Research Article

Formulation Development and Evaluation of Immediate Release Tablets Containing Atorvastatin Calcium Drug

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The present study is planned to develop amorphous form of Atorvastatin Calcium into immediate release tablets. Pre-formulation study and drug excipients compatibility study was done initially and the results obtained were directs the way and method of formulation. Preformulation and drug excipient compatibility study, prototype formulation carried out for the highest dose of Atorvastatin (80 mg) and optimized to get the final formula. All the mentioned batches were done by wet granulation method. Granules were evaluated for tests such as loss on drying (LOD), bulk density, tapped density, compressibility index and Hauser's ratio and sieve analysis before compression. Tablets were tested for weight variation, thickness, hardness, friability and dissolution. In vitro dissolutions were performed and f_1 and f_2 values were calculated. Dissolution profile of F8 was matched perfectly with marketed (innovator) formulation and f_2 value was found to be excellent. Also the impurity profile and stability result of F8 was found to be excellent. It can be concluded that the immediate release tablet was beneficial for delivering the drug which needs faster release to achieve the immediate action.

Key words: Atorvastatin Calcium (Amorphous), immediate release tablets, wet granulation method, Dissolution test, Stability study.

INTRODUCTION

Statins are the most commonly prescribed lipid-lowering agents because they are effective, well tolerated and easy to administer. They are generally effective, are supported by favorable outcome studies and have relatively few adverse effects. The six statins currently available are atorvastatin (Lipitor), cerivastatin (Baycol), fluvastatin (Lescol), lovastatin (Mevacor), pravastatin (Pravachol) and simvastatin (Zocor).[1]

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase and is commonly used as atorvastatin calcium. Atorvastatin calcium is chemically [R-(R*,R*)]-2-(4-fluorophenyl)-b,d- dihyd roxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate (**Fig.1**). Atorvastatin calcium is a white to off white amorphous powder that is insoluble in aqueous solutions of pH 4 and below, which are the conditions typically present in the stomach of a subject. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile, slightly

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soluble in ethanol, and freely soluble in methanol[2]. Atorvastatin is rapidly absorbed after oral administration, with time to reach peak concentrations (Tmax) within 1–2 h. The fraction absorbed (%) and absolute bioavailability of atorvastatin are approximately 30% and 12%, respectively[3]. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism[3-5].

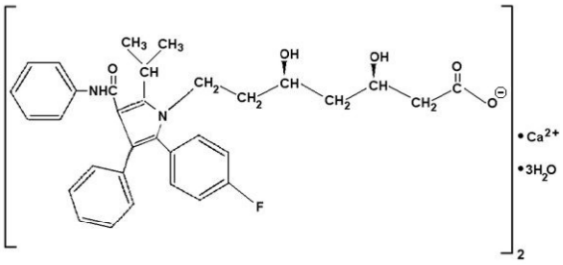

Fig. 1: Chemical structure of Atorvastatin Calcium

MATERIALS AND METHODS:

Materials

Atorvastatin calcium was obtained from Cadila Healthcare Ltd., Ahmedabad. Calcium Carbonate, HPC (KLUCEL-LF) NF, Lactose monohydrate, Croscarmellose sodium, Microcrystalline cellulose, Magnesium Stearate, Hypermellose, Titanium dioxide was purchased from Merck Chemicals, Germany. Other reagents and solvents used were of analytical grade.

Methods

1. **Preparation of Immediate Release Tablets by wet granulation technique**

Required quantity of Atorvastatin Calcium and passed through #40 mesh. Previously weighed quantities of Lactose Monohydrate, Croscarmellose sodium (CCS) and HPC were passed through 40# mesh and mixed well with Atorvastatin Calcium in Rapid Mixing Granulator (RMG) (Saral (3,5,10l, serial No=99), Vapi, India. After thorough mixing weigh the Polysorbate 80 and prepare the solution in water. Granulate the blend in RMG to obtain proper granular mass. Add extra water if require and knead the granular mass. Dry the granules in Fluid Bed Dryer (Retsch, Mumbai, India) at 60° temperature. Pass the granules through Oscillating Granular (Cadmach, Ahmedabad, India) equipped with #20 mesh. This Granule was mixed with CCS and Micro Crystalline Cellulose for 5min and then mixed with magnesium Stearate for 3min in Cage Blender (Cadmach, Ahmedabad, India) and processed for compression on D-Tooling machine by using 19.3×10.3mm oval shaped SC punch set with beveled edge, PL/PL (Cadmach, Ahmedabad, India).

