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PHYSICOCHEMICAL AND TABLET PROPERTIES OF CO-PROCESSED STARCH WITH DIFFERENT GRADES OF PVP AS DIRECT COMPRESSION EXCIPIENT

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ABSTRACT

Co-processed excipients with combination of two or more existing excipients at sub-particle level interaction will provide a means of developing high functionality excipients it is one of the most widely method for preparing directly compressible excipients. The main aim of this study was to evaluate the flowability compressibility, compactibility tablet ability and disintegration properties of tablets produced by direct compression of co-processed maize starch and polyvinyl pyrollidone using metronidazole as active ingredient. Different excipients were produced by co-fusion of maize starch and polyvinyl pyrollidone. Subsequently, the co-processed excipients were assessed for physicochemical parameters mean particle size, angle of repose, flow rate bulk, tapped densities Carr's index, Hausner's ratio, moisture content. The co-processed excipients (49%) were mixed with metronidazole (50%) and magnesium stearate (1% w/w) and directly compressed into 400mg tablets using a single punch tableting machine at 7 MT. The tablets formed were kept for 24hr to allow for elastic recovery and subsequently evaluated for weight uniformity, disintegration time and in-vitro drug release. Results obtained showed that maize starch has poor flow characteristics but improved when co-processed with different grades PVP based of indices of angle of repose (27°-45°) and Hausner's ratio (0.76-1.6). All batches of tablets released 50% and 90 % of the drug in less than 10 and 15min respectively. The results indicate that the batches of co-processed maize starch and PVP exhibit excellent powder characteristics (compressibility and flowability) and good disintegrant properties (disintegration time of less than 4 minutes).

Keywords: Direct compression, Polyvinyl pyrollidone, Co-processed, Disintegration time

INTRODUCTION

In recent years, great interest has been shown on direct compression, directly compressible excipients and co-processing in pharmaceutical industry and research institutes (Chowdaery *et al.*, 2012). Direct compression is the process of making tablets without granulation. Direct compression offers several advantages such as low cost, more suitable for moisture and heat sensitive drugs, faster dissolution rates, improved stability etc., specially processed and modified excipients are needed for direct compression. Co-processing is one of the most widely explored methods for preparing directly compressible excipients. Co-processed excipients are prepared by incorporating one excipient into the particle structure of another excipient using

processes such as co-drying (Olowosulu *et al.,* 2011).

Co-processing is interesting because the products are physically modified in a special way without altering the chemical structure. (Nachaegari *et al.,* 2004). According to International Pharmaceutical Excipient Council (IPEC), co-processed excipient is "a combination of two or more compendial or non-compendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing, and without significant chemical change" (Gohel and Jogani, 2005, Neha *et al*., 2014). Co-processing of excipients has led to the formation of excipients with superior properties compared to the simple physical mixtures of their components (Patel and Pingale, 2014). The objective of this study was to evaluate the physicochemical and tablet properties of tablets produced by direct compression of co-pressed starch with different PVP grades containing metronidazole as active ingredient.

MATERIALS AND METHODS

Materials

Maize starch obtain from Institute of Agricultural Research, ABU Zaria (Sama 17), PVP (J R S Pharma, Germany), Hydrochloric acid (Sigma-Aldrich labor chemical, Germany), Metronidazole powder (Hopkin and Williams, New Delhi, India), Magnesium stearate (BDH Chemicals LTD Poole England). All reagents were analytical grade and used without further purification.

METHODS

Co-Fusion of PVP and Maize Starch

Calculated weights of maize starch were weighed and dispersed in volumes of water (50% w/w dispersion) in labeled 500 ml beakers, into which calculated weights of PVP were added such as to obtain the ratios (4:1) of the starch to PVP. The beakers were placed on a water bath, heated to pre-gelatinization temperature of maize starch (55°C) for 15 min with intermittent stirring. The mixture was transferred onto a clean stainless-steel tray labeled respectively, and allowed to air-dry at room temperature for 30min. the dried masses were size reduced using mortar and pestle, passed through 1mm sieve and further dried in a hot air oven (Gallenkamp, UK) at 60℃ for 40-60 min.

