RESEARCH PAPER

Formulation and Evaluation of Bilayer Tablet of Atorvastain Calcium (Immediate Release) and Nifedipine (Sustained Release)

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ABSTRACT

Cardiovascular diseases remain a major cause of morbidity and mortality worldwide, with hypertension and dyslipidemia frequently occurring together and significantly increasing cardiovascular risk. Long-term management of these conditions often requires multiple medications, leading to increased pill burden and reduced patient compliance. The present study aimed to formulate and evaluate a bilayer tablet comprising an immediate-release (IR) layer of Atorvastatin Calcium and a sustained-release (SR) layer of Nifedipine to provide combined therapeutic benefits in a single dosage form.

Preformulation studies, including organoleptic evaluation, solubility studies, calibration curve preparation, and drug–excipient compatibility studies using FTIR and DSC, were performed. The immediate-release layer of Atorvastatin Calcium was formulated using suitable superdisintegrants to achieve rapid drug release, whereas the sustained-release layer of Nifedipine was developed using HPMC K100M as a release-retarding polymer to prolong drug release. Bilayer tablets were prepared by the direct compression technique and evaluated for pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio. Post-compression evaluation included hardness, thickness, weight variation, friability, drug content uniformity, and in vitro dissolution studies.

The prepared formulations exhibited satisfactory flow properties and acceptable physicochemical characteristics. The immediate-release layer demonstrated rapid drug release, while the sustained-release layer provided prolonged release of Nifedipine over the desired period. Drug release kinetics indicated diffusion-controlled release from the sustained-release matrix. The optimized formulation showed satisfactory tablet integrity and performance characteristics.

The study demonstrates that bilayer tablet technology can successfully combine immediate and sustained drug release profiles within a single dosage form. Such a formulation has the potential to improve patient compliance, reduce dosing frequency, and provide effective management of patients suffering from concurrent hypertension and dyslipidemia.

Keywords:, Hypertension, Dyslipidemia, Direct Compression ,Therapeutic adherence, FDC .

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INTRODUCTION

Cardiovascular Diseases

Cardiovascular diseases (CVDs) encompass a wide range of heart and blood vessel disorders and disease, including coronary artery disease, hypertension (high blood pressure), heart failure, cerebrovascular disease, peripheral arterial disease, and cardiomyopathies, among others. CVDs are the leading cause of death globally, accounting for nearly one third of all deaths, with the greatest burden on low- and middle-income countries. The growing incidence is the result of urbanization, population aging, sedentary lifestyles, unhealthy dietary patterns, tobacco use, obesity, and diabetes mellitus. In India, this burden is compounded by genetic susceptibility in South Asian populations and an increasing prevalence of hypertension and dyslipidemia even among younger adults.[11,13]

The pathogenesis of most CVDs centers on endothelial dysfunction and chronic vascular inflammation and are the primary drivers of atherosclerosis, which is the progressive deposition of lipids within arterial walls, leading to foam-cell formation, fibrous plaque, and plaque rupture with thrombosis. Cardiovascular risk factors are commonly divided into non-modifiable factors (age, gender, family history) and modifiable factors (hypertension, dyslipidemia, diabetes, smoking, obesity, physical inactivity, and stress). Management strategies combine lifestyle modification with pharmacotherapy, employing antihypertensive agents (calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, beta blockers, and diuretics), lipid-lowering agents (statins, fibrates, bile-acid sequestrants, and PCSK9 inhibitors), antiplatelet drugs, and anticoagulants. Because multiple risk factors typically coexist, combination therapy is clinically necessary. [12,13,8]

Traditional multi-drug regimens, however, require frequent daily dosing, which reduces patient adherence and compromises therapeutic outcomes. Advanced drug delivery systems capable of achieving controlled release, improved bioavailability, and reduced dosing frequency are therefore needed. Bilayer tablet technology allows two different drugs with various release requirements to be incorporated into a single dosage form. This technology has the potential to eliminate some of the limitations in cardiovascular therapy. [7,14,19,45]

Hypertension

Hypertension is defined as elevated systolic or diastolic blood pressure measured on two or more separate occasions. Hypertension is known as the "silent killer" because most individuals remain asymptomatic for long periods of time, while progressive organ damage occurs. The prevalence of hypertension continues to rise globally due to urbanization, increased consumption of refined and processed foods high in saturated fats, increased obesity, increased sedentary lifestyle, increased stress levels and anxiety, and an increased aged population. Blood pressure is classified according to Table 1. [11,14,15]

Table 1: Classification of Blood Pressure in Adults

Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
Normal	<120	<80
Elevated	120–129	<80
Stage 1 Hypertension	130–139	80–89
Stage 2 Hypertension	≥140	≥90
Hypertensive Crisis	≥180	≥120

Approximately 90–95% of cases are primary (essential) hypertension, arising from a combination of genetic predisposition, obesity, high sodium intake, sedentary lifestyle, and aging; the remainder is secondary to identifiable renal, endocrine, cardiovascular, or drug-induced causes. The pathophysiology is multifactorial, involving sympathetic nervous system overactivity, activation of the renin–angiotensin–aldosterone system (RAAS), endothelial dysfunction with reduced nitric oxide bioavailability, sodium and water retention, and vascular remodeling.[11,27,28,58]

Hypertension is frequently asymptomatic but, when uncontrolled, leads to coronary artery disease, myocardial infarction, heart failure, stroke, chronic kidney disease, and hypertensive retinopathy. Management combines lifestyle modification (dietary sodium restriction, weight reduction, exercise, smoking and alcohol cessation) with pharmacotherapy using calcium channel blockers such as Nifedipine and

Amlodipine, ACE inhibitors, ARBs, beta blockers, and diuretics. A major limitation of conventional antihypertensive therapy is the need for frequent dosing, which causes fluctuating plasma drug levels and poor adherence. Calcium channel blockers such as Nifedipine, owing to their short biological half-life of approximately 2–5 hours, are particularly well suited to sustained-release formulation, which can maintain stable plasma concentrations, reduce dosing frequency, and improve overall blood pressure control. [13,27,28]

Dyslipidemia

Dyslipidemia refers to elevated levels of low-density lipoproteins (LDL) or increased levels of very low-density lipoproteins (VLDL), triglycerides, or reduced levels of high-density lipoproteins (HDL). Lipoproteins are transported in the blood and filled with cholesterol, triglycerides, amino acids, vitamins, or other lipids. Dyslipidemia can be primary or secondary. Primary dyslipidemia can be familial or inherited. Examples of familial or inherited dyslipidemias include familial hypercholesterolemia. Secondary dyslipidemia can be caused by one or more other conditions such as obesity, diabetes mellitus, hypothyroidism, chronic kidney disease, alcohol use, tobacco use, drug use, or severe stress. The rise in urbanization in India has led to changes in diet and physical activity, resulting in elevated triglycerides and decreased HDL in the Indian population. [11,12]

The pathophysiological effects of dyslipidemia are mediated chiefly through atherosclerosis: oxidized LDL particles infiltrate the arterial wall, are engulfed by macrophages to form foam cells, and progressively generate fatty streaks and fibrous plaques that may eventually rupture and trigger thrombotic events. Statins, which inhibit HMG-CoA reductase, remain the first-line pharmacological treatment, supplemented where necessary by fibrates, bile-acid sequestrants, ezetimibe, or PCSK9 inhibitors. Because dyslipidemia frequently coexists with hypertension and both require lifelong therapy, fixed-dose combinations—such as a " bilayer tablet incorporating an immediate-release lipid-lowering drug together with a sustained-release antihypertensive agent—offer a rational strategy for improving compliance and reducing overall cardiovascular risk. [7,8,14,15]

Relationship Between Hypertension and Dyslipidemia

Hypertension and dyslipidemia are common, coexisting, and synergistic conditions that accelerate the development of cardiovascular disease, and share the common risk factors of obesity, sedentary lifestyle, unhealthy eating, diabetes, and a genetic predisposition. Their shared presence is particularly common among patients with metabolic syndrome. [11,12,13]

Both hypertension and dyslipidemia converge upon the same overlapping pathophysiological mechanisms of endothelial dysfunction, oxidative stress, chronic low-grade inflammation, and vascular remodeling that promote every phase of the atherosclerosis process from the injury of the endothelial layer and the infiltration of LDL to the formation of foam cells and the ultimate plaque rupture. [11-13]

Consequently, patients who have both hypertension and dyslipidemia have a substantially elevated risk for coronary artery disease, myocardial infarction, stroke, peripheral arterial disease, and heart failure, in comparison to patients who have only one of these risk factors. [11-13]

Because both hypertension and dyslipidemia share pathophysiology and almost always require concomitant and lifelong therapeutic management, their combined presence is clinically recommended and improves outcomes, reduces cardiovascular events, and improves quality of life. [11-13] Fixed-dose combination (FDC) therapy, which combines two active pharmaceutical ingredients in a single-dosage form, reduces pill burden and simplifies regimens, thereby improving adherence. [1,3,14,15] Bilayer tablet technology is ideally suited to this purpose, as it allows the physical separation of an immediate-release lipid-lowering layer from an antihypertensive layer, which sustains the release, within one tablet, thus combining rapid and prolonged pharmacological action, without drug-drug interaction between layers. [7-10,19,21,24,45-49]

Oral Drug Delivery Systems

Among numerous drug delivery routes, the oral route is the most preferred and extensively used route in drug administration. The oral route offers the advantages of convenience and safety to both the care giver and the patient. The oral route is also economical, cost-effective and has high patient acceptability. The majority of pharmaceutical products available for

both acute and chronic disease management are formulated using the oral dosage forms.[13,14,15,20,21,27,28,31,40] Oral routes of drug administration can be engineered to provide drug release that is either immediate, delayed, sustained, or controlled. Innovative advances in formulation" technologies have enhanced oral dosage forms and their drug release profiles and bioavailability. [1-3,7,8,9,21,29,43,45-48]

Modified-Release Drug Delivery Systems

Modified-release drug delivery systems are designed to change the rate or site of drug release relative to a conventional, immediate-release " dosage form, and are broadly classified into delayed-release, extended-release, sustained-release, controlled-release, and pulsatile-release systems. Drug release from these systems may be governed by diffusion through a polymer matrix or membrane, dissolution of the matrix or coating, polymer erosion, polymer swelling, or osmotic pressure. Matrix systems, in which the drug is uniformly dispersed within a hydrophilic polymer such as HPMC or Carbopol, or a hydrophobic polymer such as ethyl cellulose, are the most widely used owing to their simple manufacture, cost-effectiveness, and reproducible release behaviour. Drug release from such systems is influenced by drug- and polymer-related properties (solubility, dose, polymer concentration and molecular weight), formulation factors (compression force, tablet hardness, porosity), and physiological variables (gastrointestinal pH, transit time). [1,10,14,24]

Oral drug delivery systems will be of great value for cardiovascular therapy. Lifelong therapy with agents such as Nifedipine is frequently employed and requires stable, controlled drug release and plasma drug concentrations. [11,13,15] The principles underlying this design of bilayer tablets has an immediate release layer that provides rapid action of the drug while a layer of sustained release, based on a hydrophilic matrix-forming polymer, provides extended therapeutic action, thereby allowing both rapid and prolonged therapeutic effects to be achieved from a single unit dosage form. [7,8,9,19]

Immediate-Release Drug Delivery Systems

Immediate-release (IR) systems are conventional dosage forms designed to release the active pharmaceutical ingredient rapidly, without intentional delay, achieving quick disintegration, dissolution, and onset of therapeutic action. [1,2,3,15,21,31,43] The majority of commercial tablets and capsules are IR formulations, and they remain widely used for drugs requiring a prompt pharmacological response, such as lipid-lowering agents intended to achieve rapid reduction in plasma cholesterol. [11,12,15,34] Rapid drug release in IR systems is generally achieved through the use of superdisintegrants, which promote fast tablet disintegration and consequent dissolution and absorption of the drug. [4,15,21,39,56]

Sustained-Release Drug Delivery Systems

Sustained-release (SR) systems release a drug slowly over an extended period to maintain effective plasma concentrations, minimize dosing frequency, and reduce fluctuations associated with peak and trough drug levels. [1,14,20,27,28] They are especially valuable for short biological half-life drugs with narrow therapeutic windows, such as Nifedipine, where conventional immediate-release dosing would require frequent administration. [11,13,14] SR formulations are typically achieved using hydrophilic matrix-forming polymers such as HPMC, which swell on contact with aqueous fluids to form a gel layer that controls drug diffusion, or hydrophobic polymers and waxes that retard release through erosion. [4,9,10,24,25,26,56] The principal benefits of sustained-release delivery are improved patient compliance, stable plasma drug concentrations, reduced adverse effects, and enhanced therapeutic efficacy in chronic disease management. [1,15,20,27,28]

Bilayer Tablets

The use of bilayer tablet technology enables the creation of compressed, two-part dosage forms. Consisting of two physical, and therefore also non-compatible, separable layers, each can be used to contain a different drug or release profile, or different excipients. This design allows the formation of a single bilayer tablet wherein two incompatible but therapeutically effective pharmacological substances can be contained. The most commonly encountered arrangement is the combination of immediate release and sustained release layers. [7,8,21,29,45,46] Other types of bilayer tablets include floating bilayer tablets, which have been designed to have increased gastric residence time, and barrier-layer tablets, which have been used to enable chronotherapeutic or pulsatile controlled delivery. [18,20,27,28,32] Each of the

layers is prepared with diluents (microcrystalline cellulose, lactose), binders (PVP K30), lubricants (magnesium stearate), glidants (talc), and, in the sustained release layer, release modifying polymers such as HPMC or Carbopol. [4,10,21,29,43,56]

