Original Research Article

Development of co-processed excipients in the design and evaluation of atorvastatin calcium tablets by direct compression method

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Abstract

Introduction: Co-processed excipients were prepared to improve the process ability and efficacy of commonly used excipients and to impart multi-functional qualities to the excipients and hence that the tablets with the desired attributes can be produced. In this study, acacia and calcium carbonate ($CaCO_3$) were used to prepare a co-processing excipient suitable for the preparation of atorvastatin calcium tablets. Acacia is used as binder and $CaCO_3$ as filler. $CaCO_3$ also acts as alkalizer and thus suitable to improve the dissolution rate of pH dependent soluble drugs like atorvastatin. **Materials and Methods:** The tablets were prepared by direct compression method and the physical properties of tablets such as hardness, friability and dissolution profiles of tablets were evaluated. Acacia was used in the form of mucilage. Various ratios of the co-processing excipients were formulated by granulation technique and the blend properties were evaluated by their Hausner's ratio and Carr's index values. Based on the Kawakita plots, it was found that the formulation with 3% acacia mucilage (0.9 mg acacia and 26.6 mg of $CaCO_3$) showed good fluidity and the formulations with 4% (1.27 mg of acacia and 26.23 mg of $CaCO_3$) and 5% acacia mucilage (1.62 mg of acacia and 25.88 mg of $CaCO_3$) showed more cohesiveness. The formulations include 1-5% of the acacia mucilage as the binding agent. **Results:** The granules of formulations with low percentage of acacia mucilage (1% and 2%) failed the test for friability. The granules of the formulations with pure acacia (F_1) and pure $CaCO_3$ (F_2) showed passable flow properties. **Conclusion:** The formulation with 3% acacia mucilage (F_3, 0.9 mg acacia and 26.6 mg of $CaCO_3$) showed least dissolution time (<1 min) and is found as the best formulation among the other formulations containing 4% (F_4, 1.27 mg of acacia and 26.23 mg of $CaCO_3$) and 5% (F_5, 1.62 mg of acacia and 25.88 mg of $CaCO_3$) acacia mucilage.

Key words: Acacia, alkalizer, calcium carbonate, granulation technique

INTRODUCTION

Atorvastatin calcium is a member of the drug class known as statins, used for lowering blood cholesterol. The primary use of atorvastatin is for the treatment of dyslipidemia and the secondary use is prevention of cardiovascular diseases such as coronary heart disease, myocardial infarction, stroke, unstable angina and revascularization. Like all statins, atorvastatin also works by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase enzyme that plays a key role in production of cholesterol in the body. HMG-CoA reductase catalyzes the reduction of HMG-CoA to mevalonate, which is the rate-limiting step in hepatic cholesterol biosynthesis. Inhibition of the enzyme decreases *de novo* cholesterol synthesis, increasing low-density lipoprotein (LDL) receptors on hepatocytes. This increases LDL uptake by the hepatocytes, decreasing the amount of LDL-cholesterol in the blood. Like other statins, atorvastatin also reduces blood levels of triglycerides and slightly increases levels of high-density lipoprotein (HDL) -cholesterol.[1]

Acacia acts as an emulsifying agent (10-20%), stabilizing agent, suspending agent (5-10%), tablet binder (1-5%) and as a viscosity increasing agent.[2] However, using acacia in more concentrations may lead to increase in disintegration and dissolution times. Calcium carbonate ($CaCO_3$) is mainly used as a tablet diluent. It also acts as a buffering agent and as a dissolution aid in dispersible tablets.

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Co-processing of excipients is a novel method used in the preparation of tablet dosage forms, in which only a physical modification of excipients is done without changing their chemical nature. The aim of this technique is to improve the flow properties of the used excipients when compared to those with the individual physical mixtures. Usually most of the formulations have excipients in higher proportion than the drug. Hence, these excipients should have good flow properties and compatibility with each other which can be achieved by combining the properties of excipients through co-processing technique. Mostly binding and blending properties are enhanced by this technique than the formulations involving the individual excipients.[3-5] Usually a brittle excipient and a plastic excipient are mixed in proportions to give a synergistic action of the excipients used. Both excipients should be in such a proportion that the formed blend shows good binding properties and good flow properties. The properties are evaluated by Hausner's ratio and Carr's index values.[6-8]

The co-processed excipients were prepared by granulation technique. The blends containing the drug and co-processed excipients were formulated into a tablet by direct compression method. The direct compression method is most widely accepted process for hydrophobic drugs to be formulated into tablet dosage forms. The cost of the process is also reduced as the number of steps involved in the preparation decreases. The direct compression process is highly influenced by powder characteristics such as flow ability, compressibility and dilution potential.

