# Characterization of modified tiger nut (*Cyperus esculentus*) starches: mechanical, compaction and drug release properties

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**ABSTRACT**

**Background:** Starch is a biopolymer generally used as excipient in drug formulations due to its availability, affordability, biocompatibility, inertness and biodegradability.

**Objective:** This study evaluated the mechanical, compaction and compressibility characteristics of modified starches from *Cyperus esculentus* tubers in directly compressed metronidazole tablet formulations.

**Methods:** The native starch extracted by maceration in water was modified via acid hydrolysis (ACS), pre-gelatinization (PCS) and enzyme hydrolysis (ECS). The modified starches were used in formulating metronidazole tablets at various compression pressures by direct compression. Their powder blends were assessed using the Kawakita model whereas the tablets were assessed for mechanical (crushing and tensile strengths) and compaction (Heckel model) properties in comparison with tablets prepared with microcrystalline cellulose (MCC).

**Results:** Kawakita analysis revealed that ECS powder exhibited the highest compressibility and also the least cohesive. ECS-based tablets showed acceptable mechanical properties and also had the fastest onset of plastic deformation with low mean yield pressure value (Py (62.79 MN/m2)) and inverse measure of plastic deformation value (Pk (3.344)).

**Conclusion:** Enzyme hydrolysis of *C. esculentus* starch resulted in a filler/binder modified product with direct compressibility property, which may be a substitute to microcrystalline cellulose in direct compression of tablets.

**Keywords:** Compaction, Heckel and Kawakita analyses, modified starch

# Caractérisation des amidons de souchet (*Cyperus esculentus* ) modifiés: propriétés mécaniques, de compaction et de libération de médicaments

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**RÉSUME**

**Contexte:** L'amidon est un biopolymère généralement utilisé comme excipient dans les formulations de médicaments en raison de sa disponibilité, de son prix abordable, de sa biocompatibilité, de son inertie et de sa biodégradabilité.

**Objectif:** Cette étude a évalué les caractéristiques mécaniques, de compaction et de compressibilité des amidons modifiés issus de tubercules de *Cyperus esculentus* dans des formulations de comprimés de métronidazole directement comprimés.

**Méthodes:** L'amidon natif extrait par macération dans l'eau a été modifié par hydrolyse acide (ACS), pré-gélatinisation (PCS) et Hydrolyse enzymatique (ECS). Les amidons modifiés ont été utilisés dans la formulation de comprimés de métronidazole à différentes pressions de compression par compression directe. Leurs mélanges de poudre ont été évalués à l'aide du modèle Kawakita tandis que les comprimés ont été évalués pour les propriétés mécaniques (résistance à l'écrasement et à la traction) et de compactage (modèle Heckel) en comparaison avec les comprimés préparés avec de la cellulose microcristalline (MCC).

**Résultats:** L'analyse de Kawakita a révélé que la poudre ECS présentait la compressibilité la plus élevée et également la moins cohésive. Les comprimés à base d'ECS ont montré des propriétés mécaniques acceptables et ont également eu le début de déformation plastique le plus rapide avec une faible valeur moyenne de pression d'élasticité/ d'écoulement (Py (62,79 MN/m2 )) et une mesure inverse de la valeur de déformation plastique (Pk (3,344)).

**Conclusion:** L'hydrolyse enzymatique de l'amidon de *C. esculentus* a donné lieu à un produit modifié de charge/liant / L'hydrolyse enzymatique de l'amidon de *C. esculentus* a permis d'obtenir un produit modifié en tant que charge/liant avec une propriété de compressibilité directe, qui peut être un substitut à/ remplacer la cellulose microcristalline dans la compression directe des comprimés.

**Mots clés :** Compaction, Analyses de Heckel et Kawakita, amidon modifié

## INTRODUCTION

Starch as one of the safest and most often used adjuvants in dosage formulations may be obtained from several sources. These starches have been extensively employed in a number of drug formulation processes in the pharmaceutical industries.[1] Their roles include uses as binders, disintegrants, diluents (filler), lubricants and glidants.[2,3]

Native starches have limited applications due to their instability with changes in temperature, pH and shear forces, insolubility in common organic solvents resulting in poor processibility and functional properties.[4] Hence, their modified derivatives possessing specific properties such as solubility, flowability, texture, heat tolerance, compressibility and compactibility are often used in industrial processes .[5,6]

Compression and compaction are characteristic properties of pharmaceutical powders under pressure. Compressibility refers to the deformation and volume reduction of a powder bed under pressure while compactibility is the formation of mechanically strong compacts or tablets. Based on the hypothesis that different mechanisms operate in distinct ranges of pressure applied to a powder bed, mathematical models generated from empirical relationships have been employed to describe the volume reduction or compaction mechanisms of powders.[7]

*Cyperus esculentus* is a grass plant that produces edible nut-like tubers. Though its probable origin may have been Southern Europe, where it grows naturally, it has also been cultivated in many West African countries. In Nigeria, it is commonly grown in the northern parts and consumed locally. Its starch content has been reported to be high and comparable to rice and cassava starches.[8,9] Hence, this study aims at subjecting the extracted starch from *Cyperus esculentus* tubers to different forms of modifications and to evaluate the compactibility and compressibility characteristics of the modified starches in comparison with microcrystalline cellulose in directly compressed metronidazole tablet formulations.

## MATERIALS AND METHODS

### Materials

Metronidazole and hydrochloric acid (JHD Chemicals Ltd. Guandang, China), microcrystalline cellulose (Parachem Chemicals, India), magnesium stearate and talc (BDH Chemicals Ltd. Poole, England).

### Extraction, modification and characterization of *Cyperus esculentus* starch

The starch extraction, modifications as well as the characterization of the modified products have been previously reported.[10]

### Formulation of metronidazole powder blends

Batches of metronidazole powder blends were prepared with the modified starches and MCC using the formula in Table 1. Powder blends sufficient to produce 500 tablets per batch was produced by mixing the required quantities of metronidazole and the modified starches or MCC in a mixer for 5 min. Magnesium stearate and talc were weighed and incorporated into the powder mix in geometric proportion with continuous mixing for another 5.0 min. At this stage, the powder blends of the various batches were subjected to Kawakita analysis. The powder blend of each batch was divided into five (5) sub-batches of sufficient powder to produce 100 tablets in readiness for compression.

