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FORMULATION, DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF ATORVASTATIN CALCIUM USP

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ABSTRACT

The aim of present investigation is to develop immediate release formulation of Atorvastatin calcium for oral drug delivery by using suitable concentration of superdisingrants. Croscarmellose sodium (AC-DI-SOL), povidone, MCC, Magnesium stearate was used to formulate the immediate release tablet. Croscarmellose sodium was used as superdisintegrant and povidone was used as a binder to control the release of drug. Special care was taken for Atorvastatin calcium processing in low humidity condition and geometric mixing is applied to avoid content uniformity and segregation. The flow properties of the powdered blend for all the batches were found to be good and free flowing. The weight variation, hardness and friability of all the formulated tablets within the specified requirements. The disintegration times for the formulated tablets are within the range of USP. For Atorvastatin calcium IR tablets direct granulation was method of choice. Film coating of Protectab HP-1 Erythrocin Supra aqueous coating 3%w/w was done. Results found that release profile of batch no.ATF7 matches with Innovator product. The Percentage cumulative drug release of batch. No. ATF7 was found at 30 Minutes 103.12%. From results it can be inferred that release profile of Batch. No: ATF7matches with that of innovator product, also f1&f2 values are good enough to comply with the innovator's product INNOVATOR have reported similar kind of results for studies with Atorvastatin calcium.

KEYWORDS: Atorvastatin calcium, Immediate release, Anticholestermic agent, HMG-CoA reductase Inhibitor.

INTRODUCTION

The convenient oral drug delivery has been known for decades is the most widely utilized route of administration among all the routes. It remains the preferred route of administration in the discovery and development of new drug candidates. The popularity of oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods and generally improve the shelf life of the product.[1] Immediate release tablets are designed to disintegrate and release the drug in absence of any controlling features such as coating or other formulation techniques. Despite a rising interest in controlled-release drug delivery systems, the most common tablets are those intended to be swallowed whole, disintegrating and releasing their medicaments rapidly in the gastrointestinal tract. A Disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Such a rapid rupture of the tablet matrix increases the surface area of the tablet particles, Thereby increasing the rate of absorption of the active ingredient and producing the desired therapeutic action.[2] The proper choice of Disintegrant and its consistency of performance are critical to formulation development of immediate release tablets. In the past, starch was one of the most widely used, Inexpensive, and effective tablet disintegrants. A high concentration of starch is required to bring about effective disintegration. Scientist's search for disintegrating agents with efficient disintegrating properties at relatively low concentrations has led to the development of some new compounds with excellent disintegrating properties is called superdisintegrant. Hyperlipidemia or hyperlipoprotienemia or dylipidemia is the presence of elevated or abnormal levels of lipids or lipoproteins in the blood. Lipid and lipoprotein abnormalities are extremely common in general population and are regarded as a highly modifiable risk factor for cardiovascular disease due to influence of cholesterol. An individual's specific biochemical and metabolic profile can often work against even the healthiest lifestyle. For these "biochemically challenged" patients, lipid-lowering agents such as the statins have literally provided a new lease on life. Atorvastatin calcium is a selective competitive inhibitor of HMG CoA reductase. Atorvastatin calcium reduces total cholesterol, LDL-cholesterol in patients with homozygous and heterozygous familial hypercholesteremia, non familial hypercholesteremia and mixed dyslipidemia. It also reduces the VLDL –cholesterol and triglyceride. Atorvastatin calcium is a synthetic lipid lowering agent, which competitively inhibits 3-hydroxy-3methyl-glutryl CoA.[3-5]

MATERIALS AND METHODS

Materials: Atorvastatin calcium was received as a gift sample from Caplin Point Research Laboratory. Calcium carbonate, Lactose DCL-11 and MCC pH-102 was gifted by FMC Bio-polymer (India). Croscarmellose sodium and Cross povidone was gifted by Chetan & Chetan (India). Purified Talc, Sodium starch glycolate and calcium stearate was gifted by Cabot Sanmer (India).

IMPURITYPROFILE

Single and total impurities present in Active pharmaceutical ingredient (API) were measured by HPLC. The results are shown in Table. No: 8 & Figure. No: 2.

ASSAY: In house HPLC based method of assay was developed or both API's. The sample of drug solution was prepared and suitably diluted with mobile phase. Each sample was run and chromatograms were obtained. The concentration of drug was calculated as

$$\textbf{Concentration of sample} = \frac{\text{Peak area of sample x Concentration of reference standard}}{\text{Peak area of reference standard}}$$

The results are shown in Table. No:8 & Figure. No: 2

SPECTRAL IDENTIFICATION [6]

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate administration, to promote the consistent release and bioavailability of the drug and protect it from degradation.

Infra red spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug.

In the present study, the potassium bromide disc (pellet) method was employed. Chemical stability was confirmed by IR spectrometry.

The results are shown in Figure. No: 3-14

DIFFERENTIAL SCANNING CALORIMETER STUDIES [7]

The sample of plain drug was scanned in beginning. Than physical mixtures of drug with excipients kept for one month, were scanned. Both the drug was scanned from50 $^{\circ}$C to 250 $^{\circ}$C.

The results are shown in Figure. No: 15.

COMPATIBILITY STUDIES [8]

Drug–Excipients compatibility was performed using HPLC method and by physical observation.

Protocol for drug-excipients compatibility for Atorvastatin Calcium

Table.No:1 Ratio of Atorvastatin Calcium to Excipients Taken For Compatibility Study

S.No.	Ingredient	Ratio
1	Atorvastatin Calcium	1
2	Atorvastatin Calcium : Calcium carbonate	1:1
3	Atorvastatin Calcium : Lactose DCL-11	1:1
4	Atorvastatin Calcium : MCC pH-102	1:1
5	Atorvastatin Calcium : Croscarmellose Sodium	1:1
6	Atorvastatin Calcium : Cross povidone	1:1
7	Atorvastatin Calcium : Purified Talc	1:3
8	Atorvastatin Calcium : Sodium Lauryl Sulphate	1:3
9	Atorvastatin Calcium : Calcium Stearate	1:3
10	Atorvastatin Calcium : Erythrocin Supra	1:0.5
11	Atorvastatin Calcium : HPMC E-15	1:0.5
12	Atorvastatin Calcium : HPC	1:0.5
13	Atorvastatin Calcium : Titanium dioxide	1:0.5
14	Atorvastatin Calcium : All excipients	1:1

PREFORMULATION STUDIES OF PURE DRUG AND EXCIPIENTS [9-10]

Preformulation study relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation for the toxicological use. It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical recipients in the dosage form. Hence, the following Preformulation studies were performed on the obtained sample of drug.

The results are shown in Table. No: 13-14.

Table.no:2 Innovator Tablet Parameters to be Evaluated (Atorvastatin calcium)

S. NO.	PARAMETERSEVALUATEDFOR
1	Strength
2	Label Claim

3	Tablet Color
4	Tablet Shape
5	Description
6	Dimensions
7	Average Weight
8	Hardness
9	Dissolution Study
10	Uniformity Of Dosage Units
11	Impurity-A
12	Any Other Impurity
13	Total Impurities
14	Assay

The results are shown in Table. No: 11-12 & Figure. No:16-17

TABLET MANUFACTURING

Manufacturing of Atorvastatin Calcium

Manufacturing Procedure - Atorvastatin calcium tablets using direct compression

(A) The corresponding amount of drug (Atorvastatin Calcium) was screened using screen #40, and Lactose DCL-11 accurately weighted & screened using screen # 40. The screened powder was transferred into the poly bag in 1:10 ratio and mixed for 3 minutes. Pass it every time through #40, further mix for 2 minutes. Geometric mixing with remaining Lactose DCL is done in same proportion. MCC pH-102 pass through # 40, mix well for 3 minutes with A & pass it through #40. Calcium Carbonate pass through screen #40, was transferred into the cage blender and mixed for 5 minutes. Super-disintegrants and lubricants is accurately weighed & screen # 60 is then mixed in the poly bag or cage blender for 3 minutes. The mixture was compressed into tablets using an instrumented tablet press with 6mm punches for 100mg weight at 7-8kp hardness and tablets were collected during compression for in-process testing (weight, friability and hardness).

