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*Research article*

# BRITTLE FRACTION INDEX (BFI) AS A TOOL IN THE CLASSIFICATION, GROUPING AND RANKING OF BINDERS IN TABLET FORMULATION: PARACETAMOL TABLETS.

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**ABSTRACT:** The aim of this work was to explore the possibility of utilizing BFI as a tool for classifying, grouping and ranking binders based on performance in ameliorating capping and lamination in paracetamol tablets. Binders from different origins (starches, celluloses, natural gums, and synthetic gums) were used via wet granulation at concentrations ranging from 1.0 - 12.5% w/w to make paracetamol tablets with and without centre holes at a compression pressure of 7.5 arbitrary units. Requisite quality control tests were conducted on the tablets. The BFI values of the tablets were computed and statistically analyzed using Friedman's test and regression analysis. The analyses revealed significant differences between the BFI values of the formulations ($p < 0.05$), projected BFI as a useful tool in grouping and ranking binders based on effectiveness in ameliorating capping and lamination in paracetamol tablets, but failed to be useful in classifying the binders based on nature or origin. Furthermore, with the exception of some of the tablets formulated with the celluloses or starches, others met the official requirements for good quality and those formulated with plant gums or PVP released up to 70% of drug in 15min at low binder concentrations. The present findings may serve as a guide to formulators since they may enable quick and easy selection of the best and most economic binder(s) from an array of available binders for the conversion of paracetamol or related powders into good quality tablets.

**Key words:** BFI, grouping and ranking of binders, paracetamol tablets, capping, lamination.

## INTRODUCTION

Tablets are solid dosage preparations each containing a single dose of one or more active substances and are usually obtained by compressing uniform volumes of particles (BP, 2003). Oral tablets have remained the most common dosage form by which medicaments are usually administered to patients because of their advantages over the other dosage forms (Mattsson, 2000; Armstrong, 2002; Nachaegari and Bansal, 2004). A well formulated tablet possesses some essential properties which include its robustness in order to withstand post compaction handling and transportation (Rubinstein, 1990). The production of tablets is a complex multistage process that demands sound knowledge and experience in the art. The acquisition of these credentials notwithstanding, some problems may still be encountered during the production process. The most common ones include: binding, sticking, picking, filming, chipping, cracking, capping and lamination (Bandelin, 1989). Capping and lamination are very embarrassing problems in tablet production, packaging, transportation and dispensing. A tablet is said to have capped when the upper or lower segment of the tablet separates horizontally, either partially or completely from the main body of the tablet and comes off as a cap during ejection from the tablet press or during subsequent handling. Capping is usually caused by air entrapment in a tablet during compaction and subsequent expansion of the tablet on ejection from the die. Its other causes include presence of large amount of fines in the granulation, use of granules that have very low moisture content, insufficient amount or improper binder, high plastoelasticity of the tableting base, excessive compression force, and lack of sufficient clearance between the punch and the die wall (Okor, 2005).

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Lamination on the other hand means the separation of a tablet into two or more distinct horizontal layers, and its causes are similar to those of capping. In order to forestall tableting problems, preformulation studies are usually conducted to select suitable excipients for the production of specific active pharmaceutical ingredients (APIs). Many methods of ameliorating capping and lamination have been reported (Odeku, 2006), and one method that has been extensively studied is the use of binders (Odeku and Itiola, 2002; Olufunke et al., 2005; Eichie and Amalime, 2007). Binders act to ameliorate capping and lamination by decreasing the plastoelasticity of pharmaceutical powders. Materials used as binders predominantly display plastic compaction characteristics, and when incorporated into elastic or brittle powders there is resultant increase their plasticity and conversely reduction in their plastoelasticity. Plastoelasticity refers to the relative elastic to the plastic compression property of a pharmaceutical powder (Uhumwangho and Okor, 2004). BFI has been used as a measure of plastoelasticity of pharmaceutical powders (Ejiofor et al., 1986; Esezobo and Pilpel, 1987; Okor et al., 1998; Eichie and Okor, 2002; Onyekweli et al., 2004) and also to estimate the tendency of a tablet to cap or laminate under a diametral stress (Hiestand et al., 1977; Alebiowu and Itiola, 2002; Iwuagwu and Onyekweli, 2003; Eichie et al., 2005). BFI is measured by comparing the tensile strength ($T_o$) of a tablet with centre hole to the tensile strength (T) of a similar tablet without a centre hole. The centre hole is a built-in model defect, which simulates the actual voids formed in the tablets (due to air entrapment) during manufacture. The voids or low density regions in the tablet are weak points from which cracks propagate when stress (due to die wall pressure) is applied on the tablet during decompression. The ability of a material to relieve stress around the voids by plastic deformation is the property estimated with BFI (Williams III and McGinity, 1988). BFI is calculated with the equation (Hiestand et al., 1977):

