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Evaluation as Disintegrant, Acetone-dehydrated Pre-Gelatinized Starch of *Arthocarpus altilis* Fruits in Oral paracetamol Tablets

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Authors' contributions

This work was carried out in collaboration among all authors. Author TOU designed the study and wrote the protocol of the study. Authors GJ and IA carried out the laboratory studies. Authors DEE and IA performed the statistical analysis, managed literature search for the study and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Modifying natural polymers have imparted desirable properties making them suitable as pharmaceutical additives.
Aim: This research work was to prepare pre-gelatinized breadfruit starch using acetone to reduce drying time and energy expended. The modified starch was evaluated as a disintegrant in paracetamol oral compacts**.**
Methods: Starch from unripe mature bread fruit was pre-gelatinized, precipitated with acetone to reduce drying time. Native and pre-gelatinized starches were characterized for micromeritics, compatibility studies with test drug using Fourier Transform Infra-Red (FT-IR) and water interaction properties (viscosity, swelling power and hydration capacity). Paracetamol granules formed by wet granulation were compacted incorporating starches as disintegrant intragranularly, extragranularly and combining both methods. Disintegration and dissolution studies done.
Results: Pre-gelatinization did not alter the native starch chemically and their pH were within

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pharmaceutical limits. The disintegration efficiency ratio (DER) for the P2 and P3 (tablet batches with pre-gelatinized starches) compared favourably with that of corn starch**.** Also, the dissolution kinetics of the breadfruit starches followed the Hixson Crowel's model while that of reference corn starch was best described by the Higuchi kinetic model.

Conclusion: Breadfruit starch is edible and the properties of its pre-gelatinized form as a disintegrant compares favourably with corn starch BP. It could be an good alternative as pharmaceutical excipient.

Keywords: Arthocarpus altilis starch; acetone-dehydrated; pregelatinized; disintegrants; paracetamol tablet.

1. INTRODUCTION

Apart from determining the Active Pharmaceutical Ingredient (API), a necessary task in successful dosage form design and development, is the selection of appropriate excipient for use. Thus, excipients use is judiciously selected for incorporation into dosage forms to achieve functionality. For oral solids, the desired mechanical strength, taste, colour and release profile of dosage forms that will give a therapeutic action are achievable feats with proper selection of distinctively functional excipients compatible with the API.

Selected excipients could be used as binders, disintegrants, flow activators, fillers, dissolution modifiers or matrix formers. Disintegrants are important additives of conventional immediate-release oral compacts to allow for tablet break-up, granule de-aggregation and dissolution for timely release of API from tablets in an aqueous medium [1]. It can readily be employed (in the form of superdisintegrants) in oral dispersible tablets that are the drug of choice for paediatrics and geriatric with dysphagia. Oral solid dosage forms must go into solution in body fluids and get absorbed into the systemic circulation to elicit therapeutic action. Disintegration is a key process that precedes dissolution. The mode of incorporation of disintegrants has been reported to affect the performance and the quality of a tablet and its release profile [2,3]. Odeku and Bandelin both had published that under the same condition, use of the intra-extragranular disintegrant method gave better rate of tablet break up when compared with the other methods [3,4].

Starches of different sources (e.g., tubers, cereals,) have been employed, either in the native or modified forms, as useful excipients in dosage form development [2,5]. One readily studied starch is from *Arthocarpus altilis*. A flowering plant of the Moraceae family, *Arthocarpus altilis* (breadfruit plant) tree grows in the forest zone, having nutritious fruits which is a source of starch that has been extensively studied. Loos, Hood and Graham [6], for example, had obtained and characterized starch from breadfruit while the compression behaviour, mechanical features of compacts formed with it, pasting properties, binding effect of its mucillage and disintegrant properties of the native starch have been reported [6-10]. Pre-gelatinized breadfruit starch has been used with alginate and chitosan for controlled release microspheres of theophylline with interesting results [11].

Paracetamol, an analgesic used in this research. is expected for fast onset of action in less than 30 minutes. An effective disintegrant will be ideal to achieve this.

This work is thus focused on preparing pre-gelatinized breadfruit starch with acetone-enhanced drying, then employing the modified starch as disintegrant in paracetamol compacts. Corn starch BP was used as a reference.

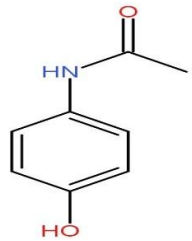

Fig. 1. Chemical structure of paracetamol

2. MATERIALS AND METHODS

2.1 Materials

Paracetamol powder (Tianjin Bofa Pharmaceuticals Co. Ltd, China), corn starch (Tianjin Tiankai, China), acetone (BDH Chemicals, UK), talc powder, magnesium stearate, methyl paraben and propyl paraben. Other materials used were of analytical grade.

2.2 Methods

2.2.1 Study area

This study was carried out in the pharmaceutics laboratory, pharmaceutical technology laboratory, tableting unit and the dosage form evaluation unit, all in pharmaceutics and pharmaceutical technology department of the faculty of pharmacy, University of Uyo, a tertiary institution in the South-South region of Nigeria, between the period of May, 2019 and March, 2020.

2.2.2 Production of starch

Freshly plucked mature, unripe breadfruit (*Arthocarpus altilis*) was obtained from Ikot Obio Odong, Ibesikpo local government area in Akwa Ibom state, a province in the south-south region of Nigeria. The fruit was prepared using method by Awokoya et al. [12] with slight modification. Briefly, 4kg of fruit, pericarp peeled out, was soaked in Sodium metabisulphite solution for an hour, thereafter wet-milled and allowed to stand for 4 hours. The mixtu re was filtered. The filtrate, allowed to stand for 12 hours, was decanted to remove the supernatant but the starch sediment washed with distilled water twice and dried in laboratory oven (Techmel & Techmel USA) at 35^{o}C for 24 hours. The dried starch was stored in an airtight container.

2.2.3 Modification of starch

The pre-gelatinization of *A. altilis* starch followed the method described by Ohwoavworhua and Osinowo [13].

2.2.4 Physicochemical evaluation of pre-gelatinized starch from *Arthocarpus altilis* fruit

Preliminary tests were carried out on the native starch and modified starch while corn starch was used as a reference standard are described as follows;

2.2.4.1 Micromeritics

The micromeritics comprising of the densities, flow rates, Hausner's and Carr's index and the angle of repose were determined in line with our earlier published method [14,15].