Table: 1 Formula for Co-Processing PVP and Maize Starch

Ingredients	Batch I	Batch II	Batch III
Maize Starch (g)	16	16	16
PVP (g)	4	4	4
Water (ml)	16	16	16

Key: **Batch I:** PVP K30: MS **Batch II:** PVP K25: MS **Batch III:** PVP VA64: MS

Characterization Co-Processed Excipient

The co-processed excipients (PVP & MS) in different ratios 1:4 were characterized for particle size analysis, angle of repose, flow rate, bulk density, tapped density, Carr's density, Hausner's ratio and moisture content and results were calculated and recorded.

Particle size analysis

Particle size analysis was carried out using the sieving method. Test sieves ranging from 500 µm to pan were arranged in a descending order of 500 µm, 250 µm, 150 µm, 90 µm, 75 µm and pan. 20 g of sample of each batch was placed on the 500 µm sieve and allowed to vibrate for 10 min at 50 cycle per minute in the Endecott test sieve shaker. The amount retained on each sieve was weighed and the mean particle size was calculated using the equation below.

$$Mean\ particle\ size = \frac{[\Sigma(\%\ retained)\ X\ (mean\ aperture)]}{100}$$

.....equation 1

Angle of repose

This was calculated using the fixed funnel method. A clean glass funnel was clamped on a retort stand such that the height from the tip of the funnel to the work bench surface was fixed at 5cm and the outlet of the funnel was plugged with a cotton wool. 20 g of sample powder as weighed using an electrical balance and poured into the funnel and the plug at the tip removed. The powder was allowed to flow freely under the influence of gravity. A conical heap of powder was formed. The dimensions of height and radius were measured and used to compute the angle of repose using equation 3 below. A mean of two measurements was obtained for each batch of sample.

$$\text{Tan}\ \theta = \frac{h}{r}$$.....equation 2

Where h is the height of the powder, r is the radius of the circular base and θ is the angle of repose.

Estimation of Flow rate

20 g of the sample was weighed and poured into the funnel of the flow rate apparatus. The time taken for the powder to flow out of the funnel was taken. This was repeated twice for each sample and average value was taken. The flow rate was calculated using the equation below.

$$Flow\ rate = \frac{mass\ of\ granules\ (g)}{time\ (s)}$$ ...equation 3

Measurement of Bulk and Tapped Densities

20 g of sample was weighed using the electronic balance, poured into a 100 ml measuring cylinder and the volume occupied was noted as V_0 as bulk volume. The cylinder was tapped 50 times at a constant rate and the tapped volume V_{50}, was noted. The bulk and tapped densities were calculated using the equation below.

$$Bulk\ density\ (BD) - \frac{weight\ of\ granules}{bulk\ volume\ (V0)}$$ …equation 4

$$Tapped\ density\ (TD) = \frac{weight\ of\ granules}{tapped\ volume}$$…equation 5

The bulk (BD) and tapped (TD) densities were used to calculate Carr's index (U) and Hausner's ratio (HR) using the equations below.

$$CI = \frac{TD-BD}{TD}\ x\ 100$$ … equation 6

$$HR = \frac{TD}{BD}$$ …. equation 7

Tableting by Direct Compression

Calculated weights of excipients were weighed in batches and mixed with calculated weights of metronidazole and magnesium stearate, and tableted by direct compression into 400mg tablets at 7 MT on a single punch tablet press using 12 mm flat faced punches.

Tablet Evaluation

The different batches of metronidazole tablets were evaluated for uniformity of weight, thickness crushing strength, disintegration time, friability, and dissolution studies and the results were calculated and recorded.

Table 2: Tablet Formula for Preparing Metronidazole Tablet

Ingredients	Amount/tablet (mg)	Amount/tablet (g)
Metronidazole	200	12
Magnesium stearate	4	0.12g
Excipients	196	11.76
Total	400	24

Weight variation test

Ten tablets were selected randomly and weighed individually. Their mean weights and standard deviation were computed calculated and recorded.

Thickness Test

Tablets should have uniform size, as this improved acceptability and makes packaging easy. It also ensures uniformity of dosage. The thickness of ten tablets was measured for each batch using a digital Vernier caliper. The values were recorded in mm, the mean and standard deviation of the ten determinations were computed, calculated and recorded.

Crushing Strength Determination

Crushing strength of a tablet determines its ability to stand mechanical pressures. The degree of hardness of a tablet depends on its size and shape. Ten tablets from each batch were taken each tablet was placed between the spindle and the anvil of the Mosanto hardness tester. The knob was screwed gradually from zero until the tablet was fractured and the force applied (kgf) was taken. The mean and standard deviation were determined.