**Table 1:** Formula used in the formulation of metronidazole powder blends and tablets

| Ingredients (mg) | Batches | | | |
|---|---|---|---|---|
| | **A** | **B** | **C** | **D** |
| Metronidazole | 200 | 200 | 200 | 200 |
| ACS | 295 | - | - | - |
| PCS | - | 295 | - | - |
| ECS | - | - | 295 | - |
| MCC PH 101 | - | - | - | 295 |
| Magnesium stearate | 2.5 | 2.5 | 2.5 | 2.5 |
| Talc | 2.5 | 2.5 | 2.5 | 2.5 |

**Drug-excipient interaction**

FTIR analysis of metronidazole drug sample and the powder blends of the modified starches was carried out to determine any reaction or interaction between metronidazole and the starches during the processes of handling and mixing. Analysis of samples was done using the potassium bromide (KBr) compact method (FTIR-4100 Spectrophotometer, Shimadzu Co. Japan). About 5.0 mg of the powder sample was mixed with KBr powder and compressed into a 200 mg tablet using a Sigma press. The compressed tablet was scanned in the spectrophotometer at a range of 4000 - 750 $cm^{-1}$.

**Kawakita analysis**

The compactibility and cohesiveness of the powder blends comprising the modified starches and MCC powder were assessed using the Kawakita analysis.[11] About 10 g of powder was poured gently into a 50 ml measure and its occupied volume (Vo) was noted. The measure was gently tapped ten times on a wooden horizontal surface and the resultant volume (VN) recorded. Tapping was continued with the powder volume recorded after every ten taps until a constant volume was obtained. The data obtained were fitted into the Kawakita Equation 1 and a plot of N/C versus N will give a slope (1/a) and intercept (1/ab). This was carried out for the modified starches and MCC powders.

$$N/C = N \cdot 1/a + 1/ab \quad \ldots . (1)$$

Where N = number of taps, C = degree of powder volume reduction (Vo-VN/Vo), a and b are constants with a = compactibility of powder and 1/b = cohesiveness of powder.

**Compression of powder blends**

A total of twenty sub-batches of 100 tablets per sub-batch were prepared using direct compression method by compressing individual powder sample weighing 500 mg on a hydraulic press at different compression pressures ranging from 49.03 MN/m2 to 147.10 $MN/m^2$ using a die of 12.5 mm in size and a flat-faced punch (Carver Inc., USA). Each compression was allotted a dwell or residence time of 30 s and after ejection, the tablets were stored in a desiccator with silica for 24 h to achieve elastic hardening and recovery.

**Tablets evaluations**

***Dimensions***

Tablet dimensions (thickness and diameter) were evaluated with a tablet hardness tester (Logan HDT-300, Logan Instruments Corp, USA) equipped with callipers. Ten (10) tablets obtained at random from the individual sub-batches were used for these determinations and their averages and standard deviation values recorded.

***Weight***

Twenty tablets obtained at random from each sub-batch were individually weighed with a Mettler analytical balance (Philip Harris Ltd., England). The weight of the individual tablet was determined and the average weight and standard deviation value recorded.

***Crushing and tensile strengths***

Ten (10) tablets picked at random from each sub-batch were assessed for hardness using an automated tablet hardness tester (Logan HDT-300, Logan instruments Corp, USA). The force required to diametrically fracture a tablet placed in between the fixed anvil and the moving hammer of the tester was recorded. The average force as

well as its standard deviation value were computed. The tensile strength of the tablets was obtained using Equation 2.

$$\tau = 2F/\pi dT \quad \ldots\ldots (2)$$

Where $\tau$ = tensile strength in $Nm^{-2}$, F = force in Newton needed to cause fracture, d = diameter of tablet in m and T = thickness of tablet in m.

***Friability***

Twenty (20) tablets taken at random from individual sub-batches were dusted to remove any surface powder. The tablets were weighed and deposited in a friabilator that was rotated at 25 rpm (100 revolutions) for 4 min (Erweka GmbH, Germany). Thereafter, they were removed from the friabilator, de-dusted and reweighed. Tablet friability was recorded as the percentage loss in weight.

***Disintegration time***

Six (6) tablets taken randomly from individual sub-batches were subjected to disintegration in distilled water at 37 ± 0.5°C using a disintegration test apparatus (Erweka, Germany). The individual tablets were introduced into the tube of the tester, followed with the placement of discs. The disintegration time was recorded as time taken for tablet break down into fragments that completely passed through the wire mesh at the base of the tube. The average time of the six tablets and its standard deviation were calculated.

***Tablet densities and porosity***

The average weight, diameter and thickness of ten (10) tablets picked at random from each sub-batch were used in calculating the compact (particle) and relative densities as well as the porosity of the tablets by applying Equations 3, 4 and 5, respectively.

$$\text{Compact density (Ps)} = \frac{4W}{\pi d^2 h} \quad \ldots\ldots (3)$$

$$\text{Relative density (D)} = \frac{W}{V \times Ps} \quad \ldots\ldots (4)$$

$$\text{Tablet porosity} = 1 - D \quad \ldots\ldots (5)$$

Where W = tablet weight (g), d = tablet diameter (cm), h = tablet thickness (cm), V = tablet volume ($cm^3$)

**Heckel analysis**

Heckel plots of the various metronidazole tablet compacts were constructed to obtain their yield pressures (Py) using the Heckel Equation 6.

$$\ln(1/1 - D) = KP + A \quad \cdots\cdots (6)$$

Where D = tablet relative density, K = a constant, P = compression pressure, A = Y-axis intercept.

A plot of ln(1/1-D) versus the various compression pressures (P) used in tablet compaction will give a straight line plot with a slope (K). Yield pressure (Py) was calculated as the reciprocal of the slope.

**Compressibility analysis**

Plots of the compact densities (Ps) of the various metronidazole tablets against their compression pressures (P) were constructed and their slope values calculated as their compressibility indices.

**Dissolution studies**

The in vitro drug dissolution profiles of the different sub-batches of tablets were assessed using the USP Type II method. A dissolution apparatus holding 900 ml of 0.1 N HCl solution set at 37 ± 0.5 C and with a paddle revolution of 50 rpm was used (Type DT, Erweka Apparatebau GmbH, Germany). At various time intervals, a 10 ml aliquot was taken from the dissolution fluid containing the tablet and immediately replenished with an equal volume of fluid held at the same condition. The absorbances of the withdrawn samples were read with a UV-Vis Spectrophotometer at 278 nm wavelength (T70, PG Instruments Ltd, USA). The amounts of drug released into the dissolution media at the various times of withdrawal as well as the percentage drug release at those time intervals were calculated from the regression equation previously generated from the calibration plot of pure metronidazole powder.