2. **Preparation of film coating**

Atorvastatin tablets were prepared by different formulas, were coated with hydroxypropylmethylcellulose (Methocel, HPMC). Methocel-based coatings in an aqueous base are the most popular coating

options. The coating solution was prepared by the following formula as in **Table 1**

Procedure: 250 mL of water was placed into a suitable container, and was heated to 60° to 70°C. Gently stirring, the hydroxypropyl methylcellulose was dispersed onto the hot water. When the cellulose was moistened, 250 mL of cold water was added quickly and stirred until the dispersion became homogenous. Polyethylene glycol 6000 was dissolved in 50 mL of water, and was added to the step above a suitable sized ball jar was filled with titanium dioxide and Talc. Water in a sufficient amount was added and stirred with mechanical stirrer (Remi International, Mumbai, India). Stirred solution was added to the base solution from the step above, and the volume was made up with cold water.

Evaluation of Granules[6]

Bulk Density (Db): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in gm/ml and is given by

$$Db = M / Vb$$

Where, M and Vb are mass of powder and bulk volume of the powder respectively.

Tapped Density (Dt): It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in gm/ml and is given by

$$Dt = M / Vt$$

Where, M and Vt are mass of powder and tapped volume of the powder respectively.

Flow properties of blend: The flow properties of blend (before compression) were characterized in terms of angle of repose, Carr's index and Hausner ratio. For determination of angle of repose (θ), the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The blends were poured till the time when

Table 1 Formula of the coating film

Material Name	F1	F2	F3	F4	F5	F6	F7	F8	Use
HPMC	18.24	16.13	15.31	15.31	15.31	15.31	15.31	15.31	Film
PEG6000	1.6	3.71	3.71	3.71	3.71	3.71	3.71	3.71	Plasticizer
Titanium Dioxide	3.48	3.48	3.48	3.48	3.48	3.48	3.48	3.48	Former Coloring agent
Talc	1.68	1.68	2.5	2.5	2.5	2.5	2.5	2.5	Antitaking Agent
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	Vehicle

upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation.

$$\tan\theta = (h/r)$$

Where, h = height of pile; r = radius of pile

Carr's index (or) % compressibility: It indicates powder flow properties. It is expressed in percentage and is given by

$$I = Dt - Db/Dt \times 100$$

Where, Dt and Db are tapped density and bulk density respectively.

Hausner ratio: Hausner ratio is an indirect index of ease of powder flow. It was calculated by the following formula.

$$\text{Hausner ratio} = Dt / Db$$

Where, Dt and Db are tapped density and bulk density respectively. The results were shown in the Table 2.

Evaluation of immediate release tablet[7]

1. **Weight variation, friability, hardness and thickness:**

Tablet weight variation, thickness and friability were measured using the USP methods and criteria. Twenty tablets were taken and their weight was determined individually and The average weight of one tablet was determined from the collective weight. Tablet friability was measured using friability tester (Roche friabilator). Thickness was measured by vernire calliper and hardness of tablet was measured by Monsanto hardness tester. Weight, drug content, hardness and thickness of tablet were representing as mean ± SD

2. Disintegration test: Randomly six disintegration test. tablets were selected from each batch for Disintegration test was performed without disc in water at 37 ± 0.5°c temperature using USP Disintegration apparatus. The mean ± SD of 6 tablets were calculated in Table 3.

