Research Article

Formulation Development and Evaluation of Atorvastatin Calcium Tablets using Co-Processed Excipients

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ABSTRACT

Direct compression is the most preferred method of tablet manufacturing owing to fewer processing steps, cost effectiveness and elimination of moisture and heat leading to better stability. In many instances, because of very poor flow and compressibility characteristics of the active Pharmaceutical ingredient (API), optimum tablet formulation cannot be achieved by direct compression using routine directly compressible vehicles. Co-processed excipient consists of two or more excipients combined in a way to attribute superior properties than simple physical admixture. Co-processed excipients have the ability to improve flow and/or compressibility characteristics of an API which otherwise is difficult to be formulated into tablets by direct compression. Present work involved the study of influence of two co-processed excipients viz. Cellactose 80 and Prosolv SMCC HD 90 (Prosolv) on pre-compression and compression characteristics of poorly flowable and compressible API, atorvastatin calcium (Atv) in comparison with routine excipients. Presence of co-processed excipients in formulations improved the flow properties of the blends remarkably in spite of being diluted with poorly flowing excipients. Disintegration time, friability & *in vitro* drug release rates of formulations containing either of the co-processed excipients were found to be significantly better than those containing regular excipients. Thus tablet formulations of Atv could be successfully formulated by direct compression using co-processed excipients.

Keywords: direct compression, co-processed excipients, Prosolv SMCC HD 90, Cellactose 80, atorvastatin calcium.

INTRODUCTION

Tablets, by far and large is the most popular dosage form for oral administration. Tablets are manufactured using various methods like direct compression, wet granulation and dry granulation known as chilsonation.

Direct compression is the most preferred method of tablet manufacturing owing to fewer processing steps, cost effectiveness and elimination of moisture and heat during processing leading to better stability.

In many instances because of very poor flow and compressibility characteristics of the API, optimum tablet formulation cannot be achieved by direct compression using routine directly compressible vehicles.

Co-processed excipient consists of two or more excipients combined in a way to attribute superior properties than simple physical admixture.[1]

Co-processed excipients have the advantages like absence of chemical change hence no regulatory concerns of safety, better flow and compressibility, suitable physico-mechanical properties, better dilution potential and lesser fill weight variation and reduced lubricant sensitivity.[2]

Co-processed excipients offer the option of using a single excipient with multiple functional properties, thereby reducing the number of excipients in inventory.

Although co-processed excipients are more costly, the overall product cost decreases because of improved functionality and fewer test requirements compared with individual excipients. Prosolv is silicified microcrystalline cellulose composed of 98% microcrystalline cellulose and 2% colloidal silicon dioxide. Silicification of the microcrystalline cellulose is achieved by a patented process, resulting in an intimate association between colloidal silicon dioxide and microcrystalline cellulose.[3,4]

In Cellactose 80 co-spray drying is used to integrate alpha-lactose monohydrate and cellulose powder into a mono-particulate system of Cellactose. Cellactose 80 comprises of 75 % alpha-lactose monohydrate and 25 % powdered cellulose.[4,5]

The purpose of present work was to study the influence of co-processed excipients on pre-compression and compression characteristics of poorly flowable and compressible API - Atv in comparison with that of routine excipients. The work also aimed at studying the impact of dilution of co-processed excipients with poorly flowable and compressible excipients on formulation characteristics.

MATERIALS AND METHODS

Atv was obtained from Zydus Cadila health care API division, Cellactose 80 from Molkerei Meggle Wasserburg GmbH, Germany, Prosolv from JRS Pharma, Gmbh. Microcrystalline cellulose pH 102(MCC 102), colloidal silicon dioxide, lactose monohydrate from Lupin Pvt. Ltd, Aurangabad, maize starch, dibasic calcium phosphate (DCP) and magnesium stearate from Pure Chem Laboratories, Pune.

