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Formulation and evaluation of atorvastatin calcium film coated tablets

G.Alagumanivasagam*, Ch.Srinivasu

Department of Pharmacy, Annamalai University, Annamalai Nagar, Tamil Nadu, India

ABSTRACT

Atorvastatin calcium is used for the treatment of secondary prevention in people with coronary heart disease and multiple risk factors for myocardial infarction, stroke, unstable angina, and revascularization. The purpose of the present work is to formulate and evaluate the Atorvastatin calcium film coated tablets. In order to obtain the best optimized product, nine different formulations were developed using diluents, binder, glidant, lubricant, and different concentrations of super disintegrant. Tablets were formulated by direct compression, slugging and wet granulation techniques. Various pre-compression parameters like bulk density, tapped density, compressibility index and Hausner's ratio and post compressional parameters like weight variation, thickness, hardness, friability, disintegration time, and drug release were studied. Comparatively granulation techniques exhibited the good powder flow than direct compression technique and wet granulation. Based on this investigation results, the drug release from tablets increased with increasing concentration of super disintegrant. The formulation F-9 was showed good drug release and selected as an optimized formulation and it was concluded that super disintegrant concentration, granulation technique, binder, and lubricants plays a key role in the formulation development and optimizing the immediate release tablet of Atorvastatin calcium formulation.

Keywords: Atorvastatin calcium, Coronary heart disease, Immediate release tablet, Super disintegrant.

INTRODUCTION

Tablets are solid dosage forms comprises medicinal substances with or without suitable diluents. They are the most endorsed form of medication both by physicians and patients. They offer preserved and convenient ways of active pharmaceutical ingredients (API) administration with magnificent physicochemical stability in relevant to some other dosage forms, and also provide means of accurate dosing. They can be mass produced with robust quality controls and offer various branding possibilities by means of coloured film coating, different shapes, sizes or logos [1, 2]. The tablet is the most widely used dosage form because of its suitableness in terms of self- administration, compactness and ease in manufacturing. In pharmaceutical industries, manufactures of generic tablets are usually concentrate on the optimization of the excipients mixture composition to obtain a product that meet established standard [3, 4]. Film coated tablets are compressed tablets coated with a thin layer of a polymer is able to forming a skin like film [5, 6]. Various types of oral controlled release formulation have been refined to recover the clinical efficacy of drugs having short half-lives as well as to increase patient compliance [7]. Solid dosage forms

Author for Correspondence:
G.Alagumanivasagam

are widely extensive due to their age old application. Especially, oral solid formulations hold a high potential as they serve to be most accetable for the administration of drugs. These have been spreaded into a wide range of formulations from conventional dosage forms for immediate release of the drug to controlled release dosage forms [8]. Conventional immediate release drug delivery is suited for drugs having long biological half life, high bioavailability, lower clearance and lower elimination half life. But main principle for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to pleasure any unwanted defect or disease [9]. Secondary prevention in people with coronary heart disease and multiple risk factors for myocardial infarction, stroke, unstable angina,[10,11] and revascularization[12,13]. Atorvastatin calcium is [R (R*, R*)]-2-(4-fluorophenyl)-b, d-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl] 1Hpyrrole- 1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O5)_2Ca«3H_2O$ and its molecular weight is 1209.42. Its structural formula was shown in figure 1.

AIM AND OBJECTIVE

The objective of the present study is to design and develop a stable, solid oral dosage form of Atorvastatin calcium tablets to deliver with the optimum concentration of drug at the desired site at specific time comparable to the innovator product with better stability, high production feasibility, and excellent patient compatibility.