2.3 Solubility Test

The solubility of each starch in different solvents (cold water, warm water, chloroform and 95% ethanol) was determined at 25^{o}C. About 1 % w/v slurry of the starch in each solvent was prepared out in clean test tubes. The slurry was allowed to stand overnight (8 hours). The slurry was thereafter centrifuged at 1500 rpm for 20minutes and 6.25 ml of the supernatant formed was decanted out the next day into an already weighed petri dishes which were evaporated to dryness in a hot air laboratory oven (Techmel & Techmel, USA) at 100^{o}C. The residue obtained was weighed and the percentage solubility in 6.25mL was calculated.

$$Solubility = \frac{weight\ of\ starch\ in\ supernatant}{weight\ of\ suprnatant} \times 100 \quad (3)$$

2.4 Hydration Capacity and Swelling Power

Hydration capacity was carried out as described by Okunlola and Adewusi [11] whereas the swelling power was determined according to the method reported by Odeniyi et al. [16] with a slight modification. Starch slurry (10%w/v) was prepared and kept at room temperature for 20 hours after which the volume of starch swelling was recorded. This test was done in triplicates and the swelling power calculated as follows;

$$Swelling\ power = \frac{Total\ volume\ of\ swollen\ starch\ or\ sedimented\ starch}{Original\ volume\ of\ dry\ weight\ starch} \times 100 \quad (4)$$

2.5 pH and Viscosity

Exactly 100mL of 1 % $^{w}/_{v}$ slurry, starch in distilled water, was prepared and the pH was determined using a pH meter (3305, Jenway). Thereafter, the viscosity of the slurry was determined using a Brookfield viscometer with spindle size 2 at 50rpm and temperature of 28 ± 2 ^{o} C. The tests were carried out in triplicates.

2.6 FTIR Analysis

The sample of pre-gelatinized breadfruit starch well size reduced was placed on KBr plate, well distributed, then covered and placed in the spectrometer (FT-IR Spectrum BX II by Perkin Elmer, Waltham, MA, USA) for scanning at a range of 4000-450 cm^{-1}. Similar scanning was done for the native starch, the corn starch BP each and the mixtures of each starch with the drug, for drug-excipient compatibility.

2.6.1 Preparation of paracetamol granules

Wet granulation method was used for granules production with gelatin (binder) used to form the

granulating fluid. With a target weight of 500 mg for tablet, granules that would cater for 100 tablets for each batch of starch was produced. The disintegrant was incorporated using 3 different methods (intra-granular, extra-granular and intra-extragranular methods). Native breadfruit starch and corn starch BP were also used as disintegrants for comparative assessment.

Table 1. Tablet composition

Ingredients	Percentage composition ($\%^{W}/_{W}$)
Paracetamol powder	86
Gelatine powder	3
Starch powder	7
Talc	1
Magnesium stearate	1
Methyl paraben	1
Propyl paraben	1

2.7 Evaluation of Granules

2.7.1 Micromeritics studies

Evaluation of the flow properties (flow rate, angle of repose, densities, and Carr's index) of the granules was done using same methods as for the starch evaluation.

2.7.2 Production of tablet compact

The granules was prepared with 1 % w/w each of talc and magnesium stearate as lubricants prior to compression. The granules were compressed into tablets using the single punch tableting press (Cadmach, Ahmedabab, India) fitted with 12.5 mm flat faced punches at a constant compression force (15 KN).

2.7.3 Tablet evaluation

2.7.3.1 Tablets weight and dimensions

Produced tablets were selected (20 for weight but 10 for dimensions) at random from each batch of tablets. Weighing was done using an electronic weighing balance (Ohaus, Galaxy) but dimensions were determined with a micrometer screw gauge (KFW Scientific industries, Ambala Cantt, India).The mean in each case was determined.

2.7.3.2 Tablet breaking force, tensile strength and friability

The tablet breaking force (crushing strength) was determined using a Monsanto hardness tester (Rolex, Chandigarh). Five tablets were used. This was determined using the formula:

$$Ts = \frac{2Bf}{\pi Dt} \quad (5)$$

Where Bf is breaking force (also known as crushing strength), D is the diameter of the tablet and t is the thickness of the tablet

The friability of 10 tablets from each batch was determined in a Roche friabilator (UNID Campbell Electronic, Mumbai, India). The friability was then calculated using the formula:

$$Fraibility = \frac{weight\ difference}{original\ weight} \times 100 \quad (6)$$

2.7.4 Drug release studies

2.7.4.1 Tablet disintegration and in-vitro dissolution study

The disintegration test was patterned after the method described in the British Pharmacopoeia for immediate-release paracetamol tablets using the digital tablet Disintegration test apparatus (Labtech, India).

The dissolution study was carried out in the dissolution apparatus (RCZ-6C3, China) employing the USP apparatus I (basket) method in 900 mL of 0.1 N HCl, agitated at 50rpm and maintained at a temperature of 37 ^{o} C ± 1 ^{o}C. Exactly 10 mL aliquots were withdrawn at intervals of 5 minutes for the first 5 withdrawals thereafter at interval of 10 minutes until 60 minutes. Withdrawn samples, filtered through Whatman filter paper no 2, were analyzed using UNICO-spectrophotometer (UV-2100PC Shanghai Instruments Co. Ltd., China) at 243 nm and the drug concentration determined.

2.7.4.2 Disintegration efficiency ratio

This was calculated using the formula:

$$DER = \frac{(Bf/Ft)}{\boldsymbol{Dt}} \quad (7)$$

Where Bf, Ft and Ds are the tablet breaking force, friability and disintegration time respectively.

The disintegration parameter, Disintegration Efficiency Ratio constant (DER_C) was also determined using the formula:

$$DERc = \frac{DER\ test}{DER\ reference} \quad (8)$$

2.7.4.3 In-Vitro kinetic release models of the tablets

The data obtained from the dissolution studies were fitted into various release kinetic models (zero order, first order, Higuchi and Korsmeyer-Peppas model) and the model with highest correlation coefficient (R^2) was considered to be the best fit to describe the kinetic drug release.

2.8 Statistical Analysis

A statistical analysis was carried out to assess the effect of starch incorporation on disintegration using the analysis of variance (ANOVA). The probability value, p ≤0.05 were considered significant at a 95% confidence interval.

3. RESULTS AND DISCUSSION

The FT-IR results of the native breadfruit starch, its pre-gelatinized form and corn starches as well as that of their physical mix with paracetamol powder are given in Figs. 2-7. The FT-IR spectra reveals the functional groups present in the native and modified starches.

