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ORIGINAL RESEARCH

Dioscorea Dumetorum and Silicified Oryza Sativa Starch Conjugates as Directly Compressible Excipients

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ABSTRACT

Background: Physical or chemical modification and co-processing, in a bid to enhance excipient functionality, have been increasingly carried out on native starches in tableting technology. In this study, starch obtained from *oryza sativa* (Family: *Poaceae*) has been modified by silicification and co-processed with starch obtained from *Dioscorea dumetorum,* (Family: *Dioscoreaceae*), in comparison with Prosolv® (silicified micro crystalline cellulose).

Methods: Silicified *oryza sativa* starch (SOsS) was conjugated with *Dioscorea dumetorum* starch (DdS) to obtain "SOsS:DdS (1:1)". The starches [SOsS, DdS, SOsS:DdS (1:1)] were characterized using Scanning Electron Micrograph (SEM), FTIR spectroscopy, density measurements, angle of repose, Carr's Indices and Hausner's ratios. The starches (or Prosolv®) were incorporated as disintegrants in paracetamol tablet formulations at concentrations of 10 %w/w – 25 %w/w. Crushing strength, Friability and Disintegration tests were used as tablet assessment criteria.

Results: The SEM indicates that enhanced thermal agglomeration during silicification increased in the particle size of *Oryza sativa* starch, while the FTIR spectra of SOsS:DdS (1:1) shows an intense broadening of the peaks occurring at 2356.70 cm^{-1}, 2092.31 cm^{-1} and 1942.28 cm^{-1} for Dds and at 2930.10 cm^{-1}, 2353.88 cm^{-1} and 2073.63 cm^{-1} for SOsS, though major characteristic peaks of native starches were retained. The ranking of the density measurements and angles of repose were DdS > SOsS:DdS (1:1) > SOsS , while Carr's indices and Hausner's ratios show that the compressibility of Dds was significantly enhanced. The crushing strength for tablets was of the order Prosolv®>Dds> SOsS:DdS (1:1)> SOsS. Friability was in the reverse order. Disintegration times were generally similar between tablets containing SOsS (alone or conjugated) and Prosolv®.

Conclusion: Conjugation of silicified *oryza sativa* and *Dioscorea dumetorum* starches showed better disintegrant properties than the native starch which are comparable with Prosolv®.

Keywords: Silicified oryza sativa, Conjugated excipients, Co-processing, Paracetamol Tablets, Enhanced Functionality.

Introduction

Excipients play very key roles in tableting technology. The choice of excipients to be employed in tablet manufacture depends on the process involved[1]. Excipients can be categorized as those that aid compression (diluents, binders, lubricants and glidants) and those that aid bioavailability (disintegrants).

Bioavailability is a term that is used to describe an estimate of the relative fraction of the administered dose that is absorbed into the systemic circulation. The oral bioavailability of a drug molecule is determined by its ability to penetrate the gastrointestinal epithelial membrane, which is mainly determined by its physico-chemical properties[2]. In the design of tablets, a major factor that contributes to bioavailability is the break-up of the tablet, thereby making the active pharmaceutical ingredient (API) available for dissolution and subsequently absorption[3] ypically, on entering the gastrointestinal tract, an uncoated tablet should breakup into fragments within 15 minutes[4]. Disintegrants are added to tablet formulations to facilitate the breakdown of the tablet into smaller particles, thereby promoting the release of the active ingredient. Thus, disintegration is critical for immediate-release tablets.

Starches have been used extensively as disintegrants in tablet formulations where they elicit their action by a number of mechanisms, which include increasing porosity and wettability of tablet matrix[5], swelling[6] and evolution of gases[7]. In recent times, formulation scientists have subjected the use of starch as a pharmaceutical excipient to various forms of modification and in some situations, starches are co-processed as excipients.

A co-processed excipient is defined by International Pharmaceutical Excipients Council (IPEC) as "any mixture of compendia or non-compendial excipients that has been designed to be physically co-processed in a way which results in functional performance attributes when used in a drug application and which are not seen if the excipients are combined using simple mixing"[8]. In co-processing excipients, only physical interactions such as hydrogen bonding or ionic interactions should be involved.