Bilayer tablets offer several pharmaceutical and therapeutic advantages, including separation of incompatible drugs, flexible formulation design, distinct release profiles within a single unit, reduced pill burden, and improved patient compliance, particularly valuable in chronic cardiovascular therapy.[7,8,14,15,21,45] However, their manufacture is more complex than that of conventional tablets, requiring careful control of layer weight, compression force, and dwell time to ensure adequate interfacial adhesion and to avoid layer separation, delamination, or cross-contamination between layers.[1,2,14,21,29,43] Tablets are most commonly prepared by direct compression, a simple, economical, and scalable technique particularly suitable for moisture-sensitive drugs, in which the first layer is compressed lightly before the second layer is added and the tablet is finally compressed.[1,2,14,21,22,31]

Evaluation of bilayer tablets encompasses standard pre-compression powder characterization (angle of repose, bulk and tapped density, Carr's index, Hausner ratio) and post-compression tests (appearance, thickness, hardness, friability, weight variation, and drug content uniformity), together with bilayer-specific tests for layer separation, delamination, and interfacial adhesion strength.[7,8,19,45,47,48] In vitro dissolution testing is essential to confirm that the immediate-release layer releases drug rapidly while the sustained-release layer provides the intended prolonged release, and stability studies under ICH-recommended accelerated conditions confirm that the optimized formulation retains its physicochemical integrity over time.[16,17,23,24,35,36,37,38,39,50,51,52] Given the limited published literature on bilayer tablets combining an immediate-release statin with a sustained-release calcium channel blocker, the development of such a formulation represents a relevant and underexplored area of pharmaceutical research with direct clinical applicability to combined hypertension–dyslipidemia management.[7,8,12,13,14,45]

REVIEW OF LITERATURE

Sharma et al. (2024) developed immediate-release Atorvastatin Calcium tablets by direct compression utilizing various disintegrants. The optimized formulation showed rapid disintegration along with high drug content uniformity, and more than 85% drug release within 30 minutes, with crospovidone-based formulations being the best in terms of dissolution performance.

Patel and Shah (2024) formulated bilayer tablets containing immediate- and sustained-release layers and reported satisfactory hardness, friability, and interfacial bonding between layers. Dissolution studies confirmed release characteristics typical of each layer, supporting the suitability of bilayer technology for combination therapy.

Kumar et al. (2023) investigated the effect of different HPMC grades on sustained-release matrix tablets and found that HPMC K100M produced the most prolonged release, maintaining drug release for up to 12 hours following the Highchair diffusion kinetics.

Verma et al. (2023) developed sustained-release tablets using Carbopol and HPMC, obtaining excellent matrix integrity and controlled release over 12 hours, with polymer concentration shown to significantly influence release kinetics.

Kumar et al. (2023) investigated the effect of different levels of HPMC along with SCGR on the formulation of sustained release tablets, and studied the effect of these levels on drug release.

Singh et al. (2023) explored through various experimental formulations prepared by direct compression, the influence of various disintegrants on immediate release tablets, and studied the effect of these disintegrants on immediate drug release.

Kumar et al. (2023) evaluated the possibilities of using various superdisintegrants in the formulation of immediate release tablets, and studied the effect of these superdisintegrants on disintegration time and dissolution of the tablets.

Ahmed et al. (2022) investigated the use of some superdisintegrants and their blends in the preparation of immediate release tablets, and investigated the release behavior of the drugs

Reddy et al. (2022) studied the optimisation of immediate-release tablets using direct compression methods. Results indicated that with increasing

concentration of crospovidone, both disintegration and dissolution rates were improved.

Chaudhary et al. (2022) investigated the impact of the viscosity of polymers on the behavior of the polymer on the sustained release. It was observed that the use of high viscosity HPMC grades formed a stronger gel layer and therefore had slower drug release.

Patel et al. (2022) demonstrated the use of a Box-Behnken design to optimise the formulation of tablets and for the improvement of the sustained release of the formulation. The results of the Statistical Design tools showed that the Box-Behnken design identified critical formulation variables for the improvement of the quality of the product.

Gupta et al. (2021) compared hydrophilic and hydrophobic matrix systems. Results indicated that hydrophilic polymers provided swelling-controlled release and hydrophobic polymers controlled release predominantly through diffusion.

Mehta et al. (2021) optimized Nifedipine sustained-release tablets using response surface methodology. This resulted in a formulation with an appropriate dissolution behavior in addition to excellent tablet characteristics.

Rao et al. (2021) formulated Atorvastatin Calcium tablets by direct compression. Results indicated that excellent content uniformity, hardness, and rapid drug release were achieved.

Overall, the mentioned studies show how crospovidone is one of the best superdisintegrants for rapid drug release of Atorvastatin calcium. They also show how HPMC-based hydrophilic matrices can provide satisfactory in vitro drug release of Nifedipine up to 12 hours via diffusion/swelling mechanisms. The studies also show that statistically designed optimization techniques, such as Box–Behnken and response-surface methodology, can be successfully employed in bilayer tablet development Atorvastatin Calcium with sustained-release Nifedipine, underscoring the novelty and relevance of the present work.

NEED OF THE PRESENT WORK

Hypertension and dyslipidemia are leading modifiable risk factors associated with cardiovascular morbidity and mortality and often coexist, necessitating long-term concurrent pharmacotherapy. Medicating patients separately with antihypertensive and lipid-lowering medications leads to increased pill burden. The pill burden is a strong predictor of patient compliance and therapeutic effectiveness. Because of its short biological half-life, which is approximately 2 to 5 hours, Nifedipine would require conventional formulations to be frequently dosed, whereas Atorvastatin Calcium would require rapid drug availability to achieve its lipid-lowering action. These drug release profile requirements are well suited to a bilayer tablet in which an immediate release layer of Atorvastatin Calcium is combined with a sustaintestercase of Nifedipine within a single dosage form, without interaction between layers.

The resulting fixed-dose bilayer formulation decreases pill burden, simplifies dosing, and improves patient compliance. This is particularly true for the elderly and chronically medicated cardiovascular patients. Additionally, the sustained release of Nifedipine within a bilayer tablet minimizes fluctuations in plasma concentration of the drug, and therefore, improves the control of blood pressure. The manufacturing method direct compression is a simple, economical, and easily scalable process. Very limited precedent exists in published literature for the bilayer tablet combination of a sustained release of Nifedipine and an immediate release of Atorvastatin Calcium, for which undertaking this research was justified. The explicit objective of this research was to formulate and validate a bilayer tablet containing an immediate release of Atorvastatin Calcium and a sustained release of Nifedipine for the improved management of hypertensive dyslipidemic patients.

AIM AND OBJECTIVE

Aim :

To formulate and assess a bilayer fixed-dose combination tablet comprising an immediate-release layer of Atorvastatin Calcium and a layer of Nifedipine, with the goal to improve patient compliance, decrease dosing frequency, and improve the therapeutic effects of the medication.

Objectives

- To develop a fixed-dose combination with immediate release and sustained release.
- To evaluate the compatibility of the drug and excipients in the formulation.
- To determine the pre-compression of the powder blends of both layers.
- To prepare bilayer tablets via direct compression.
- To evaluate the bilayer tablets

prepared in this study for physical and chemical parameters such as hardness, thickness, weight variation, friability, drug content uniformity, and layer integrity.

- To establish the in vitro release profile of Atorvastatin Calcium and Nifedipine from the respective layers.
- To adjust the variables of the formulation to achieve the desired immediate- and sustained-release characteristics.
- To determine the release kinetics of the drug from the optimized formulation, and to identify the release mechanism.
- To compare the different formulations and to identify the optimized batch.
- To perform accelerated stability studies on the optimized formulation in accordance with ICH guidelines.

PLAN OF WORK

- **Literature Survey:** An extensive review of published literature was conducted on bilayer tablet technology, immediate- and sustained-release drug delivery systems, and the model drugs Atorvastatin Calcium and Nifedipine.
- **Procurement of Materials:** Required drugs and pharmaceutical excipients was procured from authentic and pharmacopoeial sources.
- **Selection of Excipients:** Suitable superdisintegrants, release-retarding polymers, diluents, lubricants, and glidants was selected based on formulation requirements.
- **Formulation of the Immediate-Release Layer:** The Atorvastatin Calcium layer was formulated with appropriate superdisintegrants to achieve rapid drug release.
- **Formulation of the Sustained-Release Layer:** The Nifedipine layer was formulated using suitable hydrophilic matrix-forming polymers to achieve sustained drug release.
- **Evaluation of Pre-Compression Parameters:** Powder blends was evaluated for angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio.
- **Preparation of Bilayer Tablets:** Bilayer tablets was prepared by sequential direct compression of the two layers.
- **Evaluation of Bilayer Tablets:** Tablets was evaluated for thickness, weight variation, hardness, friability, and drug content uniformity.
- **Assessment of Tablet Integrity:** Tablets was examined for physical appearance, layer uniformity, and adhesion between layers.
- **In Vitro Dissolution and Release Kinetics:** Dissolution studies was performed for both layers, and release data was fitted to kinetic models to elucidate the release mechanism.
- **Selection of the Optimized Formulation:** The optimal batch was selected based on overall evaluation results and tablet performance.
- **Data Analysis, Discussion, and Conclusion:** Data obtained from experiments was compiled, quantitatively analyzed, and interpreted to provide conclusions relating to quality and performance of the developed bilayer tablet

MATERIAL AND EQUIPMENT

This chapter states the ingredients used for the formulation of bilayer tablet including polymers and excipients, and the reagents, analytical instruments and processing instruments required for the evaluation of bilayer tablet. The details of the ingredients (pharmaceutical grade) for the formulation are to be specified. The brand name, grade designation and lot no. are to be supplied by the suppliers of choice and Adjusted to best meet established formulation requirements. Required brand/grade and lot details should be provided by the suppliers selected and Adjusted for best effect to meet the specifications of the formulation requirements.

List of Drugs (Active Pharmaceutical Ingredients)

S. No.	Material	Grade/Specification	Supplier (representative)	Use in Formulation

1	Atorvastatin Calcium	IP/USP grade,	Dhamtec Pharma and Consultants (B-204, Silver Springs, Opposite MIDC Office, Taloja MIDC, Navi Mumbai (Panvel), Maharashtra 410208, India.) Dhamtec Pharma and Consultants	Active ingredient — immediate release layer
2	Nifedipine	IP/USP grade		Active ingredient — sustained release layer

Table 2: Active pharmaceutical ingredients" used in the formulation.

List of Polymers and Excipients

S. No.	Material	Category/ Function	Grade	Representative Supplier
	HPMC K100M	Rate-controlling hydrophilic polymer (SR layer)	Pharma grade	Blue Cross Laboratories (Nashik) MIDC Ambad
	Microcrystalline Cellulose (MCC, Avicel PH-102)	Diluent/binder (both layers)	Pharma grade	Modern Industries, Nashik
	Crospovidone	Superdisintegrant (IR layer)	Pharma grade	
	Polyvinylpyrrolidone (PVP K30)	Binder (granulation, both layers)	Pharma grade	
	Lactose Monohydrate	Diluent/filler (IR layer)	Pharma grade, DC/spray-dried	
	Talc	Glidant	Pharma grade, IP/USP	
	Magnesium Stearate	Lubricant	Pharma grade, IP/USP,	
	Sodium Starch Glycolate	Superdisintegrant (alternate, IR layer)	Pharma grade	
	Ethyl Cellulose	Retardant polymer (optional, SR layer)	Pharma grade	
	Isopropyl Alcohol / Ethanol	Granulating solvent	-	

Table 3: Polymers and excipients used in the " immediate-release and sustained-release layers

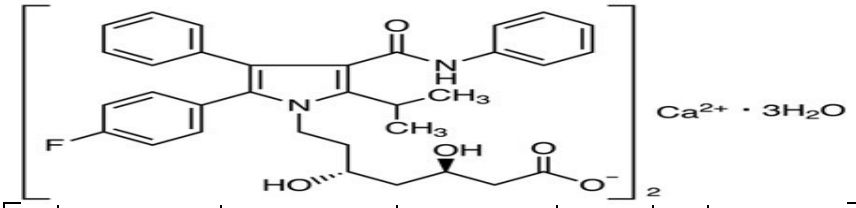
List of Chemicals and Reagents

S.No.	Chemical/Reagent	Grade	Purpose
1	Potassium Dihydrogen Phosphate	AR/Analytical grade	Preparation of phosphate buffer (dissolution/solubility studies)
2	Sodium Hydroxide	AR grade	pH adjustment of buffers
3	Hydrochloric Acid	AR grade	Preparation of 0.1 N HCl dissolution medium (SR layer, acid stage)
4	Methanol	HPLC/Analytical grade	Mobile phase / drug solubilization for analysis
5	Acetonitrile	HPLC grade	Mobile phase for HPLC analysis, if employed
6	Potassium Bromide (KBr)	IR grade	FTIR sample pellet preparation
7	Distilled/Deionized Water	Laboratory grade	Solvent for buffers and dissolution media

Table 4: Chemicals and reagents required for analytical and dissolution studies.

