

# British Journal of Pharmacy

[www.bjpharm.hud.ac.uk](http://www.bjpharm.hud.ac.uk)

## Research Article

## Comparative Analysis of Co-Processed Starches prepared by Three Different Methods

Y. E. Apeji<sup>1</sup>, D. Aluga<sup>1</sup>, O. J. Olayemi<sup>2</sup>, C. Oparaeché<sup>3</sup>, S. N. Anyebe<sup>1</sup>, M. J. Gamlen<sup>3</sup> and A. R. Oyi<sup>1\*</sup>

<sup>1</sup>Department of Pharmaceutics and Pharmaceutical Microbiology, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria; <sup>2</sup>Department of Pharmaceutical Technology and Raw Materials Development, National Institute for Pharmaceutical Research and Development (NIPRD), Idu, Abuja; <sup>3</sup>Gamlen Tableting Ltd, Biocity, Nottingham, UK.

### ARTICLE INFO


Received: 14/07/2017  
Accepted: 10/08/2017  
Revised: 07/09/2017  
Published: 01/11/2017

\*Corresponding author.  
Tel.: +234 8028283212  
E-mail:  
[pharmaroyi@yahoo.com](mailto:pharmaroyi@yahoo.com)

KEYWORDS: Co-processing;  
excipient; direct compression;  
tablet

### ABSTRACT

Co-processing is currently of interest in the generation of high-functionality excipients for tablet formulation. In the present study, comparative analysis of the powder and tableting properties of three co-processed starches prepared by three different methods was carried out. The co-processed excipients consisting of maize starch (90%), acacia gum (7.5%) and colloidal silicon dioxide (2.5%) were prepared by co-dispersion (SAS-CD), co-fusion (SAS-CF) and co-granulation (SAS-CG). Powder properties of each co-processed excipient were characterized by measuring particle size, flow indices, particle density, dilution potential and lubricant sensitivity ratio. Heckel and Walker models were used to evaluate the compaction behaviour of the three co-processed starches. Tablets were produced with paracetamol as the model drug by direct compression on an eccentric Tablet Press fitted with 12 mm flat-faced punches and compressed at 216 MPa. The tablets were stored at room temperature for 24 h prior to evaluation. The results revealed that co-granulated co-processed excipient (SAS-CG) gave relatively better properties in terms of flow, compressibility, dilution potential, deformation, disintegration, crushing strength and friability. This study has shown that the method of co-processing influences the powder and tableting properties of the co-processed excipient.

 BY 4.0 Open Access 2017 – University of Huddersfield Press

### INTRODUCTION

It has been estimated that solid dosage forms constitute about 90% of all dosage forms used in the systemic administration of therapeutic agents (Jivraj et al., 2000). The widespread use of tablets has been achieved as a result of their convenience, stability, ease of manufacture and also the diversity of tablet types. Tableting components known as excipients

contribute significantly to the successful formulation of robust tablets by modulating its processability, stability and bioavailability (Mshelia et al., 2015; Nachaegari and Bansal 2004). Hence, they are regarded as functional components of any formulation (Camargo, 2011). There has been increasing preference for direct compression (DC) as the method of choice in the formulation of tablets due to obvious advantages including shorter processing

time involving fewer unit operations and suitable for heat or moisture sensitive active pharmaceutical ingredients (API) (Odeku et al., 2008; Ogunjimi and Alebiowu 2013; Olowosulu et al., 2011). The burden of formulating poorly compressible drugs into robust tablets by DC is borne largely by the excipients utilized in this operation. These excipients constitute a greater proportion of any DC formulation relative to the active pharmaceutical ingredient (API) and so they invariably determine to a large extent the functionality of such formulations. This has therefore resulted in an increased drive to develop high-functionality excipients designed for DC formulations. Over the years, research in the area of excipient development has focussed on the co-processing of existing excipients to generate a novel excipient with improved functionality. Co-processing of excipients is a particle engineering process that involves the combination of two or more excipients at sub-particle level designed to physically modify their properties in a manner that cannot be achieved through simple physical mixing (Nachaegari and Bansal 2004; Saha and Shahiwala 2009). The outcome of this intervention has led to the development of a single-bodied composite excipient with improved functionalities like compressibility, flowability, dilution potential etc. (Nachaegari and Bansal 2004; Rojas et al., 2012). A combination of a plastic and brittle deforming material produces a co-processed excipient with desirable attributes for tableting (Wang et al., 2015). Many co-processing methods have been employed, including spray drying (Chauhan et al., 2016; Rojas and Kumar, 2011; Sharma et al., 2015), co-drying (Mshelia et al., 2015; Olowosulu et al., 2011) wet massing, spheronisation, melt extrusion (Goyanes et al., 2011), co-precipitation (Kittipongpatana and Kittipongpatana 2011), co-grinding (Adeoye and Alebiowu, 2014a; Katsuno et al., 2013), wet-, dry- and spray-granulation (Daraghmeh et al., 2010) and co-processing by crystal coating (Vanhoorne et al., 2014) among which spray drying is the most widely used and successful strategy (Rojas et al., 2012).

Not much attention has been given to the co-processing of starches compared to lactose and celluloses. Due to its versatility, starch has found application as a diluent, disintegrant and binder in the formulation of tablets by wet granulation (Odeku, 2013; Odeku et al., 2008). It is readily available in industrial quantities and can be obtained from diverse

sources. Hence, it will be economically viable to embark on a project involving starch as the major component. However, starch in its native form is not suitable for direct compression due to limitations in flowability and compressibility (Adeoye and Alebiowu 2014b; Odeku et al., 2008; Olowosulu et al., 2011). Co-processing of starch with other excipients is currently being considered as a measure to improve the functionality of starch for direct compression. Maize starch (90%) was co-processed with acacia gum (ACA, 7.5%) and colloidal silicon dioxide (CSD, 2.5%) to improve its compressibility and flowability properties respectively. Acacia gum acts as a binder in tablet formulation and an emulsifying agent in the formation of stable emulsions (Olowosulu et al., 2011). The presence of ACA in the maize starch matrix will enhance the compressibility of maize starch by creating a larger bonding area that will invariably lead to increased bonding strength. The role of CSD in the co-processed mixture is to promote flowability of maize starch by reason of its action as a glidant. It is also known to enhance compressibility when deposited on the surface of co-processed particles providing rough surfaces that facilitates particulate bonding by mechanical interlocking (Kittipongpatana and Kittipongpatana 2011). Rapid disintegration of tablets has been associated with co-processed excipients containing CSD due to its ability to create a porous network that drives water uptake into the tablet resulting in a rapid burst of the tablet in an aqueous medium during disintegration (Rojas and Kumar 2011). The target of this study therefore was to generate a co-processed excipient with multifunctional capacity designed for DC using the methods of co-dispersion, co-fusion and co-granulation. The effect of these co-processing methods on the powder, compaction and tableting properties of the co-processed excipients developed were assessed.

## MATERIALS AND METHODS

### Materials

Materials used include Maize starch (Burgoyne Burbidge & Co. India, Mumbai), Magnesium stearate (BDH Chemicals Ltd Poole, England), Colloidal silicon dioxide (Evonik Industries, Germany), Acacia gum (Kerry Ingredients and Flavours Ltd, Ireland), Paracetamol powder (BDH Chemicals Ltd Poole,

England), Potassium dihydrogen phosphate (Guandong Chemical Reagent, China), Sodium hydroxide pellets (Qualikems Laboratory Reagent, India), Liquid xylene (BDH Chemicals Ltd Poole, England), Distilled water (Department of Biological Sciences, Ahmadu Bello University, Zaria, Nigeria). All other materials used were of analytical grade.

