Assessing The Material, Compressional And Mechanical Properties Of Three Novel Excipients For Direct Compression.

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ABSTRACT

This investigation was aimed at evaluating the physical, mechanical and compressional properties of three new novel excipients (co-processed polymers of Cocoyam starch and gelatin) as sole excipients in metronidazole tablet formulations using direct compressional method of tablet preparation. Starch extracted from Cocoyam was co-fused with gelatin at different ratio: 90/10, 80/20 and 70/30. The obtained novel excipients were batched as AMI_10, AMI_20 and AMI_30; these were thereafter evaluated as direct compressible excipient in metronidazole tablet formulations. Physical and flow parameter tests were conducted on the novel excipients using standard methods, while the compressional and mechanical properties were evaluated using Heckel, Kawakita equations, and the brittle fracture index (BFI). The yields of the various batches co-processed new excipients were above 80% , no interactions were observed between the two components (starch and gelatin) as showed in the FTIR spectra and there were improvements in the flow characteristics of the novel excipients when compare to native starch. The mean yield pressure p_y an indication of onset of plastic deformations, can be ranked as, AMI_10 < AMI_30 < AMI_20, while the total plastic deformations, P_k was in the rank order of, AMI_30 < AMI_10 <, AMI_20. AMI_30, with the highest total plastic deformations, invariable also had the least brittle fracture index (BFI) and as such AMI_30 will be expected to give tablets with low or no production defects such as capping and lamination when used as a direct compressible excipient.

Key Words: Cocoyam Starch, co-processing, and direct compression.

INTRODUCTION

Direct compression (DC) method of tablet production involve compressing powdered materials directly to form tablets without pretreatment or agglomeration of powders into granules. This offers lots of cost advantages to pharmaceutical companies since fewer processing steps are involved, require less equipments and the process can be use for both heat and water sensitive pharmaceutical materials (Gohel and Jogani, 2002). The DC excipients must therefore have excellent flowability and good compressional properties to ensure consistent batch to batch production of tablets with excellent quality, (Gohel *et al*, 1999). Material flowability and compression depends on its intrinsic properties such as, particle shape/size, density, moisture content and plasticity, (Joshi, 2002), (Alebiowu and Itiola, 2002). The high cost of DC excipients presently available had made most pharmaceutical manufacturers to shy away from direct compression method of tablet manufacturing even though DC simple and cost effective (Peter *et al*, 2009). There is therefore the need to look at the possibilities of developing novel excipients for direct compression from materials that are readily available at low cost.

Starch is naturally and abundantly available at low cost, thus it's widely used in both food and pharmaceutical industries (Itiola, 1991). Despite its usefulness as binder, disintegrant and filler in pharmaceutical industries, native starch has high resistant to flow which made it not suitable for DC unless if modified via cross linking or co-processing with other materials that are compatible and can improve its functionality (Ogunjimi and Alebiowu, 2013; Adeoye and Alebiowu, 2013). This study is aimed at addressing some of the limitations of native cocoyam starch by reducing the resistant of NCS to flow and compressing through co-processing techniques.

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MATERIALS AND METHODS.

MATERIALS.

Cocoyam (*Colocasia esculenta*) was obtained from Ganmon market, Ilorin, Kwara state, Nigeria. Sodium metabisulphite (BDH limited, Poole, England). Distilled water, Metronidazole powder (Global healthcare, Nigeria). The native cocoyam starch (NCS) was prepared in our laboratory using an established method of starch extraction, Young (1984).

METHODS.

Preparation of Co-processing Starch with gelatin by co-fusion.

Batch coded AMI_90 was prepared by co-fusing 90g of Native Cocoyam starch (NCS) and 10g of gelatin. These were separately dispersed in known quantity of water and thereafter heated over a water bath. The gelatin suspension was thereafter added to the starch slurry where stirring was continued for about 30 minutes at low heat (40^oC) until a thick mass was formed. This was then sun dried to a constant weight before grinding using an Alizco milling machine (Type AZIO, Alizco Ltd, Shangai, China.). This same procedure was however repeated for the other batches with the following ratios of starch and gelatin respectively 80:20, 70:30.

