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DESIGN, FORMULATION AND EVALUATION OF BILAYER TABLETS CONTAINING ATORVASTATIN CALCIUM (IR) AND ATENOLOL (SR)

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ABSTRACT

The present study involves the formulation and evaluation of regio-selective bilayer tablets containing Atorvastatin Calcium as the immediate-release (IR) layer and Atenolol as the sustained-release (SR) layer for effective management of hyperlipidaemia and hypertension. The IR layer was developed using croscarmellose sodium to achieve rapid release of Atorvastatin, while the SR layer was optimized using a 3^2 factorial design incorporating varying concentrations of HPMC K100M and Xanthan gum to modulate the release of Atenolol. Preformulation studies including FTIR and DSC confirmed the absence of drug–excipient incompatibilities. Nine trial formulations (F1–F9) were evaluated for physicochemical parameters and *in-vitro* drug release profiles. The optimized formulation (F6) showed desirable results with drug release of 36.8% at 2 h, 73.7% at 6 h, and at 90% of 10.1 h. Drug release followed First-order and Higuchi models with non-Fickian diffusion, as indicated by the Korsmeyer–Peppas model. Stability studies confirmed the robustness of the formulation under ICH-recommended conditions. The developed bilayer tablets offer a promising approach for providing biphasic release and improving patient compliance in combination therapy.

KEYWORDS: Atorvastatin calcium, Atenolol, Bilayer tablet, Sustained release, 3^2 factorial design, Drug release kinetics.

1. INTRODUCTION

Cardiovascular diseases (CVDs), including hypertension and hyperlipidaemia, remain the foremost causes of morbidity and mortality globally.[1] These comorbid conditions often require long-term pharmacotherapy, and managing them effectively involves the use of multiple drugs, often from different pharmacological classes.[2] In such clinical scenarios, fixed-dose combination (FDC) therapy has emerged as a rational and effective strategy. Among various FDC approaches, the bilayer tablet format offers a unique advantage by enabling the delivery of two drugs with different release kinetics in a single oral dosage form.[3]

The bilayer tablet format can improve patient adherence, reduce pill burden, and provide spatial and temporal drug release by allowing one drug to be released immediately and another to be released in a sustained or delayed manner.[4] This is particularly beneficial in managing cardiovascular diseases where prompt and prolonged therapeutic action is desired from two different agents.

Atorvastatin Calcium is a lipid-lowering agent from the statin class that functions by inhibiting HMG-CoA reductase, an enzyme critical for cholesterol biosynthesis.[5] It undergoes extensive first-pass metabolism, and its bioavailability can be improved through controlled delivery systems.[6] Rapid onset of action, however, is crucial in certain acute settings, justifying its use in the immediate-release (IR) layer of a bilayer tablet.

On the other hand, Atenolol, a cardio-selective β_1-blocker, is widely prescribed for hypertension and angina pectoris.[7] It has a short half-life and requires sustained plasma levels to maintain therapeutic efficacy. Therefore, incorporating Atenolol into a sustained-release (SR) matrix layer helps maintain stable plasma concentrations and reduces dosing frequency.[8]

In this study, a regio-selective bilayer tablet was formulated to combine the IR release of Atorvastatin with the SR release of Atenolol, tailored for site-specific absorption along the gastrointestinal tract. A 3^2 factorial design was used to optimize the formulation, with HPMC K100M and Xanthan gum as the key matrix-forming polymers in the sustained layer. Comprehensive preformulation and characterization studies—including powder flow analysis, compatibility studies (FTIR/DSC), *in-vitro* dissolution, release kinetics, and stability

testing—were carried out to evaluate the pharmaceutical performance and robustness of the developed bilayer system.[9,10]

