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.
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 CaCO₃ 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 CaCO₃ until a damp mass was obtained. The damp mass with 3% acacia mucilage consists of 0.9 mg acacia and 26.6 mg of CaCO₃. The damp mass with 4% acacia mucilage has 1.27 mg of acacia and 26.23 mg of CaCO₃. The damp mass of 5% acacia mucilage has 1.62 mg of acacia and 25.88 mg of CaCO₃. 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:  
  \[ \text{Bulk density} = \frac{\text{mass}}{\text{bulk volume}} \]

- **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:  
  \[ \text{Tapped density} = \frac{\text{mass}}{\text{tapped volume}} \]

- **c. Carr’s index (%):** The Carr’s index was calculated by the formula:  
  \[ \text{Carr’s index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100 \]

- **d. Hausner’s ratio (%):** The Hausner’s ratio was calculated by the formula:  
  \[ \text{Hausner’s ratio} = \frac{\text{tapped density}}{\text{bulk density}} \]

- **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:  
  \[ \theta = \tan^{-1} \frac{\text{height}}{\text{radius}} \]

- **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:  
  \[ \% \text{friability} = \frac{\text{initial weight} - \text{final weight/initial weight}}{\text{initial weight}} \times 100 \]

All these parameters were also calculated for the co-processed excipient granules, granules of pure acacia and CaCO₃ 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 $v_0$. 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:

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

where, $n/c$ = degree of volume reduction;
$n = $ number of tapings;
$a, b = $ constants; and
$c = $ total volume reduction.

The degree of volume reduction was calculated from the formula:

$$
c = v_0 - v/v$$

where, $c = $ degree of volume reduction;
$v_0 = $ 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% to 3% acacia mucilage, pure acacia granules and pure CaCO$_3$ granules) which showed poor friability values (1% acacia mucilage, 2% acacia mucilage, pure acacia granules and pure CaCO$_3$ granules) 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

| Ingredients | Formulation code (mg) |
|-------------|-----------------------|
| Atorvastatin calcium | F1 20 20 20 20 20 |
| Acacia | 0.9 — — — — 1.27 1.62 |
| CaCO$_3$ | 2.5 2.5 2.5 2.5 2.5 |
| Starch | 26.6 26.6 26.23 25.88 |
| Lactose | — — — — — |
| Total weight of the tablet (mg) | 50 50 50 50 50 |

**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
good flow property for angle of repose. For formulation with 5% acacia mucilage (1.62 mg of acacia and 25.88 mg of CaCO₃), 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 CaCO₃ 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 CaCO₃ 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 CaCO₃) 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 CaCO₃) and 5% acacia mucilage (1.62 mg of acacia and 25.88 mg of CaCO₃) 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 CaCO₃), 4% (1.27 mg of acacia and 26.23 mg of CaCO₃) and 5% acacia mucilage (1.62 mg of acacia and 25.88 mg of CaCO₃) 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 pharmacopeial limits. The results were given in Table 4.

The co-processed granules with 1% and 2% acacia mucilage as binder solution, the granules of formulations with pure acacia and pure CaCO₃ 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 CaCO₃), 4% (1.27 mg of acacia and 26.23 mg of CaCO₃) and 5% acacia mucilage - CaCO₃ (1.62 mg of acacia and 25.88 mg of CaCO₃) 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 (F₁, 0.9 mg acacia and 26.6 mg of CaCO₃), it took less than 1 min for complete dissolution, 1.5 min for formulation with 4% acacia mucilage (F₄, 1.27 mg of acacia and 26.23 mg of CaCO₃) and 2 min for formulation with 5% acacia mucilage (F₅, 1.62 mg of acacia and 25.88 mg of CaCO₃) 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 CaCO₃ for atorvastatin calcium tablets preparation, can be given as F₃ > F₄ > F₅. The dissolution rate of atorvastatin calcium has been enhanced by using the co-processed excipients of acacia and CaCO₃. This might be possible due to the buffering tendency and dissolution aid of CaCO₃ 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 excipient showed variation in the flow properties and dissolution rates. The co-processing excipient with 3% acacia mucilage and CaCO₃ (0.9 mg acacia and 26.6 mg of CaCO₃) 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 F₁ (0.9 mg acacia and 26.6 mg of CaCO₃) the best suitable formulation for atorvastatin calcium tablets by direct compression technique.

### REFERENCES

1. Czeisler JL, Perlman KP. Diluents. In: Swarbrick TJ, Boylan JC, editors. Encyclopedia of Pharmaceutical Technology. New York, NY: Marcel Dekker Inc.; 1991. p. 37-83.
2. Rowe RC, Sheskey PJ, Owen SC, editors. Hand Book of Pharmaceutical Excipients. 5th ed. Washington, USA: Pharmaceutical Press, London and American Pharmacists Association; 2006. p. 1-3.

3. Chowdary KPR, Ramya K. Recent research on co-processed excipients for direct compression - A Review. Pharmacie Globale (IJCP) 2013;02:1-4.

4. York P. Crystal engineering and particle design for the powder compaction process. Drug Dev Ind Pharm 1992;18:677-721.

5. Gohel MC, Jogani PD. A review of co-processed directly compressible excipients. J Pharm Pharm Sci 2005;8:76-93.

6. Flores LE, Arello RL, Esquivel JJ. Study of load capacity of avicel PH-200 and cellactose, two direct-compression excipients, using experimental design. Drug Dev Ind Pharm 2000;26:465-69.

7. Schmidt PC, Rubensdorfer CJ. Evaluation of ludipress as a multipurpose excipients for direct compression part I: Powder characteristics and tableting properties. Drug Dev Ind Pharm 1994;20:2899-925.

8. Steinberg M, Blecher L, Mercill A. From Inactive ingredients to pharmaceutical excipients. Pharm. Technol 2001;25:62-4.

9. Alderborn G, Nyström C. Studies on direct compression of tablets. IV. The effect of particle size on the mechanical strength of tablets. Acta Pharm Suec 1982;19:381-90.

10. Autamashih M, Isah AB, Allagh TS, Ibrahim MA. Heckel and Kawakita analysis of granules of the crude leaves extract of vernonia galamensis prepared using poly vinyl pyrrolidone as binder. Int J Pharm Pharm Sci 2011;3:144-7.

How to cite this article: Pusapati RT, Kumar MK, Rapeti SS, Murthy T. Development of co-processed excipients in the design and evaluation of atorvastatin calcium tablets by direct compression method. Int J Pharma Investig 2014;4:102-6.

Source of Support: Nil. Conflict of Interest: None declared.