#### Preparation of co-processed excipient by co-dispersion (SAS-CD)

The co-processed excipient composed of maize starch (MS), acacia gum (ACA) and colloidal silicon dioxide (CSD) was prepared by co-dispersion technique. A suspension of MS (40% w/w) was prepared in distilled water and appropriate quantities of ACA gum in solution and CSD were added to the suspension in that sequence. The entire mixture was stirred for 5 mins and spread to dry in a tray for 24 h. The partially dried mass obtained was passed through a 0.8 mm sieve and drying completed in the hot-air oven at 40 °C for 2 h. The powder obtained was stored in an air-tight container prior to further use.

#### Preparation of co-processed excipient by co-fusion (SAS-CF)

The entire process was repeated as above except that the dispersed mixture obtained was transferred to a water bath set at 54 °C (±2 °C) for 15 mins with periodic stirring. It was allowed to cool to room temperature, stirred and the mixture spread on a tray exposed to dry partially for 24 h. The partly dried mass obtained was passed through a 0.8 mm sieve and the co-processed particles formed were dried finally in hot air oven at 40 °C for 2h.

#### Preparation of co-processed excipient by co-granulation (SAS-CG)

A powder blend of MS and CSD was prepared in a mortar using the doubling up technique. It was then granulated with a binder solution of ACA gum, force-screened through a 1 mm sieve and the granules formed were allowed to dry partially in the hot-air oven at 40 °C for 20 min. The granules were then passed through a 0.8 mm sieve and drying completed in the oven at 40 °C for 2 h. The granules were kept in an air-tight container for further studies.

### Optical microscopy

Optical images of SAS-CD, SAS-CF and SAS-CG were taken at × 400 magnification using the Amscope digital camera for microscope (MT 500, Made in Japan). The mean median particle ( $d_{50}$ ) size of each material was also determined by microscopy.

### Angle of repose

The angle of repose for each sample of co-processed excipient was measured using the fixed funnel method. The powder was allowed to flow freely from a height of 8 cm under the influence of gravity and a conical heap of powder was formed at the base. The dimensions of height and radius were measured and used to compute the angle of repose using the formula below. The mean of three determinations was reported for each sample.

$$\tan \theta = \frac{h}{r} \quad (1)$$

### Determination of bulk and tapped densities

Bulk and tapped densities were determined for each sample of the co-processed excipient using 30 g of powder. The powder was poured into a measuring cylinder at an angle of 45° and the volume occupied was recorded as bulk volume ( $V_B$ ). The cylinder was tapped to constant volume and recorded as tapped volume ( $V_T$ ). A mean of three observations was recorded for each sample. The bulk and tapped densities calculated using the equations given below were also used to determine Carr's index and Hausner's ratio.

$$BD = \frac{\text{weight}}{\text{bulk volume}(V_B)} \quad (2)$$

$$TD = \frac{\text{weight}}{\text{tapped volume}(V_T)} \quad (3)$$

$$CI = \frac{TD - BD}{TD} \times 100 \quad (4)$$

$$HR = \frac{TD}{BD} \quad (5)$$

### Particle density

Particle densities of the three samples of co-processed excipient were determined as described by Alebiowo and Femi-Oyewo (1998). An empty density bottle was weighed, filled with xylene and reweighed. A little quantity of xylene was poured out and 1g of each

sample was introduced into the density bottle containing xylene. The bottle was then filled with xylene and weighed again. The particle density was calculated using the formula given below:

$$\text{Particle density} = \frac{(W_2 \times W_3)}{50(W_3 - W_4 + W_2 + W)} \quad (6)$$

Where;  $W$  is weight of empty density bottle,  $W_2$  weight of xylene ( $w_1 - W$ ),  $W_1$  is weight of the bottle filled with xylene,  $W_3$  is weight of the sample, and  $W_4$  is weight of the bottle filled with xylene and sample.

### Moisture content determination

The amount of moisture contained in each sample was determined by drying 1 g of the sample at 105 °C to constant weight. Moisture content (%MC) was calculated using the formula below;

$$\% MC = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100 \quad (7)$$

### Lubricant sensitivity ratio (LSR)

The sensitivity of each sample of co-processed excipient to lubricant was assessed using the LSR test (Camargo, 2011). The sample powder (4.95 g) was blended with magnesium stearate (0.05 g) for 5 min. Tablets (500 mg) were produced by direct compression on an eccentric Tablet Press (Type EKO, Korsch, Germany) fitted with 12 mm flat-faced punches and compressed at 216 MPa. Tensile strength was determined after 24 h as described by Fell and Newton (Gamlen et al., 2015). The entire process was repeated for tablets prepared without lubricant. Lubricant sensitivity ratio was calculated by fitting the data obtained into Eq.9.

$$LSR = \frac{T_0 - T_1}{T_0} \times 100 \quad (8)$$

Where;  $T_0$  is the tensile strength of tablet without lubricant, and  $T_1$  is the tensile strength of tablet with lubricant

$$TS = \frac{2XC_s \times 10}{\pi dt} \quad (9)$$

Where;  $C_s$  is the crushing strength,  $\pi$  is 3.142,  $d$  is the diameter of die cavity (12 mm), and  $t$  is the thickness of the tablet.

### Dilution potential studies

Each batch of the co-processed excipient was mixed with paracetamol in the following ratios; 20:80, 40:60, 50:50, 60:40, 80:20, and compressed into tablets (500 mg) at a compression force of 10 KN using a 12 mm flat-faced punch and die set. The tablets were analysed for their tensile strength calculated using equation 10. A plot of mass fraction of the excipient against the tensile strength was generated for each material.

### Fourier Transform Infrared Spectroscopy (FT-IR) studies

FT-IR scans were collected for each sample of co-processed excipient from 650 - 4000  $\text{cm}^{-1}$  using Agilent Cary 630 FTIR Spectrometer (USA). For each spectrum, 16 scans were recorded at a resolution of 4  $\text{cm}^{-1}$ . Analysis of the spectra was done using the MicroLab software.

### Compaction studies

Compaction experiments were conducted on the three samples of the co-processed excipient using a computer-controlled portable bench-top tablet press (Model GTP-1, Gamlen Tableting Ltd, Nottingham, UK). 70 mg powder was filled manually into the die cavity measuring 5 mm and compressed at a speed of 60 mm/min at loads ranging from 100 - 500 kg (49.66 - 224.77 MPa). Tablets were ejected in the same direction as compression while the tensile strength and ejection stress were measured for each tablet with the tablet press. The tablet detachment (take-off) force was recorded using a manually operated 500 N McMesin CFG+ force transducer. Data was also collected on the weight and thickness of tablets formed and used to compute the volume, apparent density and relative density ( $D$ ) of the tablets from the equations below:

$$\text{Volume} = \pi r^2 h \quad (10)$$

$$\text{Apparent Density} = \frac{w}{\pi r^2 h} \quad (11)$$

$$D = \frac{\text{Apparent density}}{\text{Particle density}} \quad (12)$$

Where  $r$ ,  $h$  and  $w$  represents radius, thickness and weight of tablet respectively.

The data obtained from compaction studies was used to generate Heckel (Heckel, 1961) and Walker (Walker, 1923) plots from the equations below;

$$\ln\left(\frac{1}{\epsilon}\right) = PK + A \quad (13)$$

Where  $\epsilon$  is the porosity of the compact,  $P$  is the applied pressure,  $K$  is the slope of the linear portion of the plot and  $A$  is the intercept on the y axis.

$$V' = -w' \log P + V_{sp}' \quad (14)$$

Where  $V'$  is the specific volume of a compact and  $w'$  is the Walker coefficient expressing the volume reduction corresponding to one decade change in pressure  $P$  and  $V_{sp}'$  is the specific volume at pressure 1.  $W'$  is a measurement of the powder's compressibility.