Co-processing of excipients involves the incorporation of one excipient into the particle structure of another in a bid to mask some undesired properties of individual excipients while retaining or improving desired properties of individual excipients. This results in an overall improvement of performance of the excipient[8]. The vast availability of starches provides numerous possibilities to produce tailor-made co-processed excipients, meeting functional requirements. The methods employed in co-processing include spray drying, solvent evaporation, crystallization, melt extrusion, granulation/agglomeration. Basically, co-processed excipients confer improved flow properties, better compressibility, enhanced dilution potential and reduced lubricant sensitivity on the component excipients. Rice (*Oryza sativa*; Family: Poaceae) is consumed as food by over half the population of the world, for the supply of over 65% of calories[9]. Starch makes up 80% of the total constituents of rice[10]. As a result of the wide diversity in rice starch, there can be isolation of its starch with different functionalities. Starch obtained from rice is creamy, spreadable, and smooth to feel and has no distinct taste. Yam (Genus *Dioscorea*, Family: Dioscoreaceae) is the second most important root and tuber crop in Africa[11]. There are hundreds of species belonging to the genus *Dioscorea* but only about 10 are staple species. Variations in chemical composition of yam exist not only between different species but also within same species[12]. Starches obtained from native rice and yam have been used singly as excipients in various formulations, but their undesirable properties such as poor flow, poor solubility and high hydrophilicity has discouraged their use in tablet formulations[13].

In the current study, rice (*oryza sativa)* starch has been modified by silicification and co-processed with starch obtained from yam (*Dioscorea dumetorum*) in comparison with Prosolv® (silicified microcrystalline cellulose). Silicification is expected to enhance the poor flow properties of rice starch[14], while the choice of co-processing silicified rice and yam starch is expected to have better disintegrant properties

than the individual powders when incorporated as a disintegrant in directly compressed paracetamol tablets. Moreover, paracetamol cannot be tableted on its own and requires a disintegrant along with other excipients to be formulated as a tablet

Materials and Method

Materials

The materials used include analytical grade silicon dioxide (Lobachemie laboratories, China) paracetamol powder (Shangqiu Kangmeida Biotechnology Co. Ltd., China), corn starch BP (Mitushi Biopharma Ltd., Ahmedalad, India), lactose BP (Mitushi Biopharma Ltd., Ahmedalad, India), Prosolv® (Gift from BASF company, Nigeria Office) and magnesium stearate (Fooding Group Ltd, Shanxi, China. Yam tubers (*Dioscorea dumentorum,* Family: *Dioscoreaseae;* FHI No: 208173) and rice (*Oryza sativa,* Family: *Poaceae:* ; FHI No: 208671) were purchased from local markets in Ibadan, South Western Nigeria and authenticated at the Forest Herbarium, Ibadan Nigeria prior to processing for starch. Ultra-pure water (UpW) was obtained from the research laboratory of the Centre for Drug Discovery, Development and Production, Faculty of Pharmacy, University of Ibadan, Nigeria. All other materials used were of analytical grade.

Methods

Collection, extraction and purification of yam starch

The *Dioscorea dumentorum* tubers were peeled, washed with UpW and cut into tiny cubes for milling. The cut pieces were then milled to a pulp. Sufficient UpW was added to dilute the slurry and sieved until all the starch was fully extracted. The resultant mixture was allowed to stand for 48 hours then it was decanted, leaving the sediment behind. Sufficient UpW was added to the sediment with subsequent decantation twice in a day for four days. The extracted starch was dried at 50 °C for 48 h, dry blended and stored in an airtight container at 27±2 °C..

Collection, extraction and purification of rice (*Oryza sativa*) starch

Starch obtained from *Oryza sativa* was washed and soaked in UpW for 48 h to soften the grains. The grains were then milled to a pulp and sufficient UpW was added to dilute the slurry. This slurry was sieved until all the starch was extracted, leaving only the chaff. The mixture was allowed to stand for 48 h after which it was decanted leaving the sediment starch behind. Sufficient UpW was added with subsequent decantation twice in a day for four days. The starch was then dried at 50 °C for 48 h, powdered and stored in an airtight container at 27±2 °C.

