INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

PREPARATION, CHARACTERIZATION AND EVALUATION OF PGS - PVP CO-PROCESSED EXCIPIENT AS DIRECTLY COMPRESSIBLE VEHICLE IN THE FORMULATION DEVELOPMENT OF ANTIRETROVIRAL DRUGS

Sunil Kumar[1], KPR. Chowdary[2*] and P. Suresh[3]

[1]Eisai Knowledge Centre, Eisai Pharmatechnology and Manufacturing Pvt, Ltd, Ramky Pharma City (SEZ), Parawada, Visakhapatnam, Andhra Pradesh, India.

[2]Former Principal, AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, Andhra Pradesh, India.

[3]GITAM Institute of Pharmacy, GITAM University, Visakhapatnam, Andhra Pradesh, India.

ABSTRACT

Direct compression is the preferred method for the preparation of tablets. Co- processing is the one of the most widely explored and commercially utilized method for the preparation of directly compressible vehicles. The objective of the present study is to prepare and characterize pregelatinized starch-poly vinyl pyrrolidone (PGS-PVP) co-processed excipient and to evaluate its application as directly compressible vehicle in the tablet formulations of three anti-retroviral drugs namely efavirenz, ritonavir and stavudine. PGS-PVP co-processed excipient was prepared by gelatinizing potato starch in the presence of PVP and drying the resulting mass. The co-processed excipient prepared was characterized by determining melting point, solubility, swelling index in water, pH, and micromeritic characters namely particle size, bulk density, tapped density, angle of repose and compressibility index and evaluated for its application in tablet formulations.

PGS-PVP co-processed excipient prepared by gelatinizing potato starch (49 parts) in the presence of PVP (1 part) is a crystalline, discrete and free flowing powder. It is insoluble in water and aqueous fluids of pH 1.2, 4.5 and 7.4 and in several organic solvents. It exhibited high swelling (284 %) in water. PGS-PVP co-processed excipient has excellent flow properties alone and as blends with selected drugs it exhibited excellent to good flow properties. Tablets of (i) efavirenz (100 mg) (ii) ritonavir (100 mg) and (iii) stavudine (30 mg) prepared by direct compression method employing PGS-PVP co-processed excipient as DCV were of good quality with regard to drug content, hardness, friability and disintegration time. All the tablets formulated disintegrating 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. Thus PGS-PVP co-processed excipient developed in this study was found to be a promising directly compressible vehicle for the preparation of tablets of anti-retroviral drugs.

Keywords: Pre gelatinized starch, Poly vinyl pyrrrolidone , 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.

The direct compression process is mainly influenced by the properties of the excipients. The physico mechanical properties of excipients that ensure a robust and successful process are good flowability, good compressibility, low or no moisture sensitivity, low lubricant sensitivity, and good machineability even in high –speed tabletting machinery with reduced dwell times[6]. The majority of the excipients that are currently available fail to give up to these functionality requirements, thus creating the opportunity for the development of new high-functionality excipients. An efficient platform for the manipulation of excipient functionality is provided by co-processing two or more existing excipients. Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients[7]. The availability of a large number of excipients for co-processing ensures numerous possibilities to produce tailor-made “designer excipients” to address specific functionality requirements. Co-processed excipients are prepared by incorporating one excipient into the particle structure of another excipient using processes such as co-drying. Co-processing of excipients in the pharmaceutical industry can be dated back to the late 1980’s with the introduction of co-processed microcrystalline cellulose and calcium carbonate[8], followed by Cellactose (Meggle Corp., Wasserburg, Germany) in 1990, which is a co-processed combination of cellulose and lactose. A similar principle was applied in developing silicified microcrystalline cellulose (SPVP), which is the most widely used co-processed excipient[9].The objective of the present study is to prepare and characterize pregelatinized starch-poly vinyl pyrrolidone (PGS-PVP) co-processed excipient and to evaluate its application as directly compressible vehicle in tablet formulations. PGS-PVP co- processed excipeint was prepared by gelatinizing potato starch in the presence of PVP and drying the resulting mass.

EXPERIMENTAL

Materials

Efavirenz, ritonavir, stavudine and poly vinyl pyrrolidone (PVP) were gift samples from M/s Eisai Pharmatechnology and Manufacturing Pvt. Ltd., Visakhapatnam. Potato starch, lactose, talc and magnesium stearate were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

METHODS

Preparation of PGS-PVP Co-processed Excipient

Potato starch (49parts) and poly vinyl pyrrolidone (1 part) were dispersed in 20 parts of water to form a smooth slurry. Purified water (40 parts) was taken in a separate beaker and heated to boiling. Starch - PVP slurry was added to boiling water while stirring. Stirring while heating was continued for 15 to 20 minutes to form a thick mass. The product formed was collected on to stainless steel tray and dried at 80^{o}c for 12 hours. The dried product was grinded and sized to obtain -72+100 mesh sized particles.

