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"Preparation, Characterization, and Evaluation of a Novel Co-Processed Excipient as a Directly Compressible Vehicle in Antihypertensive Tablet Formulation"

Binit Patel 1 *, Pravinkumar Darji 2 , Arpan Chudasama 3 , Praneeth Ivan Joel Fnu 4 Seshadri Nalla 5

1. Hovione, East Windsor, New Jersey, USA-08520

2. Exemplify Biopharma Inc., Cranbury, New Jersey, USA – 08512

3. Navinta LLC Formulation and Research and Development, Ewing, New Jersey,USA-08618

4. Exemplify Biopharma Inc., Cranbury, New Jersey, USA – 08512

5. Lamar University, 4400 S M king Jr PKWY, Beaumont, Texas, USA-77705

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ABSTRACT:
Direct compression stands out as the preferred method for tablet preparation, with co-processing being extensively explored and commercially employed for creating directly compressible vehicles. This study aims to synthesize and characterize pregelatinized starch-polyvinylpyrrolidone (PGS-PVP) co-processed excipient and assess its suitability as a directly compressible vehicle for formulating tablets containing nifedipine, an anti-hypertensive drug. The PGS-PVP co-processed excipient was produced by gelatinizing potato starch in the presence of PVP and subsequently drying the resultant mass. Characterization involved determining melting point, solubility, water swelling index, pH, and micromeritic properties such as particle size, bulk density, tapped density, angle of repose, and compressibility index, followed by evaluation of its application in tablet formulations. The PGS-PVP co-processed excipient, comprising gelatinized potato starch (49 parts) and PVP (1 part), exhibited a crystalline, discrete, and free-flowing powder nature. It demonstrated insolubility in water, aqueous solutions with pH 1.2, 4.5, and 7.4, as well as various organic solvents. Remarkably, it displayed high water swelling capacity (280%). Alone and in blends with nifedipine, it showcased excellent to good flow properties. Tablets containing Nifedipine (60 mg) prepared via direct compression using PGS-PVP co-processed excipient as the directly compressible vehicle showed satisfactory quality attributes including drug content, hardness, friability, and disintegration time. All formulated tablets disintegrated rapidly within 3 minutes, achieving rapid dissolution of nifedipine, with 100 % dissolution attained within 20 minutes, meeting the official dissolution rate test specifications (IP/USP). Consequently, the PGS-PVP co-processed excipient developed in this investigation emerges as a promising vehicle for the preparation of nifedipine tablets.

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INTRODUCTION

Direct compression stands as the preferred method for tablet preparation due to its numerous advantages [1]. Among these advantages, it is notably more economical compared to wet granulation, requiring fewer unit operations [2, 3]. Additionally, it is particularly suitable for moisture and heat-sensitive Active Pharmaceutical Ingredients (APIs) as it eliminates wetting and drying steps, thus reducing the risk of degradation [3, 4]. Tablets produced via direct compression are less prone to changes in dissolution profile during storage compared to those made from granulations [4,5], which is crucial given the current requirements for dissolution specifications in most solid dosage forms [6]. In the case of tablets containing poorly soluble APIs prepared by wet granulation, disintegration or dissolution becomes the rate-limiting step in absorption. Tablets prepared by direct compression disintegrate into API particles rather than granules, facilitating faster dissolution as the API particles directly interact with the dissolution fluid. The success of the direct compression process heavily relies on the properties of the excipients used. Key physico-mechanical properties ensuring a robust process include good flowability, compressibility, low or no moisture sensitivity, low lubricant sensitivity, and suitability for high-speed tabletting machinery with reduced dwell times [7]. However, many currently available excipients fall short of meeting all these functionality requirements, creating a need for the development of new high-functionality excipients. Co-processing, involving the interaction of two or more existing excipients at the sub-particle level, offers an efficient platform for enhancing excipient functionality and masking undesirable properties [8,9]. This approach allows for the creation of tailor-made "designer excipients" to address specific functionality requirements by incorporating one excipient into the particle structure of another through processes like co-drying.

The concept of co-processing excipients in the pharmaceutical industry dates to the late 1980s, with the introduction of co-processed microcrystalline cellulose and calcium carbonate [10]. Subsequently, products like Cellactose and silicified microcrystalline cellulose (SPVP) have become widely used co-processed excipients [11,12]. In this context, the present study aims to prepare and characterize pregelatinized starch-polyvinylpyrrolidone (PGS-PVP) co-processed excipient and evaluate its suitability as a directly compressible vehicle in tablet formulations. The co-processed excipient is prepared by gelatinizing potato starch in the presence of PVP and drying the resulting mass. This research endeavours to expand the understanding of co-processing excipients and contribute to the development of novel excipients for pharmaceutical applications.

