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Review Article

A Comprehensive Review of Bilayer Tablet Technology for Antihypertensive Drug Delivery

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ABSTRACT

Hypertension is one of the most prevalent chronic cardiovascular disorders worldwide and remains a major cause of morbidity and mortality due to its association with stroke, myocardial infarction, heart failure, and chronic kidney disease. Conventional monotherapy often fails to achieve adequate blood pressure control because hypertension is a multifactorial disorder involving several physiological pathways. Consequently, combination therapy has become an effective strategy for improving therapeutic outcomes. Bilayer tablet technology has emerged as an advanced drug delivery system capable of incorporating two drugs with different release characteristics into a single dosage form. This technology enables one layer to provide immediate drug release for rapid onset of action, while the second layer offers sustained drug release for prolonged therapeutic efficacy. Such systems improve patient compliance by reducing dosing frequency and maintaining consistent plasma drug concentrations. The present review summarizes the recent advances in formulation development, manufacturing techniques, polymers, excipients, evaluation parameters, and applications of bilayer tablets for antihypertensive therapy. Particular emphasis is given to immediate-release Metoprolol Tartrate and sustained-release Indapamide Hemihydrate because of their complementary pharmacological mechanisms and suitability for combination therapy. Various formulation methods, including direct compression, wet granulation, and advanced bilayer compression technologies, are discussed together with pre-compression and post-compression evaluation techniques. The review also highlights quality control requirements, stability studies, in vitro dissolution testing, and current research trends in bilayer tablet development. Furthermore, recent literature describing innovations in bilayer drug delivery systems is critically analyzed to identify future opportunities for improving therapeutic performance and patient adherence. Overall,

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bilayer tablet technology represents a promising pharmaceutical approach for effective hypertension management through controlled and sequential drug delivery.

INTRODUCTION

Hypertension is a chronic non-communicable disease characterized by persistent elevation of arterial blood pressure above normal physiological levels. It affects more than one billion people globally and is recognized as one of the leading contributors to cardiovascular morbidity and premature mortality. Uncontrolled hypertension significantly increases the risk of stroke, coronary artery disease, myocardial infarction, chronic kidney disease, heart failure, and peripheral vascular disorders. Because hypertension usually progresses without noticeable symptoms during its early stages, it is widely referred to as the "silent killer." Early diagnosis and long-term pharmacological management are therefore essential for preventing serious complications.

Modern hypertension management has shifted from monotherapy to combination therapy because multiple physiological pathways contribute to elevated blood pressure. Fixed-dose combinations reduce pill burden, improve patient adherence, and provide better blood pressure control compared with administration of individual drugs. Bilayer tablet technology has become an attractive dosage form for delivering combination therapy by incorporating two drugs with different release characteristics into a single tablet. One layer is designed for immediate release to provide rapid therapeutic action, whereas the second layer ensures sustained release over an extended period.

Bilayer tablets are particularly useful when drugs possess different pharmacokinetic properties, require different release profiles, or exhibit incompatibility when mixed in a conventional formulation. The physical separation of active pharmaceutical ingredients minimizes drug–drug interactions, enhances stability, and allows independent optimization of each layer. Such systems improve therapeutic efficacy while reducing dosing frequency and plasma concentration fluctuations.

Among the various antihypertensive drug combinations investigated, the combination of Metoprolol Tartrate as an immediate-release agent and Indapamide Hemihydrate as a sustained-release agent has gained considerable attention. Metoprolol Tartrate, a selective β_1-adrenergic receptor blocker, rapidly reduces heart rate and cardiac output, whereas Indapamide Hemihydrate, a thiazide-like diuretic, provides prolonged blood pressure control through sustained natriuretic and vasodilatory effects. Their complementary mechanisms make them suitable candidates for bilayer tablet formulations.

In recent years, significant progress has been made in bilayer tablet formulation through advances in polymer science, tablet compression technology, quality-by-design principles, and controlled drug delivery strategies. This review critically discusses current developments in formulation approaches, manufacturing methods, evaluation parameters, quality control, recent research findings, and future prospects of bilayer tablets for antihypertensive therapy. The aim is to provide researchers and pharmaceutical scientists with a comprehensive overview of the design and evaluation of bilayer tablets and their role in improving hypertension management.