Silicification of rice (*Oryza sativa*) starch

Exactly 300 g of suspension containing 40% w/v of *Oryza sativa* starch was prepared in a 500 mL beaker using 180 mL UpW. Exactly 3.7 g silicon dioxide was weighed and dispersed in the slurry with stirring for 5 min. The mixture was then transferred to a thermostatic water bath set at 54 °C for 15 min with stirring. It was taken off the water bath and allowed to cool to room temperature. Ethanol (150 mL) was added to precipitate the silicified starch. The silicified starch was separated and spread on a tray to dry in open air. It was passed through a 1.00 mm sieve and dried at 40 °C for 4 h. The dry silicified *Oryza sativa* starch was stored in an air tight container at 27±2 °C.

Identification of Starch

The presence of starch in *Dioscorea dumentorum* and silicified *Oryza sativa* was confirmed using iodine. A small quantity of *Dioscorea dumentorum* (or silicified *Oryza sativa*) starch was placed on a glass slide and 2 drops of iodine added to the sample. The colour change from the reaction was recorded accordingly.

Conjugation of silicified *Oryza sativa* starch (SOsS) with *Dioscorea dumentorum* starch (DdS)

Exactly 6 g each of SOsS and DdS were weighed into a mortar and thoroughly triturated to produce an even mix of a 1:1 ratio of the two starch samples. Sufficient quantity of UpW was added to the even mix with continuous stirring to form a slurry, which was then air-dried at 27±2 °C.

Fourier Transform Infrared (FTIR) Spectroscopy

Small quantities (10 mg) each of *Dioscorea dumentorum*

Starch (DdS), silicified *Oryza sativa* starch (SOsS) and physical mixture of SOsS:DdS (1:1) were used to obtain spectra using a Magna-IR, 560 spectrophotometer (Perkin Elmer, USA).

Particle Size and Surface Morphology Determination

The particle sizes of the samples: *Dioscorea dumentorum* Starch (DdS), silicified *Oryza sativa* starch (SOsS) and physical mixtures of SOsS:DdS (1:1) were determined using a light microscope with the aid of a calibrated eyepiece. The surface morphology of the effect of silicification on *Oryza sativa* starch was carried out using a desktop scanning electron microscope (FEI-XL 30SEM, Phenom World, Netherlands)

Bulk density

The bulk densities of *Dioscorea dumentorum* starch (DdS), silicified *Oryza sativa* starch (SOsS) and physical mixture of SOsS:DdS (1:1) were determined using 30 g of powdered sample each. The powder was poured into a 100 mL measuring cylinder and the volume occupied by the powder was recorded. The bulk density was calculated using the formula:

$$\text{Bulk Density} = \frac{\text{mass}}{\text{volume}} \ (gcm^{-3}) \qquad \text{Eq (i)}$$

Tapped density

The tapped densities of DdS, SOsS and physical mixture of SOsS:DdS (1:1) were determined using 30 g of powdered sample each. The sample was poured into a 100 mL measuring cylinder and tapped for 3 min. at 2 seconds intervals. The volume at the end of 3 minutes was recorded and the tapped density determined using the following formula:

$$\text{Tapped Density} = \frac{\text{mass}}{\text{Tapped volume}} \ (gcm^{-3}) \qquad \text{Eq (ii)}$$

Carr's index

From the bulk and tapped densities of each sample of DdS, SOsS and physical mixture of SOsS:DdS (1:1), the Carr's compressibility index were calculated using the following formula:

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \qquad \text{Eq (iii)}$$

Hausner's ratio

For each sample of DdS, SOsS and physical mixture of SOsS:DdS (1:1), Hausner's ratio was calculated using the following formula:

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \qquad \text{Eq (iv)}$$

Angle of repose

Exactly 10 g each of DdS, SOsS and physical mixture of SOsS:DdS (1:1), was poured through a funnel clamped on a retort into an open ended glass tube placed on a flat surface. The tube was removed producing a cone. The height of the resultant cone and the radius was determined using a ruler and a pair of dividers. The angle of repose was then calculated using the formula:

$$\text{Angle of repose}, \theta = \tan^{-1}\frac{h}{r} \qquad \text{Eq (v)}$$

Where h= hypotenuse of cone
r= radius of cone.