Table. No: 3 Formulation of Atorvastatin Calcium Tablet

Batch. No	**ATF1**	**ATF2**	**ATF3**	**ATF4**	**ATF5**	**ATF6**	**ATF7**
Ingredient	**mg/tablet**						
Atorvastatin Calcium	10.35	10.35	10.35	10.35	10.35	10.35	10.35
Calcium Carbonate	11	11	11	11	11	11	11
Lactose DCL -11	54	52	50	54	52	50	44
MCC pH-102	19.85	19.85	19.85	19.85	19.85	19.85	19.85
Croscarmellose Sodium	2	4	6	-	-	-	6
Cross Povidone	-	-	-	2	4	6	6
Talc	1	1	1	1	1	1	1
Sodium Lauryl Sulphate	1	1	1	1	1	1	1
Calcium Stearate	0.8	0.8	0.8	0.8	0.8	0.8	0.8

Total	100mg	100mg	100mg	100mg	100mg	100mg	100mg

Table. No:4 Film Coating For Atorvastatin Calcium IR Tablets

S.NO	Ingredients	Quantity(mg)
Ingredients	**For One tablet**	
1	Erythrocin Supra	0.05
2	Protectab – HP	1.8
3	Polysorbate – 80	0.8
4	Purified Water	Qs

Table. No:5 Optimized Parameters for Film Coating for Atorvastatin IR Tablets

Conditions	Pre-heating	Coating	Drying
Inlet air temperature (°C)	55-60	60-65	50
Product temperature (°C)	55-60	50-55	55-60
Outlet air temperature (°C)	35-60	55-60	50-55
Spray rate (ml/min)	-	1-2	-
Atomizing air pressure (psi)	-	*20*	
Pan speed (rpm)	35-37	35-37	35-37

POST COMPRESSION PARAMETERS [11-14]

a) Weight Variation Test

Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet according to U.S. Pharmacopoeia. The following percentage deviation in weight variation was allowed.

Average weight of a tablet	Percentage deviation
130 mg or less	± 10
>130 mg and <324 mg	± 7.5
324mg or more	± 5

The results are shown in Table. No: 15-16.

b) Tablet Dimensions: Thickness and diameter were measured using calibrated Vernier calipers. Five tablets of each formulation were picked randomly and thickness and diameter was measured individually.

The results are shown in Table. No: 15-16.

c) Thickness: The thickness of the tablets was determined by Vernier calipers. Five tablets from each batch were used and the average values were calculated. The results are shown in Table. No: 15-16.

d) Hardness: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm2. Five tablets were randomly picked and hardness of the tablets was determined. The results are shown in Table. No: 15-16.

e) Friability test: The friability of tablets was determined by using Roche friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (Wt) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100revolutions. The tablets were weighed again (WF). The % friability was then calculated by-

$$\%F = \frac{W\ (initial)-W\ (final)}{W\ (initial)} \times 100$$

The results are shown in Table. No: 15-16.

f) Disintegration test: The disintegration time for immediate release layer was determined using the disintegration apparatus. One tablet was placed in each of six tubes placed in a beaker containing 1000 ml of purified water maintained at 37 ± 20 C and the apparatus was operated. The time taken for the tablets to disintegrate and pass through the mesh was noted. The results are shown in Table. No: 15-16.

METHOD OF ANALYSIS [15-19]

IN VITRO DISSOLUTION STUDY

Dissolution study of Immediate release of different tablet formulations and marked tablets were carried out separately.

Atorvastatin Calcium

Apparatus : Dissolution Apparatus USP Type I (Paddle)
Medium : 6.8 Phosphate buffer
Medium Volume : 900ml
Speed : 75 RPM
Time : 30 Minutes
Time intervals : 5, 10, 15, 20& 30 Minutes
Temperature : 37 ± 0.5°C.

Chromatographic Conditions

Apparatus : High Performance Liquid Chromatography system (HPLC)
Column : C18, 4.6mm × 250 cm. 5µ

Wavelength : 246nm

Detector : UV/PDA

Injection volume : 20µl.

Flow rate : 1.0ml/min

Sample cooler temp. : 30°C

Run Time : 10 minutes

Elution : Isocratic

Calculations

Dissolution of Atorvastatin in mg/tablet

$$= \frac{\text{SPL Area}}{\text{STD Area}} \times \frac{\text{STD wt in mg}}{100} \times \frac{5}{50} \times \frac{5}{20} \times \frac{900}{1\ \text{Tablet}} \times \frac{99.75}{100} \times \frac{0.9653}{100} \times 100$$

The results are shown in Table. No: 17-18 & Figure. No: 18-19.

ASSAY

Chromatographic Conditions

Apparatus : High Performance Liquid Chromatography system (HPLC)

Column : C18, 4.6mm × 250 cm. 5µ

Wavelength : 246nm

Detector : UV/PDA

Injection volume : 20µl.

Flow rate : 1.0ml/min

Sample cooler temp. : 30°C

Run Time : 10 minutes

Elution : Isocratic

Calculations

Assay of Atorvastatin in mg/tablet

$$= \frac{\text{SPL Area}}{\text{STD Area}} \times \frac{\text{STD wt in mg}}{100} \times \frac{1}{50} \times \frac{50}{\text{SPLwt1}} \times \frac{50}{100} \times \frac{99.56}{100} \times \frac{0.9653}{1} \times 100$$

The results are shown in Table. No:20 & Figure. No: 20.

STABILITY STUDIES [20-22]

Stability testing forms an integral part of formulation development. It is important to assess the effect of temperature and humidity on stability of drug and in-vitro drug release rate. It

helps to generate information for predicting the shelf life of the product and recommended storage conditions. Stability data is required to be submitted as part of the dossier submitted to the regulatory agencies.

Protocol For stability studies: Formulation was selected on the basis of in-vitro drug release profile which was comparable to that of the IR formulation under reference i.e. optimized formula for both Atorvastatin calcium batches.

Optimized formula Batch.no:AFT7 for Atorvastatin calcium (10mg),in Alu Blister Pack.
The conditions for stability are as mentioned in Table. No: 6.

Table. No: 6 Stability Condition For Atorvastatin Calcium Tablet

Study	Storage condition	Time Period Covered
Room Temperature (RT)	25°C ± 2°C/60%RH± 5%RH	3months **Testing :**If accelerated condition tablet is passed
Accelerated	40°C ± 2°C/75%RH± 5%RH	3 months Testing:1,2,3month

These were evaluated for their physicochemical characteristics, drug content, assay and in-vitro release profile of Atorvastatin calcium Tablet. In–vitro release and content of active ingredients was estimated at one month interval during to rage period. The result are shown in the table. No: 19-20 & Figure. No: 20-21.

RESULT AND DISCUSSION

Table.no:7 Standard Calibration Curve of Atorvastatin Calcium

S.No	Concentration in ppm	Area
1	10	1827247.667
2	20	3618371.667
3	50	8959876.000
4	100	18118982.333
5	120	21555409.333
6	160	29532241.333
7	200	36224779.667

*Mean±SD n=3

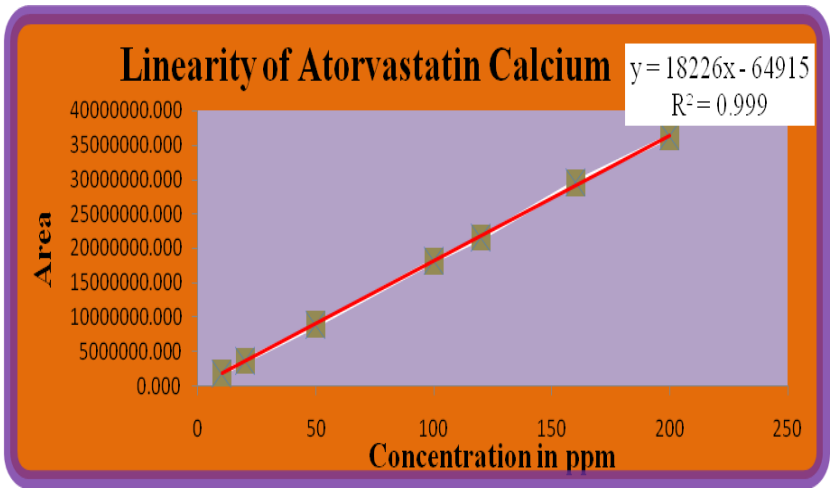

Fig. no:1 Standard Calibration Curve of Atorvastatin Calcium

IMPURITY PROFILE AND ASSAY

Table. No:8 Impurity Profile and Assay of Atorvastatin Calcium API

Impurity A	0.04%
Impurity B	Not Detected
Impurity C	Not Detected
Impurity D	0.07%
Any Other Impurity	Not Detected
Total Impurity	0.35%
Assay	99.75%
Conversional factor	1.0359