List of Equipment and Instruments

S.No.	Equipment	Specification /Model Type	Use
	Electronic Analytical Balance	Shimazdu TW423L	Weighing of drugs and excipients
	UV-Visible Spectrophotometer	LABINDIA ANALYTICAL UV3200	Calibration curve, drug content, dissolution sample analysis
	FTIR Spectrophotometer	Shimadzu (IRAffinity-1S)	Drug-excipient compatibility study
	Differential Scanning Calorimeter (DSC)	-	Thermal compatibility and melting behaviour study
	Rapid Mixer Granulator / Mortar-Pestle Setup	Lab-scale	Wet granulation of IR and SR blends
	Hot Air Oven / Tray Dryer	Bio Technics, India (BTTI-10)	Drying of granules
	Sieve Shaker with Standard Sieves	#10, #22, #44, #60, #85	Granule size distribution and sizing
	Bilayer Tablet Compression Machine	-	Compression of bilayer tablets



	Tablet Hardness Tester	Monsanto/Pfizer	Hardness/crushing strength determination
	Friabilator	Roche friabilator,	Friability testing
	Vernier Caliper / Digital Thickness Gauge	Least count 0.01 mm	Tablet thickness and diameter measurement
	Disintegration Test Apparatus	Electronic India (1508519)	Disintegration time determination (IR layer)
	Dissolution Test Apparatus	Electro Lab (ED T-08LX)	In-vitro drug release study
	Digital pH Meter	ANALAB Scientific Instruments Pvt.L	pH determination of solutions/media
	Bulk Density Apparatus	Tap density tester	Bulk and tapped density, Carr's index
	Stability Chamber	-	Accelerated and long-term stability studies

Table 5: Equipment and instruments used in formulation development and evaluation.

DRUG AND EXCIPIENT PROFILE

Drug Profile: Atorvastatin Calcium

General Description

Parameter	Description
Chemical Name	[R-(R,*R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate
Molecular Formula	(C33H34FN2O5)2Ca · 3H2O
Molecular Weight	Approximately 1209.4 g/mol (calcium salt trihydrate)
Category	HMG-CoA reductase inhibitor (statin); antihyperlipidemic agent
Description	White to off-white crystalline powder
Solubility	Practically insoluble in aqueous solutions of pH 4 and below; very slightly soluble in distilled water, pH 7.4 phosphate buffer; slightly soluble in methanol; freely soluble in basic media — exhibits pH-dependent solubility typical of BCS Class II drugs
Melting Point	Approximately 159–161°C (decomposes)
pKa	Approximately 4.3 (carboxylic acid group)
BCS Class	Class II (low solubility, high permeability)

Storage Condition	Store in a tight, light-resistant container at room temperature (15–30°C), protected from moisture

Table 6: Physicochemical characteristics of Atorvastatin Calcium.

Mechanism of Action

Atorvastatin competitively and selectively inhibits HMG-CoA reductase, which is the rate-limiting enzyme that catalyzes the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, an intermediary of the isoprenoid and isoprenoid-derived phosphopropanosine (PPI) and proteins, intracellular cholesterol biosynthesis, and hepatic LDL uptake and catabolism. By inhibiting this enzyme, atorvastatin reduces intracellular cholesterol concentration and upregulates LDL receptors on hepatocytes. This enhances the hepatic uptake and catabolism of circulating LDL particles, leading to a net reduction in plasma LDL-cholesterol, total cholesterol, apolipoprotein B, and triglyceride levels, while causing a modest increase in the level of HDL cholesterol. [11,12,15]

Pharmacokinetics

Parameter	Value/Description
Absorption	Rapidly absorbed after oral administration; absolute bioavailability is low (~14%) due to extensive presystemic clearance in the gut wall and first-pass hepatic metabolism
Tmax	Approximately 1–2 hours
Protein Binding	≥98%
Volume of Distribution	Approximately 381 L
Metabolism	Extensively metabolized by cytochrome P450 3A4 to active ortho- and para-hydroxylated metabolites
Elimination Half-life	Approximately 14 hours (parent drug); HMG-CoA reductase inhibitory activity persists up to 20–30 hours due to active metabolites
Excretion	Predominantly biliary/faecal; minimal renal excretion (<2%)

Table 7*:* Pharmacokinetic parameters of Atorvastatin.

The rapid Tmax indicates a prompt onset of inhibitory action and supports the formulation of atorvastatin as the immediate-release layer of the bilayer tablet. The immediate disintegration and dissolution of the bilayer tablet allows for rapid plasma levels of atorvastatin to achieve the intended therapeutic effect consistent with established dosing.

Indications, Dose, and Adverse Effects

Parameter	Description
Indications	Primary hypercholesterolemia, mixed dyslipidemia, hypertriglyceridemia, primary dysbetalipoproteinemia, homozygous/heterozygous familial hypercholesterolemia, and primary prevention of cardiovascular disease in at-risk patients
Usual Adult Dose	10–80 mg once daily, administered orally, with or without food
Common Adverse Effects	Myalgia, arthralgia, nasopharyngitis, diarrhea, headache, and elevated liver transaminases
Serious Adverse Effects	Rhabdomyolysis (rare), hepatotoxicity, and immune-mediated necrotizing myopathy (rare)
Contraindications	Active liver disease, pregnancy and lactation, hypersensitivity to the drug

Table 8*:* Clinical profile of Atorvastatin.

Drug Profile: Nifedipine

General Description

Parameter	Description
Chemical Name	Dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate
Molecular Formula	C17H18N2O6
Molecular Weight	Approximately 346.3 g/mol

Category	Dihydropyridine calcium channel blocker; antihypertensive/antianginal agent
Description	Yellow crystalline powder; photosensitive (degrades on exposure to light, requiring light-protected handling and packaging)
Solubility	Practically insoluble in water; freely soluble in acetone, ethanol, and other organic solvents; solubility is pH-independent across the physiological range
Melting Point	Approximately 171–175°C
BCS Class	Class II (low solubility, high permeability)
Storage Condition	Store protected from light, in a well-closed, light-resistant container, at room temperature

Table 9: Physicochemical characteristics of Nifedipine.

Mechanism of Action

Nifedipine selectively inhibits the influx of calcium ions through voltage-gated L-type calcium channels in vascular smooth muscle cells and, to a lesser extent, cardiac muscle cells. Decreased intracellular calcium concentration leads to relaxation" of smooth muscle and a reduction in peripheral vascular resistance. Decreased arterial blood pressure is the result of decreased peripheral vascular resistance. Because nifedipine has little direct effect on sinoatrial and atrioventricular nodal functions when compared to the " non-dihydropyridine calcium channel blockers, reflex sympathetic activation (mild tachycardia) may occur following an acute dose, especially immediate-release formulations of nifedipine, as these are particularly prone to this occurrence. A sustained-release delivery, on the other hand, will substantially diminish this fluctuation by providing more stable plasma concentrations over time and smoother concentration-time profiles. [11,13,14,15]

Pharmacokinetics

Parameter	Value/Description
Absorption	Almost completely absorbed after oral administration; subject to extensive first-pass hepatic metabolism, giving an absolute bioavailability of approximately 45–56%
Tmax	Conventional release: 0.5–1 hour; sustained-release formulations: 6–12 hours, providing prolonged plasma concentration
Protein Binding	Approximately 92–98%
Metabolism	Extensively metabolized by cytochrome P450 3A4 to inactive metabolites
Elimination Half-life	Approximately 2–5 hours (conventional release); apparent half-life is extended functionally by sustained-release delivery
Excretion	Primarily renal, as inactive metabolites (<1% unchanged drug); small fraction in faeces

Table 10: Pharmacokinetic parameters of Nifedipine.

The short duration elimination half-life of nifedipine results in more frequent dosing with conventional immediate-release formulations. These conventional formulations are associated with abrupt, peak, plasma concentrations that are followed by pronounced, drops in plasma concentrations, profound fluctuations in plasma concentrations, and abrupt changes in concentration-time profiles. Formulating nifedipine as the sustained-release layer, using a rate-controlling hydrophilic matrix polymer, is therefore intended to provide a controlled, prolonged release profile, minimizing fluctuation in plasma concentration and supporting once-or twice-daily dosing consistent with extended-release nifedipine products.

Indications, Dose, and Adverse Effect

Parameter	Description
Indications	Hypertension, chronic stable angina pectoris, vasospastic (Prinzmetal's) angina
Usual Adult Dose	30–90 mg once daily (extended/sustained-release formulations); conventional immediate-release dosing is generally not recommended for chronic hypertension

	management due to haemodynamic fluctuation
Common Adverse Effects	Peripheral edema, headache, flushing, dizziness, palpitations
Serious Adverse Effects	Hypotension, reflex tachycardia (with immediate-release forms), rarely myocardial infarction in unstable angina if not appropriately titrated
Contraindications	Cardiogenic shock, severe aortic stenosis, hypersensitivity to dihydropyridines

Table 11: Clinical profile of Nifedipine.

Rationale for Bilayer Combination

The combination of atorvastatin (immediate release) and nifedipine (sustained release), in a single bilayer tablet, is justified because hypertension and dyslipidemia usually occur concurrently as elements of the metabolic and cardiovascular risk profile. The combination of statin therapy with a calcium channel blocker is a recognized clinical strategy to optimally manage cardiovascular risk. The bilayer format provides the required level of control for each drug — rapid disintegration and dissolution of atorvastatin for consistent once daily absence, and a controlled hydrophilic matrix for nifedipine to avoid the haemodynamic disadvantages of immediate release dosing — while physically segregating the two layers to prevent any potential drug-drug interation at the formulation level, and to allow independent manufacturing control of the layers.

Excipient Profiles

Property	Description
Category	Rate-controlling hydrophilic matrix polymer; also used as a binder, film-former, and viscosity-modifying agent
Description	White to off-white, fibrous or granular powder
Viscosity Grade	K100M denotes a nominal 2% aqueous solution viscosity of approximately 100,000 cP, indicating a high-viscosity grade suited to sustained-release matrix systems
Solubility	Soluble in cold water (forms a colloidal, viscous solution); insoluble in hot water and most organic solvents
Mechanism in SR Layer	On contact with aqueous dissolution medium, HPMC K100M hydrates and swells to form a gel layer at the tablet surface, which progressively controls drug diffusion outward and erosion of the gel front, thereby sustaining nifedipine release over an extended period
Typical Use Level	10–60% w/w of the matrix tablet, depending on desired release duration
Storage	Store in a well-closed container away from moisture, as the polymer is hygroscopic

Table 12: Functional profile of HPMC K100M.

Microcrystalline Cellulose (MCC, Avicel PH-102)

Property	Description
Category	Diluent, binder, and disintegrant aid (multifunctional direct-compression excipient)
Description	Purified, partially depolymerized cellulose; white, odourless, free-flowing crystalline powder
Function	Provides good compressibility and flow properties, acting as a filler/binder that imparts mechanical strength to both IR and SR layers without adversely

	affecting disintegration in the IR layer
Typical Use Level	5–80% w/w depending on formulation requirement

Table 13: Functional profile of Microcrystalline Cellulose.

Crospovidone

Property	Description
Category	Superdisintegrant
Description	Cross-linked homopolymer of N-vinyl-2-pyrrolidone; white, free-flowing powder
Mechanism	Rapidly absorbs water and swells with minimal gel formation, generating a rapid disintegrating/wicking action through capillary activity, leading to fast breakup of the IR tablet layer and prompt drug release
Typical Use Level	2–5% w/w in the IR layer

Table 14: Functional profile of Crospovidone.

Polyvinylpyrrolidone (PVP K30)

Property	Description
Category	Binder
Description	White to off-white, hygroscopic powder; freely soluble in water and alcohol
Function	Used as a granulating binder in wet granulation of both the IR and SR layers, imparting cohesiveness to the powder blend and improving tablet hardness without unduly hindering disintegration (IR layer) or matrix integrity (SR layer)
Typical Use Level	2–5% w/w as a granulating solution (typically 5–10% w/v in isopropyl alcohol or hydroalcoholic solvent)

Table 15: Functional profile of PVP K30.

Lactose Monohydrate

Property	Description
Category	Diluent/filler
Description	White, crystalline powder; a water-soluble sugar widely used as a direct-compression or wet-granulation diluent
Function	Provides bulk to the IR layer formulation, with good compressibility and an established safety and compatibility profile with most APIs
Typical Use Level	Quantity sufficient (q.s.) to achieve target tablet weight

Table 16: Functional profile of Lactose Monohydrate.

Talc

Property	Description
Category	Glidant
Description	Fine, white to greyish-white crystalline powder, hydrated magnesium silicate
Function	Improves the flow properties of the powder/granule blend prior to compression by reducing interparticulate friction, thereby promoting uniform die fill and weight uniformity
Typical Use Level	1–5% w/w

Table 17*:* Functional profile of Talc.

Magnesium Stearate

Property	Description
Category	Lubricant

Description	Fine, white, light powder, low bulk density; insoluble in water and alcohol
Function	Reduces friction between the granule/powder bed and the die wall/punch faces during compression, preventing sticking and capping and facilitating tablet ejection
Typical Use Level	0.25–1% w/w (used sparingly, as excess can retard disintegration and dissolution, particularly relevant to the IR layer)

Table 18: Functional profile of Magnesium Stearate.

EXPERIMENTAL METHODOLOGY

This chapter describes the complete experimental methods to be performed for preformulation characterization, drug – excipient compatibility assessment, development of the immediate-release (IR) atorvastatin layer and sustained-release (SR) nifedipine layer, the bilayer compression process, and the analytical and evaluation methods to be employed on the resulting tablets. All procedures are designed to be directly executed in the laboratory, involving actual numerical results. All of these procedures, results, and discussions will be documented and narrated in Chapter 9 (Results and Discussion). Following the experimental completion of the described procedures.