2. HYPERTENSION: OVERVIEW AND GLOBAL BURDEN

2.1 INTRODUCTION TO HYPERTENSION

Hypertension is a chronic cardiovascular disorder characterized by persistent elevation of arterial blood pressure above normal physiological limits. It is one of the most common non-communicable diseases (NCDs) worldwide and represents a major public health challenge because of its high prevalence and strong association with cardiovascular, cerebrovascular, and renal diseases. Blood pressure is expressed as systolic blood pressure (SBP) over diastolic blood pressure (DBP) and is measured in millimeters of mercury (mmHg). According to commonly accepted clinical criteria, a normal blood pressure is approximately **120/80 mmHg**, whereas persistent elevation above the recommended range is considered hypertension. Untreated hypertension significantly increases the risk of stroke, myocardial infarction, heart failure, chronic kidney disease, peripheral vascular disease, and premature mortality. Due to its asymptomatic nature during the early stages, hypertension is widely known as the **"Silent Killer."**

2.2 GLOBAL BURDEN OF HYPERTENSION

Hypertension has become one of the leading causes of morbidity and mortality throughout the world. Rapid urbanization, unhealthy dietary habits, sedentary lifestyles, obesity, smoking, alcohol consumption, and psychological stress have contributed significantly to the increasing incidence of hypertension across both developed and developing countries.

Recent epidemiological reports indicate that more than 1.3 billion adults worldwide suffer from hypertension, and nearly half remain undiagnosed or inadequately treated. The burden is particularly high in low- and middle-income countries where access to healthcare services is limited. Persistent hypertension contributes substantially to cardiovascular mortality by increasing the risk of coronary artery disease, stroke, heart failure, chronic kidney disease, and vascular complications.

The socioeconomic burden is equally significant because hypertension requires lifelong treatment, regular clinical monitoring, and continuous medication adherence. Poor blood pressure control results in increased hospitalization, healthcare expenditure, and reduced quality of life.

2.3 CLASSIFICATION OF HYPERTENSION

Hypertension can be classified according to its etiology and severity.

A. Based on Etiology

Primary (Essential) Hypertension

Primary hypertension accounts for approximately **90–95%** of all hypertension cases. It develops gradually over many years without a single identifiable cause. Genetic predisposition, obesity, excessive salt intake, sedentary lifestyle, stress, smoking, alcohol consumption, aging, and family history are major contributing factors

Secondary Hypertension

Secondary hypertension results from identifiable medical conditions such as:

- Chronic kidney disease
- Renal artery stenosis
- Endocrine disorders
- Adrenal tumors
- Pregnancy-induced hypertension
- Drug-induced hypertension

Unlike primary hypertension, secondary hypertension often develops suddenly and may produce more severe elevations in blood pressure. Appropriate treatment of the underlying disease frequently improves blood pressure control.

B. Based on Severity

Hypertension may also be categorized according to blood pressure levels.

Category	Blood Pressure (mmHg)
Normal	<120 / <80
Elevated	120–129 / <80
Stage I Hypertension	130–139 / 80–89
Stage II Hypertension	≥140 / ≥90
Hypertensive Crisis	≥180 / ≥120

Patients with severe hypertension require immediate medical attention because prolonged elevation of blood pressure may cause irreversible damage to target organs including the heart, kidneys, retina, and brain.

2.4 ETIOLOGY AND RISK FACTORS

The development of hypertension is multifactorial and results from the interaction between genetic susceptibility and environmental influences.

Non-Modifiable Risk Factors

- Increasing age
- Family history
- Male gender
- Genetic predisposition
- Ethnicity

Modifiable Risk Factors

- Excess dietary salt
- Obesity
- Physical inactivity
- Smoking
- Alcohol consumption
- Diabetes mellitus
- Dyslipidemia
- Psychological stress
- Poor dietary habits

Modification of these risk factors through lifestyle changes has been shown to reduce the incidence and progression of hypertension.

2.5 PATHOPHYSIOLOGY OF HYPERTENSION

Hypertension develops due to complex interactions between several physiological mechanisms regulating cardiovascular function.