Table 1: Formulations of Atv containing Prosolv and Cellactose 80

Sr. No	Ingredients	Formulations											
		Prosolv						Cellactose 80					
		1		2		3		4		5		6	
		A	B	A	B	A	B	A	B	A	B	A	B
1	Atv	40	40	40	40	40	40	40	40	40	40	40	40
2	Prosolv	65	-	128	-	128	-	63	-	125	-	125	-
3	MCC 102	-	63	-	125	-	125	-	16	-	30	-	30
4	Lactose mohydrate	-	-	-	-	76	76	-	47	-	95	-	95
5	Maize starch	-	-	76	76	-	-	-	-	76	76	-	-
6	DCP	-	-	-	-	-	-	-	-	-	-	76	76
7	Colloidal silicon dioxide	-	2	-	3	-	3	2	2	3	3	3	3
8	Magnesium stearate	5	5	6	6	6	6	5	5	6	6	6	6
9	Total weight(wt.)	110	110	250	250	250	250	110	110	250	250	250	250

Preparation of powder blends:

1. Atv and excipients were sifted through BSS #40 sieve, weighed accurately and transferred to polythene bag.
2. Atv with excipients was blended in poly bag for 10 minutes.
3. Magnesium stearate was sifted through BSS # 60 sieve and transferred to the poly bag containing above blend and blended for 2-3 minutes.

Evaluation of powder blends

The blends prepared as per formulae stated in table 1 were subjected to following studies.

1. Bulk density- was determined by calculating ratio of total mass of powder to the bulk volume of powder blend.
2. Tap density- was determined by calculating ratio of total mass of powder to the tapped volume of powder blend.
3. Hausner's ratio- was measured by determining ratio of tapped density to bulk density.
4. Carr's index- was determined by using values of bulk density and tapped density and is expressed in terms of percentage using following formula.

   a. $$\text{Compressibility Index} = \frac{\text{Taped density of powder} - \text{Bulk density of powder}}{\text{Taped density}} \times 100$$

5. Angle of repose- 5 g blend was allowed to fall freely through funnel set at 2.5 cm from the base. The height and diameter of the powder heap were measured and angle of repose was determined by the formula

$\tan \theta = (h/r)$

$\theta = \tan^{-1} (h/r)$

Where, θ = angle of repose

h = height of the heap

r = radius of the heap

Preparation of tablets

The blends prepared as per the formulae mentioned in table 1 were subjected to compression using 10 station single rotary machine (Rimek-Karnavati Engineering).

1. Punch specification:
   a. Shape – Round
   b. Dimension – 10 mm s/c, 8.73 mm s/c
   c. Upper punch – Break line
   d. Lower punch – Plain
   e. Dies – 10 mm, 8.73 mm
2. Fixed the dies and punches having above mentioned specification and assembled the compression machine for compression.
3. Loading of lubricated blend was done in hopper of compression machine.
4. After achieving desired compression parameters the blend was compressed into tablets.

Evaluation of tablets

The tablets prepared by direct compression were subjected to following evaluation

1. Thickness - was determined using vernier calliper. Ten tablets from each batch were used, and average values were calculated.[6,7]

2. Weight variation – 20 tablets were selected randomly and weighed.

Average weight of the tablet was determined. These tablets were weighed individually and the weight variation was determined.[6,7]

3. Hardness **-** Orchid Scientific hardness tester was used to determine the hardness of tablets.[6,7]

4. Friability - tablets (20 No.) were carefully de-dusted, accurately weighed and placed in the drum.

Drum was rotated 100 times and tablets were removed. Loose dust was removed from the tablets as before, and weighed accurately.

Friability was determined in Veggo friabilator using formula[6,7]

$$\frac{\text{Initial Weight of tablets} - \text{Final Weight of tablets}}{\text{Initial Wt of tablets}} \times 100$$

5. Disintegration test (DT) - was performed as per IP specifications using disintegration test apparatus (EI Tablet disintegration test apparatus).[6,7]

6. Assay - tablets were finely powdered in a mortar. To the powder equivalent to 40 mg of Atv, about 10 ml of methanol was added and dissolved with the aid of sonicator for 15 minutes; The solution was filtered and 1 ml was diluted with sufficient quantity of phosphate buffer pH 6.8 to produce 100 ml in a volumetric flask, mixed well and again filtered through Whatman filter.

Filtrate, 5ml was further diluted to 10 ml using phosphate buffer pH 6.8 and mixed well.

The absorbance of the resulting solution (20µg/ml) was measured at the 241 nm with the help of UV Spectrophotometer.

The drug content in the solution was calculated with the help of standard graph. The above experiment was done in triplicate (n=3) and mean was taken.[8]

7. *In- vitro* drug release study – were undertaken using USP Dissolution apparatus type II (Electrolab Model No: TDT- 06L). The tablets containing 40 mg of Atv were added to the dissolution flasks containing 900ml of phosphate buffer pH 6.8 maintained at 37±0.5°C and stirred at 75rpm.

