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DEVELOPMENT & CHARACTERIZATION OF BILAYER IMMEDIATE AND SUSTAINED RELEASE TABLETSOF ATORVASTATIN CALCIUM AND NICOTINICACID

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ABSTRACT

The significance of controlled drug delivery systems has grown substantially in recent times, with bilayer tablets emerging as a prominent example. These tablets combine two distinct ingredients to create a dual-layered structure, enabling both immediate and sustained release of drugs. This innovative design not only addresses issues of drug incompatibility but also facilitates a gradual and consistent release of active pharmaceutical compounds in a sigmoidal pattern over an extended period. This approach ensures the maintenance of optimal plasma drug concentrations, often surpassing the maximum effective levels, for a prolonged duration. By curbing drastic dosage fluctuations commonly observed in traditional dosage forms, bilayer tablets offer a stable therapeutic outcome. Moreover, they enhance patient compliance by reducing dosing frequency. Additionally, these tablets prove advantageous by effectively treating multiple ailments in a single patient, thereby offering a holistic solution to co-morbid conditions through a singular medication format.

INTRODUCTION

The dual-release unit compressed tablet dosage form designed for oral administration embodies a distinctive approach in pharmaceutical development.[1] This innovative dosage form comprises two distinct segments: an immediate release section and a sustained release counterpart. The former ensures swift drug release, functioning akin to a loading dose facilitated by super disintegrants, while the latter upholds controlled and prolonged drug release over an extended period.[2] This dual-layer arrangement accommodates chemically incompatible substances within the same tablet, effectively addressing challenges of mixed granulation. A pivotal facet of this approach is its ability to incorporate different drugs within a single tablet, affording divergent pharmacological actions concurrently.[3] By harmonizing distinct release characteristics for each layer, the aim is to optimize therapeutic efficacy and patient convenience. A fundamental objective of controlled drug delivery systems is to diminish dosing frequency, a parameter directly linked to patient compliance.[4] Modified release drug products are strategically designed to administer medication gradually and continuously throughout the dosing interval, thereby promoting enhanced patient adherence. The formulation strategy for these bilayer tablets is meticulous. The immediate release layer is empowered by super disintegrants, which expedite drug release, ensuring swift onset of action resembling a loading dose.[5] Conversely, the sustained release layer incorporates low viscosity polymers to maintain drug bioavailability and enable prolonged, controlled drug release. This dual-release system finds particular suitability in medications like anti-histamines, anti-allergics, coronary vasodilators, and analgesics. A case in point is the research endeavor centered on developing bilayer tablets containing Atorvastatin Calcium and Nicotinic acid. The research commences with a comprehensive preformulation phase encompassing essential parameters such as angle of repose, bulk density, tapped density, physicochemical properties, compressibility index, and compactability studies.[6] This phase establishes a solid foundation for the subsequent steps. Postformulation studies, constituting the subsequent phase, are equally vital. These studies encompass drug content analysis, in vitro dissolution studies, and comprehensive evaluations, including stability assessments. The excipients utilized in formulating Atorvastatin Calcium tablets encompass an array of elements such as Calcium Carbonate,

MCCPH101, Lactose plain, Magnesium stearate, Ponceau 4R lake, CCS, HPC, polysorbate, and MCCPH102. Similarly, for the Nicotinic acid tablets, the formulation involves HPMCK100 and PVPK 90. Evaluation of the formulated bilayer tablets primarily hinges on in vitro dissolution release profiles, which serve as a criterion for selecting the most appropriate formulation for subsequent stability studies.[7] This meticulously orchestrated research holds the potential to advance pharmaceutical sciences by yielding effective, patient-centric therapeutic solutions.

METHODOLOGY

Atorvastatin calcium was received as research sample from Biocon limited Bangalore, Nicotinic acid was obtained from Aarti drugs Mumbai, Povidone K 90, Isopropyl alcohol, polysorbate 80 were received from Fisher ltd Chennai, CCS(crosscarmellose sodium), Stearic acid, Magnesium stearate from Jain Enterprises, Mumbai.

Preformulation Studies

Preformulation is the foremost stage in dosage form development, involving the study of a drug's physical and chemical attributes alone and with excipients. Key parameters assessed encompass drug's physicochemical traits, solubility, pH sensitivity, melting point, chemical characteristics, hygroscopicity, loss on drying, particle size, and flow properties.[8]

Compatibility studies of the drug with excipients

The information obtained from Preformulation studies indicates many of the subsequent events and approaches to be taken into consideration during formulation development. Parameters such as Angle of repose, Bulk and tapered density, Carr's index, Hausner ratio were observed.[9]

TABLE 1: ANGLE OF REPOSE.

S.no	Raw Material (api)	Angle of Repose (degrees)	Flow Property
1.	Atorvastatin Calcium	79.239	Very very Poor
2.	Nicotinic Acid	74.875	Very very poor

Table 2: Drug Content.

S.no	Raw Material (api)	Assay (%)
1.	Atorvastatin Calcium	99.56
2.	Nicotinic Acid	99.80

COMPATIBILITY STUDIES

This compatibility studies was carried out using the drug total excipients in different ratio and kept in stability conditions for one month in 40^0C per 75% relative humidity and 60^0C in 2 milliliters glass vial in closed condition. Excipients were mixed with Atorvastatin calcium and Nicotinic acid in the following ratio given in the table. According to compatibilities in trial and error method the formula of drug profile was conformed. The drug was mixed with the excipients in the ratio of 1:1 and 1:5 and the observation were noted.[10]

INFERENCE

Observations were concluded that the excipients selected for formulation of IR and ER compatible with Atorvastatin calcium and nicotinic acid.

ACCELERATED CONDITIONS

This study was done by including stress at different temperatures. The rate of reaction increases with in temperature. The drug was mixed with the excipients in the ratio 1:1 and 1:5 and were subjected to different temperatures.[11] The study was done for 1 month and the observations are given in the table. 40^0C, RH – 75%. Room temperature.

PREPARATION OF ATORVASTATIN CALCIUM TABLETS

Table 3: Formula For Atorvastatin Calcium Tablets with Their Specifications.

S.no	Ingredients	Specification	Qty (Mg/Tab)
1	Atorvastatin calcium	I.H.S	10.34
2	Calcium carbonate	I.P	38.00
3	MCCPH 101	I.P	55.00
4	Lactose plain	I.P	16.00
5	Ponceau 4R lake	I.H.S	0.20
6	CCS	USNF	8.50
7	HPC	I.P	1.50
8	Polysorbate 80	I.P	1.00
9	MCCPH 102	I.P	10.00
10	CCS	NF	7.50
11	Magnesium Stearate	I.P	1.50
12	Purified water		Q.S

PREPARATION OF NICOTINIC ACID TABLETS

Table 4: Formula For Nicotinic Acid Tablets Along with Their Specifications.