$$BFI = 0.5\left[\frac{T}{T_0} - 1\right] \quad \ldots (1)$$

T or $T_o$ is computed using the modified Fell and Newton equation (Lund, 1994):

$$T \text{ or } T_0 = \frac{2F}{\pi dt(1-e)} \quad \ldots (2)$$

where, T or $T_o$ = tensile strength ($MN/m^2$) of tablet without or with centre hole respectively, F = diametral compression load (MN) needed to cause tensile failure of the tablet, d = tablet diameter (m), t = tablet thickness (m), e = tablet porosity.

$$e = 1 - RD \quad \ldots (3)$$

where RD which represents tablet relative density is computed with the equation (Uhumwangho et al., 2006):

$$RD = \frac{4m}{\pi d^2 t \rho_g} \quad \ldots (4)$$

where: m = tablet weight (g), d = tablet diameter (cm), t = tablet thickness (cm), $\rho_g$ = density of the granules ($g/cm^3$).

BFI values range from 0 to 1. A high value (tending to 1) implies high fracture tendency, while a low value (tending to 0) implies low fracture tendency. Tablet formulations with BFI values ≥ 0.5 are prone to high fracture tendencies (Hiestand et al., 1977). Many pharmaceutical powders have poor compaction properties and are prone to extensive capping and lamination after production especially if inadequate or improper binder is used in their formulation. Incorporation of adequate amounts of proper binders to pharmaceutical powders reduces the BFI values of their compacts and therefore ameliorates capping and lamination tendencies. Materials used as binders in tablet production have been classified based on nature or origin (Lund, 1994; Ofuer III and Klech-Gelotte, 2002). This work aims at utilizing paracetamol, a drug with high capping and lamination tendency as a model to study the possibility of employing BFI as a tool in the classification, grouping and ranking of binders in tablet formulation.

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## MATERIAL AND METHODS

### Materials

These included paracetamol powder (Mallirickrodt Inc., USA), corn starch BP (Sigma – Aldrich, USA), D (+) – lactose monohydrate (Fluka, Netherlands). Others were acacia exudates (*Acacia senegal*), cashew exudates (*Anacardium occidentale*), that were supplied by the plant collector in National institute for pharmaceutical research and development (NIPRD) Abuja; and okra pods (*Abelmoschus esculentus*) purchased from a local market in Suleja, Niger State, Nigeria. The starches used were extracted from maize (*Zea mays*), sweet potato (*Ipomoea batatas*), cassava (*Manihot utilissima*), and wheat (*Triticum aestivum*), all purchased from a local market in Suleja. Pregelatinized starch (PGS) was prepared from corn starch BP according to BP 1993 method. The cellulose derivatives: carboxymethylcellulose sodium (CMC) - medium viscosity (Fluka, Netherlands), hydroxypropylmethylcellulose (HPMC) - viscosity: 2600mPa.s (Fluka, USA); and other binders – gelatin [gel strength (Bloom): 160] (Fluka, Germany) and polyvinylpyrrolidone (PVP) K15 (Fluka, USA), were all used as supplied by Zayo-Sigma Jos, Nigeria.

### Methods

### Extraction of gums and starches

The gums were extracted as reported by Nasipuri et al., (1996). Extraction of starches was executed as reported by Nasipuri (1979) with little modification (the maize and wheat grains were separately soaked in 0.1% sodium metabisulphite solution for 24 h before milling in order to enhance the separation of starch from the grains).

### Preparation of granules

250g batches of a basic formulation of paracetamol powder (82% w/w), lactose (8% w/w) and corn starch B.P. (10% w/w) were dry – mixed for 10 minutes in a planetary mixer ( Kenwood, model OWHM400020, Japan), moistened with the appropriate amount of binder (okra gum, cashew gum, acacia gum, gelatin, PVP, CMC or HPMC) solution or starch paste prepared according to the methods reported by previous researchers (Odeku and Itiola, 2002; Rudnic and Schwartz, 2006, Sigma-Aldreich, 2011), (except that the volume of the solutions was maintained at 30 ml**)** equivalent to 1.0, 2.0, 3.0, 4.0 and 5.0% w/w (gums, PVP, gelatin, and HPMC), 2.5, 5.0, 7.5, 10.0, and 12.5% w/w (for starches and CMC) in the final granules and granulated by wet massing with mortar and pestle. The required amount of PGS was intimately mixed with the paracetamol, corn starch and lactose and wetted with 30ml of distilled water. The homogeneous damp mass was then screened through a 1400µm sieve and the resulting damp granules dried in a hot air oven (Unitemp LTE Scientific Ltd Great Britain) at $50^0$C for 18 hours. Thereafter, the dried granules were screened through a 600µm sieve in order to generate uniformly sized granules (Armstrong, 2002) and stored in air tight containers over silica gel before subsequent tests and tableting were conducted.