Characterization of PGS-PVP Co-processed excipient

PGS-PVP co-processed excipient prepared was characterized by determining melting point, solubility, swelling index in water, pH, and micromeritic characters namely particle size, bulk density, tapped density, angle of repose and compressibility index and by FTIR spectra.

Solubility

Solubility of PGS-PVP was tested in water, aqueous buffers of pH 1.2, 4.5, and 7.4 and organic solvents such as alcohol, dichloromethane, chloroform, acetone and petroleum ether.

pH

The pH of a 1% w/v slurry was measured.

Melting point

Melting point was determined by using melting point apparatus.

Swelling Index[10]

PGS-PVP (500 mg) was added to 10 ml of water and light paraffin taken in two different graduated test tubes and mixed. The dispersion in the tubes was allowed to stand for 24 hrs. The volumes of the sediment in the tubes were recorded. The Swelling index of the material was calculated as follows.

S.I (%) = (Volume of sediment in water – Volume of sediment in light liquid paraffin)/ (Volume of sediment in liquid paraffin)

Particle size

Particle size analysis was done by sieving using standard sieves.

Bulk density[11]

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

Angle of repose[12]

Angle of repose was measured by fixed funnel method.

Compressibility index[13]

Compressibility index (CI) was determined by measuring the initial volume (V_0) and final volume (V) after hundred tappings of a sample of the product in a measuring cylinder.

CI was calculated using equation,

Compressibility index (CI) = $[(V_0-V)/V_0] \times 100$

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 formula given in the Table 2. 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, 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 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), hydrochloric acid, 0.1N (900 ml) and 0.01 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 ± 1^0C 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

Directly compressible vehicles can be prepared by various methods[14-16]. Co-processing is the one of the most widely explored and commercially utilized method for the preparation of directly compressible vehicles. Co-processing of excipients could lead to the formation of excipients with superior properties compared to the simple physical mixtures of their components. The objective of the present study is to prepare and characterize pregelatinized starch-poly vinyl pyrrolidone (PGS-PVP) co-processed excipient and to evaluate its application as directly compressible vehicle in tablet formulations.

PGS-PVP co-processed excipient was prepared by gelatinizing potato starch (49 parts) in the presence of PVP (1 part).The prepared PGS-PVP co-processed excipient was characterised by determining various physical and micromeritic properties. The PGS-PVP co-processed excipient prepared was found to be crystalline, discrete and free flowing powder. It could be ground to various particle sizes by grinding in a dry mortar. Particles of size -72+100 mesh (179.5 µm) were collected and used for further studies. The physical and micromeritic properties of

PGS-PVP co-processed excipient prepared are summarised in Table 1.

Table 1: Physical and Micromeritic Properties of PGS-PVP Co-processed Excipient

S.No.	Property/Test	Result
1.	Melting point	Charred at 250^{0}c
2.	Solubility	Insoluble in water, methanol, alcohol, acetone, chloroform, dichloromethane and petroleum ether
3.	Swelling Index (%)	High swelling in water Swelling index 284 %
4.	pH (1% aqueous dispersion)	6.8
5.	Particle size (µm)	72/100 mesh (179.5 µm)
6.	Bulk density (g/cc)	0.436
7.	Tapped density (g/cc)	0.464
8.	Angle of repose (^{o})	24.40
9.	Compressibility index (%)	7.8

The PGS-PVP co-processed excipient prepared was charred at 250^{0}C.It is insoluble in water and aqueous fluids of pH 1.2, 4.5 and 7.4 and also in several organic solvents such as alcohol, methanol, dichloromethane, acetone, chloroform and petroleum ether. It exhibited high swelling in water and the swelling index was found to be 284%.

The flow properties of the PGS-PVP co-processed excipient prepared were determined by measuring bulk density, angle of repose and compressibility index. The results given in Table 1 indicated that the excipient prepared has excellent flow properties. A directly compressible vehicle should be free flowing. Flowability is required in order 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 die cavities with reproducibility of ± 5%. As the PGS-PVP co-processed excipient possesses excellent flow properties, it is considered as a promising directly compressible vehicle for direct compression of tablets. Blends of PGS-PVP co-processed excipient and selected drugs (efavirenz, ritonavir and stavudine) also exhibited excellent to good flow properties. The estimated bulk density values of PGS-PVP co-processed excipient would also contribute to its good flow.