Characterization of AMI_10, AMI_20, AMI_30 and NCS

(i) ***Angle of repose***

This was done using a fixed load of the material which was placed in a standing open-ended dry cylindrical tube. The cylinder was gently raised to leave a heap of the powdered gum. The circumference of the base of the heap was outlined and its radius, *r*, measured. The height, *h*, of the heap was also measured. The repose angle θ was calculated using the following equation:

$$\theta = \tan^{-1}(h/r) \quad (1)$$

The procedure was carried out for the remaining two batches AMI_20 anAMI_30 and all determinations were in triplicate.

(ii) ***Flow rate.***

The flow rate in g/s was determined using a flow tube with an orifice of 10 cm (Alebiowu and Femi - Oyewo, 1998), while keeping the powdered materials load, degree of packing and height of funnel constant throughout the determination. Determinations were in triplicate and the same procedure was carried out for the remaining batches.

(iii) ***Determination of Hausner's ratio and compressibility index***

The Hausner's (1967) ratio (HR) was determined from the bulk and tapped volumes according to the relationships: Vt and Vb

$$HR = \frac{Vt}{Vb} \quad (2)$$

while the Compressibility index (CI) was obtained from the following i.e.

$$CI = 1 - \frac{Vb}{Vt} \quad (3)$$

where Vt is the tapped volume (cm^3) and Vb is the bulk volume (cm^3)

(iii) ***Determination of density parameters.***

The particle densities (ρ_{PD}) of the three novel excipients were determined by pycnometer method using xylene as the displacement fluid. The particle density (ρ_{PD}) was calculated using equation (4);

$$\rho_{PD} = (W_2 \times W_3) / 50 (W_3 - W_4 + W_2 + W) \quad (4)$$

where W = the weight of empty pycnometer

W_1 = weight of pycnometer filled with Xylene.

$W_2 = W_1 - W$

W_3 = weight of sample

W_4 = weight of sample + weight of pycnometer + Xylene.

The bulk and tapped densities(BD & TD) of Novel excipients were calculated from the ratio of the sample weight to its bulk volume and tapped volume respectively. The bulk volume was however determined by pouring known weight of powder at an angle of 45 ^{o} through a funnel into a glass measuring cylinder with a diameter of 21 mm and a volume of 50 mL. This was repeated three times and the mean value noted. This same procedure was carried out for the other two batches and native cocoyam starch for comparison.

(iv) Determination of moisture content.

A 5 g sample of the AMI_10 was placed in a porcelain dish and dried in an oven at 105 ^{o}C until a constant weight was obtained. The moisture content was obtained using the equation below;

$$\text{Moisture content (MC)} = \frac{initial\ weight - final\ weight}{final\ weight} \quad (5)$$

Same procedure was however repeated for the remaining batches.

(v) Fourier Transform Infrared (FTIR) spectra analysis

The FTIR spectra of the starch samples were recorded using an IR spectrometer (Perkin- Elmer, Model 2000, USA). 5mg of each sample were dispersed in 200mg KBr. The scanning range was conducted between1000 to 4000 cm^{-1}.

(*vi*) *Digital Photo optical microscopy*

The starch powders were observed using a digital optical microscope fitted with camera (ESKP 30, Philips, Kassel, Germany) A small drop of water on one side of a standard microscope slide. Using a narrow pointed spatula or dissecting needle about 5 mg of sample was transfer onto the water. This was mixed thoroughly to disperse the sample and cover slip was placed over the suspension taking care to avoid entrapment of air bubbles; excess water was bleed or wick off with a small piece of tissue paper held at the edge of the cover slip to obtain a thin film, the slide is then observed under 40X magnification, dimensions of about 100 particles were noted and the average particle size calculated. Images of sample were thereafter captured using the digital camera.

Preparation of tablets

The compressional and compaction properties of the excipients were studied by making them into compacts consisting of 200 mg of metronidazole and 300 mg of novel excipient each. The compacts were prepared by compressing 500 mg of each formulation, manually filled into the die cavity of 10mm flat punches, at five different pressures (40.7–203MNm^{-2}). Six compacts were prepared at each compression force and stored over silica gel for 48 h to allow elastic recovery and hardening, and to prevent false low yield values.