#### Tests conducted on the granules

#### Moisture content

The moisture contents of the granules were determined according to BP method (2009).

#### Determination of granule density

Granule density of each formulation was determined using the fluid displacement method using Xylene (Sigma – Aldrich, Germany) (Sinko, 2006) and applying the equation (Ohwoavworhua et al., 2007):

$$\rho_g = \left[\frac{w}{(w+a)-b}\right] SG \quad \ldots(5)$$

where: $\rho_g$ = granule density (g/cm$^3$), w = granule weight (g), SG = xylene specific gravity (0.879g/cm$^3$), a = pycnometer + xylene weight (g), b = pycnometer + xylene + granule weight (g).

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**Determination of bulk and tapped densities**

The bulk density of each granule sample was determined by pouring 20g (M) of the granule into a 50ml glass measuring cylinder and the bulk volume ($V_o$) determined. The bulk density ($D_B$) was then calculated from the relationship:

$$D_B = \frac{M}{V_0} \quad \ldots (6)$$

Triplicate determinations were made and the means reported (USP, 2003).

The tapped density of each granule sample was subsequently determined using Stampf Volumeter (model STAV 2003, JEF Germany). The cylinder was subjected to 750 taps mechanically and the volume $V_{750}$ of the powder column determined. $V_{750}$ was used to calculate tapped density ($D_T$) using the relationship:

$$D_T = \frac{M}{V_{750}} \quad \ldots (7)$$

Triplicate determinations were made and the means reported (USP 2003).

**Determination of angle of repose**

The static angle of repose, θ, was measured according to the BP (2009) fixed funnel and free standing cone method. A glass funnel was clamped with its tip of diameter 1.0 cm at a given height (h = 2.0cm) above a graph paper placed on a flat surface. Twenty grams of granules sample was carefully poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The diameter (d) of the base of the cone was measured. This procedure was repeated three times for each granule batch and the means were used to calculate the angle of repose for each batch using the formula:

$$\tan\theta = \frac{2h}{d} \quad \ldots (8)$$

**Evaluation of Carr's index and Hausner's ratio**

Carr's index (CI) and Hausner's ratio (HR) were evaluated using equations 9 and 10 respectively.

$$CI = \frac{D_T - D_B}{D_T} \times \frac{100}{1} \quad \ldots (9)$$

$$HR = \frac{D_T}{D_B} \quad \ldots (10)$$

**Preparation of tablets**

Immediately before tableting, each batch of granules was mixed with 0.5% w/w of talc. Tableting was done with a single punch tableting machine (Kilian Frankfurt Germany) which has a flat punch surface of diameter 12.55mm. Tablets were made by weighing accurately 500mg of granules and carefully transferring them into the die, and then compressing manually at a pre- determined pressure of 7.50 arbitrary units, with the pressure held on the granules for 30 seconds before releasing to allow consolidation to occur. The tableting procedure was repeated for tablets with centre hole of diameter, 1.5mm (made with the upper and lower adapters having a hole and a pin at their centres respectively) (Uhumwangho et al., 2006). Prelubrication of the die and punches in each stage was done by compressing some powder of pure talc before the granules were compressed (Sinka et al., 2004). And the tablets were stored in air tight containers over silica gel for 72 hours before the relevant tests were conducted.

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**Tests conducted on the tablets**

**Tablet weight and dimension measurements**

Tablet weights were determined using the electronic balance (Mettler Toledo B154, Switzerland) while the dimensions were measured with Mitutoyo gauge (Model 10C – 1012 EB Japan), to within ±1mg and ±0.01mm respectively. All the measurements were made in triplicates and the means used in relevant calculations.

**Evaluation of tablet relative density**

Tablet relative density was computed using the equation 4. The relative densities of three tablets selected at random were evaluated for each batch and the same tablets were utilized in the determination of each batch's crushing strength.

