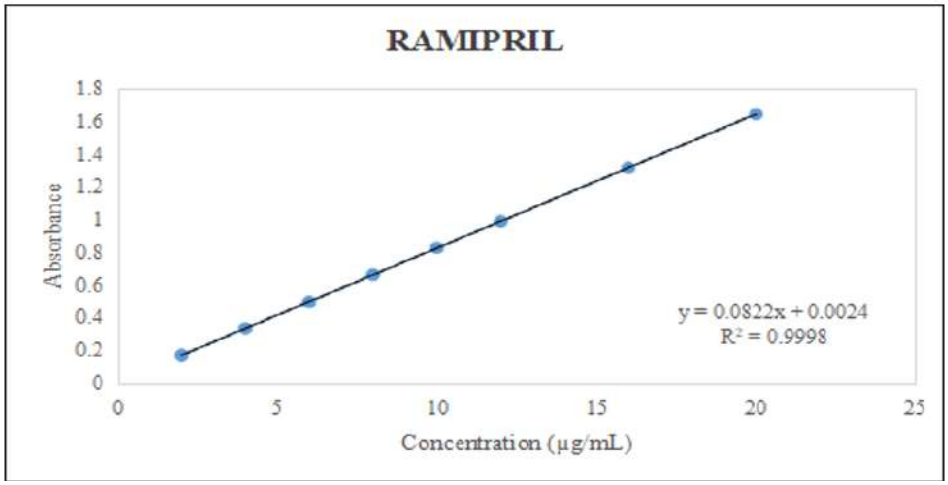

Fig 5: shows Calibration Curve of Ramipril in 0.1 N HCl (pH 1.2)

Table 10: shows Calibration Data for Ramipril in 0.1 N HCl

Concentration (µg/mL)	Absorbance (Mean ± SD)
2	0.168 ± 0.004
4	0.332 ± 0.006
6	0.495 ± 0.008
8	0.661 ± 0.007
10	0.826 ± 0.009
12	0.989 ± 0.011
16	1.318 ± 0.014
20	1.645 ± 0.016

n = 3 for each concentration

Calibration Curve of Hydrochlorothiazide in Phosphate Buffer pH (6.8)

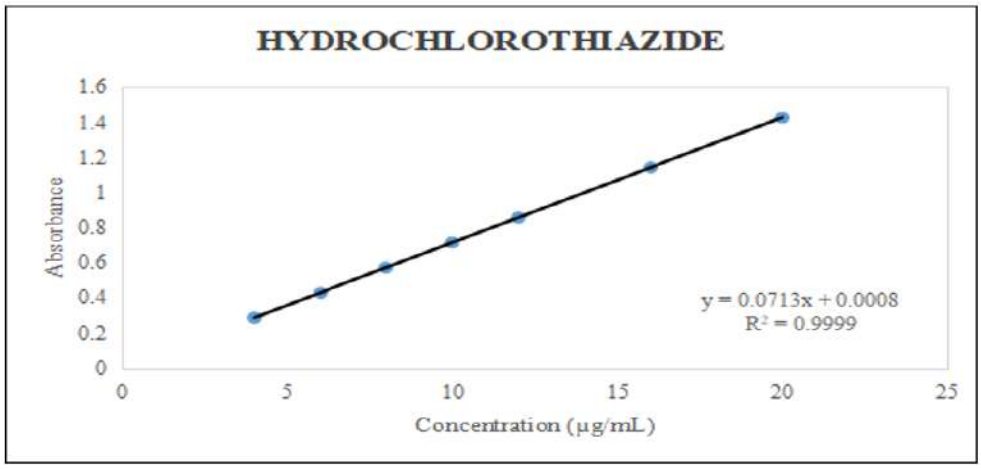

Fig 6: shows Calibration Curve of Hydrochlorothiazide in Phosphate Buffer pH

Table 11: shows Calibration Data for Hydrochlorothiazide in Phosphate Buffer

Concentration (µg/mL)	Absorbance (Mean ± SD)
2	0.142 ± 0.003
4	0.286 ± 0.005
6	0.428 ± 0.007
8	0.571 ± 0.008
10	0.714 ± 0.009
12	0.856 ± 0.010
16	1.142 ± 0.013
20	1.426 ± 0.015

n = 3 for each concentration

Drug-Excipient Compatibility Study: FTIR spectroscopy was used to check if the drugs Ramipril and Hydrochlorothiazide remained stable when mixed with various excipients.

