Formulation and Evaluation of Bilayer Tablets Containing Cilnidipine (Immediate Release) and Azilsartan Medoxomil (Sustained Release) for Antihypertensive Therapy

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doi.org/10.64643/IJIRTV12I12-203075-459

Abstract*—The present study was undertaken to formulate and evaluate bilayer tablets containing Cilnidipine as an Immediate Release (IR) layer and Azilsartan Medoxomil as a Sustained Release (SR) layer for effective management of hypertension. Hypertension is a chronic cardiovascular disorder affecting over 1.3 billion people globally and is a leading cause of stroke, myocardial infarction, and renal failure. Cilnidipine, a 4th generation calcium channel blocker (L and N-type), provides rapid blood pressure reduction, while Azilsartan Medoxomil, an angiotensin II receptor blocker, offers prolonged antihypertensive action up to 24 hours. Bilayer tablets were prepared by direct compression and wet granulation techniques using superdisintegrants (crospovidone, croscarmellose sodium, sodium starch glycolate) for the IR layer and hydrophilic/hydrophobic polymers (HPMC K4M, HPMC K15M, Carbopol 934P, ethyl cellulose) for the SR layer. Preformulation studies including FTIR and DSC confirmed drug–excipient compatibility. Pre-compression parameters showed excellent to good flow properties. Post-compression evaluation demonstrated acceptable hardness (5.8 kg/cm², friability (<1%), and drug content uniformity (99.1% for Cilnidipine; 99.5% for Azilsartan). In-vitro dissolution studies revealed ≥99% Cilnidipine release within 30 minutes and controlled Azilsartan Medoxomil release up to 24 hours. Drug release kinetics followed the Higuchi diffusion model. ICH stability studies at 40°C/75% RH for 3 months showed no significant changes. The optimized formulation (F4) achieved rapid onset and sustained antihypertensive action, improved patient compliance, and reduced dosing frequency in a single dosage form.

***Index Terms*—Azilsartan Medoxomil, Bilayer tablets, Cilnidipine, Combination therapy, Hypertension, Immediate release, Sustained release.**

I. INTRODUCTION

Hypertension is a chronic cardiovascular disorder in which blood pressure in the arteries remains persistently elevated above normal range. It affects over 1.3 billion people globally and is a major risk factor for stroke, myocardial infarction, renal failure, and other cardiovascular complications [1]. A normal blood pressure is generally around 120/80 mmHg; persistent elevation above 140/90 mmHg is considered hypertension [2].

Hypertension is often referred to as a "silent killer" because many individuals remain asymptomatic for years even when blood pressure levels are dangerously high [3]. Management requires long-term pharmacological treatment, and single-drug therapy (monotherapy) is often insufficient to achieve optimal blood pressure control [4].
Combination therapy using drugs with different mechanisms of action is widely recommended. Bilayer tablets offer a sophisticated approach by incorporating two drugs with different release profiles into a single tablet, thereby reducing pill burden, dosing frequency, and improving patient compliance [5]. Cilnidipine (a 4th generation calcium channel

blocker blocking both L and N-type channels) provides immediate vasodilation, while Azilsartan Medoxomil (an angiotensin II receptor blocker) provides prolonged antihypertensive effect through RAAS blockade [6, 7]

II. AIM AND OBJECTIVES

Aim: To formulate and evaluate bilayer tablets containing Cilnidipine as an Immediate Release (IR) layer and Azilsartan Medoxomil as a Sustained Release (SR) layer for effective management of hypertension.

Objectives:

- To develop an IR layer of Cilnidipine using superdisintegrants for rapid drug release.
- To formulate an SR layer of Azilsartan Medoxomil using hydrophilic and hydrophobic polymers.
- To perform preformulation studies including FTIR and DSC for drug–excipient compatibility.
- To evaluate pre- and post-compression parameters as per IP/USP standards.
- To conduct in-vitro dissolution studies and drug release kinetic modeling.
- To perform ICH stability studies and confirm formulation stability.