Hence, this study involves both advantages of wet granulation and direct compression as atorvastatin calcium is very slightly soluble in water. As both brittle and plastic excipients were used, problems such as capping, lamination, sensitivity to moisture and other compaction problems can be overcome. However, the main disadvantage is that, in preparation of new formulations, the fixed proportion of the co-processed excipients is to be used to get synergistic effect which is not possible in every case.

EXPERIMENTAL MATERIALS

Atorvastatin calcium was procured as a gift sample from NATCO drugs Ltd., Hyderabad. Maize starch was procured from S.D. Fine chemicals, Mumbai. Potassium di hydrogen ortho phosphate, Sodium hydroxide, lactose, acacia and $CaCO_3$ were obtained from Qualigens chemicals, Mumbai. All materials used in the study complied with pharmaceutical and analytical standards. A multi-station tablet press (CDM-3-16, Cad mach machinery Co. Pvt. Ltd., Ahmadabad); disintegration test apparatus (ED, 2 L, Electrolab, Mumbai); dissolution test apparatus (Electrolab, TDT-08 L, Dissolution tester, U.S.P), ultraviolet (UV) -visible spectrophotometer (Shimadzu, Pharmaspect, UV1700, Japan) were used in this research work.

MATERIALS AND METHODS

Development of co-processed excipients by granulation method

The co-processed excipients were prepared by granulation method using different concentrations of acacia mucilage like 1-5% respectively. The acacia mucilage (1% w/v) was formed by dispersing 100 mg of acacia in 10 ml of lukewarm water. Nearly 2-5% mucilage was also prepared by following same procedure. The mucilage was added to the $CaCO_3$ until a damp mass was obtained. The damp mass with 3% acacia mucilage consists of 0.9 mg acacia and 26.6 mg of $CaCO_3$. The damp mass with 4% acacia mucilage has 1.27 mg of acacia and 26.23 mg of $CaCO_3$. The damp mass of 5% acacia mucilage has 1.62 mg of acacia and 25.88 mg of $CaCO_3$. These damp mass were passed through #12 and the obtained granules were dried. The dried granules were passed through a series of mesh like #10, #16, #24 and #44. The granules retained on 16# were collected and stored.

Evaluation of pre-compression parameters

The following micromeritic properties were evaluated:

a. Bulk density (g/cc): 3 g of blend containing the drug and the co-processing excipients was weighed and transferred to a measuring cylinder. The bulk volume was noted. The bulk density was calculated by the formula:
   Bulk density = mass/bulk volume
b. Tapped density (g/cc): 3 g of blend containing the drug along with the excipients was weighed and transferred to a measuring cylinder and then it was subjected to 100 tapings. The tapped volume was noted. The tapped density was calculated by the formula:
   Tapped density = mass/tapped volume
c. Carr's index (%): The Carr's index was calculated by the formula:
   Carr's index = tapped density — bulk density/tapped density * 100
d. Hausner's ratio (%): The Hausner's ratio was calculated by the formula:
   Hausner's ratio = tapped density/bulk density
e. Angle of repose (θ): Blend containing the drug along with the excipients was weighed and it was kept in an open cylinder which was placed on graph sheet. Then the cylinder was slowly lifted. The angle of repose was calculated by the formula:
   Angle of repose (θ) = $\tan^{-1}$ h/r
f. Friability of granules: The friability of the granules was found out using Roche friabilator. The friabilator was rotated for 4 min or 100 revolutions. The weight of granules before friability and after friability test was noted and the % friability was found out from the formula:
   % friability = (initial weight — final weight/initial weight) × 100

All these parameters were also calculated for the co-processed excipient granules, granules of pure acacia and $CaCO_3$ in addition

to the friability of granules. Those granules of the formulations which showed poor friability values (1% acacia mucilage, 2% acacia mucilage, pure acacia granules and pure $CaCO_3$ granules) were eliminated from the study.

Construction of Kawakita plots

Estimation of degree of volume reduction

A total of 3 g of granules were weighed and transferred to a measuring cylinder. Now the volume is noted as v_o. Then they were subjected to different tapings of 25, 50, 75 and 100 and the volume was noted after each step of tapings as *v*. Kawakita plots were constructed from the formula:

$n/c = n/a + 1/ab$

n = number of tapings;

a, *b* = constants; and

c = total volume reduction.

The degree of volume reduction was calculated from the formula:

$c = v_o - v/v_o$

where, *c* = degree of volume reduction;

v_o = initial volume of granules before tapings; and

v = final volume of granules after taping.