Major mechanisms include:

Activation of the Renin–Angiotensin–Aldosterone System (RAAS)

Activation of RAAS increases production of angiotensin II, resulting in:

- Vasoconstriction
- Aldosterone secretion
- Sodium retention
- Water retention
- Increased blood volume

These effects collectively increase arterial blood pressure.

Sympathetic Nervous System Overactivity

Enhanced sympathetic activity causes:

- Increased heart rate
- Increased cardiac output
- Peripheral vasoconstriction
- Elevated blood pressure

Endothelial Dysfunction

Reduced production of nitric oxide impairs vascular relaxation, resulting in increased vascular resistance and arterial stiffness.

Oxidative Stress and Inflammation

Chronic vascular inflammation contributes to endothelial damage and accelerates progression of hypertension.

2.6 CLINICAL MANIFESTATIONS

Most patients remain asymptomatic during the early stages. When symptoms occur, they may include:

- Persistent headache
- Dizziness
- Blurred vision
- Fatigue
- Chest pain
- Palpitations
- Shortness of breath
- Nose bleeding (occasionally)

Because symptoms often appear only after target organ damage has occurred, routine blood pressure monitoring is essential for early diagnosis.

2.7 COMPLICATIONS OF HYPERTENSION

Long-term uncontrolled hypertension damages multiple organs.

Cardiovascular

- Myocardial infarction
- Heart failure
- Left ventricular hypertrophy
- Coronary artery disease

Neurological

- Stroke
- Transient ischemic attack
- Cognitive impairment

Renal

- Chronic kidney disease
- Nephropathy
- Renal failure

Ophthalmic

- Hypertensive retinopathy
- Vision impairment

Peripheral Vascular Disease

- Atherosclerosis
- Peripheral arterial disease

2.8 CURRENT MANAGEMENT OF HYPERTENSION

Effective management requires both lifestyle modification and pharmacotherapy.

Non-Pharmacological Management

- Weight reduction
- DASH diet
- Sodium restriction
- Regular physical exercise
- Smoking cessation
- Limiting alcohol intake
- Stress management

Pharmacological Therapy

Commonly prescribed antihypertensive drug classes include:

- ACE inhibitors
- Angiotensin receptor blockers (ARBs)
- Beta blockers
- Calcium channel blockers
- Diuretics
- Alpha blockers

Combination therapy is recommended for patients with moderate-to-severe hypertension because it targets multiple mechanisms simultaneously and provides superior blood pressure control compared with monotherapy.

3. NEED FOR COMBINATION THERAPY AND BILAYER TABLET TECHNOLOGY IN HYPERTENSION

3.1 NEED FOR COMBINATION THERAPY IN HYPERTENSION

Hypertension is a multifactorial cardiovascular disorder involving numerous physiological pathways responsible for maintaining blood pressure homeostasis. Activation of the renin–angiotensin–aldosterone system (RAAS), increased sympathetic nervous system activity, endothelial dysfunction, sodium retention, vascular stiffness, and increased peripheral resistance collectively contribute to the development and progression of hypertension. Because multiple mechanisms are simultaneously involved, treatment with a single antihypertensive drug often fails to achieve optimal blood pressure control in many patients. Consequently, combination therapy has become an essential strategy for effective hypertension management.

Combination therapy refers to the use of two or more antihypertensive agents with different mechanisms of action to achieve greater blood pressure reduction and improved therapeutic outcomes. Current treatment guidelines recommend combination therapy particularly in patients with stage II hypertension, resistant hypertension, and individuals at high cardiovascular risk. Combining drugs acting through different pathways not only enhances efficacy but also minimizes dose-related adverse effects by allowing lower doses of individual medications.

3.2 LIMITATIONS OF MONOTHERAPY

Although monotherapy remains useful in mild hypertension, it has several limitations.

1. Inadequate Blood Pressure Control

Many patients do not achieve target blood pressure levels with a single antihypertensive agent, especially in moderate or severe hypertension. Monotherapy frequently fails to suppress all contributing physiological mechanisms involved in blood pressure regulation.

2. Dose-Dependent Adverse Effects

Increasing the dose of a single drug to improve efficacy often increases the incidence of adverse effects such as dizziness, electrolyte imbalance, bradycardia, fatigue, and hypotension. Higher toxicity may lead to poor patient compliance and discontinuation of therapy.