### Tableting

Tablets (500 mg) containing paracetamol were prepared by direct compression on an eccentric Tablet Press (Type EKO, Korsch, Germany) equipped with a 12 mm flat-faced punches compressed at 216 MPa. Prior to tableting, the powder mix of drug and excipient was lubricated with 1% magnesium stearate. Tablets were stored for 24 h to allow for elastic recovery prior to evaluation of the tablet properties. The three batches of tablets produced were evaluated for weight variation, thickness, tensile strength, friability, disintegration and dissolution. The formula for preparing tablets is given in Table 1 below.

**Table 1.** Formula for paracetamol tablets prepared using SAS-CD, SAS-CF and SAS-CG

Ingredients	One tablet (mg)
Paracetamol (50%)	250
*DC Excipient (49%)	245
Mag. Stearate (1%)	5
Total	500

\* DC Excipient: SAS-CD, SAS-CF or SAS-CG

### Dissolution studies

The amount of drug released by paracetamol tablets was measured according to USP (2011) using rotating basket method in 900 mL of pH 5.8 buffer solution maintained at  $37 \pm 0.5^\circ\text{C}$  using a dissolution tester.

5 mL samples were withdrawn at intervals of 5, 10, 20, 30, 45, and 60 mins respectively. The dissolution medium was replaced with equal volume of the buffer solution after each withdrawal. Each sample withdrawn was filtered and 1 mL of the filtrate taken and diluted to 10 mL using the buffer solution. The absorbance values of the final solutions were taken at 244 nm using the UV spectrophotometer (Shimadzu Corporation, USA). This was done for the three batches of tablets. The concentration of paracetamol in each sample was then calculated using the equation extrapolated from the Beer-Lambert's plot of paracetamol.

## RESULTS AND DISCUSSION

### Particle and bulk properties

The goal of co-processing is to improve the functionality of the interacting excipients. There is a correlation between the powder properties of the co-processed excipient and its functionality in tableting. The performance of an excipient in terms of flow, compression and dilution potential in DC has been credited to its particle size, shape, surface properties and deformation behaviour. Changes occurring at particle level have been shown to significantly affect the functionality of the excipient (Sun et al., 2009). It is imperative therefore to characterize the powder properties of an excipient considering its impact on functionality. The particle and bulk characteristics of the co-processed excipient labelled SAS-CD, SAS-CF and SAS-CG are presented in Table 2. The mean median particle size ( $d_{50}$ ) ranged from 120 – 290  $\mu\text{m}$  with co-processed particles of SAS-CG having the largest size. This has been attributed to the method of processing which involves the agglomeration of primary particles facilitated by the formation of liquid bridges during granulation. Co-processed particles of SAS-CF were slightly bigger than those of SAS-CD owing to the fusion of particles that may have occurred in the course of heating the mixture at pregelatinization temperature. Hence, the method of co-processing influenced the outcome of the particle size of the generated co-processed excipients. Co-processing by spray-drying has yielded a significant increase in particle size compared to other methods (Chauhan et al., 2016; Rojas and Kumar 2011; Sharma et al., 2015; Vanhoorne et al., 2014). Engineering the particle size during co-processing plays a key role in

defining the functionality of the co-processed excipient. Particle size enlargement confers improvement in flowability particularly for materials designed for direct compression.

Another critical factor to be considered in the formulation of tablets by direct compression is the flowability of the powder mix. Most direct compression formulations are composed of the excipient in greater proportion compared to the API

hence the flowability of the powder mix may be directly related to the flow characteristics of the direct compression (DC) excipient. The angle of repose values presented in Table 2 ranks the three materials in the following order, SAS-CF < SAS-CD < SAS-CG with SAS-CF having the least angle of repose (28.9 °). As a general rule, angle of repose values not exceeding 30° is acceptable for good flow properties. This suggests that all three materials possessed marginal flow properties.

**Table 2.** Particle and bulk characteristics of SAS-CD, SAS-CF and SAS-CG. Values in parentheses represent standard deviation (n=3)

Parameters	SAS-CD	SAS-CF	SAS-CG
Median particle size (d <sub>50</sub> )	120 (10)	160 (13.2)	290 (20)
Angle of repose (°)	31.2 (0.21)	28.9 (0.57)	34.7 (0.21)
Bulk density (g/mL)	0.53 (0.01)	0.59 (0.0)	0.33 (0.0)
Tapped density (g/mL)	0.6 (0.0)	0.68 (0.0)	0.38 (0.0)
Hausner's ratio	1.14 (0.01)	1.13 (0.0)	1.11 (0.05)
Carr's index (%)	12.5 (1.13)	12.5 (0.99)	12 (0.0)
Particle density (g/mL)	1.44 (0.02)	1.46 (0.01)	1.46 (0.01)
Moisture content (%)	2.3 (0.2)	2.2 (0.4)	2.3 (0.3)
Lubricant sensitivity ratio (%)	63.3 (3.04)	76.8 (3.27)	-50.7 (5.17)

Optical images of the three materials displayed as Fig. 1 shows that the particles appear spherical in shape. Spherical shaped particles favour the rapid flow of powders and granules during tableting by ensuring minimal contact which lowers interparticulate friction. The bulk and tapped density values of SAS-CG were significantly lower than the other two materials owing to its larger particle size which prevents closer packing during densification resulting in more pore spaces (porosity) and more volume occupied by the powder. Lower bulk density has been associated with better dilution potential due to its ability to accommodate more of the poorly compressible drug in its pore spaces (Thoorens et al., 2014). Other parameters for assessing the flowability of a material such as Carr's index and Hausner's ratio were consistent with good flow properties for all three materials. Particle density did not differ significantly for the three materials as they were all generated from the same composition of excipients. Moisture content

ranged from 2.2 – 2.3% and did not differ significantly across the three materials. Moisture exerts a plasticizing effect and promotes flowability when present in optimal level in tableting formulations (Thapa et al., 2017). It is therefore necessary to control moisture content to optimize tablet quality.

The sensitivity of a material to lubricant is a property that is critical to the success of any formulation (Paul and Sun, 2017; Sun, 2011). Lubricants are normally added as extragranular excipients to prevent sticking of the formulation to the punch and die surfaces and facilitate smooth ejection of the tablet after compression. However, lubricants are known to exert negative effect on tablets with respect to its crushing strength and disintegration time (Patel et al., 2006; Paul et al., 2016; Sun, 2011). The coating of particles with lubricants limits bond formation leading to lower crushing strength while the hydrophobic nature of lubricants like magnesium stearate does not

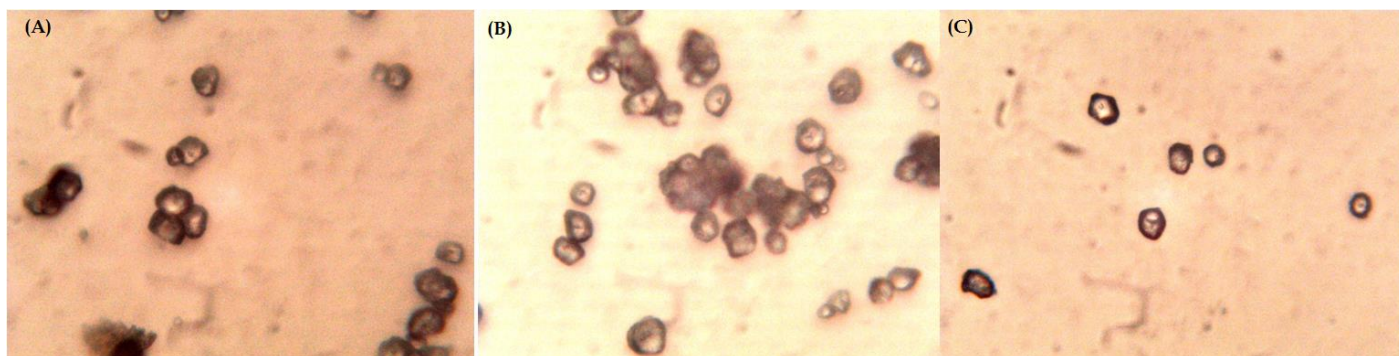


Fig. 1. Photomicrographs of (A) SAS-CD, (B) SAS-CF and (C) SAS-CG taken at magnification (x 400)

permit the influx of water during disintegration thereby extending disintegration time and by extension dissolution and bioavailability of the drug. The lubricant sensitivity ratio (LSR) determined for all three materials shows that SAS-CF was most sensitive to lubricant action while SAS-CG was least sensitive because it returned a negative value indicating that tensile strength improved in the presence of lubricants. The deformation of SAS-CG by brittle fracture during compression may have led to the formation of new surfaces which were not coated by lubricants thereby producing compacts with greater tensile strength.