S.no	Ingredients	Specification	Qty (Mg/Tab)
1	Nicotinic acid	B.P	500.00
2	HPMC K 100	B.P	120.00
3	PVP K 90-	B.P	18.60
4	IPA	B.P	Q.S
5	STEARIC ACID	B.P	46.40

RESULTS AND DISCUSSION

PRECOMPRESSION PARAMETER

BULK DENSITY

Table 5: Bulk Density Values of Granules For Bilayer Tablets.

S.NO	GRANULES	BULK DENSITY (g/ml)					
		T1	T2	T3	T4	T5	AVERAGE
1.	SR PART	0.542	0.549	0.541	0.543	0.555	0.546
2.	IR PART	0.272	0.277	0.270	0.278	0.278	0.275

TAPPED DENSITY

Table 6: Tapped Density Value of Granules For Bilayer Tablets.

S.NO	GRANULES	TAPPED DENSITY(G/ML)					
		T1	T2	T3	T4	T5	AVERAGE
1.	SR PART	0.597	0.601	0.594	0.595	0.608	0.599
2.	IR PART	0.300	0.307	0.299	0.308	0.307	0.304

CARR'S INDEX

Table 7: Carr's Index Value of Granules For Bilayer Tablets.

S.NO	GRANULES	CARR'S INDEX (%)					
		T1	T2	T3	T4	T5	AVERAGE
1.	SR PART	9.213	8.652	8.923	8.740	8.718	8.849
2.	IR PART	9.333	9.772	9.699	9.740	9.446	9.598

HAUSNER RATIO

Table 8: Hausner Ratio Values of Granules For Bilayer Tablets.

S.NO	GRANULES	HAUSNER RATIO					
		T1	T2	T3	T4	T5	AVERAGE
1.	SR PART	1.102	1.095	1.098	1.095	1.096	1.097
2.	IR PART	1.105	1.108	1.107	1.109	1.106	1.107

ANGLE OF REPOSE

Table 9: Angle of Repose Values of Granules For Bilayer Tablets.

S.NO	GRANULES	MOISTURE CONTENT (%)					
		T1	T2	T3	T4	T5	AVERAGE
1.	SR PART	29.98	30.O5	30.02	30.07	30.08	30.04
2.	IR PART	30.06	30.08	29.99	30.05	30.02	30.04

POST COMPRESSION PARAMETERS[12]

PHYSICAL PARAMETERS

Pink and white colored oblong shaped uncoated bilayer tablet with a score in the middle on the side.

WEIGHT VARIATION TEST

20 tablets selected at random were weighed individually and their deviation from the average weight of tablets by more than 5% and none deviated by more than twice that %.

% Deviation = Individual weight - Average weight/ Average weight *100

Table 10: Weight Variation Test.

S.NO	Tablet Form	%DEVIATION	
		Minimum	Maximum
1.	Bilayer Tablet	0.17	1.24

THICKNESS TEST

5 tablets were taken in random and individual thickness of each tablet was determined by Vernier Caliper. The average thickness was calculated and recorded.

TABLE 11: THICKNESS TEST

S.No	TABLET FORM	THICKNESS (mm)					
		T1	T2	T3	T4	T5	AVERAGE
1.	Bilayer Tablet	7.25	7.37	7.28	7.33	7.32	7.31

HARDNESS TEST

5 tablets were selected in random and individual hardness of each tablet was determined by hardness tester. The average hardness was calculated and recorded.

Table 12: Hardness Values For Bilayer Tablets.

S.No	Tablet Form	Hardness (kg/c^{m2})					
		T1	T2	T3	T4	T5	AVERAGE
1.	Bilayer Tablet	9.10	9.40	9.20	9.30	9.40	9.27

FRIABILITY TEST

10 tablets were taken and weighed. The tablet were placed in the drum and rotated for 100 times. Then the tablets were removed and reweighed. The maximum weight loss should not be more than 1% of weight of tablet.

Friability can be determined by the following formula,

$$F = W1 - W2 / W1 \times 100$$

Where,

W1 = Weight of the tablets before test.

W2 = Weight of the tablets after test.

Table 13: Friablity Values For Bilayer Tablets.

S.NO	Tablet Form	FRIABILITY (%)					
		T1	T2	T3	T4	T5	AVERAGE
1.	Bilayer Tablet	0.08	0.10	0.14	0.09	0.14	0.11

DISINTEGRATION TEST

The in-vitro disintegration test was carried out at 37 ± 2°c in distilled water. The in vitro disintegration time of 5 tablets from each formulation were determined using disintegration test apparatus. One tablet was placed in each of the six tubes of the apparatus containing distilled water. One disk was added to each tube. The time taken in minutes or seconds for complete disintegration of the tablet with no mass remaining in the apparatus was measured.

Table 14: Disintegration Values For Bilayer Tablets.

S.NO	TABLET FORM	DISINTEGRATION TIME (sec)					
		T1	T2	T3	T4	T5	AVERAGE
1.	Atorvastatin Calcium	368	377	370	374	366	371

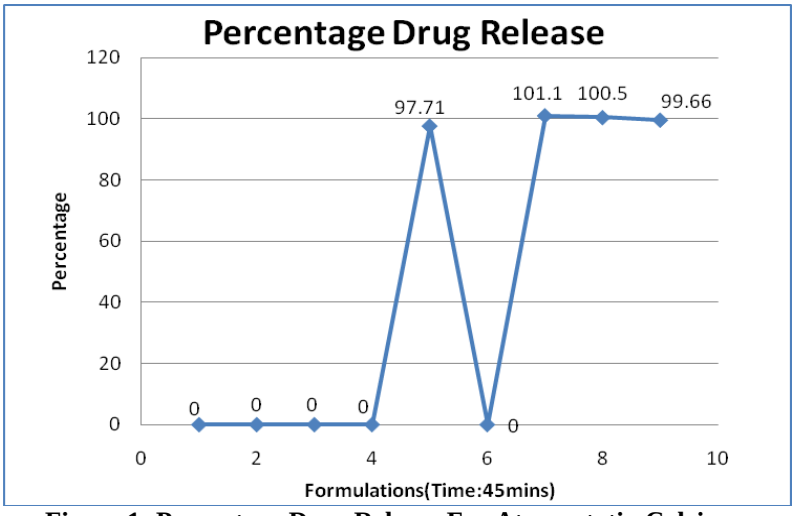

Figure 1: Percentage Drug Release For Atorvastatin Calcium.

PREPARATION OF PHOSPHATE BUFFER pH 7.0[13]

For 1 liter of medium, accurately 1.56 g of NaH2PO4 2H2O was weighed and dissolved in 900 ml of water. The pH was adjusted to 7.0 ± 0.05 with 10 N NaOH. Mixed well and volume was made upto 1000ml with water.