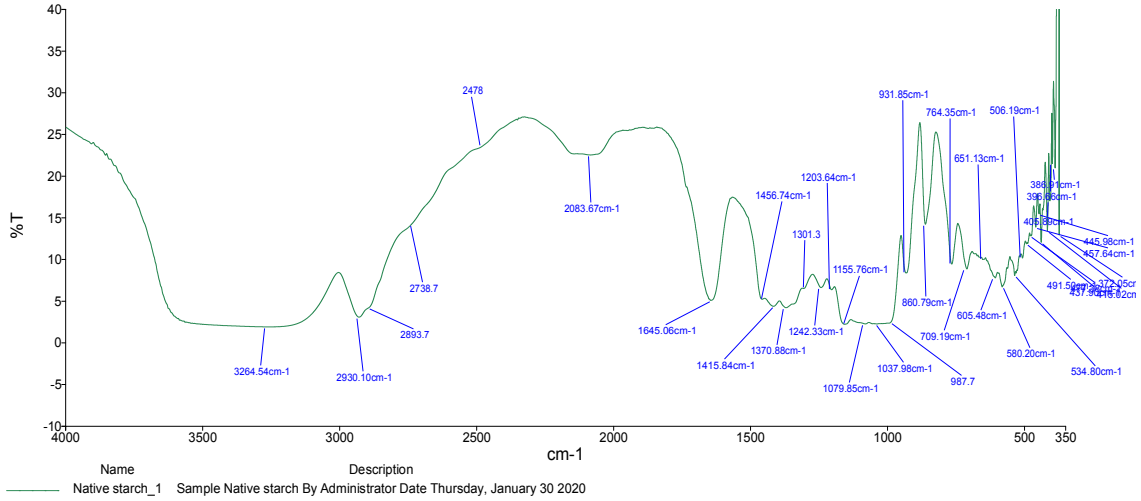

Fig. 2. FT-IR Spectrum of native breadfruit starch

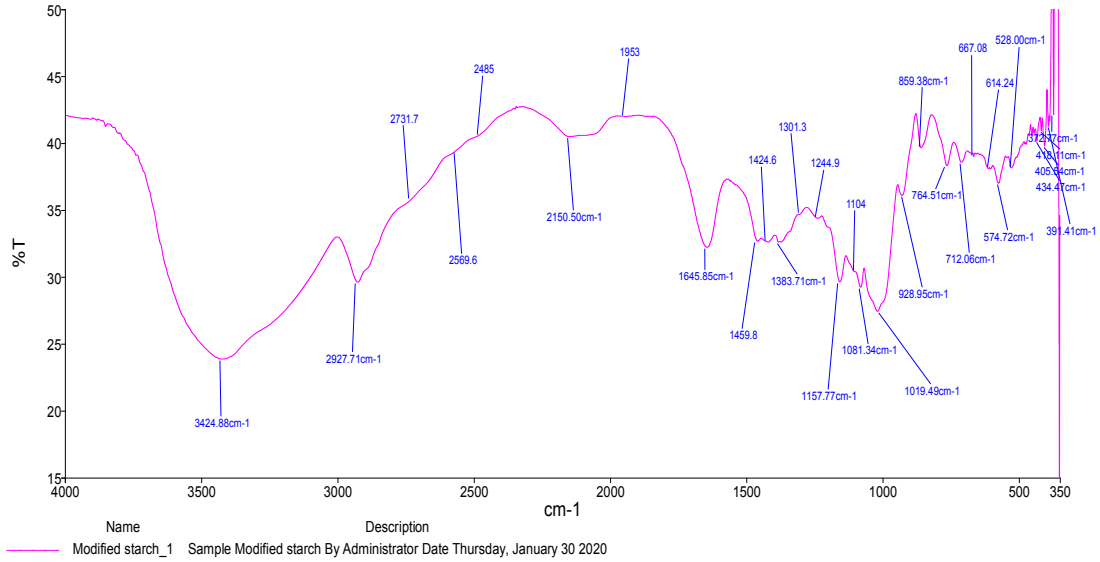

Fig. 3. FT-IR spectrum of pre-gelatinized breadfruit starch

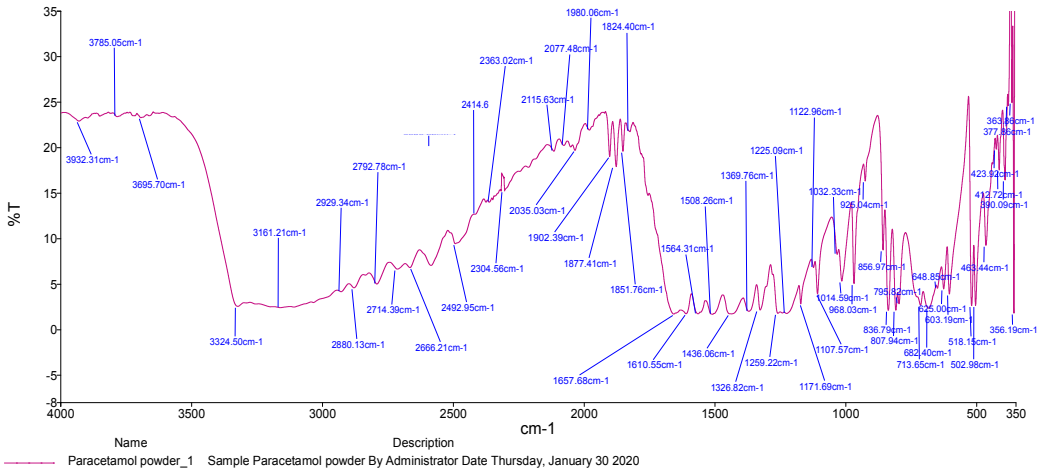

Fig. 4. FT-IR spectrum of paracetamol powder

The general and characteristic spectrum noticeable in starches and the prominent peaks of the drug and starches are presented in Table 2. The strong broad peak found at 3264 cm^{-1} (for native starch) and 3424 cm^{-1} (for pre-gelatinized) are diagnostic of –OH functional groups but the sharp peaks at 2930cm^{-1}(for native) and 2927cm^{-1} (for pre-gelatinized) are assigned the CH_2-CH_2 chains of the starches [14,17]. The medium peak seen at 2738 cm^{-1}, 2731cm^{-1} and at 1645 cm^{-1} on the native and pre-gelatinized starch spectra are attributed to the C-H and C=O stretch of the carbonyl functional group. Starches are polymers with carbonyl (specifically, aldehyde) functional groups and this explains the observations. Both the native and pre-gelatinized starches have similar functional groups. It is noteworthy that the modification by pre-gelatinization did not alter nor introduce any functional group into the starch. This was also reported in literature in our earlier work [14]. Characteristic bands seen for the pure paracetamol are the strong broad peaks of 3324cm^{-1} (O-H stretching), the weak band of 2035cm^{-1}, 1980cm^{-1},1877cm^{-1},and 1824cm^{-1} which are all assigned the aromatic group and the 1657cm^{-1} that represents the primary amide group.