III. DRUG PROFILE

A. Cilnidipine

Cilnidipine is a 4th generation dihydropyridine calcium channel blocker with dual L-type and N-type channel blocking activity. Chemical formula: $C_{27}H_{28}N_2O_7$; Molecular weight: 492.52 g/mol; BCS Class II drug; Oral bioavailability: ~10–20%; Half-life: ~2–5 hours; Protein binding: >95%; Dose: 10–20 mg once daily. It reduces vascular smooth muscle contraction via L-type channel blockade and inhibits sympathetic norepinephrine release via N-type channel blockade, thus reducing reflex tachycardia and providing renal protection [8].

B. Azilsartan Medoxomil

Azilsartan Medoxomil is a prodrug converted to active Azilsartan in the GI tract. It is a potent angiotensin II receptor blocker (ARB). Chemical formula: $C_{30}H_{24}N_4O_8$; Molecular weight: ~568.54 g/mol; BCS Class II drug; Oral bioavailability: ~60%; Half-life: ~11 hours; Protein binding: >99%; Dose: 40–80 mg once daily. It prevents vasoconstriction and aldosterone secretion by blocking AT1 receptors, making it suitable for once-daily sustained release dosing [9].

IV. MATERIALS AND METHODS

A. Materials

TABLE I: Materials Used

Sr.	Material	Category	Supplier
1	Cilnidipine	API – IR Layer	Sigma Aldrich
2	Azilsartan Medoxomil	API – SR Layer	Sigma Aldrich
3	Crospovidone (CP)	Superdisintegrant	Himedia Labs
4	Croscarmellose Sodium	Superdisintegrant	Himedia Labs
5	Sodium Starch Glycolate	Superdisintegrant	Loba Chemie
6	HPMC K4M	SR Polymer	Himedia Labs
7	HPMC K15M	SR Polymer	Himedia Labs
8	Carbopol 934P	Matrix Polymer	Himedia Labs
9	Ethyl Cellulose	Release Retardant	Loba Chemie
10	MCC PH-102	Diluent	Himedia Labs
11	Lactose Monohydrate	Diluent	SD Fine Chem
12	PVP K30	Binder	Himedia Labs
13	Magnesium Stearate	Lubricant	SD Fine Chem
14	Talc	Glidant	Local supplier
15	Sodium Lauryl Sulphate	Wetting Agent	Loba Chemie

B. Formulation Composition – IR Layer (Cilnidipine)

TABLE II: Immediate Release Layer Formula

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)
Cilnidipine	10	10	10	10	10
Crospovidone	4	6	8	10	12
Croscarmellose Sodium	8	6	4	2	—
Sodium Starch Glycolate	—	2	4	6	8
MCC PH-102	70	68	64	60	56
Lactose Monohydrate	60	60	60	60	60
PVP K30	10	10	10	10	10
SLS	2	2	2	2	2
Colloidal SiO_2	2	2	2	2	2

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)
Talc	2	2	2	2	2
Mg. Stearate	2	2	2	2	2
Total Weight (mg)	170	170	170	170	170

C. Formulation Composition – SR Layer (Azilsartan Medoxomil)

TABLE III: Sustained Release Layer Formula

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)
Azilsartan Medoxomil	40	40	40	40	40
HPMC K4M	40	50	60	70	80
HPMC K15M	20	25	30	35	40
Carbopol 934P	10	15	20	25	30
Ethyl Cellulose	10	10	10	10	10
DCP	50	40	30	20	10
MCC PH-102	50	45	40	35	30
PVP K30	10	10	10	10	10
SLS	2	2	2	2	2
Mg. Stearate	2	2	2	2	2
Total Weight (mg)	234	239	244	249	254

D. Preparation Method

Step 1 – IR Layer: All ingredients were accurately weighed and passed through sieve #60. Cilnidipine, lactose, and MCC were blended, followed by addition of superdisintegrants and SLS. Magnesium stearate and talc were added last and blended gently to avoid over-lubrication.

