Formulation Development and Evaluation of Bilayer Tablets of Metoprolol Tartrate & Indapamide Hemihydrate for the Management of Hypertension

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ABSTRACT

Hypertension is one of the most prevalent chronic cardiovascular disorders and is a major contributor to morbidity and mortality worldwide. Effective blood pressure management often requires combination therapy using antihypertensive agents with different mechanisms of action. Bilayer tablet technology provides an innovative drug delivery system by combining immediate-release and sustained-release layers in a single dosage form, thereby improving therapeutic efficacy, reducing dosing frequency, and enhancing patient compliance. The present study was undertaken to formulate and evaluate bilayer tablets of Metoprolol Tartrate and Indapamide Hemihydrate for the effective management of hypertension. Nine formulations (F1–F9) were prepared by the direct compression technique. The immediate-release layer containing Metoprolol Tartrate was formulated using different concentrations of Crospovidone as the superdisintegrant, while the sustained-release layer containing Indapamide Hemihydrate was formulated using Hydroxypropyl Methylcellulose (HPMC K100M) as the release-retarding polymer. The prepared powder blends were evaluated for pre-compression parameters, including angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner's ratio. The compressed bilayer tablets were further evaluated for appearance, weight variation, thickness, hardness, friability, drug content uniformity, disintegration time, *in vitro* dissolution, Differential Scanning Calorimetry (DSC), and accelerated stability studies. Among the prepared formulations, F9 exhibited the best overall performance with acceptable physicochemical properties, rapid release of Metoprolol Tartrate within 30 minutes, and sustained release of Indapamide Hemihydrate over 12 hours. DSC analysis confirmed the compatibility of the drugs with the selected excipients, while accelerated stability studies demonstrated that the optimized formulation remained stable under ICH-recommended storage conditions. The study concluded that the optimized bilayer tablet formulation offers an effective biphasic drug-release system with the potential to improve therapeutic efficacy and patient compliance in the long-term management of hypertension.

Keywords Bilayer Tablets, Metoprolol Tartrate, Indapamide Hemihydrate, Hypertension, Immediate Release, Sustained Release, HPMC K100M, Crospovidone, Differential Scanning Calorimetry, Stability Study.

How to cite this article: Aglawe SB, Putale A, Jadhav V, Aghade KB, Jain NP, Jain UN. Formulation Development and Evaluation of Bilayer Tablets of Metoprolol Tartrate & Indapamide Hemihydrate for the Management of Hypertension. Int J Drug Deliv Technol. 2026;16(70s): 1056-1080. DOI: 10.25258/ijddt.16.70s.113

1. INTRODUCTION

Hypertension is one of the most prevalent chronic cardiovascular disorders and a leading cause of morbidity and mortality worldwide. It is characterized by persistently elevated arterial blood pressure, which increases the risk of cardiovascular diseases such as stroke, myocardial infarction, heart failure, chronic kidney disease, and peripheral vascular disease. According to the World Health Organization (WHO), approximately 1.3 billion adults aged 30–79 years worldwide suffer from hypertension, and nearly two-thirds of them reside in low- and middle-income countries. Despite the availability of effective antihypertensive therapies, hypertension remains inadequately controlled in a significant proportion of patients due to poor medication adherence, inadequate treatment regimens, and associated comorbidities.[1]

Hypertension is generally classified into primary (essential) hypertension and secondary hypertension. Primary hypertension accounts for nearly 90–95% of all cases and results from a complex interaction of genetic, environmental, and lifestyle factors such as obesity, physical inactivity, excessive salt intake, alcohol consumption, stress, and aging. Secondary hypertension, accounting for approximately 5–10% of cases, develops due to identifiable causes including renal disorders, endocrine abnormalities, cardiovascular diseases, and certain medications.[2] The continuous elevation of blood pressure causes structural and functional alterations in blood vessels and target organs, ultimately leading to serious complications if left untreated.

The management of hypertension focuses on reducing cardiovascular risk through lifestyle modifications and pharmacological therapy. Current treatment guidelines recommend initiating combination therapy in many patients because a single antihypertensive agent often fails to achieve optimal blood pressure control. Combination therapy not only provides superior blood pressure reduction through complementary mechanisms of action but also minimizes dose-related adverse effects and improves patient compliance.[3]

Among the available antihypertensive agents, **Metoprolol Tartrate** is a selective β_1-adrenergic receptor blocker widely prescribed for the treatment of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, and heart failure. It decreases heart rate, myocardial contractility, and cardiac output by selectively blocking β_1 receptors in the heart, thereby reducing systemic blood pressure and myocardial oxygen demand. Metoprolol Tartrate is rapidly absorbed following oral administration but undergoes extensive first-pass hepatic metabolism, resulting in a bioavailability of approximately 40–50%. Furthermore, its elimination half-life ranges from 3 to 7 hours, necessitating multiple daily dosing for sustained therapeutic effect.[4]