EXPERIMENTAL SECTION

Materials

Atorvastatin Calcium (NatcoPharma Ltd., Hyderabad), Lutrol F127 (Singnet Chemicals Corporation Limited., Mumbai), Calcium Carbonate (Singnet Chemicals Corporation Limited., Mumbai), MCC PH 101 (Singnet Chemicals Corporation Limited., Mumbai), BHT (Vosco Scientifics Pvt., Secundrabad), Meglumine (Singnet Chemicals Corporation Limited., Mumbai), MCC PH 102 (Singnet Chemicals Corporation Limited., Mumbai), Opadry White (Colorcon Asia Pvt, Ltd.), Magnesium stearate (Singnet Chemicals Corporation Limited., Mumbai), SSG (KMV Enterprises., Hyderabad), Ploysorbate 80 (Vasco Scientifics Pvt, Ltd., Secundrabad), Talc (Singnet Chemicals Corporation Limited., Mumbai), HPC-EF grade (KMV Enterprises. Hyderabad), Croscarmellose Sodium (Singnet Chemicals Corporation Limited., Mumbai), Loctose Monohydrate (KMV Enterprises. Hyderabad).

Methods

Preparation of Atorvastatin Calcium Film coated tablets

Formulation Development of Atorvastatin Calcium Dispersible Tablets

- Selection of ingredients
- Selection of method
- Micronization
- Selection of Alkalizying agents

Procedure

- Atorvastatin Calcium, Lactose monohydrate, Avicel, $Caco_3$, Croscarmellose sodium, HPC EF were weighed and passed through 40# mesh.
- Atorvastatin Calcium and $Caco_3$ were geometrically mixed and remained exicipients were blended and mixed.
- The above combination was lubricated with Mg sterate, lubricated blend compressed to tablets.

Flow Properties of Blend

Density

A quantity of 25gms of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface form the height of 2.5 cm at 2sec intervals. The tapping was continued until no further change in volume was noted. Both bulk density (BD) and tapped (TD) were determined.

Compressibility Index

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations.

Hausner's ratio

It indicates the flow properties of the powder. It is usually determined from the ratio between the tapped density (TD) and the bulk density (BD).

Angle of Repose

Angle of repose (θ) is the maximum angle possible between the surface of a pile of powder and horizontal plane. It is usually determined by Fixed Funnel method and is the measure of the flowability of powder/ granules.

Evaluation of Atorvastatin Calcium tablets

Weight variation

Twenty tablets randomly selected from each formulation are weighed individually and average weight is calculated. The individual tablet weights are then compared to the average weight.

Loss on Drying

The loss on drying test is designed to measure the amount of water and volatile matters in a sample are dried under specified conditions. The loss on drying of the blend (1g) was determined by using electronic LOD (helium lamp) apparatus at 105ºC. for 5 min.

Hardness

Hardness was determined by taking ten tablets from each formulation, using a Monsanto Hardness Tester. The average hardness was calculated. It is expressed in kg or kg/cm².

Thickness

The Thickness of individual tablets are measured with a micrometer, and the average thickness was determined in mm. The thickness of the tablet is mostly related to that hardness and can be used as initial control parameter.

Friability

It is usually measured by the use of the Roche Friabilator. A 20 number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each urn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability.

Uniformity of dispersion

This test was applicable only to dispersible tablets. In this method, two tablets were placed in 100 ml of water and stirred gently until completely dispersed. A smooth dispersion must be obtained which passes through a sieve screen with a normal mesh aperture of 710 µm (sieve no. 22).

Disintegration

The disintegration test is carried out using the disintegration tester which consists of a basket rack holding 6 plastic tubes, open at the top and bottom, the bottom of the tube is covered by a 10-mesh screen. The basket is immersed in a both of suitable liquid held at 37ºC, preferably in 1L beaker.

In-vitro dissolution study

The dissolution test was performed using USP dissolution testing apparatus type II (Paddle); Medium – 0.05M Phosphate buffer, pH 6.8; Volume – 900 ml; Temperature - 37ºC; RPM-75; Time intervals - 5, 10, 15, 30 and 45 mins. Absorbance of these solutions was measured at the wavelength of UV-248nm. Separately injected equal volumes (about 10 µl) of the dissolution medium as blank, standard preparation and sample preparation into chromatograph, and the chromatograms was recorded and measure the peak area responses for the analyte peak.

