ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

DEVELOPMENT OF ATORVASATIN 10MG IMMEDIATE RELEASE FILM COATED TABLET BY DIRECT COMPRESSION PROCESS

Oneeb Hassan Javed[1], Lubna Bashir[1], Shahbaz A. Noor[1], Asif K. Sherwani[2], Shazia Naz[1], Ghazala R. Naqvi[1]

1. Department of Pharmaceutics, Federal Urdu University, Karachi

2. Department of Biochemistry, University of Karachi

Manuscript Info

Manuscript History:

Received: 15 July 2015
Final Accepted: 22 August 2015
Published Online: September 2015

Key words:

Immediate release, Direct Compression, Dissolution, Calcium Carbonate, Atorvastatin Calcium

Corresponding Author

Oneeb Hassan Javed

Abstract

Atorvastatin is a commonly used drug worldwide. The present study aims on developing formulation of Atorvastatin 10 mg immediate release film coated tablet by direct compression process. Two formulations were developed containing dual diluents in same ratio (Lactose Anhydrous and Microcrystalline Cellulose), an alkalizing agent (Calcium Carbonate) as basic medium is required for dissolution of atorvastatin, a combination of super disintegrants (Croscarmellose Sodium and Low substituted Hydroxy Propyl Cellulose), a glidant (Colloidal Silicon Dioxide) and a lubricant (Magnesium Stearate). All excipients used in core tablet were of DC grade. Calcium Carbonate was taken as the variable as it is the most critical excipient in the designed formulation. One formulation contained 50 % Calcium Carbonate and other 25 % of the total core formulation. The diluents were accordingly used to adjust the quantity of Calcium Carbonate in the two formulations. Core tablets were coated using traditional film coating materials i.e. polymer (Hydroxy Propyl Methyl Cellulose), a plasticizer (Polyethylene Glycol) and an opacifier (Titanium Dioxide). Coating solvent used was Purified Water. Both formulations showed excellent flow properties. Core tablets were tested for weight variation, hardness, thickness, friability and disintegration whereas, assay and dissolution were tested for coated tablets. Dissolution was performed at multiple points in FDA official dissolution medium. Percent release and release pattern was compared with a reference innovator brand by using the model independent method, similarity (f_2). The results revealed that both formulations show similarity in official dissolution media. Both formulations were also subjected to accelerated stability study at 40 ± 2°C and 75 ± 5% RH for 6 months and no specific change was observed.

INTRODUCTION

Atorvastatin is a synthetic lipid lowering agent. It is present as Calcium salt. Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL [1]. It reduces LDL production and the number of LDL particles. It produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles.

Immediate release solid oral tablets are those for which ≥85% of labelled amount dissolves within 30 min, either rapidly or slowly [2]. Different methods used for preparation of immediate release solid oral tablets mainly include direct compression, wet granulation and dry granulation out of which direct compression is the simplest method.

Direct compression is a process in which tablets are compressed directly from powder blend of API and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required [3]. It is more efficient and economical process as compared to other processes. It has reduced processing time, reduced labor costs and fewer manufacturing steps. Elimination of heat and moisture from the process increases not only the stability but also the suitability of the process for thermo labile and moisture sensitive API's [4].

In current study, an economical direct compression process with commonly used excipients was used. Two formulations were developed and compared with an innovator for similarity factor. The formulations were also subjected to stability studies at 40 ± 2°C and 75 ± 5% RH.

MATERIALS AND METHODS

Material

Atorvastatin is available as Calcium salt, thus, Atorvastatin Calcium from DRL was used as API . The excipients in core tablet included Lactose Anhydrous (Super Tab 21) from DMV Fonterra, Microcrystalline Cellulose (Avicel PH 102) and Croscarmellose Sodium (AcDisol) from FMC Biopolymer, Calcium Carbonate (Destab 90%) from PD Holdings, Hydroxy Propyl Cellulose (HPC LH 21) from Shin-Etsu, Colloidal Silicon Dioxide (Aerosil 200) from Evonik and Magnesium Stearate from Mallinckrodt. Coating materials used were Hydroxy Propyl Methyl Cellulose (Methocel 5CPS) from Dow Chemical, Polyethylene Glycol (PEG 6000) from Merck and Titanium Dioxide from Huntsman.