The FTIR of the physical mixtures of the drug with each starch contained all the prominent bands of the two constituents with no significant shifting of the peaks, indicating the stability and compatibility of the starches with the drug.

Table 2. Prominent peaks in the FT-IR Spectra of starches and drug

Wave numbers cm^{-1}	Representative functional group			Where present	
		Native starch	Pre-gelatinized starch	Corn starch	paracetamol
3264-3424	O-H Stretching	+	+	+	+
2931-2931	CH_2-CH_2 Symmetrical stretching	+	+	+	—
2738	C-H of CHO	+	+	+	—
1800-1700	C=O vibration peaks of CHO	+	+	+	—
1600-1400	C-H bending	+	+	+	+
2035-1610	Aromatic ring	—	—	—	+
1657	Associated primary amide group –NHCH3CO	—	—	—	+

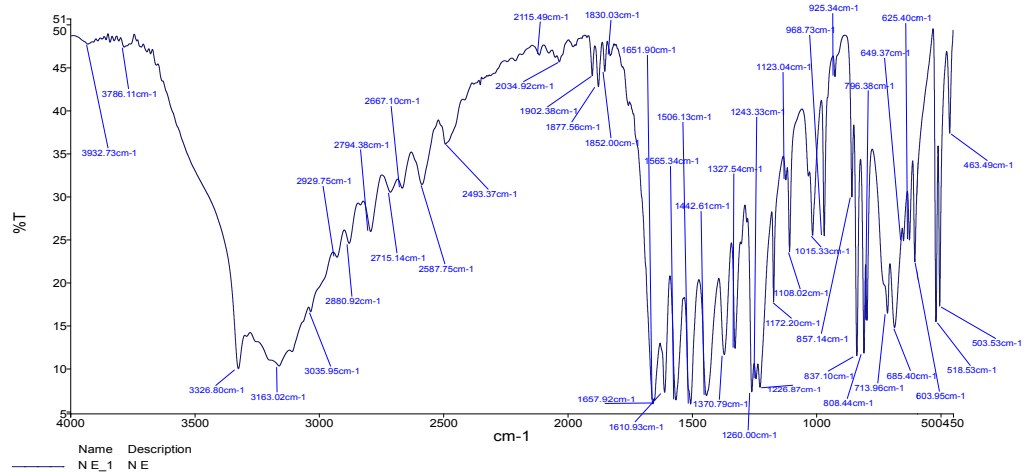

Fig. 5. FT-IR of native breadfruit starch with paracetamol powder

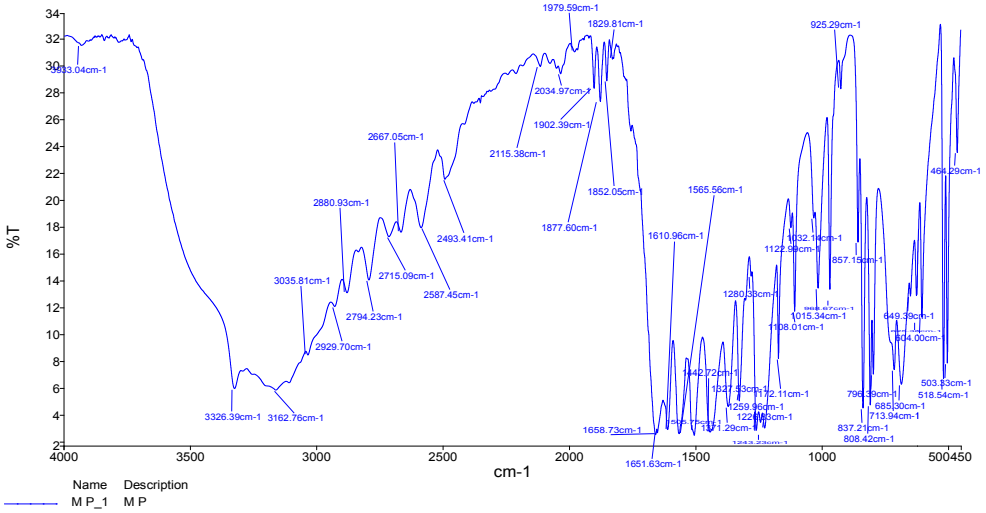

Fig. 6. FT-IR spectrum of pre-gelatinized breadfruit starch with paracetamol powder

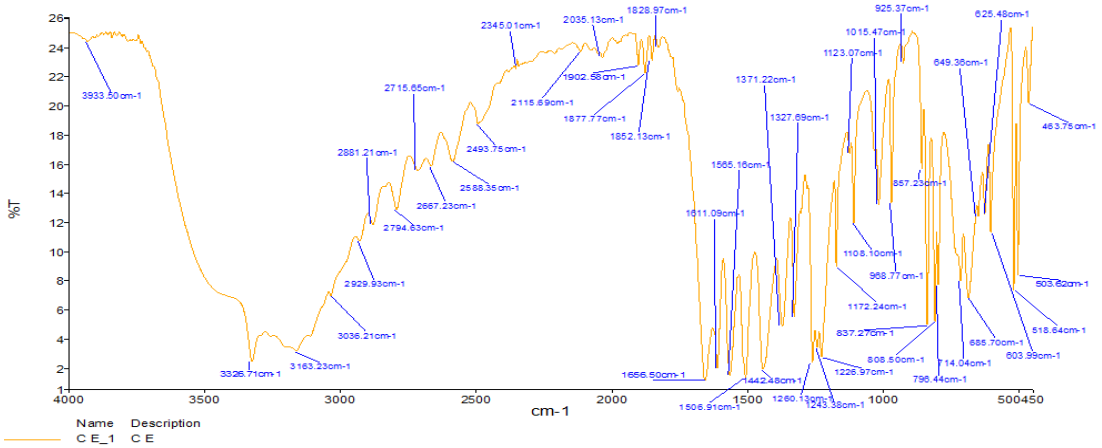

Fig. 7. FT-IR spectrum of corn starch with paracetamol powder

The organoleptic properties and micromeritics of the starches are given in Tables 3 and 4 respectively. All starch taste the same although the pre-gelatinized was grey in colour. The slightly choking smell of the modified starch was choking likely due to the acetone used to facilitate rapid drying of the pre-gelatinized starch but as the solvent evaporated the choking smell soon gave way.