2. MATERIALS AND METHODS

2.1 Materials

Atorvastatin Calcium and Atenolol were obtained as gift samples from Amoli Organics Pvt. Ltd. and Yarrow Chem Products, respectively. HPMC K100M and Xanthan Gum were used as matrix-forming polymers, while Croscarmellose Sodium was employed as a superdisintegrant. Additional excipients included lactose monohydrate, PVP K30, aerosil, magnesium stearate, talc, and coloring agents (carmine, tartrazine). All chemicals and reagents used were of analytical or laboratory grade and complied with pharmacopoeial standards.[11]

2.2 Preformulation Studies

Preformulation is a critical phase in formulation development, providing information on drug-excipient compatibility and physical properties. Melting points of the drugs were determined using a digital melting point apparatus.[12] Drug–excipient compatibility was evaluated using FTIR spectroscopy and DSC analysis.[11,13]

FTIR analysis was performed using the potassium bromide pellet method, while DSC thermograms were recorded using sealed aluminium pans under a nitrogen atmosphere.

2.3 Analytical Methods

The analytical wavelengths (λ max) for Atorvastatin Calcium and Atenolol were determined using a UV-Vis spectrophotometer (Shimadzu UV-1800) by scanning between 200–400 nm in pH 1.2 and 7.4 buffer solutions.[14] Calibration curves were constructed, and simultaneous estimation was done using Q-analysis at 226 nm and 246 nm.[14,15]

2.4 Formulation of Bilayer Tablets

Bilayer tablets were prepared using direct compression for the IR layer and wet granulation for the SR layer. The IR layer (Atorvastatin Calcium) was formulated using Croscarmellose Sodium for rapid disintegration.[16] The SR layer (Atenolol) incorporated HPMC K100M and Xanthan Gum as release-retarding polymers. Wet granulation was carried out using PVP K30 in isopropyl alcohol as a binder.[11]

The two layers were compressed sequentially using an 8-station rotary tablet press fitted with 9 mm round flat-faced punches.[11,17]

2.5 Evaluation of Tablets

Post-compression evaluation included weight variation, thickness, hardness, friability, and drug content as per IP and USP specifications.[11,18] Thickness was measured using a digital vernier caliper, hardness using Monsanto tester, and friability using a Roche friabilator. Drug content uniformity was analyzed using UV spectrophotometry at respective λmax.

2.6 *In-vitro* Dissolution Studies

Dissolution testing was performed using USP Type II (paddle) apparatus at 50 rpm. The medium consisted of 900 mL of pH 1.2 HCl buffer for the first 2 hours followed by phosphate buffer (pH 7.4) for the next 10 hours, maintained at 37 ± 0.5°C.[18,19] Samples were withdrawn at predetermined intervals, filtered, and analyzed using UV spectrophotometry.

2.7 Kinetic Modeling

Drug release data were analyzed by fitting into various kinetic models: Zero-order, First-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell models to identify the drug release mechanism.[20,23] The model with the highest regression coefficient (R^2) was considered best fitting. The *n* value from the Peppas model indicated whether the release was Fickian, non-Fickian, or Case-II transport.[22]

2.8 Statistical Optimization (3^2 Full Factorial Design)

A 3^2 full factorial design was employed to study the influence of two independent variables: amount of HPMC K100M (X_1) and Xanthan Gum (X_2), on dependent variables like cumulative drug release at 2 h, 6 h, and t_{90}%.[24] The experimental runs (F1–F9) were fitted to a second-order polynomial equation. Contour plots were generated to interpret the interactions, and statistical significance was evaluated using regression and ANOVA techniques.[19,24]

2.9 Stability Studies

The optimized bilayer tablet formulation was subjected to accelerated stability testing as per ICH Q1A(R2) guidelines at 40 ± 2°C and 75 ± 5% RH for three months.[25] Tablets were evaluated at 0, 30, 60, and 90 days for physical appearance, drug content, and dissolution profile.

Table no. 1: Composition of immediate release layer of Atorvastatin calcium.

Ingredients(Immediate release)	Quantity per tablet(mg)
Drug (Atorvastatin Calcium)	10
Lactose Monohydrate	116
Croscarmellose Sodium	6
PVPK30	8
Aerosil	5
Magnesium Stearate	3
Talc	2
Color Carmine	1-2
Total(mg)	150

Table No. 2: Composition of Sustained Release layer of Atenolol.