Accelerated Stability Studies

Atorvastatin Calcium immediate release tablets the packed formulations were stored in stability chambers maintained at 40°C and 75% relative humidity for one month.

RESULTS AND DISCUSSION

The present analysis was undertaken to formulate Atorvastatin calcium tablet for immediate release and show immediate onset of action for the treatment of Hyperchlorestremia. Pre-formulation parameters likeAngle of repose, Compressibility, Hausner ratio, Bulk density, Tapped density, LOD was carried out for the formulation F-001- F-009 and found to be within the limit. The result was prepared in table-3. The Post-compression studies like Average weight, Thickness, Hardness, Friability was prepared and the data was found to be within the limit which was

present in table-4. Disintegration Time, Moisture content, Assay was executed for the all formulation and the data was prepared in table-5. For the development and formulation of tablets, wet granulation and direct compression techniques were carried out with combination of various approved excipients. Formulation batches of Atorvastatin Calcium tablets as prepared from formula 001-009 which was given table-1. The Accelerated stability studies was prepared at 40°C at 75% rh and found to be stable up to 12 hrs. The data was presented at table-2.All the experimental formulation batches have been subjected to various evaluation parameters viz, average weight, thickness, hardness, friability, disintegration, dissolution studies, water content, assay was prepared in figure 2-10 respectly. Dissolution studies was carried out for the different formulation F001-F009 was prepared in table-6 from the table-6. It was found to be the F009 is the best formulation and found to be satisfactory From the results obtained from the study it was observed that the drug loss on storage was found to be normal.

Table 1: Formulation batches of Atorvastatin Calcium tablets

S.No.	Ingredients	F001	F002	F003	F004	F005	F006	F007	F008	F009
1	Atorvastatin Calcium	86.8	86.8	86.8	86.8	86.8	86.8	86.8	86.8	86.8
2	Loctose Monohydrate	256.0	256.0	256.0	203.0	267.2	267.2	267.16	158.0	158.0
3	Avicel pH101	-	299.1	299.1	300.0	-	-	-	-	435.2
4	SSG	-	-	-	-	-	-	-	50.0	50.0
5	HPC-EF grade	25.0	25.0	20.0	18.3	12.0	15.0	12.0	16.0	16.0
6	Polaxomer 407	-	-	-	-	-	-	-	-	-
7	Meglumine	-	-	-	-	-	-	-	11.0	12.0
8	Purified water	-	Q.S	Q.S	Q.S	-	-	-	-	Q.S
9	Avicel pH102	305.2	-	-	-	48.0	48.0	480.0	467.2	32.0
10	Mg sterate	6.0	6.0	3.00	-	6.00	3.00	6.00	6.00	6.00
11	Caco3	480.0	480.0	480.0	400.0	266.0	266.0	264.0	-	-
12	Crascarmellose sodium	61.0	61.0	69.0	121.2	84.0	84.0	84.0	-	-
13	Polysorbate 80	-	6.10	6.10	6.10	-	-	-	-	-
14	BHT	-	-	-	-	-	-	0.348	-	--
15	Polaxomer 407	-	-	-	-	-	-	-	4.00	4.00

Table 2: Accelerated stability study protocol

Condition	**40ºC/75%RH**		
Batch No.	**F009**		
Time (Hour)	0	0	0
1	28.35	27.52	26.76
2	34.15	33.72	33.76
3	39.45	39.52	40.56
4	47.45	45.12	44.36
6	57.65	53.92	62.06
8	7545	873.62	72.86
10	83	81.72	83.66
12	99.15	98.22	97.66
Assay	99.15	99.02	98.76

Table 3: Pre-formulation parameters for formulations F-001 to F-009.