Bulk and tapped densities of the starches ranged from 0.3-0.6g/mL and 0.5-0.8g/mL respectively. The pre-gelatinized breadfruit starch had bulk and tapped densities higher than both the native and the reference starches (Table 3). With a Hausner's ratio of 1.2, Carr's index of 18.3% and angle of repose of 31.4^{o}, the pre-gelatinized starch had a fair to good flow whereas the native and corn starches had poor to very poor flows with Carr's values range of 28-37% and Hausner's ratio of 1.4-1.6. These indirect measure of flow properties was corroborated by the actual measure of the flow rate where-in about 8g of the pre-gelatinized starch flowed through the funnel orifice in a second as opposed to < 2g that did for the native and corn starches. The flow properties of a dry powder can give insight into the existence and extent of cohesive forces between the particles of each starch as well as the resultant ease of flow into a tablet die and proper die cavity fill, hence, its usefulness in direct compression or the need for addition of anti-adherents. Thus on the basis of micromeritics, the starches could be ranked P>C>N but based on solely density C<N< P. Pre-gelatinization densified the breadfruit starch and improved its flow properties. A possible explanation could be that pre-gelatinized starches existed as aggregate particles thus increasing their size and density as well as flow [18]. Similar reports have been published as to effect of pre-gelatinization on starches [11,18].

Also the pH, swelling power and hydration capacity of the starches are on Table 4. The pH of the starches revolves around neutral- slight alkaline but the pharmaceutical standards is 4 -7 [19]. The swelling power and hydration capacity range 24-49% and 28-895% respectively. Pre-gelatinization improved the viscosity and significantly the hydration but not the swelling of the breadfruit starch, however these (hydration and swelling) values were significantly lesser than that of the corn starch.

Table 3. Organoleptic properties of the Starches

Starch	Colour	Odour	Taste	Texture
Native starch (N)	White	Characteristic (plant-like)	Bland	coarse powder, amorphous in nature
Pre-gelatinized starch (P)	Grey	Characteristic (slightly choking)	Bland	very fine powder with gritty feel
Corn starch (C)	Cream	Odourless	Bland	fluffy powder, amorphous in nature

Table 4. Micromeritics properties of the starches

Type of starch	Bulk density(g/mL) mean± SD	Tapped density (g/mL) mean± SD	Hausner's ratio mean± SD	Carr's index (%)	Angle of repose(θ) mean± SD	Flow rate (g/s) mean ±SD
N	0.42±0.03	0.67±0.01	1.59±0.10	36.70±4.90	40.33±0.10	1.80±0.30
P	0.63 ± 0.01	0.79 ± 0.01	1.22±0.21	18.33±1.40	31.44±2.10	7.96±1.40
C	0.38 ± 0.01	0.52 ± 0.01	1.40± 0.05	28.30±0.80	45.30±0.01	0.65±0.01

Key: Result presented as mean± SD, N= Native starch, P= Pre-gelatinized starch, C= Corn starch

Table 5. Other properties of the starches

Starch type	pH	Viscosity (mPas)	Swelling index (%)	Hydration capacity (%)
N	7.67 ± 0.01	3.24 ± 0.10	44.67 ± 27.90	28.00 ±11.00
P	8.00 ± 0.00	4.13 ± 0.10	24.33 ± 13.60	186.00 ± 58.00
C	7.04 ± 0.06	3.51 ± 0.10	49.00 ± 6.55	895.00 ± 18.50

Key: Result presented as mean± SD, N= Native starch, P= Pre-gelatinized starch, C= Corn starch

The micromeritics of the granules formed from the native, pre-gelatinized and corn starches are presented on Table 6. The pattern observable in the starches are similarly seen in that of the granules. The direct measure of flow rate shows that granules prepared from pre-gelatinized starch (P_1) incorporated intragranularly was highest, whereas the lowest value is seen in granules of pre-gelatinized starch used extragranularly. The indirect measures of the flow properties (Hausner's ratio and angle of repose) also reflects this. It is lowest in N_2 and C_1 (for Hausner's ratio), but highest in P_3 whereas the angle of repose was highest for C1 but lowest for P1. The Hausner's ratio which gives indication of densification and flow is generally fair to passable for the all batches of the granules. It is noteworthy that there was improvement in the flow of particles for native and corn starches (N and C) on use to formulate paracetamol granules. Observable too is that granules of all the starches incorporated extragranularly as disintegrant, had poor flow. This is not unexpected as flow property is related to particle size and density. Granulation increased the sizes and density, reducing interparticulate contact and cohesion thus improving their flow. However on addition of the starches (smaller particle size and density) as disintegrant to granules (extragranular incorporation), interparticle contact increased, filling the spaces between the granules and likely reduced the flow.

The physico-mechanical properties of tablets are seen on Table 7. The value of friability and breaking force ranged between 0.52 -0.71% and 66-107N respectively. The friability values reveal that all batches of tablet pass the recommended standard of ≤1% [20]. Although some literature have recommended breaking force for tablet to be within 40-150N, all batches of the tablets fall within such range [21,22]. It is clear then that the tablets formed retains a balanced tablet strength; can withstand crumbling and wear resulting from impact during transportation but not too hard to resist breakage. The weight variation of the tablets falls within the accepted range as prescribed by the official compendium. The International Pharmacopoeia specifies that for 20 randomly selected tablet, each ≥ 250 mg, 18 tablets or more must equal ± 5% mean weight deviation, but ≤2 tablets should have mean weight deviation of ± 10%.