It was necessary to determine the dilution potential of the materials because they were designed for use as direct compression excipients. Dilution potential is a measure of the material's ability to compress large amounts of a poorly compressible drug and still retain its compressibility (Adeoye and Alebiowu 2014; Camargo, 2011; Chauhan et al., 2016). The dilution potential of a material gives us an insight into the tablet formula and how much of the poorly compressible drug can be loaded to give robust tablets with the DC excipient. The dilution potential plot generated for all three materials is presented as Figure 2. Tensile strength of compacts decreased with increasing proportion of the poorly compressible drug (paracetamol). The tensile strength of compacts produced with SAS-CG was highest across the range of proportions used for all three materials. To obtain compacts of 1 MPa, about 200 mg of SAS-CG was required to produce 500 mg tablets containing 300 mg of paracetamol. However, the duo of SAS-CD and SAS-CF could not produce compacts of 1 MPa even when used in higher proportions exceeding the amount of SAS-CG that generated the 1 MPa compacts. This indicates that SAS-CG has a better

dilution potential compared to the other two and will therefore accommodate more drug in its formulation resulting in normal sized tablets. The process of obtaining SAS-CG by co-granulation technique may have improved its dilution capacity as the acacia gum forms a coat on the surface of the co-processed particles providing a better binding surface to adhere the drug (Sun, 2017).

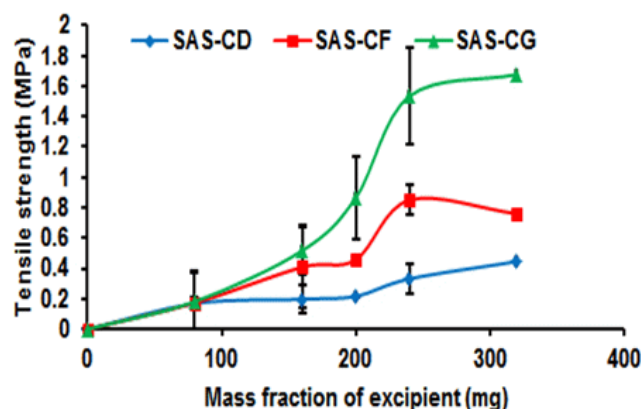


Fig. 2. Dilution potential plot showing the relationship between the proportions of excipient (mass fraction) used in the formulation and the tensile strength of tablets produced (n=5).

### FT-IR studies

The FT-IR spectra generated for SAS-CD, SAS-CF and SAS-CG are displayed as Figure 3. FT-IR was carried out to ascertain if there will be any changes occurring in the chemical structure of the co-processed excipient as a result of the method employed. The spectra for all three materials were found to be similar with major peaks/bands occurring with the same intensity and frequency. Characteristic absorption bands were observed at 3272, 2929, 1636, 1420, 1148, 1077, 991 and 928  $\text{cm}^{-1}$  positions corresponding to O-H stretch, C-H stretch, C=O stretch, O-Si-O, C-N stretch, O-H bend and =C-H bend respectively for all three materials.

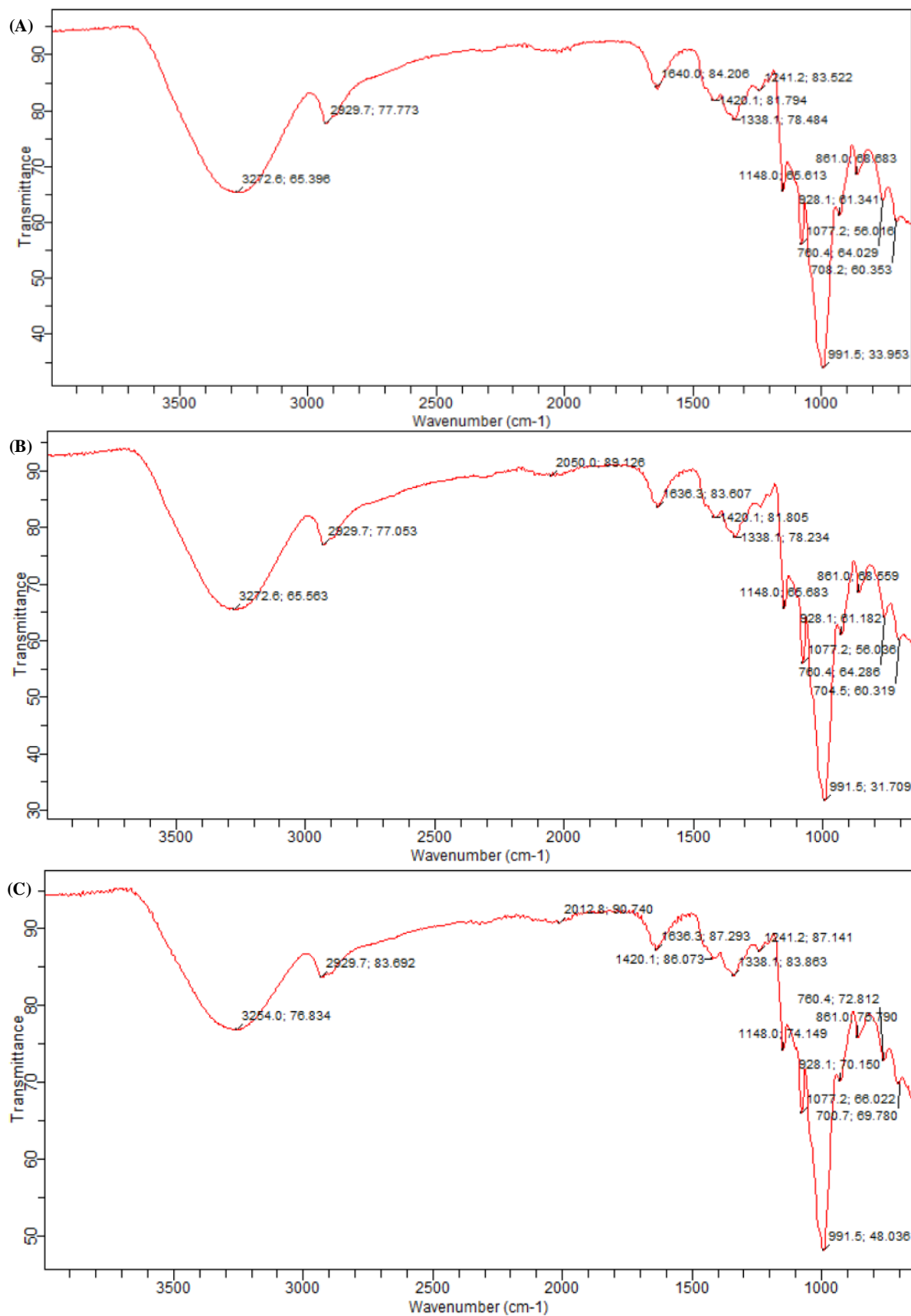


Fig. 3. FT-IR spectra of (A) SAS-CD, (B) SAS-CF, and (C) SAS-CG



This implies therefore that the methods of co-processing employed did not produce any chemical change in the excipients developed principally because they are entirely physical processes. The characteristic IR bands occurring in the individual excipients were maintained in the co-processed excipient.

