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EVALUATION OF A NEW COPROCESSED EXCIPIENT AS CARRIER FOR ENHANCING THE DISSOLUTION RATE OF POORLY SOLUBLE BCS CLASS II DRUGS

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ABSTRACT

The objective of the present study is to prepare and characterize a new co-processed excipient namely pre-gelatinized starch - PEG 1500 – Aerosil (PGS-PEG-Aerosil) and to evaluate its application as a carrier in solvent deposited (SD) dispersions for enhancing the dissolution rate of two poorly soluble BCS class II drugs namely (i) aceclofenac and (ii) valdecoxib from SD dispersions and their tablet formulations.SD dispersions of (i) aceclofenac and (ii) valdecoxib in PGS-PEG-Aerosil were prepared by kneading method. Different proportions of drug: excipient such as 4:1, 2:1 and 1:1 were used in each case to prepare SD dispersions.Tablets of (i) Aceclofenac (50mg) and (ii) Valdecoxib (50 mg) were prepared employing SD dispersions in PGS-PEG-Aerosil and commonly used tablet excipients by wet granulation method and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate.

The SD dispersions prepared were fine, discrete and free flowing powders. Low CV (< 1.5%) values ensured uniformity of the drug content in each batch of SD dispersion prepared.All SD dispersions of (i) aceclofenac and (ii) valdecoxib in PGS-PEG-Aerosil gave rapid and higher dissolution of the contained drug when compared to the corresponding pure drug. As the proportion of carrier in the SD dispersions was increased the dissolution rate was also increased. Drug dissolution from SD dispersions followed first order kinetics with both aceclofenac and valdecoxib. A 6.05 - 20.60 fold and a 14.92- 30.00 fold increase in the dissolution rate (K1) was observed respectively with SD dispersions of aceclofenac and valdecoxib. SD dispersions in PGS-PEG-Aerosil could be formulated into tablets by wet granulation method and the resulting tablets fulfilled the official specifications with regard to drug content, hardness, friability and disintegration time. All the tablets prepared disintegrated rapidly within 1-2 min and gave rapid dissolution of the contained drug, aceclofenac or valdecoxib. All aceclofenac tablets formulated employing SD dispersions fulfilled the official (IP 2010) dissolution rate specification of NLT 70% in 45 min prescribed for aceclofenac tablets.

The dissolution rate of (i) aceclofenac and (ii) valdecoxib could be markedly enhanced by solvent deposition on the new co-processed excipient (PGS-PEG-Aerosil) developed. SD dispersions of (i) aceclofenac and (ii) valdecoxib in the new co-processed excipient (PGS-PEG-Aerosil) could be compressed into tablets retaining their fast dissolution characteristics.

Key Words: Co-processing, Excipients, Aceclofenac, Valdecoxib, Solvent Deposition, Tablets, Dissolution Rate

INTRODUCTION

Co-processing is one of the most widely explored and commercially utilized method for the preparation of pharmaceutical excipients[1]. 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[2]. The objective of the present study is to prepare and characterize a new co-processed excipient namely pre-gelatinized starch - PEG 1500 – Aerosil (PGS-PEG-Aerosil) and to evaluate its application as a carrier in solvent deposited (SD) dispersions for enhancing the dissolution rate of two poorly soluble BCS class II drugs namely (i) aceclofenac and (ii) valdecoxib from SD dispersions and their tablet formulations.

Aceclofenac and valdecoxib are two widely prescribed anti-inflammatory analgesic drugs having poor solubility in water and fluids of physiological pH. As such they exhibit low

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dissolution rates leading to low and variable oral bioavailability and need enhancement in dissolution rate in their tablet formulation development to derive their maximum therapeutic efficacy. In the present study SD dispersions of these two drugs in a new co-processed excipient namely Pregelatinized starch- polyethylene glycol 1500- Aerosil (PGS-PEG-Aerosil) were prepared with a view to enhance their dissolution rates. The feasibility of formulating the SD dispersions in PGS-PEG-Aerosil into tablets with fast dissolution characteristics was also evaluated.