The content uniformity and disintegration time of the tablet batches are seen on Table 8. The former is in the range between 82- 114% w/w. The British Pharmacopoeia standard tablets is in the range of 85 % to 115% for uniformity in tablets [20]. To fall within acceptable range is an indication of good mix. Also this was expected since the tablet has a high content of the active ingredient. Higher percentage of active ingredient will translate to a good distribution of that content throughout the table even if mixing is less than ideal. The disintegration time of the tablets range from 6-59 minutes with corn starch and pre-gelatinized breadfruit starch, both incorporated extragranularly, having the least time. Cornstarch used intragranularly had the longest period for disintegration. The official compendium gives disintegration time for immediate release tablets at 15 minutes [20,21]. From the table, three batches of tablets failed the disintegration test (N_1, N_2, and P_1). Generally, intragranular incorporation of disintegrant delayed disintegration time as opposed to

Table 6. Micromeritics of granules formulated with the starches as incorporated via different methods

Batch	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (^{0})	Flow rate (g/s)
N_1	0.48± 0.01	0.64± 0.04	20.43 ± 1.80	1.25 ± 0.03	38.42± 0.20	6.15 ± 0.40
N_2	0.45 ± 0.01	0.56 ± 0.01	19.70± 0.60	1.24 ± 0.01	41.13 ± 2.90	6.27 ± 0.90
N_3	0.45 ± 0.00	0.60± 0.00	24.52 ± 0.76	1.33 ± 0.01	38.87 ± 0.50	4.38± 0.09
P_1	0.47± 0.01	0.59 ± 0.01	20.30± 0.30	1.25 ± 0.01	34.99 ± 1.70	8.05 ± 0.40
P_2	0.44± 0.01	0.57 ± 0.01	20.02 ± 2.00	1.30 ± 0.03	41.54 ± 1.30	4.18 ± 1.30
P_3	0.45 ± 0.01	0.70 ± 0.16	25.67 ± 2.70	1.35 ± 0.05	41.88± 0.80	5.06 ± 0.01
C_1	0.46 ± 0.01	0.70± 0.01	19.75 ± 1.99	1.24 ± 0.00	42.62 ± 2.70	5.62 ± 0.80
C_2	0.46 ± 0.01	0.57 ± 0.01	19.70± 2.60	1.25 ± 0.03	38.20 ± 0.40	4.43 ± 0.30
C_3	0.44 ± 0.10	0.57 ± 0.00	22.77 ± 1.80	1.29 ± 0.03	37.93 ± 0.60	5.29± 0.01

KEY: Results presented as mean± SD, N= Native starch, P= Pre-gelatinized starch, C= Corn starch, $_1$ -Intra-granular; $_2$ - Extra-granular; $_3$ - Intra-granular-extragranularly, hence N_3- granules with Native starch as disintegrant incorporated intragranular- extragranularly

Table 7. Physical properties of the formulated tablets

Tablet batch	Weight variation (g)	Thickness (mm)	Diameter (mm)	Breaking force (N)	Tensile strength (Ncm^{-2})	Friability (%)	B_f/f_t values
N_1	0.56±0.04 (7.14)	4.39±0.10	12.12±0.01	81.34±5.58	97.29± 1.00	0.63±0.10	130.37±11.98
N_2	0.55±0.01 (1.82)	4.20±0.07	12.13±0.01	95.06 ±14.41	118.74± 0.50	0.53±0.10	180.23±5.67
N_3	0.58±0.01 (1.72)	4.16±0.09	12.13±0.01	91.14±3.92	114.94± 2.20	0.71±0.08	129.05±9.07
P_1	0.58±0.03 (5.17)	4.19±0.02	12.12±0.01	100.94±21.20	126.49± 5.00	0.56±0.10	179.55±5.89
P_2	0.55±0.01 (1.82)	4.19±0.03	12.12±0.00	88.20±5.39	110.52± 0.90	0.65±0.10	137.01±12.94
P_3	0.57±0.01 (1.75)	4.21±0.01	12.13±0.01	66.64±2.74	83.04± 9.0	0.52±0.04	128.39±3.78
C_1	0.54±0.01 (1.85)	4.29±0.02	12.12±0.01	97.02±7.74	118.74± 0.10	0.58±0.10	169.11±13.10
C_2	0.56±0.02 (3.57)	4.22±0.03	12.13±0.01	102.90±14.70	127.92± 0.70	0.63±0.10	164.68±3.61
C_3	0.57±0.03 (5.26)	4.23±0.01	12.13±1.70	107.80±0.98	133.70± 1.00	0.62±0.10	176.79±22.28

KEY: Results presented as mean± SD, N= Native starch, P= Pre-gelatinized starch, C= Corn starch, $_1$ -Intra-granular; $_2$ - Extra-granular; $_3$ - Intra-granular-extragranularly, hence N_3- granules with Native starch as disintegrant incorporated intragranular- extragranularly and values bracketed is the coefficient of variation (%)

Table 8. Disintegration parameters and Content uniformity of the tablet

Batch	Disintegration time (min) Mean± SD	DER Values	DER_C values	Content uniformity (%) Mean± SD
N_1	59.23 ± 0.01	2.20	0.11	85.02±0.01
N_2	16.43 ± 0.20	10.97	0.43	85.02± 0.40
N_3	14.02 ± 0.04	9.20	0.69	114.26±0.20
P_1	33.48 ± 0.01	5.36	0.33	104.30±0.00
P_2	6.31± 0.30	21.71	0.86	82.06± 0.04
P_3	11.58 ± 0.60	11.09	0.84	112.40±0.03
C_1	8.25 ± 0.09	20.50	—	114.26±0.20
C_2	6.50 ± 0.05	25.34	—	91.92 ± 0.08
C_3	13.35 ± 0.04	13.24	—	113.97±0.05

KEY: Results presented as mean± SD, N= Native starch, P= Pre-gelatinized starch, C= Corn starch, $_1$ -Intra-granular; $_2$ - Extra-granular; $_3$ - Intra-granular-extragranularly, hence N_3- granules with Native starch as disintegrant incorporated intragranular- extragranularly.

extragranular technique whereas the effect of combining was seen the most in the pre-gelatinized starch (P_3).

3.1 Disintegration Studies

Table 8 contains the parameters for assessing disintegration. Generally, three batches (N1, N2, P1) failed the disintegration test. The British Pharmaceutical Codex prescribes 15 minutes as the time sufficient for disintegration [20]. The fastest disintegration is seen in P2 whereas the batch with longest time to experience disintegration is N1. The efficiency of disintegration is however highest for C2, followed by P2. Although the intragranular-extragranular means of disintegrant incorporation is reported as the method of disintegrant incorpration with the best disintegration effect, this work shows that disintegrant incorporated extragranularly gave a better disintegration when compared with the other methods (see P2 and C2). Disintegration breaks up solid dosage forms into small, individual particles, exposing their large surface area for drug dissolution to occur [1]. The faster the disintegration rate, the quicker dissolution and consequent release of drug.