3. Stability studies: The promising formulation was tested for a period of 8 weeks at different temperatures of 25°C

and 40°C with 60%RH and 75% RH, for their drug content.

4. In vitro dissolution study[8,9]: Dissolution test of Atorvastatin Calcium tablets was performed using USP dissolution testing apparatus II (Paddle method; Electrolab, Mumbai, India).

IR Tablet

The dissolution test was performed using 900 ml of 0.1N HCL at 37 ± 0.5°C and 50 rpm. 4 ml of aliquot samples were withdrawn in certain time intervals and filtered using 0.11 µm nylon syringe filter. At each sampling time, an equal volume of the test medium was replaced. Filtered samples were appropriately diluted with methanol and assayed for drug concentration by HPLC. [11] The HPLC system consisted of a Waters 2695 Alliance (Milford, MA, USA) separation module attached to a Waters® 2996 UV Wavelength detector.

Table 2 Flow properties

Batch No	LOD	Angle of repose (θ)* %)	Carr's compressibility Index*	Hausner's ratio*
F1	1.12	46.96	27.15	1.37
F2	1.02	47.11	29.13	1.41
F3	1.11	47.01	28.10	1.39
F4	1.14	46.79	31.42	1.45
F5	1.15	47.32	27.41	1.38
F6	0.99	46.81	27.36	1.37
F7	1.13	47.22	26.53	1.36
F8	1.01	47.05	27.41	1.37

Table 3 Tablet Evaluation

Batch No.	Friability (%)	Hardness(Kg/cm2)	Thickness(Mm)	Weight variation	Disintegration time (Min)
F1	0.16	21.7	8.2±0.01	1235.2±12.55	8.00
F2	0.17	22.1	8.5±0.03	1255.7±11.32	6.30
F3	0.20	21.5	8.9±0.02	1245.1±10.55	5.30
F4	0.21	21.2	8.6±0.06	1227.0±11.24	4.00
F5	0.21	20.6	8.2±0.07	1236.4±12.44	3.00
F6	0.22	19.7	8.4±0.04	1248.6±22.20	2.00
F7	0.29	19.3	8.8±0.06	1240.1±20.45	1.50
F8	0.22	19.1	8.7±0.09	1242.3±22.02	1.30

Table 4 Dissolution results of all Formulations

Time in min	% Cumulative Drug Released								
	Reference 80 mg	F1	F2	F3	F4	F5	F6	F7	F8
5	28.12	13.21	14.79	18.25	19.50	23.40	25.90	29.30	29.90
10	30.61	14.02	15.98	19.78	20.40	25.40	26.40	30.50	32.50
15	32.40	15.67	17.09	21.13	21.66	26.40	27.80	30.90	33.40
20	34.72	16.79	18.89	22.89	22.60	26.90	27.90	31.00	34.70
30	36.89	18.04	20.11	24.34	23.90	27.40	30.20	31.50	35.80
45	39.58	20.11	22.02	25.89	25.10	28.90	31.30	32.10	37.60
60	40.49	21.32	23.85	26.05	26.50	32.50	32.60	32.40	38.00
90	42.32	23.78	25.79	27.34	27.34	32.50	32.80	32.90	38.10
120	47.10	25.32	27.43	28.33	29.00	32.70	33.00	33.50	40.50
F1 Value		49.35	44.03	35.59	22.91	19.36	15.20	6.34	3.55
F2 Value		36.83	39.29	43.61	52.31	55.07	57.51	75.07	86.68

Table 5 First, Second & Third month Stability Data of Tablets at 40°C ± 2°C /75% RH ± 5 % RH