Ingredients (Sustained Release)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (Atenolol)	50	50	50	50	50	50	50	50	50
Lactose monohydrate	115	110	105	105	100	95	95	90	85
Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
HPMC K100M	10	10	10	20	20	20	30	30	30
Xanthan gum	5	10	15	5	10	15	5	10	15
PVP K30	9	9	9	9	9	9	9	9	9
Isopropyl alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Talc	3	3	3	3	3	3	3	3	3
Color Tartrazine	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2
Total	200	200	200	200	200	200	200	200	200

Table No. 3: Composition of factorial batches.

Batch	Variable level in coded form		
	X1		X2
F1	-1		-1
F2	-1		0
F3	-1		+1
F4	0		-1
F5	0		0
F6	0		+1
F7	+1		-1
F8	+1		0
F9	+1		+1
Independent variable	Real values		
	low(-1)	medium(0)	high(+1)
HPMC K100M (X1)	10	20	30
Xanthan gum (X2)	5	10	15
All the batches contain 50 mg of Atenolol in sustained release layer			

3. RESULTS AND DISCUSSION

3.1 Preformulation and Compatibility Studies

3.1.1 Melting Point

The melting points of Atorvastatin calcium (162 °C) and Atenolol (157 °C) fall within the standard pharmacopeial range (159–165 °C and 152–157 °C, respectively), confirming purity and compliance with official standards.

3.1.2 Drug–Excipient Compatibility

FTIR Analysis -Characteristic peaks of both drugs were retained in the physical mixture, indicating no significant chemical interaction. IR spectra confirmed the compatibility of Atorvastatin and Atenolol with formulation excipients.

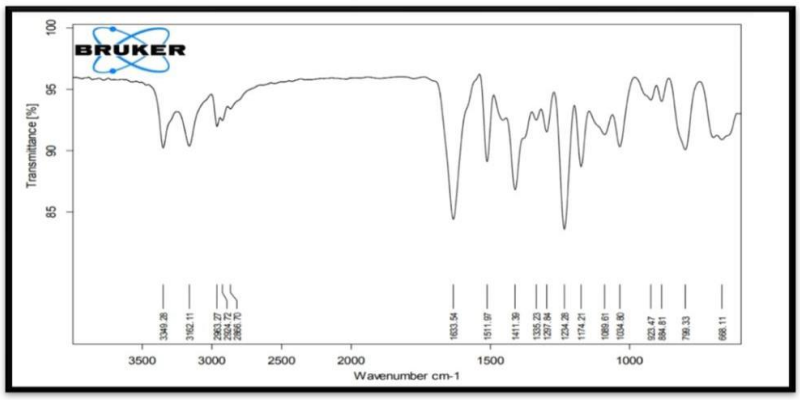

Figure No. 1: FT-IR Spectra of ATENOLOL.

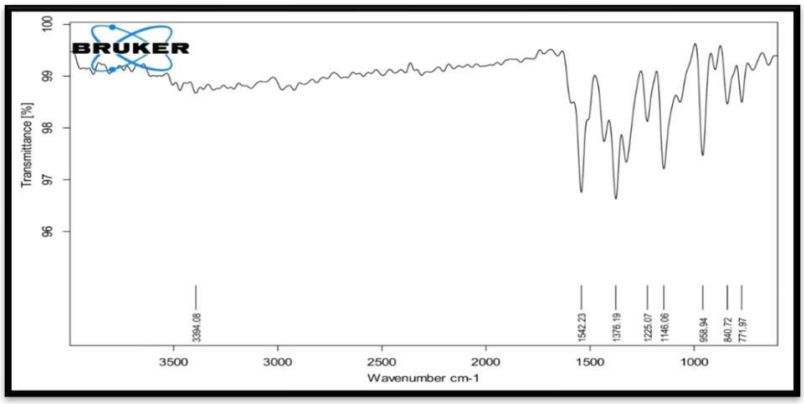

Figure No. 2: FT-IR Spectra of Atorvastatin calcium.