Aliquots of 5 ml were collected periodically and replaced by 5 ml of fresh dissolution medium.

Withdrawn samples were filtered through Whatman filter paper, diluted suitably with buffer and concentration of drug was determined spectrophotometrically at 241 nm.[9]

RESULTS AND DISCUSSION

A) Formulations containing Prosolv

Three sets of formulations were prepared. In each set formula A contained Prosolv whereas formula B contained equivalent amount of MCC 102 and colloidal silicon dioxide.

Set 1 contained only Prosolv as a diluent whereas in set 2 and set 3 maize starch and lactose monohydrate were respectively used as diluents along with Prosolv.

B) Formulations containing Cellactose 80

Three sets of formulations were prepared to compare the properties of Cellactose with that of the regular excipients viz. mixture of lactose monohydrate and microcrystalline cellulose in the ratio of 3:1 similar to Cellactose composition.

In set 4, formula A contained Cellactose 80 as a sole diluent. Cellactose 80 was used in combination with maize starch in set 5 and in combination with dibasic calcium phosphate in set 6. Maize starch, dibasic calcium phosphate or lactose used commonly as diluents in wet granulation have poor flow and compression characteristics. In present study, these diluents were used in combination with co-processed excipients in direct compression to understand their impact on pre-compression and compression behavior of co-processed excipients.

A) Formulations containing Prosolv

In set 1

As seen in table no. 2, formula 1A containing Prosolv showed good flow properties whereas formula 1B showed passable flow properties.

In set 2

Formula 2A showed passable flow characteristics. However, powder blend of formula 2B showed very poor flow behavior indicating higher influence of dilution with poorly flowing maize starch on MCC 102, whereas blend containing Prosolv upon dilution with maize starch still managed to retain passable flow properties.

In set 3

Blend of formula 3A showed passable flow properties, unlike that of formula 3B which exhibited very poor flowability owing to presence of lactose as a diluent.

From all the 3 sets of batches, set 1 formula A containing only Prosolv as a diluent showed the most favorable flow properties of powdered blend.

Evaluation of blend characteristics

Table 2: Evaluation of blend characteristics of formulations

Parameter	Formulations											
	Prosolv						Cellactose 80					
	1		2		3		4		5		6	
	A	B	A	B	A	B	A	B	A	B	A	B
Bulk Density (g/ml)	0.24	0.32	0.35	0.36	0.35	0.33	0.29	0.33	0.38	0.5	0.5	0.5
Tap Density g/ml	0.28	0.42	0.47	0.54	0.45	0.48	0.42	0.59	0.51	0.71	0.76	0.83
Hausner's Ratio	1.18	1.33	1.33	1.5	1.27	1.44	1.41	1.78	1.35	1.42	1.53	1.66
Compressibility Index	15.78	25.18	25.0	33.3	21.4	30.8	29.5	44.0	25.9	29.9	34.2	39.7
Angle of Repose (˚)	30.11	40.36	34.2	36.1	33.8	35.2	27.3	32.6	37.3	46.3	30.9	40.0

Table 3: Evaluation of tablets

Parameter	Formulations											
	Prosolv						Cellactose 80					
	1		2		3		4		5		6	
	A	B	A	B	A	B	A	B	A	B	A	B
Thickness (mm)	2.52	2.63	3.63	3.66	3.58	3.94	2.63	- -	3.57	3.61	3.55	- -
Hardness (kg/cm^2)	5.6	5.8	5.2	5.7	5.5	5.8	5.6	- -	5.2	5.6	5.6	- -
Avg. wt. (mg)	110.1 ±0.81	110.2 ±0.87	250.2 ±1.05	251.0 ±1.32	250.9 ±0.77	251.2 ±1.13	110.6 ±0.81	- -	251.5 ±0. 96	250.3 ±1.26	251.7 ±0.97	- -
Wt. Variation	0.32	0.34	0.42	0.52	0.30	0.45	0.32	- -	0.37	0.50	0.38	- -
Friability %	0.045	0.318	0.10	0.55	0.098	0.100	0.049	-	0.159	0.053	0.057	-
DT (sec)	20 Sec	85 sec	15 Sec	10 Sec	15 Sec	15 Sec	20 Sec	- -	20 Min	11 Min	30 Sec	- -
Assay (%)	98.3 ±0.72	97.7 ±1.24	100.5 ±0.5	95.3 ±1.04	99.4 ±0.7	97.1 ±1.51	96.9 ±0.9	- -	97.5 ±1.15	93.8 ±1.25	102.5 ±0.86	- -