*Mean±SD (n=6)

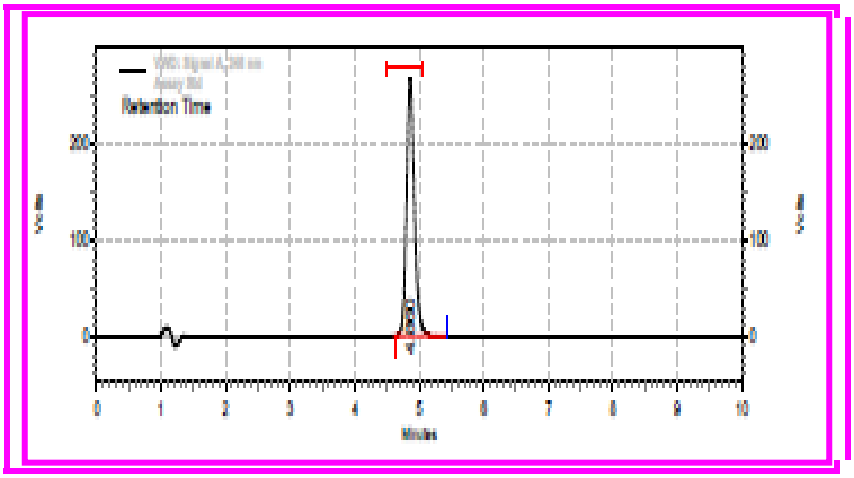

Figure. No:2 Atorvastatin calcium Assay Chromatogram

FT-IR SPECTROSCOPY

The result of FT-IR study for Atorvastatin calcium and their excipients are shown in Figure. No:3-14.