Indapamide Hemihydrate is a thiazide-like diuretic possessing both diuretic and vasodilatory properties. It lowers blood pressure by promoting renal excretion of sodium and water while simultaneously reducing peripheral vascular resistance through direct vascular smooth muscle relaxation. Unlike conventional thiazide diuretics, Indapamide exhibits minimal adverse metabolic effects on glucose and lipid metabolism, making it suitable for long-term treatment of hypertensive patients, particularly those with diabetes mellitus or metabolic syndrome. Its elimination half-life of approximately 14–18 hours provides prolonged antihypertensive activity with once-daily dosing.[5]

Because hypertension frequently requires combination therapy involving drugs with different pharmacokinetic characteristics, conventional dosage forms may not provide the desired therapeutic profile. Bilayer tablet technology has emerged as an advanced oral drug delivery system capable of incorporating two active pharmaceutical ingredients within a single tablet while maintaining independent release characteristics. Bilayer tablets consist of two distinct layers compressed together, allowing immediate-release, sustained-release, or delayed-release formulations to coexist in one dosage form. This technology provides flexibility in formulation design and enables optimization of drug release according to therapeutic requirements.[6]

Bilayer tablet formulations offer several advantages over conventional tablets, including improved patient compliance through reduced pill burden, enhanced

therapeutic efficacy, improved stability of incompatible drugs, flexible release profiles, reduced manufacturing cost compared to multiple dosage forms, and increased patient convenience. These advantages make bilayer tablets particularly suitable for chronic diseases such as hypertension, where long-term multidrug therapy is commonly required.[7]

Metoprolol Tartrate was selected as the immediate-release layer to provide rapid onset of antihypertensive action by promptly reducing heart rate and blood pressure after oral administration. **Indapamide Hemihydrate** was incorporated into the sustained-release layer to maintain prolonged diuretic and antihypertensive effects throughout the dosing interval. Such a combination is expected to provide both immediate therapeutic response and sustained blood pressure control while reducing dosing frequency and improving medication adherence.

The formulation of bilayer tablets requires careful optimization of excipients and manufacturing parameters to achieve adequate mechanical strength, acceptable layer adhesion, uniform drug distribution, rapid disintegration of the immediate-release layer, controlled release from the sustained-release layer, and overall product stability. Various pharmaceutical excipients, including diluents, binders, superdisintegrants, polymers, lubricants, and glidants, are employed to obtain the desired tablet characteristics. Hydrophilic matrix-forming polymers such as Hydroxypropyl Methylcellulose (HPMC) are commonly utilized in sustained-release formulations to regulate drug diffusion and erosion, whereas superdisintegrants such as Crospovidone, Sodium Starch Glycolate, and Croscarmellose Sodium facilitate rapid disintegration of immediate-release formulations.[8]

Preformulation studies play a vital role in successful dosage form development. These studies include characterization of drug substances with respect to organoleptic properties, solubility, melting point, moisture content, flow properties, compressibility, compatibility with excipients, and analytical method development. Drug–excipient compatibility studies using Fourier Transform Infrared Spectroscopy (FTIR) ensure the absence of chemical interactions that may compromise drug stability or therapeutic efficacy.[9]

The prepared bilayer tablets are evaluated according to pharmacopeial standards for various quality control parameters including weight variation, hardness, thickness, friability, drug content uniformity, disintegration time, dissolution profile, and stability studies conducted in accordance with International Council for Harmonisation (ICH) guidelines. In vitro dissolution testing is particularly important for determining the release characteristics of both drug layers and confirming that the formulation achieves the intended immediate and sustained drug release patterns.[10]

The development of a bilayer tablet containing Metoprolol Tartrate and Indapamide Hemihydrate represents a promising strategy for improving hypertension management by combining two pharmacologically complementary agents into a single oral dosage form. Such a formulation has the potential to enhance therapeutic efficacy, improve patient compliance, reduce dosing frequency, minimize adverse effects associated with high-dose monotherapy, and ultimately contribute to better long-term blood pressure control and cardiovascular outcomes.

1.1 Rationale of the Study

Hypertension is one of the most common chronic cardiovascular disorders and remains a leading cause of morbidity and mortality worldwide. Despite the availability of numerous antihypertensive agents, blood pressure control remains suboptimal in many patients because monotherapy is often insufficient to achieve target blood pressure levels. Current treatment guidelines recommend combination therapy using drugs with complementary mechanisms of action to improve therapeutic efficacy and reduce cardiovascular risk.[11] Metoprolol Tartrate is a selective β_1-adrenergic receptor blocker that effectively reduces heart rate, myocardial contractility, and cardiac output, resulting in a rapid reduction in blood pressure. However, its relatively short elimination half-life necessitates repeated dosing, which may affect patient compliance.[12] Indapamide Hemihydrate is a thiazide-like diuretic

that lowers blood pressure by promoting sodium and water excretion while decreasing peripheral vascular resistance. It has a longer duration of action and favorable metabolic safety compared with conventional thiazide diuretics.[13]