Storage Condition		Room Temp.		40°C/75%RH						Specification
Period		Initial		1 Month		2 Month		3 Month		
Formulations		Innovator	F8	Innovator	F8	Innovator	F8	Innovator	F8	
Parameters		Observation								
Physical appearance		White	White	White	White	White	White	White	White	No Change
Hardness (Kp)		19.6	19.1	19.5	19.3	19.2	19.6	19.6	19.5	NLT 220N
%LOD		1.01	1.0	1.03	1.01	1.04	1.03	1.07	1.05	NMT 6%
D.T. (Min)		1.39	1.30	1.33	1.32	1.38	1.31	1.36	1.36	NMT 15min.
Impurities	Unknown Impurity	0.02	0.04	0.03	0.04	0.04	0.06	0.06	0.07	NMT 0.1%
	Total Impurity	0.30	0.27	0.34	0.29	0.38	0.46	0.42	0.55	NMT 1.0%
Assay		98.32	99.52	98.89	98.95	98.95	99.67	99.45	100.4	98.0% - 101.0%

Phenomenex luna C_{18} (2) (250×4.6), µm Column was used for the analysis. The mobile phase system, consisting of reservoir A (3.5 buffer), reservoir B (3.5 buffer: Acetonitrile: THF) and diluents (Acetonitrile: Buffer pH 4.8) with a total flow rate of 1.5 mL/min through the column to elute the analytes. The eluate was monitored by the UV Wavelength detector (scan 248 nm) and data integration was carried out by Millennium32 software (version 4)[9, 10]

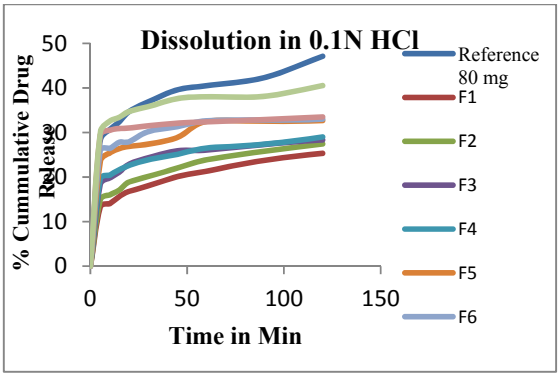

Fig. 2 Dissolution profile of Atorvastatin

CONCLUSION:

Pre-formulation study and drug excipient compatibility study results were directs the way and method of formulation. All the mentioned formulations were done by wet granulation method.

Table 6 Stability dissolution results for F8 at the condition 40/75° C

Time Point (min)	Initial	1 Month	2 Month	3 Month
5	29.50	29.98	30.04	30.45
10	33.40	33.11	32.93	33.51
15	35.00	33.50	33.12	33.87
20	35.30	34.56	34.76	34.21
30	36.60	35.34	35.21	36.23
45	38.00	36.76	37.00	37.78
60	41.20	39.89	39.56	40.04
90	43.10	42.02	43.67	44.79
120	46.00	46.55	47.37	48.45

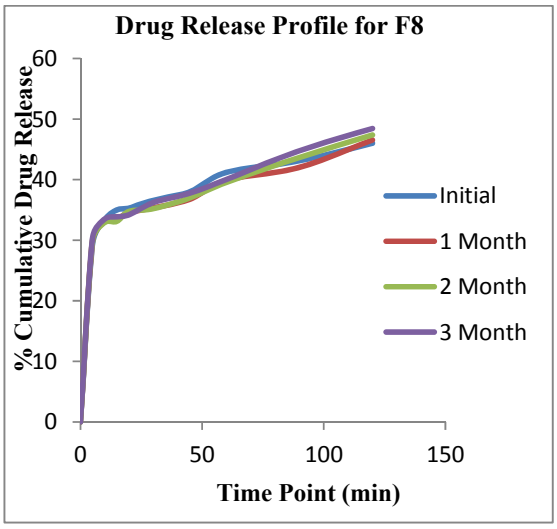

Fig. 3: Drug Release profile for F8

Dissolution profile of F8 was matched perfectly with marketed (innovator) formulation and *f*2 value was found to be excellent. Also the stability result of F8 was found to be excellent. But in F8 calcium carbonate is used. It can be concluded that the immediate release tablet was beneficial for delivering the drug which needs faster release to achieve the immediate action.

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