EXPERIMENTAL

Materials

Aceclofenacand valdecoxib were gift samples from M/s Hetero Drugs Ltd., Hyderabad. Rice starch(I.P.), Poly ethylene glycol 1500, Aerosil,Crospovidone, PVP K 30and lactose were procured from commercial sources.All other materials used were of Pharmacopoeial grade.

Preparation of PGS-PEG-Aerosil Co-processed Excipient:

Rice starch (15 parts) and PEG 1500 (5 parts) and Aerosil (0.4 parts) were dispersed in 40 parts of water to form smooth slurry. Purified water (40 parts) was taken in a separate beaker and heated to boiling. Starch-PEG-Aerosil slurry was added to boiling water while stirring. Stirring and heating was continued for 15 to 20 minutes to form a thick mass. To the mass formed, acetone (40 parts) was added and mixed thoroughly to remove the water in the product formed. The product formed was collected by filtration and further dried at 85^{o}C until dry. The dried product was grinded and sized to obtain -36+80 mesh (302.5 µm) sized particles.

Estimation of Aceclofenac:

An UV spectrophotometric method based on the measurement of absorbance at 275nm in phosphate buffer of pH 6.8 was used for the estimation of aceclofenac. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 1-10 µg/ml. Low RSD values (less than 1.7%) ensured reproducibility of the method. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.95 % and 1.4 % respectively. No interference by excipients used in the study was observed.

Estimation of Valdecoxib:

An UV spectrophotometric method based on the measurement of absorbance at 246 nm in of 0.1 N hydrochloric acid was used for the estimation of valdecoxib. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 1-10 µg/ml. Low RSD values (less than 1.4%) ensured reproducibility of the method. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.1 % and 1.73 % respectively. No interference by excipients used in the study was observed.

Preparation of Solvent Deposited (SD) Dispersions:

Solvent deposited dispersions of (i) aceclofenac and (ii) valdecoxib in the new co-processed excipient developed (PGS-PEG-Aerosil) were prepared by kneading method. Solvent deposited dispersions in each case were prepared at 4:1, 2:1 and 1:1 ratios of drug: excipient.

The required quantity of drug was dissolved in the solvent alcohol (10 ml) to get a clear solution in a dry mortar. The excipient, PGS_PEG-Aerosil, powder (80 mesh) was added to the drug solution in the mortar and mixed. The mixture was kneaded for 30 min by continuous tirturation. Small volume of the solvent was added to maintain the mixture as a thick slurry during kneading process. Tirturation was continued until a dried mass was obtained. The mass obtained was further dried at 45^{0}c for 1 h in a hot air oven. The dried product was powdered and passed through mesh number 100.

Estimation of Drug Content of SD Dispersions:

SD dispersion 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 upto 100 ml with methanol. The solution was then suitably diluted with phosphate buffer of pH 6.8 in the case of aceclofenac and with 0.1 N HCl in the case of valdecoxib. The absorbance of the solutions was measured at

275nm in the case of aceclofenac and at 246nm in the case of valdecoxib. Drug content of the SD dispersions was calculated using the standard calibration curve in each case.

Preparation of Tablets Employing SD Dispersions:

SD dispersions of aceclofenac and valdecoxib in the new co-processed excipient (PGS-PEG-Aerosil) were compressed into tablets along with commonly used tablet excipients. The tablets were prepared by wet granulation method as per the formulae given in Table 1.

The required quantities of SD dispersions, lactose and PVP as per the formula were blended thoroughly in a dry mortar. The blend of powders was then mixed with water (qs.) to obtain a dough mass. The wet mass was pressed through mesh number 12 to obtain wet granules. The wet granules were dried at 70^0C for 1 h. The dried granules were passed through mesh number 14 to break the aggregates and to obtain discrete granules. Superdisinte grantcro spovidone, talc and magnesium stearate were passed through mesh number 60 and blended with the dried tablet granules. The tablet granules were compressed into 250 mg tablets on a 8- station rotary tablet punching machine (Karnavathi "RIMEK" minipress II) to a hardness of 3-4 kg/cm^2. The prepared tablets were evaluated for dug content, hardness, friability, disintegration time and dissolution arte characteristics.