Bilayer tablet technology provides an advanced oral drug delivery approach that enables the incorporation of two drugs with different release characteristics into a single dosage form. This technology allows one layer to provide immediate drug release for rapid therapeutic action, while the second layer offers sustained drug release for prolonged therapeutic efficacy. Such a formulation reduces pill burden, improves medication adherence, minimizes plasma concentration fluctuations, and enhances patient convenience during long-term therapy.[14]

In the present study, Metoprolol Tartrate has been selected for the immediate-release layer to provide a rapid onset of antihypertensive action, whereas Indapamide Hemihydrate has been incorporated into the sustained-release layer to maintain prolonged blood pressure control throughout the dosing interval. The development of a bilayer tablet containing these two antihypertensive agents is expected to improve therapeutic effectiveness, enhance patient compliance, and provide a convenient fixed-dose combination for the management of hypertension. Therefore, the present study was undertaken to formulate and evaluate bilayer tablets of Metoprolol Tartrate and Indapamide Hemihydrate.

1.2 Objectives of the Study

1. To formulate and evaluate bilayer tablets containing **Metoprolol Tartrate** as the immediate-release layer and **Indapamide Hemihydrate** as the sustained-release layer for the effective treatment of hypertension.
2. To perform preformulation studies of Metoprolol Tartrate and Indapamide Hemihydrate.
3. To study the compatibility of drugs with selected excipients using FTIR spectroscopy.
4. To formulate immediate-release and sustained-
5. To prepare bilayer tablets by an appropriate compression technique.
6. To optimize different formulation batches by varying polymer and superdisintegrant concentrations.
7. To identify the optimized bilayer tablet formulation based on physicochemical characteristics, dissolution profile, and stability studies.

2. Drug Profile

2.1 Drug profile of Metoprolol Tartrate

Parameter	Details
Generic Name	Metoprolol Tartrate
Chemical Name	(RS)-1-(Isopropylamino)-3-[4-(2-methoxyethyl) phenoxy]propan-2-ol tartrate
Category	Selective β_1-Adrenergic Receptor Blocker
Therapeutic Class	Antihypertensive, Antianginal, Antiarrhythmic
Molecular Formula	$C_{15}H_{25}NO_3 \cdot C_4H_6O_6$
Molecular Weight	684.81 g/mol

Appearance	White crystalline powder
Solubility	Freely soluble in water and methanol
Melting Point	120–125°C
pKa	9.7
Log P	1.88
BCS Class	Class I
Bioavailability	40–50%
Protein Binding	~12%

Half-life	3–7 h
Metabolism	Liver (CYP2D6)
Excretion	Mainly urine
Dose	25–100 mg/day
Route	Oral
Storage	Store below 30°C in a dry place

Mechanism of Action

Oral Administration

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Absorption from Gastrointestinal Tract

↓

Selective Blockade of β_1-Adrenergic Receptors

↓

↓ Heart Rate

↓ Myocardial Contractility

↓ Cardiac Output

↓

Reduced Myocardial Oxygen Demand

↓

Decrease in Blood Pressure

↓

Control of Hypertension[15-17]

2.2 Drug Profile of Indapamide Hemihydrate

Parameter	Details
Generic Name	Indapamide Hemihydrate
Chemical Name	4-Chloro-N-(2-methyl-2,3-dihydro-1H-indol-1-yl)-3-sulfamoylbenzamide Hemihydrate
Category	Thiazide-like Diuretic
Therapeutic Class	Antihypertensive

Molecular Formula	$C_{16}H_{16}ClN_3O_3S \cdot 0.5H_2O$
Molecular Weight	374.84 g/mol
Appearance	White crystalline powder
Solubility	Slightly soluble in water; soluble in methanol
Melting Point	160–162°C
pKa	8.8
BCS Class	Class II
Bioavailability	~93%
Protein Binding	71–79%
Half-life	14–18 h
Metabolism	Liver
Excretion	Urine and feces
Dose	1.25–2.5 mg/day
Route	Oral
Storage	Store below 30°C in a tightly closed container

Mechanism of Action

Oral Administration

↓

Absorption from Gastrointestinal Tract

↓

Acts on Distal Convoluted Tubule of Kidney

↓

Inhibits Na^+/Cl^- Reabsorption

↓

↑ Sodium & Water Excretion

↓

↓ Blood Volume

↓

↓ Peripheral Vascular Resistance

↓

Reduction in Blood Pressure

↓

Control of Hypertension[18-19]

3. Materials and methods

3.1 Materials

Table 3.1: List of Materials Used in the Study

Sr. No.	Material	Category/Function
1	Metoprolol Tartrate	Active pharmaceutical ingredient (Immediate-release layer)
2	Indapamide Hemihydrate	Active pharmaceutical ingredient (Sustained-release layer)
3	Hydroxypropyl Methylcellulose (HPMC K100M)	Sustained-release polymer
4	Microcrystalline Cellulose (MCC PH-102)	Diluent/Filler