B) Formulations containing Cellactose 80

Powder characteristics of blends containing Cellactose 80 were favorable for direct compression as compared to blends containing lactose and microcrystalline cellulose (basic components of Cellactose 80). Dilution with poorly flowable maize starch or dicalcium phosphate affected the flow properties of blends containing cellactose to lesser extent as compared to that of blends containing routine excipients. (Table no: 2)

Evaluation of tablets

A) Formulations containing Prosolv

Tablets of formulae 1A, 2A and 3A prepared using Prosolv exhibited lesser thickness, lesser friability, lesser weight variation as compared to the tablets of formulae 1B, 2B

and 3B respectively prepared using regular excipients. Lesser thickness could be attributed to the better compaction of blend containing Prosolv. Though hardness range for all the formulations was similar i.e. 5-6 kg/cm^2 the overall compaction and cohesively of the tablet mass was better for the tablets prepared with co-processed excipients which reflected in minimal friability of these formulations. (Table no. 3)

A.) *In-vitro* drug release studies

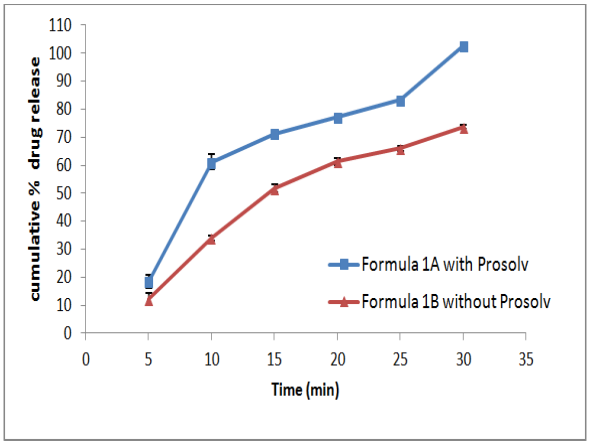

Figure 1: Comparative *In-vitro* drug release profiles of Atv from tablets of set 1A and 1B.

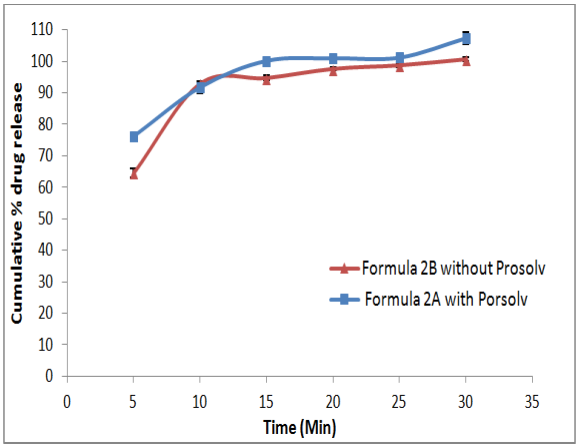

Figure 2: Comparative *In-vitro* release profiles of Atv from tablets of set 2A and 2B.

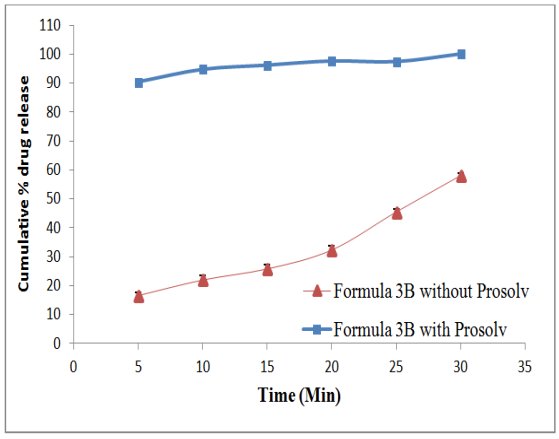

Figure 3: Comparative *In-vitro* release profiles of Atv from tablets of set 3A and 3B.

In vitro drug release profiles of tablets of set 1A and 1B, 2A and 2B, 3A and 3B (Figure No. 1, 2, 3) when compared using student's t test at $P < 0.05$ showed significant difference in drug release at all the time points.