Step 2 – SR Layer (Wet Granulation): Azilsartan Medoxomil was blended with HPMC K4M, HPMC K15M, Carbopol, and DCP. Binder solution (PVP K30 in isopropyl alcohol) was added to form wet mass, granulated through sieve #22, and dried in a hot air oven at 40–50°C. Magnesium stearate and talc were added post-drying.

Step 3 – Bilayer Compression: SR layer granules were filled into the die cavity and pre-compressed. IR layer blend was added over the SR layer and final compression was applied using a bilayer tablet punching machine.

V. EVALUATION PARAMETERS

A. Pre-Compression Parameters

Powder blends were evaluated for angle of repose ($\tan\theta = h/r$), bulk density (mass/bulk volume), tapped density (mass/tapped volume), Carr's index [(TD−BD)/TD × 100], and Hausner's ratio (TD/BD) to assess flowability and compressibility [10].

B. Post-Compression Parameters

Tablets were evaluated for weight variation (20 tablets, IP limits), thickness (Vernier caliper), hardness (Monsanto tester, acceptance: 4–8 kg/cm²), friability (Roche friabilator, limit: <1%), and drug content uniformity (UV spectrophotometry, limit: 85–115%) [11].

C. Disintegration and Dissolution

Disintegration of IR layer was determined using USP apparatus. In-vitro dissolution was performed in USP Type II (Paddle) apparatus using pH 6.8 phosphate buffer at 37°C ± 0.5°C, 50 rpm, 900 mL. Samples were withdrawn at predetermined intervals and analyzed by UV spectrophotometry. Drug release kinetics were assessed using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models [12].

D. FTIR and DSC Studies

FTIR spectroscopy (KBr pellet method, 4000–400 cm^{-1}) and Differential Scanning Calorimetry (30–300°C, 10°C/min, nitrogen atmosphere) were used to assess drug–excipient compatibility [13].

E. Stability Studies

Stability studies were conducted as per ICH guidelines at accelerated conditions (40°C/75% RH) for 3 months. Drug content, hardness, friability, and dissolution profile were evaluated at 1, 2, and 3-month intervals [14].

VI. RESULTS AND DISCUSSION

A. Pre-Compression Parameters

TABLE IV: Pre-Compression Evaluation Results

Batch	Angle of Repose (°)	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Carr's Index (%)	Hausner Ratio	Flow Property
F1	30.2	0.42	0.51	17.6	1.21	Good
F2	29.4	0.44	0.53	16.9	1.20	Good
F3	28.8	0.46	0.54	14.8	1.17	Excellent
F4	27.5	0.48	0.55	12.7	1.14	Excellent
F5	26.9	0.49	0.56	12.5	1.14	Excellent

All powder blends showed good to excellent flowability. Batches F4 and F5 exhibited the best flow characteristics, indicating suitability for direct compression.

B. Post-Compression Parameters

TABLE V: Post-Compression Evaluation Results

Parameter	F1	F2	F3	F4	F5
Avg. Weight (mg)	408	413	416	421	426
Thickness (mm)	4.2	4.3	4.4	4.5	4.6
Hardness (kg/cm²)	4.8	5.1	5.4	5.8	6.0
Friability (%)	0.82	0.75	0.68	0.58	0.54
Drug Content – Cilnidipine (%)	96.2	97.4	98.5	99.1	98.8
Drug Content – Azilsartan (%)	97.1	98.2	99.0	99.5	99.2
Disintegration Time (sec)	62	51	42	28	25

All batches complied with IP/USP limits. Friability values were below 1%. Drug content uniformity was within the acceptable range (85–115%). Batch F4 showed optimal disintegration time (28 sec) and satisfactory mechanical strength (5.8 kg/cm²).