Tablets with a hole (1.54mm diameter) at their center were made using an upper punch with a hole through the center and a lower punch fitted with a pin, (Itiola 1991).The compacts were there after evaluated for thickness, diameter and weight uniformity.

Heckel and Kawakital analysis of compacts.

The compression behaviour of the excipients was characterized using both the Heckel and Kawakita models as shown in Equation (6 and7) respectively;

$$\ln \frac{1}{1-D} = kP + A \qquad (6)$$

where D is the relative density of the tablets at applied pressure P and K is the material dependent constant, i.e. the slope of the straight line portion of the Heckel plot and the reciprocal of K is the mean yield pressure (P_y), Heckel (1964).

The Kawakita equation however, is used to study powder compression using the degree of volume reduction, *C*, and is written as;

$$C = (V_o - V_p)/V_o = abP/(1 + bP) \qquad (7)$$

The equation, in practice, can be rearranged to give

$$P/C = P/a + 1/ab \qquad (8)$$

Where V_o is the initial bulk volume for granular materials and V_p is the bulk volume after compression. The constant ***a*** is equal to the minimum porosity of the material before compression; the constant *b*, which is termed the coefficient of compression is related to the plasticity of the material. The reciprocal of *b* is related to the pressure term P_k, which is the pressure required to reduce the powder bed by 50 %, (Kawakita and Ludde, 1970; Shivanand and Sprockel, 1992).

Determination of tablet crushing strength, tensile strength and Brittle fracture Index

The tensile strength of the compacts was determined using the method of Fell and Newton. An Erweka digital hardness tester (G.B CALEVA, Dorset, England) was used at room temperature to determine the force required to diametrically break the tablets into two equal halves. The tensile strength (T) was then calculated according to formula:

$$T = \frac{2F}{\pi dt} \qquad (9)$$

where **F** denotes the crushing strength (N), **d** and **t** are the tablet diameter (m) and thickness (m), respectively.

The Brittle Fracture index values of tablets were calculated using the Hiestand equation (Hiestand, *et al* 1977);

BFI = 0.5[(T/ To) - 1] (10)

T_o and T represent the tensile strength of tablet with and without hole respectively

RESULTS AND DISCUSSION

The microscopies of the three novel excipients, AMI_10, AMI_20 and AMI_30 are presented in fig 1,2, and 3, respectively. While AMI_30 particles are polygonal in shape, have the highest granular diameter and the particle are free from each other, these suggests material with low forces of attraction between the particles. AMI_10 particles are spherical and possessed the least granule diameter. AMI_20 particles are irregularly shape with granular diameter of about 16.48 micron. Increasing the concentration of gelatin incorporated has being observed to increase the mean granule size of the excipients, and a reduction in sphericity of the excipient.