3. COMPENSATORY MECHANISMS

The body frequently activates compensatory pathways that oppose the pharmacological action of antihypertensive drugs. For example, diuretic therapy may stimulate RAAS activation, reducing its long-term effectiveness. Combination therapy helps overcome these compensatory mechanisms.

3.3 Rationale for Combination Therapy

The scientific rationale behind combination therapy includes:

- Targeting multiple blood pressure regulatory pathways simultaneously.
- Producing additive or synergistic antihypertensive effects.
- Reducing dose-related toxicity.
- Blocking compensatory physiological responses.
- Achieving faster and more sustained blood pressure control.
- Reducing cardiovascular complications.
- Improving patient adherence.

Different classes of antihypertensive drugs exert their effects through distinct mechanisms. Calcium channel blockers primarily cause vasodilation, angiotensin receptor blockers inhibit the action of angiotensin II, and diuretics reduce plasma volume by promoting sodium and water excretion. Combining these mechanisms provides superior therapeutic outcomes compared with single-drug therapy.

4. BILAYER TABLET TECHNOLOGY

4.1 Introduction to Bilayer Tablets

Bilayer tablets are advanced solid oral dosage forms consisting of two separate layers compressed into a single tablet. Each layer may contain different active pharmaceutical ingredients (APIs), different excipients, or the same drug formulated with different release characteristics. This technology enables the delivery of immediate-release and sustained-release medications within a single dosage form, thereby achieving sequential or controlled drug release according to therapeutic requirements.

In hypertension therapy, bilayer tablets can provide rapid blood pressure reduction through an immediate-release layer while maintaining prolonged antihypertensive activity using a sustained-release layer. This approach offers better therapeutic control, reduces dosing frequency, and improves patient compliance.

4.2 SCIENTIFIC RATIONALE FOR BILAYER TABLETS

A. Separation of Incompatible Drugs

Some drugs may undergo physical or chemical interactions when combined in a conventional single-layer formulation. Bilayer tablets physically separate these drugs into distinct layers, thereby minimizing incompatibility and improving stability.

B. Dual Drug Release Profile

Bilayer tablets provide:

- Immediate drug release for rapid therapeutic action.
- Sustained drug release for prolonged therapeutic effect.

This dual-release capability is one of the most important advantages of bilayer tablet systems.

C. Improved Pharmacokinetic Profile

Sustained-release layers help maintain consistent plasma drug concentrations and minimize peak–trough fluctuations, thereby reducing adverse effects while maintaining efficacy.

D. Enhanced Patient Compliance

By incorporating multiple drugs into a single tablet, bilayer formulations reduce pill burden and dosing frequency, which significantly improves patient adherence.

E. Synergistic Therapeutic Action

Drugs with different mechanisms of action may work synergistically when delivered together, resulting in superior clinical outcomes.

4.3 TYPES OF BILAYER TABLETS

Bilayer tablets may be classified according to their release characteristics:

1. Immediate Release–Sustained Release Bilayer Tablets

One layer rapidly releases the drug to achieve an immediate therapeutic effect, whereas the second layer provides sustained release for prolonged action.

2. Immediate Release–Immediate Release Bilayer Tablets

Both layers release the drug rapidly but contain different active pharmaceutical ingredients.

3. Sustained Release–Sustained Release Bilayer Tablets

Both layers are designed to maintain prolonged drug release.

4. Sequential Release Bilayer Tablets

One drug is intentionally released before the second drug to achieve a desired therapeutic sequence.

5. Floating Bilayer Tablets

These tablets remain buoyant in gastric fluid and prolong gastric residence time, thereby improving drug absorption.

4.4 ADVANTAGES OF BILAYER TABLETS

Bilayer tablet technology offers several advantages:

1. Dual drug release pattern.
2. Improved therapeutic efficacy.
3. Reduced dosing frequency.
4. Better patient compliance.
5. Separation of incompatible drugs.
6. Controlled and sustained drug release.
7. Improved bioavailability.

8. Reduced plasma concentration fluctuations.
9. Enhanced formulation flexibility.
10. Suitable for chronic diseases such as hypertension and diabetes.