**Tablet crushing strength and friability tests**

Crushing strengths of tablets were determined at room temperature by diametral compression using a hardness tester (Kal Kolb, Erweka Germany). Results were taken from tablets that split cleanly into two halves without any sign of lamination. All measurements were made in triplicates and their means used to calculate tablets' tensile strengths. The percentage friabilities of ten tablets (without centre holes) selected at random from each batch were determined using Roche Friabilator (Copley/Erweka, Type, TAR 20, GMBH Germany), operated at 25rpm for 4 minutes and evaluated with equation 11.

$$\text{Friability} = \frac{W_i - W_f}{W_i} \times \frac{100}{1} \quad \ldots(11)$$

where $W_i$ = initial weight of the tablets before test, $W_f$ = final weight of the tablets after test.

**Evaluation of tablet tensile strength and brittle fracture index (BFI)**

Tablet tensile strength and BFI were evaluated using equations 2 and 1 respectively.

**Tablet disintegration and dissolution tests**

The disintegration times of the tablets (without centre holes) were determined in distilled water at 37±0.5$^0$C using the disintegration tester (Manesty, Model: MK 4, UK). Six tablets were selected at random from each batch and the machine operated till all the tablets disintegrated. The results reported are the means ± standard deviation.

Before the dissolution test, 10µg/ml of paracetamol solution in 0.1N HCl was scanned between 200nm and 800nm using UV-Visible spectrophotometer (UV– 160A Shimadzu Corporation Japan). Maximum absorbance (0.791) was shown at a wavelength of 296nm. Tablet dissolution test was then carried out using the USP XXIII basket method (Erweka Germany Type: DT 80) operated at 50rpm for 30 minutes in 900ml of 0.1N HCl maintained at 37±0.5$^0$C . At 5 minutes intervals, 5ml of dissolution fluid was withdrawn and replaced with 5ml of fresh 0.1N HCl. Each withdrawn sample was filtered and the amount of paracetamol released determined using the UV–Visible spectrophotometer, at 296nm with 0.1N HCl as blank in conjunction with calibration curve equation: $y = 0.0034x - 0.0019$, $r^2 = 0.9998$.

**Statistical analyses**

**Friedman's test**

Friedman's test was employed to test the null hypotheses ($H_o$): there are no significant differences between the BFI values of paracetamol tablets formulated with (a) okra gum, cashew gum, acacia gum, gelatin, PVP, or HPMC at fixed concentrations within the range 1.0%w/w – 5.0%w/w, (b) CMC or the starches, (c) okra gum, cashew gum, acacia gum, gelatin, PVP, HPMC, CMC, or the starches. Alternate hypothesis ($H_A$): there are considerable differences between the tablets' BFI values.

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Level of significance (α): 0.05.

Friedman test is executed with the formula (Jones, 2002):

$$X_R^2 = \frac{12}{N_{rows}\, N_{columns}\,(N_{columns}+1)} \sum R^2 - 3N_{rows}(N_{columns}+1) \quad \ldots \quad (12)$$

where: $N_{rows}$ = number of rows in table, $N_{columns}$ = number of columns in table, R = sum of ranks in each column, $X_R^2$ = calculated Friedman's statistic.

**Regression analysis**

This was carried out using Microsoft excel 2007 regression analysis tool pack.

## RESULTS AND DISCUSSION

### Results

### Moisture content and flow indices of granules

The moisture contents of the granules ranged from 2.85 % (granules formulated with cashew gum at 1%w/w) - 3.15 % (granules formulated with CMC at 12.5%w/w). The granules' angle of repose fall within the range: $32.4^0$ for formulations containing PVP at 1%w/w and $24.7^0$ for those containing cassava starch at 12.5%w/w. The lowest Carr's index value, 17.5%, and the highest, 21.9%, were manifested by formulations containing PGS 7.5%w/w and CMC 12.5%w/w respectively. Hausner's ratio results followed the order of Carr's index values (1.21 for PGS 7.5%w/w and 1.28 for CMC 12.5%w/w).

### Effects of binder type and concentration on tablets' BFI values

The highest BFI value of 0.4486 was displayed by paracetamol tablets containing acacia gum 1%w/w, while the lowest value, 0.0815, was from those containing CMC 12.5%w/w (Table 1).

The application of Friedman's test on the BFI values revealed that there was no significant difference between the BFI values of tablets formulated with starches or CMC at fixed binder concentration within the range 2.5%w/w – 12.5%w/w ($p < 0.05$). Tablets formulated with binders within the range of 1.0%w/w – 5.0%w/w however displayed statistically significant differences between their BFI values ($p < 0.05$). Results of regression analyses revealed dissimilarity in the effectiveness of the various binder classes in reducing BFI. With a correlation coefficient (r) > 0.9 for all plots and slope values between the range 0.01- 0.03 (Table 2a ) and 0.03 - 0.1 (Table 2b ), the analyses show that gums, gelatin, PVP, and HPMC at lower concentrations between the range, 1.0 – 5.0% w/w, performed thrice better than starches and CMC at concentrations between the range 2.5 – 12.5% w/w. By this the binders may be grouped (Table 3) and ranked in terms of effectiveness.