Ramipril Compatibility Results

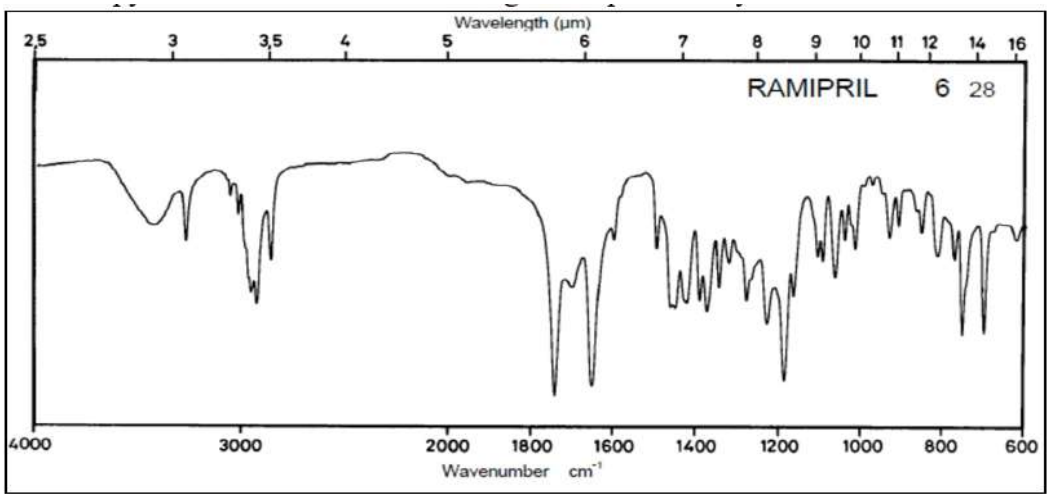

Fig 7: shows FTIR Spectra of Ramipril with excipients

Hydrochlorothiazide Compatibility Results

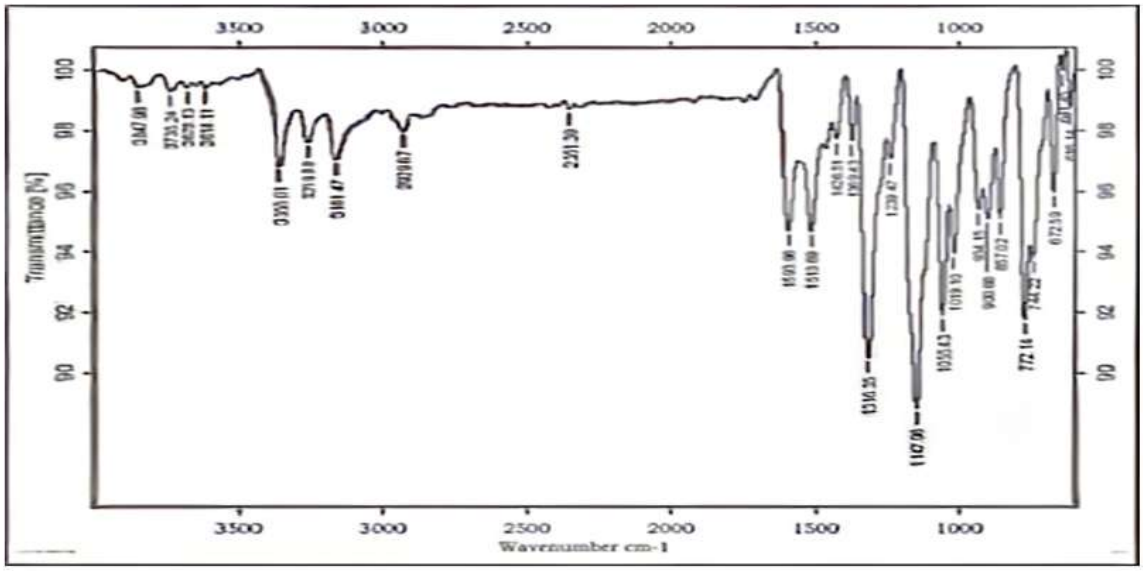

Fig 8: shows FTIR Spectra of Hydrochlorothiazide with excipients

Evaluation of pre-compression parameters: The powder blends for the immediate release layer and granules for the sustained release layer were systematically evaluated for flow and compaction properties before bilayer tablet compression. These parameters are critical indicators of material behavior during manufacturing and directly influence tablet quality attributes.

Pre-compression Parameters of Immediate Release Layer (Ramipril Layer)

Table 12: shows Pre-compression Parameters of Immediate Release Layer Powder Blends

Batch	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)	Flow Property
F1	0.48 ± 0.02	0.62 ± 0.02	22.58	1.29	32.4 ± 0.8	Passable
F2	0.46 ± 0.02	0.58 ± 0.02	20.69	1.26	31.2 ± 0.9	Fair to Passable
F3	0.44 ± 0.02	0.55 ± 0.02	20.00	1.25	29.8 ± 0.7	Good
F4	0.47 ± 0.02	0.60 ± 0.02	21.67	1.28	31.8 ± 0.8	Fair to Passable
F5	0.45 ± 0.02	0.56 ± 0.02	19.64	1.24	30.4 ± 0.9	Good
F6	0.43 ± 0.02	0.53 ± 0.02	18.87	1.23	28.6 ± 0.7	Good
F7	0.46 ± 0.02	0.58 ± 0.02	20.69	1.26	31.0 ± 0.8	Fair to Passable
F8	0.44 ± 0.02	0.54 ± 0.02	18.52	1.23	29.2 ± 0.7	Good
F9	0.42 ± 0.02	0.51 ± 0.02	17.65	1.21	27.4 ± 0.8	Good

Values expressed as mean ± SD, n = 3