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 single unit disintegration test apparatus (Make: Paramount) using water as a test fluid.

Dissolution Rate Study on SD Dispersions and Their Tablets:

Dissolution rate of the SD dipersions and their 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 6.8 (900ml) and 0.1N HCl (900ml) were used as dissolution fluids for aceclofenac and valdecoxib respectively. SD dispersion equivalent to 50 mg of drug or one tablet containing 50 mg of drug was used in each test. A temperature 37 ± 1^0c was maintained throughout. Samples of dissolution medium (5ml) were withdrawn through a filter (0.45 µ) at different time intervals and assayed for aceclofenac at 275 nm and for valdecoxib at 246 nm. All the dissolution experiments were conducted in triplicate (n=3).

Analysis of Data:

Dissolution data were analyzed as per zero order and first order kinetics. Dissolution rates (K_1) were estimated from the slope of the first order linear plots. Dissolution efficiency (DE_{30}) values were estimated as suggested by Khan[3].

RESULTS AND DISCUSSION

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.

PGS-PEG-Aerosil, a new co-processed excipient was prepared by gelatinizing rice starch in the presence of PEG 1500 and Aerosil and drying the resulting mass and 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 the resukts are reported earlier [4].

In the present study the new co-processed excipient developed (PGS-PEG-Aerosil) was evaluated as a "carrier" in SD dispersions for enhancing the dissolution rate of two poorly soluble BCS class II drugs namely (i) Aceclofenac and (ii) Valdecoxib. SD dispersions of the selected drugs in PGS-PEG-Aerosil were prepared by kneading method. Different proportions of drug: excipient such as 4:1, 2:1 and 1:1 were used in each case to prepare SD dispersions. The SD dispersions prepared were fine, discrete and free flowing powders. The drug content of the SD dispersions was found to be within 100±5% of

the theoretical amount. Low CV (< 1.5%) values ensured uniformity of the drug content in each batch of SD dispersion prepared.

The dissolution rate of (i) aceclofenac and (ii) valdecoxib from the SD dispersions prepared was studied in phosphate buffer of pH 6.8 and 0.1N hydrochloric acid respectively.The dissolution profiles of SD dispersions of aceclofenac and valdecoxib are shown in Figs.1and 2. The dissolution parameters of the SD dispersions prepared are given in Table1.

All the SD dispersions of (i) aceclofenac and (ii) valdecoxib in PGS-PEG-Aerosil gave rapid and higher drug dissolution when compared to the corresponding pure drug. As the proportion of carrier in the SD dispersions was increased the dissolution rate was also increased in both the cases. Drug dissolution from SD dispersions followed first order kinetics with co-efficient of determination (R^2) values greater than 0.936 in all the cases. All the dissolution parameters estimated (PD_{10}, T_{50}, DE_{30} and K_1) indicated rapid dissolution of aceclofenac and valdecoxib from the SD dispersions prepared when compared to pure drug. A 6.05, 15.13 and 20.60 fold increase in the dissolution rate (K_1) of aceclofenac was observed with SD dispersions ASD1, ASD2, ASD3 respectively when compared to that of pure drug (F1). A 14.92, 18.40 and 30.00 fold increase in the dissolution rate (K_1) of valdecoxib was observed with SD dispersions VSD1, VSD2, VSD3 respectively when compared to that of pure drug (F2).Thus the dissolution rate of both aceclofenac and valdecoxib could be markedly enhanced by solvent deposition on the new co-processed excipient (PGS-PEG-Aerosil) developed.

