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Design and Evaluation of Amlodipine Besilate and Atorvastatin Calcium Tablets

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ABSTRACT

Amlodipine besilate is a calcium channel blockers used for the treating high blood pressure, certain types of angina and coronary heart failure. Atorvastatin calcium known as Statins is used for lowering blood cholesterol and in the treatment of primary hypercholesterolemia and dyslipidemia. The objective of the present investigation was to formulate and evaluate an oral administrable tablet containing Amlodipine besilate and Atorvastatin calcium by wet granulation method. The tablets were prepared using Microcrystalline cellulose, Calcium carbonate, polysorbate 80, Hydroxypropyl cellulose, Pregelatinized starch, Croscarmellose sodium, Colloidal anhydrous silica and Magnesium stearate. Preformulation studies were performed prior to compression. The prepared tablets were evaluated for various pre-compression characteristics like angle of repose, bulk density, tapped density, cars index and hausner's ratio, loss on drying and post-compression characteristics like Appearance, Weight variation, Hardness, Thickness, Disintegration, Friability, In vitro Dissolution studies. The stability studies were carried out for the optimized batch for three months and it showed no significant changes in the physicochemical parameters and *in vitro* release pattern. The present study concludes that combined pill has the potential to improve the management of hypertensive patients with additional cardiovascular risk factors, especially dyslipidemia by reducing pill burden and prescription costs.

Keywords: Amlodipne besilate, Atorvastatin calcium, Wet granulation, Hypertensive, Dyslipidemia.

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INTRODUCTION

The oral dosage form is the most popular way of taking medication. Oral delivery of drugs is the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation [1] and by this administration normally the drug dissolves in the stomach fluids or intestinal fluids and absorbs form these regions of the gastrointestinal tract (GIT) depends upon the physicochemical properties of drug [2].

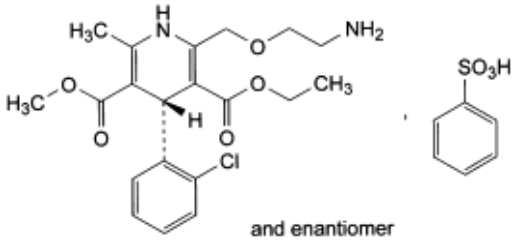

Figure 1: Structure of Amlodipine Besilate

Combination therapy have various advantages over monotherapy such as problem of dose-dependent side effect is minimized, a low dose combination of two different agents reduces the dose related risk, the addition of one agent may counteract some deleterious effects of the others, minimize the clinical and metabolic effects that occurs with maximal dosage of individual components of the combined tablets [3].

Amlodipine besilate is a white crystalline powder which is slightly soluble in water, sparingly soluble in ethanol and freely soluble in methanol. Chemically, amlodipine besilate is 3-ethyl-5- methyl (4RS)- 2- [(2- Aminoethoxy) methyl]- 4- (2-Chlorophenycl)-6-Methyl-1,4-Dihydropyridine-3,5-pyridine Dicarboxylate Benzenesulphonate [4] (Figure 1). Amlodipine besilate is a dihydropyridine derivative is a long acting calcium channel blockers [5]. It is used in the management of hypertension, chronic stable angina pectoris and prinzmetal variant angina [6]. It acts by inhibiting the transmembrane influx of calcium ions into vascular smooth muscles and cardiac muscles and also acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

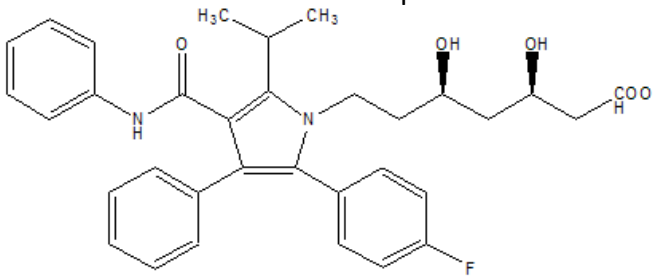

Figure 2: Structure of Atorvastatin Calcium

Atorvastatin calcium is synthetic hydroxyl methyl glutaryl coenzyme A (HMG- CoA) reductase inhibitors that has been used as a lipid lowering agent [7]. Chemically, [R-(R*, R*)]-2-