The area under the dissolution curve (AUCT) was calculated using the trapezoidal rule (Equation 7). Dissolution efficiency (DE) was computed as the area of the trapezium depicting a 100 % dissolution (Equation 8).

$$AUC_T = \frac{1}{2}(a+b)h \quad \ldots\ldots (7)$$

$$\text{Dissolution Efficiency } (DE_T) = \frac{AUC_T}{AUC_O} \times 100 \quad \ldots\ldots (8)$$

Where AUCT = Area under the dissolution curve at time t, a = time at start of section under consideration, b = time at end of section under consideration, h = concentration of the dissolution fluid, AUCo = Area under the curve over the entire course of release.

**Statistical analysis**

Data are presented as mean ± standard deviation. Analysis of variance (2-way) was used in analysing differences between means. Multiple comparison was carried out using Dunnett's test at 95 % confidence interval with p-values ≤ 0.05 considered as statistically significant (Graphpad Prism 7.0® (Graphpad Software Inc. USA)).

## RESULTS

**Physicochemical properties of tablets**

Results from the evaluations of the metronidazole tablets compressed at various compression loads are outlined in Table 2. The average weight of the tablets ranged from 0.500 - 0.509 g while their diameters and thickness ranged from 0.0037 - 0.0049 and 0.0120 - 0.0122 m, respectively. The tablet's crushing strength and friability values were between 22 - 200 N and 0.15 - 5.29 %, respectively. Also, the tablets exhibited disintegration times ranging from 0.35 to 38.59 min.

**Table 2:** Physicochemical characteristics of the metronidazole tablets

| Batch | Sub-batch | Compression pressure ($MNm^{-2}$) | Tablet weight (g) | Dimensions (m) | | Crushing strength (N) | Friability (%) | Disintegration time (min) |
|---|---|---|---|---|---|---|---|---|
| | | | | Diameter | Thickness | | | |
| A (ACS) | A1 | 49.03 | 504 ± 12.8 | 0.0046 ± 0.0010 | 0.0121 ± 0.0001 | 22.31 ± 1.32 | 5.03 ± 0.22 | 4.51 ± 0.55 |
| | A2 | 73.54 | 508 ± 8.99 | 0.0046 ± 0.0012 | 0.0121 ± 0.0001 | 27.84 ± 3.43 | 1.66 ± 0.11 | 5.35 ± 0.20 |
| | A3 | 98.07 | 500 ± 9.85 | 0.0039 ± 0.0011 | 0.0120 ± 0.0001 | 33.82 ± 3.83 | 2.26 ± 0.21 | 7.85 ± 0.58 |
| | A4 | 122.58 | 503 ± 8.15 | 0.0039 ± 0.0011 | 0.0121 ± 0.0001 | 40.27 ± 1.03 | 0.52 ± 0.12 | 8.48 ± 0.99 |
| | A5 | 147.10 | 506 ± 9.83 | 0.0037 ± 0.0013 | 0.0121 ± 0.0003 | 57.85 ± 5.21 | 0.67 ± 0.22 | 11.59 ± 1.71 |
| B (PCS) | B1 | 49.03 | 507 ± 7.54 | 0.0049 ± 0.0010 | 0.0121 ± 0.0001 | 27.67 ± 3.85 | 4.86 ± 0.13 | 0.35 ± 0.07 |
| | B2 | 73.54 | 504 ± 8.27 | 0.0042 ± 0.0010 | 0.0120 ± 0.0002 | 39.14 ± 6.83 | 5.29 ± 0.21 | 0.52 ± 0.04 |
| | B3 | 98.07 | 506 ± 8.56 | 0.0041 ± 0.0010 | 0.0121 ± 0.0001 | 46.20 ± 6.21 | 1.66 ± 0.31 | 1.17 ± 0.04 |
| | B4 | 122.58 | 507 ± 6.37 | 0.0041 ± 0.0010 | 0.0121 ± 0.0001 | 62.62 ± 5.81 | 2.29 ± 0.11 | 1.49 ± 0.07 |
| | B5 | 147.10 | 502 ± 7.01 | 0.0038 ± 0.0014 | 0.0121 ± 0.0001 | 81.04 ± 7.66 | 0.83 ± 0.11 | 3.27 ± 0.72 |
| C (ECS) | C1 | 49.03 | 503 ± 7.40 | 0.0046 ± 0.0010 | 0.0121 ± 0.0001 | 69.26 ± 0.72 | 0.72 ± 0.04 | 9.98 ± 0.64 |
| | C2 | 73.54 | 508 ± 8.54 | 0.0043 ± 0.0010 | 0.0121 ± 0.0001 | 92.05 ± 1.29 | 0.44 ± 0.02 | 13.25 ± 0.81 |
| | C3 | 98.07 | 505 ± 9.97 | 0.0042 ± 0.0010 | 0.0121 ± 0.0002 | 138.8 ± 1.28 | 0.85 ± 0.24 | 16.66 ± 1.39 |
| | C4 | 122.58 | 504 ± 6.39 | 0.0040 ± 0.0010 | 0.0121 ± 0.0001 | 165.1 ± 5.95 | 0.15 ± 0.30 | 35.19 ± 3.15 |
| | C5 | 147.10 | 503 ± 8.43 | 0.0039 ± 0.0014 | 0.0121 ± 0.0001 | 200.7 ± 1.77 | 0.19 ± 0.21 | 38.59 ± 4.37 |
| D (MCC) | D1 | 49.03 | 505 ± 10.1 | 0.0048 ± 0.0012 | 0.0122 ± 0.0001 | 41.22 ± 1.23 | 1.15 ± 0.10 | 7.63 ± 0.62 |
| | D2 | 73.54 | 502 ± 7.46 | 0.0047 ± 0.0010 | 0.0121 ± 0.0001 | 64.27 ± 1.06 | 0.61 ± 0.10 | 8.95 ± 0.32 |
| | D3 | 98.07 | 509 ± 4.53 | 0.0047 ± 0.0010 | 0.0121 ± 0.0002 | 93.35 ± 0.95 | 0.85 ± 0.11 | 11.46 ± 0.92 |
| | D4 | 122.58 | 506 ± 6.47 | 0.0044 ± 0.0010 | 0.0121 ± 0.0001 | 130.8 ± 1.10 | 1.03 ± 0.22 | 16.22 ± 1.17 |
| | D5 | 147.10 | 504 ± 6.39 | 0.0042 ± 0.0010 | 0.0121 ± 0.0001 | 200.1 ± 1.53 | 0.28 ± 0.23 | 21.38 ± 1.87 |

± Standard deviation

**Comparative mechanical parameters of tablets**

The relationships between some mechanical parameters of the metronidazole tablets are shown in Table 3. The tablets had crushing strength-friability ratio (CSFR) of 5.04 - 1100 N/%. They also had crushing strength-friability/disintegration time ratio (CS/FR/DT) values that ranged from 1.12 - 33.43 N/%min while their tensile strengths showed a decreasing order of ECS > MCC > PCS > ACS.