STANDARD PREPARATION

50 mg of Atorvastatin calcium was weighed and taken in 200 ml volumetric flask. It was diluted with methanol upto the mark. From this 2 ml was diluted to 50 ml with dissolution medium.

TEST PREPARATION

At specified time interval 10 ml of aliquot was withdrawn into the test tube.

PROCEDURE

Standard and test preparation was filtered through 0.45 µ membrane filter. Inject the standard in replicate and test in single.

Table 15: Percentage Drug Release.

S.NO	TABLET FORM	% DRUG RELEASE				
		0mins	5 min	15 min	30 min	45 min
1.	Atorvastatin Calcium	0.00	12.74	37.62	79.48	98.23

STANDARD PREPARATION

50 mg of Nicotinic acid was accurately weighed and taken in a 100 ml volumetric flask. To this 70 ml of 0.1 N Hydrochloric Acid was added and sonicated. The solution was diluted upto the mark with 0.1 N Hydrochloric Acid and filtered through Whattman NO-41 filter paper. First few ml of the filtrate was discarded and from the remaining filtrate, 10 ml was diluted with 0.1N hydrochloric acid for acid stages.

TEST PREPARATION

10 ml aliquot was withdrawn at specific time and filtered through Whattman NO-41. First few ml of filtrate was discarded and from the remaining filtrate 5 ml was taken and diluted to 50 ml with 0.1N hydrochloric acid for acid stage.

Table 16: % Durg Release of Nicotinic Acid in Bilayer Tablet.

S.NO	TABLET FORM	% DURG RELEASE			
		1hour	3hour	6hour	9hour
1.	Nicotinic Acid	17.09	36.88	55.16	71.38

Standard atorvastatin calcium drug[14]

50 mg of Atorvastatin Calcium was accurately weighed and taken in a 200 ml volumetric flask. 30 ml of methanol was added and sonicated for 5 minutes. It was then diluted to volume with methanol.

Standard Nicotinic acid drug

500 mg of nicotinic acid was accurately weighed and taken in a 200 ml volumetric flask. 30 ml of methanol was added and sonicated for 5 minutes. It was then diluted to volume with methanol.

Preparation of Standard solution

2ml of Atorvastatin Calcium and 10 ml of Nicotinic Acid standard solution was diluted with 50 ml of mobile phase and mixed.

Preparation of test solution

About 20 tablets were crushed and powder. Weight of the tablet powder equivalent to 10mg of Atorvastatin Calcium and 500 mg of Nicotinic Acid was taken in a 200 ml volumetric flask. It was sonicated for 5 minutes with cool water and volume was made up with methanol. It was then centrifuged for 10 minutes to get clear supernatant liquid. 5ml of the Supernatant liquid was further diluted to 25 ml with mobile phase and mixed.

Table: 17 % Drug Content In Bilayer Tablet.

S.no	Parameter	Atorvastatin Calcium	Nicotinic Acid
1.	Drug Content (%)	100.04	100.63

ATORVASTATIN CALCIUM TABLETS

The drug and the excipients were studied for their preformulation parameter and the granules were prepared by using different binders and solvents with variable concentration. The prepared granules were thoroughly evaluated for their bulk and tapped density. It was found that the values of bulk and tapped densities increased after the addition of HPC and it was further optimized by enhancing the solubility of HPC in water by usage of Tween 80. The concentration of HPC was altered and optimized until value of compressibility index and Hauser ratio come within the limits. The compatibility of granules were enhanced by the usage of MCC pH 101(35%), lactose (10 %) and calcium carbonate (25 %) as diluents. Since the drug has poor flow property, preferences were given in the formulation for the addition of flow enhancers such as Talc, Aerosol, and Magnesium Stearate and MCC pH102. The flow of the granules was optimized in formulation F9 by the usage of magnesium Stearate at a concentration of 1% and MCC pH 102 at concentration of 6%. The disintegration time of the tablets obtained from each formulation was monitored and it was optimized and brought within the limits by the addition of superdisintegrant (CSS) at a concentration of 5.55 at pre-granulation stage and at a concentration of 5% in post granulation. Finally Ponceau 4R Lake was mixed with granules at 0.1% concentration to distinguish it from Nicotinic Acid granulation and make it viable for a bilayer tablet. The formula, pre-compression and post-compression parameter for

Atorvastatin Calcium different formulation are given below.

Table 18: Formulation of Atorvastatin Calcium Immediate Release Tablet.

S.No	INGREDIENTS	QUANTITIES (mg/tab)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Atorvastatin Calcium	10.34	10.34	10.34	10.34	10.34	10.34	10.34	10.34	10.34
2.	Starch	30.00	20.00	-	-	-	-	-	-	-
3.	Water	q.s	q.s	q.s	q.s	q.s	-	q.s	q.s	q.s
4.	MCC pH 101	60.00	60.00	60.00	80.00	80.00	40.00	40.00	40.00	55.00
5.	Magnesium Stearate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.50
6.	Gelatin	-	10.00	-	-	-	-	-	-	-
7.	Talc	-	2.00	2.00	2.00	2.00	2.00	-	-	-
8.	Aerosil	-	-	1.00	1.00	1.00	1.00	-	-	-
9.	PVP K 30	-	-	30.00	-	-	-	-	-	-
10.	PVP K 90	-	-	-	30.00	-	-	-	-	-
11.	Lactose	-	-	-	-	20.00	20.00	20.00	20.00	16.00
12.	Hydroxy Propyl Cellulose LF	-	-	-	-	2.50	2.50	2.50	2.00	1.50
13.	Methylene Chloride	-	-	-	-	-	q.s	-	-	-
14.	Calcium carbonate	-	-	-	-	-	40.00	40.00	40.00	38.00
15.	Polysorbate 80	-	-	-	-	-	-	1.00	1.00	1.00
16.	MCC pH 102	-	-	-	-	-	-	10.00	10.00	10.00
17.	Croscarmellose sodium	-	-	-	-	-	-	-	16.00	8.50
18.	Croscarmellose sodium	-	-	-	-	-	-	-	-	7.50
19.	Ponceau 4R lake	-	-	-	-	-	-	-	-	0.20
	Total weight (mg/tab)	101.34	103.34	104.34	124.34	116.84	116.84	124.84	140.34	149.54

Table 19: Precompression Parameter of Atorvastatin Calcium Granules.