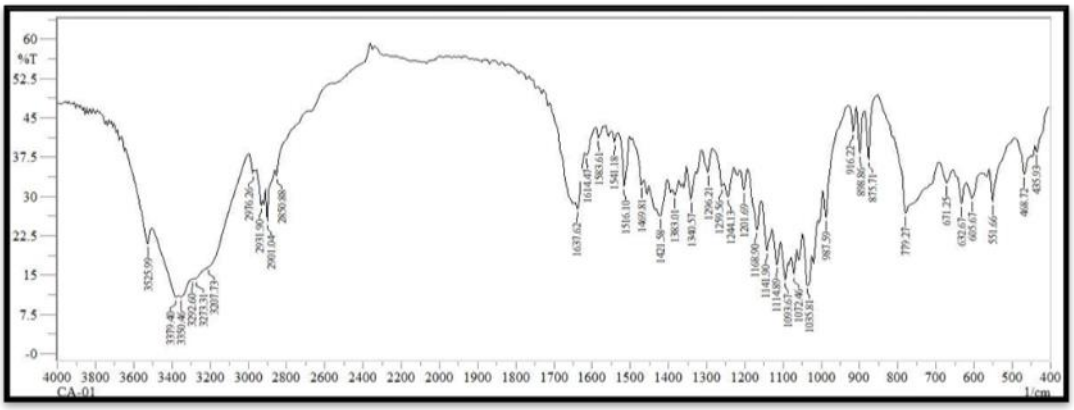

Figure No. 3: FT-IR Spectra of physical mixture of AT+ATV + polymers.

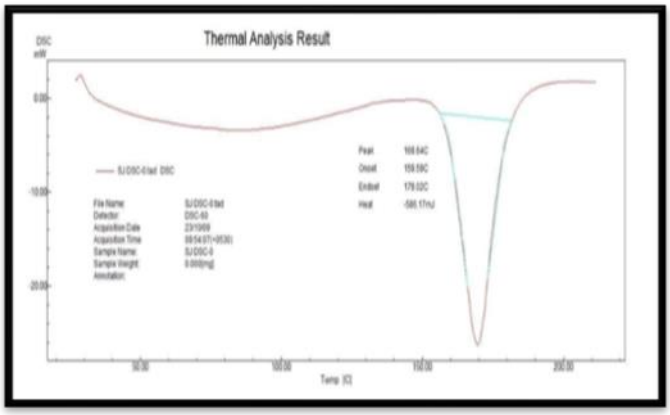

Figure No. 4: DSC of Atenolol.

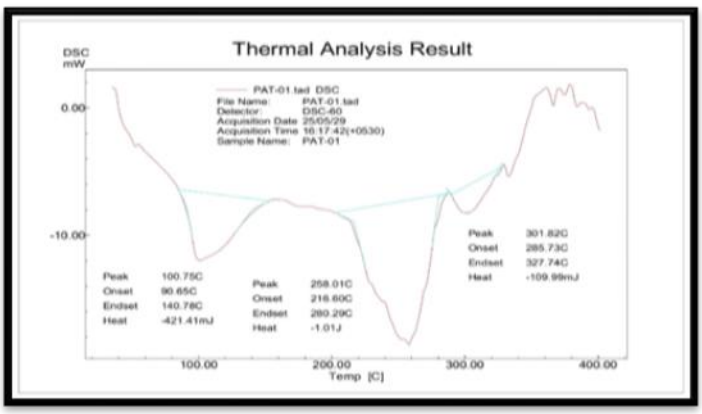

Figure No. 5: DSC of Atorvastatin calcium.

DSC Analysis-Sharp endothermic peaks of pure Atorvastatin and Atenolol were observed at 169.38 °C and 169.64 °C, respectively. The physical mixture showed negligible shift, further confirming no interaction between drug and polymers.