To evaluate the PGS-PVP co-processed excipient 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 PGS-PVP co-processed excipient as DCV at strength of 60% in the formula. The tablets were prepared as per the formulae given Table 2. 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 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 the PGS-PVP co-processed excipient were of good quality with regard to drug content ,hardness, friability and disintegration time.

Table 2: Formulae of Tablets Prepared By Direct Compression Method Employing PGS-PVP Co- processed Excipient

Ingredient (mg/tablet)	Tablet Formulation		
	Efavirenz	Ritonavir	Stavudine
Efavirenz	100	-	-
Ritonavir	-	100	-
Stavudine	-	-	30
PGS-PVP Co-processed excipient (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 3: Physical Properties of Various Tablets Prepared By Direct Compression Method Employing PGS-PVP Co-processed Excipient

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

The results of the dissolution rate study are given in Table 4.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 4: Dissolution Rate of Various Tablets Formulated by Direct Compression Method Employing PGS-PVP Co-processed Excipient 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)

CONCLUSION

PGS-PVP co-processed excipient prepared by gelatinizing potato starch (49 parts) in the presence of PVP (1 part) is a crystalline, discrete and free flowing powder. It is insoluble in water and aqueous fluids of pH 1.2, 4.5 and 7.4 and in several organic solvents. It exhibited high swelling (284%) in water. PGS-PVP co-processed excipient has excellent flow properties alone and as blends with selected drugs it exhibited excellent to good flow properties. Tablets of (i) efavirenz (ii) ritonavir and (iii) stavudine prepared by direct compression method employing PGS-PVP co-processed excipient as DCV were of good quality with regard to drug content, hardness, friability and disintegration time. All the tablets formulated disintegrating 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. Thus PGS-PVP co-processed excipient developed in this study was found to be a promising directly compressible vehicle for the preparation of tablets of antiretroviral drugs.

REFERENCES

1. Shangraw RF. Direct Compression Tableting, Encyclopedia of Pharmaceutical Technology. Newyork: Marcel Dekker, USA, Edition 2, Vol.4, 1988: 85-160.
2. Armstrong NA. Selection of excipients for direct compression tablet formulation. Pharm.Technol.Eur.1989; 24-30.
3. Jivraj M, Martini LG and Thomson CM. An Overview of the Different Excipients Useful for the Direct Compression of Tablets. PSTT. 2000;3:58-63.
4. Rubinstein MH: Tablets. Pharmaceutics: The Science of Dosage of Form. Churchill, UK, Edition 1, 1998;304-321.
5. Banker UV. Role of Ingredients and Excipients in Developing Pharmaceuticals. Manuf Chem.1994; 65: 32-34.
6. Armstrong NA and Palfrey LP. The Effect of Machine Speed on the Consolidation of Four Directly Compressible Tablet Diluents. J Pharm Pharmacol. 1989;41:149-151.

7. Reimerdes D.The Near Future of Tablet Excipients. Manufacturing Chemist. 1993; 64(7):14-15.
8. Dev KM. Coprocessed Microcrystalline Cellulose and Calcium Carbonate and Its Preparation. US Patent No.4, 744, 987 to FMC Corporation (Philadelphia,PA) 1988.
9. Bolhius GK and Chowhan ZT. Materials for Direct Compaction. Pharmaceutical Powder Compaction Technology. G.Alderborn and C.Nystron, Eds. Marcel Dekker Inc., New York, NY, 1996;419-500.
10. Chowdary KPR and Sunil Kumar. Formulation development of selected drugs by direct compression method. IJPRD. 2011;3(6):273-279.
11. Martin A: Physical Pharmacy. Lippincott Williams &Wilkins. Baltimore, 2001:423-454.
12. Cooper J and Gunn C. Powder flow and compaction. Tutorial Pharmacy. CBS Publications, New Delhi, India.1986;211-233
13. Aulton ME and Wells TI: Pharmaceutics; The Science of dosage form design. Churchill Livingstone, London, England, Edition 2,1988;89-90.
14. Reimedes D. The Near Future of Tablet Excipients. Manuf chem. 1993;64:14-15.
15. Shangraw RF, Wallace JW and Bowes FM. Morphology and functionality in Tablet Excipients for Direct Compression. Pharm. Technol. 1987;11:136-143.
16. Bolhuis GK and Chowhan ZT. Materials for Direct Compression. Pharmaceutical Powder Compaction Technology. Marcel Dekker, USA. 1996:7:419-499.