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Formulation and stabilization of Atorvastatin tablets

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ABSTRACT

The present study is planned to develop Atorvastatin calcium amorphous 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 calcium (80 mg) and optimized to get the final formula. Atorvastatin calcium (amorphous) is highly susceptible to hydrolysis and oxidation. So wet granulation method was avoided. All the mentioned batches were done by dry granulation method by roller compaction. 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 Formulation 1 (F1) and Formulation 2 (F2) values were calculated. Dissolution profile of F5 was matched perfectly with marketed (innovator) formulation and F2 value was found to be excellent. Also the impurity profile and stability result of F5 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, Immediate release tablets, Dry granulation method, Dissolution test, Stability study.

INTRODUCTION

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Clinical and pathologic studies showed that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased

levels of HDL-C are associated with a decreased cardiovascular risk. As it has long half life (14 hrs), it is not suitable drug for controlled release formulation. Tablet dosage form is preferable because other dosage form don't have good shelf life in case of atorvastatin due to its degradation and impurity issue. Different processing parameters on final formulation & worst case study were carried out for optimization of the best condition of the formulation [1, 2].

Atorvastatin calcium is highly susceptible to heat, moisture, a low pH environment and light. Again the amorphous form is many times unstable than its counterpart crystalline form. In acidic environment it degrades into corresponding lactone. The *in-vitro* evaluation of an immediate release dosage form by using Atorvastatin calcium in amorphous form was used in tablets prepared by Dry granulation/Roller compaction techniques. The percent drug releases at 0, 5, 10, 15 and 30 mins were selected as responses. The release of Atorvastatin was immediate within 2-3 mins, indicating the usefulness of the formulations for once daily dosage forms [3].

EXPERIMENTAL SECTION

Materials:

Atorvastatin calcium (Biocon Ltd.), Magnesium oxide (Signet Dead-sea, Israel),Sodium bicarbonate (Merck), Calcium carbonate (Signet Specialty minerals,UK), Lactose monohydrate DMV (Pharmatose vaghel, Netherlands), Dicalcium phosphate (Signet rhodia/Innophos, USA), Microcrystalline cellulose (Signet FMC Biopolymers, USA), Pregelatinised Starch (Colorcon Asia Pvt. Ltd.), Mannitol (Signet Roquette France), Croscarmellose Sodium (Signet FMC Biopolymer, USA), Butylated hydroxy anisole (Merck), Polysorbate 80 (Merck), Magnesium Stearate (Signet Ferro, Portugal), Opadry White YS-1-7040 (Colorcon Ltd.).

Method:

Lactose monohydrate was passed through 40 meshes. Then dissolve Polysorbate 80 and butylated hydroxyl anisole in ethanol (5ml). Apply the solution on lactose monohydrate and dried in tray drier at 40-45^{0}C until desired LOD is reached and again it was passed through 40 meshes. All the ingredients was passed through 40 meshes, except magnesium stearate, added with the earlier mixture and mixed for 25 mins in octagonal blender. Then magnesium stearate was passed through 40 meshes and mixed with the blend in same blender for further 5 mins. After compaction theoretical weight of dry mix and practical weight of flakes was determined. Then milling is done with 2mm sieve, slow speed and forward direction. Granules were passed through 24 meshes. At this stage sieve analysis is done and the % fines and granules were adjusted**.** Extra granularly microcrystalline cellulose were passed through 40 meshes and mixed with milled blend for 10 mins. Then magnesium stearate were passed through 40 meshes and mixed with the above blend in same blender for further 5 mins. Final parameters are measured and strategy taken for its optimization [4, 5].

Preformulation study

The present investigation was carried out to develop and formulate stable oral solid dosage form of Atorvastatin calcium amorphous. The dosage form was developed as tablets and they were prepared by using different excipients along with stabilizer.

Compatibility study

From the results obtained for Drug-excipients compatibility study, it was found that the drug is compatible with the respective excipients under evaluation based on physical observation. So chosen excipients can be used in the formulation. The result showed that, the impurity level with drug and some excipients combination increased and also slight changes in appearance but most excipients are found to be compatible with Atorvastatin calcium, the total impurities do not exceed two times than impurities of initial, so these are selected.