Pre-compression Parameters of Sustained Release Layer (Hydrochlorothiazide Granules)

Table 13: shows Pre-compression Parameters of Sustained Release Layer Granules

Batch	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)	Flow Property

F1	0.52 ± 0.02	0.64 ± 0.02	18.75	1.23	26.8 ± 0.6	Good
F2	0.51 ± 0.02	0.62 ± 0.02	17.74	1.22	26.2 ± 0.7	Good
F3	0.50 ± 0.02	0.60 ± 0.02	16.67	1.20	25.4 ± 0.6	Good
F4	0.53 ± 0.02	0.66 ± 0.02	19.70	1.25	27.6 ± 0.8	Fair to Good
F5	0.52 ± 0.02	0.64 ± 0.02	18.75	1.23	26.8 ± 0.7	Good
F6	0.51 ± 0.02	0.62 ± 0.02	17.74	1.22	26.0 ± 0.6	Good
F7	0.54 ± 0.02	0.68 ± 0.02	20.59	1.26	28.4 ± 0.8	Fair to Good
F8	0.53 ± 0.02	0.66 ± 0.02	19.70	1.25	27.8 ± 0.7	Fair to Good
F9	0.52 ± 0.02	0.64 ± 0.02	18.75	1.23	27.2 ± 0.7	Good

Values expressed as mean ± SD, n = 3

Evaluation of Bilayer Tablets

Physical and Chemical Properties of Bilayer Tablets

To develop optimized bilayer tablet formulations containing Ramipril and Hydrochlorothiazide, multiple batches (F1-F9) were prepared with varying polymer and excipient concentrations.

The primary objective was to identify the optimal balance between polymers that would provide immediate release characteristics for Ramipril while maintaining sustained release for Hydrochlorothiazide. Preliminary investigations demonstrated that lower polymer concentrations led to rapid disintegration without adequate sustained release, while excessive polymer content delayed the immediate release phase.

