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Research Article

FORMULATION DEVELOPMENT OF SELECTED ANTIRETROVIRAL DRUGS BY DIRECT COMPRESSION METHOD

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ABSTRACT

Direct compression is the preferred method for the preparation of tablets. Though several directly compressible vehicles (DCVs) are available commercially, literature on their evaluation and application in formulation development is rather scanty. The objective of the present study is to make a comparative evaluation of three commercially available DCVs namely Lubritose AN, Lubritose SD, Lubritose MCC and one laboratory made DCV namely starch phosphate, a new modified starch in the formulation development of three antiretroviral drugs by direct compression method. Tablets of (i) Efavirenz (100 mg) (ii) Ritonavir (100 mg) and (iii) Stavudine (30 mg) were formulated employing the four directly compressible vehicles and the tablets were evaluated for various physical properties and dissolution rate. All the DCVs tested possess excellent to good flow properties as evidenced by their angle of repose and compressibility index values. Blends of DCVs and the selected APIs also exhibited good flow characteristics suitable for direct compression. The estimated bulk densities for different DCVs ranged from 0.385 – 0.520 g/cc also contribute to their good flow. All the tablets prepared employing various DCVs were of good quality with regard to drug content, hardness, friability and disintegration time and fulfilled the official requirements of uncoated tablets. All the tablets formulated employing various DCVs and prepared by direct compression method gave rapid dissolution of the contained drug. The dissolution was complete (100%) within 15 – 30 min with all the drugs and the dissolution was much higher than the official requirement in each case. Stavudine tablets exhibited faster dissolution than those of efavirenz and ritonavir with all the four DCVs. Hence these DCVs are recommended for the preparation of tablets of antiretroviral drugs by direct compression method.

Keywords: Directly compressible vehicles, Direct compression, Efavirenz, Ritonavir, Stavudine

INTRODUCTION

Direct compression is the preferred method for the preparation of tablets[1]. It offers several advantages[2-3]. Notable among them are (i) It is economical compared to wet granulation since it requires fewer unit operations (ii) More suitable for moisture and heat sensitive APIs since it eliminates wetting and drying steps (iii) Changes in dissolution profiles are less likely to occur in tablets made by direct compression method on storage than in those made from granulations[4]. This is extremely important because the official compendium now requires dissolution specifications in most solid dosage forms[5]. Disintegration or dissolution is the rate limiting step in absorption in the case of tablets of poorly soluble API prepared by wet granulation. The tablets prepared by direct compression disintegrate into API particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution.

Though several directly compressible vehicles are available commercially, literature on their evaluation and application in formulation development is rather scanty. Starch phosphate, a modified starch is recently reported[6] as a promising directly compressible vehicle. In the present study three commercially available directly compressible vehicles namely Lubritose AN, Lubritose SD and Lubritose MCC and one laboratory made directly compressible vehicle namely starch phosphate were evaluated for their application in formulation development. Tablets of (i) Efavirenz (100 mg) (ii) Ritonavir (100 mg) and (iii) Stavudine (30 mg) were formulated employing four directly compressible vehicles and the tablets were evaluated for various physical properties and dissolution rate. The results are reported in this paper.

MATERIALS AND METHODS

Efavirenz, Ritonavir and Stavudine were gift samples from M/s Eisai Pharmatechnology and Manufacutring Pvt., Ltd., Parawada, Visakhapatnam. Lubritose AN, Lubritose SD and Lubritose MCC were procured from commercial sources. Starch phosphate was prepared in the laboratory. All other materials used were of Pharmacopoeial grade.

Preparation of Starch Phosphate

Starch phosphate was prepared based on the method of Choi et al[7] with some modifications. Potato starch (100 mg) and di- sodium hydrogen orthophosphate anhydrous (30 g) were suspended in 100 ml of water and continuously stirred for 20 min. This starch slurry was then filtered and the wet starch mixture was conditioned for 12 h at room temperature (28^0c). To enhance phosphorylation, this mixture was heated in a forced air oven at 130^0c for 3 h. The product obtained was ground and sized.