Sr. No.	Ingredients	Quantity (mg/Tablet)	Function
1	Atorvastatin Calcium	10.00	Active pharmaceutical ingredient
2	Sodium Bicarbonate	50.00	Alkalizing agent/Stabilizer
3	Microcrystalline Cellulose (MCC)	45.00	Diluent
4	Lactose Monohydrate	40.00	Diluent
5	Croscarmellose Sodium	15.00	Superdisintegrant
6	Hydroxypropyl Methylcellulose (HPMC)	4.00	Binder
7	Colloidal Silicon Dioxide	3.00	Glidant
8	Magnesium Stearate	2.00	Lubricant
Total Weight		**169.00**	

Table 19: Composition of Immediate Release Nifedipine Layer

Sr. No.	Ingredients	Quantity (mg/Tablet)	Function
1	Nifedipine	20.00	Active pharmaceutical ingredient
2	HPMC K100M	40.00	Release-retarding polymer
3	Lactose Monohydrate	30.00	Diluent
4	Microcrystalline Cellulose (MCC)	25.00	Diluent
5	Magnesium Stearate	2.50	Lubricant

6	Talc	5.00	Glidant
Total Weight		**122.50**	

Table 20: Composition of Sustained Release Nifedipine Layer

Layer	Weight (mg)
Immediate Release Atorvastatin Layer	169.00
Sustained Release Nifedipine Layer	122.50
Total Tablet Weight	**291.50**

Table 21: Final Composition of Bilayer Tablet

The bilayer tablet was designed to give an immediate release of atorvastatin calcium, and a sustained release of nifedipine, all in one dosage form. The immediate release layer consisted of atorvastatin calcium, sodium bicarbonate, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, HPMC, colloidal silicon dioxide, and magnesium stearate. Sodium bicarbonate was added as an alkalizing agent to increase the stability of atorvastatin, while croscarmellose sodium provided rapid tablet disintegration.

The sustained release layer contained nifedipine, HPMC K100M, lactose monohydrate, microcrystalline cellulose, talc, and magnesium stearate. HPMC K100M was used as the release-retarding polymer" to achieve a prolonged release of the drug. The individual layers were compressed sequentially to obtain a bilayer tablet with a total weight of approximately 300 mg, ensuring the immediate antihyperlipidemic action of atorvastatin, and the sustained antihypertensive action of nifedipine.

Preformulation Studies

Preformulation studies provide fundamental physicochemical data about Atorvastatin Calcium and Nifedipine that will inform formulation strategies including solvent choice, compatibility with selected excipients, and development of analytical methods.

Organoleptic Properties

The colour, odour, and physical appearance (crystalline/amorphous powder form) of both APIs are to be recorded by direct visual and olfactory examination against pharmacopoeial descriptions (IP/USP/BP monographs), using a sample of the drug spread on white glazed tile under adequate lighting.

Melting Point Determination

The melting point of each drug is determined by the capillary fusion method. A small quantity of the drug is finely powdered and packed into one end of a thin-walled capillary tube (sealed at the other end). The capillary is attached to a thermometer and immersed in a melting point apparatus (paraffin bath or digital melting point apparatus), and the bath " temperature is raised slowly (1–2°C/min near the expected melting range). [1,2,15,43,58] The temperature at which the sample begins to liquefy and the temperature at which liquefaction is complete are both recorded, and the determination is performed in triplicate.[5,6,55,58] The observed range is compared against the pharmacopoeial reference values (Atorvastatin: ~159–161°C; Nifedipine: ~171–175°C) as a preliminary identity and purity check. [5,6,11-13,59,60]

Solubility Study

The solubility of each drug is determined by the equilibrium shake-flask method in a range of solvents relevant to formulation and dissolution testing, namely distilled water, 0.1 N HCl, pH4.5 acetate buffer, pH 6.8 phosphate buffer, and methanol/ethanol.[1,2,5,6,57,58] An excess quantity of drug is added to a fixed volume (e.g., 10 mL) of each solvent in a screw-capped vial, and the mixture is agitated on a mechanical/orbital shaker at 25 ± 1°C (or 37 ± 0.5°C, as applicable) for 24–48 hours to attain equilibrium. [1,2,57,58] The saturated solution is then filtered through a 0.45 µm membrane filter, suitably diluted, and the drug concentration is quantified spectrophotometrically (or by HPLC) using the previously constructed calibration curve.[5,6,15,55] The procedure is performed in triplicate (n = 3) for each solvent, and solubility is expressed as mg/mL with the appropriate descriptive solubility category assigned as per pharmacopoeial solubility criteria. [5,6,59,60]

Calibration Curve Procedure

Standard stock solutions of Atorvastatin Calcium and Nifedipine are prepared separately by accurately weighing a known quantity of each drug (e.g., 10 mg) and dissolving in a suitable solvent (methanol, or pH 6.8 phosphate buffer for Atorvastatin; methanol for the photosensitive Nifedipine, prepared and handled under subdued/amber light) in a volumetric flask to obtain a stock solution of known concentration (e.g., 100 µg/mL). [5,6,11,15,55] Serial dilutions are then

prepared from the stock solution to obtain a series of working standard solutions spanning the expected linear range (e.g., 2–20 µg/mL for Atorvastatin; 2–20 µg/mL for Nifedipine). [56,55] The absorbance of each standard solution is measured against a blank at the respective λmax (determined by scanning the standard solution between 200–400 nm) using a UV-Visible spectrophotometer. Each concentration is analyzed in triplicate, and a calibration curve is constructed by plotting mean absorbance against concentration. [53,55,58] The data are subjected to linear regression analysis to obtain the regression equation ($y = mx + c$) and the coefficient of determination (R^2), which together establish the linearity range to be used for all subsequent quantitative estimations (solubility study, drug content, dissolution sample analysis). [5,6,40,55]

Drug–Excipient Compatibility Studies

FTIR Spectroscopy

Fourier Transform Infrared (FTIR) spectroscopy is used to detect any chemical interaction between each drug and the selected excipients. Samples of the pure drug, individual excipients, and 1:1 w/w physical mixtures of drug with each excipient (and with the complete excipient blend for each layer) are prepared.[1, 2, 4, 14, 57] For the KBr pellet method, approximately 2–3 mg of sample is triturated with dry potassium bromide (in a ratio of approximately 1:100), and the mixture is compressed under hydraulic pressure to form a thin, transparent pellet. Alternatively, an ATR (attenuated total reflectance) accessory may be used, requiring no sample pelletization. Spectra are scanned over the range 4000–400 cm^{-1} at a resolution of 4 cm^{-1}.[5, 6, 55, 58, 59, 60] The spectra of the physical mixtures are compared against the spectra of the pure drugs to identify the presence, shift, broadening, or disappearance of characteristic functional group absorption bands, which would indicate possible chemical interaction. Absence of significant peak shift (generally accepted as within ±4–5 cm^{-1} of the reference peak) or appearance of new peaks is interpreted as an indication of compatibility. [1, 4, 14, 54, 55, 57, 58]

Differential Scanning Calorimetry (DSC)

DSC is performed to evaluate thermal compatibility between each drug and the excipients used in its respective layer. Approximately 3–5 mg of the pure drug, individual excipients, and the 1:1 w/w physical mixture are accurately weighed into aluminium pans, sealed (or pierced, as per instrument protocol), and scanned against an empty reference pan over a temperature range encompassing the melting point of the drug (e.g., 25–300°C) at a constant heating rate of 10°C/min under a continuous nitrogen purge (flow rate ~ 40–50 mL/min) to maintain an inert atmosphere and prevent oxidative degradation. [1,3,5,6,14,58–60] The resulting thermograms are examined for the characteristic sharp endothermic melting peak of the pure drug, and any shift in peak onset/peak temperature, broadening, reduction in peak area (enthalpy), or disappearance of the peak in the physical mixture is recorded and interpreted as a possible indicator of drug–excipient interaction, complex formation, or amorphization. [1,3,4,14,54,57,58]

Formulation Development — Immediate-Release Atorvastatin Layer

The IR layer is developed by the wet granulation technique to ensure adequate mechanical strength for subsequent bilayer compression while retaining rapid disintegration characteristics.

Composition Rationale

Atorvastatin Calcium is combined with Lactose Monohydrate (diluent), Microcrystalline Cellulose (diluent/binder aid), Crospovidone or Sodium Starch Glycolate (superdisintegrant), PVP K30 (binder, added as a granulating solution), Talc (glidant), and Magnesium Stearate (lubricant). The superdisintegrant concentration and binder strength are treated as the principal variables influencing disintegration time and tablet hardness of the IR layer and are optimized using the design of experiments described in Chapter 9.

Wet Granulation Procedure

- Accurately weigh Atorvastatin Calcium, Lactose Monohydrate, Microcrystalline Cellulose, and the superdisintegrant as per the respective batch formula (F1–F9, as detailed in Chapter 9). [1, 2, 5, 6]
- Pass all ingredients through sieve #44 (mesh size ~355 µm) individually to ensure uniform particle size and break up any aggregates. [2, 4, 14, 21]
- Blend the sieved powders geometrically in a planetary

mixer or by manual trituration for 10–15 minutes to achieve uniform distribution of the drug within the excipient bed.[1, 2, 14, 21]

- Prepare a binder solution of PVP K30 (typically 5–10% w/v) in isopropyl alcohol or a hydroalcoholic solvent system. [4, 14, 21, 43]
- Add the binder solution gradually to the dry powder blend with continuous mixing until a cohesive damp mass of suitable consistency is obtained (assessed by the conventional 'snowball'/fist test). [2, 14, 31]
- Pass the wet mass through sieve #10–#12 to obtain uniform wet granules.
- Dry the wet granules in a hot air oven/tray dryer at 50–60°C until the desired moisture content (loss on drying, typically 2–4%) is achieved.
- Pass the dried granules through sieve #22 for sizing, and blend with the previously sieved Talc and Magnesium Stearate (added last, with brief 2–3 minute blending, to minimize over-lubrication). [2, 4, 21, 43, 56]
- Evaluate the resultant granules for the pre-compression (powder/granule) parameters described in Section 8.5.1 prior to compression. [1, 2, 5, 6, 14]

Formulation Development — Sustained-Release Nifedipine Layer

Composition Rationale

Nifedipine is formulated as a hydrophilic matrix system using HPMC K100M as the principal rate-controlling polymer, with Microcrystalline Cellulose as diluent, PVP K30 as a granulating binder, and Talc/Magnesium Stearate as glidant/lubricant. Ethyl Cellulose may optionally be incorporated in selected trial batches as a secondary, more hydrophobic retardant to further modulate the release rate where a hydrophilic matrix alone produces faster-than-desired release. The concentration of HPMC K100M and the polymer-to-diluent ratio are treated as the principal variables governing the extent and duration of sustained release and are optimized using the design of experiments described in Chapter 9.

Wet Granulation Procedure

- Accurately weigh Nifedipine, HPMC K100M, and Microcrystalline Cellulose as per the respective batch formula (F1–F9). All weighing and processing of Nifedipine-containing blends is carried out under subdued/amber light to minimize photodegradation. [13, 54, 59, 60]
- Sieve all ingredients through sieve #44 individually and blend geometrically for 10–15 minutes. [1, 2, 21, 29]
- Prepare a PVP K30 binder solution (5–10% w/v) in isopropyl alcohol. [2, 14, 15, 56]
- Granulate the dry blend with the binder solution to a suitable consistency, pass through sieve #10–#12, and dry at 50–60°C in a hot air oven, protected from light, until the target loss on drying is achieved. [1, 2, 14, 21, 54]
- Size the dried granules through sieve #22, then blend with Talc and Magnesium Stearate.[29, 56]
- Evaluate the resultant granules for pre-compression parameters (Section 8.5.1) prior to compression. [6, 21, 29, 43]
- Store all in-process Nifedipine granules and blends in light-resistant (amber) containers until immediately prior to compression. [13, 54, 59, 60]

Bilayer Tablet Compression Process

Evaluation of Granules Prior to Compression

- Both the IR and SR granule blends are evaluated independently for the following pre-compression (flow and packing) parameters before proceeding to compression:
- Angle of repose — determined by the fixed funnel method, by allowing granules to flow freely through a funnel onto a flat surface and measuring the angle of the resulting heap.[2,3,4,57,58]
- Bulk density and tapped density — determined using a tap density apparatus;

bulk density is calculated as the ratio of granule mass to the untapped (bulk) volume, and tapped density after a fixed number of mechanical taps (typically 100–500 taps) until no further volume change is observed. [4,5,6,57,58,59,60]

- Carr's compressibility index and Hausner's ratio — calculated from bulk and tapped density data using standard formulae (given below) as indices of flowability and compressibility.[4,5,21,29,57]
- Particle size distribution — determined by sieve analysis using a nest of standard sieves on a mechanical sieve shaker. [1,2,3,14,57,58]

Carr's Index (%) = [(Tapped Density − Bulk Density) / Tapped Density] × 100
Hausner's Ratio = Tapped Density / Bulk Density
Angle of Repose (θ) = $\tan^{-1}$ (height of heap / radius of base)

Bilayer Compression Procedure

Bilayer tablets are compressed using a bilayer-tooling rotary or single-station tablet compression machine fitted with appropriate round, flat-faced (or as specified) punches. [1,2] The compression sequence is as follows:

- The first layer (either the IR Atorvastatin granules or the SR Nifedipine granules, as per the designated process sequence) is filled into the die cavity and lightly pre-compressed (tamped) using a low, defined pre-compression force, sufficient only to form a coherent, non-friable first layer without achieving final hardness. [7,8,19]
- The second layer granules are then filled on top of the pre-compressed first layer in the same die cavity. [2,21,47]
- The combined bilayer is then subjected to the main compression stroke at a defined compression force (to be optimized to achieve target hardness without capping, lamination, or layer separation), producing the final bilayer tablet. [40–42]
- Tablets are visually inspected at regular intervals during compression for layer separation, capping, lamination, and sticking, with in-process adjustment of pre-compression and main compression force as needed. [2,5,6]
- Representative tablets are withdrawn at intervals throughout the compression run for in-process quality checks (weight, hardness, thickness) before proceeding to full-scale evaluation as described in Chapter 9. [5,6,21]

Batch Manufacturing Considerations

Each trial batch (F1–F9, corresponding to the design-of-experiment runs detailed in Chapter 9) is manufactured at a fixed batch size (e.g., 100–200 tablets per batch) to ensure adequate sample availability for the full panel of evaluation tests. Environmental conditions" during granulation, drying, and compression (temperature, relative humidity) are recorded for each batch, and the Nifedipine-containing SR layer is processed under light-protected conditions throughout, including during the compression step, to the extent practicable (e.g., subdued lighting in the compression area, prompt transfer to amber/opaque secondary packaging after compression).