Based on optimization studies, formulations incorporating 22.22-38.89% total polymer content (HPMC K4M and HPMC K100M) were selected for comprehensive evaluation as they demonstrated the desired release characteristics. The tablets were prepared according to the composition. These optimized batches were evaluated using various physicochemical parameters, and the results are presented below.

The formulations prepared as per the composition Table and were thoroughly evaluated, and results showed that all batches possessed acceptable physical characteristics with appropriate mechanical strength and dimensional uniformity. Drug content analysis confirmed consistent delivery of both active ingredients across all formulations.

Friability testing revealed good mechanical resistance for all batches. Results of all physicochemical evaluations are presented in the below table.

Physical Characteristics and Drug Content

All bilayer tablet batches demonstrated excellent compliance with quality specifications. Tablet thickness ranged from 4.74-4.90 mm with low variability. Average weights ranged from 299.4-301.4 mg, representing minimal deviation from the 300 mg target. Hardness values ranged from 6.2-7.2 kg/cm², confirming adequate mechanical strength. Friability values remained below 1% for all formulation.

Table 14: shows Physical characteristics of Ramipril and Hydrochlorothiazide bilayer tablet

Batch	Thickness (mm)	Avg. Weight (mg)	Hardness (kg/cm²)	Friability (%)	Ramipril Content (%)	Hydrochlorothiazide content (%)
F1	4.82±0.08	301.2±3.8	6.2±0.4	0.66	98.6±1.8	99.2±1.6
F2	4.78±0.07	299.8±3.2	6.4±0.3	0.57	99.4±1.6	100.4±1.8
F3	4.74±0.06	300.4±2.9	6.6±0.4	0.50	100.2±1.4	98.8±1.4
F4	4.86±0.09	300.6±3.5	6.5±0.4	0.57	99.8±1.5	99.6±1.7
F5	4.80±0.07	299.4±2.8	6.7±0.3	0.53	101.2±1.6	100.8±1.5

F6	4.76±0.06	300.2±2.6	6.9±0.4	0.47	98.4±1.7	101.2±1.6
F7	4.90±0.10	301.4±3.6	6.8±0.5	0.43	100.6±1.5	99.4±1.8
F8	4.84±0.08	300.8±3.0	7.0±0.4	0.40	99.2±1.4	100.2±1.7
F9	4.78±0.07	299.6±2.5	7.2±0.4	0.37	101.4±1.8	98.6±1.5

n=3, values expressed as mean ± SD; Target weight: 300 mg.

Table 15: shows Disintegration Time of Immediate Release Layer

Batch	Disintegration Time (minutes)	Standard Deviation
F1	12.4	± 1.2
F2	10.8	± 0.9
F3	8.6	± 0.8
F4	11.2	± 1.0
F5	9.4	± 0.9
F6	7.8	± 0.7
F7	10.6	± 1.1
F8	8.8	± 0.8
F9	6.4	± 0.6

Interpretation

All bilayer formulations met immediate release requirements with disintegration times between 6.4–12.4 minutes. Batch F1 (3.33% disintegrant) showed maximum disintegration at 12.4 minutes, while Batch F9 (10.0% disintegrant) demonstrated minimum at 6.4 minutes, representing 48% faster breakdown.

A negative correlation between disintegrant concentration and disintegration time confirmed croscarmellose sodium's effectiveness as a superdisintegrant. Importantly, visual observation during disintegration testing revealed that only the immediate release layer (white layer) disintegrated, while the sustained release layer (yellowish-white layer) remained largely intact, gradually swelling but not disintegrating within the test timeframe. This confirmed successful bilayer design, where the two layers functioned independently with distinct release mechanisms.