**Table 1: BFI of paracetamol tablets formulated with different binders at 1.0%w/w – 12.5% w/w and compression pressure of 7.5 arbitrary unit.**

| | Brittle fracture index (BFI) | | | | | | | | Brittle fracture index (BFI) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Binder conc. (%w/w) | PCOS | PCAS | PMAS | PPOS | PWES | PPGS | PCMC | Binder conc. (%w/w) | PACG | PCAG | POKG | PGEL | PPVP | PHPMC |
| 2.5 | 0.2641 | 0.2759 | 0.3537 | 0.2939 | 0.3167 | 0.3904 | 0.3271 | 1.0 | 0.4486 | 0.3015 | 0.2960 | 0.3376 | 0.4362 | 0.3517 |
| 5.0 | 0.2398 | 0.2608 | 0.2490 | 0.2463 | 0.2925 | 0.2849 | 0.2778 | 2.0 | 0.3431 | 0.2713 | 0.2292 | 0.3198 | 0.3614 | 0.3131 |
| 7.5 | 0.1581 | 0.2400 | 0.2316 | 0.2365 | 0.1228 | 0.1691 | 0.1153 | 3.0 | 0.2052 | 0.1700 | 0.2238 | 0.2383 | 0.2622 | 0.2857 |
| 10.0 | 0.1065 | 0.1482 | 0.1558 | 0.1362 | 0.1168 | 0.1438 | 0.1052 | 4.0 | 0.1931 | 0.1448 | 0.2015 | 0.2147 | 0.2408 | 0.2282 |
| 12.5 | 0.1032 | 0.1272 | 0.1178 | 0.1241 | 0.1065 | 0.1111 | 0.0815 | 5.0 | 0.1773 | 0.1391 | 0.1667 | 0.2081 | 0.2057 | 0.2064 |

PACG: Paracetamol tablets formulated with Acacia gum as binder. PCAG: Paracetamol tablets formulated with Cashew gum as binder. POKG: Paracetamol tablets formulated with Okra gum as binder. PGEL: Paracetamol tablets formulated with Gelatin as binder. PPVP: Paracetamol tablets formulated with Povidone as binder. PCOS: Paracetamol tablets formulated with Corn starch B.P. as binder. PCAS: Paracetamol tablets formulated with Cassava starch as binder. PMAS: Paracetamol tablets formulated with Maize starch as binder. PPOS: Paracetamol tablets formulated with Potato starch as binder. PWES: Paracetamol tablets formulated with Wheat starch as binder. PPGS: Paracetamol tablets formulated with Pregelatinized starch as binder. PCMC: Paracetamol tablets formulated with Carboxymethylcellulose Sodium as binder. PHPMC: Paracetamol tablets formulated with Hydroxypropylmethylcellulose as binder.

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**Table 2a: Summary of regression analyses of BFI on binder concentration for paracetamol tablets formulated with binders at fixed concentrations within the range 2.5%w/w – 12.5%w/w.**

| Tablet type | R | r2 | F | Sign F | Slope |
|---|---|---|---|---|---|
| PCOS | 0.9644 | 0.9301 | 39.9024 | 0.0080 | -0.0182 |
| PCAS | 0.9533 | 0.9088 | 29.8818 | 0.0120 | -0.0164 |
| PMAS | 0.9776 | 0.9556 | 64.5879 | 0.0040 | -0.0226 |
| PPOS | 0.9620 | 0.9255 | 37.2754 | 0.0088 | -0.0180 |
| PWES | 0.9048 | 0.8187 | 13.5515 | 0.0347 | -0.0238 |
| PPGS | 0.9566 | 0.9150 | 32.3047 | 0.0108 | -0.0280 |
| PCMC | 0.9325 | 0.8695 | 19.9861 | 0.0209 | -0.0266 |

**Table 2b: Summary of regression analyses of BFI on binder concentration for paracetamol tablets formulated with binders at fixed concentrations within the range 1.0%w/w – 5.0%w/w.**

| Tablet type | R | r2 | F | Sign F | Slope |
|---|---|---|---|---|---|
| PACG | 0.9265 | 0.8583 | 18.1744 | 0.0237 | -0.0693 |
| PCAG | 0.9431 | 0.8894 | 24.1313 | 0.0162 | -0.0451 |
| POKG | 0.9544 | 0.9108 | 30.6504 | 0.0116 | -0.0286 |
| PPGEL | 0.9482 | 0.8990 | 26.7086 | 0.0141 | -0.0364 |
| PPVP | 0.9675 | 0.9360 | 43.8808 | 0.0070 | -0.0582 |
| PHPMC | 0.9921 | 0.9843 | 188.1986 | 0.0008 | -0.0376 |