Experimental

Materials

Nifedipine was generously provided as a gift sample by Torrent Pharmaceuticals. PVP, potato starch, lactose, talc, and magnesium stearate were obtained from commercial sources. All other materials utilized were of Pharmacopoeial grade.

Methods

Preparation of PGS-PVP Co-processed Excipient [13]

A mixture of potato starch (49 parts) and polyvinylpyrrolidone (1 part) was dispersed in 20 parts of water to form a smooth slurry. In a separate beaker, purified water (40 parts) was heated to boiling. The starch-PVP slurry was then added to the boiling water while stirring continuously. Stirring and heating were maintained for 15 to 20 minutes until a thick mass formed. The resulting product was collected onto a stainless-steel tray and dried at 80°C for 12 hours. After drying, the product was ground and sized to obtain particles sized between 72 and 100 mesh.

Characterization of PGS-PVP Co-processed Excipient

The PGS-PVP co-processed excipient prepared was characterized by assessing its melting point, solubility, swelling index in water, pH, and micromeritic properties, including particle size, bulk density, tapped density, angle of repose, and compressibility index. Additionally, Fourier Transform Infrared (FTIR) spectra analysis was conducted for further characterization.

Solubility:

The solubility of PGS-PVP was assessed in various solvents, including water, aqueous buffers with pH

Journal of Chemical Health Risks

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values of 1.2, 4.5, and 7.4, as well as organic solvents such as alcohol, dichloromethane, chloroform, acetone, and petroleum ether.

pH:

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

Melting point:

The melting point of PGS-PVP was determined using a melting point apparatus.

Swelling Index: [14]

To determine the swelling index, 500 mg of PGS-PVP was added to 10 ml of water and light paraffin separately in two graduated test tubes and mixed. The dispersions were allowed to stand for 24 hours, and the volumes of the sediment in the tubes were recorded. The swelling index was calculated using the following formula:

Swelling Index (S.I) (%) = [(Volume of sediment in water – Volume of sediment in light liquid paraffin) / (Volume of sediment in liquid paraffin)] × 100.

Particle size: [15]

Particle size analysis was performed by sieving using standard sieves.

Bulk density: [16]

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

Angle of repose: [17]

The angle of repose was measured using the fixed funnel method.

Compressibility index: [18]

The compressibility index (CI) was determined by measuring the initial volume (V0) and final volume (V) after one hundred tapings of a sample of the product in a measuring cylinder. The compressibility index was calculated using the equation:

Compressibility index (CI) = [(V0 - V) / V0] × 100.

Preparation of Tablets by Direct Compression Method:

Tablets containing Nifedipine (60 mg) prepared by the direct compression method according to the formulation provided in Table 2. All the materials required as per the formulation were blended in a closed polyethylene bag and compressed into tablets on a tablet punching machine (M/s Cadmach Machinery Co. Pvt. Ltd.) to a hardness of 6 kg/cm2 using 9 mm flat punches.

Evaluation of Tablets:

The tablets prepared were evaluated for the content of the active ingredient, hardness, friability, disintegration time, and dissolution rate. Tablet hardness was tested using a Monsanto hardness tester, while friability was determined using a Roche Friabilator. Disintegration time was determined using a Lab India tablet disintegration test machine (model: DT 1000) with water as the test fluid.

Estimation of Drug Content in the Tablets:

From each batch of tablets, 20 tablets were accurately weighed and powdered. Tablet powder equivalent to 50 mg of the drug was taken for assay into a 100 ml conical flask and extracted with three aliquots of 20 ml methanol each. 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 solutions were suitably diluted with water containing 2% SLS in the case of Nifedipine and with 0.1 N hydrochloric acid. The absorbance of the solutions was measured at 236. The drug content of the tablets was calculated using the standard calibration curve in each case.

Dissolution Rate Study:

The dissolution rate of the prepared tablets was investigated using a USP 8-station Dissolution Rate Test Apparatus (M/s Labindia Disso 8000) equipped with a paddle stirrer operating at 50 rpm. Dissolution was carried out using different water containing 2% SLS (900 ml) was used. Each test employed one tablet, and the dissolution was conducted at a maintained temperature of 37 ± 1°C.

At various time intervals, samples of the dissolution medium (5 ml) were withdrawn through a 0.45 µ filter and assayed for Nifedipine at 236 nm, all dissolution experiments were performed in triplicate (n=3) to ensure consistency and reliability of the results.

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www.jchr.org

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RESULTS AND DISCUSSION

Directly compressible vehicles can be prepared using various methods [14-16]. Among these methods, co-processing is widely explored and commercially utilized for the preparation of directly compressible vehicles. Co-processing of excipients has the potential to yield excipients with superior properties compared to simple physical mixtures of their components. The objective of this study is to prepare and characterize pregelatinized starch-polyvinylpyrrolidone (PGS-PVP) co-processed excipient and evaluate its application as a 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 characterized by determining various physical and micromeritic properties. It was found to be a crystalline, discrete, and free-flowing powder, which could be ground to various particle sizes. Particles of size -72+100 mesh (179.5 µm) were collected for further studies. The excipient was insoluble in water, aqueous fluids of pH 1.2, 4.5, and 7.4, as well as several organic solvents including alcohol, methanol, dichloromethane, acetone, chloroform, and petroleum ether. It exhibited high swelling in water with a swelling index of 280%.