FOR ATORVASTATIN CALCIUM

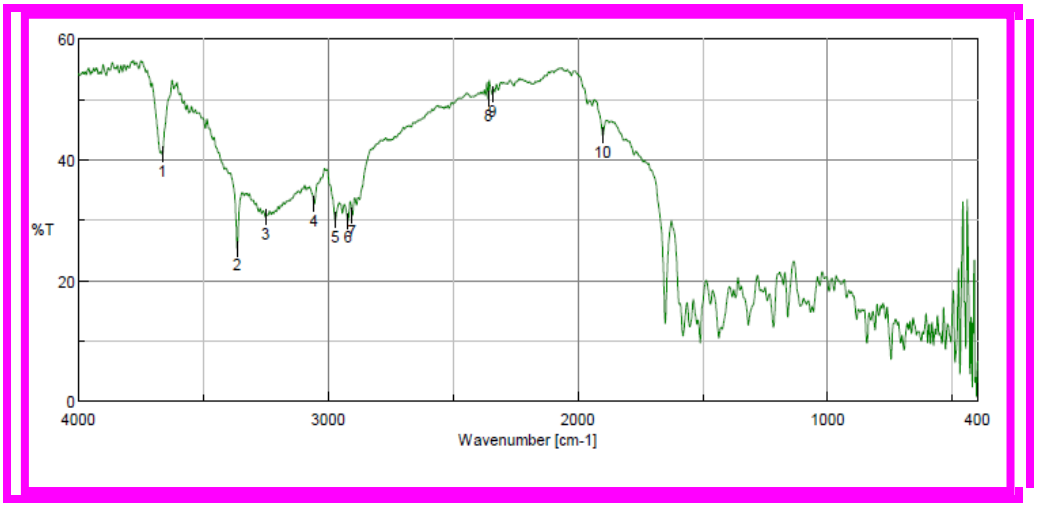

Figure.No:3 FTIR Spectrum of Pure Atorvastatin Calcium

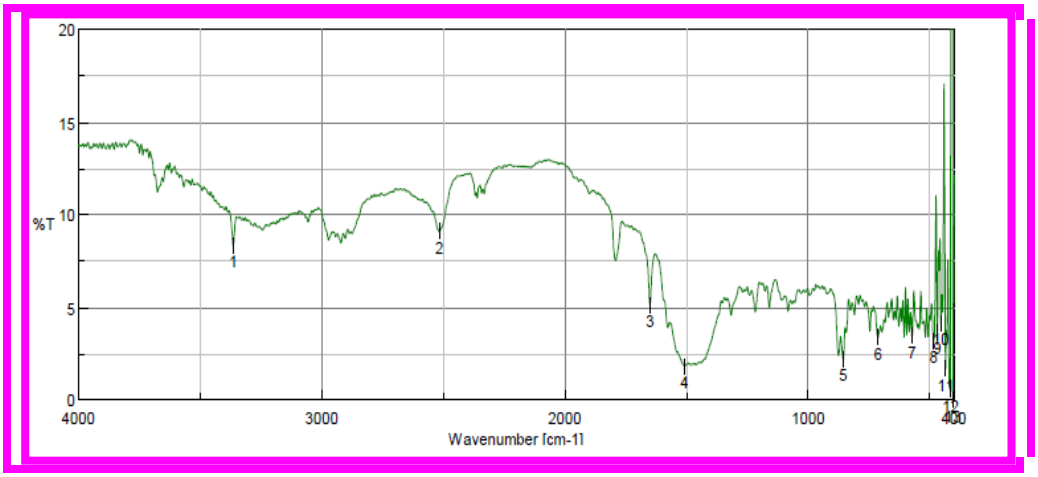

Figure. No: 4 FTIR Spectrum of Atorvastatin Calcium + Calcium Carbonate

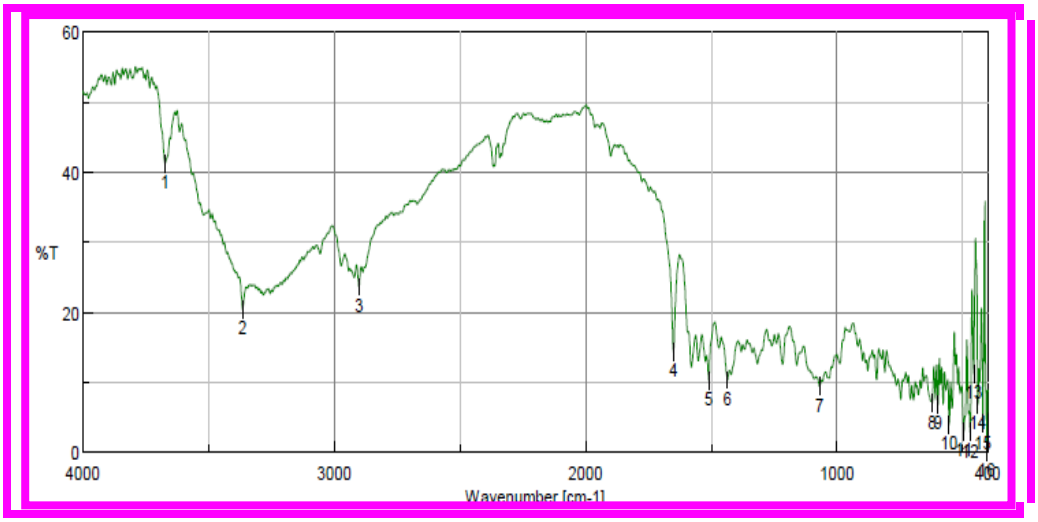

Figure.No: 5 FTIR Spectrum of Atorvastatin calcium + Lactose

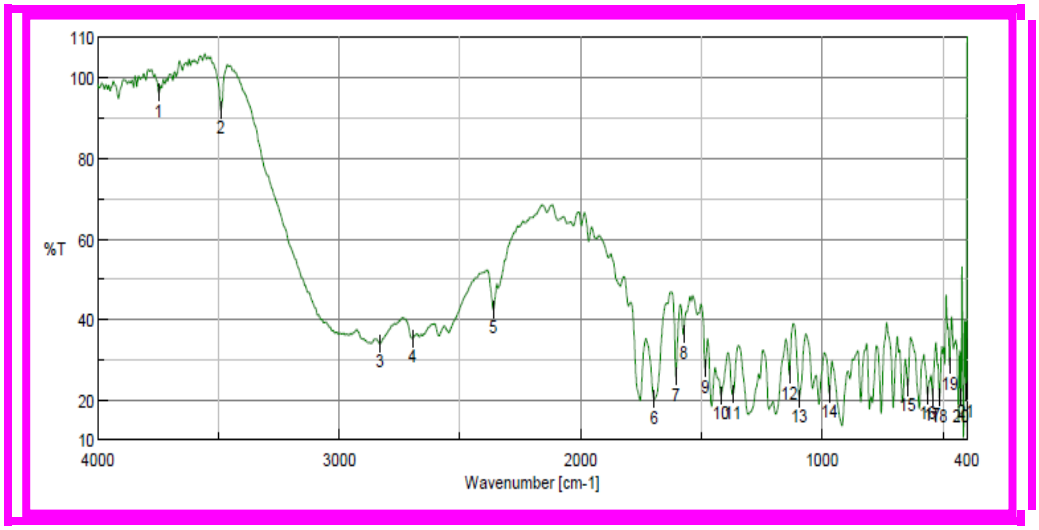

Figure.No:6 FTIR Spectrum of Atorvastatin Calcium + MCC pH-102

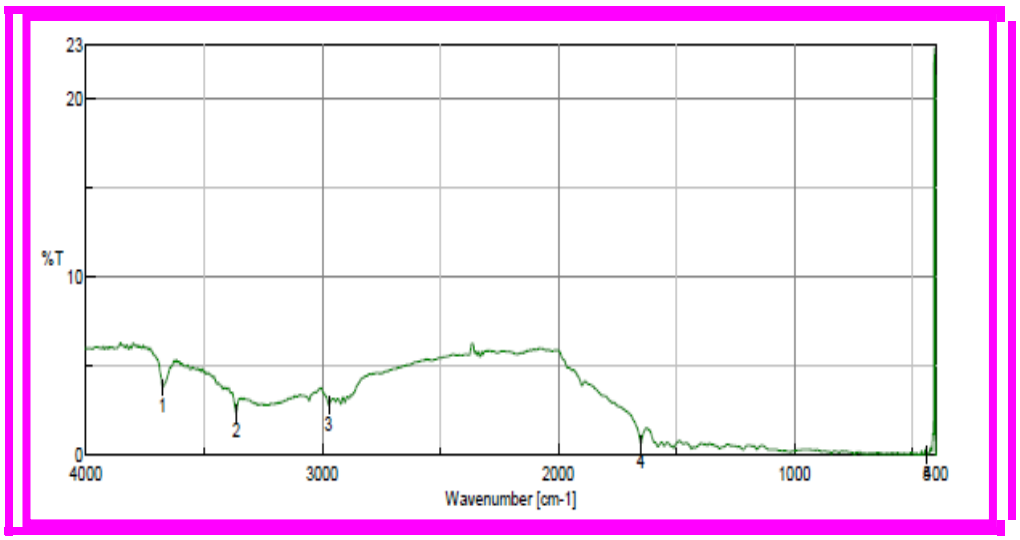

Figure.No:7 FTIR Spectrum of Atorvastatin Calcium + Croscarmellose Sodium

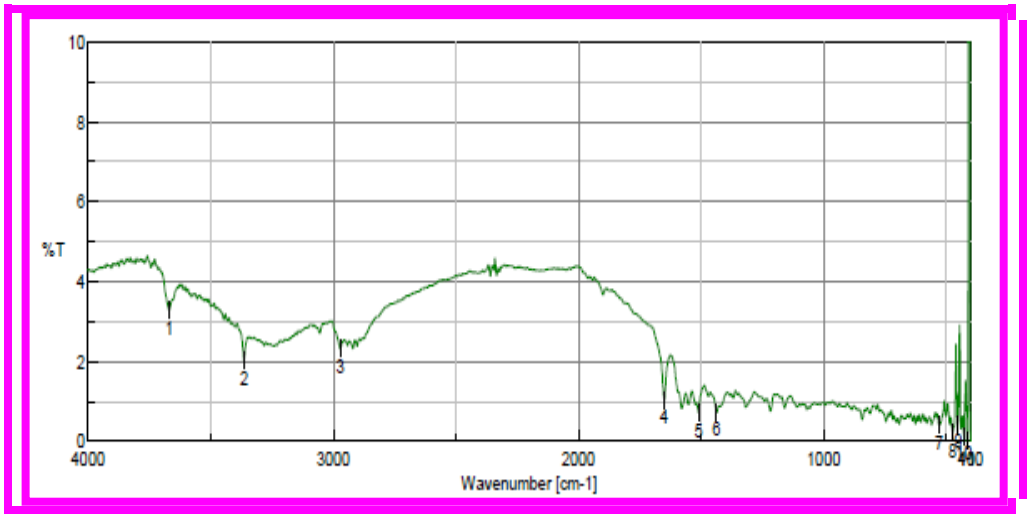

Figure.No: 8 FTIR Spectrum of Atorvastatin Calcium + Cross povidone

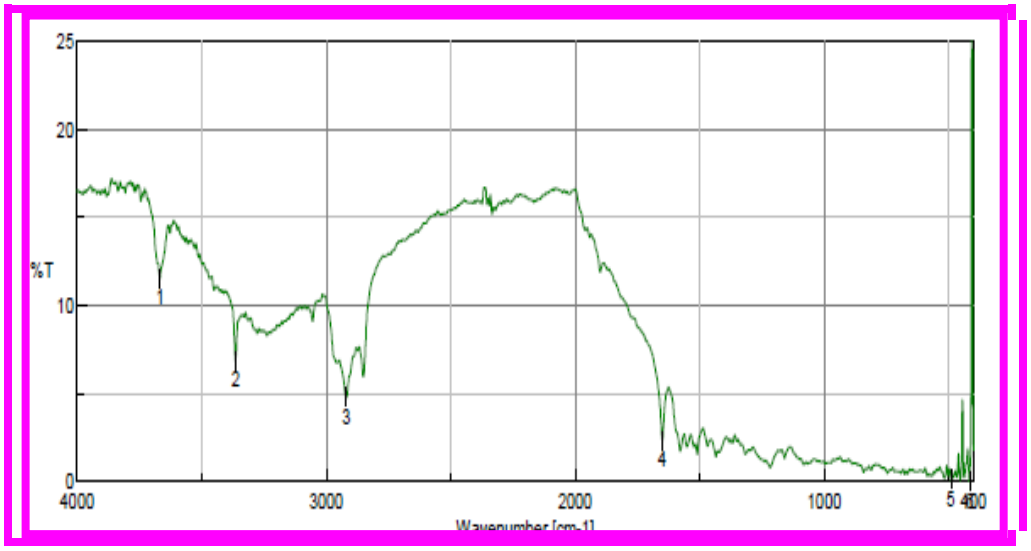

Figure.No: 9 FTIR Spectrum of Atorvastatin Calcium + Purified Talc

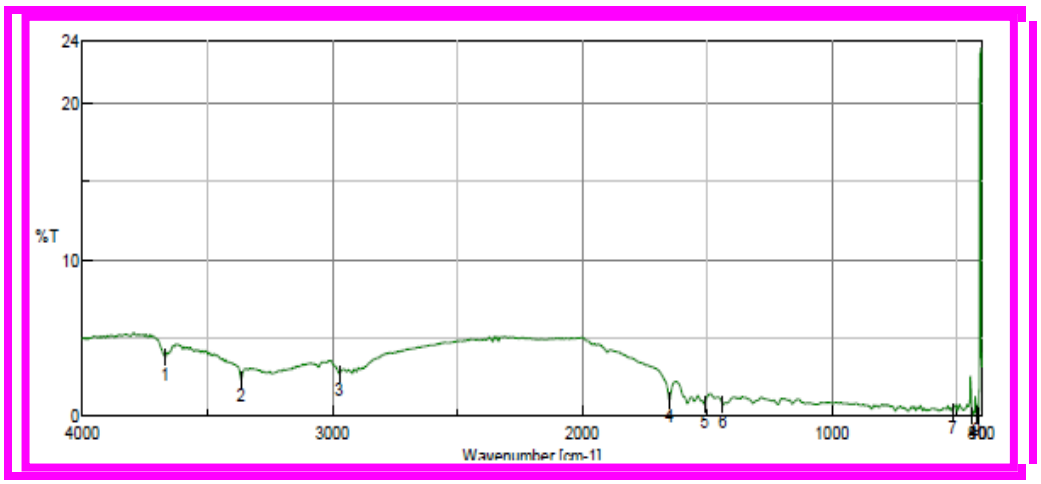