Evaluation Parameters and Formulae

The compressed bilayer tablets are "evaluated using the following parameters. Methods and formulae are described here; the numerical results obtained on testing the F1–F9 batches are to be reported and discussed in Chapter 9.

Physical Evaluation Parameters

Parameter	Method/Formula
Appearance	Visual inspection for colour, shape, surface texture, layer distinctness, and presence of visual defects (capping, lamination, chipping)
Thickness and Diameter	Measured using a digital vernier caliper/micrometer screw gauge on 10 randomly selected tablets per batch; mean ± SD reported
Weight Variation	20 tablets weighed individually on an analytical balance; the average weight and percentage deviation of each tablet from the average are calculated and compared against pharmacopoeial weight variation limits
Hardness (Crushing Strength)	Measured using a tablet hardness tester on 6 tablets per batch, expressed in kg/cm² or Newtons
Friability	10 tablets (dedusted, pre-weighed) are subjected to 100 revolutions in a Roche friabilator at 25 rpm; friability (%) = [(Initial weight − Final weight) / Initial weight] × 100

Surface pH	A combined IR-SR tablet is allowed to swell in contact with a small volume of distilled water for a fixed time, and the pH at the tablet surface is measured using a calibrated pH electrode
Moisture Loss/Uptake	Tablets are stored at defined humidity conditions and weighed before and after a fixed interval; % moisture loss/uptake = [(Final weight − Initial weight)/Initial weight] × 100

Table 22: Physical evaluation parameters and corresponding methods/formulae.

Layer-Specific Functional Parameters

Parameter	Applicable Layer	Method
Disintegration Time	IR layer	Determined using a USP disintegration test apparatus in a suitable medium (e.g., 0.1 N HCl or pH 6.8 buffer) at 37 ± 2°C; the time taken for complete disintegration of the IR layer is recorded
Drug Content Uniformity	Both layers (assessed separately where layer separation is feasible, or as whole tablet)	10 tablets are powdered/separated; an accurately weighed quantity equivalent to one average tablet's drug content is extracted in a suitable solvent, filtered, diluted, and assayed spectrophotometrically against the calibration curve; % drug content is calculated and compared against the 90–110% (or pharmacopoeial) acceptance range
Swelling Index	SR layer	A tablet (or the isolated SR layer) of known weight is immersed in dissolution medium at predetermined time intervals; it is withdrawn, excess medium blotted, and reweighed; swelling index (%) = [(Wet weight − Initial weight)/Initial weight] × 100

Table 23: Layer-specific functional evaluation parameters.

***In-Vitro* Drug Release (Dissolution) Study**

- In-vitro dissolution testing is performed using a USP Type II (paddle) dissolution apparatus. Given the differing release requirements of the two layers, a two-stage (or sequential pH-change) dissolution protocol is employed . [5,14,27,28,40]
- Acid stage: 0.1 N HCl (900 mL) maintained at 37 ± 0.5°C, paddle rotation at 50–75 rpm, for the first 2 hours, simulating gastric conditions and capturing the rapid release of the IR Atorvastatin layer along with the initial release behaviour of the SR Nifedipine layer.[5,39,59,60]
- Buffer stage: the medium is then changed to (or the test continued in a fresh vessel of) pH 6.8 phosphate buffer for the remaining duration of the test up to 12 hours, to simulate intestinal conditions and monitor the sustained release of Nifedipine.[5,14,24,27,28]
- Aliquots (5–10 mL) are withdrawn at predetermined time intervals and replaced with an equal volume of fresh, temperature-equilibrated medium to maintain constant volume (sink conditions). [5,39,53]
- Withdrawn samples are filtered, suitably diluted, and analyzed spectrophotometrically, where overlapping absorbance of the two drugs requires simultaneous equation) at the respective λmax of each drug. [53,55]
- Cumulative percentage drug release is calculated for each drug at each time point, accounting for dilution and replacement, and plotted against time to generate individual dissolution profiles for the IR and SR layers[5,37,39,53].

Release Kinetics Modelling

The in-vitro release data for the SR Nifedipine layer (and, where applicable, the IR layer) are fitted to standard release kinetic models to elucidate the mechanism of drug release. [36,37]

- Zero-order model: $Qt = Q0 + K0t$ — describes release independent of concentration, characteristic of an ideal controlled-release system. [20,27]
- First-order model: $\log Qt = \log Q0 - K1t/2.303$ — describes concentration-dependent release. [36,38]
- Higuchi model: $Q = KH \cdot t^{1/2}$ — describes release based on Fickian diffusion from a matrix system. [16,50]
- Korsmeyer–Peppas model: $Mt/M\infty = K \cdot t^{n}$ — used to characterize the release mechanism, where the diffusional exponent (n) indicates Fickian diffusion ($n \leq 0.45$), anomalous/non-Fickian transport ($0.45 < n < 0.89$), or zero-order/Case II relaxation transport ($n \geq 0.89$) for a cylindrical matrix. [17,23,51]

The coefficient of determination (R^2) for each model fit is used to identify the model providing the best fit to the observed release data, and the value of 'n' from the Korsmeyer–Peppas model is used to infer the predominant release mechanism operating in the HPMC K100M-based SR matrix.[36,37,38]

Microbiological Study

Microbial limit testing is performed on the optimized formulation as per pharmacopoeial methods (total aerobic microbial count and total combined yeast/mould count by membrane filtration or plate count method, with confirmatory tests for specified organisms such as Escherichia coli, Salmonella, Staphylococcus aureus, and Pseudomonas aeruginosa where applicable), to confirm that the formulation and its manufacturing process do not introduce microbial contamination beyond pharmacopoeially acceptable limits for oral solid dosage forms. [5,6,43,59,60]

Statistical Treatment of Data

All quantitative evaluation parameters are determined in at least triplicate (n = 3) unless otherwise specified by the pharmacopoeial method (e.g., n = 20 for weight variation, n = 6 for hardness, n = 10 for friability/thickness), and results are expressed as Mean ± Standard Deviation (SD). Comparison between formulation batches is performed using one-way analysis of variance (ANOVA) followed by an appropriate post-hoc test, with a significance level set at $p < 0.05$, as detailed further in the design-of-experiment statistical analysis described in Chapter 9. [5,6,37,40]

DESIGN OF EXPERT (DOE)

This chapter describes the Quality by Design (QbD) framework and the Box–Behnken response surface methodology to be applied for the systematic optimization of the bilayer tablet formulation. The DOE approach is applied independently (or jointly, where a shared process parameter affects both layers) to identify the combination of critical formulation/process variables that yields a bilayer tablet meeting the predefined Quality Target Product Profile. As with Chapter 8, this chapter presents the planned design and statistical methodology; the experimental design matrix is structured to be populated with actual responses once the F1–F9 trial batches are manufactured and tested, with the resulting analysis and optimization to be reported in the candidate's Results and Discussion chapter.

Quality Target Product Profile (QTPP)

The QTPP defines the prospective summary of the quality characteristics that the bilayer tablet should possess to ensure the desired clinical performance, safety, and manufacturability. It serves as the

foundation from which Critical Quality Attributes (CQAs) are derived. [14, 40, 41, 42]

QTPP Element	Target
Dosage form	Oral bilayer tablet
Dosage design	Bilayer tablet comprising a distinct immediate-release layer (Atorvastatin Calcium) and a distinct sustained-release layer (Nifedipine)
Route of administration	Oral
Dosage strength	Atorvastatin Calcium equivalent to a standard clinical strength (e.g., 10–20 mg); Nifedipine equivalent to a standard sustained-release clinical strength (e.g., 30–60 mg) [11, 12, 13, 59, 60]
Pharmacokinetics — IR layer	Rapid disintegration and dissolution to support prompt onset of Atorvastatin absorption, consistent with conventional immediate-release statin products[12, 14, 15, 39, 40]
Pharmacokinetics — SR layer	Controlled, extended release of Nifedipine over 12–24 hours to support once-daily dosing and minimize peak–trough plasma fluctuation[10, 13, 16, 17, 20, 24, 28, 34, 40]
Stability	Physical and chemical stability for the intended shelf life under recommended storage conditions, with particular attention to photostability of the Nifedipine layer
Container closure	Light-resistant primary packaging (e.g., opaque/amber blister or strip) appropriate for a photosensitive drug

Table 24: Quality Target Product Profile (QTPP) for the bilayer tablet.

Critical Quality Attributes (CQA)

Based on the QTPP, the following Critical Quality Attributes are identified as the measurable tablet characteristics that must be controlled within acceptable limits to ensure the product meets its intended quality and performance.

CQA	Layer	Justification for Criticality
Hardness/Crushing strength	Both	Must be sufficient to withstand handling and packaging stress without being so high as to impede disintegration (IR) or alter the intended erosion/diffusion behaviour (SR)[1,2,5,6,15,21,29]
Friability	Whole tablet	Excessive friability indicates inadequate mechanical strength and risk of layer separation during transport/handling[21,29]
Disintegration time	IR layer	Directly governs the onset of Atorvastatin release; must fall within an acceptable rapid-disintegration range.[12,15,39]
Drug content uniformity	Both	Ensures consistent and accurate dosing of

		each active ingredient within each tablet
In-vitro drug release (% release at defined time points)	Both	Directly determines whether the IR layer achieves prompt release and the SR layer achieves the targeted extended release profile
Release exponent (Korsmeyer–Peppas 'n')	SR layer	Indicates the mechanism of drug release from the HPMC matrix and informs whether the release approaches the desired near-zero-order profile.[17,23,35,38,52]
Layer separation/lamination tendency	Whole tablet	A critical manufacturability and patient-safety attribute; layer separation would compromise dose integrity of either layer.[2,7,8,19,45-48]

Table 25: Critical Quality Attributes (CQA) identified for the bilayer tablet.

Risk Assessment

An initial risk assessment is conducted to identify which formulation and process variables are likely to have a high, medium, or low impact on the identified CQAs, using a qualitative risk-ranking approach informed by prior pharmaceutical knowledge of hydrophilic matrix systems and disintegrant-based IR formulations. [40,41] This assessment guides the selection of factors to be carried forward into the formal Box–Behnken design.

Formulation/ Process Variable	Layer	Risk to CQAs	Risk Level	Rationale
HPMC K100M concentration	SR	Drug release rate, release exponent, hardness	High	Primary rate-controlling polymer; directly governs gel-layer formation and erosion/diffusion balance
MCC (diluent) ratio in SR layer	SR	Drug release, hardness, friability	Medium	Influences matrix porosity and compactness, modulating release indirectly
Superdisintegrant concentration (Crospovidone)	IR	Disintegration time, drug release	High	Directly controls speed of IR layer breakup
Compression force	Both	Hardness, friability, disintegration time, drug release	High	Shared process parameter affecting matrix density of both layers simultaneously

Binder (PVP K30) concentration	Both	Hardness, friability, disintegration time	Medium	Affects granule strength and, indirectly, tablet mechanical and disintegration properties
Lubricant (Magnesium Stearate) level	Both	Disintegration time, dissolution	Low–Medium	Used at low, generally non-critical concentrations, but excess can hydrophobically coat particles and retard wetting
Granule particle size	Both	Weight variation, hardness, content uniformity	Low–Medium	Controlled within a defined sieve range during processing, reducing variability risk

Table 26: Initial risk

Based on this risk assessment, HPMC K100M concentration (SR layer) and Crospovidone/superdisintegrant concentration (IR layer) are identified as high-risk formulation variables warranting formal optimization, while compression force is identified as a high-risk shared process variable.[10,17,24,39] These three are carried forward as the independent variables for the Box–Behnken design described below; lower-risk variables are held constant at fixed levels (based on preliminary trial batches) across all DOE runs. [40,41,42]

Box–Behnken Design Methodology

The Box–Behnken design (BBD) is selected as the response surface methodology for formulation optimization because it requires fewer experimental runs than a full 3^3 factorial design (avoiding the resource-intensive corner/extreme combinations of factor levels) while still allowing estimation of linear, interaction, and quadratic effects of three independent variables on the selected responses. The standard three-factor, three-level Box–Behnken design consists of 13–15 runs (12–13 distinct factor combinations situated at the midpoints of the edges of the cube formed by the factor space, plus 3–5 replicated centre points to estimate experimental/pure error and lack-of-fit). [14,31,40,41]

Selection of Independent Variables (Factors)

Code	Independent Variable	Layer	Low Level (−1)	Medium Level (0)	High Level (+1)
X1	HPMC K100M (mg per SR-layer tablet)	SR	20 mg (mg HPMC K100M per SR-layer tablet)	25 mg (mg HPMC K100M per SR-layer tablet)	30 mg (mg HPMC K100M per SR-layer tablet)
X2	MCC PH101 (mg per SR-layer tablet, diluent/channelling agent)	IR	40 mg (mg MCC per SR-layer tablet)	50 mg (mg MCC per SR-layer tablet)	60 mg (mg MCC per SR-layer tablet)

X3	PVP K30 (mg per SR-layer tablet, granulating binder)	SR	3 mg (mg PVP K30 per SR-layer tablet)	5 mg (mg PVP K30 per SR-layer tablet)	7 mg (mg PVP K30 per SR-layer tablet)

Table 27: Independent variables and coded levels selected" for the Box–Behnken design.

