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FORMULATION DEVELOPMENT OF SELECTED ANTIRETROVIRAL DRUGS BY DIRECT COMPRESSION METHOD EMPLOYING A NEW MODIFIED STARCH

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ABSTRACT

Direct compression is the preferred method for the preparation of tablets. Formulation of tablets by direct compression method requires an excipient with good flow and compressible characteristics. We have earlier reported preparation and evaluation of directly compressible vehicles by co-processing and chemical modification methods. The newly developed excipients were suitable for formulation of tablets by direct compression method. The objective of the study is formulation development of selected antiretroviral drugs by direct compression method employing Starch phosphate, a new modified starch developed. Tablets of (i) efavirenz (ii) ritonavir and (iii) stavudine prepared by direct compression method employing Starch phosphate as DCV were of good quality with regard to drug content, hardness, friability and disintegration time. All the tablets formulated disintegrated rapidly within 3.5 min. With all the three drugs, the tablets prepared gave rapid dissolution of the contained drug, 100 % within 20 min and fulfilled the official (IP/USP) dissolution rate test specification prescribed in each case. Starch phosphate developed was found to be a promising directly compressible vehicle for the preparation of tablets of antiretroviral drugs. Tablets of three antiretroviral drugs could be prepared by direct compression method employing starch phosphate, a new modified starch.

Keywords: Direct compression, Directly compressible vehicle, Starch phosphate, 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 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.

Formulation of tablets by direct compression method requires an excipient with good flow and compressible characteristics. Though several directly compressible excipients are available commercially there is a continued need for development of new efficient and cost effective excipients for direct compression. We have earlier reported[6, 7] preparation and evaluation of directly compressible vehicles by co-processing and chemical modification methods. The newly developed excipients were suitable for formulation of tablets by direct compression method. The objective of the study is formulation development of selected antiretroviral drugs by direct compression method employing a new modified starch, Starch phosphate.

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EXPERIMENTAL

Materials:

Efavirenz, ritonavir and stavudine were gift samples from M/s Eisai Pharmatechnology and Manufacturing Pvt. Ltd., Visakhapatnam. Lactose, talc and magnesium stearate 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 etal.[8]with some modifications. Potato starch (100 g) 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 ovenat 130°C for 3 h. The product obtained was ground and sized.

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 using Starch phosphate as per the formula given in the Table 1. All the materials required as per the formula 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 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 tablets was tested using Monsanto hardness tester. Friability of the tablets was determined in a Roche Friabilator. Disintegration time was determined in a Lab India 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 3×20 ml quantities of methanol. The methanolic extracts were filtered and collected into a 100 ml volumetric flask and the volume was then 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 245nm in the case of efavirenz; at 210 nm in the case of ritonavir and at266 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/sLabindia Disso 8000) with a paddle stirrer at 50 rpm. Water containing 2% SLS (900 ml), hydrochloric acid, 0.1N (900 ml) and0.01 M hydrochloric acid (900 ml) were used as dissolution fluids for efavirenz, ritonavir and stavudine respectively. One tablet was used in each test. A temperature 37±1^{0}C was maintained throughout. Samples of dissolution medium (5 ml) were withdrawn through a filter (0.45 µ) at different time intervals and assayed for efavirenz at 245 nm, ritonavir at 210 nm and stavudine at 266 nm. All the dissolution experiments were conducted in triplicate (n=3).

RESULTS AND DISCUSSION

Direct compression is the preferred method for the preparation of tablets. Formulation of tablets by direct compression method requires an excipient with good flow and compressible characteristics. We have earlier reported preparation and evaluation of directly compressible vehicles by co-processing and chemical modification methods. The newly developed excipients were suitable for formulation of tablets by direct compression method. The objective of the study is formulation development of selected antiretroviral drugs by direct compression method employing Starch phosphate, a new modified starch developed.

To evaluate the starch phosphate prepared as directly compressible vehicle (DCV), tablets of (i) efavirenz (100 mg) (ii) ritonavir (100 mg) and (iii) stavudine (30 mg) were prepared by direct compression method employing starch phosphate as DCV at strength of 60% in the formula. The tablets were prepared as per the formulae given Table 1. All the tablets prepared were evaluated for content of active ingredient, hardness, friability, and disintegration time and dissolution rate. The results are given in Tables 2-3. Hardness of the tablets was in the range 4.0 - 5.0 Kg/sq.cm. Weight loss in the friability test was in the range 1.45 – 2.10%.The drug content of the tablets was within 100 ± 3% of the labelled claim. All the tablets formulated disintegrating rapidly within 3.5 min. As such all the tablets prepared employing starch phosphate were of good quality with regard to drug content, hardness, friability and disintegration time. The results of the dissolution rate study are given in Table 3.With all the three drugs; the tablets prepared gave rapid dissolution of the contained drug. The dissolution was complete (100 %) within 20 min and fulfilled the official (IP/USP) dissolution rate test specification prescribed in each case**.**

Table 1: Formulae of Tablets Prepared By Direct Compression Method Employing Starch Phosphate

Ingredient (mg/tablet)	Tablet Formulation		
	Efavirenz	Ritonavir	Stavudine
Efavirenz	100	-	-
Ritonavir	-	100	-
Stavudine	-	-	30
Starch phosphate (72/100 mesh)	264	264	264
Lactose	58.4	58.4	128.4
Talc	8.8	8.8	8.8
Magnesium stearate	8.8	8.8	8.8
Tablet weight(mg)	440	440	440

Table 2: Physical Properties of Various Tablets Prepared by Direct Compression Method

Formulation	Hardness (kg/sq.cm)	Friability (% weight loss)	Disintegration time (min-sec)	Drug content (mg/tablet)
Efavirenz tablets	4.0	1.45	3-00	98.5
Ritonavir tablets	5.0	2.10	3-15	99.2
Stavudine tablets	5.0	1.95	3-20	101.6

Table 3: Dissolution Rate of Various Tablets Formulated by Direct Compression Method Employing Starch phosphate Prepared

Formulation	Percent Drug Dissolved (%) at Time (min)				Official Dissolution Rate Specification
	5	10	15	20	
Efavirenz tablets	74.50	88.50	97.20	100	NLT 70 % in 60 min in water containing 2% SLS (I.P, 2010)
Ritonavir tablets	78.40	98.80	99.90	100	NLT 75 % in 60 min in 0.1 N HCl (I.P, 2010)
Stavudine tablets	71.62	100	100	100	NLT 70 % in 45 min in 0.01 M HCl (I.P, 2010)

CONCLUSIONS

1. Tablets of (i) efavirenz (ii) ritonavir and (iii) stavudine prepared by direct compression method employing Starch phosphate as DCV were of good quality with regard to drug content, hardness, friability and disintegration time.
2. All the tablets formulated disintegrated rapidly within 3.5 min.
3. With all the three drugs, the tablets prepared gave rapid dissolution of the contained drug, 100 % within 20 min and fulfilled the official (IP/USP) dissolution rate test specification prescribed in each case.
4. Starch phosphate developed was found to be a promising directly compressible vehicle for the preparation of tablets of antiretroviral drugs.
5. Tablets of three antiretroviral drugs could be prepared by direct compression method employing starch phosphate, a new modified starch

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