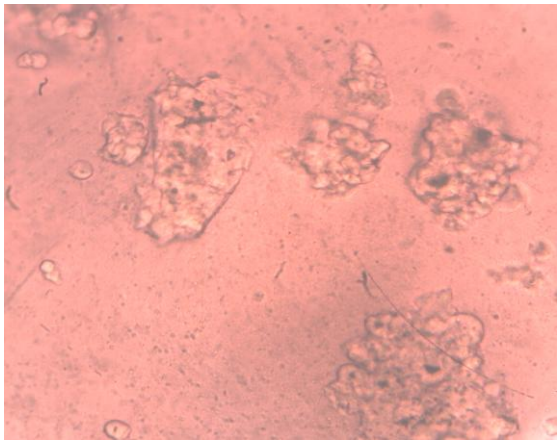


Figure 1: Photomicrograph for ami_10

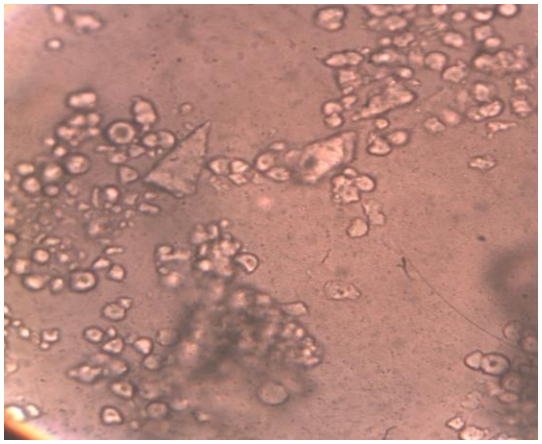


Figure 2; Photomicrograph for ami_20

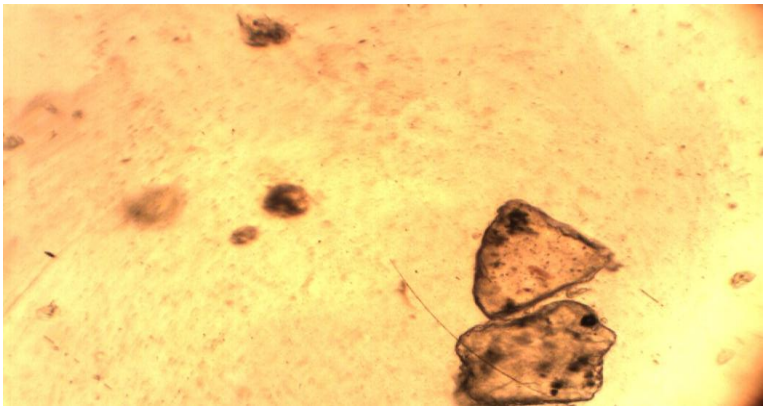


Figure 3; Photomicrograph For Ami_30

Table 1 Density and flow properties of native and co-processed excipients.

Materials	Angle of repose(º)	Flow rate (gs^{-1})	TD (gcm^{-3})	BD (gcm^{-3})	CI	HR	MGD (µm)
AMI_10	$36.86^{\pm0.002}$	$0.67^{\pm0.000}$	$0.036^{\pm0.002}$	$0.028^{\pm0.004}$	22.2	1.36	$14.90^{\pm0.003}$
AMI_20	$33.65^{\pm0.000}$	$0.79\pm^{0.001}$	$0.029^{\pm0.001}$	$0.023^{\pm0.002}$	20.7	1.26	$16.48^{\pm0.003}$
AMI_30	$32.01^{\pm0.002}$	$1.07^{\pm0.001}$	$0.028^{\pm0.001}$	$0.024^{\pm0.002}$	14.3	1.17	$17.20^{\pm0.001}$
NCS	$63.10^{\pm0.001}$	$0.34^{\pm0.000}$	$0.661^{\pm0.001}$	$0.506^{\pm0.002}$	23.0	1.31	$14.88^{\pm0.004}$

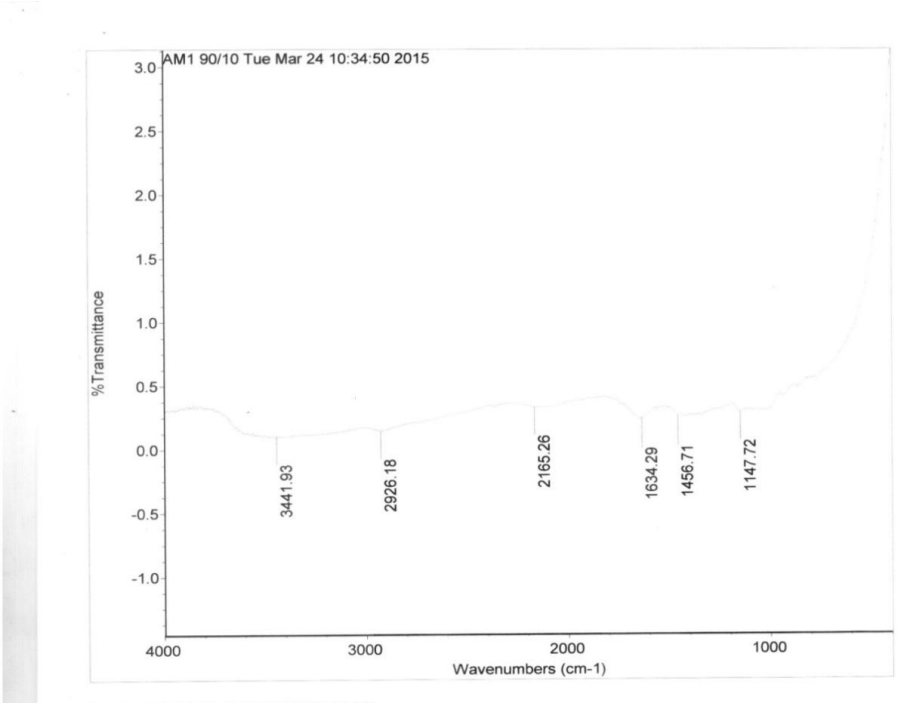
Where MGD and NCS, represent the mean granular diameter and the native cocoyam starch respectively.