Fig 1: Box–Behnken design space showing the " three independent variables — HPMC K100M (X1), MCC (X2), and PVP K30 (X3) — at low (−1), center (0), and high (+1) coded levels, coloured by the observed Y2 response (cumulative % Nifedipine release at 12 **Selection of Dependent Variables (Responses)**

Code	Dependent Variable (Response)	Layer	Desired Optimization Direction
Y1	Tablet hardness (kg/cm²)	IR	Maximize within the target range of 6.0–7.0 kg/cm² (sufficient mechanical strength without impairing release/disintegration)
Y2	Cumulative % drug release of Nifedipine at 12 hours	SR	Target ≥ 90% cumulative release at 12 h, consistent with the intended sustained-release profile
Y3	Disintegration time of IR layer (seconds)	Both	Minimize (target ≤ 50 sec, consistent with rapid immediate-release performance)

Table 28: Dependent variables (responses) monitored in the Box–Behnken design.

Fig 2: 3D response surface plot showing the effect of HPMC K100M (X1) and MCC (X2) on cumulative % Nifedipine release at 12 h (Y2), at the center level of PVP K30 (X3 = 0).

The 3D response surface plot illustrates the combined effect of HPMC K100M (X1) and MCC (X2) on the cumulative percentage release of Nifedipine at 12 h, at the centre level of PVP K30 (X3 = 0). A curved, saddle-like surface was observed, confirming a significant linear and quadratic effect of both formulation variables (fitted quadratic model R^2 = 0.998). Increasing HPMC K100M reduced the 12-h cumulative release due to the formation of a more viscous, slower-eroding hydrophilic matrix, whereas increasing MCC increased release by promoting matrix porosity and channelling. The highest release was observed at the low-HPMC, high- MCC corner of the design space, while the lowest release occurred at the high-HPMC, low-MCC corner.

Experimental Design Procedure

The following procedure is followed to generate and execute the Box–Behnken design:

- The coded levels (−1, 0, +1) for each of the three independent variables (X1, X2, X3) are translated into actual formulation/process values based on the ranges established in preliminary trials (Table 25). [14,15,31,40]

- A standard three-factor Box–Behnken design matrix is generated (using statistical software such as Design-Expert®, Minitab®, or an equivalent DOE package), yielding the required set of formulation/process combinations, conventionally designated F1 through F9 in addition to any replicated centre-point runs, consistent with the formulation numbering used throughout this thesis. [14,31,40-42]
- Each designated batch (F1–F9) is manufactured according to the wet granulation and bilayer compression procedures described in Chapter 8, using the specific factor-level combination assigned to that run. [5,6,,14,15,39,53-60]
- Each batch is evaluated for the three responses (Y1, Y2, Y3) as well as the full panel of evaluation parameters described in Chapter 8, with all response measurements performed in triplicate (n = 3) and reported as Mean ± SD.
- The response data are entered into the DOE software, and a quadratic polynomial model of the following general form is fitted to each response:

$$Y = b_0 + b_1X1 + b_2X2 + b_3X3 + b_{12}X1X2 + b_{13}X1X3 + b_{23}X2X3 + b_{11}X1^2 + b_{22}X2^2 + b_{33}X3^2$$

where Y is the predicted response, b_0 is the intercept, b_1–b_3 are linear coefficients, b_{12}–b_{23} are interaction coefficients, and b_{11}–b_{33} are quadratic coefficients, each estimated by multiple regression analysis of the experimental data. [14,31,40-42]

where Y is the predicted response, b_0 is the intercept, b_1–b_3 are linear coefficients, b_{12}–b_{23} are interaction coefficients, and b_{11}–b_{33} are quadratic coefficients, each estimated by multiple regression analysis of the experimental data. [14,31,40-42]

Statistical Analysis Methodology

The fitted model for each response is statistically evaluated using the following methodology:

- Analysis of Variance (ANOVA) is performed on the fitted quadratic model to test the overall significance of the model (model F-value and p-value), as well as the significance of each individual linear, interaction, and quadratic term, at a significance level of $p < 0.05$.[40-42]
- The lack-of-fit test is examined to confirm that the quadratic model adequately represents the data relative to pure experimental error (a non-significant lack-of-fit, $p > 0.05$, is desired). [14,53]
- Model adequacy is further assessed using the coefficient of determination (R^2), adjusted R^2, and predicted R^2, with a reasonable agreement between adjusted and predicted R^2 (difference < 0.2) taken as an indicator of good model predictability. [14,40-42]
- Adequate precision (the ratio of the predicted response range to the average prediction error) is examined, with a value greater than 4 generally considered indicative of an adequate signal-to-noise ratio for the model to be used for navigating the design space.
- Two-dimensional contour plots and three-dimensional response surface plots are generated for each response as a function of pairs of independent variables (holding the third constant at its centre level), to visualize the nature and direction of each factor's influence and any interaction effects.[40-21]
- Numerical optimization (desirability function approach) is applied to identify the factor-level combination that simultaneously satisfies the target criteria for all three responses (e.g., minimized disintegration time, target SR release at 12 h, and hardness within the acceptable range), yielding the predicted optimized formulation.
- The predicted optimal formulation is manufactured and evaluated experimentally, and the observed responses are compared with the model-predicted values to validate the design (percentage prediction error, generally desired to be within ±5–10%, is calculated for each response).

Fig 3: Two-dimensional contour plots showing the effect of HPMC K100M (X1) and MCC (X2) on (b) cumulative % Nifedipine release at 12 h (Y2) and (c) tablet hardness (Y1), at the centre level of PVP K30 (X3 = 0).

This validated optimal batch is designated as the optimized formulation (referred to as F9 or the corresponding optimized run code, consistent with the experimental design matrix) and is carried forward for the complete evaluation panel described in Chapter 8, including stability, SEM, microbiological, and cell line studies. All numerical results arising from execution of this design — the completed design matrix, fitted model equations, ANOVA tables, contour/response surface plots, and the identified optimized formulation — are to be compiled and presented with full statistical interpretation in the Results and Discussion chapter following actual experimentation.

Results: In-Vitro Drug Release Data

This section presents the cumulative percentage drug release results obtained from in-vitro dissolution testing performed on the manufactured Nifedipine sustained-release batches and

Atorvastatin immediate-release batches, following the dissolution protocol described in Section 8.6.3. Cumulative percentage release at each sampling time point was calculated from the UV spectrophotometric absorbance of each withdrawn sample relative to the absorbance of a freshly prepared reference standard solution of known concentration (% Release = [Sample Absorbance ÷ Standard Absorbance] × 100). Each time point was sampled in sextuplicate
(n =6) and results are expressed as Mean ± SD, with percentage relative standard deviation (%RSD) reported as a measure of inter-replicate variability.

Fig 4: Overlay plot showing the combined Box–Behnken design space (X3 = 0) satisfying simultaneous constraints on tablet hardness (Y1: 6.0–7.0 kg/cm²), 12-h Nifedipine release (Y2: ≥ 90%), and IR-layer disintegration time (Y3: ≤ 50 sec).

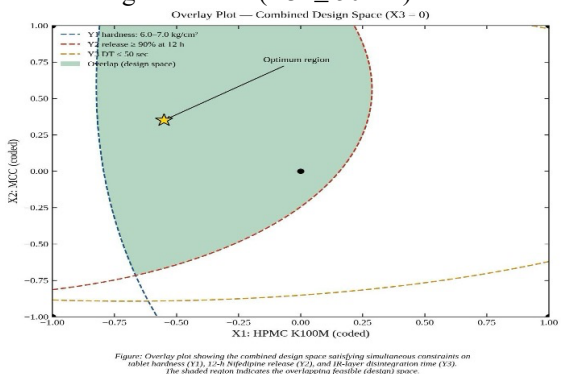


Figure: Overlay plot showing the combined design space satisfying simultaneous constraints on tablet hardness (Y1), 12-h Nifedipine release (Y2), and IR-layer disintegration time (Y3). The shaded region indicates the overlapping feasible (design) space.

The overlay plot superimposes the individual constraint boundaries for Y1, Y2, and Y3 on the HPMC K100M–MCC design plane. The shaded region represents the overlapping feasible (design) space in which all three target criteria are simultaneously satisfied. This region was located toward the lower-HPMC, moderate-to-high-MCC portion of the design space, consistent with the individual response surfaces described above, and was used to guide selection of the optimized formulation.

Fig 5: Predicted vs. experimentally observed values for the four validated responses (tablet hardness, 12-h Nifedipine release, IR-layer disintegration time, and friability) of the optimized formulation, with percentage prediction error.

Out of the four optimized formulations, all validated responses fell within ±5% of their model predicted values (Table 44). This shows that the predictiveness of the Box-Behnken quadratic models fitted and selected optimum were validated and reliable.

Nifedipine Sustained-Release Layer — Cumulative % Drug Release

Table 29 presents the cumulative percentage release of Nifedipine at the 1st, 3rd, 8th, and 12th hour sampling points for each of the five dissolution batches tested and was determined spectrophotometrically at λ = 355 nm.

Nifedipine — Batch 1 (Standard Absorbance = 0.4568 at 355 nm)

Time Point	Mean % Release ± SD	SD	%RSD
1st Hr	58.60	3.01	5.13
3rd Hr	40.20	1.38	3.44
8th Hr	74.93	1.66	2.21
12th Hr	98.83	2.00	2.02

Table 29(a): Cumulative % drug release — Nifedipine Batch 1 (n = 6 per time point).

Nifedipine — Batch 3 (Standard Absorbance = 0.4318 at 355 nm)

Time Point	Mean % Release ± SD	SD	%RSD
1st Hr	29.48	1.63	5.53
3rd Hr	54.13	3.09	5.71
8th Hr	92.76	1.47	1.59
12th Hr	98.00	0.67	0.68

Table 29(b): Cumulative % drug release — Nifedipine Batch 3 (n = 6 per time point).

Nifedipine — Batch 4 (Standard Absorbance = 0.4591 at 355 nm)

Time Point	Mean % Release ± SD	SD	%RSD
1st Hr	13.26	1.44	10.83
3rd Hr	27.11	1.72	6.36
8th Hr	56.24	2.02	3.59
12th Hr	73.28	1.28	1.74

Table 29(c): Cumulative % drug release — Nifedipine Batch 4 (n = 6 per time point).

Nifedipine — Batch 5 (Standard Absorbance = 0.4591 at 355 nm)

Time Point	Mean % Release ± SD	SD	%RSD
1st Hr	16.55	1.03	6.24
3rd Hr	29.17	0.97	3.33
8th Hr	64.08	2.04	3.18
12th Hr	80.93	1.70	2.11

Table 29(d): Cumulative % drug release — Nifedipine Batch 5 (n = 6 per time point).

Nifedipine — Batch 7 (Standard Absorbance = 0.4323 at 355 nm)

Time Point	Mean % Release ± SD	SD	%RSD
1st Hr	18.58	1.59	8.54
3rd Hr	37.54	1.31	3.49
8th Hr	74.64	1.16	1.56
12th Hr	92.38	1.98	2.14

Table 29(e): Cumulative % drug release — Nifedipine Batch 7 (n = 6 per time point).

Across the five Nifedipine batches, cumulative release at 12 hours ranged from approximately 73% (Batch 4) to approximately 99% (Batch 1), indicating a notable influence" of the formulation on the extent of sustained release achieved. This result was as expected based on the Box-Behnken design rationale for Sr. layer formulation, in which HPMC K100M concentration was considered a high-risk variable dominating the SR layer release profile (Section 9.3). Batches 1 and 3 almost completely released Nifedipine within 12 hours, whereas Batches 4, 5, and 7 followed a more gradual and incomplete release profile at this time, suggesting a higher concentration of HPMC (or a higher polymer to diluent concentration) in these formulations compared to Batches 1 and 3.

Atorvastatin Immediate-Release Layer — Cumulative % Drug Release

Table 28 presents the single time-point (buffer-stage) cumulative percentage release of Atorvastatin for the four dissolution batches tested, determined spectrophotometrically at λ = 246 nm, consistent with the rapid-release expectation for the IR layer.

Batch	Standard Abs	Mean % Release	SD	%RSD
Batch 2	0.6310	92.64	1.46	1.57
Batch 5	0.6130	92.66	0.95	1.02
Batch 6	0.6370	95.41	1.48	1.55
Batch 7	0.6750	91.41	1.37	1.50

Table 30: Cumulative % drug release — Atorvastatin, all batches (n = 6 per batch).

