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PREPARATION, CHARACTERIZATION AND EVALUATION OF A NEW CO-PROCESSED EXCIPIENT AS DIRECTLY COMPRESSIBLE VEHICLE IN TABLET FORMULATION

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ABSTRACT

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. The objective of the present study is to prepare and characterize pregelatinised starch-polyethylene glycol 1500-Aerosil (PGS-PEG-Aerosil) co-processed excipient and to evaluate its application as directly compressible vehicle in tablet formulations. PGS-PEG-Aerosil 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, P^H and micromeritic characters namely particle size, bulk density, tapped density, angle of repose and compressibility index and evaluated for its application as directly compressible vehicle in tablet formulations.

The new co-processed excipient prepared was crystalline, discrete, fine 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 (500%) in water. The new excipient developed (PGS- PEG-Aerosil) exhibited excellent flow properties alone and as blends with selected drugs. Tablets of i) Paracetamol, ii) Aceclofenac and iii) Sulphamethoxazole prepared employing PGS-PEG-Aerosil co-processsed excipient alone as directly compressible vehicle were found to be soft and fragile. Blends of PGS-PEG-Aerosil co-processed excipient-Lubritose (1:1) and PGS-PEG-Aerosil co-processed excipient-Starch 1500 (1:1) exhibited good flow characteristics.Tablets of i)Paracetamol, ii)Aceclofenac and iii)Sulphamethoxazole prepared by direct compression method employing blends (1:1) of PGS-PEG-Aerosil co-processed excipient with Lubritose and Starch-1500 as directly compressible vehicles were found to be of good quality with regard to drug content, hardness, friability, disintegration time and dissolution rate. All the tablets disintegrated rapidly within 15-30 sec and gave rapid dissolution of the contained drug fulfilling the official dissolution rate test specification prescribed in each case. Thus PGS-PEG-Aerosil co-processed excipient developed was found to be a promising directly compressible vehicle for the preparation of compressed tablets with fast dissolution characteristics.

Key words: Co-processing, Direct compression, Directly compressible vehicles, Tablets, Paracetamol, Sulphamethoxazole, Aceclofenac

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.

Direct compression requires excipients with good flowability and compressibility. Though,

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several directly compressible vehicles such as Ludipress(lactose, PVP, Crosspovidone), Pharmatose DCL 40 (anhydrous lactose, lactitol), Avicel CE 15 (MCC, guar gum), Di-Pac (sucrose, dextrin) etc., are available; there is a continued need to develop new and efficient directly compressible vehicles. Literature on directly compressible vehicles and their application in formulation development is rather scanty.

Co-processing is one of the most widely explored and commercially utilized methods for the preparation of directly compressible vehicles[6]. 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 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 directly compressible vehicle in the formulation development of selected drugs by direct compression method.

EXPERIMENTAL

Materials:

Paracetamol, sulphamethoxazole and aceclofenac were gift samples from M/s Hetero Drugs Ltd., Hyderabad. Rice starch (I.P.), Poly ethylene glycol 1500, Aerosil, Lubritose SD, Starch 1500, croscarmellose sodium was procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Methods:

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.

Characterization of New Co-Processed Excipient Prepared:

The new co-processed excipient prepared was evaluated for the following:

Solubility:

Solubility of PGS-PEG-Aerosil coprocessed excipient 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 1% w/v slurry was measured.

Melting Point:

Melting point was determined by using melting point apparatus (Digimelt).

Swelling Index[8]:

The new excipient prepared(200 mg) was added to 10 ml of water and light liquid paraffin taken in two different graduated test tubes and mixed. The dispersions in the tubes were allowed to stand for 12 h. The volume of the sediment in the tubes was recorded. The swelling index of the material was calculated as follows.

$$S.I\ (\%) = \frac{\text{Volume of sediment in water} - \text{Volume of sediment in light liquid paraffin}}{\text{Volume of sediment in light liquid paraffin}} X100$$

Moisture Absorption:

The hygroscopic nature of the new excipient prepared was evaluated by moisture absorption studies in a closed desiccator at 84% relative humidity and room temperature.

Particle Size:

Particle size analysis was done by sieving using standard sieves.

Density:

Density (g/cc) was determined by liquid displacement method using benzene as liquid.

Bulk Density[9]:

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

Angle of Repose[10]:

Angle of repose was measured by fixed funnel method.