The feasibility of formulating SD dispersions in PGS-PEG-Aerosil excipient in to compressed tablets with fast dissolution characteristics was also evaluated. Aceclofenac (50mg) tablets and Valdecoxib (50 mg) tablets were formulated employing SD dispersions in PGS-PEG-Aerosil and commonly used tablet excipients as per the formulae Table 2. The tablets were prepared by wet granulation method and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate. Formulations ASF1 and VSF1 were prepared using crospovidone, a superdisintegrant and ASF2 and VSF2 were prepared without crospovidone. Formulations AC and VC were prepared using drug alone (control) in each case.

All the tablets prepared contained drug within 100 ± 3% of the labeled claim. Hardness of the tablets was in the range 3.2-5.0 kg/cm^2. Weight loss in the friability was less than 0.648 %. All the aceclofenac and valdecoxib tablets formulated employing SD dispersions in PGS-PEG-Aerosil excipient disintegrated rapidly within 1 min 50 sec. Formulations ASF2 and VSF2 prepared without using superdisintegrant also disintegrated rapidly with in 1min 10 sec. The rapid disintegration observed with ASF2 and VSF2 formulations is due to the high swelling nature of the new co-processed excipient used as carrier in the SD dispersions.

The dissolution parameters of various tablets prepared are given in Table 3. All dissolution parameters estimated (PD_{10},T_{50},DE_{30} and K_1) indicated rapid and higher dissolution of drug from the tablets formulated employing SD dispersions with both aceclofenac and valdecoxib when compared to control formulations.All aceclofenac tablets formulated and commercial fulfilled the official (IP 2010) dissolution rate specification of NLT 70% in 45 min prescribed for aceclofenac tablets. Thus the results of the study indicated that SD dispersions of (i) aceclofenac and (ii) valdecoxib in the new co-processed excipient (PGS-PEG-Aerosil) developed could be compressed into tablets retaining their fast dissolution characteristics.

CONCLUSIONS

1. The SD dispersions prepared were fine, discrete and free flowing powders. Low CV (< 1.5%) values ensured uniformity of the drug content in each batch of SD dispersion prepared
2. All SD dispersions of (i) aceclofenac and (ii) valdecoxib in PGS-PEG-Aerosil gave rapid and higher dissolution of the contained drug when compared to the corresponding pure drug.
3. As the proportion of carrier in the SD dispersions was increased the dissolution rate was also increased.
4. Drug dissolution from SD dispersions followed first order kinetics with both aceclofenac and valdecoxib.

5. A 6.05 - 20.60 fold and a 14.92- 30.00 fold increase in the dissolution rate (K_1) was observed respectively with SD dispersions of aceclofenac and valdecoxib.
6. SD dispersions in PGS-PEG-Aerosil could be formulated into tablets by wet granulation method and the resulting tablets fulfilled the official specifications with regard to drug content, hardness, friability and disintegration time.
7. All the tablets prepared disintegrated rapidly within 1-2 min and gave rapid dissolution of the contained drug, aceclofenac or valdecoxib.
8. All aceclofenac tablets formulated employing SDdispersions fulfilled the official (IP 2010) dissolution rate specification of NLT 70% in 45 min prescribed for aceclofenac tablets.
9. The dissolution rate of (i) aceclofenac and (ii) valdecoxib could be markedly enhanced by solvent deposition on the new co-processed excipient (PGS-PEG-Aerosil) developed. SD dispersions of (i) aceclofenac and (ii) valdecoxib in the new co-processed excipient (PGS-PEG-Aerosil) could be compressed into tablets retaining their fast dissolution characteristics.