The densities and the flow parameter of the three novel excipients are as presented in table 1.The angle of repose, flow rate, and the HR are use to quantified the flow properties of the excipients. The

angle of repose (^{o}) gives an indication of the inter-particulate frictional forces operating within the powder system by quantifying the intrinsic resistance of the powder bed to flow, Staniforth and Aulton (2007).

Generally, powder material with values of (^{o}) less than 25^{o} have excellent flow rate, B.P (1998), (Armstrong, 1997). However values greater than 50 ^{o} suggests a material of high internal resistant to flow, while values falling between 30 to 35 ^{o}, are considered to be appropriate for solid dosage from technology, (Shangraw *et al*,1987). Co-processing of cocoyam starch with gelatin had significantly improved the flow of NCS as indicated by reduced angle of repose and a corresponding increase in the flow rate of the new novel excipients.

A form of correlation (inverse proportion) is now established by the fact that the novel excipient, AMI_30 with a least value of HR, and angle of repose among the co-processed excipients, also had the highest flow rate. Various researcher had also reported similar complex interplay between particle size, particle shape, particle size distribution and the intra- and inter-particulate forces at work within the particles makes it difficult to describe how these parameters individually affect the flowability of powders (Vasilenko *et al*, 2011; IIic *et al*,2009).



- **Figure 4: FTIR for AMI_10**

Figures 4,5 and 6 shows the FTIR spectral for the three new novel excipients with no visible interaction between gelatin and native Cocoyam starch.

The compaction data were analysis using Heckel model. Heckel analysis is a method for transforming a parametric view of the force and displacement signals to a linear relationship for materials undergoing compaction. The equation is based on the assumption that the densification on compaction pressure is first order (Fell, 1968; Bolhuis *et al* 2005). Values of mean yield pressure *Py* were calculated from the region of the plots (Figure 7) showing the highest correlation coefficient for linearity of >0.93 for all excipients.

AMI_20 , with the least Py values that is the fastest on set of plastic deformation, The Py values can be ranked, AMI_20 < AMI_10 < NCS < AMI <30.