Friability Test

This measures tablets strength relative to its ability to withstand shock and abrasion and other physical injuries during processing packaging, handling and shipment. Five tablets were weighed and recorded before transferring into Roche Friabilator (TA3R Erweka, Germany). The apparatus was allowed to rotate at 25 rpm for 5 min. The tablets were collected and reweighed collectively. Loss in weight calculated using the equation below.

$$\text{Friability} = \frac{\textit{initial weight} - \textit{final weight}}{\textit{initial weight}} \times 100 \quad \text{....equation 8}$$

Disintegration test

The time taken for six tablets from each of tablet to disintegrate was determined using the USP disintegration test apparatus (ZT3, Erweka, Germany). The entire experiment was set to run at 37 ^{O}C in distilled water as the medium for disintegration. The mean and standard deviation of six replicates was computed and recorded for each batch.

Dissolution Test

An in-vitro dissolution study was carried out to measure the availability of drug to be absorbed when taken orally; it was carried out on all batches using 0.1N HCL as dissolution medium. A single tablet was placed in the vessel containing 900ml of 0.1N HCL regulated at 37 ^{O}C and allowed to rotate at 50 rpm. Ten (10) mL samples were withdrawn at 15sec, 30sec, 1min, 2min 30 sec, 5min, 10min, 15min, 30min and 45min respectively and replaced with equal volume of 0.1N HCL after each withdrawal. The samples collected were sufficiently diluted

with 0.1N HCL (1 in 10 dilutions) before taking the absorbance at 277 nm using the UV spectrophotometer (UV – 1800 Spectrophotometer Shimadzu Corporation, USA). The amount of drug released (%) was calculated using the regression equation (y = 4.8343x + 0.0048, R 2 = 0.9998) obtained from the calibration curve of the pure metronidazole powder.

RESULTS

Physicochemical Properties of Maize Starch and Co-Processed Excipients

Physical properties of all excipients are presented in table 3.

The angle of repose of the maize starch is above 49 ^{O}C indicating poor flow characteristics. The angle of repose ranged from 27.0 – 49.2 with PVP K30 having the lowest and Maize starch having the highest value. Alternatively, the flow rate increase in ascending order: Maize starch > PVP K25 > PVP VA64 > PVP K30. The moisture content, bulk and tapped densities were also analyzed.

Table 3: Physicochemical Properties of Maize Starch and Different Co-Processed Excipients

Parameter	Batch I	Batch II	Batch III	Maize starch (MS)
Angle of repose (°)	27.0	30.0	28.0	49.2
Bulk density(g/ml)	0.40	0.50	0.33	0.40
Tap density(g/ml)	0.46	0.52	0.47	0.66
Carr's index (%)	19.0	16.2	13.3	39.3
Hausner's ratio	0.80	0.76	0.86	1.60
Flow rate(g/sec)	4.00	3.50	3.90	2.60
Moisture content (%)	2.60	3.10	3.97	3.23

Key: **Batch 1:** PVP K30: MS **Batch II:** PVP K25: MS **Batch III:** PVP VA64: MS

Tablet Analysis of All Batches of Metronidazole Tablets

Maize starch alone did not form metronidazole tablets by direct compression. All Formulation of tablets resulted in mean tablet weights of (393-403mg) of 400mg.The mean crushing strength of all Formulations are within 3-4kgf, and all tablets pass the friability test of less than 1%. All the Formulations show mean disintegration time of 2-3min.

Table 4: Tableting Properties of Metronidazole Tablets Prepared Using Different PVP Grades

Tablets Parameters	Batch 1	Batch II	Batch III
Weight Variation (Mg)	393 ± 8.23	393 ± 6.75	403 ± 6.75
Thickness (Mm)	2.81 ± 0.04	2.71 ± 0.03	6.78 ± 0.06
Crushing Strength (Kgf)	4.0 ± 0.35	3.8 ± 0.27	3.9 ± 0.42
Diameter (Mm)	12.12 ± 0.0	12.06 ± 0.0	12.01 ± 0.02
Disintegration Time	3.5 ± 0.37	2.6 ± 0.67	2.1 ± 0.33
Friability (%)	0.57	0.93	0.91