Table 16: shows Swelling Index of Bilayer Tablets at Different Time Intervals

Batch	1 hr	2 hr	4 hr	6 hr	8 hr
F1	45 ± 3%	68 ± 4%	92 ± 5%	108 ± 6%	115 ± 7%
F2	46 ± 3%	70 ± 4%	95 ± 5%	112 ± 6%	120 ± 7%
F3	48 ± 3%	72 ± 4%	98 ± 5%	116 ± 6%	124 ± 8%
F4	58 ± 4%	88 ± 5%	125 ± 7%	148 ± 8%	162 ± 9%
F5	60 ± 4%	92 ± 5%	130 ± 7%	154 ± 8%	168 ± 9%
F6	62 ± 4%	95 ± 5%	135 ± 7%	160 ± 9%	175 ± 10%
F7	72 ± 5%	112 ± 6%	162 ± 9%	195 ± 11%	218 ± 12%
F8	75 ± 5%	118 ± 7%	170 ± 9%	205 ± 11%	230 ± 13%
F9	78 ± 5%	124 ± 7%	178 ± 10%	215 ± 12%	242 ± 14%

Medium: 0.1 N HCl at 37 ± 0.5°C; Values expressed as mean ± SD; n = 3

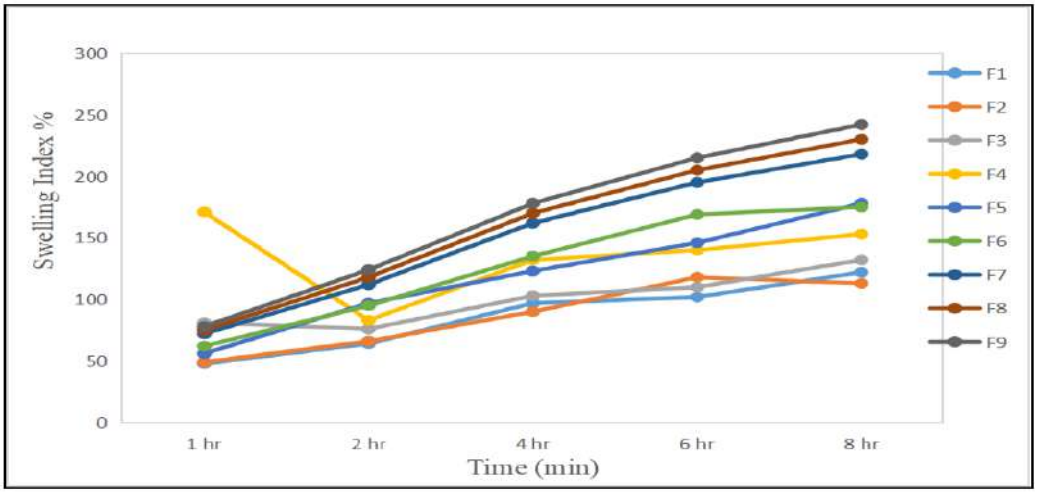

Fig 9: shows Swelling Index of Bilayer Tablets at Different Time Intervals

Interpretation

Swelling tests demonstrated that higher polymer concentrations led to increased tablet expansion over 8 hours. Formulation F1 (lower polymer content) achieved 115% swelling, while F9 (higher polymer) reached 242%, indicating a 2.1-fold variation dependent on HPMC quantity. HPMC absorbs water, causing polymer chains to expand and form protective gel layers; increased polymer concentrations generate thicker, stronger gel barriers. Swelling occurred in two phases: rapid uptake during the first 2 hours followed by gradual expansion as water penetrated deeper. Lower-swelling batches (F1-F3) exhibited faster Hydrochlorothiazide release due to thin gel formation, whereas high-swelling batches (F7-F9) provided sustained release through thicker diffusion barriers, with swelling behavior accurately predicting drug release kinetics.