Preparation of Tablets

All materials were weighed accurately. Core tablets were prepared by passing all materials through appropriate sieves. Atorvastatin Calcium and Calcium Carbonate were passed through 30 mesh, whereas, remaining excipients were passed through 40 mesh. Atorvastatin Calcium, Colloidal Silicon Dioxide, Croscarmellose Sodium and Hydroxy Propyl Cellulose were first mixed for 5 mins. Calcium Carbonate was then added to the blend and mixed for 5 mins followed by addition of Lactose Anhydrous and Microcrystalline Cellulose and further mixing for 15 mins. The blend was than lubricated with Magnesium Stearate for 5 mins.

All materials were mixed in a tumbler mixer and compressed using a single punch machine. Core tablets were coated using coating solution prepared in Purified Water with HPMC 5CPS, PEG 6000 and Titanium Dioxide.

Table 1 – Composition of formulations of Atorvastatin 10 mg Film Coated Tablet (F01 and F02)

Ingredients	Quantity (mg / tablet)	
	Trial 01 (F01)	Trial 02 (F02)
Atorvastatin Calcium	10.36	10.36
Calcium Carbonate (Destab 90%)	75.00	37.50
Microcrystalline Cellulose (Avicel PH 102)	21.57	40.32
Lactose Anhydrous (Super Tab 21)	21.57	40.32
Croscarmellose Sodium (AcDisol)	12.00	12.00
Hydroxy Propyl Cellulose (HPC LH 21)	4.50	4.50
Colloidal Silicon Dioxide (Aerosil 200)	3.00	3.00
Magnesium Stearate	2.00	2.00
Total (Core Tablet)	150.00	150.00
Hydroxy Propyl Methyl Cellulose (Methocel 5CPS)	2.56	2.56
Polyethylene Glycol (PEG 6000)	0.72	0.72
Titanium Dioxide	0.72	0.72
Purified Water	25.6	25.6
Total (Coated Tabet)	154.00	154.00

Table 2 – Selected variable in the formulations

Ingredients	Quantity (%)

	F01	F02
Calcium Carbonate (Destab 90%)	50.00	25.00
Diluents	21.72	40.59

Evaluation of powder blend

Angle of repose [5]

Angle of repose was calculated using standard fixed funnel method. It is the angle formed by base (diameter) of the bench surface and edge (height) of the cone like pile of powder. Height and diameter of the cone was measured when poured through the funnel and angle of repose was calculated using following formula:

$$\Theta = \tan^{-1} \frac{h}{r}$$

Bulk Density [6, 7]

Bulk density was measured using method of measurement in graduated cylinder. A known mass of powder blend (M) was leveled in 100 mL graduated cylinder without compacting and unsettled apparent volume (V_0) was measured. Bulk density was calculated as per following formula:

$$\text{Bulk Density} = \frac{M}{V_0}$$

Tapped Density [6, 7]

A known mass of powder blend (M) leveled in 100 mL graduated cylinder was subjected to 250 taps per minute (USP method II) using Electrolab tap density tester (Model ETD - 1020). Final tapped volume (V_f) was measured and tapped density was calculated as per following formula:

$$\text{Tapped Density} = \frac{M}{V_f}$$

Compressbility Index and Hausner Ratio [6, 7]

Compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the powder's ability to settle and simplest ways for measurement of powder flow.

Compressibility index and Hausner ratio were calculated using following formula:

$$\text{Compressibility Index} = \frac{V_0 - V_f}{V_0} \times 100$$

$$\text{Hausner Ratio} = \frac{V_0}{V_f}$$

Evaluation of Core Tablets

Weight Variation [8]

Weight variation was performed using randomly selecting twenty tablets. A comparison between average weight of the tablets and each tablet's weight was performed. Limit of % weight variation was $\pm$7.5% considering pharmacopoeial requirements.

Hardness [9]

Hardness of a tablet, also known as tablet crushing strength was performed using a Vankel Tablet Hardness Tester (Model VK200) and results were calculated.

Disintegration Test [6, 7]

Disintegration test was performed using basket-rack assembly from Electrolab (Model ED - 2L). 1 tablet was placed in each of six tubes of the basket and test was performed using water as the immersion fluid maintained at 37 ± 2°C. Time for complete disintegration of all six tablets was noted.