Particle density

The particle densities of DdS, SOsS and physical mixture of SOsS:DdS (1:1) were determined using the liquid pycnometer method with xylene as the replacement fluid. The 50 mL capacity pycnometer was dried and weighed empty (W), filled completely with xylene, closed up and the excess solvent wiped. The pycnometer filled with xylene was weighed and recorded (W_1). The weight of the xylene (W_2) was determined as the difference between W and W_1. Each sample (2 g) was weighed (W_3) and transferred into the pycnometer. The pycnometer was closed up and excess solvent wiped off. It was weighed and recorded (W_4). The density was evaluated using the following formula:

$$\text{Particle density} = \frac{W_2 W_3}{50(W_3 - W_4 + W_2 + W)} \qquad \text{Eq (vi)}$$

Preparation of powder mix

The basic formulation for preparing the powder mix is shown in Table 1. Exactly 25 g powder mix was prepared by weighing dry powders into a dry mortar and triturating using a pestle until a uniform mix was obtained. The different batches of powder were stored in air-tight containers at 27±2 °C.

Production of tablets

Using the Carver hydraulic hand press (model C Carver Inc., Menomonee Falls, Wisconsin, USA), 500±

Table 1: Basic formulation for preparation of 500±20 mg Paracetamol tablets

Component	Ingredient	Batch 1	Batch 2	Batch 3	Batch 4
		(%w/w)	(%w/w)	(%w/w)	(%w/w)
API	Paracetamol	50	50	50	50
Binder	Corn starch	20	20	20	20
Disintegrant	Prosolv® or SOsS or DdS or *SOsS:DdS (1:1)	10	15	20	25
Filler	Lactose	19.5	14.5	9.5	4.5
Lubricant	Magnesium stearate	0.5	0.5	0.5	0.5

Code: API= Active pharmaceutical ingredient, SOsS= Silicified *oryza sativa* starch
DdS= *Dioscorea dumentorum* starch,

RESULTS

Characterization of Starch

Identification of Starch

The starches obtained from both *Dioscorea dumentorum* and silicified *Oryza sativa* were identified using iodine. A blue-black colour change confirmed the presence of starch in the two samples of the powders used. Silicification did not erode the starch content of the powdered *Oryza sativa*.

Fourier Transform Infrared (FTIR) Spectroscopy

The FTIR spectra obtained for *Dioscorea dumentorum* starch (DdS), silicified *Oryza sativa* starch (SOsS) and physical mixtures of SOsS:DdS (1:1) are shown in Figs. 1, 2 and 3.

Particle size and surface morphology

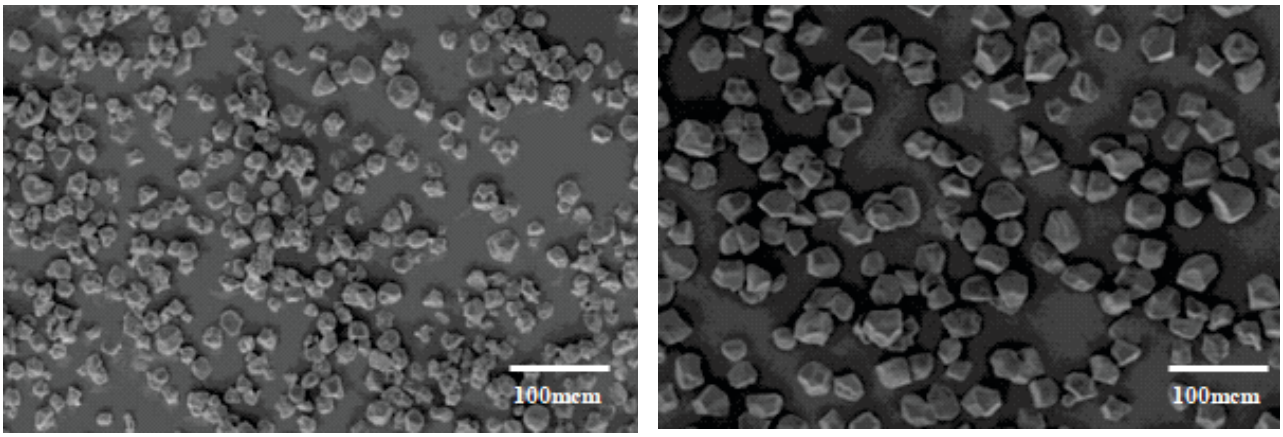
The particle size distribution of *Dioscorea dumentorum* starch (DdS), silicified *Oryza sativa* starch (SOsS) and physical mixtures of SOsS:DdS (1:1) and the morphological characteristics of native and silicified *Oryza sativa* starches are shown in Table 2 and Fig. 4 respectively.