**Table 3: Binders' groups according effectiveness in ameliorating capping and lamination in paracetamol tablets**

| | Binder Concentration (% w/w) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| BFI | 1.0 | 2.0 | 2.5 | 3.0 | 4.0 | 5.0 | 7.5 | 10.0 | 12.5 |
| 0.05 – 0.10 | | | | | | | | | CMC |
| 0.10 – 0.15 | | | | | CAG | CAG | WES<br>CMC | COS<br>CAS<br>POS<br>WES<br>PGS<br>CMC | COS<br>CAS<br>MAS<br>POS<br>WES<br>PGS |
| 0.15 – 0.20 | | | | CAG | ACG | ACG,<br>OKG | COS<br>PGS | MAS | |
| 0.20 – 0.25 | | OKG<br>CAG | OKG<br>CAG | ACG<br>OKG<br>GEL | OKG<br>GEL<br>PVP<br>HPMC | COS<br>MAS<br>POS<br>GEL<br>PVP<br>HPMC | CAS<br>MAS<br>POS | | |
| 0.25 – 0.30 | OKG | CAG | COS<br>CAS<br>POS | PVP<br>HPMC | | CAS<br>WES<br>PGS<br>CMC | | | |
| 0.30 – 0.35 | GEL<br>CAG | ACG<br>GEL<br>HPMC | WES<br>CMC | | | | | | |

COS – Corn Starch B.P. MAS – Maize Starch PGS – Pregelatinized Starch
CAS – Cassava Starch POS – Potato Starch CMC – Carboxymethyl cellulose
CAG – Cashew gum PVP – Povidone OKG – Okra gum
WES – Wheat Starch ACG- Acacia gum GEL – Gelatin
HPMC – Hydroxypropylmethyl cellulose

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**Tablets' friabilities, disintegration times, and dissolution profiles**

Tablets' friability values were within the range 0.55% (PCOS at 12.5%w/w binder concentration) to 2.05% (PHPMC at 1.0%w/w binder concentration) (Table 4); while disintegration times ranged from 0.39min (PPVP and PGEL at 1.0%w/w binder concentration) to > 480.00min (PHPMC at 5.0%w/w binder concentration) (Table 5). The amount of drug released from the various formulations in 15min ranged from 2.6% (PCMC at 12.5%w/w binder concentration) to 85.6% (PACG at 1.0%w/w binder concentration) (Table 6).

**Table 4: Friability values of paracetamol tablets (without centre holes) formulated at compression pressure of 7.5 arbitrary units.**

| Friability (%) | | | | | | | Friability (%) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PCOS | PCAS | PMAS | PPOS | PWES | PPGS | PCMC | Binder conc.(%w/w) | PACG | PCAG | POKG | PGEL | PPVP | PHPMC |
| 0.74 | 0.69 | 0.93 | 0.91 | 0.80 | 0.80 | 0.82 | 1.0 | 0.89 | 0.91 | 0.397 | 0.83 | 0.95 | 2.05 |
| 0.69 | 0.69 | 0.84 | 0.87 | 0.76 | 0.74 | 0.80 | 2.0 | 0.78 | 0.76 | 0.84 | 0.75 | 0.88 | 0.93 |
| 0.66 | 0.65 | 0.75 | 0.81 | 0.75 | 0.68 | 0.70 | 3.0 | 0.76 | 0.70 | 0.75 | 0.75 | 0.78 | 0.75 |
| 0.62 | 0.64 | 0.70 | 0.75 | 0.68 | 0.68 | 0.66 | 4.0 | 0.70 | 0.68 | 0.72 | 0.74 | 0.66 | 0.70 |
| 0.55 | 0.58 | 0.68 | 0.73 | 0.59 | 0.60 | 0.62 | 5.0 | 0.64 | 0.68 | 0.67 | 0.70 | 0.65 | 0.65 |