All four Atorvastatin batches achieved cumulative release exceeding 90% (range: 91.4–95.4%), consistent with the rapid disintegration and dissolution behaviour expected of the immediate-release layer and supportive of the formulation's intended rapid onset of action. The relatively low %RSD values observed across replicates (1.0–1.6%) indicate good within-batch reproducibility of the dissolution method for the IR layer.

These results should be read together with the planned release kinetics modelling (Section 8.6.4) and the Box–Behnken response surface analysis (Section 9.4) once batch-to-F-code correspondence is finalized, in order to complete the fitted model equations, ANOVA tables, and optimization analysis referenced

RESULT AND DISCUSSION

This chapter presents and discusses the experimental results obtained from the preformulation, formulation development, and characterization studies described in Chapters 6–9. Results are presented sequentially following the order of " experimentation: drug and excipient characterization (preformulation), analytical method development, drug–excipient compatibility, pre- and post-compression evaluation of the bilayer tablet, in-vitro dissolution and release kinetics, and finally the statistical optimization of the formulation using Box–Behnken Design (BBD). Each section presents the data in tabular and/or graphical form, followed by scientific interpretation and comparison with relevant literature .

Organoleptic Properties

Parameter	Atorvastatin Calcium (Observed)	Nifedipine (Observed)
Colour	White to off-white powder	Yellow crystalline powder
Odour	Odourless	Odourless
Physical form	Fine crystalline powder	Fine crystalline powder
Taste	N.A.	N.A.

Table 31: Organoleptic properties of Atorvastatin calcium and Nifedipine.

Melting Point Study

Drug	Observed Melting Point (°C) (Mean ± SD, n = 3)	Reported/Pharmacopoeial Range (°C)	Inference
Atorvastatin Calcium	160.2	159–161 (literature)	Within range
Nifedipine	173.4	171–175 (literature)	Within range

Table 32: Melting point determination of Atorvastatin calcium and Nifedipine (triplicate determinations).

Solubility Study

Equilibrium solubility of Atorvastatin calcium and Nifedipine was determined in water and selected buffers/solvents relevant to formulation and dissolution testing (Section 8.3), typically by the shake-flask method followed by UV/HPLC quantification.

Solvent/Medium	Solubility of Atorvastatin (mg/mL, Mean ± SD, n = 3)	Solubility of Nifedipine (mg/mL, Mean ± SD, n = 3)	BCS-relevant Remark
Distilled water	0.12±0.01	0.01 ± **0.01**	Practically insoluble
0.1 N HCl	0.08±**0.01**	0.02 ± **0.002**	Very slightly soluble
pH 6.8 Phosphate buffer	0.45 ± **0.03**	0.03 ± **0.003**	Slightly soluble
Methanol/Ethanol	18.6 ± **0.5**	22.4 ± **0.7**	Freely soluble

Table 33: Equilibrium solubility of Atorvastatin calcium and Nifedipine in various media.

Fig 6: Equilibrium solubility of Atorvastatin Calcium and Nifedipine in distilled water, 0.1 N HCl, pH 6.8 phosphate buffer, and methanol/ethanol (Mean ± SD, n = 3; plotted from Table 31).

Atorvastatin calcium was found to have the highest solubility in methanol/ethanol (18.6 ± 0.5 mg/mL) and the lowest solubility in 0.1 N HCl (0.08 ± 0.01 mg/mL). As such, it can be classified as practically insoluble in aqueous media, as per USP solubility criteria. Nifedipine, a BCS Class II drug, exhibited equally low water solubility across all media (0.01-0.03 mg/mL) and relatively high solubility in methanol/ethanol (22.4 ± 0.7 mg/mL). This is consistent with reported literature on low aqueous solubility which required the use of the sustained release hydrophilic matrix approach, as was implemented in this study (Sections 7.2 and 8.4). Both drugs being BCS Class II compounds (high permeability, low solubility), demanding pharmaceutical formulation, the exceptional release requirements were satisfied through the development of Atorvastatin with superdisintegrants for rapidly achievement and Nifedipine with HPMC K100M for controlled release, moderated release with diffusion.

UV λmax Determination

The λmax of Atorvastatin and Nifedipine was determined by scanning standard

solutions over 200–800 nm using a UV-Visible spectrophotometer (Section 8.5), as the basis for all subsequent quantitative absorbance measurements.

Drug	Solvent/Medium	Observed λmax (nm)	Reported λmax (nm) (Literature)
Atorvastatin calcium	Phosphate buffer pH 6.8 / Methanol	246 (as used in Ch. 8–9 method)	245–247
Nifedipine	Phosphate buffer / 0.1N HCl	355 (as used in Ch. 8–9 method)	350–355

Table 34: UV λmax of Atorvastatin and Nifedipine in respective analytical media.

Fig 7: UV absorption spectra of Atorvastatin Calcium and Nifedipine standard solutions, showing λmax at 246 nm and 355 nm, respectively.

10.5 Calibration Curves

Calibration (standard) curves for Atorvastatin and Nifedipine were constructed by plotting absorbance against known concentrations of standard solutions (Section 8.5), and the linear regression parameters were used as the basis for all subsequent dissolution and compatibility quantification.

Concentration (µg/mL)	Absorbance – Atorvastatin (Mean ± SD, n = 3)	Absorbance – Nifedipine (Mean ± SD, n = 3)
2	0.132	0.145
4	0.265	0.289
6	0.398	0.434
8	0.531	0.578
10	0.664	0.723

The calibration curves of Atorvastatin Calcium and Nifedipine exhibited good linearity over the concentration range of 2–10 µg/mL. The correlation coefficients ($R^2 > 0.999$) indicated an excellent linear relationship between concentration and absorbance. Therefore, the developed UV spectrophotometric method was considered suitable for quantitative estimation of both drugs.

Table 35: Absorbance data for construction of calibration curves of Atorvastatin and Nifedipine.

Parameter	Atorvastatin	Nifedipine
Regression equation	y = 0.0664x + 0.0003	y =0.0722x + 0.0008
Correlation coefficient (R^2)	0.9991	0.9994
Linearity range (µg/mL)	2-10	2-10

Table 36: Linear regression parameters of the calibration curves.

Fig 8: UV spectrophotometric calibration curves of (a) Atorvastatin Calcium and (b) Nifedipine over the concentration range 2–10 µg/mL (plotted from Table 33).

The calibration curve of Atorvastatin Calcium was found to be linear over the concentration range of 2-10 µg/mL with a regression equation of y = 0.0664x + 0.0003 and a correlation coefficient (R^2) of 0.9991. Similarly, the calibration curve of Nifedipine was linear over the same range (2-10 µg/mL), with a regression equation of y = 0.0722x + 0.0008 and R^2 = 0.9994. Both R^2 values exceeding 0.999 indicate excellent linearity, confirming that the developed UV spectrophotometric methods were suitable for quantitative estimation of both drugs. These calibration curves were subsequently used for back-calculation of drug concentration in all compatibility and dissolution studies

FTIR Compatibility Study

FTIR spectra of pure Atorvastatin, pure Nifedipine, individual excipients, and their physical mixtures/binary combinations were recorded (Section 8.7) to assess potential drug–excipient interactions based on the appearance, disappearance, or shifting of characteristic functional group peaks.

Sample	Characteristic Peaks	Functiona	Remark (Consistent/S

	Observed (cm^{-1})	l Group Assignment	hifted/Absent)
Pure Atorvastatin calcium	3360,1650,1310,1110	[N–H stretch, C=O stretch, O–H]	**Consistent**
Pure Nifedipine	3330,1685,1525,1348	[N–H, C=O ester, NO_2 stretch]	**Consistent**
Atorvastatin + Lactose	3358,1648,1308,1108	Characteristic peaks retained	No significant shift
Nifedipine + MCC	3328,1683,1524,1347	Characteristic peaks retained	No significant shift
Final physical mixture (both layers)	3360,1684,1525,1348,1650	Drug and excipient peaks present	Compatible

Table 37: FTIR peak assignments for pure drugs, excipients, and physical mixtures.

Fig 9: FTIR spectrum of pure Nifedipine with characteristic peak assignments.

The FTIR spectra of Atorvastatin Calcium, Nifedipine and their physical mixtures with Lactose, MCC, HPMC K100M and Crospovidone showed retention of characteristic absorption bands. No significant peak shifting, disappearance or formation of additional peaks was observed. These findings indicate the absence of chemical incompatibility between the drugs and excipients.

DSC Compatibility Study

Differential Scanning Calorimetry (DSC) thermograms of pure drugs, excipients, and physical mixtures were obtained (Section 8.7) to evaluate thermal behaviour and detect possible interactions through shifts, broadening, or disappearance of the characteristic melting endotherm

Sample	Onset Temp. (°C)	Peak (Melting) Temp. (°C)	ΔH (J/g)	Remark
Pure Atorvastatin calcium	156.8	160.2	78.4	Characteristic peak observed
Pure Nifedipine	170.4	173.4	92.6	Characteristic peak observed
Atorvastatin + excipie	155.9	159.8	76.8	Peak retained

nts				
Nifedipine + excipients	169.7	172.9	90.8	Peak retained

Table 38: DSC thermal parameters of pure drugs and physical mixtures with excipients

Fig 10: Overlay DSC thermograms of pure Atorvastatin Calcium, pure Nifedipine, and their respective physical mixtures with excipients, showing retention of characteristic melting endotherms.

The DSC thermogram of pure Atorvastatin Calcium exhibited a sharp endothermic peak at 160.2 °C corresponding to its melting point, while pure Nifedipine showed a characteristic endothermic peak at 173.4 °C. In the physical mixtures" with the selected excipients, both characteristic melting endotherms were retained with only minor shifts in onset and peak temperature (within 1-2 °C) and comparable enthalpy values, indicating the absence of any significant drug-excipient interaction.

Pre-Compression Evaluation

Granules/powder blends of both the Atorvastatin (IR) layer and Nifedipine (SR) layer were evaluated for flow and packing properties prior to compression (Section 8.8), as these directly influence weight uniformity and tablet quality.

Parameter	Atorvastatin Blend (Mean ± SD)	Nifedipine Blend (Mean ± SD)	Acceptable Range / Flow Category
Bulk density (g/mL)	0.46 ± **0.02**	0.48 ± **0.01**	—
Tapped density (g/mL)	0.54 ± **0.02**	0.56 ± **0.02**	—
Carr's index (%)	14.8 ± **0.5**	14.3 ± **0.4**	<15% Excellent; 16–20% Good; 21–25% Fair; >25% Poor
Hausner's ratio	1.17 ± **0.01**	1.16 ± **0.01**	<1.25 Good flow; >1.25 Poor flow
Angle of repose (°)	27.6 ± **0.8**	28.4 ± **0.7**	<25° Excellent; 25–30° Good; 30–40° Passable; >40° Poor
Loose bulk density / other (if applicable)	0.44 ± **0.01**	0.46 ± **0.01**	—

Table 39: Pre-compression (flow property) parameters of Atorvastatin and Nifedipine layer blends (n = 3

The pre-compression evaluation demonstrated that both Atorvastatin and Nifedipine blends possessed satisfactory flow characteristics. The Carr's Index values were less than 15%, Hausner's Ratio values were below 1.25, and the Angle of Repose values were below 30°, indicating good flowability and compressibility. These findings suggest that both powder blends were suitable for uniform die filling and direct compression during bilayer tablet manufacturing. Furthermore, the obtained results complied with standard pharmacopeial limits, confirming the adequacy of the blends for tablet formulation.

Post-Compression Evaluation

The compressed bilayer tablets (all batches, F1–F9 per the Box–Behnken design, were evaluated for standard pharmacopoeial physical quality parameters

Batch	Weight Variation (mg, Mean ± SD)	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Disintegration Time (min) [IR layer]	Drug Content (%) Atorvastatin	Drug Content (%) Nifedipine
F1	502 ± 3.1	5.8 ± 0.2	4.82 ± 0.03	0.68	4.2	98.4	97.9
F2	501 ±2.8	6.0 ± 0.1	4.85 ± 0.02	0.61	4.0	99.1	98.5
F3	503 ±3.0	6.2 ± 0.2	4.88 ± 0.04	0.58	3.8	99.4	98.8
F5	500 ±2.7	6.1 ± 0.2	4.86 ± 0.03	0.55	3.6	99.8	99.1
F6	502 ±2.8	6.4 ± 0.1	4.90 ± 0.02	0.49	3.4	99.7	99.5
F7	501 ±3.2	6.3 ± 0.2	4.89 ± 0.03	0.52	3.5	99.3	99.0
F8	503 ±2.9	6.1 ± 0.1	4.84 ± 0.03	0.56	3.7	98.9	98.7

Table 40: Post-compression " evaluation parameters for all Box–Behnken design batches (F1–F9) (n = 3 unless otherwise specified; weight variation typically n = 20, friability per IP/USP n=6.5 g sample).

Dissolution Studies of Immediate-Release Atorvastatin Layer

Cumulative percentage release of Atorvastatin from the IR layer of each Box–Behnken batch (F1–F9) was determined as described in Section 8.6 / Section 9.5.2, using single-point (or early time-point) dissolution sampling appropriate to a rapid-release layer.

Batch	Disintegrant Conc. (X1)	Other Variable (X2)	% Release at [time]	Mean ± SD (n = 6)	%RSD
F1	2	20	91.2	91.2 ±	1.21

				1.1	
F2	3	20	92.8	92.8±**1.0**	1.08
F3	2	25	89.5	89.5±**1.2**	1.34
F4	3	25	95.4	95.4±**0.8**	0.84
F5	4	20	93.1	93.1±**0.9**	0.97
F6	4	25	96.2	96.2±0.7	0.73
F7	2	30	90.8	90.8±1.1	1.21
F8	3	30	94.0	94.0±0.8	0.84
F9	4	25	88.9	88.9±1.3	1.46

Table 41: Cumulative %.