S.NO	PARAMETER	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Bulk density(g/ml)	0.188	0.201	0.203	0.237	0.257	0.269	0.282	0.280	0.275
2.	Tapped density(g/ml)	0.295	0.287	0.263	0.289	0.301	0.311	0.310	0.308	0.304
3.	Compressibility index (%)	36.271	29.965	22.813	17.993	14.618	13.505	9.032	9.177	9.598
4.	Hausner ratio	1.570	1.427	1.295	1.218	1.173	1.156	1.099	1.100	1.107
5.	Angle of repose (degrees)	42.440	37.582	33.875	31.660	31.921	30.760	30.172	30.111	30.040
6.	Moisture content (%)	1.22	1.30	1.18	1.25	1.11	0.92	1.36	1.14	1.27

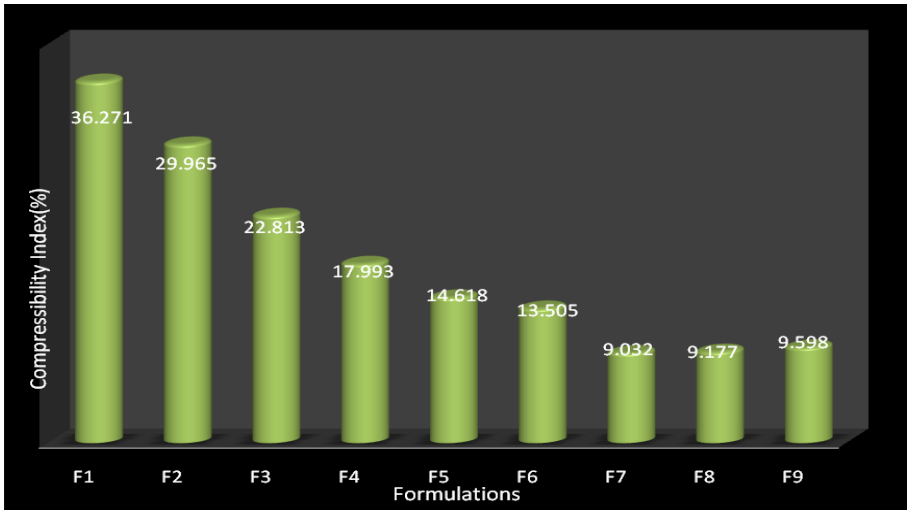

Figure 2: Compressibility Index Values of Atorvastatin Calcium Formulation.

NOTE: [X AXIS – FORMULATION: Y AXIS- COMPRESSIBILITY INDEX]
INFERENCE: The above bar diagram represent the C.I values of various formulations carried out for Atorvastatin Calcium granules. Form the diagram it could be inferred that the values of formulation F9 came within the limits by using HPC as binder and MCC, lactose and calcium carbonate as filter.

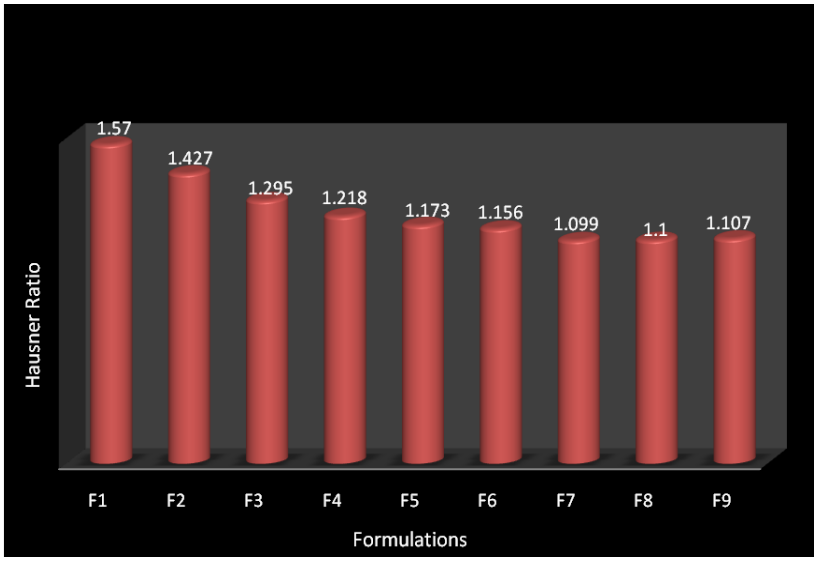

Figure 3: Hausner Ratio Values Of Atorvastatin Calcium Formulation.

(X AXIS – FORMULATION: Y AXIS – HAUSNER RATIO)
INFERENCE: From the above bar diagram it could be inferred that the Hausner ratio of the optimized formula F9 was bought within the limit.

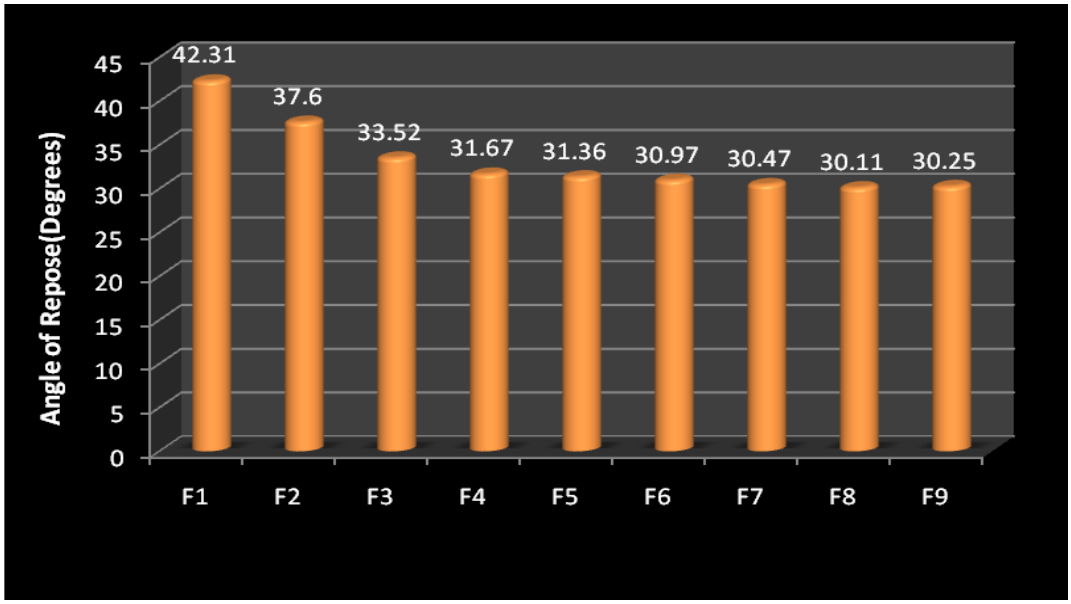

Figure 4: Angle of Repose Values of Atorvastatin Calcium Formulation.

INFERENCE: The flow property was enhanced from F1 to F9 by increasing the % of Magnesium Stearate and inclusion of MCC pH 102.

Table: 20 Post Compression Parameter of Atorvastatin Calcium Immediate Release Tablets.