### Compaction profile

The compaction profiles of the three co-processed excipients were evaluated using the Heckel (Heckel, 1961) and Walker (Walker, 1923) models. Heckel and Walker are empirically based models and differ in the parameter by which they describe deformation behaviour (Egart et al., 2014). The Heckel plot which illustrates a porosity-pressure relationship is presented as Figure 4A.

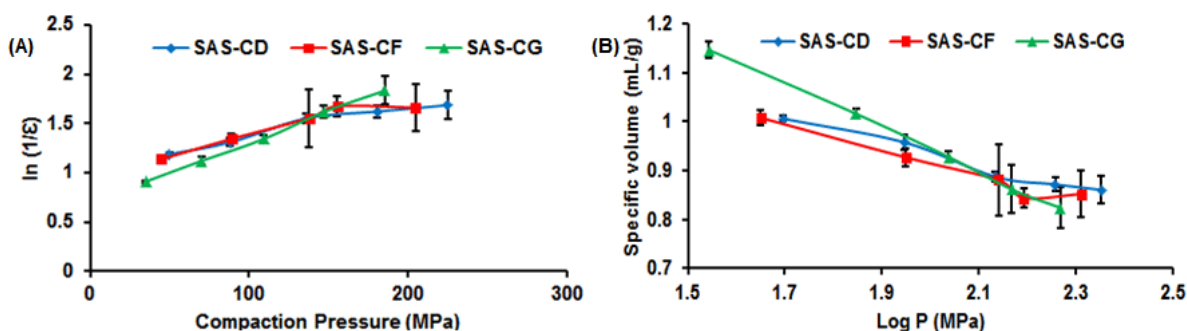
Porosity of the compacts decreased as the compaction pressure increased for all the materials. The material's ability to deform during compaction was quantified using the yield pressure calculated as the reciprocal of the slope of the linear portion of the plot. The yield pressure ( $P_Y$ ) alongside other Heckel parameters is given in Table 3. This is the pressure that characterizes the onset of deformation and lower values indicate a higher degree of plasticity in the material. Comparing the Heckel profile of the three materials, SAS-CG had the least  $P_Y$  (160.9 MPa) suggesting a faster onset of deformation during compaction. Plastic deformation facilitates the formation of tablets because particles are brought in close proximity to each other as a result of the irreversible deformation which increases the contact area available for bonding. The total degree of densification ( $D_A$ ) attributed to particle

rearrangement at low pressures was slightly higher with SAS-CD and SAS-CF in comparison to SAS-CG. This can be attributed to the larger surface area due to smaller particle size of both materials which occupied less volume during die-filling and particle rearrangement at low pressure resulting in a greater degree of densification. The extent of densification occurring as a result of particle fragmentation ( $D_B$ ) did not differ significantly across the three materials.

**Table 3.** Heckel and Walker parameters for SAS-CD, SAS-CF and SAS-CG

Material	Heckel			Walker	
	$P_Y$ (MPa)	$D_A$	$D_0$	$D_B$	$W'$
SAS-CD	234.4	0.62	0.37	0.25	26.7
SAS-CF	211.3	0.60	0.4	0.20	28.7
SAS-CG	160.9	0.47	0.23	0.24	45.5

The Walker plot shown in Figure 4B considers changes in the specific volume of the compact as a function of compaction pressure. The plot shows a trend of decreasing specific volume with increase in compaction pressure for all three materials. The Walker coefficient ( $W'$ ) which measures the compressibility of the material is also given in Table 3. Higher values of  $W'$  implies better compressibility, hence, SAS-CG had a better compression profile compared to the other two materials. This is consistent with the observations recorded with the Heckel analysis. The Walker model may be considered as a better tool in classifying the deformation behaviour of a material because of its highly discriminative power



**Fig. 4.** Compaction plots of SAS-CD, SAS-CF and SAS-CG. (A) Heckel Plot and (B) Walker Plot ( $n=3$ )

compared to Heckel analysis. Some criticisms have been recorded against the Heckel model with regards to its accuracy and robustness (Sonnergaard, 1999). Contrastingly, the Walker model is more robust and less sensitive to the approach used (Ilić et al., 2013). Notwithstanding, Heckel and Walker analysis have been able to predict and determine optimum tableting properties usually obtained with plastic and brittle fracture deforming materials (Alakayleh et al., 2016).

Compressibility and compactibility are two vital indicators that contribute to the tableability of a material (Egart et al., 2014). The compressibility-tabletability-compressibility (CTC) profile of all three materials is illustrated in Figure 5A-C. Compressibility is the measure of the ability of a material to contract in volume under the effect of compaction pressure and it is represented as a tablet porosity-pressure relationship (Ghori and Conway 2016; Khomane et al., 2013; Patel et al., 2006; Upadhyay et al., 2013) as seen in Fig. 5A. The trend observed shows that the porosity of the compact

decreases with increasing compaction pressure for all the materials. This occurred as a result of extensive packing occurring at higher compaction pressures leading to lower porosities (Alakayleh et al., 2016). There was a slight difference in the extent of porosity reduction obtained with SAS-CG compared with the other two materials. At lower pressures, the porosities of compacts obtained with SAS-CD and SAS-CF were lower than that of SAS-CG. This has been attributed to the larger particle size of SAS-CG which requires more work of compression to rearrange the particles, deform and finally to fragment them (Alakayleh et al., 2016). However, at higher pressures where particle fragmentation must have taken place to fill up the interparticulate pores during rearrangement coupled with plastic deformation, the extent of porosity reduction observed with SAS-CG seem to surpass the other two yielding compacts with lower porosity. The reduction in porosity as a measure of compressibility suggests that more surface area of particles will be available for bonding (Osei-Yeboah and Sun 2015; Sun 2011).

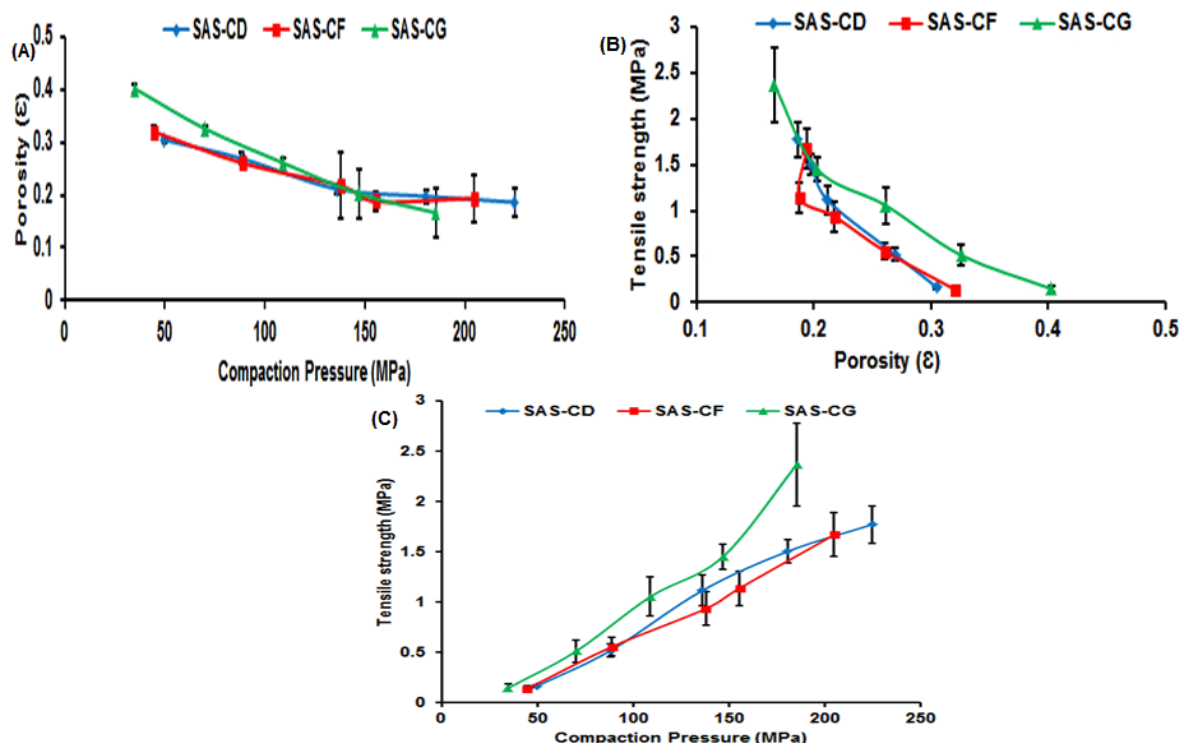


Fig. 5. CTC plots for SAS-CD, SAS-CF and SAS-CG. (A) Compressibility Plot (B) Compactability Plot and (C) Tabletability Plot (n=3)