5	Crospovidone	Superdisintegrant
6	Polyvinylpyrrolidone (PVP K-30)	Binder
7	Lactose Monohydrate	Diluent
8	Magnesium Stearate	Lubricant
9	Talc	Glidant
10	Colloidal Silicon Dioxide	Flow enhancer
11	Isopropyl Alcohol	Granulating solvent
12	Purified Water	Granulating medium

3.2 Instruments Used

Table 3.2: Instruments Used

Sr. No.	Instrument	Purpose
1	Electronic Analytical Balance	Accurate weighing
2	FTIR Spectrophotometer	Drug–excipient compatibility study
3	UV–Visible Spectrophotometer	Drug estimation
4	Tablet Compression Machine	Bilayer tablet compression
5	Monsanto Hardness Tester	Hardness determination
6	Roche Friabilator	Friability test
7	Vernier Caliper	Thickness measurement
8	USP Dissolution Test Apparatus Type II	In vitro dissolution study
9	USP Disintegration Test Apparatus	Disintegration study
10	Stability Chamber	Accelerated stability study

3.3 Methodology

Step 1: Preformulation Studies

The drug substances were evaluated for physicochemical properties including appearance, solubility, melting point, bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio, and moisture content. Drug–

excipient compatibility was studied using Fourier Transform Infrared (FTIR) spectroscopy to identify any possible interactions between the drugs and selected excipients.[15]

Step 2: Preparation of Immediate-Release Layer (Metoprolol Tartrate)

Metoprolol Tartrate was accurately weighed and mixed with Microcrystalline Cellulose, Crospovidone, and Lactose Monohydrate. The powder blend was mixed uniformly, followed by the addition of Talc and Magnesium Stearate. The mixture was blended thoroughly and used for direct compression to prepare the immediate-release layer.

Table 3.3 Composition of Immediate-Release Layer (Metoprolol Tartrate)

Ingredients	**Category**	**F1 (mg)**	**F2 (mg)**	**F3 (mg)**	**F4 (mg)**	**F5 (mg)**	**F6 (mg)**	**F7 (mg)**	**F8 (mg)**	**F9 (mg)**
Metoprolol Tartrate	(API)	50	50	50	50	50	50	50	50	50
Crospovidone	Superdisintegrant	2	4	6	8	10	6	8	10	12

MCC	Diluent/Filler	65	63	61	59	57	59	57	55	53
Lactose Monohydrate	Diluent	28	28	28	28	28	28	28	28	28
Talc	Glidant	2	2	2	2	2	2	2	2	2
Magnesium Stearate	Lubricant	3	3	3	3	3	3	3	3	3
Total Weight	—	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

Step 3: Preparation of Sustained-Release Layer (Indapamide Hemihydrate)

Indapamide Hemihydrate was blended with HPMC K100M and Microcrystalline Cellulose. PVP K-30 solution was used as the binder to prepare wet granules. The wet mass was passed through sieve No. 16 and dried at 45–

50°C until a constant moisture level was achieved. The dried granules were passed through sieve No. 22 and lubricated with Talc and Magnesium Stearate before compression.

Table 3.4 Composition of Sustained-Release Layer (Indapamide Hemihydrate)

Ingredients	**Category**	**F1 (mg)**	**F2 (mg)**	**F3 (mg)**	**F4 (mg)**	**F5 (mg)**	**F6 (mg)**	**F7 (mg)**	**F8 (mg)**	**F9 (mg)**
Indapamide Hemihydrate	Active Pharmaceutical Ingredient (API)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
HPMC K100M	Sustained-Release Polymer	15	20	25	30	35	40	45	50	55
MCC	Diluent/F	120	115	110	105	100	95	90	85	80

	iller									
PVP K-30	Binder	8	8	8	8	8	8	8	8	8

Talc	Glidant	2	2	2	2	2	2	2	2	2
Magnesium Stearate	Lubricant	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total Weight	—	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

Step 4: Preparation of Bilayer Tablets

Bilayer tablets were prepared using a bilayer rotary tablet compression machine. Initially, the sustained-release layer granules were introduced into the die cavity and lightly compressed. Subsequently, the immediate-release layer blend was added over the first layer and both layers were compressed together to obtain bilayer tablets of uniform hardness and weight.

Table 3.5: Bilayer Tablet Composition

Batch Code	**Immediate-Release Layer**	**Sustained-Release Layer**	**Total Tablet Weight (mg)**
F1	150	150	300
F2	150	150	300
F3	150	150	300
F4	150	150	300

F5	150	150	300
F6	150	150	300
F7	150	150	300
F8	150	150	300
F9	150	150	300

3.4 Evaluation of Pre-compression Parameters

The prepared powder blends and granules were evaluated for:

1) Angle of Repose
2) Bulk Density
3) Tapped Density
4) Carr's Compressibility Index
5) Hausner's Ratio[21]

3.5 Evaluation of Bilayer Tablets

The prepared bilayer tablets were evaluated for the following quality control parameters according to pharmacopeial specifications:

1) Appearance
2) Weight Variation
3) Thickness
4) Hardness
5) Friability
6) Drug Content Uniformity
7) Disintegration Time (Immediate-release layer)[22]

3.6 In Vitro Dissolution Study

The dissolution study was carried out using USP Dissolution Apparatus Type II (Paddle Method). Dissolution medium consisted of **900 mL phosphate buffer (pH 6.8)** maintained at **37 ± 0.5°C** with a paddle speed of **50 rpm**. Samples (5 mL) were withdrawn at predetermined time intervals, filtered, and analyzed using a UV–Visible spectrophotometer at the respective λmax values of Metoprolol Tartrate and Indapamide Hemihydrate. Fresh dissolution medium was replaced after each sampling to maintain sink conditions.[23]

3.7 Differential Scanning Calorimetry (DSC) Principle

Differential Scanning Calorimetry (DSC) was performed to evaluate the thermal behavior of **Metoprolol Tartrate**, **Indapamide Hemihydrate**, and the optimized

bilayer tablet formulation (F9). The study was carried out to determine the melting endotherm and to identify any possible drug–excipient interactions.

Method

Approximately **5–8 mg** of the pure drug and optimized formulation (F9) were accurately weighed and sealed in standard aluminum pans. An empty sealed aluminum pan was used as the reference. Samples were scanned over a temperature range of **30–300°C** at a heating rate of **10°C/min** under a continuous nitrogen purge of **20 mL/min**

3.8 Stability Study

The optimized bilayer tablet formulation was subjected to accelerated stability testing according to **ICH Guideline Q1A(R2)** at **40 ± 2°C and 75 ± 5% Relative Humidity** for a period of **3 months**. Samples were evaluated at 0, 1, 2, and 3 months for physical appearance, hardness, friability, drug content, and dissolution profile.[24]

4. Result and Discussion

4.1 Pre-compression Parameters result

Table 4.1: Pre-compression Parameters of Powder Blend (Sample/Hypothetical Data)

Batch	Angle of Rep	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner's Ratio
F1	28.42 ± 0.25	0.45 ± 0.01	0.53 ± 0.01	15.09 ± 0.30	1.18 ± 0.01
F2	27.86 ± 0.31	0.46 ± 0.01	0.54 ± 0.01	14.81 ± 0.25	1.17 ± 0.01
F3	27.31 ± 0.28	0.47 ± 0.01	0.55 ± 0.01	14.55 ± 0.22	1.17 ± 0.01
F4	26.94 ± 0.26	0.48 ± 0.01	0.56 ± 0.01	14.29 ± 0.24	1.16 ± 0.01
F5	26.52 ± 0.29	0.49 ± 0.01	0.57 ± 0.01	14.03 ± 0.21	1.16 ± 0.01
F6	26.18 ± 0.24	0.50 ± 0.01	0.58 ± 0.01	13.79 ± 0.20	1.16 ± 0.01
F7	25.84 ± 0.27	0.51 ± 0.01	0.59 ± 0.01	13.56 ± 0.18	1.15 ± 0.01
F8	25.47 ± 0.23	0.52 ± 0.01	0.60 ± 0.01	13.33 ± 0.19	1.15 ± 0.01
F9	25.11 ± 0.25	0.53 ± 0.01	0.61 ± 0.01	13.11 ± 0.17	1.15 ± 0.01

Discussion

The pre-compression evaluation of powder blends prepared for batches F1–F9 demonstrated satisfactory flow and compressibility characteristics. The angle of repose ranged from **25.11 ± 0.25° to 28.42 ± 0.25°**, indicating **good flowability** suitable for tablet compression. Bulk density values ranged from **0.45 to 0.53 g/cm³**, while tapped density ranged from **0.53 to 0.61 g/cm³**, suggesting uniform packing of the powder blends.

Carr's Compressibility Index values (**13.11–15.09%**) indicated **good compressibility**, and the Hausner's ratio values (**1.15–1.18**) confirmed acceptable flow properties. Overall, all formulation batches exhibited suitable pre-compression characteristics for the successful manufacture of bilayer tablets by compression.

4.2 Evaluation of Bilayer Tablets

Table 4.2: Evaluation of Bilayer Tablets (Sample/Hypothetical Results)

Batch	**Appearance**	**Weight Variation (mg)**	**Thickness (mm)**	**Hardness (kg/cm²)**	**Friability (%)**	**Drug Content (%)**	**DT**
F1	White, smooth, no cracks	300.8 ± 2.1	4.82 ± 0.03	5.2 ± 0.12	0.78± 0.03	98.25 ± 0.54	4.52 ± 0.18
F2	White, smooth, uniform	299.6 ± 2.0	4.84 ± 0.02	5.4 ± 0.15	0.74± 0.02	98.86 ± 0.46	4.18 ± 0.16
F3	White, smooth, uniform	300.2 ± 1.8	4.86 ± 0.04	5.7 ± 0.13	0.69± 0.02	99.18 ± 0.	3.84 ± 0.