Formula	Angle of repose	Compressibility Index (%)	Hausner ratio	Bulk density (m/ml)	Tapped density (g/ml)	LOD (%)
F-001	35.65	35.52	1.536	0.551	0.853	1.24

F-002	26.56	20.75	1.261	0.420	0.530	1.43
F-003	28.42	34.50	1.527	0.486	0.742	1.31
F-004	30.12	26.15	1.354	0.461	0.625	1.96
F-005	34.76	31.81	1.467	0.568	0.833	2.62
F-006	32.56	34.69	1.536	0.510	0.781	2.72
F-007	26.43	37.80	1.608	0.426	0.656	1.60
F-008	27.87	31.91	1.469	0.531	0.781	1.53
F-009	26.15	22.85	1.290	0.584	0.757	1.17

Table 4: Post-compression studies.

Formula	Average weight (mg)	Thickness (mm)	Hardness (kp)	Friability (%)
F-001	1221.7	6.25	16.6	0.64
F-002	1223.8	6.53	16.9	0.57
F-003	1221.6	7.27	18.6	0.43
F-004	1222.5	7.01	15.4	0.35
F-005	804.4	6.89	22.5	0.19
F-006	802.9	6.46	22.3	0.17
F-007	1221.8	6.76	21.7	0.16
F-008	804.9	5.34	16.8	0.13
F-009	**802.6**	**6.94**	**22.5**	**0.07**

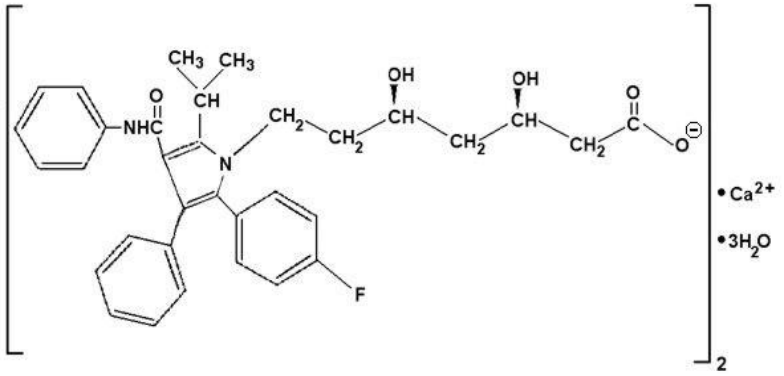
Table 5: Disintegration Time, Water content and Assay values for the formulations F-001 to F-009.

Formula	Disintegration time (mins)	Water content (w/w)	Assay (%)
F-001	1.70	2.5	97.8
F-002	2.27	3.1	98.4
F-003	1.45	2.2	91.0
F-004	1.67	3.7	97.5
F-005	1.34	2.8	99.7
F-006	1.26	3.0	99.1
F-007	1.15	4.2	100.7
F-008	1.22	3.6	101.2
F-009	**1.05**	**2.7**	**100.2**

Table 6: Dissolution profile of different formulations (F-001 to F-009).

Sample Time (minutes)	Cumulative Percentage Drug Release								
	F-001	**F-002**	**F-003**	**F-004**	**F-005**	**F-006**	**F-007**	**F-008**	**F-009**
5	43.2	43.9	45.2	45.4	48.0	50.2	51.4	50.1	**56.3**
10	45.6	46.7	48.1	50.4	51.1	51.5	53.1	55.8	**61.9**
15	47.9	49.1	50.6	53.3	55.4	58.7	60.6	61.4	**68.1**
30	52.1	53.8	54.2	57.7	60.4	62.4	66.3	67.7	**73.9**
45	62.3	62.7	64.2	66.2	68.7	72.9	71.4	74.3	**79.4**
60	70.1	70.6	72.6	73.2	76.5	81.3	80.7	81.7	**87.2**

