

**FORMULATION DEVELOPMENT OF SELECTED DRUGS BY DIRECT COMPRESSION METHOD****K. P. R. Chowdary^{*1}, Sunil Kumar¹**¹Eisai Knowledge Centre, Eisai Pharmatechnology and Manufacturing Pvt.,Ltd., Ramky Pharma City (SEZ), Parawada, Visakhapatnam-531019, India**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 medicaments by direct compression method. Tablets of (i) Nimesulide (50 mg) (ii) Piroxicam (20 mg) and (iii) Diethyl carbamazine citrate (100 mg) were formulated employing 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 0.345 – 0.545 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 – 20 min with all the drugs

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INTRODUCTION

Direct compression is the preferred method for the preparation of tablets¹. It offers several advantages²⁻³. 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 granulations⁴. This is extremely important because the official compendium now requires dissolution specifications in most solid dosage forms⁵. 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 reported⁶ 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) Nimesulide (50 mg) (ii) Piroxicam (20 mg) and (iii) Diethyl carbamazine citrate (100 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.

EXPERIMENTAL MATERIALS:

Nimesulide, piroxicam and diethyl carbamazine citrate (DEC) 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.

METHODS:

Preparation of Starch Phosphate:

Starch phosphate was prepared based on the method of Choi et al⁷ 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°C). To enhance phosphorylation, this mixture was heated in a forced air oven at 130°C 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 density⁸

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

Angle of repose⁹

Angle of repose was measured by fixed funnel method.

Compressibility index¹⁰

Compressibility index (CI) was determined by measuring the initial volume (V_0) and final volume (V) after hundred tapings of a sample of starch citrate in a measuring cylinder. CI was calculated using equation

$$\text{Compressibility index (CI)} = \frac{V_0 - V}{V_0} \times 100$$

Preparation of Tablets by Direct Compression Method:

Tablets of (i) Nimesulide (50 mg) (ii) Piroxicam (20 mg) and (iii) Diethyl carbamazine citrate (100 mg) were prepared by direct compression method as per the formulae given in Tables 3-5.

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/cm² 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, disintegration time and dissolution rate. Hardness of 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 phosphate buffer of pH 7.4 in the case of nimesulide; with 0.1 N hydrochloric acid in the case of piroxicam and with water in the case of diethyl carbamazine citrate. The absorbance of the solutions was measured at 230 nm in the case of nimesulide; at 333 nm in the case of piroxicam and at 220 nm in the case of diethyl carbamazine citrate. 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. Phosphate buffer of pH 7.4 (900 ml), 0.1 N hydrochloric acid (900 ml) and water (900 ml)

were used as dissolution fluids respectively for nimesulide, piroxicam and diethyl carbamazine citrate tablets. One tablet was used in each test. A temperature 37±1°C was maintained throughout. Samples of dissolution medium (5 ml) were withdrawn through a filter (0.45µ) at different time intervals and assayed for nimesulide at 230 nm; for piroxicam at 333 nm and for diethyl carbamazine citrate at 220 nm. For comparison, dissolution rate of one commercial brand in each case was also studied. All the dissolution experiments were conducted in triplicate (n=3).

RESULTS AND DISCUSSION

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 Table 1. 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 24°-30° 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 0.345- 0.545 g/cc. The bulk densities of the DCVs would also contribute to their good flow.

Table 1: Micromeritic Properties of Directly Compressible Vehicles Tested

DCV	Bulk Density(g/cc)	Angle of Repose(°)	Compressibility Index (%)
Lubritose AN	0.425	26.2	9.85
Lubritose SD	0.412	24.5	12.15
Lubritose MCC	0.345	23.6	11.62
Starch Phosphate (80/120 mesh; 152µm)	0.545	22.5	9.51

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

DCV- API* Blend	Angle of Repose (°)	Compressibility Index (%)
Lubritose AN- N	24.5	9.6
Lubritose SD- N	26.8	11.5
Lubritose MCC- N	29.2	12.4
Starch Phosphate- N	26.7	12.6
Lubritose AN- P	25.6	10.8
Lubritose SD- P	27.2	12.6
Lubritose MCC- P	28.5	13.4
Starch Phosphate- P	25.3	13.8
Lubritose AN- DEC	26.2	13.2
Lubritose SD- DEC	27.8	12.8
Lubritose MCC- DEC	26.5	11.4
Starch Phosphate- DEC	25.8	10.5

Tablets of (i) Nimesulide (50 mg) (ii) Piroxicam (20 mg) and (iii) Diethyl carbamazine citrate (100 mg) were prepared by direct compression method employing the four directly compressible vehicles as per the formulae given in Tables 3-5. All the tablets prepared were evaluated for content of active ingredient, hardness, friability, disintegration time and dissolution rate. The results are given in Table 6. Hardness of the tablets was in the range 4.5 – 6.5 Kg / sq.cm. Weight loss in the

friability test was in the range 0.65 – 1.3 %. The drug content of the tablets was within $100 \pm 3\%$ of the labelled claim. Tablets formulated employing Lubritose MCC disintegrated rapidly within seconds, 19 – 55 seconds. Tablets formulated with other DCVs were disintegrated within 1 – 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.