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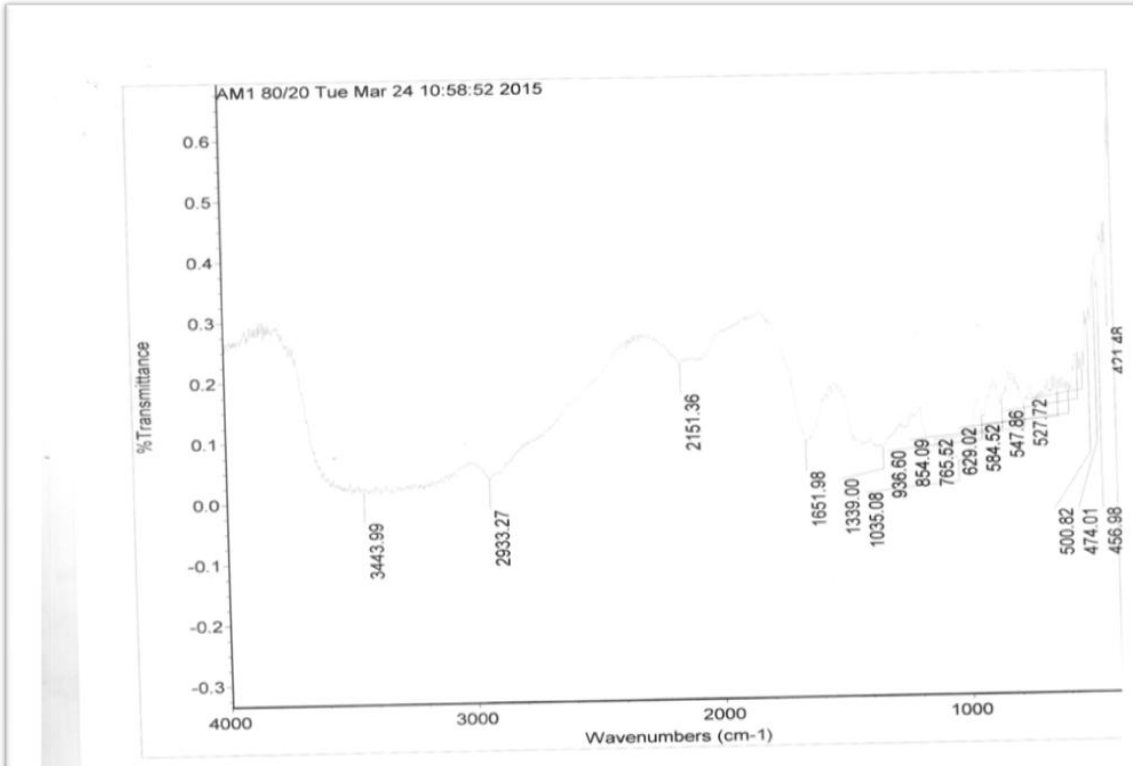