In set 1, drug release from tablets of formula 1A containing Prosolv was faster and complete at the end of 30 minutes whereas tablets of formula 1B containing routine excipients showed incomplete and slower drug release.

In set 2, tablets prepared with Prosolv showed significantly faster drug release rate as compared to tablets containing routine excipients. Presence of starch, a disintegrant helped in increasing the release rate of the drug in this formula and thus 100% release was achieved in 15 minutes.

In set 3, tablets prepared with Prosolv showed faster drug release rate in spite of presence of slow dissolving lactose monohydrate unlike that of formula 3B where lactose affected the drug release significantly.

B) Formulations containing Cellactose 80

Tablets compressed using Cellactose 80 showed lesser thickness, lower friability, lesser weight variation than the tablets prepared using regular excipients. Cellactose 80, owing to its better particle size, morphology and closer size distribution range, shows better flow, compressibility and cohesivity of the blend thus imparting low weight variation and friability to the tablets. Powder blends of set 4B and 6B containing regular excipients could not be compressed into tablets owing to very poor compressibility of lactose and DCP respectively. Hence further studies on these two formulations were discontinued. (Table No: 3)

***In-vitro* Drug Release Studies**

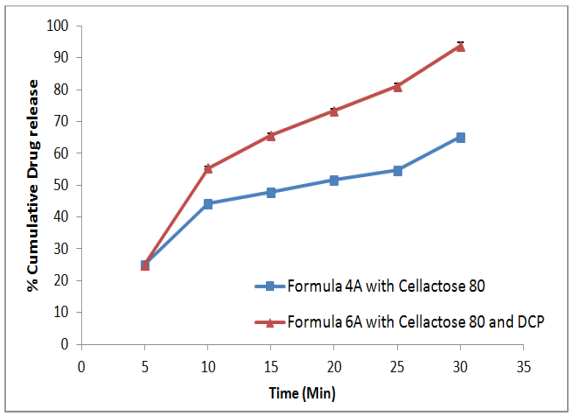

Figure 4: *In-vitro* drug release profile of Atv tablets of set no. 4A and 6A containing Cellactose

Drug release from tablets of formula 4A was found to be only 65% within 30 minutes which could be attributed to presence of larger proportion of lactose in Cellactose 80. However when DCP was used along with Cellactose 80 in formula 6A, drug release rate was improved significantly showing more than 90 % release in 30 minutes. (Figure No. 4)

In vitro drug release profiles of 5A and 5B when compared using student's t test at $P < 0.05$ showed significant difference in drug release at all the dissolution time points. Tablets prepared with Cellactose 80 and starch showed remarkable improvement in drug release rate resulting in complete release at the end of 30 minutes.(Figure No. 5)

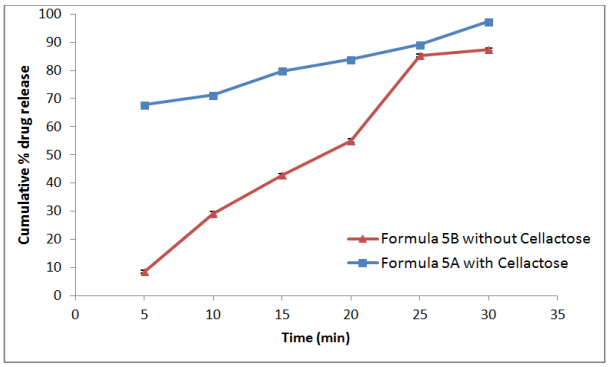

Figure 5: *In-vitro* drug release profiles of Atv from tablets of set. no. 5A and 5B

Overall compression parameters of formulations containing co-processed excipients were better than the formulations containing regular excipients. Uniform particle size, close range of size distribution and near spherical morphology of these co-processed excipients could be the major traits responsible for better mixing of contents, flow, compaction behavior and even faster *in vitro* release of drug.[10]

CONCLUSION

Immediate release tablets of Atv when prepared by direct compression using co-processed excipients showed better pre-compression and compression characteristics as compared to tablets prepared with regular excipients. Formulations prepared with Prosolv showed lower friability and faster *in vitro* release as compared to formulations made using Cellactose 80.

Unlike routine excipients, co-processed excipients could tolerate dilution with poorly flowable and compressible excipients in better manner and retained acceptable pre-compression and compression characteristics thus proving advantage of using co-processed excipients for direct compression of poorly flowable and compressible APIs.

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