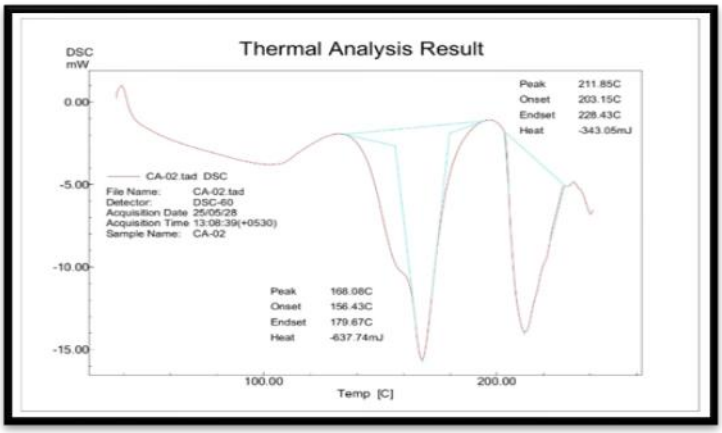

Figure No. 6: DSC of physical mixture of Drugs and Polymers.

3.2 Analytical Method and Calibration

3.2.1 λmax Determination

Atorvastatin calcium: 246 nm (λmax in both pH 1.2 and 7.4 buffer)

Atenolol: 226 nm (λmax in both pH 1.2 and 7.4 buffer)

3.2.2 Calibration Curves

Standard calibration curves were linear

Atorvastatin: 5–25 µg/mL (R^2 = 0.9994–0.9996)

Atenolol: 2–12 µg/mL (R^2 = 0.999–0.9998)

3.3 Evaluation Parameters

3.3.1 Pre-compression Evaluation

IR and SR blends showed excellent flow and compressibility:

Table No. 4: Precompression study of powder blend of immediate release layer.

Parameters	Immediate release layer
Bulk Density(g/ml)	0.444±0.014
Tapped Density(g/ml)	0.5188±0.024
Carr's Compressibility Index (%)	14.41±0.841
Hausner's Ratio	1.16±0.0763
Angle of Repose(θ)	30.12±0.661

Table No. 5: Precompression parameters of granules of sustain release layer.

FC	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Compressibility Index (%)	Hausner's Ratio	Angle of Repose (θ)
F1	0.488±0.005	0.563±0.011	13.32±0.773	1.15±0.015	23.87±0.233
F2	0.443±0.017	0.530±0.017	9.21±0.840	1.09±0.011	24.21±0.411

F3	0.448±0.007	0.515±0.009	13.13±0.773	1.14±0.007	25.12±0.433
F4	0.437±0.043	0.514±0.012	14.81±0.773	1.17±0.005	24.12±0.143
F5	0.398±0.004	0.447±0.004	10.96±0.003	1.12±0.012	23.88±0.933
F6	0.438±0.007	0.511±0.007	14.21±0.631	1.16±0.005	24.23±0.898
F7	0.441±0.006	0.515±0.017	14.38±0.873	1.16±0.009	22.92±0.360
F8	0.433±0.004	0.516±0.011	14.24±0.443	1.16±0.013	23.22±0.960
F9	0.398±0.006	0.448±0.007	11.16±0.773	1.12±0.005	24.19±0.260

6.3.2 Post-compression Evaluation

All nine bilayer formulations met pharmacopeial specifications:

Table No. 6: Post compressional parameters of Atorvastatin calcium and Atenolol bilayer tablet.