Figure 5: FTIR for AMI_20

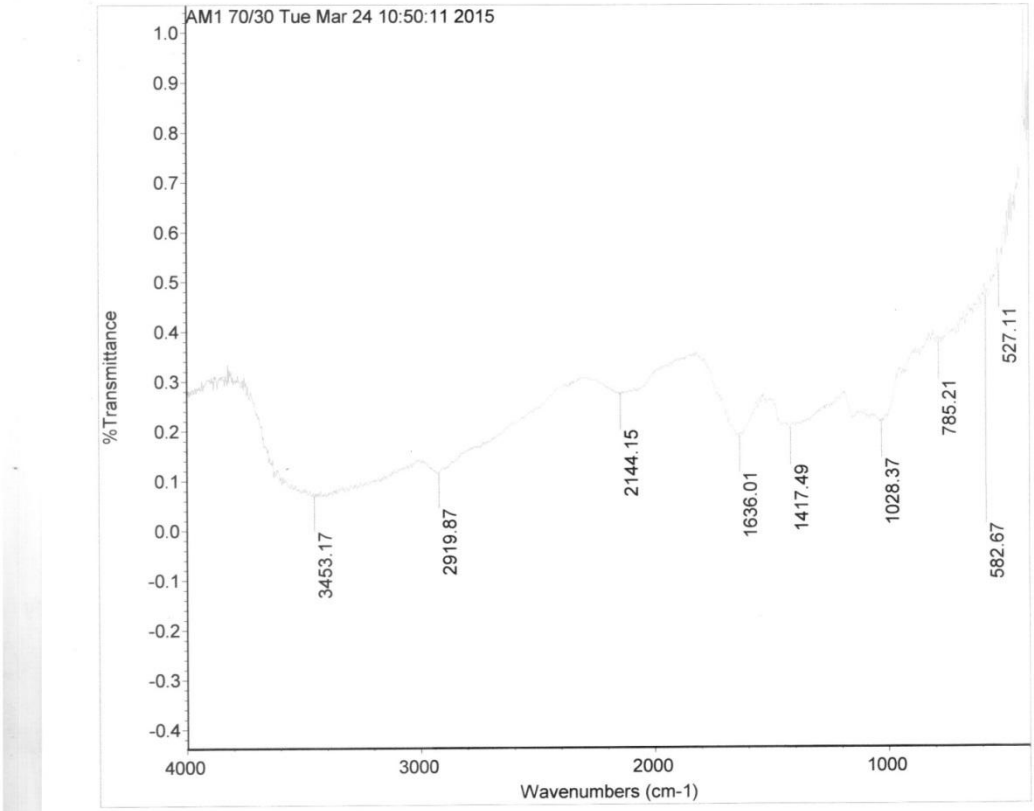

Figure 6: FTIR for AMI_30

Kawakita equation relates the volume reduction during compression to the applied pressure and a plot of P/C versus applied pressure gave a linear relationship at all compression pressures with a correlation coefficient of 0.999 for all the excipient, (figure 8). Values of a and ab were obtained from the slope and intercept of the Kawakita plot respectively. Pk values (total plastic deformation) were calculated from the reciprocal of values of b, and its inversely related to the total plastic deformation of a material during compression, the Pk values for the NCS and three novel excipients are of the ranking order of AMI_30 < AMI_10< AMI_20 < NCS. Therefore low Pk values are generally desirable for materials intended for use as direct compressible excipient, since plastic deformation create more binding points within compacts, and this invariably contribute to an increased mechanical properties of compacts (Alebiowu and Itiola, 2002;, Alebiowu, 2007)

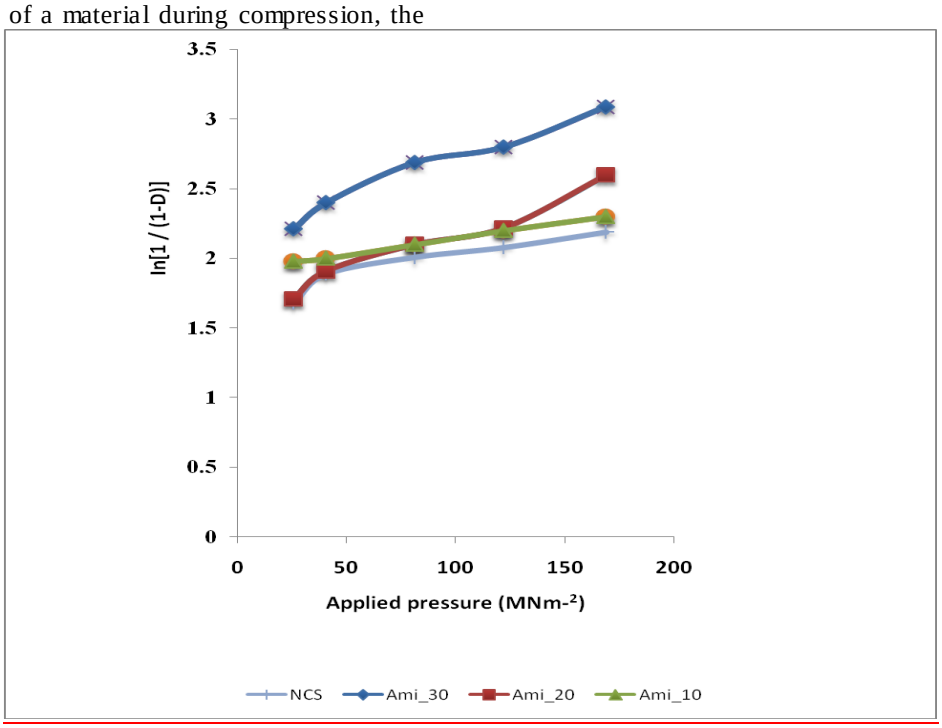

Figure 7: Plot of ln (1/1-D) against applied pressure (MNm^{-2})

Table 2: Heckel and Kawakita parameters

Material	D_A	D_O	D_B	P_y	D_1	P_{KI}
AMI_10	0.795	0.0070	0.791	260.4	0.993	3.01
AMI_20	0.877	0.0078	0.8692	236.9	0.990	3.64
AMI_30	0.850	0.0079	0.8421	276.2	0.991	2.34
NCS	0.761	0.3160	0.4450	267.9	0.899	3.70

Table 2 shows the values of the mean yield pressure Py for NCS and the three novel excipients. High Py is indication of higher yield strength, or higher forces of compaction are needed to initiate plastic deformations.