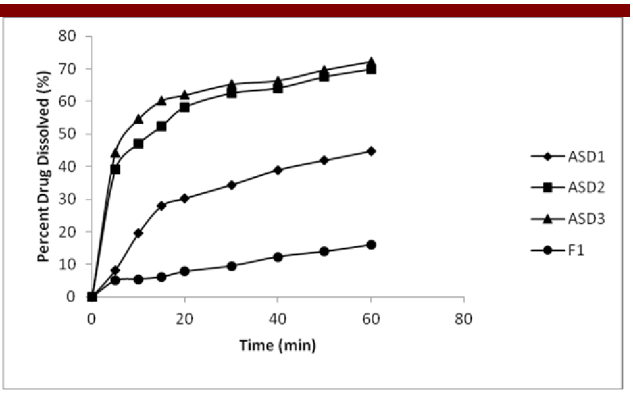

Fig. 1: Dissolution Profiles of SD Dispersions of Aceclofenac in PGS-PEG-Aerosil Co-processed Excipient

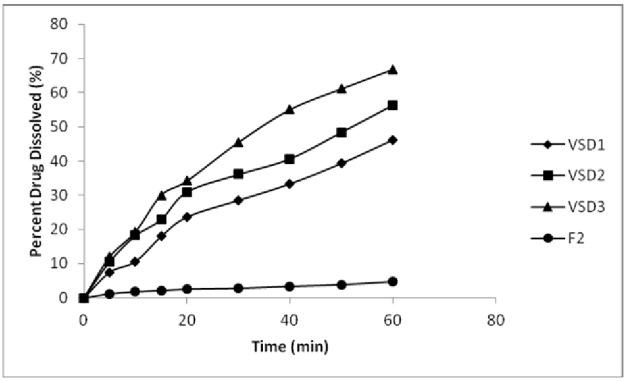

Fig.2: Dissolution Profiles of SD Dispersions of Valdecoxibin PGS-PEG-Aerosil Co-processed Excipient

Table 1: Dissolution Parameters of SD Dispersions of
(i) Aceclofenac and
(ii) Valdecoxib in PGS-PEG –Aerosil Co-Processed Excipient

Formulation	PD_{10} (%)	T_{50} (min)	DE_{30} (%)	Dissolution Rate K_1 (min^{-1})	Increase in K_1 (no. of folds)
F1	5.47	> 60	6.31	0.0038	-
ASD1	19.48	> 60	18.49	0.0230	6.05
ASD2	47.01	13	48.06	0.0575	15.13
ASD3	54.57	8	52.86	0.0783	20.60
F2	1.78	> 60	1.970	0.00069	-
VSD1	10.68	> 60	16.71	0.01030	14.92
VSD2	18.21	53	22.38	0.01270	18.40
VSD3	19.31	35	26.34	0.0207	30.00

Table 2: Formulae of Tablets Prepared Employing SD Dispersions of Aceclofenac and Valdecoxib in the New Co-Processed Excipient (PGS-PEG-Aerosil)

Ingredient (mg/tablet)	FORMULATIONS					
	AC	ASF1	ASF2	VC	VSF1	VSF2
Aceclofenac	50	-	-	-	-	-
Aceclofenac new DCV (1:1) SD	-	100	100	-	-	-
Valdecoxib	-	-	-	50	-	-
Valdecoxib new DCV (1:1) SD	-	-	-	-	100	100
Lactose	175	125	135	175	125	135
PVP	5	5	5	5	5	5
Crospovidone	10	10	-	10	10	-
Talc	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5
Total weight(mg)	250	250	250	250	250	250

Table 3: Dissolution Parameters of (i)Aceclofenac Tablets and (ii) Valdecoxib TabletsPrepared Employing SD Dispersions of Aceclofenac in the New Co-Processed Excipient (PGS-PEG-Aerosil)

Formulation	PD_{10} (%)	PD_{45} (%)	T_{50} (min)	DE_{30} (%)	Dissolution Rate K_1 (min^{-1})	Official dissolution rate test specification
ASF1	65.99	90.63	4.5	65.50	0.0736	NLT 70 % of the stated amount in 45 min
ASF2	35.35	89.11	14.5	24.70	0.0515	
AC	36.42	91.83	14.5	23.71	0.0552	
AFENAK	51.28	74.56	9.5	51.74	0.0227	
VSF1	28.47	56.20	37.5	14.73	0.0160	No Official Dissolution Rate Test
VSF2	11.53	31.20	> 60	13.76	0.0078	
VC	12.62	23.52	> 60	14.56	0.0039	

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