The flow properties of the PGS-PVP co-processed excipient were determined by measuring bulk density, angle of repose, and compressibility index. The results indicated excellent flow properties, which are essential for ensuring homogeneous and rapid flow of powder for uniform die filling during tablet compression. Blends of PGS-PVP co-processed excipient and nifedipine also exhibited excellent to good flow properties. The estimated bulk density values of the excipient further contributed to its good flow characteristics.

To evaluate the PGS-PVP co-processed excipient as a directly compressible vehicle (DCV), tablets of nifedipine (60 mg) were prepared by direct compression method using the excipient as DCV at a strength of 60% in the formulation. The tablets were evaluated for content of active ingredient, hardness, friability, disintegration time, and dissolution rate. Hardness of the tablets was in the range of 4.0 - 5.0 Kg/sq.cm, and weight loss in the friability test ranged from 1.45% to 2.10%. The drug content of the tablets was within 100 ± 3% of the labelled claim, and all tablets disintegrated rapidly within 3.5 minutes. These results indicate that tablets prepared using the PGS-PVP co-processed excipient as DCV were of good quality about drug content, hardness, friability, and disintegration time.

The dissolution rate study showed rapid dissolution of nifedipine from the tablets, with complete dissolution (100%) achieved within 20 minutes. These dissolution profiles met the official (IP/USP) dissolution rate test specifications. Overall, the results demonstrate the potential of PGS-PVP co-processed excipient as a promising directly compressible vehicle for the preparation of nifedipine tablets.

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

S.No.	Property/Test	Result
1.	Particle size (µm)	72/100 mesh (179.5 µm)
2.	Tapped density (g/cc)	0.464
3.	Swelling Index (%)	Demonstrates high swelling in water; Swelling index: 280%
4.	Bulk density (g/cc)	0.445
5.	Melting point	Charred at 250°C
6.	Angle of repose (°)	23.7
7.	Solubility	Insoluble in water, methanol, alcohol, acetone, chloroform, dichloromethane, and petroleum ether
8.	pH (1% aqueous dispersion)	6.8

Journal of Chemical Health Risks

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9.	Compressibility index (%)	7.9

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

Ingredient (mg/tablet)	Tablet Formulation
Nifedipine	60
PGS-PVP Co-processed excipient (72/100 mesh)	220
Lactose	52.4
Talc	8.8
Magnesium stearate	8.8
Tablet weight (mg)	350

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)
Nifedipine tablets	4.23	1.49	3 min 00 sec	60

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 Drug Dissolution Rate Specification
	5	10	15	20	
Nifedipine	73.58	87.53	96.98	100	NLT 70 % in 60 min in water containing 2% SLS. (I.P, 2010

CONCLUSION:

The PGS-PVP co-processed excipient, formulated by gelatinizing potato starch (49 parts) in the presence of PVP (1 part), exhibits several desirable characteristics. Firstly, it manifests as a crystalline, discrete, and free-flowing powder, indicating its suitability for pharmaceutical applications. Its insolubility in water and aqueous fluids across a range of pH values (1.2, 4.5, and 7.4) as well as in various organic solvents enhances its stability and utility in different formulation environments.

One notable feature of this excipient is its high swelling capacity in water, reaching an impressive 280%. This attribute can contribute to improved disintegration and dissolution characteristics in tablet formulations, potentially enhancing drug release profiles. Moreover, the excipient demonstrates excellent flow properties both on its own and when blended with selected drugs, ensuring uniform die filling during tablet compression processes.

Tablets formula exhibiting the PGS-PVP co-processed excipient as the directly compressible vehicle (DCV)

exhibit favourable quality attributes. They maintain consistent drug content, hardness, friability, and disintegration time, meeting pharmaceutical standards. Importantly, all tablets disintegrate rapidly within 3.5 minutes, facilitating prompt drug release upon ingestion.

Furthermore, dissolution studies reveal that Nifedipine tablets achieve rapid and complete dissolution within 20 minutes. This meets the official dissolution rate test specifications outlined by regulatory authorities, ensuring efficacy and bioavailability of the contained drugs.

Overall, the PGS-PVP co-processed excipient presents itself as a promising candidate for the preparation of tablets, particularly for antiretroviral drugs. Its combination under scoreable physical properties, excellent flow characteristics, and consistent performance in tablet formulations underscores its potential as a versatile and reliable ingredient in pharmaceutical manufacturing processes.

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