Values of T and BFI for the excipients at 0.90 relative density, are presented in Table 3. The ranking order of T for the novel excipients was AMI_30 >AMI_20 >AMI_10. > While the ranking order of BFI was AMI_10 >AMI_30 > AMI_20. A low BFI value is desired for the minimization of lamination and capping during tablet production. Furthermore, there is an inverse relationship between the Pk values and the T of tablets. Low Pk values ensures high plastic deformation of materials which would lead to more contact points for inter-particulate bonding within tablets, Itiola and Pilpel (1991) , Odeku et al 2007

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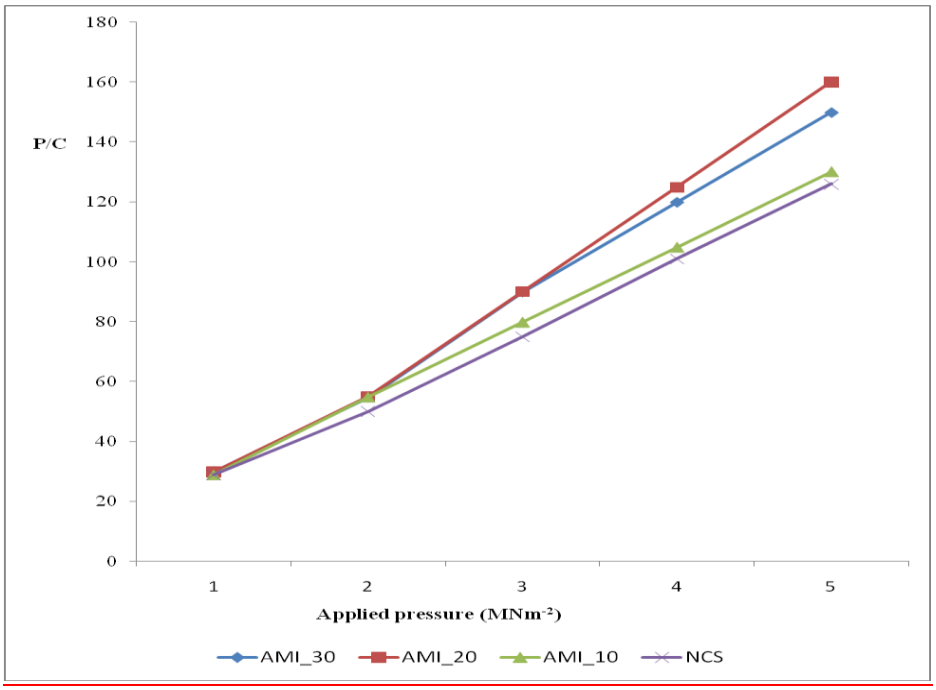

Figure 8: Plots of P/C versus applied pressure

Table 3; Values of Brittle Fracture index and Tensile strength of materials

Materials	T	T_o	BFI
AMI_10	0.749	0.281	0.832
AMI_20	1.131	1.067	0.029
AMI_30	1.511	1.229	0.114

The results of the tensile tests on the metronidazole tablets fit the general equation:

Log T (or To) = AD + B (11)

with a correlation coefficient > 0.991. A and B are constants which depend on the nature of materials involved and on the presence of a hole in the tablet.

CONCLUSION

The results obtained from this work revealed the followings: NCS (Native Cocoyam) and GLT (gelatin) can be co-processed to produce a novel excipient with enhanced flow and compressional properties better the starting materials. The morphological and physical properties of the novel excipients exert significant influence on the flow rate, compressional and mechanical properties of the novel excipients. The obtained novel excipients potential as direct compressible excipients was greater than those of the starting materials this is reflected in the compressibility and tensile strength of compacts.

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