S.NO	PARAMETER		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	% DEVIATION	MAX	1.12	0.96	1.05	0.88	1.02	1.10	1.14	0.85	0.91
		MIN	0.28	0.22	0.41	0.25	0.36	0.17	0.31	0.37	0.19
2.	HARDNESS (kg/cm2)		1.07	1.58	2.50	2.50	4.00	4.50	5.24	5.19	5.12
3.	THICKNESS (mm)		1.86	1.74	1.69	1.68	1.56	1.53	1.50	1.52	1.52

4.	MOISTURE CONTENT (%)	1.24	1.31	1.18	1.27	0.92	1.11	1.39	1.15	1.21
5.	DISINTEGRATION TIME (seconds)	012	021	039	044	377	451	528	394	360
6.	FRIABILITY (%)	failed	failed	0.87	0.65	0.30	failed	0.17	0.06	0.06
7.	DRUG CONTENT (%)	-	-	-	-	100.42	-	99.97	100.13	100.07
8.	DISSOLUTION (%) (AT 45 MINS)	-	-	-	-	97.71	-	101.1	100.05	99.66

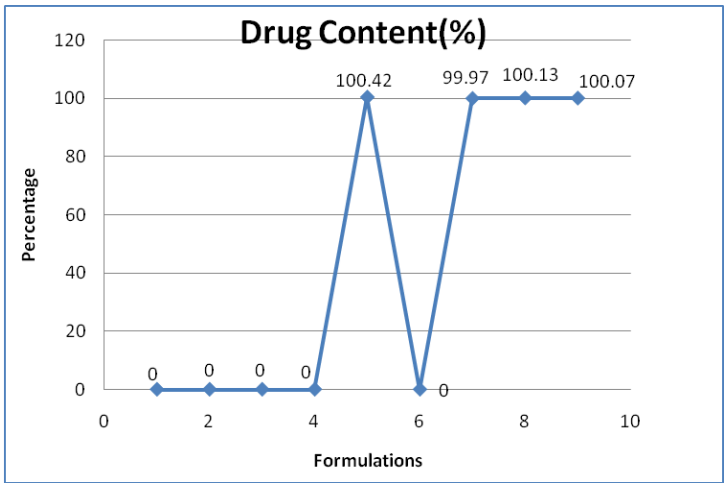

Figure 5: Percentage Drug Content Values of Atorvastatin Calcium Tablet Formulation.

INFERENCE: The drug content was not estimated for the formulation which failed in physical parameters. The drug content values of final formula F9 was found to be within the limits.

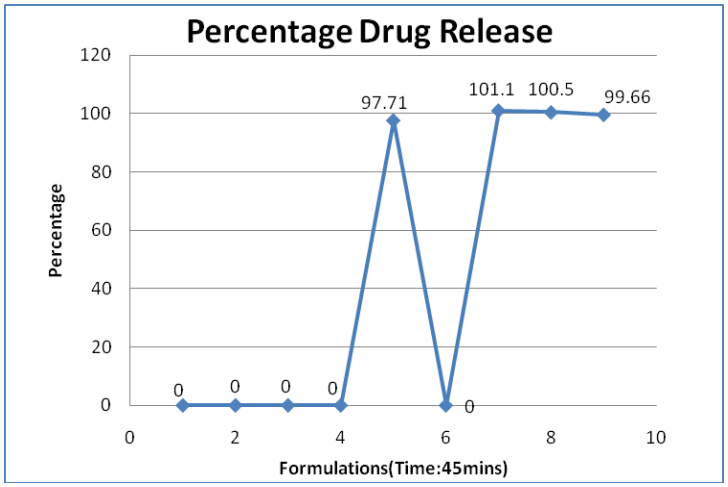

Figure 6: % Drug Release Values For Atorvastatin Calcium Tablet Formulation.

INFERENCE: InVitro studies were carried out only for that formulation which passed in their physical parameters. The % drug release of final formulation F 9 was found to be within the limits.

TABLE 21: PRECOMPRESSION PARAMETERS FOR F9 OF ATORVASTATIN CALCIUM GRANULES.

S.NO	PARAMETERS	T1	T2	T3	T4	T5	AVERAGE (F9)
1	Bulk density(g/ml)	0.272	0.277	0.270	0.278	0.278	0.275
2	Tapped density(g/ml)	0.300	0.307	0.299	0.308	0.307	0.304
3	Compressibility (g/ml)	9.333	9.772	9.699	9.740	9.446	9.598
4	Hausner ratio	1.105	1.108	1.107	1.109	1.106	1.107
5	Angle of repose (degrees)	30.06	30.08	29.99	30.05	30.02	30.04
6	Moisture Content (%)	1.30	1.23	1.27	1.25	1.30	1.27

Table 22: Post Compression Parameter For F9 of Atorvastatin Calcium Immediate Release Tablets.

S.N0	PARAMETERS		T1	T2	T3	T4	T5	AVERGE (F9)
1.	% DEVIATION	MAX	0.90	0.92	-	-	-	0.91
		MIN	0.17	0.20	-	-	-	0.19
2.	HARDNESS (kg/cm2)		5.10	5.10	5.10	5.20	5.10	5.12
3.	THICKNESS (mm)		1.48	1.55	1.50	1.53	1.54	1.52
4.	MOISTURE CONTENT (%)		1.18	1.23	1.20	1.21	1.23	1.21
5.	DISINTEGRATION TIME (seconds)		358	361	356	361	364	360
6.	FRIABILITY (%)		0.04	0.06	0.07	0.06	0.05	0.06
7.	DRUG CONTENT (%)		-	-	-	-	-	100.07
8.	DISSOLUTION (%)		-	-	-	-	-	99.66

Table 23: Percentage Drug Release For F9 of Atorvastatin Calcium Tablet.

S.NO	TIME (min)	% Drug Release
1.	0	0
2.	5	14.65
3.	15	42.17
4.	30	81.33
5.	45	99.66

NICOTINIC ACID TABLETS

Studies from various journals revealed that HPMC when used at a concentration of 14% made an effective sustained release of the active pharmaceutical ingredient and maximum it can be used upto 80% of the drug although this may vary depending upon the amount of drug used. Studies were done on the maximum allowable dosage of nicotinic acid and daily allowable intake of HPM. Initially formula was prepared by taking 14% of HPMC. Even though HPMC plays a dual of sustained release of the drug and binder for the granules, PVP was also included in the formula since preformulation studies showed that nicotinic acid has very poor density values. Stearic acid was used as lubricant and IPA was used as the carrier solvent for the binder. Precompression and post compression studies relegated that satisfactory hardness and thickness was obtained. Problem were faced in granulation flow property and drug release. Accordingly the % of HPMC was increased from 14% to 24%. Increase in HPMC concentration was balanced by altering the concentration of PVP to maintain optimum hardness to the compressed tablets. Flow properties of the granules were increasing the concentration of Stearic acid from 5% to 7%. Various formulation studies taken for the nicotinic acid tablet and their parameter including stability studies are shown below,

Table 24: Formulation of Nicotinic Acid Sustained Release Tablet.