Compressibility Index[11]:

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

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

Estimation of Paracetamol:

An UV spectrophotometric method based on the measurement of absorbance at 253 nm in phosphate buffer of pH 5.8 was used for the estimation of paracetamol. 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. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.8 % and 1.2 % respectively. No interference by excipients used in the study was observed.

Estimation of Sulphamethoxazole:

An UV spectrophotometric method based on the measurement of absorbance at 254 nm in 0.1 N HCl was used for the estimation of sulphamethoxazole. 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. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 1.1 % and 1.6 % respectively. No interference by excipients used in the study was observed.

Estimation of Aceclofenac:

An UV spectrophotometric method based on the measurement of absorbance at 275 nm 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. 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.

Preparation of Tablets by Direct Compression Method:

Tablets of (i) paracetamol (120 mg) (ii) sulphamethoxazole (100 mg) and (iii) aceclofenac (100 mg) were prepared by direct compression method as per the formulae given in the Table 2 employing PGS-PEG-Aerosil co-processed excipient as directly compressible vehicle. All the materials required as per the formula were blended in a closed polyethylene bag. The blends were directly compressed into tablets on a 10-station tablet punching machine (Rimek) to a hardness of 3-4 kg/cm^2 using 12 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 single unit disintegration test apparatus (Make: Paramount) using water as a test fluid.

Estimation of Drug Content in the Tablets:

From each batch of tablets prepared 10 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 upto 100 ml with methanol. The solution was then suitably diluted with phosphate buffer of pH 5.8 in case of paracetamol, with 0.1 N HCl of in the case of sulphamethoxazole and with phosphate buffer of pH 6.8 in the case of aceclofenac. The absorbance of the solutions was measured at 253 nm, 254 nm and 275nm respectively in the cases of paracetamol, sulphamethoxazole and aceclofenac. 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 5.8 (900ml), 0.1N HCl (900ml), phosphate buffer of pH 6.8 (900ml) were used as dissolution fluids for paracetamol, sulphamethoxazole and aceclofenac

respectively. One tablet was used in each test. A temperature 37±1^{0}c was maintained throughout. Samples of dissolution medium (5ml) were withdrawn through a filter (0.45 µ) at different time intervals and assayed for paracetamol at 253 nm, for sulphamethoxazole at 254 nm and for aceclofenac at at 275 nm. All the dissolution experiments were conducted in triplicate (n=3).

RESULTS AND DISCUSSION

Directly compressible vehicles are prepared by various methods[12-14]. Co-processing is one of the most widely explored and commercially utilized methods 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.

PGS-PEG-Aerosil co-processed excipient was prepared by gelatinizing rice starch (15 parts) in the presence of PEG 1500 (5 parts) and Aerosil (0.4 parts) The prepared PGS-PEG-Aerosil co-processed excipient was characterized by determining various physical and micromeritic properties. The PGS-PEG-Aerosil co-processed excipient prepared was found to be crystalline, discrete and free flowing powder. It could be grinded to various particle sizes in a dry mortar. Particles of size -36 +80 mesh (302.5 µm) were collected and used for further studies. The physical and micromeritic properties of PGS-PEG-Aerosil co-processed excipient prepared are summarized in Table 1 .

The PGS-PEG-Aerosil co-processed excipient prepared was charred at 220^{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 500%.

The flow properties of the PGS-PEG-Aerosil 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 new excipient prepared has excellent flow properties.

Directly compressible vehicles 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-PEG-Aerosil co-processed excipient possesses excellent flow properties, it is considered as a promising directly compressible vehicle for direct compression of tablets. Blends of PGS-PEG-Aerosil co-processed excipient and selected drugs (paracetamol, sulphamethoxazole and aceclofenac) also exhibited excellent to good flow properties.. The estimated bulk density values of PGS-PEG-Aerosil co-processed excipient would also contribute to its good flow.

Tablets of (i) Paracetamol (120 mg) (ii) Sulphamethoxazole (100 mg) and (iii) Aceclofenac (100 mg) were prepared by direct compression method employing the new DCV developed (PGS- PEG-Aerosil) alone and in combination with other commercial DCVs as per the formulae given in 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 Tables 3-4. Tablets prepared by direct compression method employing the new DCV developed (PGS- PEG-Aerosil) alone (PF1,SF1 and AF1) were found to be very soft and fragile and these tablets disintegrated within 10-20 sec with all the three drugs. As such the new DCV developed alone is considered not suitable for preparing tablets by direct compression method. Blends of new DCV and two commercial DCVs (Lubritose SD and Starch 1500) in 1:1 ratio were tried for preparing tablets by direct compression method. The physical parameters of tablets prepared by direct compression method employing blends of new DCV and commercial DCVs are given in Table 3.