Micromeritic Evaluation

Particle size

Particle size analysis was done by sieving using standard sieves.

Bulk density[8]

Bulk density (g/cc) was determined by three tap method in a graduated cylinder.

Angle of repose[9]

Angle of repose was measured by fixed funnel method.

Compressibility index[10]

Compressibility index (CI) was determined by measuring the initial volume (V_o) and final volume (V) after hundred tapings of a sample of starch citrate in a measuring cylinder. CI was calculated using equation

$$\text{Compressibility index (CI)} = \frac{V_o - V \times 100}{V_o}$$

Preparation of Tablets by Direct Compression Method

Tablets of (i) Efavirenz (100 mg) (ii) Ritonavir (100 mg) and (iii) Stavudine (30 mg) were prepared by direct compression method as per the formulae given in Tables 3-4.

All the materials required as per the formulae were blended in a closed polyethylene bag. The blends were compressed into tablets on a tablet punching machine (M/s Cadmach Machinery Co. Pvt. Ltd)

to a hardness of 6 kg/cm ^{2} using 9 mm concave punches. In each case 100 tablets were compressed.

Evaluation of Tablets

All the tablets prepared were evaluated for content of active ingredient, hardness, friability, and disintegration time and dissolution rate. Hardness of the tablets was tested using Monsanto Hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time was determined in a Labindia tablet disintegration test machine (Model: DT 1000) using water as test fluid.

Estimation of Drug Content in the Tablets

From each batch of tablets prepared 20 tablets were accurately weighed and powdered. Tablet powder equivalent to 50 mg of drug was taken for assay into a 100 ml conical flask and extracted with 3x20 ml quantities of methanol. The methanolic extracts were filtered and collected into a 100 ml volumetric flask and the volume was made up to 100 ml with methanol. The solution was then suitably diluted with water containing 2% SLS in the case of efavirenz and with 0.1 N hydrochloric acid in the case of ritonavir and stavudine. The absorbance of the solutions was measured at 245 nm in the case of efavirenz; at 210 nm in the case of ritonavir and at 266 nm in the case of stavudine. Drug content of the tablets was calculated using the standard calibration curve in each case.

Dissolution Rate Study

Dissolution rate of the tablets prepared was studied employing USP 8 station Dissolution Rate Test Apparatus (M/s Labindia Disso 8000) with a paddle stirrer at 50 rpm. Water containing 2% SLS (900 ml), 0.1N hydrochloric acid (900 ml) and 0.01 M hydrochloric acid (900 ml) were used as dissolution fluids respectively for efavirenz, ritonavir and stavudine tablets as prescribed in I.P 2010. One tablet was used in each test. A temperature 37+1^{o}C was maintained throughout. Samples of dissolution medium (5 ml) were withdrawn through a filter (0.45µ) at different time intervals and assayed for efavirenz at 245 nm; for ritonavir at 210 nm and for stavudine at 266 nm. All the dissolution experiments were conducted in triplicate (n=3).

RESULTS AND DISCUSSION

The objective of the present study is to make a comparative evaluation of three commercially available DCVs namely Lubritose AN, Lubritose SD, Lubritose MCC and one laboratory made DCV namely starch phosphate, a new modified starch in the formulation development of three antiretroviral drugs namely efavirenz, ritonavir and stavudine by direct compression method.

The directly compressible vehicles (DCV) should be free flowing. Flowability is required in order to ensure homogeneous and rapid flow of powder for uniform die filling. During the short dwell-time (milliseconds), the required amount of powder blend should be transferred into the die cavities with reproducibility of ± 5%. The flow properties of the DCVs, as determined by their angle of repose and compressibility index values, are summarized in Tables 1 -2.