Figure 1: Structure of Atorvastatin calcium



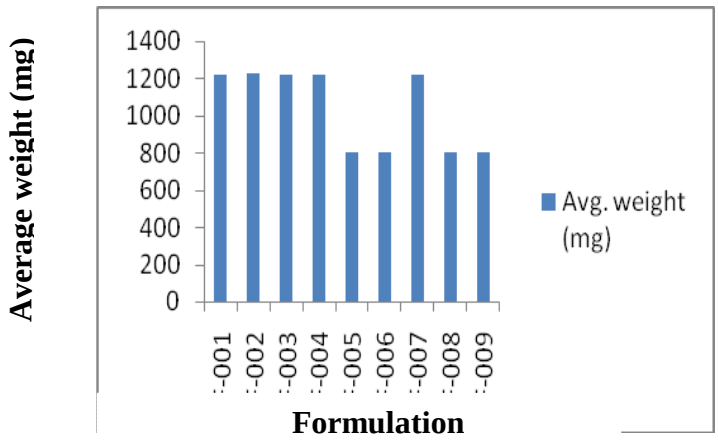


Figure 2: Average weight of the various formulation

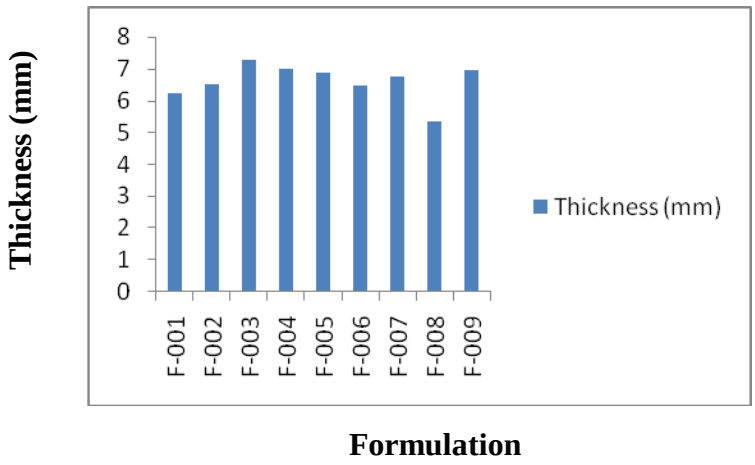


Figure 3: Thickness of the various formulation

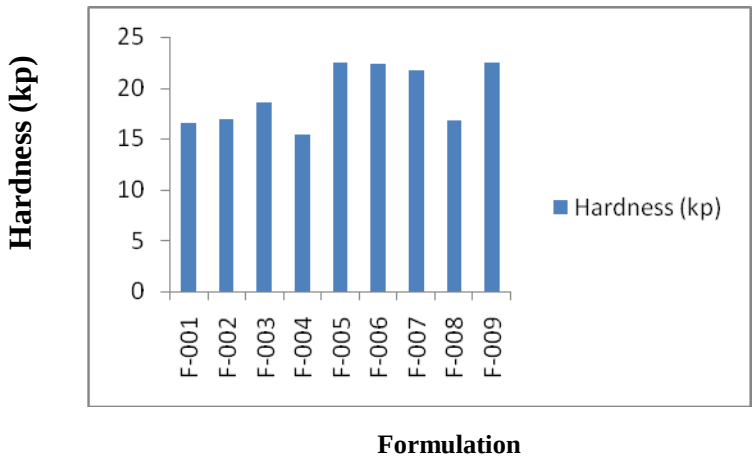


Figure 4: Hardness of the various formulation

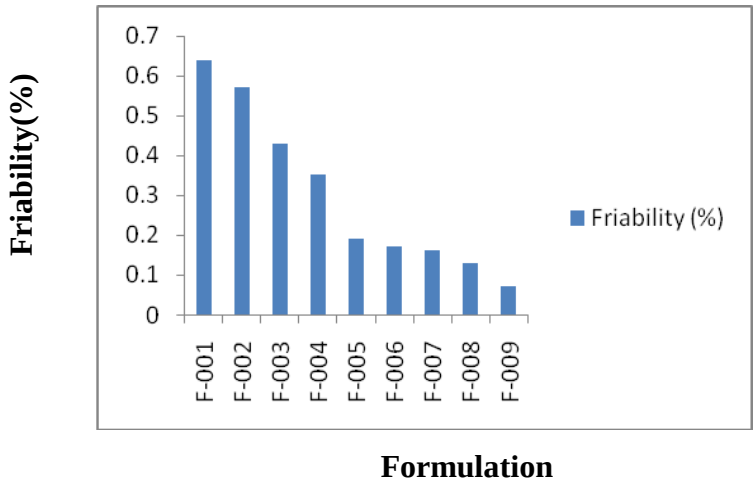


Figure 5: Friability of the various formulation

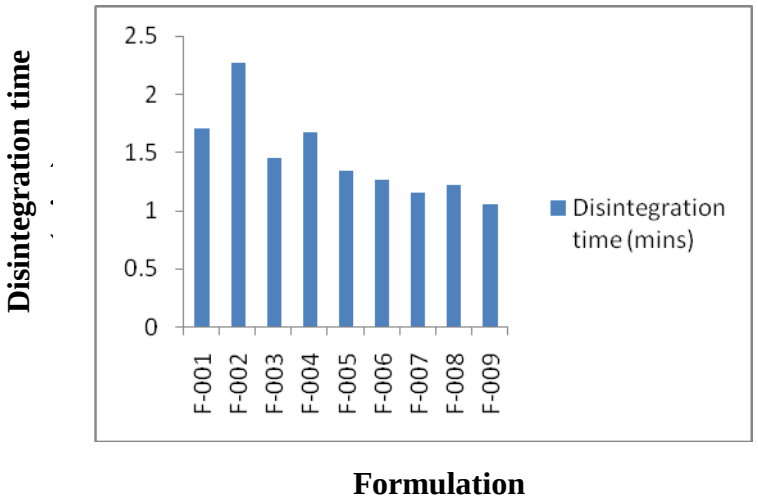