C. In-Vitro Dissolution Studies

TABLE VI: % Cilnidipine Release from IR Layer

Time (min)	F1	F2	F3	F4	F5
5	38%	45%	52%	60%	64%
10	55%	66%	75%	84%	88%
20	72%	82%	90%	95%	97%
30	84%	91%	96%	99%	99.5%

TABLE VII: % Azilsartan Medoxomil Release from SR Layer

Time (hr)	F1	F2	F3	F4	F5
1	25%	22%	18%	16%	14%
4	60%	52%	45%	40%	35%
8	88%	78%	70%	65%	60%
12	99%	94%	92%	86%	80%
24	—	99%	99%	95%	90%

The IR layer of F4 released approximately 99% Cilnidipine within 30 minutes. The SR layer of F4 provided controlled Azilsartan Medoxomil release up to 24 hours, confirming the dual-release behavior of the bilayer system. F1 showed faster release unsuitable for sustained action, while F5 showed overly retarded release. F4 demonstrated the most optimized release profile. Drug release kinetics of the SR layer followed the Higuchi diffusion model (R^2 = 0.9921), indicating diffusion-controlled release with non-Fickian transport mechanism.

D. FTIR and DSC Results

TABLE VIII: FTIR Characteristic Peaks of Optimized Formulation (F4)

Functional Group	Cilnidipine (cm^{-1})	Azilsartan (cm^{-1})	F4 Formulation (cm^{-1})	Interpretation
N–H Stretching	3342	3320	3338	Peak retained
C=O Stretching	1702	1712	1705	No significant shift
Aromatic C=C	1576	1542	1568	Stable peak observed

Functional Group	Cilnidipine (cm^{-1})	Azilsartan (cm^{-1})	F4 Formulation (cm^{-1})	Interpretation
C–O Stretching	1248	—	1245	Compatible
O–H Stretching	—	3385	3380	No interaction

FTIR spectra of the optimized formulation (F4) showed retention of all characteristic peaks of both drugs without significant shifting or disappearance, confirming absence of chemical interaction. DSC thermograms revealed endothermic peaks for Cilnidipine at 173.24°C and Azilsartan at 145.68°C in pure drug samples. The F4 formulation showed both peaks retained (173.10°C and 146.02°C) with negligible shift, confirming thermal compatibility and drug–excipient compatibility.

E. Stability Study Results

TABLE IX: ICH Stability Study Results (F4, 40°C/75% RH)

Parameter	Initial	1 Month	2 Months	3 Months
Appearance	Intact, smooth	No change	No change	No change
Avg. Weight (mg)	421	421	420	420
Hardness (kg/cm^2)	5.8	5.7	5.6	5.5
Friability (%)	0.58	0.59	0.60	0.62
Cilnidipine Content (%)	99.1	98.9	98.7	98.4
Azilsartan Content (%)	99.5	99.2	98.9	98.6
% Drug Release – IR	99%	98.8%	98.5%	98.1%
% Drug Release – SR	99%	98.7%	98.4%	98.0%

No significant changes were observed in drug content, hardness, friability, or dissolution profile over 3 months of accelerated stability testing, indicating excellent formulation stability under ICH-prescribed conditions.

VII. CONCLUSION

Bilayer tablets containing Immediate Release Cilnidipine and Sustained Release Azilsartan Medoxomil were successfully formulated and evaluated for antihypertensive therapy. The optimized formulation F4 demonstrated rapid disintegration and ~99% Cilnidipine release within 30 minutes from the IR layer, and controlled Azilsartan Medoxomil release up to 24 hours from the SR layer. FTIR and DSC studies confirmed drug–excipient compatibility. Post-compression evaluation parameters were within pharmacopeial limits. Drug release followed Higuchi diffusion kinetics. ICH stability studies confirmed formulation stability. The developed bilayer tablet system offers a promising patient-friendly single dosage form providing rapid onset and prolonged antihypertensive action with improved patient compliance and reduced dosing frequency for effective long-term hypertension management.

ACKNOWLEDGMENT

The authors are thankful to the Principal and Management of BSS's Tatyaraoji More College of Pharmacy, Umerga, and Dr. Babasaheb Ambedkar Technological University (DBATU), Lonere, for providing laboratory facilities and guidance to carry out this research work.

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