Parameters						
FC	**Thickness (mm)**	**Hardness (kg/cm2)**	**Friability (%)**	**Weight Variation (mg)**	**Drug Content of ATV (%)**	**Drug Content of AT (%)**
F1	4.16±0.01	4.9±0.26	0.74±0.8	345±0.52	99.66±0.4	98.70±0.7
F2	4.21±0.08	5.32±0.2	0.49±0.3	346±0.52	98.43±0.8	98.13±0.2
F3	4.14±0.01	5.13±0.3	0.43±0.7	344±0.66	99.36±0.6	99.92±0.7
F4	4.22±0.01	5.03±0.2	0.44±0.8	347±0.4	99.03±0.8	99.63±0.2
F5	4.23±0.02	5.24±0.1	0.43±0.9	345±0.67	98.73±0.2	98.82±0.7
F6	4.17±0.01	5.26±0.2	0.48±0.5	349±0.43	98.01±0.3	98.91±0.7
F7	4.22±0.01	5.32±0.3	0.43±0.8	349±0.52	99.34±0.4	98.11±0.92
F8	4.24±0.02	5.24±0.3	0.53±0.4	350±0.99	98.42±0.8	98.41±0.8
F9	4.20±0.02	5.40±0.2	0.55±0.3	351±0.92	98.11±0.8	97.51±0.91

3.3 Optimization via 3^2 Design

A 3^2 full factorial design was employed with two independent variables (HPMC K100M and Xanthan gum) and three dependent responses (% drug release at 2 and 6 hours, and t_{90}%).

The polynomial equations for each response demonstrated significant model fit ($p < 0.05$) and $R^2 > 0.97$ for all responses. Formulation F6 was identified as optimized.

Table No. 7: Response variables (R1–R3) obtained from various trial formulations of Atenolol 50 mg SR tablets.

			Factor X_1	Factor X_2	Response Y_1	Response Y_2	Response Y_3
Std	**Run**	**Space type**	**A:HPMCK100M**	**B:XANTHANGUM**	**Drug release after 2 hr**	**Drug release after 6 hr**	**Time for 90% drug release**
			mg	**mg**	**%**	**%**	**hr**
1	**3**	Factorial	10	5	52.55	90.3	6
2	**1**	Axial	10	10	45.87	85.7	7.2
3	**6**	Factorial	10	15	43.8	84.4	7.8
4	**8**	Axial	20	5	42.1	83.5	8.9
5	**2**	Centre	20	10	39.6	81.3	9.2
6	**5**	Axial	20	15	36.8	73.7	10.1
7	**4**	Factorial	30	5	32.7	71.9	9.8
8	**7**	Axial	30	10	28.5	69.4	10.2
9	**9**	Factorial	30	15	26.8	62.7	12.2

6.4 *In-vitro* Dissolution Study

Immediate Release Layer: Atorvastatin released >90% within 60 minutes in all formulations due to efficient disintegration via croscarmellose.

Sustained Release Layer: Atenolol release was inversely related to HPMC K100M concentration.

F6 showed ideal release profile

36.8% at 2 h

73.7% at 6 h

t_{90}% = 10.1 h

This confirms matrix control via HPMC and Xanthan gum.

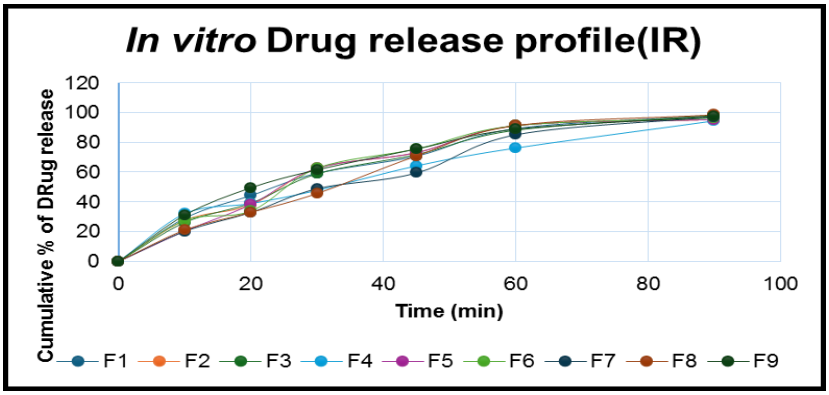

Figure No. 7: *In vitro* dissolution profile of IR layer of Atorvastatin calcium.

