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A COMPARATIVE EVALUATION OF DIRECT COMPRESSION AND WET GRANULATION METHODS FOR FORMULATION OF STAVUDINE TABLETS

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ABSTRACT

The objective of the present study is to make a comparative evaluation of direct compression and wet granulation methods for formulation of stavudine tablets. Stavudine is a widely prescribed antiretroviral drug used for treating HIV infections. Stavudine tablets are official in IP 2010 which prescribed a dissolution rate specification of NLT 70% in 45 min for stavudine tablets. Stavudine (30 mg) tablets were prepared by two methods namely (i) direct compression method employing the seven directly compressible vehicles and (ii) wet granulation method employing usual tablet excipients. All the tablets prepared were evaluated for content of active ingredient, hardness, friability, and disintegration time and dissolution rate. Tablets of good quality fulfilling the official specifications with regard to drug content, hardness, friability and disintegration time could be prepared by both the methods. The tablets prepared by direct compression method disintegrated very rapidly when compared to those prepared by wet granulation method. Tablets prepared by direct compression method gave very rapid dissolution of the contained drug, 100% within 20 min. In the case of wet granulation method, the tablets gave relatively low dissolution. When compared to those prepared by direct compression method. The dissolution was complete (100%) in 60 min. Stavudine tablets prepared by both the methods fulfilled the official IP 2010 dissolution rate test specification prescribed.

Keywords: Stavudine tablets, direct compression method, Wet granulation method, Dissolution rate

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 profile 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. The objective of the present study is to make a comparative evaluation of direct compression and wet granulation methods for the formulation of stavudine tablets. Stavudine is a widely prescribed antiretroviral drug used for treating HIV infections. Stavudine tablets are official in IP 2010 which prescribed a dissolution rate specification of NLT 70% in 45 min for stavudine tablets.

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EXPERIMENTAL

Materials:

Stavudine was a gift samples from M/s Eisai Pharmatechnology and Manufacturing Pvt., Ltd., Parawada, Visakhapatnam. Acacia, PVP K30, Crospovidone, Lactose, Lubritose AN, Lubritose SD, Lubritose MCC, Talc and Magnesium stearate were procured from commercial sources. PGS-MCC, PGS-PVP, Starch phosphate and starch citrate were prepared in the laboratory. All other materials used were of Pharmacopoeial grade.

Methods:

Preparation of Tablets by Direct Compression Method:

Tablets of Stavudine (30 mg) were prepared by direct compression method as per the formulae given in Tables 1. 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.

Preparation of Tablets by Wet Granulation Method:

Tablets of Stavudine (30 mg) were prepared by wet granulation method as per the formulae given in Tables 2. Drug (stavudine), acacia, PVP K30 and lactose were thoroughly blended in a dry mortar and granulated with water (q.s.). The water (q.s.) was added and mixed thoroughly to form dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60°C for 2 h. The dried granules were passed through mesh No. 16 to break the aggregates. Crospovidone and the lubricants (talc and magnesium stearate) were passed through mesh No 100 on to dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a Cadmach tablet punching machine (M/s Cadmach Engineering Co. Pvt. Ltd., Mumbai) to a hardness of 6 kg/cm^2 using 9 mm round and flat punches.

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 0.01 M hydrochloric acid. The absorbance of the solution was measured at 266 nm. Drug content of the tablets was calculated using the standard calibration curve.

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. Hydrochloric acid, 0.01 M (900 ml) was used as dissolution fluid as prescribed for stavudine tablets in I.P 2010. 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 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 direct compression and wet granulation methods for formulation of stavudine tablets. Stavudine (30 mg) tablets were prepared by two methods namely (i) direct compression method employing the seven directly compressible vehicles and (ii) wet granulation method employing usual tablet excipients as per the formulae given in Tables 1-2. All the tablets prepared were evaluated for content of active ingredient, hardness, friability, and disintegration time and dissolution rate.

The physical properties of the tablets prepared are given in Table 3. 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 – 1.65 %. The drug content of the tablets was within 100 ± 3% of the labeled claim. All the tablets formulated by direct compression method disintegrated very rapidly.

Lubritose MCC, Starch citrate and Starch phosphate gave very rapid disintegration of the tablets within 1 min. Co-processed excipients, PGS-MCC and PGS-PVP also gave rapid disintegration within 2-3 min. Thus, the new co-processed excipients and modified starches were found to provide rapid disintegration quality to the tablets formulated. The disintegration time of the tablets prepared by wet granulation method was in the range 5-30 min-sec to 6-10 min-sec. As such all the tablets prepared by direct compression and wet granulation methods fulfilled the official requirements with regard to drug content, hardness, friability and disintegration time.