Figure 6: Disintegration time of the various formulation

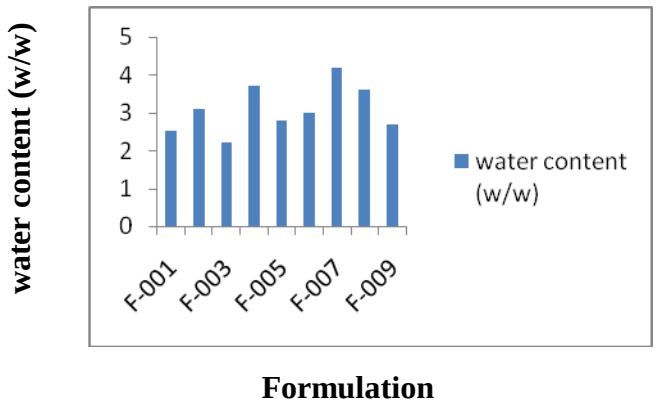


Figure 7: Water content of the various formulation

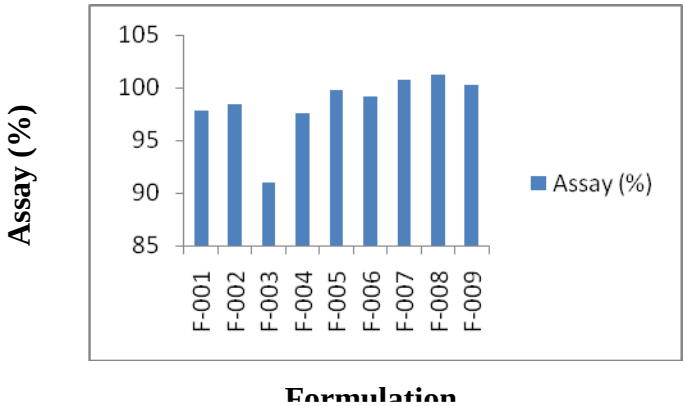


Figure 8: Assay of the various formulation

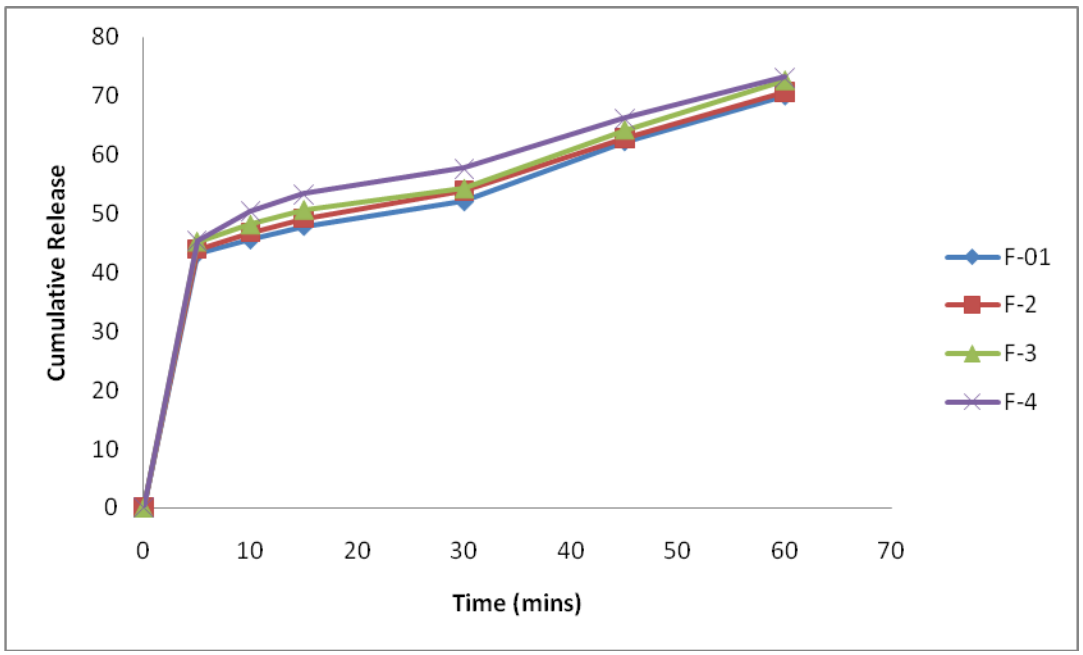


Figure 9a: Dissolution Profile of F-001-F-004

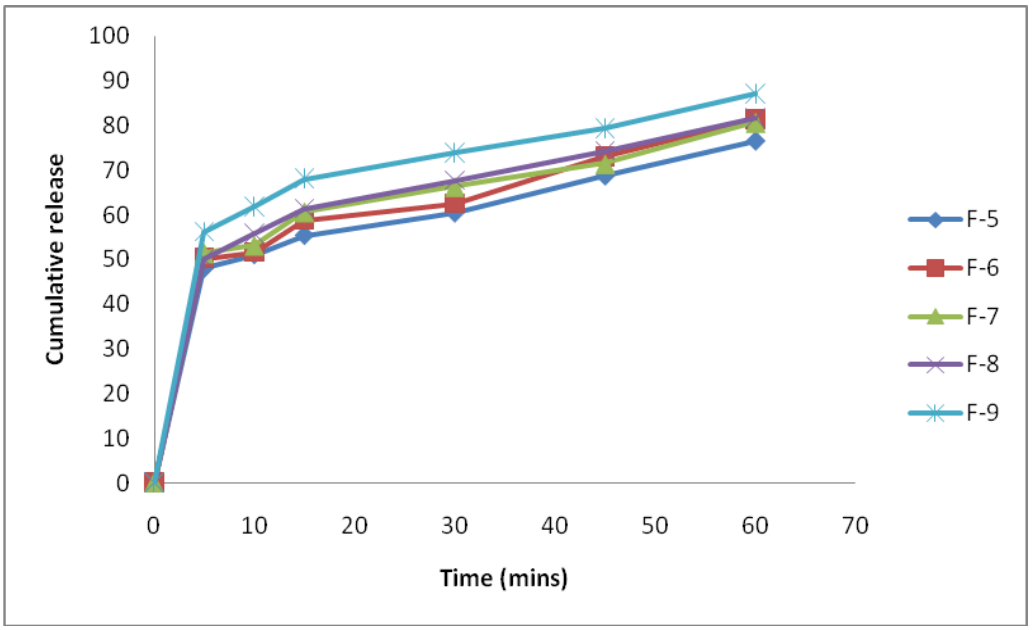


Figure 9b: Dissolution Profile of F-005-F-009.