Bulk and Tapped densities, Carr's indices, Hausner's ratio, Particle Densities and angles of repose

The bulk and tapped densities, Carr's indices, Hausner's ratios, particle densities and angles of repose of *Dioscorea dumentorum* starch (DdS), silicified *Oryza sativa* starch (SOsS) and physical mixtures of SOsS:DdS (1:1) samples are shown in Table 2.

Evaluation of Tablets

The results of the crushing strength, friability, crushing strength-friability ratio (CSFR) and disintegration time tests conducted on the tablets are shown in Table 3.



(a) (b)

Fig. 4: Micrographs for native (a) and silicified (b) *Oryza sativa* starch

Table 2: Powder properties of *Dioscorea dumentorum* starch (DdS), silicified *Oryza sativa* starch (SOsS) and conjugates of SOsS:DdS (1:1)

Powder property	*Dioscorea dumentorum* starch	Silicified *Oryza sativa* starch	Conjugates of SOsS:DdS (1:1)
Bulk density (gcm^{-3})	0.67	0.42	0.62
Tapped density (gcm^{-3})	0.83	0.47	0.69
Carr's index	19.28	10.60	10.10
Hausner 's ratio	1.24	1.12	1.32
Angle of repose (°)	49.42	22.67	34.73
Particle density (gcm^{-3})	1.47	1.43	1.49

Table 3: Values of Disintegration time, Crushing Strength, Friability, crushing strength-friability ratio (CSFR) of Paracetamol tablets

Disintegrant	Concentration (% w/w)	Disintegration time (secs)	Crushing strength (N)	Friability (%)	CSFR
Prosolv®	10.0	68	14.23±1.01	19.83	0.72
	15.0	67	24.37±1.40	13.21	1.84
	20.0	77	25.66±0.83	13.13	1.95
	25.0	76	40.13±1.66	12.50	3.21
SOsS:DdS (1:1)	10.0	79	10.57±0.42	27.89	0.38
	15.0	78	12.63±1.82	20.25	0.62
	20.0	77	14.83±1.80	14.72	1.01
	25.0	77	17.43±1.29	13.53	1.29
SOsS	10.0	74	6.23±2.37	33.01	0.19
	15.0	74	9.73±0.70	31.55	0.31
	20.0	72	11.30±1.2	27.70	0.41
	25.0	79	13.77±1.80	28.07	0.49
DdS	10.0	134	10.63±0.93	33.95	0.31
	15.0	134	17.53±1.66	33.96	0.52
	20.0	130	19.97±0.46	29.89	0.67
	25.0	129	21.63±0.49	28.26	0.77

Silicified *Oryza sativa* starch: SOsS, *Dioscorea dumentorum* starch: DdS, Conjugates of SOsS:DdS (1:1)