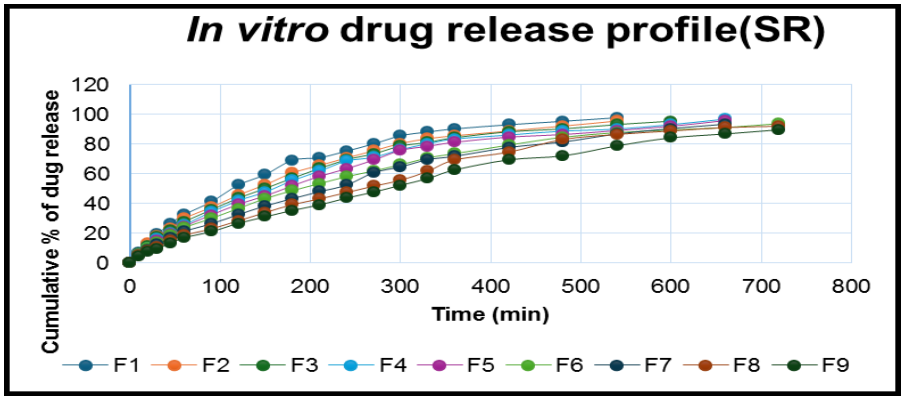

Figure No. 8: *In vitro* dissolution profile of SR layer of Atenolol.

3.5 *In-Vitro* Drug Release and Kinetics

The immediate-release layer of Atorvastatin Calcium disintegrated rapidly, releasing over 95% of drug content within 30 minutes. The sustained-release layer of Atenolol demonstrated controlled release over 12 hours. Drug release data of F6 was best described by:

- **First-order model** (R^2 = 0.9978), indicating concentration-dependent release,
- **Higuchi model** (R^2 = 0.9893), signifying diffusion-controlled mechanism,
- **Korsmeyer–Peppas model** with an 'n' value of 0.7405, suggesting anomalous (non-Fickian) transport involving both diffusion and erosion.

These results confirm that the selected polymers effectively controlled the release of Atenolol over an extended period.

Table No. 8: Release kinetics data of all the formulations.

Formulation code	Zero order	First order	Higuchi	Korsmeyer peppas	
	R^2	R^2	R^2	n	R^2
F1	0.8699	0.9914	0.9769	0.9969	0.9969
F2	0.9008	0.9953	0.9864	0.9948	0.9948
F3	0.8874	0.9980	0.9820	0.9969	0.9969
F4	0.8730	0.9879	0.9766	0.7788	0.9976
F5	0.8877	0.9899	0.9799	0.7666	0.9978
F6	0.9053	0.9978	0.9893	0.7405	0.9982
F7	0.9441	0.9878	0.9897	0.7216	0.9990
F8	0.9541	0.9833	0.9823	0.7047	0.9997
F9	0.9684	0.9860	0.9843	0.6993	0.9992

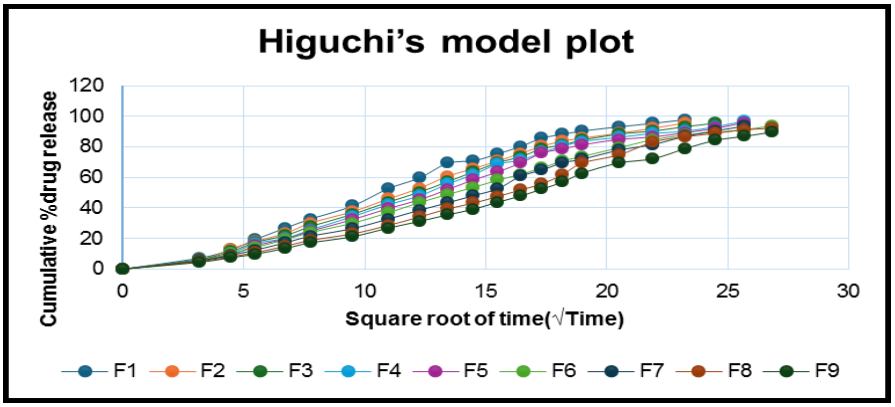

Figure No. 10: Higuchi Release Plot of All Formulations.