4.5 APPLICATIONS OF BILAYER TABLETS

Bilayer tablets are widely used in:

- Hypertension management
- Diabetes mellitus
- Cardiovascular diseases
- Pain management
- Chronotherapeutic systems
- Gastro-retentive systems
- Sequential drug delivery
- Controlled release formulations
- Combination therapy
- Extended-release formulations

4.6 LIMITATIONS OF BILAYER TABLETS

Despite numerous advantages, bilayer tablets have certain limitations:

- Complex manufacturing process.
- Layer separation (delamination).
- Higher production cost.
- Compression challenges.
- Scale-up difficulties.
- Stability problems.
- Weight variation issues.
- Cross-contamination between layers.
- Large tablet size.
- Requirement for specialized compression machinery.

4.7 IMPORTANCE OF BILAYER TABLETS IN HYPERTENSION

Hypertension requires both rapid reduction of elevated blood pressure and prolonged maintenance of normal blood pressure. Bilayer tablet systems effectively satisfy these requirements by delivering an immediate-release antihypertensive agent followed by sustained drug release for long-term control. Such formulations provide improved therapeutic efficacy, better patient compliance, reduced pill burden, and enhanced quality of life, making them highly suitable for chronic hypertension management.

5.1 METOPROLOL TARTRATE

5.1.1 INTRODUCTION

Metoprolol Tartrate is a selective β_1-adrenergic receptor blocker (beta-blocker) widely used for the treatment of hypertension, angina pectoris, myocardial infarction, cardiac arrhythmias, and chronic heart failure. Because of its cardioselective nature, Metoprolol primarily acts on β_1 receptors located in the myocardium with minimal influence on β_2 receptors found in bronchial and vascular smooth muscles. This selectivity reduces undesirable respiratory adverse effects and makes Metoprolol one of the preferred β-blockers in cardiovascular therapy.

Although Metoprolol exhibits excellent antihypertensive activity, its relatively short elimination half-life necessitates repeated administration to maintain therapeutic plasma concentrations. Consequently, incorporation of Metoprolol Tartrate into the immediate-release (IR) layer of bilayer tablets ensures rapid onset of action and immediate reduction of blood pressure.

5.1.2 PHYSICOCHEMICAL PROPERTIES

Parameter	Description
Generic Name	Metoprolol Tartrate
Drug Class	Selective β_1-Adrenergic Blocker
Pharmacological Class	Antihypertensive Agent
BCS Classification	Class I
Molecular Formula	$C_{15}H_{25}NO_3 \cdot C_4H_6O_6$
Molecular Weight	684.81 g/mol
Solubility	Freely soluble in water
Half-life	3–7 hours
Bioavailability	Approximately 50%
Route	Oral

5.1.3 MECHANISM OF ACTION

Metoprolol selectively blocks β_1-adrenergic receptors in cardiac tissue.

The pharmacological sequence is:

Metoprolol Tartrate

↓

β_1-Receptor Blockade

↓

Reduced Heart Rate

↓

Reduced Myocardial Contractility

↓

Reduced Cardiac Output

↓

Reduced Blood Pressure

By decreasing cardiac output and suppressing renin secretion from the kidneys, Metoprolol effectively lowers systemic blood pressure while reducing myocardial oxygen demand.

5.1.4 PHARMACOLOGICAL ACTIONS

Metoprolol produces several beneficial cardiovascular effects:

- Selective β_1 receptor blockade.
- Reduction in heart rate.
- Decreased myocardial contractility.
- Suppression of renin secretion.
- Reduced cardiac workload.
- Lower myocardial oxygen consumption.
- Prevention of sympathetic overactivity.
- Effective control of hypertension.

5.1.5 THERAPEUTIC APPLICATIONS

Metoprolol Tartrate is indicated for:

- Essential hypertension
- Angina pectoris
- Acute myocardial infarction
- Cardiac arrhythmias
- Chronic heart failure
- Tachycardia
- Prevention of cardiovascular mortality

5.1.6 ADVANTAGES

Major advantages include:

- Rapid onset of antihypertensive activity.

- Good oral absorption.
- Cardioselective action.
- Well-established safety profile.
- Effective reduction in cardiovascular mortality.
- Suitable for immediate-release formulations.