**Table 5: Disintegration times of paracetamol tablets (without centre hole) formulated at compression pressure of 7.5 arbitrary units.**

| Disintegration time (min) | | | | | | | Disintegration time (min) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PCOS | PCAS | PMAS | PPOS | PWES | PPGS | PCMC | Binder conc.(%w/w) | PACG | PCAG | POKG | PGEL | PPVP | PHPMC |
| 0.56 | 1.00 | 0.40 | 0.69 | 0.61 | 0.44 | 24.98 | 1.0 | 1.56 | 0.39 | 0.69 | 0.51 | 0.51 | 8.63 |
| 2.09 | 5.43 | 0.66 | 7.35 | 1.31 | 0.62 | 74.17 | 2.0 | 2.43 | 0.41 | 1.22 | 1.24 | 0.86 | 74.61 |
| 2.57 | 7.00 | 1.04 | 12.61 | 1.45 | 0.94 | 85.21 | 3.0 | 4.01 | 2.04 | 1.49 | 5.00 | 0.97 | 155.92 |
| 1.11 | 14.00 | 1.46 | 3.85 | 2.03 | 2.04 | 102.54 | 4.0 | 11.12 | 3.80 | 2.78 | 6.61 | 1.61 | 410.88 |
| 0.71 | 8.88 | 0.59 | 0.58 | 1.57 | 1.03 | 117.84 | 5.0 | 19.29 | 9.51 | 3.54 | 11.28 | 3.70 | >480.00 |

**Table 6: Amount of paracetamol released from tablets (without centre hole) in 15min.**

| Cumulative amount of drug released (%) in 15 min | | | | | | | Cumulative amount of drug released (%) in 15 min | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PCOS | PCAS | PMAS | PPOS | PWES | PPGS | PCMC | Binder conc.(%w/w) | PACG | PCAG | POKG | PGEL | PPVP | PHPMC |
| 16.4 | 29.17 | 15.8 | 12.5 | 28.2 | 21.9 | 4.9 | 1.0 | 85.8 | 77.0 | 79.8 | 81.0 | 81.8 | 36.8 |
| 16.0 | 26.9 | 15.0 | 12.2 | 25.4 | 20.4 | 4.7 | 2.0 | 78.1 | 73.8 | 72.4 | 64.1 | 79.3 | 10.4 |
| 35.9 | 29.6 | 17.0 | 15.7 | 29.5 | 31.9 | 4.4 | 3.0 | 66.9 | 70.9 | 70.7 | 43.7 | 79.0 | 6.1 |
| 45.6 | 30.3 | 30.2 | 18.3 | 35.8 | 46.3 | 3.5 | 4.0 | 33.8 | 40.3 | 68.0 | 29.2 | 78.3 | 5.2 |
| 67.4 | 34.3 | 74.1 | 25.2 | 68.7 | 78.1 | 2.6 | 5.0 | 26.6 | 26.8 | 66.1 | 22.8 | 77.1 | 4.4 |

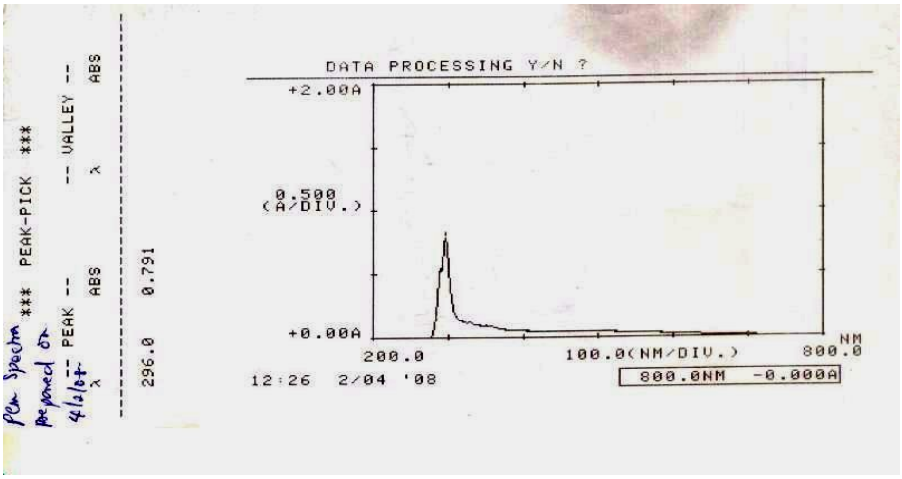


**Fig. 1: Paracetamol spectrum in 0.1N HCl.**

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## DISCUSSION

The moisture contents of the granules did not differ appreciably and therefore might not have contributed significantly to their dynamic and compaction properties. The dynamic properties of the granules all lie within the passable grade with respect to angle of repose, Carr's index, and Hausner's ratio characterizations (Wells and Aulton, 1990). These flow properties are traceable to the aperture size (600µm) of the sieve used in dry screening the granules. Reports from previous works (Armstrong, 2000; Powders and Granules, 2011) revealed that sieving with such sieve size generates uniformly sized and moderately coarse granules. It was noted during the experiment that the granules had small amount of fines and this resulted to moderate tapped volume reductions and consequently moderate flow characteristics, which however may be improved by glidant incorporation.