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(4-fluorophenyl)-β, δ-dihydroxy- 5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1Hpyrrole-1-heptanoic acid [8] (Figure 2). Atorvastatin calcium is a competitive inhibitor of HMG-CoA reductase. This enzyme catalyzes the reduction of 3-hydroxy-3methyl glutaryl-coenzyme-A to mevolonate, which is the rate determining step in hepatic cholesterol synthesis. Atorvastatin calcium intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia. Because, cholesterol synthesis decreases, hepatic cells increase the number of LDL receptors on the surface of the cells, which inturn increase the amount of LDL uptake by the hepatic cells and decrease the amount of LDL in the blood [9-11].

The rational of combination therapy is to minimize dose dependent side effects and adverse reactions. Side effect of Atorvastatin calcium was reduced 60% by combining with Amlodipine besilate. It has potency to promote the activity of Atorvastatin calcium [12]. The present study was aimed to formulate an immediate release tablets of Amlodipine besilate and Atorvastatin calcium tablets by wet granulation method.

MATERIALS AND METHODS

Amlodipine Besilate (Cadila Pharmaceutial Ltd.India), Atorvastatin Calcium (vitalite lab,India) were received as gift sample. Microcrystalline Cellulose (Vijlak Pharma, India), Calcium carbonate (Shubham Pharmaceuticals, India), Polysorbate 80 (SD Fine Chem Ltd.India), Hydroxypropyl Cellulose (Ruitai, China), Pregelatinised Starch (Colorcon Asia Pvt. Ltd, India), Croscarmellose Sodium (Vijlak Pharma, India), Colloidal anhydous Silica (P.D.Fine, India), Magnesium Stearate (Amishi Drugs Ltd) were commercially procured and used in this study.

FORMULATION OF TABLETS

Table 1: Formulation of Amlodipine besilate and Atorvastatin calcium tablets

Sl. No	Ingredients	Quantity per tablet (mg)			
		F1	F2	F3	F4
01	Amlodipine besilate	13.980	13.980	13.980	13.980
02	Atorvastatin calcium	92.875	92.875	92.875	92.875
03	Microcrystalline cellulose	43.375	43.375	40.375	39.375
04	Calcium carbonate	26.770	26.770	19.770	19.770
05	Hydroxypropyl cellulose	4.000	4.000	4.000	4.000
06	Polysorbate 80	-	-	-	7.000
07	Pregelatinized starch	12.000	12.000	12.000	12.000
08	Croscarmellose sodium	4.000	8.000	8.000	8.000
09	Colloidal anhydrous silica	2.000	2.000	2.000	2.000
10	Magnesium Stearate	1.000	1.000	1.000	1.000
	Total	200	200	200	200

Formation of Amlodipine besilate and Atorvastatin calcium tablets were prepared by a conventional wet granulation technique, employing various excipients as per the formula given in table 1. Atorvastatin calcium was passed through mesh no #30, Calcium carbonate and Microcrystalline cellulose (MCC 101) were passed through mesh no #40. The above sifted

materials were blended for 10 min. Binder solution was prepared separately by adding weighed quantity of Hydroxypropyl cellulose and Polysorbate 80 to a required quantity of purified water under continuous stirring. Then the mixture was granulated using prepared binding solution by rapid mixing granulator for 2 min. The wet mass was unloaded from rapid granulator and it was dried in tray drier at 50°C till the Loss on Drying (LOD) becomes NMT 5% w/w. The dried granules were passed through mesh no#30. Then the pre-lubricant materials like Amlodipine Besilate, Pregelatinized Starch, Croscarmellose Sodium and Colloidal anhydrous silica were passed through mesh no #40 and blended with the above granules for 25 min at slow speed using Octagonal blender. Finally, mixture was lubricated with magnesium stearate passed through mesh no #60 for 2 min in Octagonal blender and the tablets were compressed in 8 station Rotary tablet compression machine using 8mm standard concave punch (Pacific tools, India) [13].

CHARACTERIZATION OF BLEND

Prior to compression, the blend was evaluated for their characteristics parameters such as Bulk Density, Tapped Density, Carr's Index and Hausner's ratio [14].