Friability Test [6, 7]

Friability was determined using Electrolab friability tester (Model EF - 2). Around 6.5 g tablets were subjected to friability at 25 rpm for 4 min (100 rotations). Initial and final weight of the tablets was measured and calculated as per following formula:

$$\% \text{ Friability} = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Assay

Assay was performed on coated tablets by randomly selecting and crushing twenty tablets. 80 mg of crushed powder was dissolved in a 100 mL volumetric flask, sonicated for 15 mins and shaked for 30 mins in a flask shaker. The solution was diluted to volume with diluent and mixed. Solution was than filtered through ordinary filter paper. 5 mL of solution was transferred into 50 mL volumetric flask, solution was diluted to volume with diluent and mixed. This solution contained 0.08 mg of Atorvastatin per mL. Standard solution having same concentration was prepared. Solutions were filtered through 0.45µm membrane filter and injected into HPLC system.

Mobile phase was prepared using 50 volume of phospahte buffer, 48 volume of acetonitrile and 2 volume of methanol (50:48:2, v / v), fitered through 0.45 µm membrane filter and degased.

Chromatographic conditions were taken as Agilent Eclipse XDB-C18, 150 x 4.6 mm, 5µm or equivalent HPLC column and measured at 238 nm with 1.0 mL / min flow rate and 10 µL injecting volume using HPLC Shimadzu 20A.

Dissolution

Multi point dissolution was carried out on coated tablets using USFDA drug database, recommended dissolution method for atorvastatin calcium tablet. Randomly selected twelve tablets were analyzed for dissolution in 900 mL volume, 0.05 M phosphate buffer, pH 6.8 using USP apparatus II (paddle) at 75 rpm [10]. Temperature was maintained at 37± 0.5ºC. Samples were collected at 5, 10, 15, 20 and 30 min time intervals and concentration was calculated by measuring absorbance at 241 nm in a UV-Vis spectrophotometer, Shimadzu (Model UV-1800).
Similarity factor (f_2) for dissolution was also calculated. Following formula was used [11].

$$f_2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{j-1}^{n}\left|R_j - T_j\right|^2\right]^{-0.5} \times 100\right\}$$

Where,
'n' is the sample number, 'Rj' is the % of reference drug release and 'Tj' is the % of test drug release at different time intervals.

Stability Studies

Accelerated stability study at 40 ± 2°C and 75 ± 5% RH was performed for both formulations and samples were tested at 3 and 6 months [12]. Stability chamber (Model TH-1000G) was used for stability.

RESULTS AND DISCUSSION

Two formulations of Atorvasatin 10mg immediate release film coated tablet were developed. Calcium Carbonate, used as alkalyzing agent, was taken as the variable as it is the most critical excipient in the designed formulation. The diluents were accordingly used to adjust the quantity of Calcium Carbonate as shown in Table 2. Tablet formulations were developed using direct compression process followed by traditional film coating of the tablets.
Pre compression properties of the powder blend were evaluated. Both formulations had excellent powder flow with angle of repose of 26 and 29, and, hausner ratio of 1.23 and 1.25 as shown in Table 3, indicating that increase or decrease in concentration of variables does not have much impact on powder flow.

Table 3 – Evaluation of powder blend

Test	Results	
	F01	F02

Angle of repose (^{0})	26	29
Bulk density (g / mL)	0.62	0.58
Tapped density (g / mL)	0.76	0.73
Compressibility Index (%)	19	20
Hausner ratio	1.23	1.25

The tablets were compressed and evaluated for physical parameters and found satisfactory as shown in Table 4. Weight variation of both formulations was found well with in limit of ±7.5%. Optimum hardness around 6.5 kp with around 0.2% friability and 3 minutes DT was easily achieved for both formulations which is within pharmacopoeial limits.