The inverse relationship between binder concentration and BFI (Table 1) is consistent with earlier reports (Alebiowu and Itiola, 2002; 2003; Odeku et al., 2005) and can be explained in terms of the plasticizing effects of binders on paracetamol powder as their concentrations increased. Similarity in the mechanism of increase in plasticity of paracetamol granules as starch pastes or CMC concentration increased may account for the insignificant difference between the BFI values of tablets formulated with starches or CMC as binder. In contrast, binders from different classes (plant origin, semi-synthetic, and animal origin) with possibly dissimilar plasticizing mechanisms manifested significant differences in their effectiveness in reducing BFI. Previous researches (Odeku and Itiola, 2002; Alebiowu and Itiola, 2003; Odeku et al., 2005; Uhumwangho et al., 2006; Eichie and Amalime, 2007) also revealed dissimilarities in BFI reductions by different binders, however non used binders from varied classes as is the case in the present study and no statistical analysis was conducted by the workers to verify the significance of such finding. The regression analyses revealed that some classes of binders are superior to others in ameliorating capping and lamination in paracetamol tablets. The steeper slopes of plant gums, PVP, gelatin and HPMC, are indications of their greater effectiveness in BFI reductions than starches and CMC. By this, the binders were grouped as shown in table 3. It is evident from table 3 that no particular class of binders occupied a unique group within the range of BFI values realised in this study. Rather, binders from various classes at different/similar concentrations appear within each range. This grouping is very significant in formulation development in that it may serve as a guide for scientists to narrow their search for appropriate binders and suitable concentrations to be applied in formulating not only paracetamol but also other elastic natured powders into tablets with highly reduced tendencies to fracture. Furthermore, within each group, binders possess dissimilar abilities in the reduction of BFI; hence they can be ranked based on their effectiveness. For example, paracetamol tablets formulated with gelatin, PVP, HPMC, corn starch BP, maize starch, or potato starch, at 5.0%w/w, target BFI value range being 0.20 – 0.25 (Table 3), ranking is therefore- PVP > HPMC > GEL > COS > POS > MAS (Table 1). From this ranking, it is evident that from an array of binders that can impart the same range of BFI value at the same concentration, choice may still be made based on the level of effectiveness of each binder. However, it must be stressed that this choice should also be guided by the dissolution profile desired from the formulation. For example, HPMC ranked better than GEL, COS, POS, and MAS, but it is not suitable for the formulation of immediate release tablets. This ranking can also help a formulator to choose based on economic gains since some binders are cheaper and easier to source than others.

All the tablet batches except PHPMC (at 1.0%w/w HPMC) fulfilled the requirement on friability having displayed values less than 1% (USP, 2004). Tablets formulated with CMC, HPMC (except at 1.0%w/w), and PACG at 5.0%w/w ACG failed the BP requirement (< 15min) for conventional tablets' disintegration (Roohullah et al., 2003; Akin-Ajani et al., 2005). Tablets formulated with starches displayed lowest disintegration times at 12.5%w/w binder concentration. This resulted from the added disintegrant effect that starches have been established to manifest when they are incorporated as pastes during granulation (Rudnic and Schwartz, 2000).

The amount of drug released in 15min was used as a discriminating test to judge the release profile of tablets. It is obvious from table 6 that from 1.0 – 3.0%w/w binder concentration, tablets formulated with plant gums released about 70% of the drug whereas starches achieved the same fit at 12.5%w/w, an observation that can be explained by starches' added disintegrant activity when incorporated as a paste (Rudnic and Schwartz, 2000). Beyond 3.0%w/w plant gums imparted negatively on the dissolution profile of the drug, unlike PVP whose concentration increase resulted to very minimal reduction in the amount of drug released in 15min.

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It is desirable that fast onset of action should characterise paracetamol formulations since it is an antipyretic and analgesic drug, therefore putting into consideration the issues of economy and effectiveness, plant gums which even at low concentrations performed better than PVP, gelatin, CMC, HPMC, and starches in the reduction of BFI and released higher amount of drug at much lower concentration than starches can be adjudged to be better binders for paracetamol tablet formulation than starches.

## CONCLUSION

It is evident from this work that brittle fracture index is a useful tool for the grouping of binders based on their abilities to ameliorate capping and lamination in tablets. Its usefulness also extends to the ranking of binders based on their levels of effectiveness in solving the problem of capping and lamination. However, 'families' of binders based on nature or origin could not be classified using BFI since no 'family' occupied a unique range of BFI values within the concentration ranges used in the present study.

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