Pre compression parameters

Loss on drying, density analysis, compressibility index and Hausner's ratio, sieve analysis, angle of repose was carried out.

Post compression parameters

Weight variation test for the tablets was carried out, thickness of tablets was observed by Vernier Caliper, hardness of the tablet was measured in 'Newton' unit in digital hardness tester and disintegration test was carried out in Electro lab (ED-2AL). The friability was carried out by using Roche Friabilator.

Dissolution (in-vitro drug release) studies [6]

Atorvastatin calcium tablets were subjected to *in-vitro* drug release studies at pH 6.8 phosphate buffer for 30 mins. The drug release studies carried out in USP dissolution test apparatus II (paddle) 75 RPM speed, using 900 ml of dissolution medium, maintained at 37°C ± 0.5°C. *In-vitro* release profiles of Atorvastatin calcium from all prepared batches of tablet was evaluated using different excipients combination. These different batches of tablets were prepared using different excipient at various ratios at different stages.

Accelerated Stability Studies [7]

Exposure study:

Exposure study was done for finding the degradation pathways of drug formulation by exposing formulation to stress conditions like 80°C temperature for 2 days & in Autoclave for 15 mins at 121°C after these tests formulation was compared with innovator formulation which was also kept in same conditions. If any measurable difference seen then that formulation, was rejected otherwise selected.

Stability study:

Stability study was done by exposing the formulation to different conditions including stress conditions of temperature & pressure. Stability study was done at 40°C/75% RH (for 1, 2, 3, 6 months), 30°C/75% RH (for 1, 2, 3, 6, 9, 12, 24 months), 2-8°C (1, 2, 3, 6, 9, 12, 24 months). After that study was over formulation was checked for its physical & chemical parameters. For those formulations, parameters were present within the specification was selected.

Worst case study:

Worst case study was done for optimizing the final process of formulation by changing different processing variables which seems to be critical. In our formulation, dry mixing time, granulation parameters, compression force was selected as critical steps.

RESULTS AND DISSCUSION

Bulk density was found to be in the range 0.473 – 0.512 gm/ml, Tapped density in the range 0.582-0.631 gm/ml, Carr's index ranging 18.73-20.13 and Hauser's ratio in the range 1.19-1.25 and they showed the good flow characteristics. The results were shown in the Table 1.

Table 1: Powder flow characterization

Parameters	Observations
Angle of repose	46.960
Bulk density	0.279 gm/ml
Tapped density	0.383 gm/ml
Hausenr's ratio	1.37
Compressibility index	27.15%
LOD	-4.258%

Drying time for achieve LOD in particular limit. Tablet weight was ranging 1197-1209 mg for core tablets (Target wt – 1200 mg/tablet) which is less than 5% indicates that the variation in the weight of the tablets is within standard official limits. No weight variation was observed, as the blend characteristics were maintained through the development process.

Table 2: Post compression parameters of all formulation

Formulation	Avg. wt. (mg)	Thickness(mm)	Hardness(N)	Disintegration time (min)	Friability (%w/w)
1	1199-1210	7.43-7.56	228-250	5-7	0.092
2	1199-12109	7.43-7.56	230-250	5-6	0.132
3	1197-1208	7.41-7.53	222-255	3-4	0.125
4	1197-1210	7.42-7.56	231-256	1-2	0.197
5	1196-1208	7.40-7.53	230-250	2-3	0.296
6	1198-1209	7.43-7.54	230-252	4-5	0.301
7	1199-1212	7.44-7.57	220-250	2-3	0.281
8	1196-1209	7.40-7.54	231-252	2-3	0.288
9	1198-1209	7.43-7.53	222-245	2-3	0.295
10	1197-1209	7.41-7.53	220-242	2-3	0.321

The hardness of tablets was found to be uniform within range 225-255 (N) for final formulation. Disintegration time for 6 tablets was found to be 1.30-2.50 min indicating that disintegration time within the specification limit. The percentage friability of tablet was ranging 0.004% - 0.321% which was less than the standard limit of 1% indicates that the prepared tablets are mechanically stable.