**Compaction profile**

The Kawakita and Heckel plots are presented in Figures 1 and 2, respectively while the various parameters derived from the analyses of the plots are shown in Table 4. The parameters derived from the Kawakita plot includes 'a' (0.053 - 0.067), 'b' (0.194 - 0.299), 'DI' (0.933 - 0.947) and 'Pk' (3.344 - 5.155) while the 'Py' (62.79 - 217 $MN/m^2$), 'Do' (0.230 - 0.389), 'DA' (0.457 - 0.646) and 'DB' (0.068 - 0.360) were gotten from the Heckel plot.

**Table 3:** Comparative mechanical parameters of the metronidazole tablets

| Batch | Sub-batch | Compression pressure ($MNm^{-2}$) | CS/FR ratio (N/%) | CS/FR/DT ratio (N/%min) | Tensile strength ($Nm^{-2}$) |
|---|---|---|---|---|---|
| A (ACS) | A1 | 49.03 | 5.04 | 1.12 | $2.52 \times 10^5$ |
| | A2 | 73.54 | 16.77 | 3.13 | $3.20 \times 10^5$ |
| | A3 | 98.07 | 14.96 | 1.91 | $4.62 \times 10^5$ |
| | A4 | 122.58 | 77.44 | 9.13 | $5.40 \times 10^5$ |
| | A5 | 147.10 | 86.34 | 7.45 | $8.25 \times 10^5$ |
| B (PCS) | B1 | 49.03 | 5.69 | 16.26 | $3.01 \times 10^5$ |
| | B2 | 73.54 | 7.40 | 14.23 | $4.93 \times 10^5$ |
| | B3 | 98.07 | 27.83 | 23.79 | $5.90 \times 10^5$ |
| | B4 | 122.58 | 27.34 | 18.35 | $8.08 \times 10^5$ |
| | B5 | 147.10 | 97.64 | 29.86 | $11.21 \times 10^5$ |
| C (ECS) | C1 | 49.03 | 96.19 | 9.64 | $7.89 \times 10^5$ |
| | C2 | 73.54 | 209.20 | 15.79 | $11.26 \times 10^5$ |
| | C3 | 98.07 | 163.29 | 9.80 | $17.41 \times 10^5$ |
| | C4 | 122.58 | 1100.67 | 31.28 | $21.70 \times 10^5$ |
| | C5 | 147.10 | 1056.32 | 27.37 | $27.11 \times 10^5$ |
| D (MCC) | D1 | 49.03 | 35.84 | 4.70 | $4.45 \times 10^5$ |
| | D2 | 73.54 | 105.36 | 11.77 | $7.16 \times 10^5$ |
| | D3 | 98.07 | 109.82 | 9.58 | $10.41 \times 10^5$ |
| | D4 | 122.58 | 126.99 | 7.83 | $15.66 \times 10^5$ |
| | D5 | 147.10 | 714.64 | 33.43 | $25.05 \times 10^5$ |