Figure. No: 10 FTIR Spectrum of Atorvastatin Calcium +Sodium Lauryl Sulphate

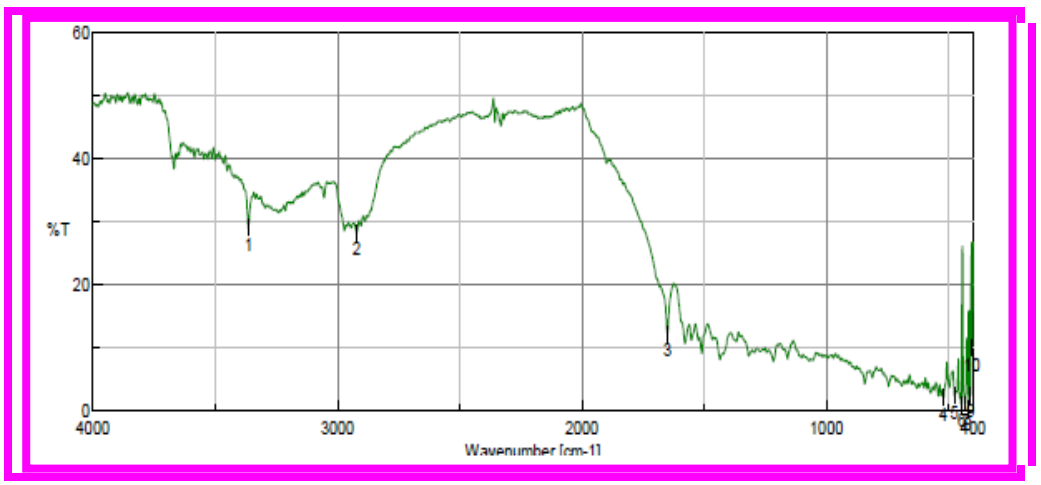

Figure.No:11 FTIR Spectrum of Atorvastatin Calcium +Calcium Stearate

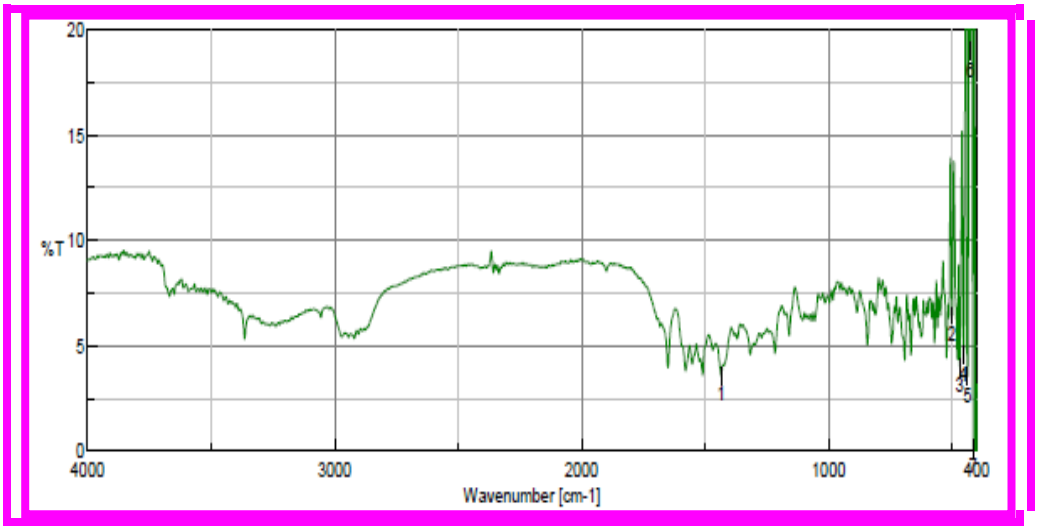

Figure.No:12 FTIR Spectrum of Atorvastatin Calcium + Film Coating Polymer

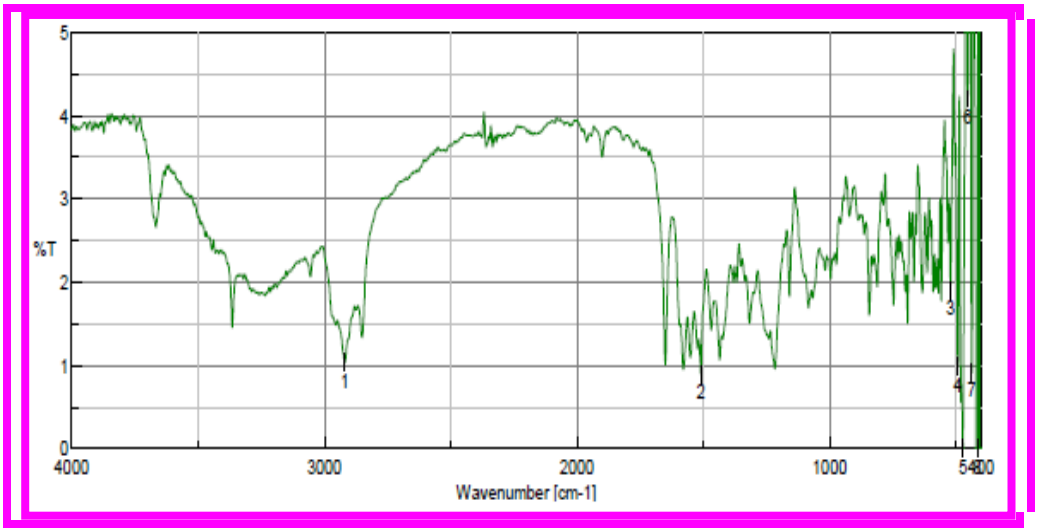

Figure.No:13 FTIR Spectrum of Atorvastatin Clacium + All excipients

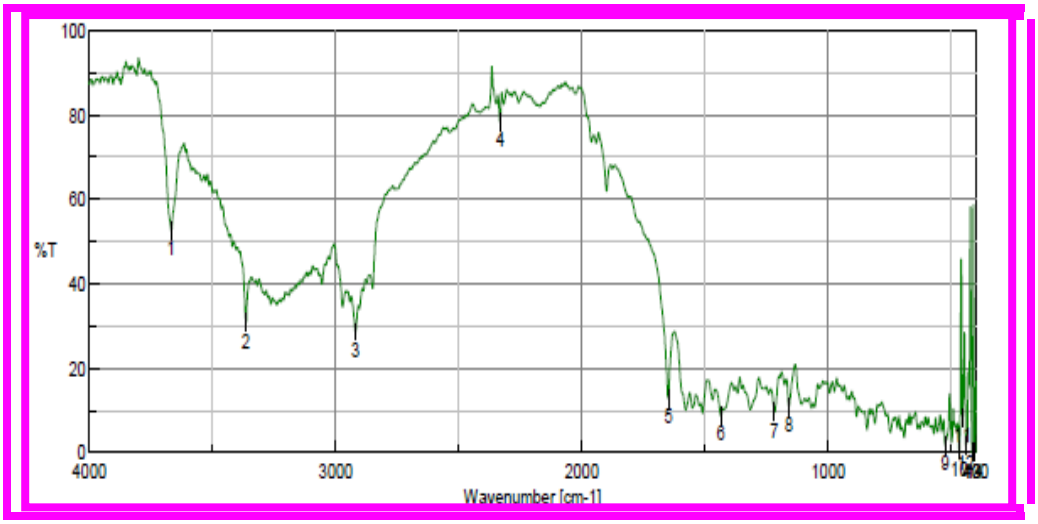

Figure.No:14 FTIR Spectrum of Atorvastatin calcium + Colour

DIFFERENTIAL SCANNINGCALORIMETERSTUDIES

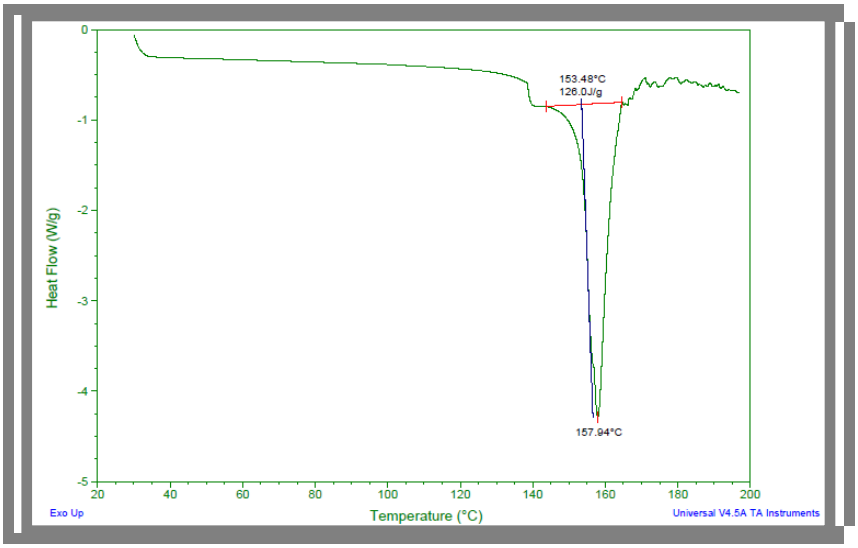

Figure. No: 15 DSC Graph of Atorvastatin calcium

DISCUSSION

From this figure. No:15 it can be seen that peak value of Atorvastatin Calcium was found to be 157.94°C in DSC thermogram. This value matches with that given in the literature and confirm the purity of API.