The results of dissolution rate study are given in Table 7. 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 – 20 min with all the drugs. In the case of DEC, a water soluble drug Lubritose MCC and starch phosphate gave relatively higher dissolution than the others. In the case of piroxicam, a poorly soluble drug commercial DCVs gave higher dissolution than starch phosphate. With nimesulide all DCVs gave equally rapid dissolution. The official dissolution rate specifications for various tablets are shown in Table 7. All piroxicam and diethyl carbamazine citrate tablet formulations prepared by direct compression method employing various DCVs gave dissolution much higher than the official requirement. Nimesulide is not official in pharmacopoeias and it is used as a model drug.

Table 3: Formulae of Nimesulide Tablets Prepared by Direct Compression Method

Ingredient (mg/tablet)	NF1	NF2	NF3	NF4
Nimesulide	50	50	50	50
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	154.7	-	-	-
Lubritose SD	-	154.7	-	-
Lubritose MCC	-	-	154.7	-
Starch Phosphate	-	-	-	154.7
Total weight (mg)	230	230	230	230

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

Ingredient (mg/tablet)	PF1	PF2	PF3	PF4
Piroxicam	20	20	20	20
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	184.7	-	-	-
Lubritose SD	-	184.7	-	-
Lubritose MCC	-	-	184.7	-
Starch Phosphate	-	-	-	184.7
Total weight (mg)	230	230	230	230

Table 5: Formulae of Diethyl Carbamazine Citrate Tablets Prepared by Direct Compression Method

Ingredient(mg/tablet)	DECF1	DECF2	DECF3	DECF4
Diethyl carbamazine citrate	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 6: 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)
NF1	Lubritose AN	4.5	0.85	5-00	50.2
NF2	Lubritose SD	5.0	0.65	1-30	50.1
NF3	Lubritose MCC	4.5	0.95	0-45	49.5
NF4	Starch Phosphate	5.5	1.01	2-30	49.6
PF1	Lubritose AN	5.0	0.92	4-25	19.8
PF2	Lubritose SD	5.5	0.95	1-28	20.1
PF3	Lubritose MCC	5.5	1.20	0-18	19.6
PF4	Starch Phosphate	4.5	1.30	2-15	20.3
DECF1	Lubritose AN	6.0	0.86	5-20	98.5
DECF2	Lubritose SD	6.5	0.98	4-30	98.9
DECF3	Lubritose MCC	5.0	1.25	0-40	99.2
DECF4	Starch Phosphate	5.5	1.16	3-35	101.2

Table 7: 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	
NF1	Lubritose AN	100	-	-	-	Not Official Used as a model Drug
NF2	Lubritose SD	94.6	100	-	-	
NF3	Lubritose MCC	92.5	99.2	100	-	
NF4	Starch Phosphate	95.2	98.6	100	-	
PF1	Lubritose AN	64.9	99.1	100	-	NLT 75 % in 45 min in 0.1 N HCl (I.P, 2010)
PF2	Lubritose SD	77.9	95.3	97.4	100	
PF3	Lubritose MCC	78.9	94.8	100	-	
PF4	Starch Phosphate	78.2	83.1	96.5	100	
DECF1	Lubritose AN	83.8	89.6	95.9	98.2	NLT 75 % in 45 min in Water (I.P, 2010)
DECF2	Lubritose SD	93.1	97.1	100	-	
DECF3	Lubritose MCC	91.6	100	-	-	
DECF4	Starch Phosphate	97.5	101.4	-	-	

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 nimesulide, piroxicam and diethyl carbamazine citrate formulated employing the above mentioned DCVs by direct compression method fulfilled all official specifications apart from giving a rapid dissolution of the contained drug. All piroxicam and diethyl carbamazine citrate tablet formulations prepared by direct compression method employing various DCVs gave dissolution much higher than the official requirement. Hence these DCVs are recommended for the preparation of tablets by direct compression method, an economical method for the preparation of tablets

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