5.1.7 LIMITATIONS

Despite its advantages, Metoprolol has certain limitations:

- Short biological half-life.
- Multiple daily dosing requirement.
- Bradycardia.
- Fatigue.
- Dizziness.
- Contraindicated in severe bradycardia and cardiogenic shock.

5.1.8 RATIONALE FOR SELECTION IN BILAYER TABLETS

Metoprolol Tartrate is highly suitable for the Immediate Release Layer because:

- Rapid onset of therapeutic action.
- Excellent aqueous solubility.
- Fast gastrointestinal absorption.
- Need for immediate blood pressure reduction.
- Compatibility with superdisintegrants such as Crospovidone and Croscarmellose Sodium.
- Complements the sustained action of Indapamide Hemihydrate.

5.2 INDAPAMIDE HEMIHYDRATE

5.2.1 INTRODUCTION

Indapamide Hemihydrate is a thiazide-like diuretic extensively used for long-term treatment of essential hypertension. Unlike conventional diuretics, Indapamide not only promotes sodium and water excretion but also possesses direct vasodilatory activity, resulting in prolonged antihypertensive effects.

Because hypertension requires continuous blood pressure control throughout the day, Indapamide is an ideal candidate for incorporation into the Sustained Release (SR) layer of bilayer tablets. Sustained release maintains relatively constant plasma drug concentrations, minimizes fluctuations, reduces adverse effects, and improves patient adherence.

5.2.2 PHYSICOCHEMICAL PROPERTIES

Parameter	Description
Generic Name	Indapamide Hemihydrate
Drug Class	Thiazide-like Diuretic
Pharmacological Class	Antihypertensive Agent
BCS Classification	Class II
Molecular Weight	374.84 g/mol
Solubility	Slightly soluble in water
Half-life	14–18 hours
Bioavailability	>90%
Route	Oral

5.2.3 MECHANISM OF ACTION

The pharmacological pathway is:

Indapamide Hemihydrate

↓

Inhibition of Na^+/Cl^- Transport

↓

Increased Sodium and Water Excretion

↓

Reduced Plasma Volume

↓

Reduced Peripheral Resistance

↓

Lower Blood Pressure

Besides its diuretic effect, Indapamide directly relaxes vascular smooth muscles, contributing to long-lasting antihypertensive action.

5.2.4 PHARMACOLOGICAL ACTIONS

Indapamide:

- Produces diuresis.
- Promotes sodium excretion.
- Reduces extracellular fluid volume.
- Causes peripheral vasodilation.
- Lowers peripheral vascular resistance.
- Maintains long-term blood pressure control.

5.2.5 THERAPEUTIC APPLICATIONS

Indapamide is widely prescribed for:

- Essential hypertension.
- Mild-to-moderate hypertension.
- Edema associated with cardiovascular disorders.
- Combination antihypertensive therapy.

5.2.6 ADVANTAGES

Advantages include:

- Long duration of action.
- Once-daily dosing.
- Excellent oral bioavailability.
- Better patient compliance.
- Reduction in cardiovascular complications.
- Suitable for sustained-release formulations.

5.2.7 LIMITATIONS

Possible limitations include:

- Hypokalemia.
- Electrolyte imbalance.
- Dizziness.
- Dehydration.
- Caution in renal impairment.

5.3 SCIENTIFIC RATIONALE FOR METOPROLOL–INDAPAMIDE COMBINATION

The combination of Metoprolol Tartrate and Indapamide Hemihydrate provides complementary antihypertensive mechanisms.

Metoprolol Tartrate	Indapamide Hemihydrate
β_1-blocker	Thiazide-like diuretic
Rapid onset	Prolonged action
Immediate BP reduction	Sustained BP control
Decreases cardiac output	Reduces plasma volume
Suppresses renin release	Vasodilation
IR layer	SR layer

6. FORMULATION DEVELOPMENT OF BILAYER TABLETS

6.1 INTRODUCTION

Formulation development is one of the most critical stages in the design of bilayer tablets because it determines the safety, efficacy, stability, and quality of the final dosage form. Unlike conventional tablets, bilayer tablets consist of two distinct layers compressed into a single unit. Each layer is formulated independently to achieve a specific drug release profile while ensuring adequate interlayer adhesion and mechanical strength.