Table. No: 9 Compatibility study of Atorvastatin Calcium with Excipients

The RS Data of Atorvastatin calcium (By HPLC) of 1 month excipients Compatability @ 40°C-75% RH

S.No	Ingredient	Ratio	Related substance %w/w
1	Atorvastatin Calcium	1	0.15
2	Atorvastatin Calcium : Calcium carbonate	1:1	0.21
3	Atorvastatin Calcium : Lactose DCL-11	1:1	0.23
4	Atorvastatin Calcium : MCC pH-102	1:1	0.22
5	Atorvastatin Calcium : Croscarmellose Sodium	1:1	0.19
6	Atorvastatin Calcium : Cross povidone	1:1	0.18
7	Atorvastatin Calcium : Purified Talc	1:3	0.19
8	Atorvastatin Calcium : Sodium Lauryl Sulphate	1:3	0.20
9	Atorvastatin Calcium : Calcium Stearate	1:3	0.19
10	Atorvastatin Calcium : Erythrocin Supra	1:0.5	0.20
11	Atorvastatin Calcium : HPMC E-15	1:0.5	0.17
12	Atorvastatin Calcium : HPC	1:0.5	0.16
13	Atorvastatin Calcium : Titanium dioxide	1:0.5	0.17
14	Atorvastatin Calcium : All excipients	1:1	0.24

*Mean±SD (n=6)

Discussion: From this table. No:9 it can be seen the Atorvastatin calcium is compatible with all the excipients used in the study.

Table. No: 10 Compatibility study of Atorvastatin calcium with Excipients:

The RS Data of Atorvastatin calcium (By HPLC) of 1 month excipients Compatability @ 40°C-75% RH

Ingredient	Ratio	Description		
		Related substance %w/w	1 Month 25°C/60 %RH	1 Month 40°C/75%RH
Atorvastatin Calcium	1	White to pale yellow, granular powder	*	*
Atorvastatin Calcium : Calcium carbonate	1:1	White to pale yellow, granular powder	*	*
Atorvastatin Calcium : Lactose DCL-11	1:1	White to pale yellow, granular FF powder	*	*
Atorvastatin Calcium : MCC pH-102	1:1	White to pale yellow, granular powder	*	*
Atorvastatin Calcium : Croscarmellose Sodium	1:1	White to Greyish white , granular powder	*	*
Atorvastatin Calcium : Cross povidone	1:1	White to Grayish white , granular powder	*	*
Atorvastatin Calcium : Purified Talc	1:3	White to pale yellow, granular powder	*	*
Atorvastatin Calcium : Sodium Lauryl Sulphate	1:3	White to pale yellow, granular powder	*	*
Atorvastatin Calcium : Calcium Stearate	1:3	White to pale yellow, granular powder	*	*
Atorvastatin Calcium : Erythrocin Supra	1:0.5	White to pale yellow, granular FF powder	*	*
Atorvastatin Calcium : HPMC E-15	1:0.5	White to pale yellow, granular powder	*	*
Atorvastatin Calcium : HPC	1:0.5	White to pale yellow, granular powder	*	*
Atorvastatin Calcium : Titanium dioxide	1:0.5	White to pale yellow, granular powder	*	*
Atorvastatin Calcium : All excipients	1:1	White to pale yellow, granular powder	*	*

Result: * Indicated That No Change Was Observed

ATORVASTATIN CALCIUM INNOVATORTABLET CHARACTERIZATION

Table. No: 11 Atorvastatin calcium Innovator Tablet Characterization

Brand Name	INNOVATOR (10mg)
Strength	10 mg TABLET
Label Claim	Each tablet contains Atorvastatin 10 mg
Tablet Color	Sunset yellow Colour
Tablet Shape	Round Shape

Description	Debbosed with 'z' on one side & 'sz' on other side, Film Coated tablets
Dimensions	DIAMETER : 5.50-5.55mm THICKNESS : 3.40-3.80mm
Average Weight	201.8
Hardness	7-8kp
Uniformity of Dosage Unit	MEAN : 102.12 SD: 2 RSD :2
Assay	102.67%(10.56mg/Tablet)

*Mean±SD (n=6)

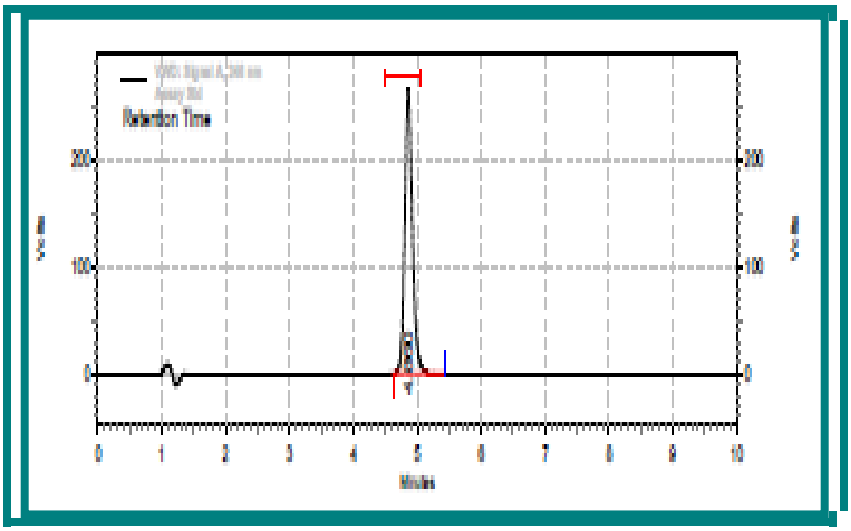

Figure. No: 16 Assay Chromatogram of the Atorvastatin calcium Innovator

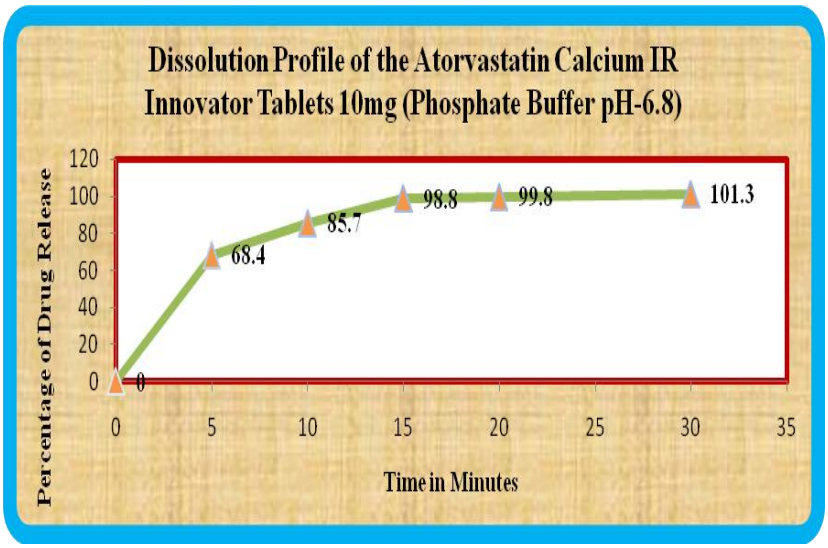

Figure. No: 17 Dissolution Profile of the Atorvastatin Calcium IR Innovator Tablets 10mg (Phosphate Buffer pH-6.8)

Table. No: 12 Dissolution Profile of the Atorvastatin Calcium IR Innovator Tablets 10mg (Phosphate Buffer pH-6.8)

Dissolution Media (900mL Media, at 75RPM)	Number of Units Used 6	Percentage of Drug Dissolved in Minutes				
		5	10	15	20	30
Phosphate Buffer pH-6.8	Mean	68.4	85.7	98.8	99.8	101.3
	±SD	1.7	1.8	1.8	1.8	1.9
	±RSD	1.7	1.8	1.8	1.8	1.9

*Mean±SD (n=6)

Discussion: The dissolution was found to be rapid with more than 85% drug being released in15 minutes under moderate agitation (75rpm) in 6.8 Phosphate Buffer (Table. No: 12). From this figure. No: 17 it can be seen that amount of Atorvastatin calcium IR dissolved in 5 & 30 Minutes is NLT 75% respectively. So, the above criteria as acceptance limit.