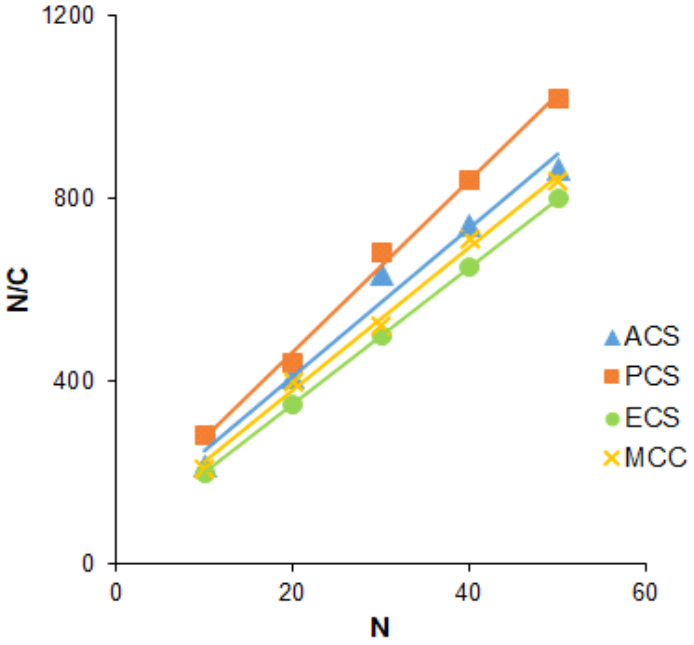


**Figure 1:** Kawakita plots of the powder blends of the modified starches (ACS, PCS, ECS) and MCC

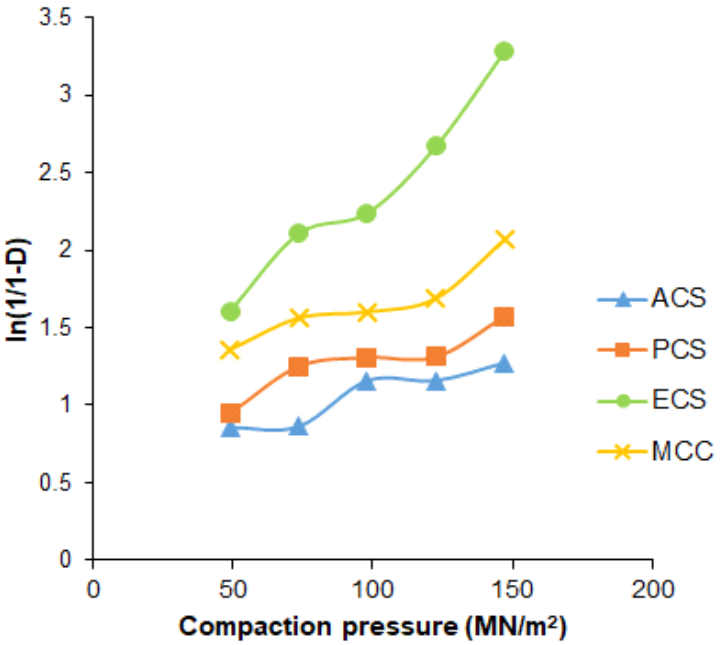


**Figure 2:** Heckel plots of compacts prepared with the modified starches (ACS, PCS, ECS) and MCC

**Table 4:** Parameters derived from the Kawakita and Heckel plots

| Material | Kawakita plot | | | | Heckel plot | | | |
|---|---|---|---|---|---|---|---|---|
| | a | B | $D_I$ | $P_k$ | $P_y$ (MN/m²) | $D_0$ | $D_A$ | $D_B$ |
| ACS | 0.061 | 0.194 | 0.939 | 5.155 | 217.02 | 0.389 | 0.457 | 0.068 |
| PCS | 0.053 | 0.214 | 0.947 | 4.673 | 186.86 | 0.239 | 0.529 | 0.290 |
| ECS | 0.067 | 0.299 | 0.933 | 3.344 | 62.79 | 0.230 | 0.559 | 0.329 |
| MCC | 0.064 | 0.240 | 0.936 | 4.167 | 159.04 | 0.286 | 0.646 | 0.360 |

**Compressibility indices**

The compressibility plots of the metronidazole tablets prepared with the modified starch products and MCC are presented in Figure 3. The compressibility indices of the tablets obtained from the plot follows the ranking ECS (0.539) > MCC (0.461) > PCS (0.364) > ACS (0.263). The result showed increased tablet density with increased compression load or pressure of the materials.

**Drug release profiles of tablets**

The in vitro dissolution profiles and some dissolution parameters generated from the profiles of the metronidazole tablets compressed at different compaction pressures (49.03 - 147.1 $MNm^{-2}$) are shown in Figure 4 and Table 5 respectively. The results showed a graded response in drug release with respect to compaction pressure. A decreased release in the amount of metronidazole from the tablets corresponded with increased compaction pressure. Tablets formulated with pre-gelatinized starch exhibited the highest drug release at all compression pressures with a total area under the curve ranging from 4255.2 - 4660.7 mg/ml min. Dissolution efficiency (DE) of the tablets ranged from 35.26 - 50.18 with comparable values among tablets formulated with PCS, ECS and MCC.

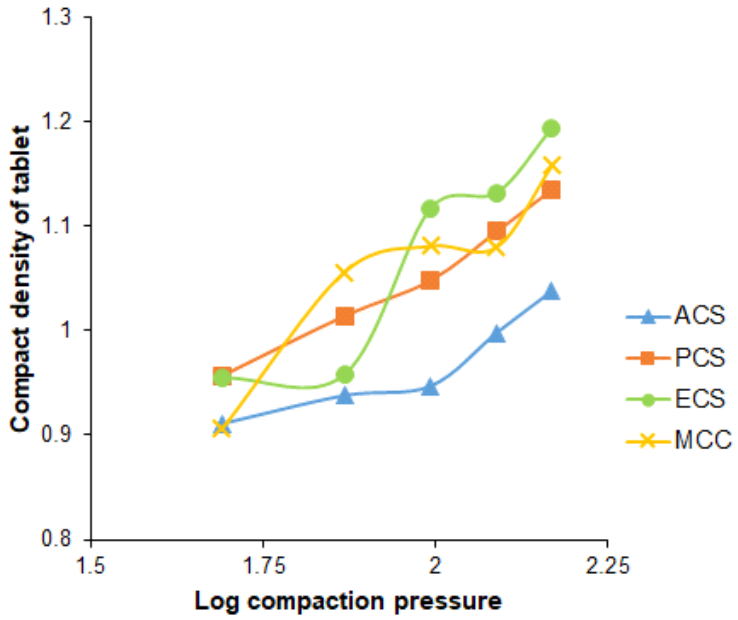


**Figure 3:** Compressibility plot of the metronidazole tablets prepared with the modified starches (ACS, PCS, ECS) and MCC