The results of dissolution rate study are given in Table 4. All the tablets formulated employing various DCVs and prepared by direct compression method gave rapid dissolution of stavudine. Dissolution data were analyzed as per zero order and first order kinetics. The R^2 values were higher in the first order model than in the zero order model indicating that the drug dissolution from all the tablets prepared first order kinetics. The dissolution was complete (100%) within 10–15min. Lubritose MCC, starch phosphate and starch citrate gave relatively higher dissolution than the others. Stavudine dissolution from the tablets prepared by wet granulation method was rapid and complete within 60 min. Tablets prepared using PVP as binder gave higher dissolution than those prepared using acacia as binder. All the stavudine tablet formulations prepared by both direct compression and wet granulation methods fulfilled the official (IP 2010) dissolution rate test specification prescribed for stavudine tablets.

Comparison of Tablets Made by Wet Granulation and Direct Compression Methods:

In the present study stavudine tablets were formulated and prepared by direct compression and wet granulation methods. Seven directly compressible excipients were used to prepare tablets in the case of direct compression method. Stavudine tablets were also prepared by wet granulation method employing commonly used tablet excipients. The tablets prepared by the two methods were evaluated. The following conclusions are drawn by comparing the properties of the tablets prepared by the two methods.

Table 1: Formulae of Stavudine Tablets Prepared by Direct Compression Method

Ingredient (mg/tablet)	SF1	SF2	SF3	SF4	SF5	SF6	SF7
Stavudine	30	30	30	30	30	30	30
Acacia	4.6	4.6	4.6	4.6	4.6	4.6	4.6
Crospovidone	11.5	11.5	11.5	11.5	11.5	11.5	11.5
Talc	4.6	4.6	4.6	4.6	4.6	4.6	4.6
Magnesium stearate	4.6	4.6	4.6	4.6	4.6	4.6	4.6
Lubritose AN	174.7	-	-	-	-	-	-
Lubritose SD	-	174.7	-	-	-	-	-
Lubritose MCC	-	-	174.7	-	-	-	-
Starch Phosphate	-	-	-	174.7	-	-	-
Starch Citrate	-	-	-	-	174.7	-	-
PGS-MCC	-	-	-	-	-	174.7	-
PGS-PVP	-	-	-	-	-	-	174.7
Total weight (mg)	230	230	230	230	230	230	230

Table 2: Formulae of Stavudine Tablets Prepared by Wet Granulation Method

Ingredient (mg/tablet)	WSF1	WSF2
Stavudine	30	30
Acacia	4.6	-
PVP K30	-	4.6
Crospovidone	11.5	11.5
Talc	4.6	4.6
Magnesium stearate	4.6	4.6
Lactose	174.7	174.7
Granulating Fluid (Water)	qs	Qs
Total weight (mg)	230	230

Table 3: Physical Properties of Stavudine Tablets Formulated by Direct Compression and Wet Granulation Methods

Formulation	DCV Used	Hardness (Kg/sq.cm)	Friability (% weight loss)	Disintegration Time (min – sec)	Drug Content (mg / tablet)
SF1	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
SF5	Starch Citrate	5.0	1.20	1-40	30.2
SF6	PGS-MCC	5.0	1.65	2-30	29.8
SF7	PGS-PVP	6.5	1.20	2-10	29.6
WSF1		5.5	0.85	6-10	30.1
WSF2		5.0	0.94	5-30	29.4

S: Stavudine; WSF1 and WSF2 are tablets made by wet granulation method

Table 4: Dissolution Rate of Stavudine Tablets Formulated by Direct Compression and Wet Granulation Methods

Formulation	DCV Used	Percent Dissolved (%) at Time (min)					Official Dissolution Rate Specification
		5	10	15	20	30	
SF1	Lubritose AN	83.2	92.5	96.2	99.8	99.6	NLT 70% in 45 min. in 0.01 M HCl (IP 2010)
SF2	Lubritose SD	89.5	94.2	96.8	99.6	100	
SF3	Lubritose MCC	95.4	98.6	99.8	100	100	
SF4	Starch Phosphate	92.6	97.5	100	100	100	
SF5	Starch Citrate	89.5	94.6	99.6	100	100	
SF6	PGS-MCC	85.6	92.8	99.4	100	100	
SF7	PGS-PVP	71.62	100	100	100	100	
WSF1	-	58.9	65.9	77.8	89.2	98.9	
WSF2	-	59.8	78.7	80.2	88.9	100	

S: Stavudine; WSF1 and WSF2 are tablets made by wet granulation method

CONCLUSIONS

1. Tablets of good quality fulfilling the official specifications with regard to drug content, hardness, friability and disintegration time could be prepared by both the methods.
2. The tablets prepared by direct compression method disintegrated very rapidly when compared to those prepared by wet granulation method.
3. Tablets prepared by direct compression method gave very rapid dissolution of the contained drug, 100% within 20 min. In the case of wet granulation method, the tablets gave relatively low dissolution. When compared to those prepared by direct compression method. The dissolution was complete (100%) in 60 min.
4. Stavudine tablets prepared by both the methods fulfilled the official IP 2010 dissolution rate test specification prescribed.

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