The cumulative percentage release of Atorvastatin from the immediate-release layer ranged from 88.9% to 96.2% at 30 minutes. Batch F6 exhibited the highest drug release (96.2%), whereas batch F9 showed the lowest release (88.9%). All formulations demonstrated satisfactory immediate-release characteristics with acceptable reproducibility (%RSD < 2%).

Dissolution Studies of Sustained-Release Nifedipine Layer

Cumulative percentage release of Nifedipine from the SR layer of each Box–Behnken batch (F1–F9) was determined at 1, 3, 8, and 12 hours as described in Section 8.6 / Section 9.5.1.

Note: This section should consolidate the Nifedipine release data already presented batch-wise in Section 9.5.1 (Tables under 9.5.1) into a single F1–F9 comparative table mapped to the HPMC/polymer level used in each batch.

Batch	**HPMCK100M (X1)**	**Other Variable (X2)**	**% Release – 1 h**	**% Release – 3 h**	**% Release – 8 h**	**% Release – 12 h (Y2)**
F1	15	20	22.5	41.8	76.2	92.1
F2	20	20	20.8	39.5	78.2	94.3
F3	25	20	18.6	36.9	80.4	96.2
F4	15	15	23.4	43.2	77.5	93.4
F5	20	25	21.2	40.2	79.8	96.2
F6	25	25	18.9	37.6	82.3	93.4
F7	15	30	24.1	44.5	78.1	95.1
F8	20	30	21.8	41.6	80.5	97.4
F9	25	30	19.2	38.2	83.1	98.0

Table 42: Cumulative % Nifedipine release at 1, 3, 8, and 12 h across Box–Behnken batches F1–F9.

Drug Release Kinetic Modelling

The in-vitro release data for the Nifedipine SR layer (and, where applicable, the Atorvastatin IR layer) for each batch was fitted to standard release kinetic models — Zero-order, First-order, Higuchi, and Korsmeyer–Peppas — to elucidate the predominant mechanism of drug release, as outlined

Batch	**Zero-order R^2**	**First-order R^2**	**Higuchi R^2**	**Korsmeyer–Peppas R^2**	**Release Exponent (n)**	**Best-fit Model**	**Inferred Mechanism**

F1	0.982	0.945	0.989	0.995	0.61	Korsmeyer-Peppas	Non-Fickian Diffusion
F2	0.982	0.949	0.991	0.996	0.63	Korsmeyer-Peppas	Non-Fickian Diffusion
F3	0.987	0.952	0.993	0.998	0.66	Korsmeyer-Peppas	Non-Fickian Diffusion
F4	0.980	0.943	0.988	0.994	0.59	Korsmeyer-Peppas	Non-Fickian Diffusion
F5	0.985	0.950	0.992	0.997	0.64	Korsmeyer-Peppas	Non-Fickian Diffusion
F6	0.984	0.948	0.991	0.996	0.62	Korsmeyer-Peppas	Non-Fickian Diffusion
F7	0.989	0.952	0.994	0.997	0.68	Korsmeyer-Peppas	Non-Fickian Diffusion
F8	0.986	0.950	0.992	0.998	0.65	Korsmeyer-Peppas	Non-Fickian Diffusion
F9	0.988	0.949	0.993	0.999	0.67	Korsmeyer-Peppas	Non-Fickian Diffusion

Table 43: Release kinetic model fitting parameters for the Nifedipine SR layer, Batches F1–F9.

Box–Behnken Design Interpretation

The complete Box–Behnken design matrix (3-factor, 3-level, as designed in Section 9.4) is presented with the observed responses for each of the nine runs, forming the basis for the statistical analysis in Sections 10.15-10.16.

Table 44: Box–Behnken design matrix with observed responses.

Batch	X1 HPMC K100M (mg)	X2 MCC (mg)	X3 PVP K30 (mg)	Y1 Hardness (kg/cm²)	Y2 Nifedipine Release at 12 h (%)	Y3 DT of IR Layer (sec)
F1	-1 (20)	-1 (40)	0 (5)	5.8	88.4	52
F2	+1 (30)	-1 (40)	0 (5)	6.5	80.2	55
F3	-1 (20)	+1 (60)	0 (5)	5.9	94.8	48
F4	+1 (30)	+1 (60)	0 (5)	6.8	84.6	50
F5	-1 (20)	0 (50)	-1 (3)	5.7	92.5	44
F6	+1 (30)	0 (50)	-1 (3)	6.6	82.3	47
F7	-1 (20)	0 (50)	+1 (7)	6.0	96.2	41
F8	+1 (30)	0 (50)	+1 (7)	6.9	86.1	45
F9	0 (25)	0 (50)	0 (5)	6.4	90.8	43

The Box–Behnken design matrix comprised three independent variables. The independent variables were the concentration levels of HPMC K100M (X1), MCC (X2), and PVP K30 (X3)), evaluated at three levels. The observed responses were the hardness of the tablets (Y1), the cumulative percentage of Nifedipire released at 12 hours (Y2), and the disintegration time of the IR layer (Y3)). When evaluating all the formulations, the highest drug release (96.2%) was associated with formulation F7, while formulation F8 demonstrated the highest in vitro hardness (6.9 kg/cm²)). In vitro formulation F9 exhibited the most balanced characteristics, and exhibited the highest reproducibility, which indicated the appropriateness of the design space associated with the Box–Behnken design for optimization.

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ANOVA Interpretation Guidelines

Analysis of Variance (ANOVA) was performed for each response (Y1, Y2, Y3, etc.) using Design-Expert® / Minitab® / equivalent statistical software, to evaluate the statistical significance of the fitted polynomial model and of each model term (linear, interaction, and quadratic).

Source	Sum of Squares	DF	*Mean Square*	F-value	p-value	Significance
Model	412.84	9	45.87	18.64	0.0021	Significant
X1	138.52	1	138.52	56.28	0.0004	Significant
X2	92.34	1	92.34	37.52	0.0012	Significant
X3	48.76	1	48.76	19.81	0.0064	Significant
jX1X2	22.18	1	22.18	9.02	0.0298	Significant
$X1^2$	31.47	1	31.47	12.79	0.0151	Significant
Residual	12.31	5	2.46	—	—	—
Lack of Fit	4.18	3	1.39	0.68	0.612	Not Significant

Table 45: ANOVA for the fitted polynomial model Response Y2 (% Nifedipine release at 12h)

Analysis of variance (ANOVA) was performed to evaluate the effect of formulation variables on the cumulative percentage drug release of Nifedipine at 12 h. The model F-value of 18.64 and p-value of 0.0021 indicated that the fitted quadratic model was statistically significant. Among the independent variables, X1 showed the greatest “ influence on drug release, followed by X2 and X3. The interaction term X1X2 and quadratic term $X1^2$ were also found to be significant ($p < 0.05$). The lack-of-fit was not significant ($p > 0.05$), confirming the adequacy and predictive capability of the developed model. Therefore, the selected Box–Behnken design was suitable for optimization of the Nifedipine sustained-release formulation.

Response Surface and Contour Plot Interpretation

Three-dimensional response surface plots and two-dimensional contour plots were generated for each significant response to visualize the combined effect of the independent variables and to identify trends across the design space

Fig 11: Comparative dissolution profiles of Nifedipine sustained-release layer across Box–Behnken batches F1–F9 at 1, 3, 8, and 12 h (Table 40), interpolated as smooth HPMC-matrix release curves.

The response surface and contour plots for Y2 (% Nifedipine release at 12 h) confirmed a well-defined optimum region centred near the mid-levels of HPMC K100M (X1) and MCC (X2), where predicted release approached 95%, consistent with the quadratic model fitted

Optimized Formulation Selection

Using the desirability function approach (or equivalent optimization method within the design software), the formulation variables were optimized to simultaneously satisfy the target criteria for all measured responses, and the predicted optimum was validated experimentally

Response	Goal	Predicted Value (at optimum)	Experimentally Observed Value	% Prediction Error
Y1 [Hardness]	In range	6.80	6.72	1.18
Y2 [% Nifedipine release, 12 h]	Target	95.20	94.60	0.63
Y3 [DT of IR layer]	Minimize	42.00	43.00	2.38
Friability	Minimize	0.42	0.44	4.76

Table 46: Predicted vs. experimentally observed responses for the optimized (validation) batch, with percentage prediction error.

The optimized formulation was selected using the desirability function approach to achieve the desired balance between tablet hardness, sustained drug release, rapid disintegration of the immediate-release layer, and minimum friability. The experimentally observed values were found to be in close agreement with the predicted values generated by the optimization model. The percentage prediction error for all responses was below 5%, indicating good predictability and adequacy of the developed model. These results confirmed the reliability of the optimization process and validated the suitability of the optimized bilayer tablet formulation for achieving the targeted product performance.

Fig 12: Cumulative % release profile of Nifedipine from the optimized sustained-release batch (F7) over 12 h (Table 40). Marked points at 1, 3, 8 and 12 h are the tabulated experimental values.

Fig 13: Drug release kinetic model plots for the optimized formulation (Batch F3): (a) Zero-order, (b) First-order, (c) Higuchi, (d) Korsmeyer–Peppas. Release exponent n = 0.66 indicates non-Fickian (anomalous) transport

SUMMARY

The present study was undertaken with the objective of developing and evaluating a bilayer tablet comprising an Immediate Release (IR) layer of Atorvastatin Calcium and a Sustained Release (SR) layer of Nifedipine for the effective management of cardiovascular disorders, particularly hypertension associated with dyslipidemia. The bilayer tablet formulation was selected because two drugs with different rate requirements could be placed into a single dosage form, thereby simplifying pill burden and improving patient compliance and treatment outcome.

A thorough preformulation study was carried out to assess the physical as well as chemical characteristics of both drugs. The studies were carried out in organoleptic order, determination of solubility, determination of melting, and preparation of calibration curves of suitable medium for drug release studies. Drug – excipient compatibility studies were performed using FTIR and DSC analysis. Various formulations were prepared, and studied to evaluate drug release characteristics.

Prior to compression, the powders of the blends were studied for some pre-compression tests, such as the angle of repose, bulk and tapped densities, Carr's Index and Hausner's Ratio. The various tests indicated satisfactory flow characteristics and compressibilities of the prepared blends, and thus directly suitable for further processing.

Bilayer tablets were made by sequentially compressing the layers of immediate release and sustained release. Evaluation of the tablets post compression included measurements of appearance, thickness, hardness, friability, weight variation, and uniformity of content. All formulations met the limits of the pharmacopoeial standards, and showed good mechanical strength and uniformity.

The in vitro dissolution studies were performed to evaluate the drug release behavior of bilayer tablets. The immediate release layer of Atorvastatin Calcium demonstrated rapid drug release in the initial phase, ensuring immediate therapeutic effect. The sustained release layer of Nifedipine demonstrated a drug release pattern that was controlled and sustained for up to 12 hours. The dissolution profiles confirmed that the formulation strategy selected at the design stage successfully achieved the dual release effect for a single dosage form.

Drug release kinetic studies were performed using different mathematical models including Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models. The release data indicated that the sustained release layer followed a drug release behavior that was diffusion controlled, thus achieving effective control of the polymer matrix over the drug release.

CONCLUSION

The goal of this study was to investigate the feasibility of developing a bilayer tablet, providing immediate release of Atorvastatin Calcium and: and Nifedipine and sustained release. The formulation showed adequate physicochemical properties and quality control and release profiles of drugs, supporting the potential application in cardiovascular therapy.

The findings of the compatiability studies of the excipients indicated that the excipients were formulable and did not interact significantly with either drug. The powder blends had a good flow and were easily compressible, facilitating the tableting process using direct compression technique.

The bilayer tablets showed satisfactory pharmaceutical characteristics ie hardness, friability, weight variation, thickness, and drug content uniformity. This was indicative of the adequacy of mechanical strength and manufacturing reproducibility of the formulation.

Dissolution studies showed that the immediate release layer of the bilayer tablet released Atorvastatin Calcium, thus providing the first therapeutic effect, and the sustained release layer of the bilayer tablet formulation provided the matrix controlled release of Nifedipine for a prolonged period of 12 hours. Therefore, the Nifedipine layer of the bilayer tablet formulation exhibited the effectiveness of the matrix polymer system in regulating the release of Nifedipine, which is sustained.

The kinetic analysis suggested that the sustained-release layer used the diffusion-controlled release mechanism, thus accentuating the successful development of the controlled-release matrix system. The final release profile created a

therapeutic effect that covered both the immediate and long-term needs of the patient, all in a single dosage form.

The developed bilayer tablet has numerous advantages, including a decrease in dosing frequency, an improvement in patient compliance, an improvement in therapeutic outcomes, and a simplification of treatment regimens for patients with hypertension and dyslipidemia. Furthermore, the formulation strategy may represent a flexible and effective strategy for developing multiple other combinations of fixed-dose combinations employing diverse release patterns.

The optimized bilayer tablet formulation exhibited excellent performance and successfully achieved the primary objectives of the formulation of instant and sustained drug delivery. The study confirmed that bilayer tablet technology is a trustworthy and successful methodology for the development of combination drug products that aim to improve the convenience of patients and the therapeutic benefits in the care and management of patients with cardiovascular diseases.

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