Bulk Density

Blend was poured gently through a glass funnel into a graduated cylinder exactly to 10ml mark. The weight of the cylinder along with granules required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2 cm until the time when there was no more decrease in the volume (Tap density tester USP, Campbell Electronics). Bulk Density (gm/ml) and Tapped Density (gm/ml) were calculated using the following equation [15]

$$\text{Bulk Density (gm/ml)}\ D_b = M / V_b$$

Where, M=Weight of Blend taken and $V_{b=}$ Bulk Volume

$$\text{Tapped Density (gm/ml)}\ D_t = M / V_t$$

Where, M =Weight of Blend taken and V_t=Tapped Volume

Carr's Index

Table 2: Carr's Index with corresponding Flow character

Carr's Index	Type of Flow
1-10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very Poor
>38	Extremely Poor

This was measured to know the property of the blend to be compressed; as such they measured for relative importance of interparticulate interactions. Carr's Index was calculated using the following equation (Table 2)

$$\text{Carr's Index (\%)} = D_t - D_b \times 100 / D_t.$$

Where, D_t = Tapped Density
D_b = Bulk Density

Hausner's Ratio

Table 3: Hausner's ratio with corresponding Flow character

Hausner's ratio	Type of Flow
1-1.1	Excellent
1.12 – 1.18	Good
1.19 – 1.25	Fair
1.26 – 1.34	Passable
1.35 – 1.45	Poor
1.46 – 1.59	Very Poor
>1.6	Extremely Poor

Hausner's ratio indicates the flow property of powder Hausner's ratio was calculated by following equation (Table 3). .

$$\text{Hausner's ratio} = D_t / D_b$$

Where, D_t = Tapped Density
D_b = Bulk Density

EVALUATION OF TABLETS

The prepared Amlodipine besilate and Atorvastatin calcium tablets were evaluated for Hardness, Thickness, Friability, Uniformity of Weight, Disintegration time, In vitro release studies, Stability studies.

Hardness [13-16]

The hardness test was performed to provide a measure of tablet strength. The resistance of tablet from shipping or breakage, under conditions of storage, transportation and handling before usage depends on its hardness. A Monsanto tablet hardness tester (P32, Tab machines, India) was employed to determine the hardness of the tablets for each batch three tablets were tested [16].

Thickness [13]

Thickness of tablets was important for uniformity of tablet size. It was measured by using Vernier caliper scale (Mitutoyo, Japan).

Friability [13]

Friability was determined using a Friabilator (Digital test apparatus, model DFI-1, India), it is expressed in terms of weight loss and is calculated in percentage. Twenty tablets were randomly selected, dusted and weighed accurately and placed in the plastic chamber and subjected to its tumbling action at 25 rpm for 4 mins, dropping the tablets through a distance of six inches with each evaluation. After 100 revolutions the tablets were once again dusted and reweighed to determine the percentage loss of weight. The weight loss should not be more than 1%.

$$\% \text{ loss} = \frac{\text{Initial weight of tablets} - \text{Final weight of}}{\text{Initial weight of tablets}} \times 100$$

Uniformity of Weight [17]

Table 4: Average weight of tablets with % deviation

Average weight of tablets (mg)	% Deviation
80mg or less	10
More than 80mg but less than 250 mg	7.5
250 mg or more	5

Twenty tablets were randomly selected and weighed individually. The average weight was determined then percentage deviation from the average weight was calculated (Table 4).

Disintegration time [18,19]

The disintegration time was performed using an USP disintegration test apparatus (TD2, Tab machines, India) with distilled water at 37±0.5°C. The disintegration time was taken to be the time when no granules of any tablets were left on the mesh of the apparatus. The time reported to obtain complete disintegration of six tablets were recorded and mean value was reported.

***In vitro* release studies** [1, 20]

The release rate of Amlodipine besilate and Atorvastatin calcium tablets were determined using USP dissolution testing apparatus II (Electro lab, India). The dissolution testing was performed using 900ml of pH 6.8 phosphate buffer at 37±0.5°C temperature and speed 75 rpm. Sample of 10ml was withdrawn at regular interval and replaced with fresh medium to maintain sink condition.