Compactibility is a measure of the ability of a material to form compacts of sufficient tensile strength under the effect of densification (Ghori Conway 2016; Joiris et al., 1998; Upadhyay et al., 2013; Yadav et al., 2017). It is illustrated as a plot of tensile strength against

porosity in Fig. 5B. For all three materials, tensile strength of compacts increased with a decrease in porosity. The particles were brought in close proximity to each other at low porosity to facilitate bonding which results in an increase in tensile

strength (Ogunjimi and Alebiowu 2014). The tensile strength of a tablet is an outcome of the bonding area between adjacent particles and bonding strength (strength of the interaction over a unit area) (Osei-Yeboah et al., 2016). The plot shows that compacts of higher tensile strength were obtained with SAS-CG at the same level of porosity when compared to SAS-CD and SAS-CF. This is consistent with Heckel analysis that showed a lower yield pressure because of plasticity. A greater degree of plasticity brings particles in close proximity to each other allowing stronger bond formation at higher compaction pressures. More contact points were therefore generated in compacts involving SAS-CG. Certain extrinsic powder characteristics such as particle size, size distribution, surface area, bulk density and porosity may have impacted on the compressibility and compactibility of these materials as seen in other studies (Egart et al., 2014; Khomane et al., 2013).

Tabletability is the capacity of a powdered material to be transformed into a tablet of specified strength under the effect of compaction pressure (Ghori and Conway, 2016; Joiris et al., 1998; Upadhyay et al., 2013; Yadav et al., 2017). It is represented by a plot of tensile strength against compaction pressure (Fig. 5C). The plot shows that tensile strength of compacts produced increased across the range of compaction pressures utilized for all three materials. This was expected as increasing the compaction pressure led to more

energy being transmitted to the powder bed during the compaction process and allowing more interparticulate bond formation (Xu et al., 2016). The tensile strength of compacts obtained with SAS-CD and SAS-CF were lower than that of SAS-CG at the same compaction pressure indicating that a greater degree of tabletability was attained with SAS-CG due to the combined effect of bonding area (compressibility) and bonding strength (compactibility). It also implies that a greater degree of elastic recovery may have occurred with SAS-CD and SAS-CF compacts during decompression that may have lowered the tensile strength relative to SAS-CG compacts. The tabletability of a material is crucial to the formation of robust tablets devoid of tableting defects like capping and lamination. Hence, only excipients that will enhance the tabletability of a formulation should be selected.

To evaluate the lubrication potential of the three materials, the parameters of ejection shear stress and detachment force were obtained during powder compaction. Figure 6A and B represents the ejection shear stress and detachment force plots respectively. Ejection shear stress is the stress generated during the tablet ejection process and it is represented by a plot of ejection shear stress against compaction pressure (Gamlen, 2017; Pitt et al., 2015). The plot shows an increase in ejection shear stress as the compaction pressure increases for all three materials.

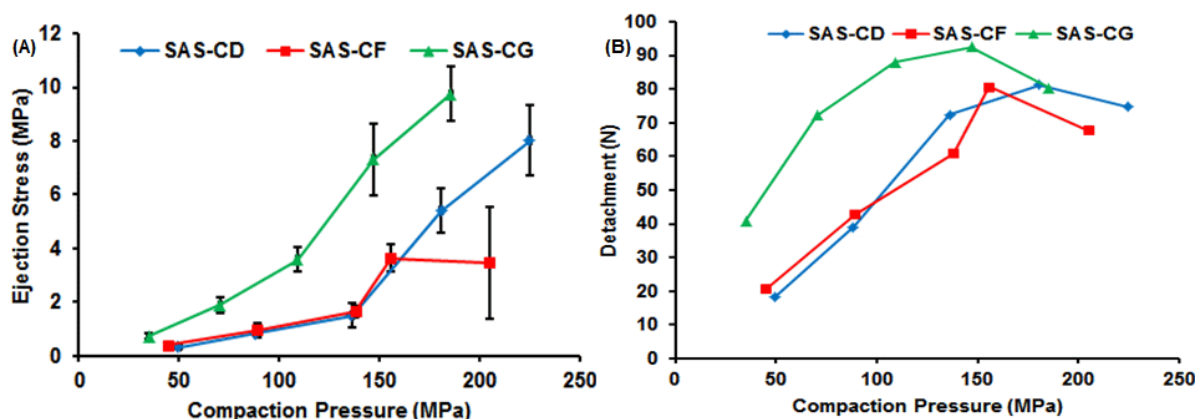


Fig. 6. (A) Ejection and (B) Detachment Plots for SAS-CD, SAS-CD and SAS-CG (n=3)

Similarly, the detachment force plot shows an increase in detachment force as compaction pressure increases for all three materials. This parameter describes the force required to detach a tablet from the punch face once it is ejected from the die. Of the three materials,

SAS-CG gave the highest ejection shear stress and detachment force across the range of compaction pressures employed indicating that it had limited self-lubricating property. This could be attributed to the high tensile strength of tablets produced by SAS-CG

which increases the stress and force for ejection and detachment respectively during tableting. SAS-CD and SAS-CF had lower ejection shear stress and detachment force suggesting a greater degree of self-lubricating potential. Ejection shear stress > 5 MPa has been associated with manufacturing problems like capping and lamination (Gamlen, 2017; Pitt et al., 2015). To avoid the occurrence of tableting defects with the use of these materials in tableting, it will be necessary to properly lubricate formulations containing these materials.

### Tablet properties

The physical properties of paracetamol tablets produced by direct compression with the developed co-processed excipients are given in Table 4. Mean tablet weight ranged between 499.2 - 511.3 mg. Based on the target tablet weight of 500 mg, the % limit allowed for variation is 5%. Hence, all the batches passed the weight variation test according to the USP requirements. Uniformity in weight of tablets has been attributed to the uniform flow of the formulation mix during the filling of the die leading to compression. This is a critical stage as poor flow will lead to a wide variation in tablet weight that may adversely affect content uniformity of tablets. The thickness values obtained for each batch of tablets correlated well with the mean tablet weight as higher thickness values corresponded to higher mean tablet weight. Tensile strength of tablets did not differ significantly across the batches even though the CTC profile revealed slight differences among the three materials. Notwithstanding, the friability of tablets showed some degree of variation among the three materials. The widely acceptable limit for friability is 1% and only tablets of SAS-CG satisfied the

requirement. This may be attributed to the predominant plastic deformation profile of SAS-CG that facilitated the formation of stronger bonds during compression resulting in tablets of sufficient mechanical strength. The higher yield pressure ( $P_y$ ) obtained for SAS-CD and SAS-CF during Heckel analysis is an indication that a greater degree of deformation occurred by fragmentation (brittle fracture). Hence, it is more likely that weaker tablets will be formed by these materials as reflected in the friability. Evaluation of disintegration time shows that all the batches of tablets disintegrated within 1 min which is typical for co-processed excipients containing colloidal silicon dioxide (El-Barghouthi et al., 2008; Nagpal et al., 2012; Rojas and Kumar, 2011). A more rapid disintegration was observed in SAS-CG tablets. This may have occurred as a result of the low bulk density of SAS-CG characterized by the presence of intergranular pore spaces creating more room for water uptake. There is also the likelihood of a preferential distribution of colloidal silicon dioxide on the surface of the co-processed particles of SAS-CG generated by co-granulation that creates a network of channels on the surface of tablets facilitating the rapid uptake of water during disintegration. The drug-release profiles of SAS-CD, SAS-CF and SAS-CG is presented as Fig. 7. Maximum drug release did not exceed 45% after 60 mins suggesting that more time will be required to attain 100% released. Even though disintegration of tablets was rapid, dissolution did not follow the same pattern as expected. There is a remote possibility that the drug, paracetamol was tightly bound by the excipient and so a longer time will be required to release the drug into solution. It goes to say that rapid disintegration does not always translate into rapid dissolution as tablets only disintegrate into