Table 4 – Evaluation of core tablets

Test	Specification	Results	
		F01	F02
Weight variation (%)	± 7.5	150 ± 2.0	150 ± 3.0
Hardness (kp)	5 – 10	6.8 ± 0.5	6.5 ± 0.4
Thickness (mm)	2.8 – 3.8	3.13 ± 0.04	3.20 ± 0.06
Disintegration Time (min)	NMT 15	2.5	3.0
Friability (%)	NMT 1	0.21	0.18

Core tablets were coated using coating solution prepared in Purified Water with HPMC 5CPS, PEG 6000 and Titanium Dioxide. % weight gain and appearance of the tablets was found satisfactory after coating. Assay of the tablets was performed using randomly selecting 20 tablets and found near 100% for both formulations i.e. 99.5% for F01 and 98.9% for F02. Dissolution was performed using USFDA drug database dissolution method and found 99.4 for F01 and 98.6 for F02 as shown in Table 5.

Dissolution was performed at multiple time points (5, 10, 15, 20 and 30 minutes) and compared with the reference innovator product. Similarity factor (f_2) was calculated which was found as 87.2 for F01 and 81.7 for F02 as shown in Table 6. Generally, f_2 values greater than 50 (50 - 100) ensure sameness or equivalence of the two products, the test product and the reference product [13]. In this case, both formulations show f_2 value greater than 50 which indicates that the both formulations are equivalent to the reference innovator product.

Accelerated stability studies showed no major change in physico-chemical properties as quality of drug product varies with time under the influence of variety of environmental factors and storage condition [14]. All parameters were satisfactory and within limits for both formulations when tested up to 6 months as shown in Table 6.

Table 5 – Initial evaluation of coated tablets and results of accelerated stability studies at 40 ± 2°C and 75 ± 5% RH

Test	Specification	Results					
		F01			F02		
		Initial	3	6	Initial	3	6
Appearance	White colored, oval shaped, biconvex, film coated tablet	Complies	Complies	Complies	Complies	Complies	Complies
Hardness (kp)	NLT 5	7.9 ± 0.5	7.8 ± 0.4	7.6 ± 0.4	7.6 ± 0.4	7.5 ± 0.4	7.5 ± 0.4
Thickness (mm)	NLT 2.8	3.21±0.04	3.23±0.03	3.23±0.04	3.30±0.05	3.31±0.05	3.30±0.03
Assay (%)	90 – 110	99.5	99.0	98.4	98.9	98.5	98.1
Dissolution (%)	NMT 80	99.4	98.5	97.6	98.6	98.0	97.1