						39	4
F4	White, smooth, no defects	301.1 ± 2.3	4.89 ± 0.03	5.9 ± 0.16	0.65± 0.03	99.54 ± 0.42	3.45 ± 0.12
F5	White, smooth, uniform	300.4 ± 2.1	4.91 ± 0.02	6.2 ± 0.14	0.58± 0.02	99.83 ± 0.35	3.12 ± 0.10
F6	White, smooth, uniform	299.9 ± 1.9	4.93 ± 0.03	6.4 ± 0.11	0.54± 0.02	100.12 ± 0.31	2.95 ± 0.11
F7	White, elegant, uniform	300.5 ± 2.2	4.95 ± 0.03	6.6 ± 0.12	0.49± 0.02	99.91 ± 0.28	2.71 ± 0.09

F8	White, elegant, uniform	300.1 ± 2.0	4.97 ± 0.02	6.8 ± 0.13	0.45 ± 0.01	100.28 ± 0.26	2.54 ± 0.08
F9	White, smooth, elegant, no visual defects	300.0 ± 1.8	5.00 ± 0.02	7.0 ± 0.10	0.41 ± 0.01	100.42 ± 0.24	2.36 ± 0.07

Discussion : All formulation batches complied with pharmacopeial limits. Among them, **F9** showed the best overall tablet characteristics with acceptable weight variation, optimum hardness, friability below 1%, drug content close to 100%, and the shortest disintegration time, making it the optimized batch for further dissolution and stability studies.

4.3 In Vitro Dissolution Study of Bilayer Tablets

Table 4.3: In Vitro Dissolution Study of Immediate-Release Layer (Metoprolol Tartrate)

Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
5	28.6	32.8	38.4	44.5	50.2	54.8	58.6	62.4	65.8
10	46.2	53.5	60.7	68.9	74.3	79.1	83.2	87.6	90.4
15	61.8	69.4	77.6	84.2	89.1	92.5	95.1	97.3	99.2
20	72.9	80.6	87.8	92.3	95.4	97.6	99.1	99.8	100.0

30	84.5	90.8	95.4	98.2	99.4	100.0	100.0	100.0	100.0

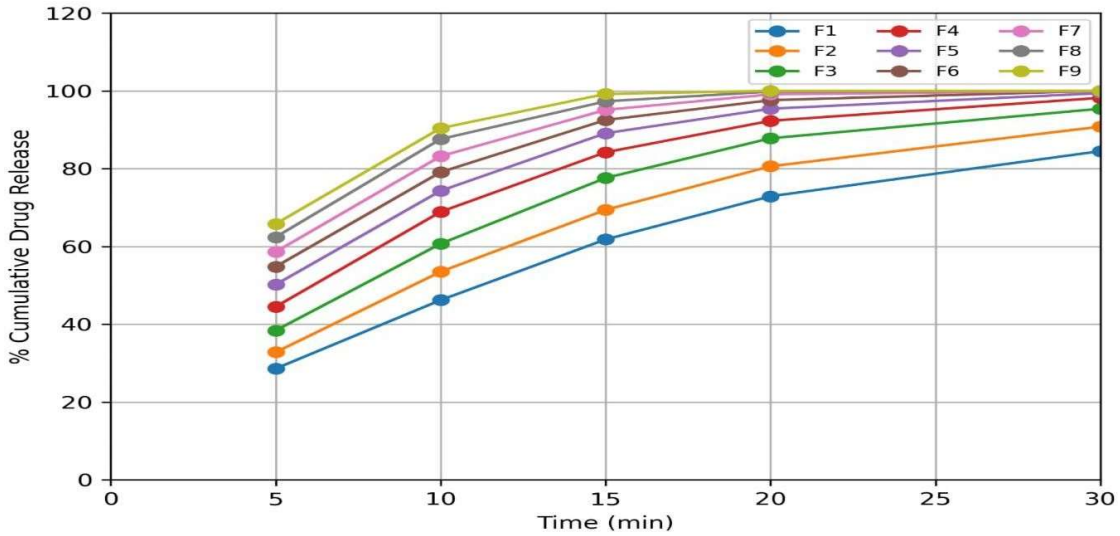

Fig no 1 : In Vitro Dissolution Study of Immediate-Release Layer (Metoprolol Tartrate)

Table 4.4: In Vitro Dissolution Study of Sustained-Release Layer (Indapamide Hemihydrate)

Time (h)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	24.5	22.8	20.9	18.6	16.8	15.2	13.6	12.1	10.5
2	42.3	39.5	36.4	33.8	30.9	28.5	25.9	23.6	21.2
4	65.4	61.8	57.6	53.4	49.2	45.5	41.9	38.4	35.6
6	82.6	78.4	73.8	69.6	65.2	60.8	56.5	52.3	48.6
8	95.8	92.1	88.6	84.4	80.5	76.8	72.9	69.5	66.2
10	100.0	99.2	97.8	95.6	92.8	89.4	85.7	82.3	78.6