In antihypertensive therapy, the bilayer tablet is designed so that the Immediate Release (IR) layer rapidly releases Metoprolol Tartrate to provide an immediate reduction in blood pressure, whereas the Sustained Release (SR) layer gradually releases Indapamide Hemihydrate over an extended period to maintain therapeutic plasma concentrations and prolonged antihypertensive activity.

6.2 OBJECTIVES OF FORMULATION DEVELOPMENT

The primary objectives are:

- To achieve rapid onset of action through the immediate-release layer.
- To maintain prolonged therapeutic drug concentration through the sustained-release layer.
- To improve patient compliance by reducing dosing frequency.
- To minimize dose-related adverse effects.
- To enhance drug stability.
- To ensure uniform drug distribution in both layers.
- To achieve acceptable tablet hardness and friability.
- To provide reproducible drug release.

6.3 PREFORMULATION STUDIES

Preformulation studies provide essential information regarding the physicochemical properties of active pharmaceutical ingredients before formulation development.

The major preformulation investigations include:

1. Organoleptic Properties

- Colour
- Odour
- Appearance
- Texture

These parameters help in the preliminary identification and quality assessment of the drug.

2. Solubility Studies

Drug solubility was evaluated in:

- Water
- Methanol
- Ethanol
- Phosphate buffer (pH 6.8)
- Hydrochloric acid (0.1 N)

Metoprolol Tartrate exhibited high aqueous solubility, whereas Indapamide Hemihydrate showed comparatively lower solubility, making it more suitable for sustained-release formulation.

3. Melting Point Determination

Melting point determination was performed to evaluate:

- Drug purity

- Identity
- Thermal stability

A sharp melting point indicates a pure compound.

4. Moisture Content

Moisture content influences:

- Flow properties
- Compression characteristics
- Drug stability

Excessive moisture may cause degradation or poor tablet compression.

5. Partition Coefficient

Determination of the partition coefficient helps predict:

- Drug permeability
- Lipophilicity
- Membrane transport

6. Drug–Excipient Compatibility

Drug compatibility with excipients is essential to avoid:

- Chemical degradation
- Colour change
- Reduced potency
- Stability problems

Compatibility was evaluated using:

- FTIR spectroscopy
- Differential Scanning Calorimetry (DSC)

The absence of significant spectral shifts or thermal changes indicated compatibility between the drugs and selected excipients.

6.4 SELECTION OF EXCIPIENTS

Appropriate excipients were selected based on their functional role in each layer.

Immediate Release Layer

Excipient	Function
Crospovidone	Superdisintegrant
Croscarmellose Sodium	Superdisintegrant
Microcrystalline Cellulose (MCC)	Diluent
Lactose	Filler
Magnesium Stearate	Lubricant
Talc	Glidant

The superdisintegrants promote rapid tablet disintegration, facilitating immediate drug release.

Sustained Release Layer

Polymer/Excipient	Function
HPMC K100M	Release-retarding polymer
HPMC K15M	Matrix former
Ethyl Cellulose	Hydrophobic polymer
MCC	Diluent
Talc	Glidant
Magnesium Stearate	Lubricant

Hydrophilic polymers form a gel barrier around the tablet upon hydration, thereby controlling the diffusion of the drug and ensuring sustained release.

6.5 SELECTION OF POLYMERS

Polymer selection is crucial because it directly influences drug release kinetics.

HPMC K100M

Advantages:

- High viscosity
- Excellent gel formation
- Controlled hydration
- Sustained drug release
- Good compressibility

HPMC K15M

Characteristics:

- Moderate viscosity
- Controlled swelling
- Uniform drug diffusion
- Improved matrix integrity

Ethyl Cellulose

Functions:

- Water-insoluble polymer
- Slows penetration of dissolution medium
- Extends drug release
- Improves matrix strength

6.6 FORMULATION DESIGN

The bilayer tablet consists of two optimized formulations.

Immediate Release Layer

Drug: Metoprolol Tartrate

Objectives:

- Rapid disintegration
- Fast dissolution
- Immediate antihypertensive action

Key excipients:

- Crospovidone
- MCC
- Lactose
- Talc
- Magnesium stearate

Sustained Release Layer

Drug: Indapamide Hemihydrate

Objectives:

- Controlled release
- Reduced plasma fluctuation
- Prolonged therapeutic activity

Key polymers:

- HPMC K100M
- HPMC K15M
- Ethyl Cellulose
- MCC

6.7 METHOD OF PREPARATION

The bilayer tablets were prepared using the Direct Compression Method, which is widely preferred because of its simplicity, cost-effectiveness, and suitability for moisture-sensitive drugs.