From the obtained *n*/*c* values, a graph was plotted, *n*/*c* versus *n* from which "*a*" and "*b*" values were obtained. The constants of Kawakita equation can be used to estimate the flow and cohesiveness properties of powders. Constant "*a*", describes the compressibility and constant "1/*b*" describes cohesive properties of powders or the fastness of how the final packing stage is achieved.[9] Smaller the values of "*a*", better is the fluidity. The low value of 1/*b* is indicative that the materials are soft and that they readily deform plastically under pressure.[10]

Preparation of atorvastatin calcium tablets

The co-processed excipients were used in the proportion of 55% in the tablet. The tablet weight was fixed as 50 mg of which 20 mg was drug and starch was used as disintegrant (5%). This blend was mixed well and was compressed in a rotary tablet machine using 5 mm punch die.

Evaluation of post-compression parameters

The following post-compression parameters were evaluated:

a. % weight variation
   The weight of the tablets was determined individually and the % weight variation was calculated using the formula:
   % weight variation = (average weight − individual weight/average weight) × 100

b. Determination of drug content
   A total of 20 tablets were powdered and the quantity of powder equivalent to 20 mg of atorvastatin calcium was utilized for assay. The drug was extracted with methanol, filtered and the volume was made up to the volume using 6.8 pH phosphate buffer. Suitable dilutions were made and analyzed spectrophotometrically by measuring the absorbance at 244 nm. Drug content was determined from the standard graph.

c. Tablet friability
   The friability test was performed using Roche friabilator. Ten randomly selected tablets were weighed and placed in the friabilator. The friabilator was rotated for 4 min. The tablets were dusted to remove the adherent particles and then reweighed. The percentage friability was calculated with the following formula:
   % friability = (initial weight — final weight/initial weight) × 100

d. *In vitro* disintegration time
   The disintegration for all formulations was carried out using tablet disintegration test apparatus. 6 tablets were placed separately in each tube of disintegration test apparatus and discs were placed. The water was maintained at a temperature of 37°C ± 2°C and time taken for the entire tablet to disintegrate completely was noted.

e. *In vitro* dissolution characterization
   In vitro dissolution studies were performed for all tablet formulations by using United States Pharmacopeia dissolution apparatus type-II. Dissolution test was carried out at 75 rpm using 900 ml of 6.8 pH phosphate buffer as dissolution media.

RESULTS AND DISCUSSION

The present study has been carried out to develop the co-processed excipients in the design and development of atorvastatin calcium tablets using direct compression method. The excipients acacia and $CaCO_3$ were used in the present study. The composition of the tablets was represented in Table 1. Atorvastatin calcium was used at a dose of 20 mg/tablet. Hence, the excipients were needed to get formulated into a tablet. Both individual excipients showed very poor flow properties, whereas the drug showed moderate flow properties. However, in presence of co-processed excipients, the drug showed good flow properties. Atorvastatin calcium shows pH dependent solubility and is soluble in alkaline medium. Hence, $CaCO_3$ which gives alkaline medium is added as the co-processing excipient by which the disintegration and dissolution profiles were improved. Both excipients have very poor flow properties. But for formulation with 3% acacia mucilage (0.9 mg acacia and 26.6 mg of $CaCO_3$), showed excellent flow properties based on Carr's index, Hausner's ratio and angle of repose. For formulation with 4% acacia mucilage, the values of Carr's index, Hausner's ratio showed fair flow properties and

Table 1: Composition of atorvastatin calcium tablets

Ingredients	Formulation code (mg)				
	F_1	F_2	F_3	F_4	F_5
Atorvastatin calcium	20	20	20	20	20
Acacia	0.9	—	0.9	1.27	1.62
$CaCO_3$	—	26.6	26.6	26.23	25.88
Starch	2.5	2.5	2.5	2.5	2.5
Lactose	26.6	0.9	—	—	—
Total weight of the tablet (mg)	50	50	50	50	50