**Table 4.** Physical properties of tablets produced with the three co-processed excipients. Values in parentheses represent  $\pm$ SD, (n=6)

Properties	SAS-CD	SAS-CF	SAS-CG
Weight uniformity (g)	511.3 (9.2)	502.8 (14.3)	499.2 (10.1)
Thickness (mm)	4.32 (0.1)	4.27 (0.04)	4.11 (0.15)
Crushing strength (N)	76 (11.4)	85 (8.7)	85 (7.1)
Tensile strength (MN/m <sup>2</sup> )	0.93 (0.14)	1.06 (0.11)	1.1 (0.09)
Friability (%)	1.54 (0.03)	1.91 (0.06)	0.81 (0.04)
Disintegration time (min)	0.85 (0.08)	0.62 (0.1)	0.37 (0.04)

fragments containing the drug which has to be released into solution. This agrees with the findings of Odeku (2005) where 100% release of paracetamol was achieved in 120 mins.

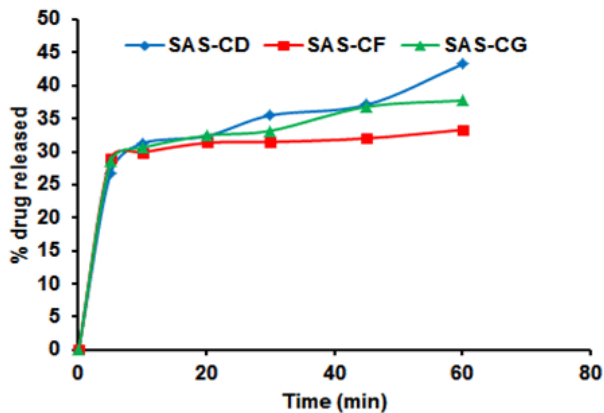


Fig. 7. Dissolution plot showing the *in vitro* drug release profiles of SAS-CD, SAS-CF and SAS-CG

## CONCLUSIONS

A comparative study was carried out to evaluate the effect of different co-processing methods on the powder and tableting properties of a co-processed excipient consisting of MS (90%), ACA (7.5%) and CSD (2.5%). The methods of co-processing evaluated generated SAS-CD (co-dispersion), SAS-CF (co-fusion) and SAS-CG (co-granulation) as co-processed excipients. Characterization of the powder properties of the three excipients revealed similarities in the flow parameters, particle density and moisture content while differences were observed in the particle size, dilution potential and LSR which can be attributed to the method of co-processing. FT-IR analysis did not reveal any chemical change occurring in the material as a result of the method of co-processing. Compaction and tableting properties of the three excipients showed that SAS-CG exhibited a greater degree of plastic deformation owing to the lower yield pressure obtained in comparison to the other two excipients. This facilitated the formation of tablets with sufficient mechanical strength, rapid disintegration and minimal friability.

Summarily, the findings reveal that SAS-CG produced by co-granulation performed better in terms of powder, compaction and tableting properties owing to the effect of particle size, bulk density, surface properties and deformation behaviour modulated by the method of co-processing. This

study therefore highlights the importance of selecting a robust method for co-processing that will deliver the desired functionality in tableting.

## ACKNOWLEDGEMENTS

The authors will like to thank Gamlen Tableting Ltd, UK for carrying out the compaction analysis. The authors also thank Kerry ingredients and flavours Ltd, Ireland and Evonik industries, Germany for the gift samples of acacia gum and colloidal silicon dioxide respectively.

## REFERENCES

- Adeoye, O., Alebiowu, G. (2014a). Evaluation of co-processed disintegrants produced from tapioca starch and mannitol in orally disintegrating paracetamol tablets. *Acta Poloniae Pharmaceutica N Drug Research*, 71(5), 803-811.
- Adeoye, O., Alebiowu, G. (2014b). Flow, packing and compaction properties of novel coprocessed multifunctional directly compressible excipients prepared from tapioca starch and mannitol. *Pharmaceutical Development and Technology*, 7450(8), 901-910.
- Alakayleh, F., Rashid, I., Al-Omari, M. M. H., Al-Sou'od, K., Chowdhry, B. Z., Badwan, A. A. (2016). Compression profiles of different molecular weight chitosans. *Powder Technology*, 299(May), 107-118.
- Alebiowu, G., Femi-Oyewo, M. N. (1998). Further studies on Datura metel Linn powder I: effect of surfactants on the granule and compact properties. *Phytotherapy Research*, 12(2), 123-126.
- Camargo, J. J. R. (2011). Assessment of co-processing of cellulose II and silicon dioxide as a platform to enhance excipient functionality. University of Iowa.
- Chauhan, S. I., Nathwani, S. V., Soniwala, M. M., Chavda, J. R. (2016). Development and characterization of multifunctional directly compressible co-processed excipient by spray drying method. *AAPS PharmSciTech*, Aug(1), 1-9.
- Daraghme, N., Rashid, I., Al Omari, M. M. H., Leharne, S. A., Chowdhry, B. Z., Badwan, A. (2010). Preparation and characterization of a novel co-processed excipient of chitin and crystalline mannitol. *AAPS PharmSciTech*, 11(4), 1558-1571.
- Egart, M., Ilic, I., Jankovic, B., Lah, N., Srcic, S. (2014). Compaction properties of crystalline pharmaceutical ingredients according to the Walker model and nanomechanical attributes. *International Journal of Pharmaceutics*, 472, 347-355.
- El-Barghouthi, M., Eftaiha, A., Rashid, I., Al-Remawi, M., Badwan, A. (2008). A novel superdisintegrating agent made from physically modified chitosan with silicon dioxide. *Drug Development and Industrial Pharmacy*, 34(4), 373-383.