Hardness of these tablets (PF2, PF3, SF2, SF3, AF2 and AF3) was in the range 2.0-2.5 Kg / sq. cm. Weight loss in the friability test was in the range 0.42-0.70 %. The drug content of the tablets was within 100 ± 3% of the labeled claim. All the tablets prepared by direct compression method employing blends of new DCV and commercial DCVs disintegrated very rapidly.

The disintegration time of these tablets was in the range 40-140 sec. Thus tablets of good quality with regard to drug content, hardness, friability and disintegration time could be prepared by direct compression method employing blends of new DCV and the two commercial DCVs in 1:1 ratio.

The results of dissolution rate study are given in Table 4 and Fig 1. All the tablets formulated employing blends (1:1) of new and commercial DCVs and prepared by direct compression method gave rapid dissolution of the contained drug. 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 models indicating that the drug dissolution from all the tablets formulated followed first order kinetics. The corresponding first order dissolution rate constants (K_1) were estimated from the slope of the first order linear plots. Dissolution efficiency (DE_{30}) values were determined as suggested by Khan[15]. The dissolution parameters are summarized in Table 4. All the tablets formulated employing blends of new and commercial DCVs gave rapid and higher dissolution of the contained drug. Paracetamol tablets (PF2 and PF3) gave more than 80% dissolution in 30 min fulfilling the official (IP 2010) dissolution rate test specification of paracetamol tablets.

Sulfamethoxazole tablets (SF2 and SF3) gave more than 95 % dissolution in 30 min fulfilling the official (USP 2008) dissolution rate test specification of NLT 80% in 30 min. In the case of aceclofenac tablets, formulation (AF2) gave 73 % dissolution in 45 min fulfilling the official (IP 2010) dissolution rate test specification of NLT 70% in 45 min. Whereas aceclofenac tablets formulated employing blend of new DCV and Starch 1500 (AF3) gave dissolution less than the official dissolution rate prescribed. Paracetamol and aceclofenac tablets formulated employing blends of new and commercial DCVs (PF2, PF3, AF2, and AF3) gave higher dissolution of the contained drug when compared to the corresponding commercial brand tested.

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

PROPERTY	RESULT
Melting point	Charred at 220^0c
Solubility	Insoluble in water and aqueous fluid of acidic and alkaline pH
Swelling Index	500%
pH(1% Aqueous dispersion)	6.78
Particle size	36/80 mesh
Bulk density(g/cc)	0.748
Tapped Density(g/cc)	0.868
Angle of Repose	28.77
Compressibility Index	13.82

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

Ingredient (mg/tablet)	FORMULATIONS								
	PF1	PF2	PF3	SF1	SF2	SF3	AF1	AF2	AF3
Paracetamol	50	120	120	-	-	-		-	-
Aceclofenac	-	-	-	-	-	-	50	100	100
Sulfamethoxazole	-	-	-	50	100	100	-	-	-
New DCV	180	-	-	180	-	-	180	-	-
New DCV: Lubritose (1:1)	-	350	-	-	370	-	-	370	-
New DCV: Starch1500 (1:1)	-	-	350	-	-	370	-	-	370
Croscarmellose sodium	10	20	20	10	20	20	10	20	20
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
Total weight (mg)	250	500	500	250	500	500	250	500	500

Table 3: Physical Properties of Various Tablets Prepared by Direct Compression Method Employing PGS –PEG-Aerosil Co-processed Excipient

Formulation	Hardness (kg/cm^2)	Friability (%)	Disintegration Time (min-sec)	Drug content (mg/tab)
PF2	2.5	0.542	0-40	117.3
PF3	2.0	0.702	1-5	118.6
CROCIN	5.5	0.254	1-45	498
SF2	2.0	0.624	0-50	102.8
SF3	2.0	0.521	2-20	98.5
AF2	2.5	0.424	0-56	97.9
AF3	2.5	0.702	1-12	98.4
AFENAK	4.5	0.172	1-10	98.8