good flow property for angle of repose. For formulation with 5% acacia mucilage (1.62 mg of acacia and 25.88 mg of $CaCO_3$), the Carr's index and the Hausner's ratio values showed very poor flow property whereas the angle of repose showed fair flow property. All the pre-compression parameters were calculated for the co-processed excipient granules, granules of pure acacia and $CaCO_3$ in addition to the friability of granules. Those granules of the formulations which showed poor friability values (1% acacia mucilage, 2% acacia mucilage, pure acacia granules and pure $CaCO_3$ granules) were eliminated from the study. The co-processed excipients were formed using granulation technique. The results were given in Table 2. The Kawakita plots were found out for the co-processed excipient granules from the data obtained from the tapings. From the *n*/*c* versus *n* graph, the constants "*a*" and "*b*" were found out and concluded that the formulation with 3% acacia mucilage (0.9 mg acacia and 26.6 mg of $CaCO_3$) has better fluidity as "*a*" value is more than "1/*b*" value and the granules of formulations with 4% (1.27 mg of acacia and 26.23 mg of $CaCO_3$) and 5% acacia mucilage (1.62 mg of acacia and 25.88 mg of $CaCO_3$) have higher cohesiveness as "1/*b*" value is more than "*a*" value. The results were represented in Table 3. The formulations with 55% co-processed excipients involving 3% (0.9 mg acacia and 26.6 mg of $CaCO_3$), 4% (1.27 mg of acacia and 26.23 mg of $CaCO_3$) and 5% acacia mucilage (1.62 mg of acacia and 25.88 mg of $CaCO_3$) were fabricated using direct compression method and then were subjected to various quality control tests such as weight variation, drug content determination, friability, disintegration and dissolution. All the results of the post-compression tests were satisfactory and were within the pharmacopoeial limits. The results were given in Table 4.

Table 2: Micromeritic properties of co-processing excipients formulated with different ratios of acacia mucilage and calcium carbonate

Parameters	Formulation code		
	F_3	F_4	F_5
Bulk density (g/cc)	0.67	0.45	0.39
Tapped density (g/cc)	0.74	0.54	0.58
Carr's index (%)	9.45	16.67	32.76
Hausner's ratio	1.10	1.2	1.49
Angle of repose	28.39	32.38	35.89

Table 3: Data for Kawakita plots of co-processed excipient granules

No. of tapings	N/C values			a			1/b		
	F_3	F_4	F_5	F_3	F_4	F_5	F_3	F_4	F_5
25	5.17	1.33	1.33	59.17	53.76	46.3	286.9	47.58	40.51
50	5.81	1.78	2						
75	6.19	2.4	2.67						
100	6.45	2.67	2.91						

Table 4: Post-compression properties of formulated atorvastatin calcium tablets

Parameters	Formulation code		
	F_3	F_4	F_5
Hardness (kg/cm^2)	4-5	4-5	4-5
Percentage friability index	0.8	0.9	0.8
Average weight (mg)	50±0.25	50±0.25	50±0.25
Disintegration time	<1 min	<1 min	1-2 min
Dissolution time	<1 min	1.5 min	2 min

The co-processed granules with 1% and 2% acacia mucilage as binder solution, the granules of formulations with pure acacia and pure $CaCO_3$ failed to meet the limits for friability. So, these were eliminated from the study. The remaining study was continued with 3% (0.9 mg acacia and 26.6 mg of $CaCO_3$), 4% (1.27 mg of acacia and 26.23 mg of $CaCO_3$) and 5% acacia mucilage - $CaCO_3$ (1.62 mg of acacia and 25.88 mg of $CaCO_3$) granules. Among the 3 formulations with 55% of co-processing excipients, the best formulation was chosen based on the dissolution rate of the formulations. For formulation with 3% acacia mucilage (F_3, 0.9 mg acacia and 26.6 mg of $CaCO_3$), it took less than 1 min for complete dissolution, 1.5 min for formulation with 4% acacia mucilage (F_4, 1.27 mg of acacia and 26.23 mg of $CaCO_3$) and 2 min for formulation with 5% acacia mucilage (F_5, 1.62 mg of acacia and 25.88 mg of $CaCO_3$) in the pH 6.8 phosphate buffer.

As the proportion of acacia mucilage increased, the dissolution rate decreased to an extent. Hence, the order of preferring the proportion of co-processed excipients of acacia and $CaCO_3$ for atorvastatin calcium tablets preparation, can be given as $F_3 > F_4 > F_5$.

The dissolution rate of atorvastatin calcium has been enhanced by using the co-processed excipients of acacia and $CaCO_3$. This might be possible due to the buffering tendency and dissolution aid of $CaCO_3$ in the formulations which created an alkaline medium for better dissolution of atorvastatin calcium.

CONCLUSION

The present study concludes that the proportion of the co-processing excipients showed variation in the flow properties and dissolution rates. The co-processing excipient with 3% acacia mucilage and $CaCO_3$ (0.9 mg acacia and 26.6 mg of $CaCO_3$) showed excellent micromeritic properties than the individual excipients used in the study. The more is the binder used, the more is the disintegration time for the tablets. The optimum proportion of the binder and diluent used and the proportion of co-processed excipients used in the formulation made F_3 (0.9 mg acacia and 26.6 mg of $CaCO_3$) the best suitable formulation for atorvastatin calcium tablets by direct compression technique.

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