Dissolution Profile of Ramipril (Immediate Release Layer)

Table 17: shows Cumulative Percentage Drug Release of Ramipril

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	28.4	32.6	38.2	30.8	36.4	42.6	32.4	38.8	45.2
10	45.6	52.4	61.8	48.2	58.6	68.4	50.6	62.2	72.8
15	62.8	71.6	82.4	66.4	78.2	88.6	68.8	82.6	92.4
20	76.4	84.8	94.6	80.2	90.4	98.2	82.6	94.8	99.6
30	86.2	93.4	99.8	89.6	97.8	100.4	91.8	99.4	101.2
45	92.8	98.6	101.2	95.4	100.6	101.8	97.2	101.4	102.4
60	97.4	100.8	102.4	99.2	102.2	102.6	100.4	102.8	103.2

Medium: 0.1 N HCl (pH 1.2), 37 ± 0.5°C, 50 rpm; Values expressed as mean, n = 3

Interpretation: The dissolution study revealed rapid and complete release of Ramipril from all bilayer tablet batches, typical of immediate-release formulations. Over 85% of the drug was released within 30 minutes, with several batches (F3, F5, F6, F8, F9) exceeding 90% and reaching nearly complete release by 45–60 minutes. A direct link was observed between disintegrant concentration and dissolution rate.

Batch F9 (10% croscarmellose sodium) showed the fastest release, achieving 99.6% in 20 minutes with T_{80} around 14 minutes, while F1 (3.33%) showed slower release with T_{80} near 24 minutes.

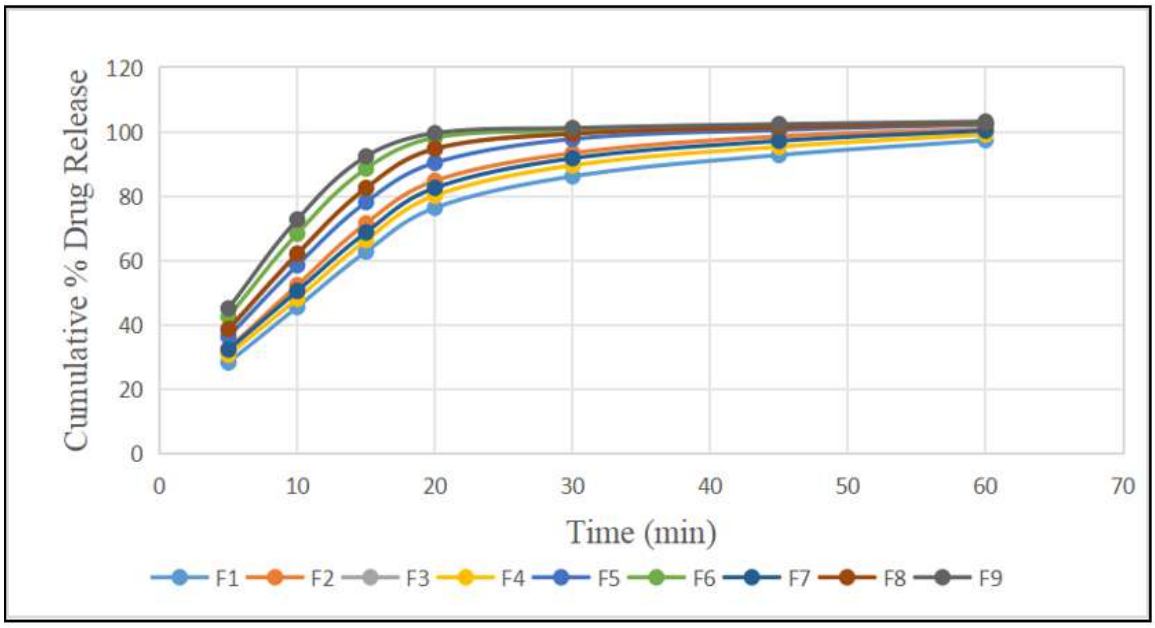

Fig 10: shows Cumulative Percentage Drug Release of Ramipril

Dissolution Profile of Hydrochlorothiazide (Sustained Release Layer)

Table 18: shows Cumulative Percentage Drug Release of Hydrochlorothiazide

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	8.4	8.2	8.6	6.2	6.4	6.8	4.6	4.8	5.2
1	18.6	18.2	19.4	14.8	15.2	16.6	11.4	12.2	13.6
2	32.8	33.2	35.6	26.4	28.6	30.8	21.2	23.4	26.2
3	45.2	46.8	49.4	37.6	40.8	43.6	30.8	34.2	37.8
4	56.4	58.6	62.2	47.8	51.6	55.4	39.6	44.2	48.6
6	72.8	76.4	81.2	62.4	68.2	73.6	52.8	59.4	65.2
8	84.6	89.2	94.6	74.8	81.4	87.8	64.2	72.6	79.4
10	92.8	97.4	101.8	84.6	91.8	97.2	73.8	83.2	90.6
12	98.4	102.6	104.2	92.4	98.6	102.8	81.6	91.4	98.2