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Stability studies [19, 21, 22]

In order to determine the change on storage, stability study was carried out a 25°C / 60% RH and 40°C / 75% RH in a stability chamber. Samples were withdrawn at regular intervals. Formulation was evaluated for changes in Hardness, Thickness, Disintegration time and *in vitro* release studies.

RESULTS AND DISCUSSION

Evaluation of Granules

Table 5: Flow properties of Tablet Blend.

Formulation	F1	F2	F3	F4
Bulk Density (gm/ml)	0.429	0.407	0.419	0.480
Tapped Density (gm/ml)	0.536	0.543	0.531	0.589
Carr's Index (%)	19.96	25.04	21.09	18.50
Hausner's Ratio	1.2	1.3	1.2	1.2

The granules thus prepared were evaluated and the results thus obtained are given in table 5. The flow property was found to be good in all the formulations. In particular, F4 formulation showed good flow property compared to other formulations. The Hausner's ration and Carr's index were found to be good.

Physical evaluation of tablets [23-25]

Table 6: Physical characteristics of tablets.

Formulation	F1	F2	F3	F4
Hardness (kg/cm^2)	4.5	4.8	4.5	4.6
Thickness (mm)	3.8	4.0	3.9	3.85
Friability (%)	0.08	0.09	0.07	0.09
Uniformity weight (mg)	200	199	200	200
Disintegration time (mins)	12	6.5	7	6.5
In vitro Dissolution (%)	60.02	69.29	92.15	99.04

The formulated tablets met the pharmacopoeial requirements of uniformity of Weight. All the tablets confirmed to the required Hardness, Friability, Thickness and Disintegration time were within acceptable limits and the results are shown in table 6. It was clear that the weight variation holds good for all the formulation. In the design of Amlodipine besilate and Atorvastatin calcium immediate release tablets, Formulation F_1 has a problem in the disintegration time due to the less amount of disintegrant. Hence, in formulation F_2 the amount of croscarmellose sodium was increased in order to decrease the disintegration time. It showed good tablet integrity and disintegration time but the drug release was only 69.29%. In formulation F_3, Polysorbate 80 is used as a surfactant in the binder solution. It showed a drug

release of 92.15%. So, we planned to increase the polysorbate 80 in the next batch to get a good drug release and in formulation F_4 polysorbate 80 were increased and it shows marked increase in drug release of 99.04% and hence optimized as immediate release tablets.

Stability studies

Table 7: Stability Data for the formulation F4

S.No	Test	Specification	Initial Analysis	Stability Results		
				1 Month	2 Month	3 Month
				25°C / 60% RH, 40°C / 75% RH	25°C / 60% RH, 40°C / 75% RH	25°C / 60% RH, 40°C / 75% RH
1	Appearance	Round white biconvex, film coated tablets plain on both side	Complies	Complies	Complies	Complies
2	Disintegration	NMT 10 mins	6.5	6.5	6.5	7.0
3	Hardness	5 ± 0.5 Kg/cm^2.	4.5	4.5	4.4	4.4
4	Thickness	4 mm	4.0	4.0	3.9	3.9
4	Friability	Less than 1% W/W	0.09	0.09	0.09	0.09
5	Dissolution	Amlodipine Besilate 95.0% - 105.0%	99.04	98.34	97.23	97.11
		Atorvastatin Calcium 95.0% - 105.0%	98.54	97.78	97.02	96.98

Formulation F_4 was charged for stability studies at 25°C / 60% RH and 40°C / 75% RH and the results are presented in table 7. There were no significant changes in stability results of F_4 formulation. In case of Hardness and friability there were no changes in both the conditions. No significant changes were seen in case of disintegration time and the release profile was similar as that of the initial data.

CONCLUSION

The present research work was carried out to design and evaluate Amlodipine besilate and Atorvastatin calcium tablets by wet granulation method. The prepared tablets shown satisfactory results for various physicochemical evaluation tests like hardness, thickness, weight variation and *in vitro* dissolution study.

Among all the formulations, F4 formulation was better in all the terms of pre-compression and post-compression parameters, prepared by wet granulation method which has given good flow properties and post compression studies of all parameters like hardness, friability, thickness were good. No significant change was observed in drug content, physical properties and dissolution rate of these tablets after the storage period of 3 months at 25°C / 60% RH and 40°C / 75% RH.