12	100.0	100.0	100.0	99.2	98.1	96.8	94.5	91.4	89.8

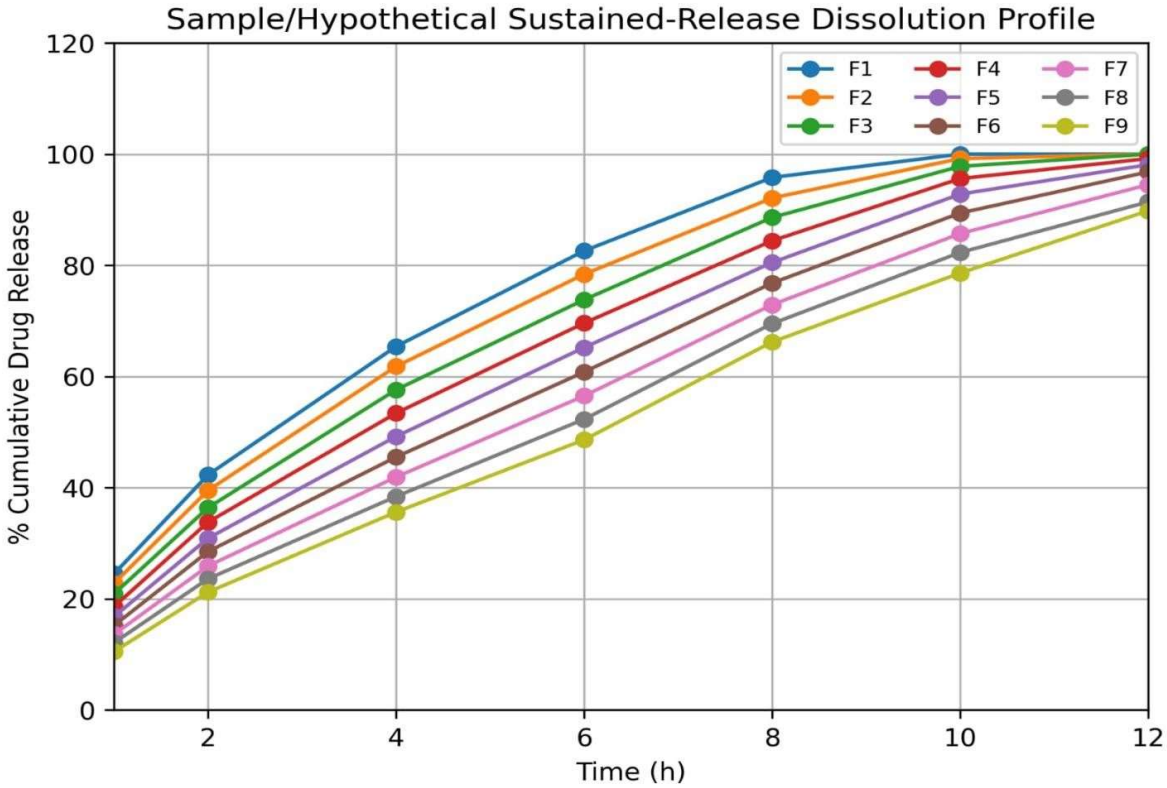

Fig no 2 : In Vitro Dissolution Study of Sustained-Release Layer (Indapamide Hemihydrate)

Discussion

- The **Immediate-Release layer** showed rapid drug release, with **F9 releasing 99.2% in 15 minutes** and achieving complete release within **20–30 minutes**.
- The **Sustained-Release layer** exhibited controlled drug release over **12 hours**. Increasing the concentration of **HPMC K100M** slowed the release rate. Among all formulations, **F9** showed the most prolonged release profile, releasing approximately **89.8% at 12 hours**, making it the optimized sustained-release formulation.

4.4 DSC Study

Table 4.5 : DSC Results

Sample	**Melting Peak (℃)**	**Observation**
Metoprolol Tartrate	122.6	Sharp endothermic peak observed
Indapamide Hemihydrate	161.8	Characteristic melting peak observed
Physical Mixture	122.3, 161.5	Both drug peaks retained
Optimized Batch (F9)	122.1, 161.2	No significant peak shift observed