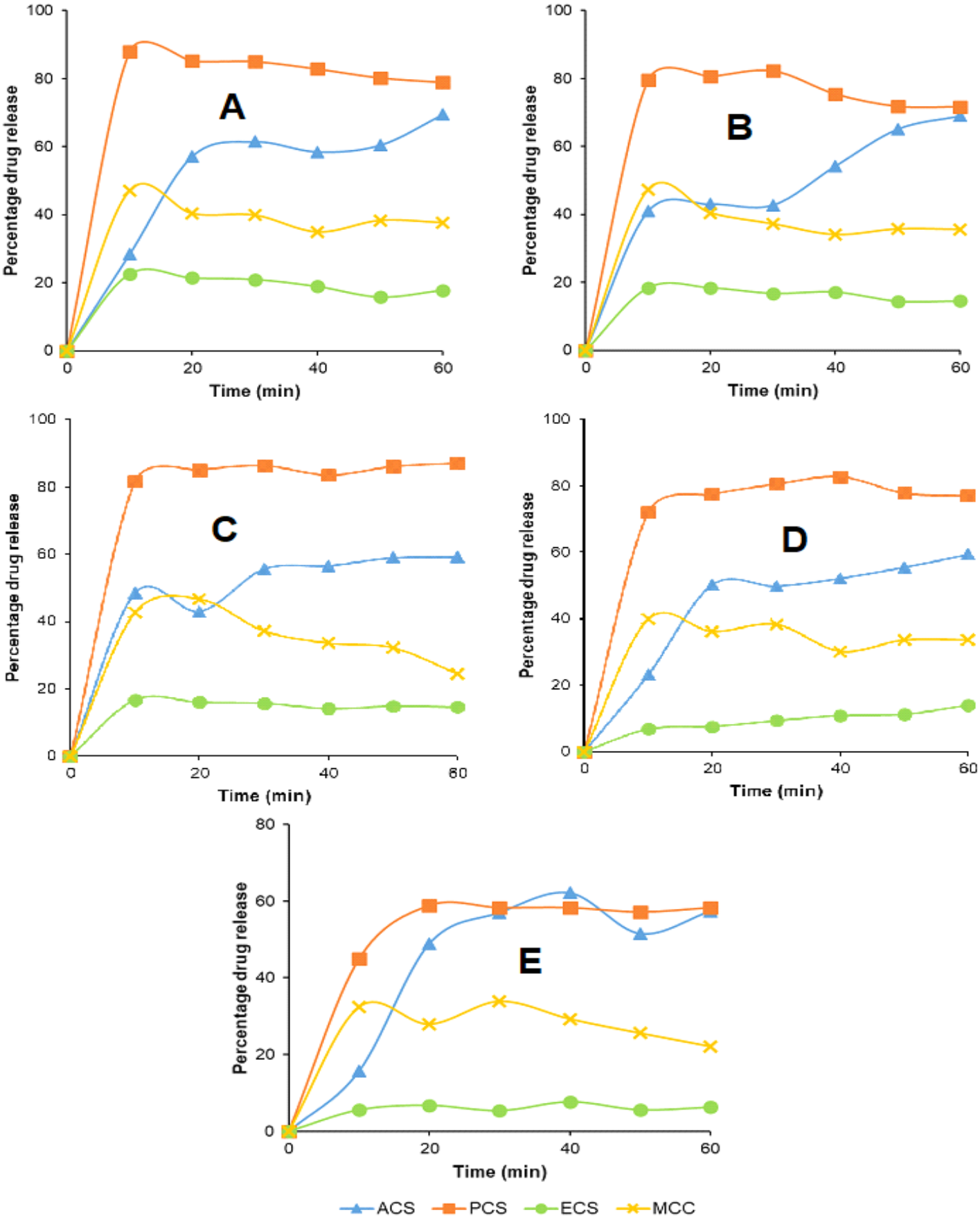


Figure 4: Drug release profile of metronidazole tablets compressed at different pressures (49.03 (A), 73.54 (B), 98.07 ©, 122.58 (D) and 147.1 (E)) $MNm^{-2}$

**Table 5:** Some dissolution parameters of the metronidazole tablets

| Batch | Sub-batch | $AUC_{30}$ (mg/ml min) | $AUC_T$ (mg/ml min) | DE |
|---|---|---|---|---|
| A (ACS) | A1 | 1161.9 | 3004.45 | 38.67 |
| | A2 | 1052.8 | 2804.4 | 37.54 |
| | A3 | 1191.55 | 2919.5 | 40.81 |
| | A4 | 982.2 | 2603.15 | 37.73 |
| | A5 | 930.7 | 2639.5 | 35.26 |
| B (PCS) | B1 | 2155.2 | 4604.6 | 46.81 |
| | B2 | 2012.9 | 4255.2 | 47.30 |
| | B3 | 2097.8 | 4660.7 | 45.01 |
| | B4 | 1897.75 | 4291.4 | 44.22 |
| | B5 | 1329.75 | 3068.1 | 43.34 |
| C (ECS) | C1 | 544.75 | 1085.5 | 50.18 |
| | C2 | 451.75 | 924.5 | 48.86 |
| | C3 | 404.75 | 844.8 | 47.91 |
| | C4 | 1031.25 | 2148 | 48.01 |
| | C5 | 151 | 342.5 | 44.09 |
| D (MCC) | D1 | 1074.20 | 2195.20 | 48.93 |
| | D2 | 1064.35 | 2127.1 | 50.04 |
| | D3 | 1079.35 | 2044.45 | 52.79 |
| | D4 | 951.6 | 1948.75 | 48.83 |
| | D5 | 773.1 | 1602.35 | 48.25 |

$AUC_{30}$ (Area under the curve at 30 min), $AUC_T$ (Total area under the curve), DE (Dissolution efficiency)

**Drug-excipient interaction**

The FTIR spectral of metronidazole (Figure 5 (a)) exhibited characteristic absorption bands at 3948, 3721, 3262, 2481, 949.00 and 644.00 $cm^{-1}$. These absorption bands are present in a more or less degree on comparing the spectral data of the powder blends containing the combination of metronidazole and the modified ACS (Figure 5 (b)), PCS (Figure 5 (c)) and ECS (Figure 5 (d)) starches. The probability of any interaction between metronidazole and the modified starches during the powder blend mixing can be ruled out from this observation.