Hence, the study resulted in developing a Amlodipine besilate and Atorvastatin calcium commercially by reducing formulation cost fulfilling the objective of the study.

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REFERENCES

[1] Anilkumar J Shinde, Manojkumar S. Patil, Harinath N. More Ind J Pharm Edu Res 2010; 44(3): 54-58

[2] Pragnesh Patel, Anupkumar Roy, Vinod Kumar SM, Martand kulkarni. Int J Drug Dev and Res 2011; 3(1): 52-61.

[3] Jitendra R. Amrutkar, Mohan G. Kalaskar, Varsha G. Shrivastav, Yeole PG. Int J Pharma Res Dev 2009; 1: 1-11.

[4] Budawari S. The Merck index, 23rd Ed, White house station, New Jersey, 2008, pp.516,

[5] Martindale, Sweetman SC. The Complete Drug Reference, 32nd Ed. Pharmaceutical Press, 1999, pp.822, 907.

[6] Oniel MJ, Smith A, Heckelman PE, Budawari S, The Merck index on encyclopedia of chemicals, Drugs & Biologicals. 13th Ed; Merck & Co Inc., White house station, New Jersey 2001, pp.488,865.

[7] Mohammadi A, Razonour N, Ansari M, Dogaheh, Ghorbani F, Bidhorbeh, Hashem M, Walker RB. J Chrom B 2007; 846: 215-221.

[8] Desager JP, Hormans Y. Clin Pharmacokinet 1996; 31: 348-371.

[9] Malinowshi JM. J Health Syst Pharm 1998; 15: 2253-2267.

[10] Lipitor product information. Park-Davis/Pfizer Inc 2002.pp.105

[11] Burnham TM. HMG-CoA redcutase inhibitors: Drug facts and comparisons. Louis: Facts and comparisons, 2002. Inc pp. 536-542a.

[12] Suganeswari M, Anto shering, Azhagesh Raj K, Bharathi P, Sathish B. Int J Pharm and Bio Archives 2011; 2(3): 949-953.

[13] Libermann A, Lachmann L, Kinig JL. The Theory and Practice of Industrial Pharmacy, Varghese Publishing house, 1991, pp 67-68.

[14] Jaimini Mani, Rana AC, Tanwar YS. Curr Drug Deliv 2007; 4: 51-55.

[15] Shabaraya AR, Narayanacharyulu R. J Pharm Pharm Sci 2007; 8(1): 231-236.

[16] The United State of Pharmacopoeia 24/ NF19 Asian Edition, The official compendia of standard United States Pharmacopoeial convection Inc. Rockville. 1995, pp. 1015, 1016, 1791.

[17] Indian Pharmacopoeia, 4th edition. Ministry of Healthy and Family welfare, Govt of India. The controller of Publicaitons, New Delhi, 1996 pp.A-54.

[18] Swati Jagdale, Mahesh Gattani, Dhaval Bhavsar, Bhanudas Kuchekar, Aniruddha Chabukswar. Int J Res Pharm Sci 2010; 1(3): 282-289.

[19] Rajalakshmi G, Vamsi CH, Balachandar R, Damodharan N. Int J Pharm Biomed Res 2011; *2*(4): 237-243.

[20] Pragnesh Patel, Anupkumar Roy, Vinod kumar SM, Martand kulkarni. Int J Drug Dev & Res 2011; 3(1): 52-61.

[21] Carstensen JT. Drug Stability: Principle and Practices, Marcel Dekker, 2nd Ed, 1995, pp.538- 550.

[22] NC Ngwuluka, BA Idiakhoa, EI Nep, I Ogaji and IS Okafor. Res Pharm Biotech 2010; 2(3): 25-32.

[23] Shiva S Krishna, Subhabrata Ray and RS Thakur. Pak J Pharm Sci 2006; 19(3): 208-213.

[24] Biljana Govedarica, Rade Injac, Rok Dreu and Stane Srcic. Afr J Pharm and Pharm 2001; 5(1): 31-41.
[25] S Jayaprakash, S Mohamed Halith, K Kulathuran Pillai, Priya. Der Pharmacia Lettre 2011; 3 (4): 143-154.