Dissolution report of F1 showed that, overall drug release is so much less. It was also found that, the disintegration time is more, though it is within limit. It took time to disintegrate the tablet into granules and therefore to release drug. The F2 was taken by increasing the small amount of concentration of superdisinstegrant croscarmellose sodium. The result showed that there is just small amount of increase in drug release. Initial drug release is matched but not up to the last point. There is also no improvement in reduction of disintegration time. In F3, the concentration of superdisintegrant was increased and also half amount was added extargranularly to improve

the drug release. The result shows that the drug release was more than previous, but alkalinity not maintained.

F4 was taken with increase amount of alkalizer. The hardness of tablets obtained was able to provide sufficient strength to avoid friability up to certain limit. If the hardness was reduced beyond the value, tablets were susceptible to friability. But in the above process multicompaction (upto 3 times) was required to produce required flow as a result the production of fines was more as well as the production loss is more. F5 was taken by using pre gelatinized starch as dry binder to increase the compatibility and palatability property of blend. So multicompaction is avoided and production of fine is minimized. Slight increase in DT is observed but no impact on drug release (dissolution profile) is excellent with F2 value = 97.69. For F6 the disintegration time also increased (5-6 mins). F7 was taken by trying anhydrous lactose in place of mannitol. Similar result was found as F5.

At this stage different formulations are taken by using different alkalizer as stabilizer at different concentration in order to optimize. F8 was taken by using sodium hydrogen carbonate as stabilizer in place of calcium carbonate at low concentration, but desired alkalinity was not maintained. F9 was taken by increasing the concentration of stabilizer Sodium hydrogen carbonate which was able to provide sufficient basic environment to dissolve the active pharmaceutical ingredient. The dissolution profile matched in all media. But the results obtained from stress studies showed that related substances were present more than the limit. F10 which was taken by magnesium oxide as stabilizer was just below its IIG limit. The result was found to be satisfactory.

Table 3: Dissolution results of all Formulations

Time point	Innovator	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0	0
5	85.6	52	83	80	82	85	62	89	86	85	85
10	94.1	68	85	88	90	94	70	92	94	90	90
15	96.7	72	87	93	97	96	79	96	98	95	95
30	99.8	75	89	94.1	98.9	99	81	98.2	98.9	97.9	98
F2	NA	28.17	53.80	64.27	76.80	97.69	33.86	82.15	70.3	72.4	80.2

Table 4: Exposure study of F5

Storage condition	Room temperature		80^0 c		Autoclave	
Period	Initial		2 days (open)		At 121^0C for 15 mins	
Formulations	Innovator	F5	Innovator	F5	Innovator	F5
Parameters		Observations				
Physical parameters	White	White	White	White	White	White
Hardness (N)	264	279	290	298	Not applicable	
LOD (%)	7.48	7.54	6.10	6.22	12.27	12.97
D.T. (min)	2-3	2-3	5-6	6-7	Not applicable	
Assay (%)	99.24	99.56	94.25	93.72	95.85	94.99
Dissolution (at 30 min)	99.6	99	97	95	Not applicable	
Total impurity (%)	0.931	.934	1.41	1.83	5.45	6.38

Exposure studies were carried out of selected F5, F7, F9 and F10. In exposure study, in house formulation and marketed (innovator) product are used. Formulation was subjected to different environmental stress conditions like 80°C for 2 days and in autoclave at 121°C for 15 mins. The result of F5 showed similar behavior between our formulation and marketed product in different conditions. The stability studies of final formulation were done for 3 months by packing in HDPE container in humidity chamber (40°C/75% RH). Anhydrous silica gel canisters as well as oxygen absorbers are incorporated into the bottle to protect the drug from oxidation and moisture.

The results given in table for 1 month, 2 month and 3 months stability result shows that all parameters of formulation including physical parameters, impurity profile, content uniformity or dissolution profile were within specification limit. So it indicates optimized formulation is stable. Worst case study for final formulation was performed to optimize the critical stages during the formulation process. In this case dry mixing, granulation and compression force were considered as critical stages which may cause problem if the set parameters vary.