Medium: Phosphate buffer pH 6.8, 37 ± 0.5°C, 75 rpm; Values expressed as mean, n = 3

Interpretation

Hydrochlorothiazide dissolution from bilayer tablets demonstrated polymer-dependent sustained release over 10–12 hours. An inverse relationship existed between HPMC concentration and release rate. Lower polymer batches (F1–F3, 22.22%) released 94.6–101.8% by 10 hours, intermediate batches (F4–F6, 30.56%) released 84.6–97.2%, while higher polymer batches (F7–F9, 38.89%) showed slowest release with only 73.8–90.6% at 10 hours.

Sustained release occurred through hydration-induced gel formation, drug diffusion through the polymer matrix, gradual erosion, and polymer chain relaxation. Higher polymer concentrations created thicker gel barriers with longer diffusion pathways, slowing drug release.

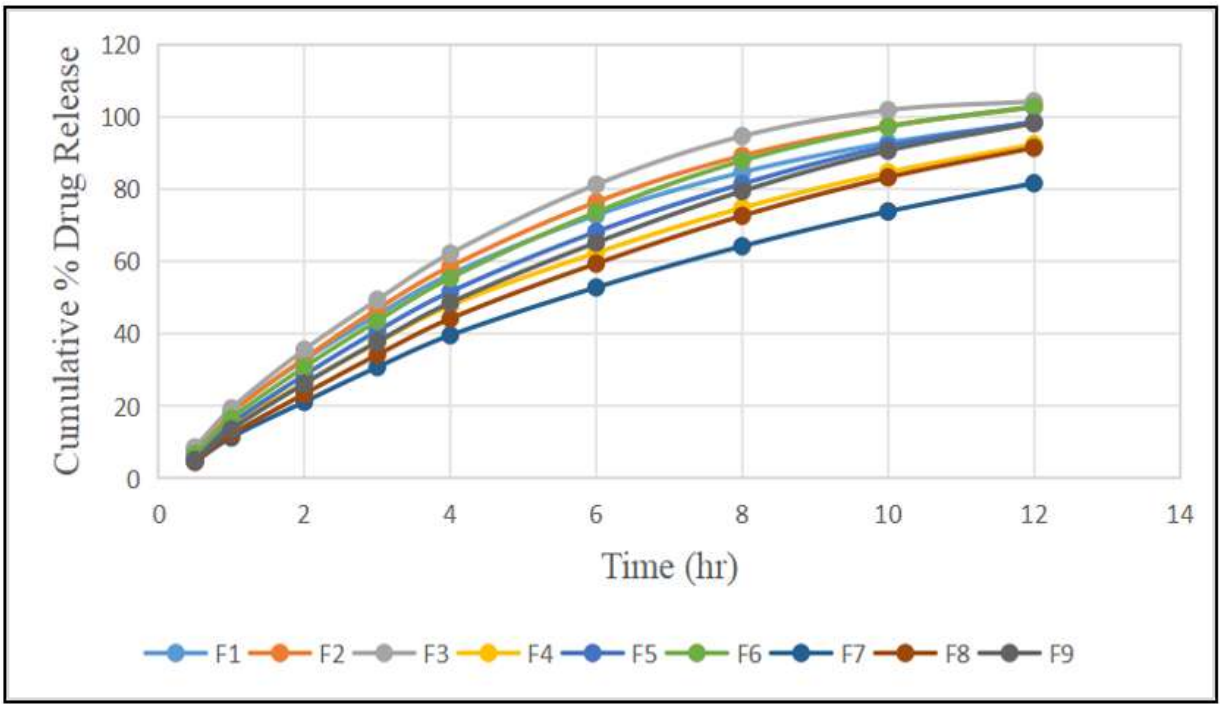

Fig 11: shows Cumulative Percentage Drug Release of Hydrochlorothiazide

Table 19: shows Drug Release Kinetics for Ramipril (Immediate Release Layer)