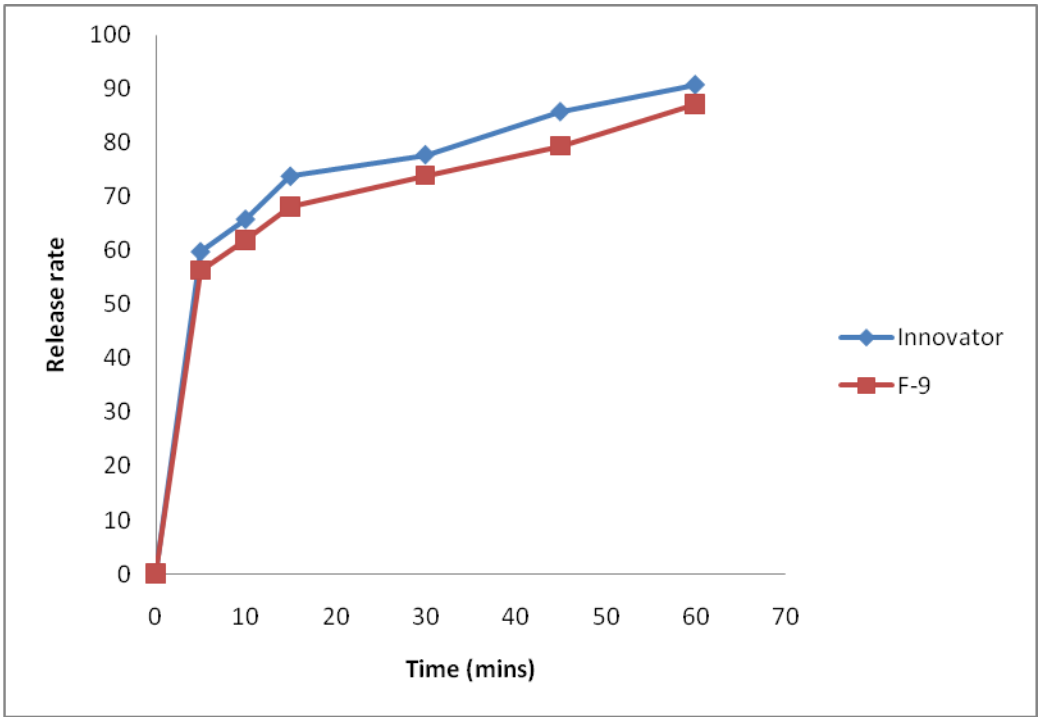


Figure 10: Comparison of Drug Release of Innovator and F-009

Pre-formulation study results of formulations

CONCLUSION

From the preceding investigation it can be finalised that, the "Formulation Development and Evaluation of Atorvastatin calcium tablets", were formulated in this research investigation was found to be pharmaceutical equivalent to that of the reference drug. In this research concentration of wet granulation and direct compression techniques, were taken a major role in the formulation development and optimizing the immediate release tablet formulation of Atorvastatin calcium. Accelerated stability studies were conducted for the optimized formulation F-9 as per ICH guidelines; the results were revealed that the formulation exhibit the no notable changes.

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