S.NO	INGREDIENTS (mg/tab)	F1	F2	F3	F4	F5	F6
	NICOTINIC ACID	500.00	500.00	500.00	500.00	500.00	500.00
2.	HPMC K 100	70.00	80.00	90.00	100.00	110.00	120.00
3.	PVP K 90	114.00	87.00	59.00	30.00	24.40	18.60
4.	IPA	q.s	q.s	q.s	q.s	q.s	q.s
5.	STEARIC ACID	34.20	36.68	38.94	40.95	44.40	46.40
	TOTAL WEIGHT (MG/TAB)	718.20	703.68	687.94	670.95	678.80	685.00

TABLE 25: PRECOMPRESSION PARAMETERS OF NICOTINIC ACID GRANULES.

S.NO	PARAMETER	F1	F2	F3	F4	F5	F6
1.	BULK DENSITY (G/ML)	0.548	0.555	0.547	0.559	0.550	0.546
2.	TAPPED DENSITY (G/ML)	0.676	0.669	0.639	0.638	0.615	0.599
3.	COMPRESSIBILITY INDEX (%)	18.935	17.040	14.397	12.382	10.569	8.849
4.	HAUSNER RATIO	1.234	1.205	1.168	1.141	1.118	1.097
5.	ANGLE OF REPOSE (DEGREE)	37.446	36.120	34.783	33.171	30.835	30.040
6.	MOISTURE CONTENT (%)	0.67	0.58	0.55	0.41	0.38	0.36

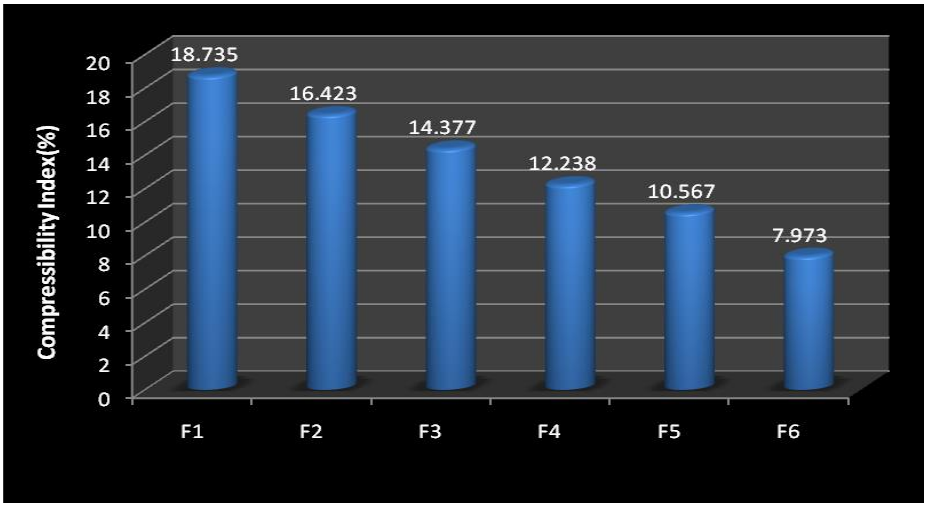

Figure 6: Compressibility Index Values of Nicotinic Acid Formulation.

INFERENCE: The compressibility index values were optimized from each formulation by altering the concentrations of HPMC & PVP.

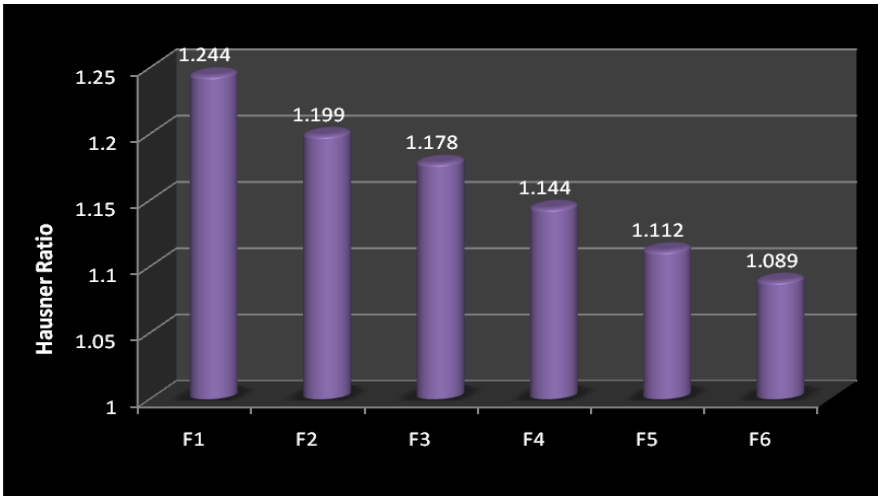

Figure 7: Hausner Ratio Values of Nicotinic Acid Formulation.

(X AXIS – FORMULATION : Y AXIS – HAUSNER RATIO)

INFERENCE: The Hausner ratio values were optimized from each formulation by altering the concentration of HPMC & PVP and brought within the limits in formulation F6.

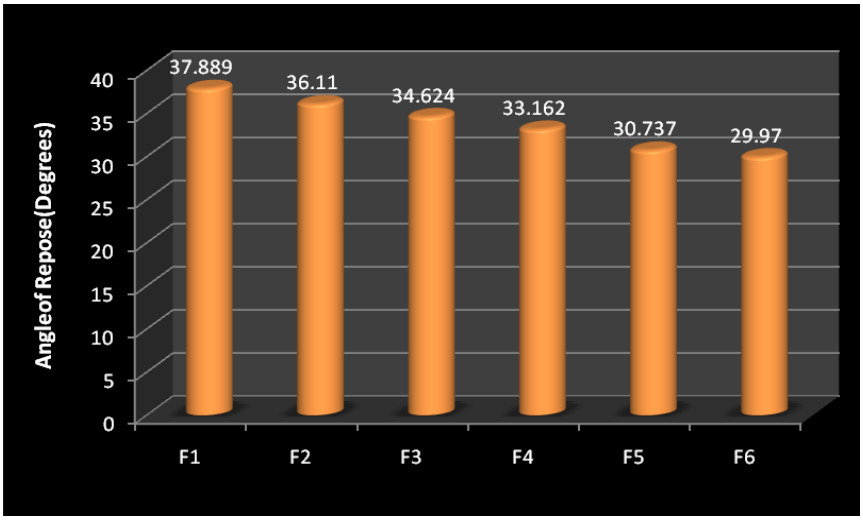

Figure 8: Angle of Repose Values of Nicotinic Acid Formulation.