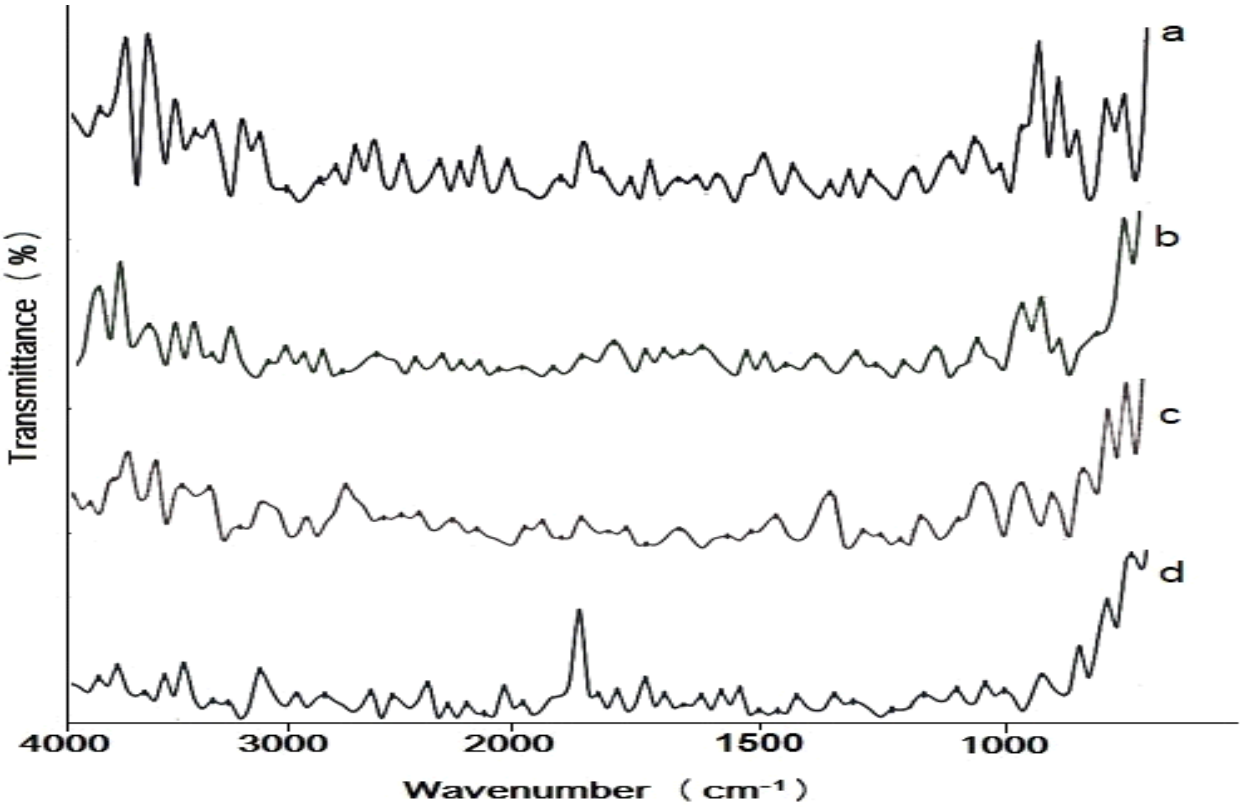


**Figure 5**: FTIR spectra of metronidazole (a) and admixtures of the drug with the modified starches ACS (b), PCS © and ECS (d)

**DISCUSSION**

All the tablet batches passed the weight variation test. Weight uniformity is one of the characteristics of good tablets, which can be affected by powder properties and equipment.[12] The British Pharmacopeia recommends for tablets with mean weight greater than 250 mg, that not more than two (2) tablets should have a weight deviation of more than 5.0% and none should deviate greater than 10 % from the mean.[13] This test is significant in ensuring that tablet batches fall within the required size range as this affects the drug or chemical content of the tablets.

Generally, the hardness (crushing strength) values of the tablets increased with increased compression pressure while their friability decreased with increased pressure. Crushing strength is an index used in measuring the hardiness or resilience of a tablet while friability gives information about the weakness of the tablet. Tablet hardness is a function of several factors such as compaction force, moisture content, particle size and shape. Though pharmacopeia specifications for tablet hardness are not available, values falling within certain range of 40 - 70 N can be generally accepted for immediate release tablets.[14]

On the other hand, friability, which is a tablet mechanical property that uses a disruptive force to evaluate tablet ability to resist or withstand abrasion during use, has a British Pharmacopeia specification of 0.8 - 1.0 %.[15] While crushing strength test involves bulk tablet deformation, friability is limited to surface deformation and is greatly influenced by tablet morphology.[16] Tablets having friability values exceeding 1.0 % may not be able to tolerate the mechanical stress associated with its packaging and transportation as well as handling by end users. The failure of some batches to meet friability specification may be due to the use of low compression pressure.

Tablet disintegration is the net outcome of the disintegrating and adhesive forces that come into play when a tablet is subjected to an aqueous environment. Also, it is a critical preliminary step for drug dissolution and consequently, it can be the rate limiting step in drug absorption process.[17] Two of the tablet batches formulated with ECS at higher compaction pressures failed the British Pharmacopeia disintegration time test specification of 15 min.[15] This can be attributed to the predetermined hardness of the batches. There were no significant differences between the disintegration times

of the control ($p > 0.05$) and all batches formulated with PCS at all compaction pressures and ACS batches at 49.03 - 98.07 $MNm^{-2}$ compression pressure.

Generally, a correlation was observed between tablet hardness and disintegration time. Tablet formulated at higher compaction pressures and having higher crushing strength values, gave higher disintegration times. Tablets formulated with PCS exhibited rapid disintegration time when compared to the other modified starches and MCC at same compaction pressure.

The comparative mechanical parameters of the tablets gave three useful indices; crushing strength friability ratio (CSFR), crushing strength-friability/disintegration time ratio (CS/FR/DT) and tensile strength. CSFR is an index of tablet quality as it gives a measure of both tablet weakness and strength. Some authors have reported that the stronger the tablet, the higher the value of this index and vice versa.[18,19] Results of this parameter showed that tablet batches formulated with ECS had significantly higher CSFR values. This suggests a possible superior binding ability of ECS over the other modified starches. While CS/FR/DT does not only measure tablet strength (crushing) and weakness (friability) which are strong indicators of bond strength but also takes into consideration, the adverse effect of these two parameters on tablet disintegration time which provides indication of bond disruption.[12] CS/FR/DT have been described as a more appropriate index for evaluating the performance of a tablet with respect to its disintegration because it not only measures tablet strength and weakness but also the combined impact of these parameters on disintegration time.[19] Usually, the higher the value, the better the combined disintegrant and binding activity in a tablet. The results obtained showed that the PCS and ECS batches had higher values of CS/FR/DT than those containing the other modified starches. The CS/FR/DT values were very low for the MCC and ACS indicating poor combined binding and disintegrating effect of the starches.

The tensile strength values of the tablets followed the series of ECS > MCC > PCS > ACS in decreasing order. It was noted that higher compaction pressure resulted in tablets with higher tensile strength. The ECS based tablet's tensile strength was statistically significant from the control ($p < 0.0001$) at all compaction pressures. Thus, ECS produced tablets with the highest mechanical strength as evidenced by its high crushing strength, crushing strength friability ratio and tensile strength values.

In studying the compaction characteristics of the modified starch powders, the Kawakita model uses the extent of reduction in volume of a powder bed under compression. However, the model suffers a limitation of being able to describe the compaction process to certain levels of pressure and beyond these levels, the equation becomes non-linear. Therefore, since the Heckel model shows linearity at high pressure and the Kawakita model generally displays linearity at low pressure, a combination of both models provide a more accurate description of the compaction characteristics of pharmaceutical materials.

Kawakita plots of the modified starch products and MCC showed a linear proportionality with the value of 'a' derived from the slope of the plots and 'b' from their intercepts. The values of 'a' provides the maximum achievable volume reduction which describes the powder compressibility. The values obtained for the materials were in the order of ECS > MCC > ACS > PCS. This implies that ECS exhibited the highest compressibility. The values of 'b' on the other hand, describes the tendency or inclination of the powder to undergo volume reduction. Thus, "1/b" describes the cohesive nature of the powders or how fast the final packing stage is achieved. The values of 'b' obtained for the materials was in the order of ECS > MCC > PCS > ACS implying that ECS exhibited the highest inclination toward volume reduction while the values obtained for "1/b" ranked as follows ECS < MCC < PCS < ACS implying that ECS was the least cohesive of the materials.