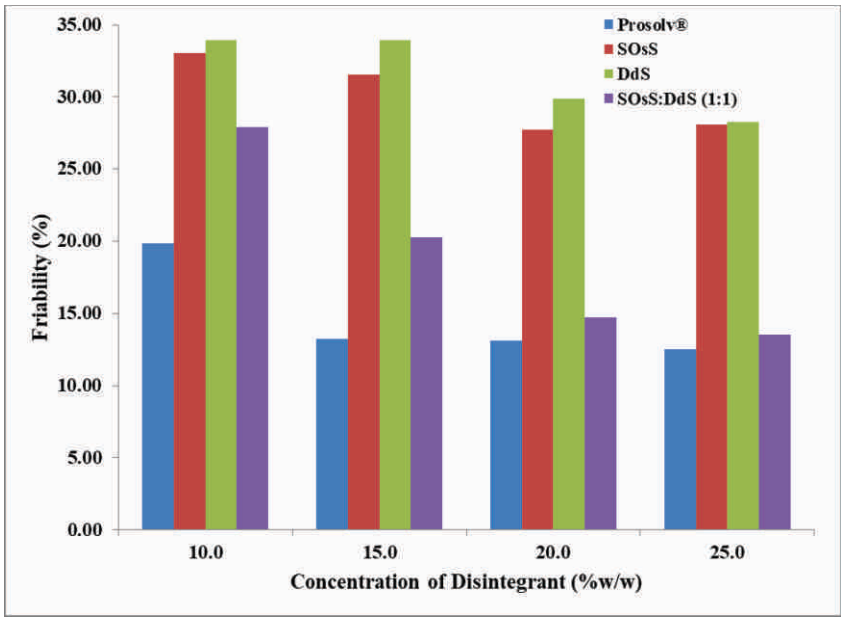


Fig. 4: Representative plot showing the effect of Concentration of Disintegrant (%w/w) on Friability (%)

DISCUSSION

Starch yield or recovery from yam tubers depends on factors such as the starch content in the original tubers, structure and composition of the tubers, postharvest storage conditions and the efficiency of the method of isolation[15]. Starch from *Dioscorea dumentorum* is composed of small granules and more difficult to extract than those from other yam species[11]. This can be as a result of two reasons; small granules settle more slowly during extraction and get entrapped in the fibrous matrix more easily than starches of larger granules. The starch component of *oryza sativa* makes up 80% of its total constituents with proteins, lipids and phosphorus available as other minor constituents[10]. Chemical modification of starch could lead to changes in the chemical reactivity of the amylose proportion of starch[10]. Silicification of *oryza sativa* starch did not affect the integrity of the starch due to the blue-black colouration on addition of N/50 iodine, thus confirming the presence of starch in the powders.

Ganim *et al* documented the use of Fourier Transform Infrared (FTIR) spectroscopy in analyzing the secondary and tertiary structures of compounds based on harmonic oscillations associated with the bending and stretching of bonds[17]. Significant changes in a sample can be detected from significant changes in functional groups that are associated with the sample as a result of bending and stretching of bonds due to intimate cohesion of the sample with other components.

The FTIR spectra for the silicified *oryza sativa* starch (Fig.2) indicates characteristic peaks (3440.44 cm^{-1}, 2930.10 cm^{-1} and 2353.88 cm^{-1}) in the functional group region, which can be assigned to O-H stretching vibration in $CH_{2=}$C-H, stretching vibration in CH_3, CH_2 and C-H stretching vibration in C-O-C respectively. Other significant peaks are shown in the fingerprint region within the range 1421.04 cm^{-1} and 465.73 cm^{-1}; peaks within this range are associated with aromatic C-H bending vibrations. The presence of O-H stretching vibrations is also seen in the peaks occurring at 3407.63 cm^{-1} and 2928.87 cm^{-1} in the FTIR spectra of *Dioscorea dumetorum* starch (DdS) (Fig.1). Co-processing of SOsS with DdS caused an intense broadening of the peaks occurring at 2356.70 cm^{-1}, 2092.31 cm^{-1} and 1942.28 cm^{-1} for Dds and at 2930.10 cm^{-1}, 2353.88 cm^{-1} and 2073.63 cm^{-1} for SOsS, but has been replaced by a single broad peak (2164.00 cm^{-1}) occurring in the spectra for the conjugates SOsS:DdS (1:1). The broadening did not affect the integrity of the starches as major characteristic peaks were replicated in the FTIR spectra for the conjugates. SRS:DdS (1:1) as seen in Fig. 3. Particle size increase of rice starch has been linked to enhanced flow properties [9,10] The micrographs for the native and modified *oryza sativa* starch (Fig. 4) show an increase in particle size

of the starch on silicification, and thus, it is expected that the flow properties of the *oryza sativa* starch will be enhanced as a result of silicification.