Table 4: Dissolution Parameters of Tablets Prepared by Direct Compression Method Employing PGS-PEG-Aerosil Co-processed Excipient and Commercial Tablets

Formulation	Dissolution Parameter				
	PD_{10} (%)	T_{50} (min)	DE_{30} (%)	K_1 (min^{-1})	official dissolution rate test specification
PF2	36.85	14	50.03	0.0687	NLT 80% of stated amount in 30 min (IP 2010)
PF3	35.60	15.5	49.74	0.0429	
CROCIN	32.04	18	47.53	0.0333	
SF2	83.50	3.5	80.55	0.1980	NLT 80% of labeled amount in 30 min(USP 2008)
SF3	69.56	3.0	73.87	0.1220	
AF2	53.93	8.5	52.96	0.0255	NLT 70% of the stated amount in 45 min (IP 2010)
AF3	50.44	10	49.82	0.0181	
AFENAK	51.28	9.5	51.74	0.0227	

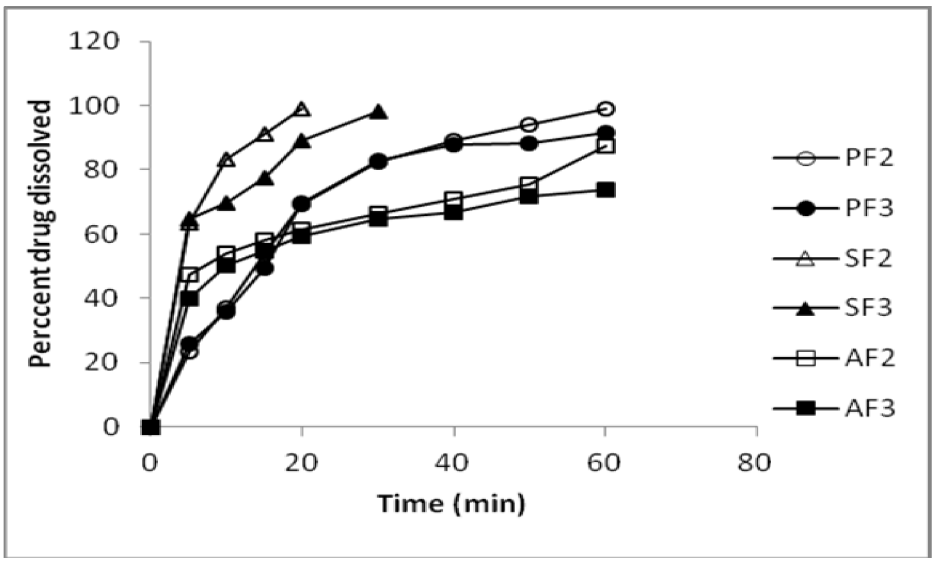

Fig. 1: Dissolution Profiles of Tablets Prepared by Direct Compression Method Employing PGS-PEG-Aerosil Co-processed Excipient

CONCLUSIONS

1. The new co-processed excipient prepared was crystalline, discrete, fine and free flowing powder.
2. It is insoluble in water and aqueous fluids of pH 1.2, 4.5 and 7.4 and in several organic solvents.
3. It exhibited high swelling (500%) in water.
4. The new excipient developed (PGS- PEG-Aerosil) exhibited excellent flow properties alone and as blends with selected drugs.
5. Tablets of i) Paracetamol, ii) Aceclofenac and iii) Sulphamethoxazole prepared employing PGS-PEG-Aerosil co-processsed excipient alone as directly compressible vehicle were found to be soft and fragile.
6. Blends of PGS-PEG-Aerosil co-processed excipient-Lubritose (1:1) and PGS-PEG-Aerosil co-processed excipient-Starch 1500 (1:1) exhibited good flow characteristics.
7. Tablets of i)Paracetamol, ii)Aceclofenac and iii)Sulphamethoxazole prepared by direct compression method employing blends (1:1) of PGS-PEG-Aerosil co-processed excipient with Lubritose and Starch-1500 as directly compressible vehicles were found to be of good quality with regard to drug content, hardness, friability, disintegration time and dissolution rate.
8. All the tablets disintegrated rapidly within 15-30 sec and gave rapid dissolution of the contained drug fulfilling the official dissolution rate test specification prescribed in each case.
9. Thus PGS-PEG-Aerosil co-processed excipient developed was found to be a promising directly compressible vehicle for the preparation of compressed tablets with fast dissolution characteristics.

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