All Results are presented in Standard Deviation (SD)
Key: **Batch I:** PVP K30: MS **Batch II:** PVP K25: MS **Batch III:** PVP VA64: MS
Result from fig 1: Shows co-processed maize starch with PVP V64 has shorter disintegration time, followed by PVP K25, then, PVP K30

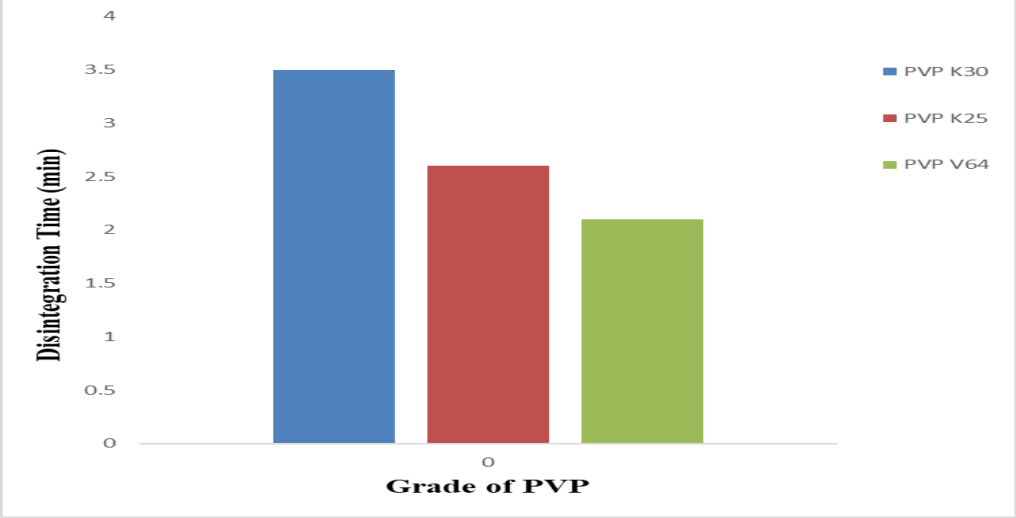

Fig 1: Show the disintegration time of co-processed maize starch with different grades of PVP

Figure2 shows the percentage drug release of metronidazole tablet formulated by different grades of co-processed excipient. All batches of tablets released 50% and 90 % of the drug in less than 10 min and 15 min respectively.

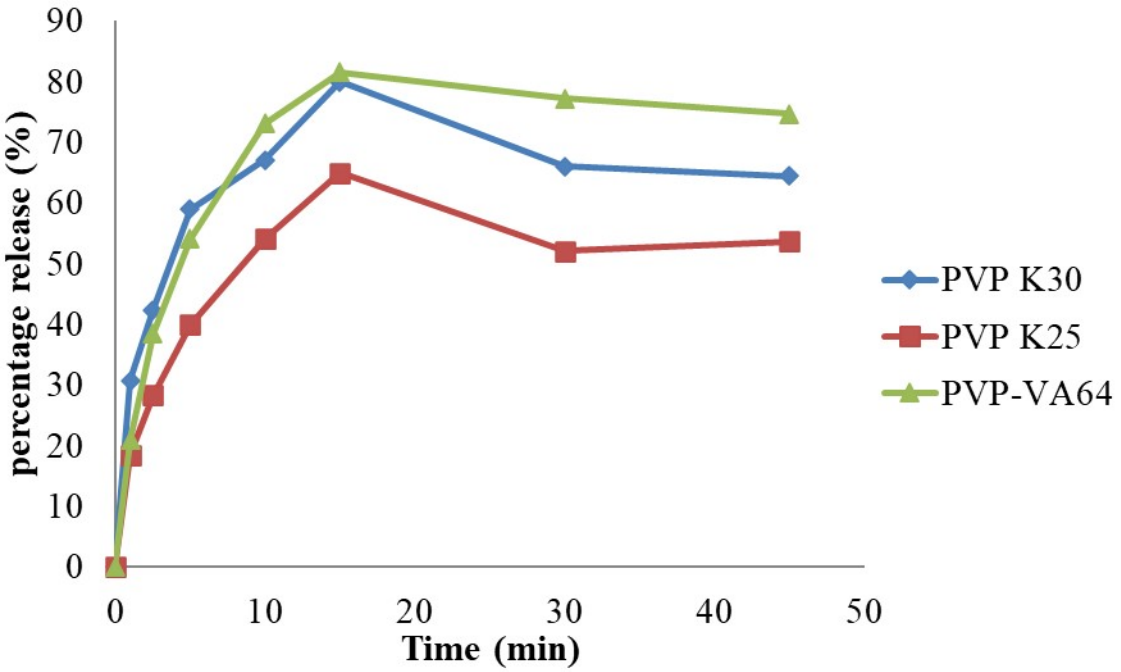

Figure 2: Percentage drug release of metronidazole tablet formulated by different grades of co-processed excipient