Table 1: Micromeritic Properties of Directly Compressible Vehicles Tested

DCV	Bulk Density (g/cc)	Angle of Repose (^{0})	Compressibility Index (%)
Lubritose AN	0.452	26.4	10.20
Lubritose SD	0.440	25.6	12.40
Lubritose MCC	0.385	24.2	10.35
Starch Phosphate (80/120 mesh; 152µm)	0.520	23.2	10.21

Table 2: Micromeritic Properties of Blends of Directly Compressible Vehicles and APIs

DCV- API* Blend	Angle of Repose (^{0})	Compressibility Index (%)
Lubritose AN- E	25.2	9.85
Lubritose SD- E	26.4	10.25
Lubritose MCC- E	26.3	11.45
Starch Phosphate- E	25.6	11.50
Lubritose AN- R	25.4	10.45
Lubritose SD- R	26.8	11.50
Lubritose MCC- R	27.2	12.25
Starch Phosphate- R	24.6	13.26
Lubritose AN- S	25.8	12.36
Lubritose SD- S	27.2	12.45
Lubritose MCC- S	24.6	11.50
Starch Phosphate- S	22.8	10.85

* E: Efavirenz; R: Ritonavir and S: Stavudine

Table 3: Formulae of (i) Efavirenz and (ii) Ritonavir Tablets Prepared by Direct Compression Method

Ingredient (mg/tablet)	EF1/RF1	EF2/RF2	EF3/RF3	EF4/RF4
Efavirenz/ Ritonavir	100	100	100	100
Acacia	5.7	5.7	5.7	5.7
Crospovidone	11.5	11.5	11.5	11.5
Talc	4.6	4.6	4.6	4.6
Magnesium stearate	4.6	4.6	4.6	4.6
Lubritose AN	158.6	-	-	-
Lubritose SD	-	158.6	-	-
Lubritose MCC	-	-	158.6	-
Starch Phosphate	-	-	-	158.6
Total weight (mg)	285	285	285	285

Table 4: Formulae of Stavudine Tablets Prepared by Direct Compression Method

Ingredient (mg/tablet)	SF1	SF2	SF3	SF4
Stavudine	30	30	30	30
Acacia	4.6	4.6	4.6	4.6
Crospovidone	11.5	11.5	11.5	11.5
Talc	4.6	4.6	4.6	4.6
Magnesium stearate	4.6	4.6	4.6	4.6
Lubritose AN	174.7	-	-	-
Lubritose SD	-	174.7	-	-
Lubritose MCC	-	-	174.7	-
Starch Phosphate	-	-	-	174.7
Total weight (mg)	230	230	230	230

It is obvious from these results that all the DCVs tested possess excellent to good flow properties. Blends of DCVs and the selected APIs (Table 2) also exhibited angle of repose values in the range 22^0-28^0 and compressibility index values in the range 9 -14 % indicating good flow of the blends. The results, thus, indicated that the commercial and laboratory prepared DCVs tested possess good flow characteristics suitable for direct compression. The estimated bulk densities for the different DCVs are tabulated in Table 1. The bulk densities were ranged from 0.385- 0.520 g/cc. The bulk densities of the DCVs would also contribute to their good flow.

Tablets of (i) Efavirenz (100 mg) (ii) Ritonavir (100 mg) and (iii) Stavudine (30 mg) were prepared by direct compression method employing the four directly compressible vehicles as per the formulae given in Tables 3-4.

Table 5: Physical Properties of Various Tablets Formulated by Direct Compression Method

Formulation	DCV Used	Hardness (Kg/sq.cm)	Friability (% weight loss)	Disintegration Time (min – sec)	Drug Content (mg / tablet)
E*F1	Lubritose AN	5.5	0.95	5-10	98.5
EF2	Lubritose SD	6.0	1.20	4-20	99.6
EF3	Lubritose MCC	5.5	0.85	0-40	97.4
EF4	Starch Phosphate	6.5	0.65	0-55	98.2
R*F1	Lubritose AN	5.0	0.85	5-20	101.2
RF2	Lubritose SD	5.5	0.90	3-30	100.5
RF3	Lubritose MCC	6.5	1.10	0-25	98.2
RF4	Starch Phosphate	6.0	0.95	0-45	99.2
S*F1	Lubritose AN	6.0	0.75	4-15	30.2
SF2	Lubritose SD	6.5	0.85	3-25	30.1
SF3	Lubritose MCC	5.0	1.15	0-30	29.6
SF4	Starch Phosphate	5.5	0.90	0-40	29.2

E: Efavirenz; R: Ritonavir and S: Stavudine

All the tablets prepared were evaluated for content of active ingredient, hardness, friability, and disintegration time and dissolution rate. The results are given in Table 5.