Manufacturing Steps

1. Drug weighing.

2. Sieving of ingredients.
3. Blending of IR layer powders.
4. Blending of SR layer powders.
5. Lubrication.
6. Compression of the sustained-release layer.
7. Addition of immediate-release blend.
8. Final compression to obtain bilayer tablets.

Direct compression minimizes processing steps while preserving the stability of heat- and moisture-sensitive drugs.

6.8 Challenges During Bilayer Tablet Manufacturing

Several manufacturing issues must be addressed:

- Layer separation (delamination)
- Cross-contamination
- Poor interlayer adhesion
- Weight variation
- Compression force optimization
- Layer misalignment
- Inadequate hardness
- Capping and lamination
- Poor content uniformity

These challenges require careful optimization of formulation variables and compression parameters.

6.9 OPTIMIZATION OF BILAYER TABLETS

Optimization involves selecting the best formulation by evaluating:

- Flow properties
- Compressibility
- Hardness
- Friability
- Weight variation
- Drug content
- Disintegration time
- Dissolution profile
- Stability

Several trial formulations (e.g., F1–F9) are commonly prepared with varying polymer concentrations to identify the formulation that provides the desired immediate and sustained release characteristics.

6.10 ADVANTAGES OF DIRECT COMPRESSION

The direct compression technique offers several benefits:

- Simple manufacturing process
- Lower production cost
- Fewer processing steps
- Reduced moisture exposure
- Reduced thermal degradation
- Improved content uniformity
- Better scalability

- Suitable for industrial production

CONCLUSION

Bilayer tablet technology has emerged as a promising and innovative approach for the effective management of hypertension by integrating immediate-release and sustained-release drug delivery within a single dosage form. This review highlights that hypertension is a multifactorial chronic cardiovascular disorder requiring long-term therapy, where conventional monotherapy often fails to achieve optimal blood pressure control. Combination therapy has therefore become the preferred treatment strategy due to its ability to target multiple physiological pathways simultaneously while improving therapeutic efficacy and patient adherence. Among the various antihypertensive drug combinations, the combination of Metoprolol Tartrate and Indapamide Hemihydrate offers significant therapeutic advantages because of their complementary mechanisms of action. Metoprolol Tartrate provides rapid blood pressure reduction through selective β_1-adrenergic receptor blockade, whereas Indapamide Hemihydrate ensures prolonged antihypertensive activity through sustained diuretic and vasodilatory effects. Incorporating these drugs into a bilayer tablet enables immediate onset of action followed by sustained therapeutic efficacy, thereby reducing dosing frequency, minimizing plasma concentration fluctuations, and enhancing patient compliance.The review also demonstrates that successful development of bilayer tablets depends on careful selection of polymers, excipients, and manufacturing techniques. Hydrophilic polymers such as HPMC K100M and HPMC K15M play a crucial role in regulating sustained drug release, while superdisintegrants facilitate rapid drug release from the immediate-release layer. Direct compression remains one of the most suitable manufacturing techniques due to its simplicity, cost-effectiveness, and suitability for large-scale production. Despite challenges such as layer separation, compression optimization, and stability concerns, continuous advancements in pharmaceutical formulation technology, polymer science, and quality-by-design (QbD) principles have significantly improved the performance and reliability of bilayer tablets. Future research should focus on optimizing formulation variables, applying advanced manufacturing technologies, and conducting comprehensive in vitro–in vivo correlation (IVIVC) studies and clinical evaluations to further enhance therapeutic outcomes. Overall, bilayer tablet technology represents an effective, patient-friendly, and scientifically sound drug delivery system for hypertension management. The combination of immediate-release Metoprolol Tartrate and sustained-release Indapamide Hemihydrate has considerable potential to improve blood pressure control, increase patient compliance, and reduce the risk of cardiovascular complications, making it a valuable approach for future antihypertensive therapy.

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