DISCUSSION

It is important to note that no single and simple test method can adequately characterize the flow properties of pharmaceutical powders, but a combination of different test methods and analysis provide sufficient information on the flow properties, as well of tablet ability, disintegration properties of pharmaceutical powders (Chowdary *el.,* 2012) commonly reported methods important in testing powder characteristic of pharmaceutical excipients and active ingredients include angle of repose, particle size, moisture content, similarly, tests on solid tablet formulation commonly reported in understanding compatibility of combinations of active ingredients and excipients include crushing strength disintegration time and content uniformity (Bodhmage, *et al,.* 2016).

The particle size analysis of maize starch using sieve method gave a mean particle size of 117.93Nm. It is observed that particle size of co-processed PVP and MS are way larger than either of individual components. The change in particle of co-processed excipients is attributable to both the type of co-processing procedure used and intermolecular forces between different materials resulting in particular changes.

The parameters of angle of repose, Hausners ratio and Carris index are used to measure the flow property of the powder. The angle of repose is the measure of the interparticulate frictional forces in a powder or in the granules. The angle of repose of maize starch obtained is $49^{O}C$ which shows high value indicating poor flow characteristics, all co-processed excipients (MS and PVP) show lower angle of repose (better flow) than MS alone. Flowability is an important property especially in direct compression because this tableting method requires very good flow to obtain optimum weight and content of active ingredient (Patel *et al,* 2016). Tapped density of MS was found to be (0.66/l ml) has the highest value compared with the co-processed

excipient (0.4-0.5g/ml), whereas the bulk densities of all the excipients were within the same range (0.33-0.5g/ml). Tapping or vibrating a loose powder induces movement and separation and lowers the friction between the powder particles. Tapped density is always higher than the free flow bulk density. Tapped density is a function of particle shape, particle porosity and particle distribution (Gohel *et al*., 2015). For Hausners ratio, values greater than 1.25 indicates poor flow property from the result gotten MS have value greater than 1.25 showing that it has poor flow. Carrs index indicates the ability of a material to diminish in volume when pressure is applied. As the values of the index decreases, the flow of the powder decreases.

Metronidazole tablets were unable to form by direct compression using maize starch only. This supports the established knowledge that maize starch is only suitable as a multifunctional excipient in granulation method of tableting. Analysis of tablets formed ratios of the excipients (PVP and MS) shows result of crushing strength values in tablet batches are within the range indicating better binding properties by direct compression. For friability testing, it is stated in USP (2011) that tablets should not lose more than (1%) of their total weight. Friability testing shows the resistance of tablet to chipping abrasion of breakage under conditions of storage, transportation and handling before use and these parameters depend on its hardness (Philip *et al.,* 2016).). The results obtained from the tablet analysis of this project work shows that the presence of MS in direct compression increases friability of tablets, though they have passed the test. Disintegration of tablets formed by co-processed MS and PVP show very rapid disintegration. Disintegration time less than 3min complies with USP (2011) specification (15min) for uncoated tablets. Figure 1.1 show Plot of result from dissolution tests, (MS PVP) in ratio 1:4 show percentage release of drug at less than 15min for all the batches with its peak at 45min. co-processing maize starch with polyvinyl pyrollidone of different grades at a fixed ration (4:1) using co-fusion technology, produced excipients with improved characteristics and tablet properties than individual excipients.

CONCLUSION

From the results obtained showed that the co-processed excipients (PVP K25: MS, PVP K30: MS and PVP VA64: MS) had good flow properties and swelling capacity. The co-processed excipients when used in the formulation of tablets would be effective filler-binder for direct compression. The new co-processed excipient compared favorably and better than maize starch as a filler-binder.

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