Batch	Zero Order R^2	First Order R^2	Higuchi R^2	Korsmeyer-Peppas R^2	n value	Best Fit Model
F1	0.8846	0.9624	0.9782	0.9856	0.62	Korsmeyer-Peppas
F2	0.8952	0.9698	0.9824	0.9902	0.58	Korsmeyer-Peppas
F3	0.9108	0.9756	0.9868	0.9924	0.54	Korsmeyer-Peppas
F4	0.8894	0.9648	0.9798	0.9878	0.60	Korsmeyer-Peppas
F5	0.9042	0.9724	0.9846	0.9912	0.56	Korsmeyer-Peppas
F6	0.9186	0.9784	0.9892	0.9938	0.52	Korsmeyer-Peppas
F7	0.8924	0.9672	0.9812	0.9886	0.59	Korsmeyer-Peppas
F8	0.9096	0.9748	0.9862	0.9918	0.55	Korsmeyer-Peppas
F9	0.9224	0.9806	0.9908	0.9946	0.50	Korsmeyer-Peppas

Table 20: shows Drug Release Kinetics for Hydrochlorothiazide (Sustained Release Layer)

Batch	Zero Order R^2	First Order R^2	Higuchi R^2	Korsmeyer-Peppas R^2	n value	Best Fit Model
F1	0.9824	0.9486	0.9762	0.9896	0.56	Korsmeyer-Peppas
F2	0.9848	0.9512	0.9788	0.9908	0.54	Korsmeyer-Peppas
F3	0.9872	0.9536	0.9806	0.9922	0.52	Korsmeyer-Peppas
F4	0.9902	0.9584	0.9846	0.9948	0.62	Korsmeyer-Peppas
F5	0.9918	0.9606	0.9868	0.9956	0.58	Korsmeyer-Peppas
F6	0.9932	0.9624	0.9884	0.9964	0.54	Korsmeyer-Peppas
F7	0.9946	0.9658	0.9908	0.9976	0.68	Korsmeyer-Peppas
F8	0.9954	0.9672	0.9918	0.9982	0.64	Korsmeyer-Peppas
F9	0.9962	0.9686	0.9926	0.9988	0.60	Korsmeyer-Peppas

Stability Studies

Table 21: Optimized batch F5 stability testing at 40 ± 2°C/75 ± 5% RH for 3 months.

Parameter	Initial	3 Months	Limit
Appearance	White-yellowish bilayer	No change	No defects
Layer Integrity	Distinct	Intact	No separation
Hardness (kg/cm²)	6.7 ± 0.3	6.9 ± 0.4	5–8
Friability (%)	0.53	0.51	<1.0
Ramipril Drug release %	99.2 ± 1.6	98.0 ± 1.7	90–110
HCTZ Drug release %	98.8 ± 1.5	97.6 ± 1.6	90–110
Disintegration Time (min)	9.4	10.2	<15
f_2 Ramipril	—	94.8	>50
f_2 HCTZ	—	98.2	>50

Conclusion

The optimized bilayer tablet design (particularly batch F5) provides an effective two-component system for hypertension management.

The immediate release layer delivers Ramipril quickly for rapid blood pressure control, while the sustained release layer maintains steady

Hydrochlorothiazide levels throughout the day, reducing the need for multiple doses and improving patient compliance.

Batch F5 (containing 30.56% total polymer and 6.67% disintegrant) represents the best balance, offering rapid initial drug action combined with extended therapeutic coverage.

All formulations demonstrated excellent physical, chemical, and thermal stability, meeting pharmacopoeial standards.

The factorial design approach effectively identified how polymer and disintegrant concentrations influence tablet performance.

Higher polymers create thicker gel layers that slow drug release, while increased disintegrants accelerate immediate release.

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