- Gamlen, M. (2017). Analysis of PROSOLV® EASYtab with added Ascorbic Acid.
- Gamlen, M. J. D., Martini, L. G., Al Obaidy, K. G. (2015). Effect of repeated compaction of tablets on tablet properties and work of compaction using an instrumented laboratory tablet press. *Drug Development and Industrial Pharmacy*, 41(1), 163-169.
- Ghori, M. U., Conway, B. (2016). Powder compaction: Compression properties of cellulose ethers. *British Journal of Pharmacy*, 1, 19-29.
- Goyanes, A., Souto, C., Martínez-pacheco, R. (2011). Co-processed MCC-Eudragit E excipients for extrusion - spheronization. *European Journal of Pharmaceutics and Biopharmaceutics*, 79, 658-663.
- Heckel, R. W. (1961). Density-Pressure relationships in powder compaction. *Transactions of the Metallurgical Society of AIME*, 221, 671-675.
- Ilić, I., Govedarica, B., Šibanc, R., Dreu, R., Srčić, S. (2013). Deformation properties of pharmaceutical excipients determined using an in-die and out-die method. *International Journal of Pharmaceutics*, 446(1), 6-15.
- Jivraj, M., Martini, L. G., Thomson, C. M. (2000). An overview of the different excipients useful for the direct compression of tablets. *Pharmaceutical Science and Technology Today*, 3(2), 58-63.
- Joiris, E., Di Martino, P., Berneron, C., Guyot-Hermann, A., Guyot, J. (1998). Compression behavior of orthorhombic paracetamol. *Pharmaceutical Research*, 15(7), 1122-1130.
- Katsuno, E., Tahara, K., Takeuchi, Y., Takeuchi, H. (2013). Orally disintegrating tablets prepared by a co-processed mixture of micronized crospovidone and mannitol using a ball mill to improve compactibility and tablet stability. *Powder Technology*, 241, 60-66.
- Khomane, K. S., More, P. K., Raghavendra, G., Bansal, A. K. (2013). Molecular understanding of the compaction behavior of indomethacin polymorphs. *Molecular Pharmaceutics*, 10(2), 631-639.
- Kittipongpatana, O. S., Kittipongpatana, N. (2011). Preparation and physicomachanical properties of co-precipitated rice starch-colloidal silicon dioxide. *Powder Technology*, 217, 377-382.
- Mshelia, J., Apeji, Y., Olayemi, O. (2015). Powder, compaction and tableting properties of co-processed silicified starch. *British Journal of Pharmaceutical Research*, 6(2), 131-140.
- Nachaegari, S. K., Bansal, A. K. (2004). Coprocessed excipients for solid dosage forms. *Pharmaceutical Technology*, (January), 52-64.
- Nagpal, M., Goyal, A., Kumar, S., Singh, I. (2012). Starch-silicon dioxide coprecipitate as superdisintegrant : formulation and evaluation of fast disintegrating tablets. *International Journal of Drug Delivery*, 4, 164-174.
- Odeku, O. A. (2005). Assessment of Albizia zygia gum as a binding agent in tablet formulations. *Acta Pharm.*, 55, 263-276.
- Odeku, O. A. (2013). Potentials of tropical starches as pharmaceutical excipients: A review. *Starch/Staerke*, 65(1-2), 89-106.
- Odeku, O. A., Schmid, W., Picker-Freyer, K. M. (2008). Material and tablet properties of pregelatinized (thermally modified) Dioscorea starches. *European Journal of Pharmaceutics and Biopharmaceutics*, 70(1), 357-71.
- Ogunjimi, A. T., Alebiowu, G. (2013). Flow and consolidation properties of neem gum coprocessed with two pharmaceutical excipients. *Powder Technology*, 246(60), 187-192.
- Ogunjimi, A. T., Alebiowu, G. (2014). Material and tableting properties of Azadirachta Indica gum with reference to official acacia gum. *Acta Poloniae Pharmaceutica - Drug Research*, 71(1), 107-118.
- Olowosulu, A. K., Oyi, A., Isah, A. B., Ibrahim, M. A. (2011). Formulation and evaluation of novel coprocessed excipients of maize starch and acacia gum ( StarAc ) for direct compression tableting. *International Journal of Pharmaceutical Research and Innovation*, 2, 39-45.
- Osei-Yeboah, F., Chang, S., Sun, C. C. (2016). A critical examination of the phenomenon of bonding area - bonding strength interplay in powder tableting. *Pharmaceutical Research*, 1-7.
- Osei-Yeboah, F., Sun, C. C. (2015). Tabletability modulation through surface engineering. *Journal of Pharmaceutical Sciences*, 1-4.
- Patel, S., Kaushal, A. M., Bansal, A. K. (2006). Compression physics in the formulation development of tablets. *Critical Reviews in Therapeutic Drug Carrier Systems*, 23(1), 1-65.
- Paul, S., Sun, C. C. (2017). Lubrication with magnesium stearate increases tablet brittleness. *Powder Technology*, 309, 126-132.
- Paul, S., Taylor, L. J., Murphy, B., Krzyzaniak, J., Dawson, N., Mullarney, M. P., Meenan, P., Sun, C. C. (2016). Mechanism and kinetics of punch sticking of pharmaceuticals. *Journal of Pharmaceutical Sciences*, 305, 1-8.
- Pitt, K. G., Webber, R. G., Hill, K. A., Dey, D., Gamlen, M. J. (2015). Compression prediction accuracy from small scale compaction studies to production presses. *Powder Technology*, 270, 490-493.
- Rojas, J., Buckner, I., Kumar, V. (2012). Co-processed excipients with enhanced direct compression functionality for improved tableting performance. *Drug Development and Industrial Pharmacy*, 38(10), 1159-1170.
- Rojas, J., Kumar, V. (2011). Comparative evaluation of silicified microcrystalline cellulose II as a direct compression vehicle. *International Journal of Pharmaceutics*, 416(1), 120-128.
- Saha, S., Shahiwala, A. F. (2009). Multifunctional coprocessed excipients for improved tableting performance. *Expert Opinion on Drug Delivery*, 6(2), 197-208.
- Sharma, P., Modi, S. R., Bansal, A. K. (2015). Co-processing of hydroxypropyl methylcellulose (HPMC) for improved aqueous dispersibility. *International Journal of Pharmaceutics*, 485(1), 348-356.

- Sonnergaard, J. M. (1999). A critical evaluation of the Heckel equation. *International Journal of Pharmaceutics*, 193, 63–71.
- Sun, C. C. (2009). Materials Science Tetrahedron – A useful tool for pharmaceutical research and development. *Journal of Pharmaceutical Sciences*, 98(5), 1671–1687.
- Sun, C. C. (2011). Decoding powder tabletability: Roles of particle adhesion and plasticity. *Journal of Adhesion Science and Technology*, 25(4–5), 483–499.
- Sun, C. C. (2017). Microstructure of tablet – Pharmaceutical significance, assessment, and engineering. *Pharmaceutical Research*, 34(5), 918–928.
- Thapa, P., Lee, A. R., Choi, D. H., Jeong, S. H. (2017). Effects of moisture content and compression pressure of various deforming granules on the physical properties of tablets. *Powder Technology*, 310(January), 92–102.
- Thoorens, G., Krier, F., Leclercq, B., Carlin, B., Evrard, B. (2014). Microcrystalline cellulose , a direct compression binder in a quality by design environment – A review. *International Journal of Pharmaceutics*, 473, 64–72.
- United States Pharmacopeial Convention. (2011). USP Protocol for Dissolution studies. In USP/NF.
- Upadhyay, P., Khomane, K. S., Kumar, L., Bansal, A. K. (2013). Relationship between crystal structure and mechanical properties of ranitidine hydrochloride polymorphs. *CrystEngComm*, 15(19), 3959–3964.
- Vanhoorne, V., Peeters, E., Snick, B. Van, Remon, J. P., Vervaet, C. (2014). Crystal coating via spray drying to improve powder tabletability. *European Journal of Pharmaceutics and Biopharmaceutics*, 88(3), 939–944.
- Walker, E. E. (1923). The properties of powders. Part VI. The compressibility of powders. *Transactions of the Faraday Society*, 19(July), 73.
- Wang, S., Li, J., Lin, X., Feng, Y., Kou, X., Babu, S., Panicucci, R. (2015). Novel coprocessed excipients composed of lactose , HPMC , and PVPP for tableting and its application. *International Journal of Pharmaceutics*, 486(1), 370–379.
- Xu, M., Heng, P. W. S., Liew, C. V. (2016). Formulation and process strategies to minimize coat damage for compaction of coated pellets in a rotary tablet press: A mechanistic view. *International Journal of Pharmaceutics*, 499(1), 29–37.
- Yadav, J. A., Khomane, K. S., Modi, S. R., Ugale, B., Yadav, R. N., Nagaraja, C. M., Kumar, N., Bansal, A. K. (2017). Correlating Single Crystal Structure , Nanomechanical , and Bulk Compaction Behavior of Febuxostat Polymorphs. *Molecular Pharmaceutics*, 14, 866–874.