Table.No: 13 Preformulation Study of Pure Drug (ATORVASTATIN CALCIUM).

S.NO.	Parameters	Result	Conclusion
1	Bulk Density*	0.675 gm/ml	------
2	Tapped Density*	0.75 gm/ml	-----
3	Angle of Repose*	19.61	Excellent
4	Carr's Index*	10 %	Excellent Flow
5	Hausner Ratio*	1.11	Better Flow
6	Melting Point*	159.2-160.7 °C	----
7	Solubility*	Freely soluble in methanol, slightly soluble in ethanol, very slightly soluble in water	

*Mean±SD (n=6)

Table No: 14 Preformulation Study of the blend (ATORVASTATIN CALCIUM)

Batch Code	Bulk Density*	Tapped Density*	Angle of repose*	% Compressibility*	Hausner Ratio*	Loss on Drying*
ATF1	0.41	0.47	24.58	12.76	1.15	2.1
ATF2	0.44	0.52	25.91	15.38	1.18	1.9
ATF3	0.44	0.51	26.86	13.72	1.16	1.8
ATF4	0.47	0.54	24.43	12.96	1.14	1.7
ATF5	0.45	0.50	24.10	12.00	1.06	1.6
ATF6	0.46	0.53	24.77	13.20	1.15	1.7
ATF7	0.47	0.52	25.42	9.61	1.11	1.5

*Mean±SD (n=6)

The physical parameters of drug as well as blends concluded that these were considerably good to formulate the tablet using direct compression technique.

Table No: 15 Evaluation of Atorvastatin calcium Core-Tablets

Batch No	Weight variation (mm)**	Diameter (mm)*	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)*	Disintegration Time*
ATF1	102±6.5	5.39±0.02	3.32±0.03	3.45±0.21	0.25	53 seconds
ATF2	101±6.5	5.28±0.01	323±0.04	3.51±0.20	0.31	47 seconds
AFT3	102±5.6	5.39±0.03	3.34±0.04	3.45±0.14	0.28	49 seconds
AFT4	102±6.5	5.47±0.02	3.25±0.05	3.57±0.13	0.32	51 seconds
AFT5	101±5.8	5.38±0.03	3.36±0.04	3.67±0.12	0.34	48 seconds
AFT6	102±6.8	5.39±0.02	3.28±0.05	3.56±0.11	0.33	50 seconds
AFT7	102±6.8	5.49±0.01	3.25±0.06	3.87±0.15	0.35	51 seconds

*Mean±SD (n=6) **Mean±SD (n=20)

Table No: 16 Evaluation of Atorvastatin calcium Film Coated-Tablets

Batch No	Weight variation (mm)**	Diameter (mm)*	Thickness (mm)*	Hardness (kg/cm^2)*	Disintegration Time*
ATF1	105±6.5	5.69±0.01	3.42±0.03	4.15±0.21	1 mts 23 sec
ATF2	104±7.5	5.68±0.02	343±0.04	4.17±0.20	1 mts 33 sec
AFT3	104±6.6	5.69±0.02	3.44±0.04	3.75±0.14	1 mts 33 sec
AFT4	105±7.5	5.57±0.01	3.45±0.05	3.87±0.13	1 mts 35 sec
AFT5	104±7.8	5.68±0.02	3.46±0.04	3.87±0.12	1 mts 32 sec
AFT6	104±6.8	5.69±0.01	3.48±0.05	3.76±0.11	1 mts 31 sec
AFT7	104±7.8	5.69±0.03	3.45±0.06	3.87±0.15	1 mts 12 sec

*Mean±SD (n=6) **Mean±SD (n=20)

Table.No:17 Dissolution Profile of the Atorvastatin calcium IR Tablets AFT1-AFT7

% Cumulative Amount of Drug Release							
Time (Minutes)	**ATF1**	**ATF2**	**ATF3**	**ATF4**	**ATF5**	**ATF6**	**ATF7**
5	58.34	59.13	60.54	59.78	60.67	61.89	65.19
10	78.98	79.45	80.56	79.67	80.19	81.89	84.12
15	92.14	94.45	95.19	91.78	93.18	94.87	97.01
20	93.45	95.76	96.87	93.17	95.48	96.67	100.17
30	97.45	98.13	98.78	96.67	97.87	98.89	103.12

*Mean±SD (n=6)

Table.No:18 Dissolution Profile of the Atorvastatin calcium IR Tablet Optimized Formulation AFT7 with Innovator Tablet

% Cumulative Amount of Drug Release		
Time in (Minutes)	**AFT7**	**INNOVATOR**
5	65.19	68.4
10	84.12	85.7
15	97.01	98.8
20	100.17	99.8
30	103.12	101.30

*Mean±SD (n=6)

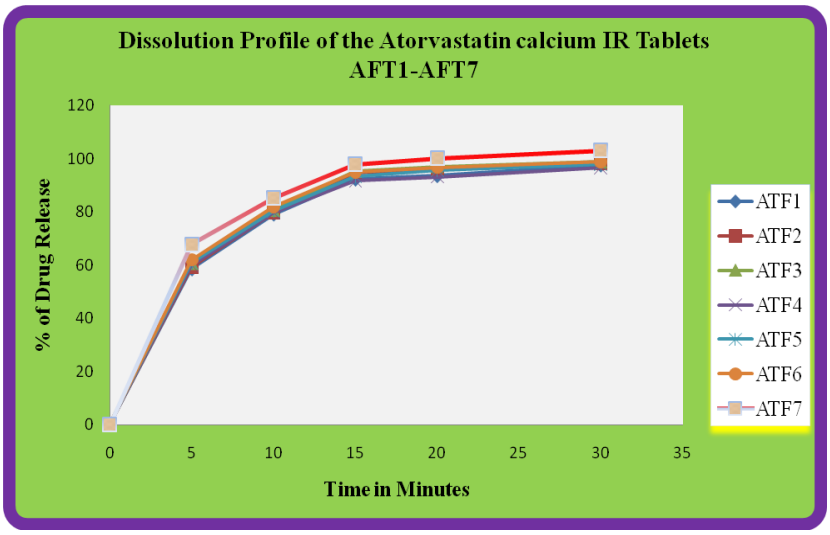

Figure.No:18 Dissolution Profile of the Atorvastatin calcium IR Tablets AFT1-AFT7

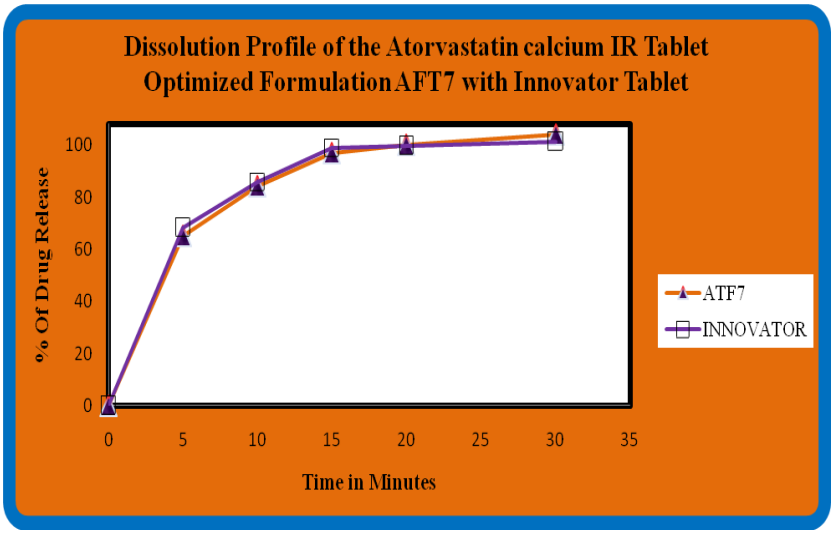

Figure. No: 19 Dissolution Profile of the Atorvastatin calcium IR Tablet Optimized Formulation AFT7 with Innovator Tablet

Discussion: From table. No:17 & figure. No:18 it can be seen that the variation of concentration of Super disintegrant and different disintegrant is affecting the release in same proportion. Different approaches were tried in batches ATF7 it was found with two super disintegrant was showing good release pattern. ATF7 shows a similar release profile to that of the Innovator with f2 value of 64. From the above results it is seen that Batch ATF7 is showing best f2 & f1 value. From Fig.no: 19 it can be inferred that release profile of Batch ATF7 matches with that of innovator product, also f1&f2 values shown in Table. No:18 are good enough to comply with the innovator's product INNOVATOR have reported similar kind of results for studies with Atorvastatin Calcium.