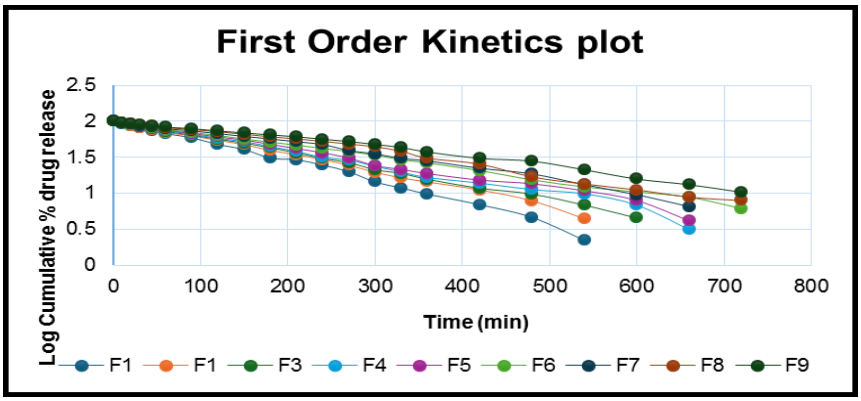

Figure No. 9: First Order Release Plot of All Formulations.

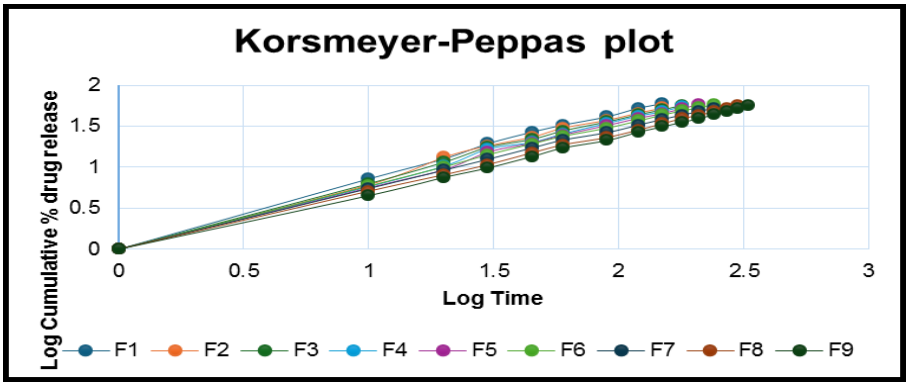

Figure No. 11: Korsmeyer-Peppas Release Plot of All Formulations.

3.5 Stability Study

The optimized formulation (F6) was subjected to accelerated stability testing at 40 ± 2°C and 75 ± 5% RH for three months. There were no significant changes in physical appearance, drug content, or dissolution profile, confirming the stability of the bilayer tablets under stress conditions.

Table No. 9: Stability study of formulation F6.

Time (month)	Drug content (%) of ATV	Drug content (%) of AT
Zero	99.36±0.52	99.11±0.92
First	99.12±0.44	99.16±0.22
Second	99.55±0.13	99.32±0.87
Third	99.13±0.42	99.36±0.11

4. CONCLUSION

The study successfully developed a bilayer tablet incorporating Atorvastatin Calcium in an immediate-release layer and Atenolol in a sustained-release layer. The use of a 3^2 factorial design enabled effective optimization of the matrix layer using HPMC K100M and Xanthan gum. The optimized formulation (F6) showed desirable release characteristics and followed First-order and Higuchi kinetics with anomalous diffusion as per the Korsmeyer–Peppas model. Stability studies confirmed formulation integrity under accelerated conditions. The developed bilayer tablet represents a promising approach for fixed-dose combination therapy in the treatment of hypertension and hyperlipidemia, improving therapeutic efficacy and patient compliance.

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