The reciprocal of 'b' gave values of 'Pk' while '1-a' afforded 'DI' values which are the initial relative density of the starch powders (Table 4). The 'Pk' values measures inversely the plastic deformation of powder under compaction i.e. the lesser the value, the greater the degree of plastic deformation in the material. The values obtained from the Kawakita plots are ranked as follows; ECS < MCC < PCS < ACS. The 'DI' values quantifies the initial relative density of the packed starch powders due to minute compaction pressures of tapping. These values were observed to increase in the following order; ECS < MCC < ACS < PCS.

As powder compaction involves volume reduction, the Heckel equation is centred on a powder bed's change in volume when under compression.[20] It reflects the densification of a powder column and it is used to describe the relationship between a powder bed's relative density under compression and the applied compression pressure.[21]

A linear fit was obtained for all the formulations at the various compaction pressures (49.03 - 147.10 $MNm^{-2}$), indicating deformation primarily by plastic flow.[22] The mean yield pressure 'Py' was obtained from the stretch of the line curve with highest linearity while the intercept was obtained by extending the line curve. Mean yield pressure is that pressure where the plastic deformation of a material starts. It has an inverse relationship with the ability of a material to deform plastically under an applied load. ACS exhibited the maximum 'Py' value while ECS had the least. These values indicated that ECS wound undergo the fastest onset of plastic deformation i.e. readily deforms plastically during compression, at low pressures.

Generally, the 'Py' values were presented in ascending order as follows; ECS < MCC < PCS < ACS. These results are in agreement with those of tensile strengths (Table 3) which showed that ECS had the highest tensile strength and with the lowest 'Pk' value obtained from the Kawakita plot for ECS, thus confirming that ECS exhibited the highest plastic deformation. Plastic deformation is irreversible and affords more intimate points of contact and formation of inter-particulate bonds resulting in tablets with sufficient mechanical strength.[23] The 'Do' value which represents the relative density of powder at zero pressure i.e. the extent of initial die packing resulting from the filling of the die was found to be in the order of ECS < PCS < ACS < MCC. This revealed that MCC displayed maximum degree of densification or die packing while ECS demonstrated the least degree of densification. These results confirmed what was noticed in the Kawakita plots where ECS exhibited a lower value for "1/b" in comparison to the other materials.

The 'DA' values denotes the sum total of particle packing at zero and low pressures and they were in the order of MCC > ECS > PCS > ACS. This parameter furnishes data on the total deformation occurring at the powder compression phase. The ordering of the 'DA' values of the materials implies that MCC had a higher total deformation than the other materials. On the other hand, 'DB' values denote particle rearrangement phase or packing in the initial compression stages at low pressure. It also indicates the extent of particle fragmentation. The 'DB' value was highest in MCC which explains why MCC had the highest total deformation even though ECS had a higher plastic deformation. This implies that MCC does not deform exclusively by plastic deformation but also undergoes a significant amount of brittle fracture.[24] Generally, the 'DB' values were in the order of PCS < ACS < ECS < MCC. This result indicates that MCC required the least pressure to experience fragmentation and rearrangement while on the other hand, PCS needed high amount of pressure because it had the least value.

Compressibility is the capacity of a material to decrease in volume under an applied pressure. A direct correlation is found between the density of a tablet and the logarithm of compaction pressure. Hence, the extent to which the density of a tablet increases with a corresponding increase in applied pressure is a depiction of the compression properties of the tablet material.[25] The slope value derived from the plot of tablet density versus log of compression pressure is deemed to indicate the compressibility index of a material, such that the larger the value, the more compressible the material. The compressibility indices result showed a comparable increase in density of tablets with increased compression pressure of the materials. ECS exhibited the highest value, indicating that it had the highest compressibility and this confirms the results obtained from the Kawakita analysis of their powder blends.

Furthermore, the drug release data from the dissolution studies of the tablets showed variable low drug release among the batches. The British Pharmacopeia stipulates that not less than 85 % of the labelled amount of metronidazole must be dissolved in 30 min.[13] Only the tablet batches formulated with PCS at the lowest compaction pressure (49.03 MNm-2) used met this criterion. This could be as a result of the hardness (> 70 N) of some of the tablets and also the lack of disintegrant in the formulation. Previous researches have shown an inverse correlation between tablet hardness and rate of dissolution.[26,27] As tablet hardness increased with increase in compression pressure, there was a corresponding increase in tablet density resulting in decreased tablet porosity, so that the dissolution medium could not penetrate the tablets. However, the release profile did not follow the disintegration time-dissolution trend exactly and this correlates with previous reports that there may not always be an automatic correlation between disintegration and dissolution.[28]

Also, it was observed that metronidazole tablets formulated with PCS (pre-gelatinized) gave the best drug release profile with their total area under the curve (AUCT). This is in contrast to a number of previous researches. Rahman *et al*. showed that fully pre-gelatinized starches lose much of their disintegration properties due to gelatinization.[29] They observed slower drug release from tablets with pre-gelatinized starch and attributed it to slower penetration of fluid into the tablet

due to the formation of intermolecular hydrogen bonds in the highly branched amylopectin. Some authors have also reported an increase in relative density such as found in pre-gelatinized starches leads to a reduction in disintegration time.[30,31] Park and Kim showed that low amylose content (25 % and below), as found in pre-gelatinized starches, produces very strong tablets due to strong gel layer.[32] The contrary result obtained in this study may be attributed to the fact that there was no tablet binder in the formulation.

## CONCLUSIONS

Modification of native Cyperus esculentus starch resulted in products with improved mechanical and compaction properties. Results from the Kawakita analysis revealed that the enzyme hydrolysed Cyperus esculentus starch (ECS) exhibited the highest compressibility and was also the least cohesive of the materials. Tablets formulated with ECS had the highest mechanical strength (crushing strength and tensile strength values) and compactibility, as it had the fastest onset of plastic deformation with low mean yield pressure value and inverse measure of plastic deformation value. Therefore, to meet the ever growing need for specific and functional excipients in the pharmaceutical market, enzymatic hydrolysis of *C. esculentus* starch can be explored to produce a filler/binder modified product with direct compressibility property, which may be a substitute to microcrystalline cellulose in direct compression of tablets.

## ACKNOWLEDGEMENT

The authors are grateful to the laboratory staff of the Department of Pharmaceutics and Pharmaceutical Technology, University of Benin, Benin City for their technical support. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors and we declare no conflict of interest.

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