(X AXIS – FORMULATION: Y AXIS – ANGLE OF REPOSE)
INFERENCE: The flow property of granules from each formulation was enhanced by increasing the concentration of Stearic acid and optimized in formulation F6 at a concentration of 6.5%.

Table 26: Post Compression Parameter of Nicotinic Acid Sustained Release Tablets.

S.NO	PARAMETERS		F1	F2	F3	F4	F5	F6
1.	% DEVIATION	MAX	0.66	0.59	0.60	0.54	0.51	0.47
		MIN	0.13	0.15	0.10	0.07	0.11	0.09
2.	HARDNESS (KG/CM2)		7.64	7.70	7.83	7.85	7.91	7.94
3.	THICKNESS (MM)		5.44	5.38	5.61	5.45	5.57	5.53
4.	MOISTURE CONTENT (%)		0.49	0.45	0.38	0.36	0.31	0.27
5.	FRIABILITY (%)		0.17	0.12	0.10	0.10	0.09	0.07
6.	DRUG CONTENT		101.38	101.08	101.44	101.27	101.15	101.24
7.	DISSOLUTION (%) AT 9 HOURS		-	-	99.72	90.37	78.12	71.67

TABLE 27: % DRUG RELEASE VALUES OF NICOTINIC ACID FORMULATION.

S.NO	TIME (Hours)	F1	F2	F3	F4	F5	F6
1.	1	41.26	34.15	27.10	23.65	20.61	18.20
2.	3	68.02	61.30	54.87	48.42	44.05	39.68
3.	6	95.16	89.47	77.08	73.14	62.77	60.49
4.	9	-	-	99.37	90.37	78.12	71.67

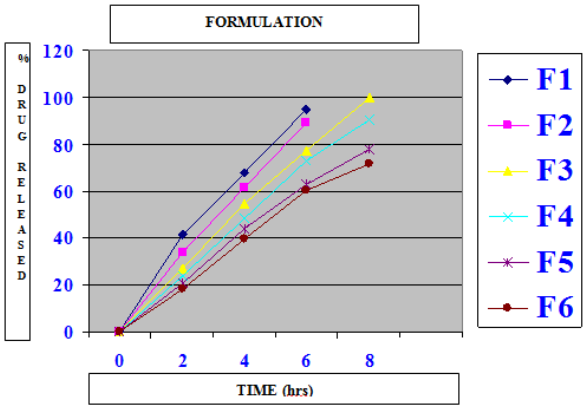

Figure 9: Percentage Drug Release Values For Nicotinic Acid Tablet Formulations.

INFERENCE: The %drug release was optimized and brought within the limit of 65% - 75% in formulation F6 by increasing concentration of HPMC from 14% - 24%.

Table 27: Pre Compression Parameters For F6 of Nicotinic Acid Granules.

S.NO	PARAMETERS	T1	T2	T3	T4	T5	AVERAGE (F6)
1.	Bulk Density (g/ml)	0.542	0.549	0.541	0.543	0.555	0.546
2.	Tapped Density (g/ml)	0.597	0.601	0.594	0.595	0.608	0.599
3.	Compressibility Index (%)	9.213	8.652	8.923	8.740	8.718	8.849
4.	Hausner Ratio	1.102	1.095	1.098	1.095	1.095	1.097
5.	Angle of Repose	29.98	30.05	30.02	30.07	30.08	30.040
6.	Moisture Content	0.31	0.35	0.42	0.41	0.31	0.36

Table 28: Post Compression Parameters For F6 of Nicotinic Acid Sustained Release Tablets.

S.No	PARAMETERS		T1	T2	T3	T4	T5	AVERAGE (F6)
1.	% Deviation	Max	0.49	0.46	-	-	-	0.47
		Min	0.10	0.08	-	-	-	0.09
2.	Hardness (kg/cm2)		7.50	8.10	7.40	8.30	8.40	7.94
3.	Thickness (mm)		5.66	5.51	5.59	5.54	5.35	5.53
4.	Moisture Content (%)		0.33	0.30	0.28	0.24	0.20	0.27
5.	Friability (%)		0.09	0.06	0.07	0.06	0.08	0.07

6.	Drug Content (%)	-	-	-	-	-	101.24
7.	Dissolution (%)	-	-	-	-	-	71.67

Table 29: Drug Release For F6 of Nicotinic Acid Tablets.

S.No	TIME	%DRUG RELEASE	%RSD
1	1	18.20	4.02
2	3	39.68	3.51
3	6	60.44	2.92
4	9	71.67	2.80

FORMULATION OF BILAYER TABLET CONTAINING ATORVASTATIN CALCIUM (IR) AND NICOTINIC ACID (SR).

As showed above various trials were undertaken for granular formulation of Atorvastatin calcium and Nicotinic acid and the successful granules were compressed into tablets. Since Precompression and post compression results for both the drugs were found to be satisfactory, these granules were subjected to be compressed as a bilayer tablet. Maximum affordable pressure were given to punches and tablets were compressed containing Nicotinic acid [SR] as bottom layer and Atorvastatin calcium [IR] as upper layer. No problem was observed in physical parameters of the compressed tablets. Initially minute problems were observed during compression such as mottling and sticking. The problem was overcome by pre drying and sieving of the granules prior to compression. Various parameters determined after the compression of the bilayer tablets were shown below.

Table 30: Parameters For Compressed Bilayer Tablet Containing Atorvastatin Calcium [Ir] & Nicotinic Acid [Sr].

S.No	PARAMETERS		T1	T2	T3	T4	T5	AVERAGE
1.	% Deviation	Max	1.31	1.30	1.25	1.19	1.15	1.24
		Min	0.15	0.17	0.21	0.16	0.16	0.17
2.	Hardness (Kg/cm2)		9.10	9.40	9.20	9.30	9.40	9.27
3.	Thickness (mm)		7.25	7.37	7.28	7.33	7.32	7.31
4.	Friability (%)		0.08	0.10	0.14	0.09	0.14	0.11
5.	Disintegration time (seconds)Atorvastatin calcium)		368	377	370	374	366	371
6.	Drug content (%) (Atorvastatin calcium)		100.04	-	-	-	-	100.04
7.	Drug content (%) (Nicotinic acid)		100.63	-	-	-	-	100.63
8.	Dissolution (%) (Atorvastatin calcium)		98.23	-	-	-	-	98.23
9.	Dissolution (%) (Nicotinic acid)		71.38	-	-	-	-	71.38

Table 31: % Drug Release Of Atorvastatin Calcium In Bilayer Tablet.