Table 6 – Results of similarity factor (f_2) in 0.05 M phosphate buffer, pH 6.8

Test	Results	
	F01	F02
Similarity factor (f_2)	87.2	81.7

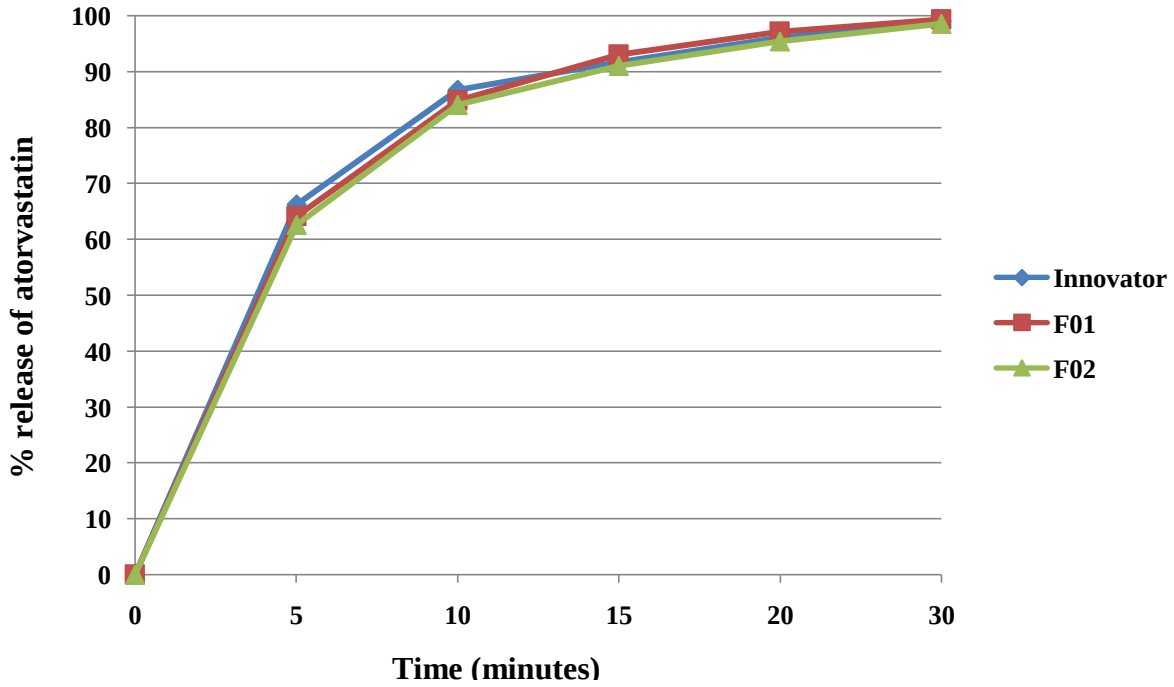

Figure 1 – % release of innovator, F01 and F02 in 0.05 M phosphate buffer, pH 6.8.

CONCLUSIONS

Two formulations of atorvastatin 10 mg immediate release film coated tablet by direct compression process were successfully developed using Calcium Carbonate in different concentrations. Both formulations showed excellent blend properties and all critical tablet parameters were found satisfactory. Similarity factor (f_2) was more than 80% for both formulations which shows that both formulations were equivalent to innovator product. Both formulations were also stable for 6 months at accelerated condition. More than 80% f_2 value for both formulations indicate that use of Calcium Carbonate in 25% concentration i.e. Trial 02 (F02) is sufficient for achieving a satisfactory and equivalent dissolution to reference innovator product. The developed formulation is also advantageous in having a simple manufacturing process.

REFERENCES

1. Human prescription drug label of Lipitor (atorvastatin calcium) film coated tablet, (http://dailymed.nlm.nih.gov/dailymed/).
2. Vishal G. Rathod, Vaishali Kadam, S. B. Jadhav, Md. Zamiruddin, V. B. Bharkad, Suprabha P. Biradar; World Journal of Pharmacy and Pharmaceutical Sciences, Volume 3, Issue 6, 545-558.
3. Rabia Bushra, Muhammad H. Shoaib, Nousheen Aslam, Durriya Hashmat, Masud-ur-Rehman; Pak. J. Pharm. Sci., Vol.21, No.2, April 2008, pp.113-120.
4. Gowtham K. Dokala, Ch. Pallavi; International Journal of Research in Pharmaceutical and Biomedical Sciences, Vol. 4 (1) Jan– Mar 2013
5. Rakhi B. Shah, Mobin A. Tawakkul and Mansoor A. Khan; AAPS PharmSciTech. 2008 Mar, 9(1): 250–258.
6. Pharmacopoeia, USP 37 – NF 32.
7. Pharmacopoeia, BP 2013.
8. T.N.V.S Narayana Reddy*, S.Divya Teja.Banda, G. Diwaker Srinivas; Int. J. Pharm. Sci. Rev. Res., 23(1), Nov – Dec 2013, nº 54, 290-294.

9. Umesh L. Chaudhari, Shashikant D. Barhate, Rajesh G. Patil, Chandrashekhar B. Borase, Pratibha A. Mali, Prafulla D. Chaudhari; IJPRD, 2011, Vol 3(10), Dec 2011 (143 – 151).
10. USFDA drug database, recommended dissolution method for atorvastatin calcium tablet (http://www.accessdata.fda.gov/scripts/cder/dissolution/)
11. Uzma Asif, Asif K. Sherwani, Naheed Akhtar, Muhammad H. Shoaib, Muhammad Hanif, Muhammad I. Qadir, Muhammad Zaman; Advances in Polymer Technology, Vol. 00, No. 0, 2015, DOI 10.1002/adv.21536 2015 Wiley Periodicals, Inc.
12. ICH Quality guidelines, stability testing of new drug substances and products Q1A(R2), (http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html).
13. FDA Guidance for Industry, dissolution testing of immediate release solid oral dosage forms, (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070237.pdf).
14. E. Sayar, S. Sahin, S. Cevheroglu S., Hincal; A. A. Fabad J Pharm Sci 2008, 33, 87–94.