Hardness of the tablets was in the range 5. 0–6.5 Kg / sq. cm. Weight loss in the friability test was in the range 0.65 – 1.2 %. The drug content of the tablets was within 100 ± 3% of the labelled claim. Tablets formulated employing Lubritose MCC and starch phosphate disintegrated rapidly within seconds, 25 – 55 seconds. Tablets formulated with other DCVs were disintegrated within 3 – 6 min. As such, all the tablets prepared employing various DCVs were of good quality with regard to drug content, hardness, friability and disintegration time and fulfilled the official (I.P) specifications of uncoated tablets.

Table 6: Dissolution Rate of Various Tablets Formulated by Direct Compression Method

Formulation	DCV Used	Percent Dissolved (%) at Time(min)					Official Dissolution Rate Specification
		5	10	15	20	30	
E*F1	Lubritose AN	66.5	82.1	89.4	96.2	99.8	NLT 70 % in 60 min in water containing 2% SLS
EF2	Lubritose SD	75.3	81.4	89.6	95.2	98.4	(I.P, 2010)
EF3	Lubritose MCC	85.6	92.8	96.2	99.8	100	
EF4	Starch Phosphate	90.4	97.5	99.8	100	100	
R*F1	Lubritose AN	64.2	69.2	80.6	89.5	92.1	NLT 75 % in 60 min in 0.1 N HCl
RF2	Lubritose SD	62.5	70.2	79.4	86.5	96.0	(I.P, 2010)
RF3	Lubritose MCC	82.6	91.4	95.6	99.2	99.6	
RF4	Starch Phosphate	87.2	94.5	98.9	99.2	99.4	
S*F1	Lubritose AN	83.2	92.5	96.2	99.8	99.6	NLT 70 % in 45 min in 0.01 M HCl
SF2	Lubritose SD	89.5	94.2	96.8	99.6	100	(I.P, 2010)
SF3	Lubritose MCC	95.4	98.6	99.8	100	100	
SF4	Starch Phosphate	92.6	97.5	100	100	100	

***** E: Efavirenz; R: Ritonavir and S: Stavudine

The results of dissolution rate study are given in Table 6. All the tablets formulated employing various DCVs and prepared by direct compression method gave rapid dissolution of the contained drug. The dissolution was complete (100%) within 15 – 30 min with all the drugs. In the case of stavudine, a water soluble drug the dissolution from all the tablets formulated was very rapid and complete with in 15 min. In the case of poorly soluble drugs, efavirenz and ritonavir, the dissolution was relatively slow but complete with in 20- 30 min. Lubritose MCC and starch phosphate gave relatively higher dissolution than the others with all the three drugs. The official (I.P 2010) dissolution rate specifications of various tablets are shown in Table 6. All the tablet formulations of the three antiretroviral drugs prepared by direct compression method employing various DCVs gave dissolution much higher than the official requirement.

CONCLUSION

The results of the present study indicated that the three commercial DCVs namely Lubritose AN, Lubritose SD, Lubritose MCC and the starch phosphate, a new modified starch prepared in the laboratory posses excellent to good flow characteristics suitable for direct compression. The tablets of efavirenz, ritonavir and stavudine formulated employing the above mentioned DCVs by direct compression method fulfilled all official specifications apart from giving a rapid dissolution of the contained drug. Hence these DCVs are recommended for the preparation of tablets of antiretroviral drugs by direct compression method.

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