The DER values which incorporates more parameters in the assessment of disintegrant property reveals that C2 and P2 had the highest values for the DER. The DERc on the other hand is highest for P2 (0.86) followed by P3 (0.84). DERc measures more accurately the disintegrant effect of an excipient intended at tablet disintegration because it encompases tablet parameters that assesses tablet strength and weaknesses [23]. There was a significant difference between the DERc of the pre-gelatinized starch and the native as seen by rhe higher value. However, corn starch DERc is with no values as they are used as the reference standards in each case. P2 and P3 proved to be better disintegrants than the native starch but were slightly less effective as the corn starch as disintegrant.

3.2 Dissolution

The calibration curve of paracetamol is given in Fig. 9 while the dissolution profile is shown in Figs. 10-12. From the Fig. 7, the linear equation for calibration is y=0.4429x + 0.0235 and the corelation coefficient being 0.9916. All batches of the paracetamol formulation, except C_1, released more than 90% of their content in 60 minutes. C_1 only released about 80 % at the same time. The release were fitted into kinetics model and the values are given in Table 9 and the parameters for evaluation of the kinetics presented in Table 10. As for the release kinetics, all the batches with native and pregelatinized breadfruit starch followed Hixson Crowel model except native incorporated intra extragranularly and the pregelatinized starch employed intragranularly which were described by Higuchi and Korsemeyer Peppas model. All batches of the corn starch irrespective of mode of incorporation followed the Higuchi model. This means that drug release from batches of tablet made with the corn starch (irrespective of mode of incorporation) and that with native starch incorporated intra extragranularly is dependent on the square root of time. While the generality of the batches with breadfruit starch both native and modified released their content depending on th cube root of the amount remaining per unit time.

Using the t_{50} and t_{90} values (Table 10) for further assessment, it becomes obvious that both P2 and P3 would take the shortest time of 3 minutes

to release 50% and 90**%** of their content whereas it will take C2 17 minutes and more than 1 hour respectively to release the same amount . At the same rate use of tablets P2 and P3 gives an early onset of action. The values resonates well with the high value of DERc of the tablet batches P2 and P3 as disintegration precedes dissolution. P1 definitely failed the dissolution test since less than 70% was dissolved in 45 minute [21].

The seeming inconsistency of C1 and C2 batches when the disintegration time are compared with their kinetic parameters could be a function of the behavior of the corn starch after the disintegration.