S.No	TIME (Mins)	% DRUG RELEASE
1.	0	0
2.	5	12.74
3.	15	37.62
4.	30	79.48
5.	45	98.23

INFERENCE: The percentage of drug release was checked according to In House Specifications at time intervals of 0, 5, 15, 30, and 45 minutes. Not less than 75 % of drug has to be released at 45 minutes and the formulated tablet showed drug release according to the limits. The above graph shows that the drug release follows first order release.

Table 32: % Drug Release Of Nicotinic Acid In Bilayer Tablets.

S.no	Time (Hours)	% Drug Release	% rsd
1.	1	17.09	4.20
2.	3	36.88	3.60
3.	6	55.16	3.43
4.	9	71.38	2.96

COMPATIBILITY STUDIES

This compatibility studies was carried out using the drug total excipients in different ratio and kept in stability conditions for one month in 40^0C per 75% relative humidity and 60^0C in 2 milliliters glass vial in closed condition.[15,16]

Excipients were mixed with Atorvastatin calcium and Nicotinic acid in the following ratio given in the table. According to compatibilities in trial and error method the formula of drug profile was conformed.

The samples were withdrawn at periodic intervals and given to analytical development for analysis of following parameters.

Moisture content.

Assay.

IR.

Compatibility studies were done to find out whether there is any interaction between drug and excipients.

The drug was mixed with the excipients in the ratio of 1:1 and 1:5 and the observation were noted.

INFERENCE

Observations were concluded that the excipients selected for formulation of IR and ER compatible with Atorvastatin calcium and nicotinic acid.

ACCELERATED CONDITIONS

This study was done by including stress at different temperatures. The rate of reaction increases with in temperature. The drug was mixed with the excipients in the ratio 1:1 and 1:5 and were subjected to different temperatures. The study was done for 1 month and the observations are given in the table. 40^0C, RH – 75%. Room temperature.

RESULT AND DISCUSSION

After the preformulation studies of active ingredients and excipients, incompatibility and stability studies were carried out. From the result obtained and from the literary knowledge of all the drug and excipients for which the above studies were carried out, an optimized formula was evaluated and the formulation of bilayer tablet was carried out.

Nine formulations F1, F2, F3, F4, F5, F6, F7, F8, and F9 were carried out for Atorvastatin calcium granules and F9 was found to be successful as it meets all the requirements. Similarly six formulations F1, F2, F3, F4, F6, and F6 were formulated and performed for nicotinic acid granules and formulation F9 meet all requirements in a successful way.

STABILITY STUDY

The stability parameters for all the formulations were evaluated after 30 days and 45 days for both 25° C and 40° C with their respective RH and the values were been tabulated below.[17]

Table 34: Stability Datas For Optimized Formulations At 25° C & 60 % Rh For Atorvastatin Calcium Tablets.

S.No	Tablet Form and Parameters	STORAGE CONDITION (25° C &60 %RH)		
		INITIAL	30 DAYS	45 DAYS
1.	Description	Pink color circular tablet	N.D	N.D
2.	% Deviation	< 1%	< 1%	< 1%
3.	Hardness (kg/cm2)	5 - 5.5	Within limits	Within limits
4.	Thickness (mm)	1.52	1.52	1.52
5.	Friability (%)	0.06	0.06	0.06
6.	Disintegration Time (seconds)	363	358	345
7.	Moisture Content (%)	1.21	1.29	1.33
8.	Drug Content (%)	100.07	99.73	99.61
9.	Drug Release (%)	99.66	99.60	99.58

Table 35: Stability Datas For Optimized Formulations At 25° C & 60 % Rh For Nicotinic Acid Tablets.

S.No	TABLET FORM AND PARAMETERS	STORAGE CONDITION (25° C &60 %RH)		
		INITIAL	30 DAYS	45 DAYS
1.	Description	White color round tablet	N.D	N.D
2.	% Deviation	< 1%	< 1%	< 1%
3.	Hardness (kg/cm2)	7.5 – 8	Within limits	Within limits
4.	Thickness (mm)	5.53	5.53	5.53
5.	Friability (%)	0.07	0.08	0.10
6.	Moisture Content (%)	0.27	0.28	0.30
7.	Drug Content (%)	101.24	101.08	99.97
8.	Drug Release (%)	71.67	70.98	70.67

SUMMARY AND CONCLUSION

In the pursuit of formulating effective Bilayer tablets comprising Atorvastatin calcium and Nicotinic acid, a comprehensive project encompassing a total of 9 formulations for Atorvastatin calcium and 6 for Nicotinic acid was undertaken. The primary objective was to systematically evaluate the pre-compression and post-compression attributes of these formulations to identify the most optimal composition for both drugs. For Atorvastatin calcium, the formulations underwent rigorous scrutiny for various parameters encompassing both pre-compression and post-compression aspects. Among the tested formulations, the ninth variant (F9) exhibited consistently favorable outcomes across all measured parameters. This formulation, deemed the final optimized version, demonstrated the highest level of performance and subsequently underwent stability studies to assess its long-term viability. Similarly, for Nicotinic acid, a parallel series of six formulations was meticulously prepared and subjected to comprehensive pre-compression and post-compression evaluations. The sixth formulation (F6) emerged as the most promising, showcasing satisfactory results in various studied parameters. This selected formulation was subsequently advanced to stability studies to gauge its resilience under varying conditions. The project further elaborated on the manufacturing procedure, detailing the specific formulations and methodologies employed for the trial batches. Diverse iterations featuring distinct excipients were created to explore a range of possibilities. The granules optimized for both Atorvastatin calcium and Nicotinic acid were then seamlessly compressed into bilayer tablets. The compressed bilayer tablets were subjected to an array of evaluations, encompassing

description, hardness, thickness, friability, disintegration, assay, and dissolution. These critical assessments provided insights into the tablets' physical attributes, mechanical strength, and dissolution profiles. Upon meticulous evaluation, the compressed bilayer tablets were meticulously packaged in blister packs and exposed to stability studies conducted at varying environmental conditions: 40°C & 75% relative humidity, and 25°C & 60% relative humidity. Samples were consistently and systematically analyzed at predefined intervals, following a robust stability protocol. The collective findings of the study underscored the success of the Bilayer tablet formulation containing both Atorvastatin calcium and Nicotinic acid. The formulation demonstrated its efficacy in achieving both immediate release and sustained extended release profiles. Moreover, the study affirmed the potential for consistent manufacturability, offering reproducible characteristics across batches.

In conclusion, the undertaken project validated the feasibility and efficacy of the formulated Bilayer tablets comprising Atorvastatin calcium and Nicotinic acid. The rigorous evaluation, optimization, and stability analysis collectively corroborated the formulation's potential for practical application, promising a consistent therapeutic outcome.

FUTURE SCOPE

Stability studies of the developed formulation to be continued. Scale up trial to be carried out to confirm the reproducible results in batch to batch.

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