Table 5: Stability observations of F5

Storage condition		Room temp.		40ºC/75%RH						Specifications
Period		Initial		1 Month		2 Months		3 Months		
Formulations		*Innovator*	*F5*	*Innovator*	*F5*	*Innovator*	*F5*	*Innovator*	*F5*	
Parameters					Observations					
Physical appearance		White	White	White	White	White	White	White	White	*No change*
Hardness (N)		234	239	248	240	253	248	249	239	*NLT 220N*
LOD (%)		7.48	7.54	7.52	7.57	7.43	7.57	7.52	7.36	*NMT 8.0%*
D.T. (min.)		2-3	2-3	2-3	2-3	2-3	2-3	2-3	2-3	*NMT 15 min.*
Impurities (%)	*unknown Impurity*	0.03	0.12	0.038	0.13	0.04	0.13	0.04	0.14	*NMT 0.2%*
	Total Impurity	0.93	.934	0.94	1.35	1.02	1.48	1.60	1.70	*NMT 3%*
Assay (%)		99.24	100.7	101.8	100.72	100.12	101.36	99.25	101.32	*95-105%*
Dissolution (at 30 min)		99.6	99	98.9	97.7	98.6	97.25	98.1	96.9	*NLT 85% in 30 min.*

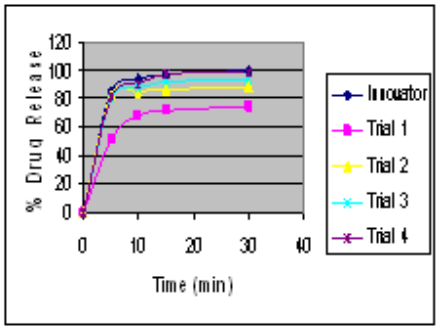

Fig.1: Drug release pattern F1-F4.

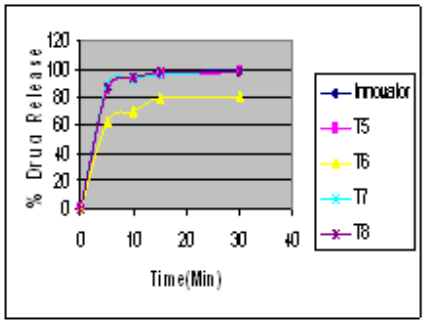

Fig.2: Drug release pattern of F5-F8

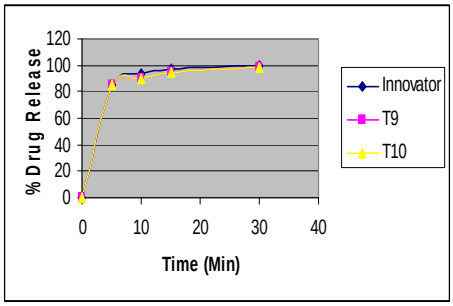

Fig. 3: Drug release pattern of F9 and F10.

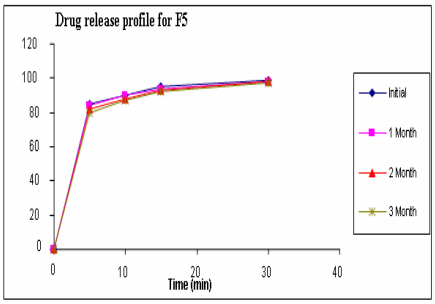

Fig.4: Drug release pattern of F5 with 1, 2 and 3 months stability study

Table 6: Stability dissolution results for F5 at the condition 40/75 ^{0} C

Time point (min)	Initial	1 Month	2 Month	3 Month
0	0	0	0	0
5	85	84	82	80
10	90	90	88	87
15	95	94	93	92
30	99	98	98	97

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 dry granulation method by roller compaction. Dissolution profile of F5 was matched perfectly with marketed (innovator) formulation and F2 value was found to be excellent. Also the impurity profile and stability result of F5 was found to be excellent. But in F5 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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