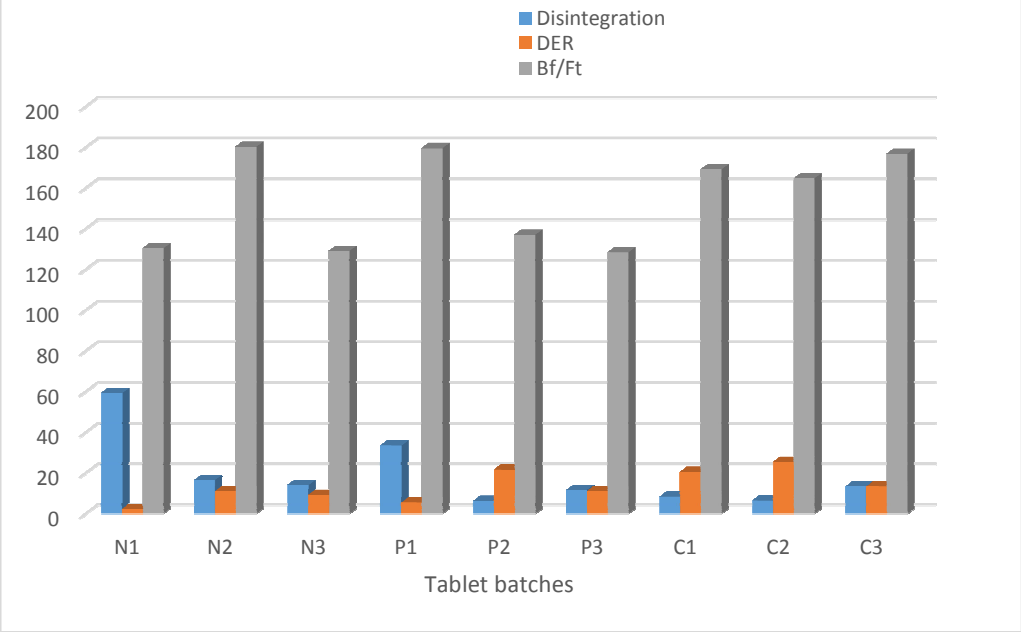

Fig. 8. Disintegration parameters of the tablet batches formed from the starches

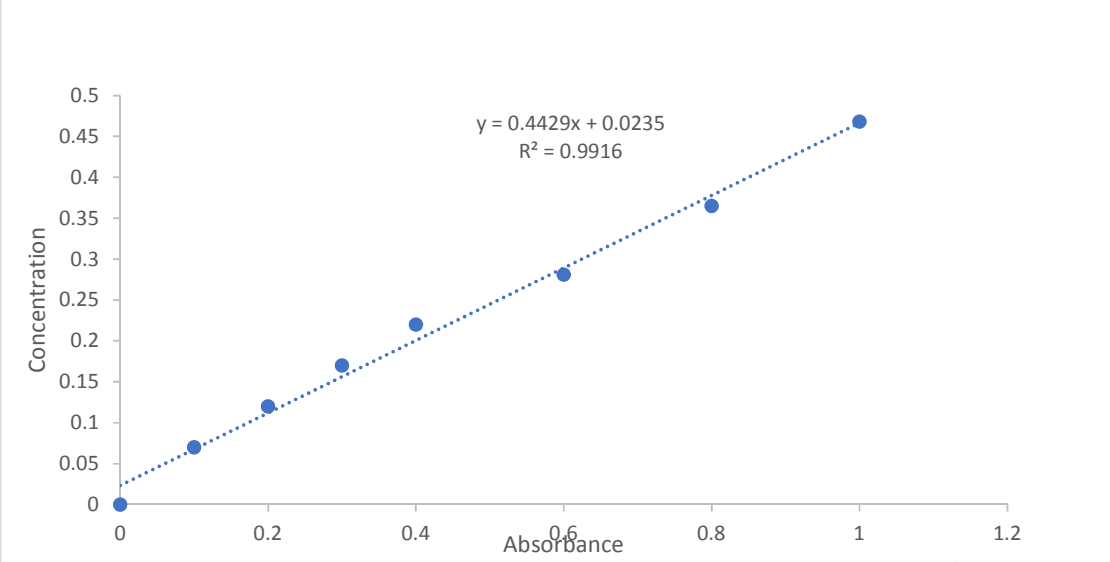

Fig. 9. Calibration curve of Paracetamol

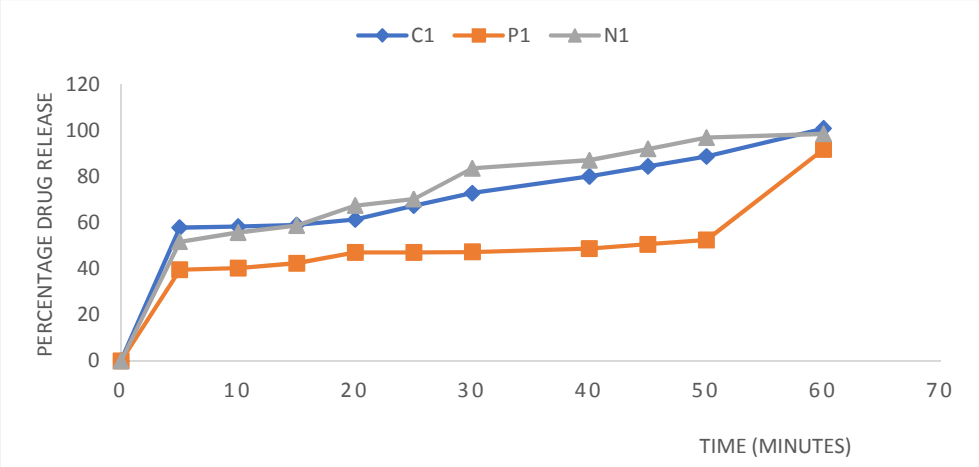

Fig. 10. Release profile of tablets with disintegrants (starches) incorporated intra-granularly

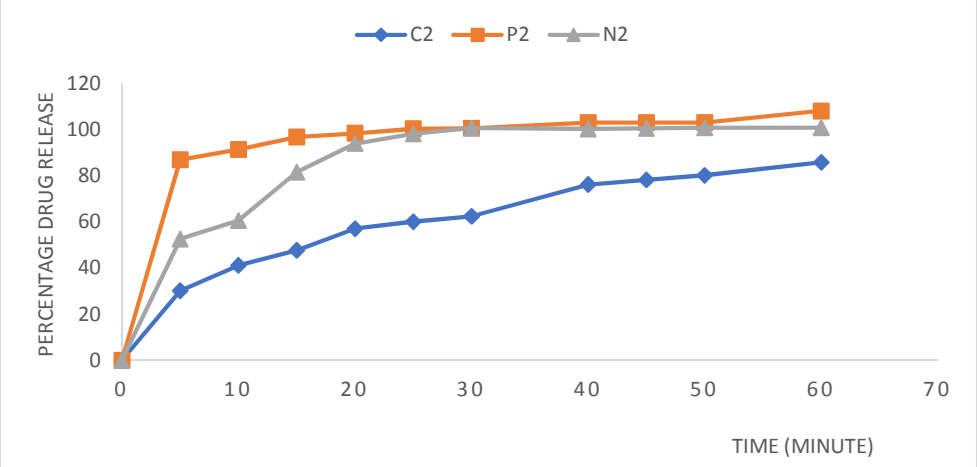

Fig. 11. Release profile of tablets with disintegrants incorporated extra-graularly

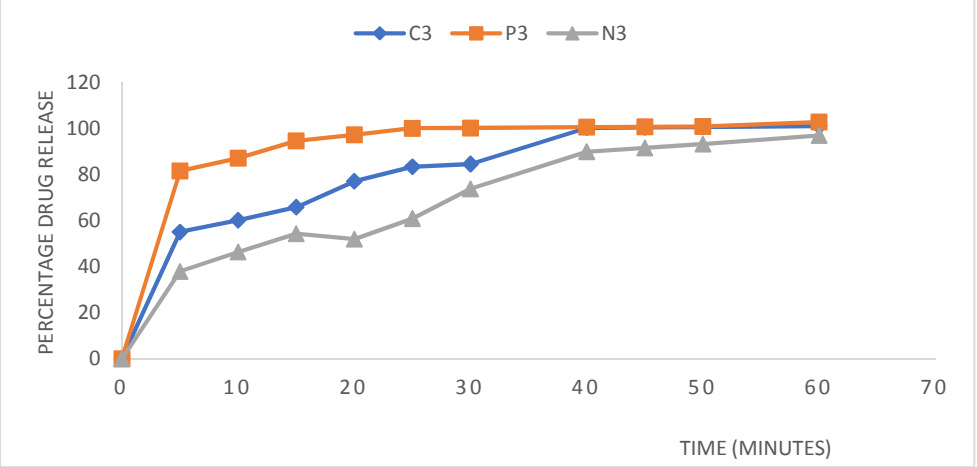

Fig. 12. Release profile of tablets with disintegrant (starches) employed intra-extragranularly

Table 9. Release kinetic models for the batches of paracetamol

Batch	Zero-order	First-order	Higuchi	Hixon crowel	Korsemeyer-peppas model
N_1	0.7828	0.9389	0.9475	0.9599*	0.7733
N_2	0.5928	0.8104	0.842	0.8725*	0.7608
N_3	0.8782	0.9621	0.9732*	0.9703	0.8287
P_1	0.6505	0.5367	0.7298	0.5987	0.7365*
P_2	0.3748	0.6324	0.6437	0.8541*	0.6631
P_3	0.377	0.7179	0.6535	0.856*	0.6693
C_1	0.7428	0.7595	0.898*	0.7099	0.7405
C_2	0.8632	0.9844	0.99*	0.9615	0.8407
C_3	0.7355	0.9058	0.9306*	0.9159	0.767

Key: values with asterisk show the highest values for correlation coefficient of all the 5 release kinetic models each batch of tablet was subjected

Table 90. Parameters for assessing release kinetics of the batches of the tablets

Time/Batch	N_1	N_2	N_3	P_1	P_2	P_3	C_1	C_2	C_3
t_{50} (min)	04	05	13	45	03	03	05	17	05
t_{90} (min)	43	19	40	59	08	13	51	>60	33

4. CONCLUSION

Pre-gelatinization improved the hydration, viscosity and micromeritics of the native starch of the breadfruit and this translated to a better disintegration efficiency in tablets formed by it. Although the disintegration efficiency of the pre-gelatinized starch is comparable to that of corn starch, irrespective of the mode of incorporation, it did significant better in dissolution and release kinetics. As product manufacturers and excipient developers contemplate fast onset of action for their immediate-release oral compacts and needed excipients in this regards, the use of pre-gelatinized breadfruit starch will be a good option to consider.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by any producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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