ASSAY

FOR ATORVASTATIN CALCIUM

Content Uniformity	Atorvastatin Calcium Optimized (ATF7) (ALU BLISTER PACK)		
	Mean	SD	RSD
	101.56	1.7	1.7

*Mean±SD (n=6)

Tablet (Batch No)	% of Drug Release*	Assay**s
ATF7	103.12	101.267±0.435
INNOVATOR	101.30	100.564±0.347

*Mean±SD (n=6) & ***Mean=Not less than 75% ; **Mean = Not less than 80%**

STABILITY STUDIES

Table. No: 19 Stability Studies Data of the Atorvastatin Calcium Optimized Formulations (ATF7) (ALU BLISTER PACK)

Parameters	Initial	1st Month		2nd Month		3rd Month	
		RT	40°C	RT	40°C	RT	40°C
Weight variation (mm)**	104±7.8	104± 7.8	103.5± 7.6	103.5± 7.8	103.5± 7.2	103.5± 7.8	103.2± 7.1
Diameter (mm)*	5.69±0.03	5.68± 0.03	5.67± 0.03	5.68± 0.03	5.67± 0.02	5.67± 0.03	5.66± 0.01
Thickness (mm)*	3.45±0.06	3.44± 0.06	3.45± 0.06	3.45± 0.06	3.44± 0.05	3.45± 0.06	3.43± 0.04
Hardness (kg/cm2)*	3.87±0.15	3.86± 0.15	3.86± 0.14	3.86± 0.15	3.86± 0.12	3.86± 0.15	3.85± 0.10
Disintegration Time*	1 mts 12 sec	1 mts 12 sec	1 mts 11 sec	1 mts 11 sec	1 mts 11 sec	1 mts 11 sec	1 mts 10 sec

*Mean±SD (n=6) **Mean±SD(n=20)

Table. No: 20 Stability Studies Data of the Assay & Dissolution Study of Atorvastatin Calcium Optimized Formulations (ATF7), With INNOVATOR (ALU BLISTER PACK)

Parameters	Initial	1st Month		2nd Month		3rd Month	
		RT	40°C	RT	40°C	RT	40°C
*Assay	101.267±0.435	101.260 ±0.435	101.204 ±0.421	101.260 ±0.435	101.120 ±0.435	101.260 ±0.435	101.001 ±0.435
*INNOVATOR (Assay)	100.564±0.235	100.554±0.435		100.545±0.243		100.555±0.256	
*% of Cumulative Release	103.12	102.67	102.76	102.67	102.01	102.67	101.65
*INNOVATOR (% of Cumulative Release)	101.30	101.21		101.05		101.31	

*Mean±SD (n=6)

Discussion: Assay*Mean=Not less than 75% ; DissolutionMean = Not less than 80%.** The results indicated that the, optimized formulated tablets were within the Pharmacopeial specifications.

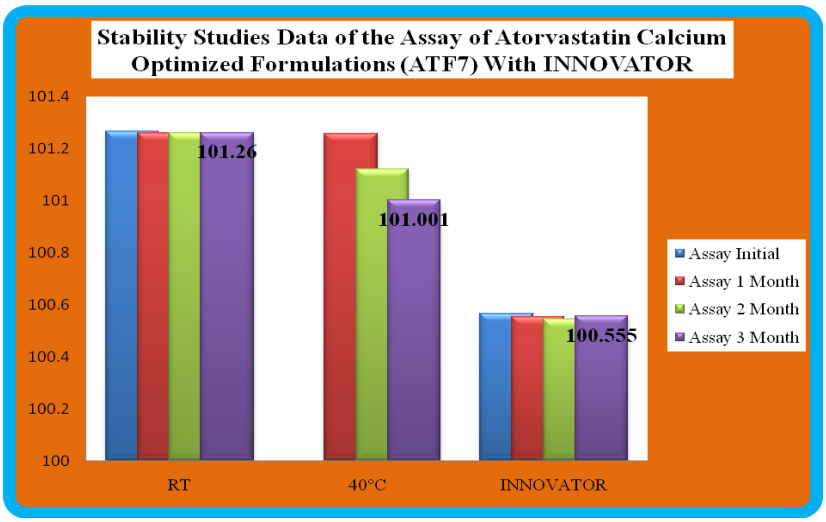

Figure. No: 20 Stability Studies Data of the Assay of Atorvastatin Calcium Optimized Formulations (ATF7) With INNOVATOR

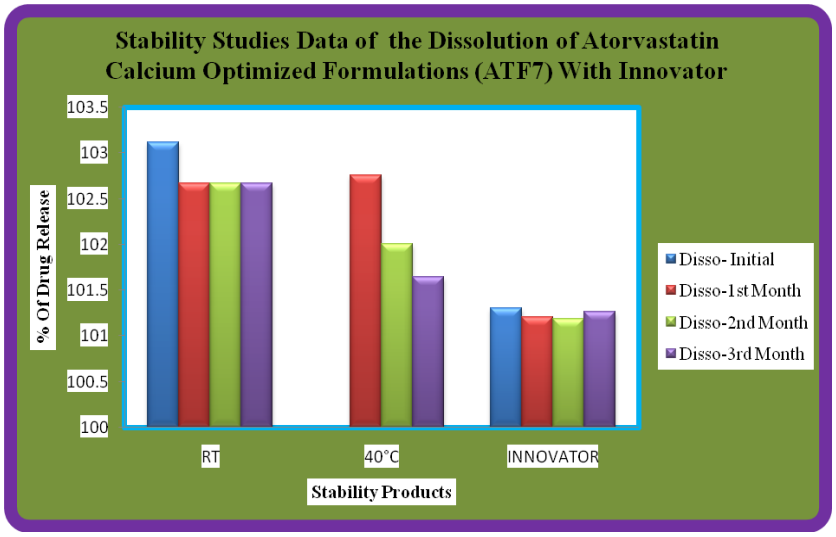

Figure. No:21 Stability Studies Data of the Dissolution of Atorvastatin Calcium Optimized Formulations (ATF7) With Innovator

Discussion: From this Table and Figure, it was seen that Atorvastatin calcium IR Tablets Batch. No: ATF7 was showing good stability for three months accelerated condition @ 40°C &75%RH. It was found that dissolution and assay value are not affected for the batch, and total impurity is also less than 1%.

SUMMARY AND CONCLUSION

The research work was aimed with formulation, development and evaluation of immediate release tablet of Atorvastatin calcium. The Assay and Impurity drug were carried out by HPLC method. The drug powders were subjected to Preformulation studies. The Preformulation characteristics are within the Pharmacopeial specifications. The Preformulation studies were carried out and the results were found to be satisfactory. The drugs and excipients compatibility were carried out by FT-IR studies and DSC. The spectra showed that there was no interaction between them. The drugs and excipients compatibility were carried out by HPLC method and by physical observation showed that there was no interaction between them. The drugs Assay and impurity were carried out by HPLC method. Special care was taken for Atorvastatin calcium processing in low humidity condition and geometric mixing is applied to avoid content uniformity and segregation. The bulk density of the powdered blend was found to be 0.41 - 0.47 gm/cm^3, tapped density between 0.47 – 0.54gm/cm^3 for all formulations. % Compressibility, Hausner's ratio to be found between USP limit. Angle of Repose was found in the range of (28) º. Hardness was found to be (3-4) kg/cm^2. The flow properties of the powdered blend for all the batches were found to be good and free flowing. The weight variation, hardness and friability of all the formulated tablets within the specified requirements. The disintegration times for the formulated tablets are within the range of USP. The Atorvastatin calcium IR tablets direct granulation was method of choice. Optimization was done and it was found that release profile was found to be best with two super disintegrants i.e. Croscarmellose sodium and Crospovidone. Film coating of Protectab HP-1 Erythrocin Supra aqueous coating 3%w/w was done on Atorvastatin calcium tablets as to avoid the humidity. Results found that release profile of batch no.ATF7 matches with Innovator product . The Percentage cumulative drug release of batch. No. ATF7 was found at 30 Minutes 103.12%. From results it can be inferred that release profile of Batch. No: ATF7matches with that of innovator product, also f1&f2 values are good enough to comply with the innovator's product INNOVATOR have reported similar kind of results for studies with Atorvastatin calcium.

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