The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume expressed in grams per millilitre (g/mL). The bulk density is therefore a subject of the powder properties and the arrangement of the particles in the powder bed[17]. Reproducibility is often a problem with bulk density because slight disturbance of the powder bed changes the bulk density. The bulk density of a powder determines its packing behavior during die filling, mixing, granulation and compression[18]. Light powders leave large gaps between individual particles and have low bulk densities whereas heavy powders have smaller particles sitting between larger particles with resultant high bulk density. Tapped density is obtained by mechanically tapping a graduated measuring cylinder containing the powder sample. The tapped density of a powder determines the rate and extent of packing during the unit operations of tableting. From the results obtained, the ranking of the bulk and tapped densities was DdS > SOsS:DdS (1:1) > SOsS , thus indicating that SOsS had the highest fill volume.

Flow properties of powders are key considerations in the formulation of tablets. The flow of the powder from the hopper into the die determines the weight, hardness and content uniformity of the tablets[19]. Angle of repose, Carr's compressibility index and Hausner ratio are evaluated as measures of flow. The angle of repose is the angle formed by the horizontal base of the bench surface and the edge of a cone-like pile of granules. It is a function of the strength of the interparticulate forces, which is an indication of how cohesive the powder particles are. Angle of repose and flowability have an inverse relationship[20]. The Hausner's ratio ranked SOsS:DdS (1:1) > DdS > SOsS, while the ranking of the angle of repose was DdS > SOsS:DdS (1:1) > SOsS, thus implying that the conjugation of Dds with SosS led to an enhancement of flow, though not supported by the values of the Hauner's ratio. It will be recalled that the dynamics involved in arriving at the values for the Hauner's ratios and the angles of repose differ ,thus, re-arrangement of particles due to different sizes could occur differently as a result of the different pattern of motion. The values obtained for the Carr's indices show that the compressibility (an indicator of the tendency of the powder to flow) of Dds was significantly enhanced after it was conjugated with SosS.

Crushing strength of a tablet is a measure of the tablet hardness and it is the force required to break up a tablet. The crushing strength of a tablet is dependent on the concentration (and type) of the binder (and lubricant), compression force, dwell time and the powder properties, while Friability is a measure of the tendency for a tablet to chip, crumble or break after compression. From the results, tablets containing Prosolv® had the highest crushing strength values (and were the least friable) at all the disintegrant concentrations used, while tablets containing SOsS had the least crushing strength with friability values comparable with tablets containing DdS.

Disintegration is the mechanical breakdown of a tablet into smaller particles as a result of the breakage of inter-particle interactions generated during tablet compression[21]. If disintegration does not occur, only the active ingredients that are close to the tablet surface are available for absorption and activity. Disintegration is, thus, an important prerequisite for dissolution and absorption of tablets[22]. The values obtained from the disintegration test shows that tablets containing SOsS as disintegrants either singly or as a conjugate with DdS disintegrated faster than tablets containing DdS as disintegrants and had results comparable with the official disintegrant (Prosolv®). The results, exemplified by the representative plot in Fig. 4, shows that there was a direct relationship between the concentration of disintegrants and disintegration

for tablets containing SOsS:DdS (1:1) and DdS. It was proposed that a viscous gel layer that will enhance rapid capillary activity will be formed at higher concentrations of the disintegrants [23], thus the conjugation shows an enhancement on the disintegration profile of the tablets when compared with the other disintegrants used.

CONCLUSION

In this study, conjugates of silicified *Oryza staiva* starch and *Dioscorea dumentorum* starch (obtained after co-processing at ratio 1:1) were evaluated for disintegrant properties in paracetamol tablets. The flow properties of native *Dioscorea dumentorum* starch were enhanced by conjugating it with silicified *Oryza staiva* starch, while the disintegrant properties of the conjugates were better than native *Dioscorea dumentorum* starch and comparable with Prosolv®, thus indicating the potential of the conjugates as a disintegrant. Further studies on the conjugates may offer unique advantages in the formulation of fast dissolving oral dosage forms.

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