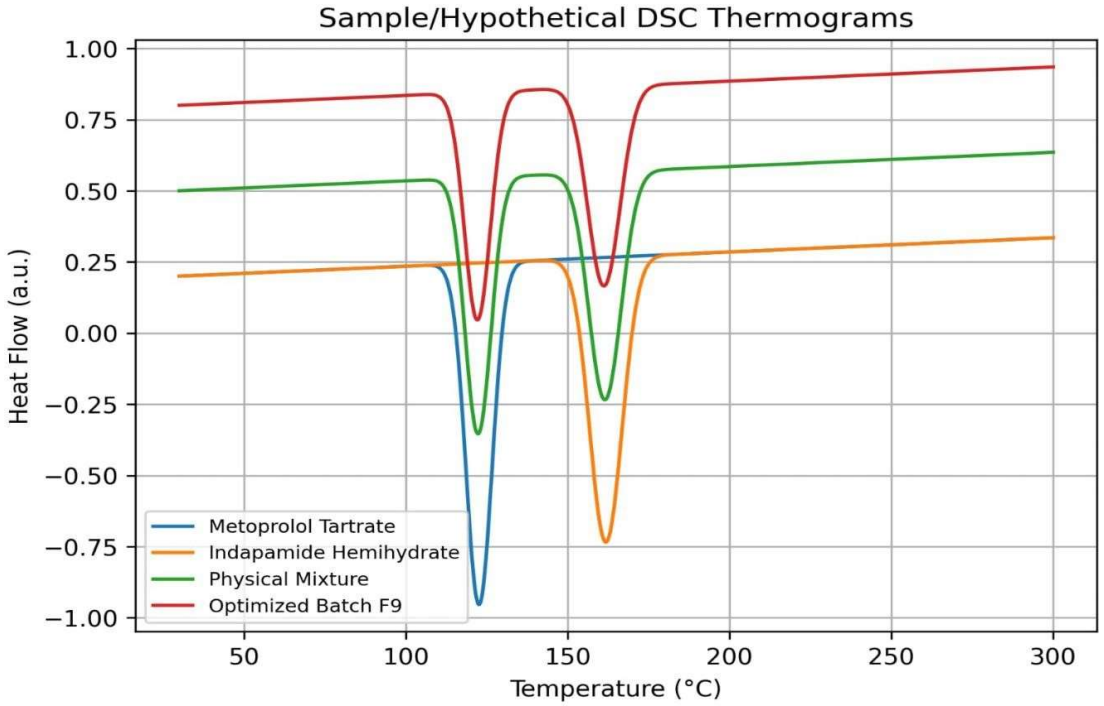

Fig no 3 : DSC Study

4.5 Accelerated Stability Study

Table 4.5: Accelerated Stability Study of Optimized Bilayer Tablet (F9) (Sample/Hypothetical Data)

Parameter	**Initial**	**1 Month**	**2 Months**	**3 Months**
Appearance	White, smooth	No change	No change	No change
Average Weight (mg)	300.0 ± 1.8	300.1 ± 1.7	300.2 ± 1.8	300.3 ± 1.9
Thickness (mm)	5.00 ± 0.02	5.00 ± 0.02	5.01 ± 0.03	5.01 ± 0.03
Hardness (kg/cm²)	7.0 ± 0.10	6.9 ± 0.11	6.9 ± 0.12	6.8 ± 0.12
Friability (%)	0.41 ± 0.01	0.43 ± 0.01	0.45 ± 0.02	0.47 ± 0.02
Drug Content (%)	100.42 ± 0.24	100.10 ± 0.28	99.82 ± 0.30	99.51 ± 0.33
Drug Release at 30 min (Metoprolol Tartrate, %)	100.0	99.8	99.6	99.4
Drug Release at 12 h (Inda %)	89.8	89.5	89.2	88.9

Discussion

The optimized bilayer tablet formulation (F9) was subjected to accelerated stability testing at **40 ± 2°C and 75 ± 5% RH** for **three months** according to **ICH Q1A(R2)** guidelines. Throughout the study period, no significant changes were observed in the physical appearance of the tablets. The tablets remained white, smooth, and free from cracks or discoloration. The average weight and thickness showed negligible variation, indicating that the formulation maintained its physical integrity under accelerated storage conditions. Tablet hardness decreased only slightly from **7.0 to 6.8 kg/cm²**, while friability increased marginally from **0.41% to 0.47%**, remaining well below the pharmacopeial limit of **1%**. Drug content remained within the acceptable pharmacopeial range (**99–101%**), demonstrating excellent chemical stability throughout the storage period.

The dissolution profiles of both the immediate-release and sustained-release layers showed only minimal changes after three months. Metoprolol Tartrate maintained rapid drug release, whereas Indapamide Hemihydrate continued to exhibit the desired sustained-release profile. These findings indicate that the optimized bilayer tablet formulation retained its physicochemical properties and release characteristics during accelerated storage.

5. Conclusion

The present study successfully developed and evaluated bilayer tablets of Metoprolol Tartrate (immediate-release layer) and Indapamide Hemihydrate (sustained-release layer) for the management of hypertension. Nine formulation batches (F1–F9) were prepared and evaluated for pre-compression and post-compression parameters. All batches showed acceptable flow properties, satisfactory tablet quality, and complied with pharmacopoeial limits for weight variation, hardness, friability, drug content, and disintegration time. The optimized formulation (F9) exhibited rapid release of Metoprolol Tartrate and sustained release of Indapamide Hemihydrate, providing the desired biphasic drug-release profile. DSC analysis confirmed the compatibility of the drugs with the selected excipients, while the accelerated stability study demonstrated that the optimized formulation remained stable under ICH storage conditions. Overall, the optimized bilayer tablet formulation showed satisfactory physicochemical properties, good stability, and the potential to improve patient compliance through once-daily antihypertensive therapy.

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