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Evaluation of the Effects of Co-processed *Manihot Esculenta* Starch on the Tablet Properties of Directly Compressed Diclofenac and Paracetamol Formulations

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ABSTRACT

Advancements in tablet manufacture has increased the demand for versatile excipients with multifunctional applications. Co-processing is fast evolving into the tool for development of these excipients with unique functional properties. The aim of this study is to evaluate the effect of co-processed *Manihot esculenta* starch and povidone on tablet properties of diclofenac and paracetamol formulations. Starch extracted from *Manihot esculenta* tubers was modified either by pre-gelatinization or gelatinization and then co-processed by co-dispersion with povidone to yield EXP-A and EXP-B respectively. The developed excipients were assessed for their flow properties, moisture contents, swelling indices, hydration capacities and particle densities. The co-processed excipients and a physical mixture of the excipients were incorporated into diclofenac and paracetamol tablet formulations by direct compression. The tablets were evaluated for uniformity of weight, hardness, friability, disintegration time and *in vitro* drug release. Possible drug-excipient interaction was also investigated by Fourier Transform Infrared Spectroscopy (FT-IR). Results showed that EXP-B possessed better flow properties, higher swelling index and hydration capacity and lower moisture content than EXP-A. All the tablets had uniform weights, tablet hardness was between 4.5 and 11 kp; tablets containing higher amounts of EXP-A or EXP-B had higher hardness. Friability was between 0.45 and 4.02 with tablets containing EXP-A having lower values than the other batches. Disintegration time was between 1.45 and 12.77 min with tablets containing unmodified starch in both formulations having the least values. Dissolution profile was similar for tablets containing co-processed excipients. Co-processing starch from *Manihot esculenta* tubers with povidone produced robust tablets which may be better suited for modified-release tablet formulations.

Keywords: co-processed excipients, starch, *Manihot esculenta*, povidone, direct compression
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INTRODUCTION

Pharmaceutical excipients play a vital role in the manufacture of drug products however, the development of these excipients is a herculean task because it is an expensive and time-consuming venture. Furthermore, some of the currently available excipients do not meet the formulation demands of drug development any longer nor do they enable optimization of formulation processes. In addition, the many regulatory pathways through which new excipients go through further increases the challenges faced with development of novel excipients [1]. These challenges have led to researches involving modification of already existing excipients as such, starch which is by far the most commonly used excipient in the pharmaceutical industries or employing other formulation techniques.

Co-processing is the combination of two or more established excipients by an appropriate process, which involves interaction at the sub-particle level. The aim of co-processing is to provide synergistic functionality of the combined excipients, minimize the flaws of the individual excipients without altering their chemical nature and to provide a singular multifunctional excipient [2]. These developed co-processed excipients, mostly possess superior flowability, compressibility, filler-binder characteristics compared to the simple physical mixtures of individual components [3,4]. Most pharmaceutical industries utilize co-processing techniques to develop new excipients for drug formulation [5]. Co-processed excipients are popular for direct compression tablet formulations making them of great economic value in tablet production. Typically, the combination of plastic and brittle-deforming materials produces preferable attributes for tablet manufacture [7].

Literature reveals several studies that have been conducted to investigate the co-processing processes or the functionality of the developed co-processed excipients. Co-processing maize starch with sodium carboxymethyl cellulose and microcrystalline cellulose was reported to produce a novel multifunctional excipient with capability to improve drug release from paracetamol tablet formulation [7]. In another study, co-processing of corn starch with gelatin and colloidal silicon dioxide was reported to improve tensile strength and disintegration of ibuprofen tablet formulations better than Prosolv® or StarLac® in the tablet formulations [8]. The study by Halim *et al*., [9] showed that co-processing purple sweet potato starch with Avicel PH 101 produced a material with improved flowability. Olayemi and Anyebe [10] have also reported co-fusion of starch from *Cyperus esculentus* tubers with mannitol caused rapid disintegration of aspirin tablet formulations. In a completely different study [11], co-processing of a poorly soluble drug with gelatin and microcrystalline cellulose showed rapid tablet disintegration and improved tabletability. In a recent study, Yerima *et al*., [12] co-processed cow bone powder with maize starch and khaya

gum producing a directly compressible material with favorable tensile strength and better disintegration profile than StarLac®.

In this study, starch was extracted from the tubers of *Manihot esculenta* (cassava), modified (by pre-gelatinization and by gelatinization) and both modified starches were co-processed with povidone USP K-90 (polyvinylpyrrolidone) by co-dispersion. The aim of this study was to evaluate the effect of the co-processed starches on the physical and mechanical (physico-mechanical) properties of paracetamol and diclofenac tablet formulations.

MATERIALS AND METHODS

Materials

Diclofenac potassium and paracetamol powders (Edo Pharmaceutical Limited, Benin City, Nigeria), Povidone USP K-90; polyvinylpyrrolidone (ISP Technologies Incorporated, NJ, USA), Lactose (Sigma Chemicals, St. Louis, USA). *Manihot esculenta* (cassava) starch was processed from its tubers in the Department of Pharmaceutics and Pharmaceutical Technology Laboratory, University of Benin, Nigeria.

Methods

Collection of *Manihot esculenta* tubers and extraction of starch from the tubers

Fresh tubers of *Manihot esculenta* (cassava) were bought from a village market in Benin City, Nigeria and identified in the Herbarium Unit of the Department of Plant Biology and Biotechnology, Faculty of Life Sciences, University of Benin, Nigeria and assigned a voucher number UBH-P404.

An earlier method [13] was adopted for extraction of starch with some modification. The tubers were washed with water, the skin was peeled off, then chopped into small cubes which were blended with sufficient water in a high-speed blender (Moulinex, France) until a smooth paste was obtained. The paste was suspended in water (1 in 10 volume), stirred to ensure proper mixing for about 5 min and filtered with a muslin cloth. The filtrate was left to stand for about 2 h to allow for sedimentation of the starch. The supernatant was decanted, the sediment was re-suspended in water, stirred and the process of filtration and decantation of the liquid was carried out again as already described. The resulting sediment which is the starch was dried in the hot air-oven (Gallenkamp, United Kingdom) at 55 ^{o}C for 1 h. The dried starch powder coded as MES was packaged in an air-tight container and kept in a desiccator until further use.

Evaluation of starch from *Manihot esculenta* tubers (MES)

Organoleptic properties

The odour, color and texture of MES was assessed using the sensory organs.

Solubility

MES (100 mg) was weighed into in a test tube containing 2 mL of water, the test tube was shaken to disperse the starch at room temperature. The dispersion was filtered using a pre-weighed Whatman filter paper. The filter paper with residue on it was dried in a hot air oven

(Gallenkamp, United Kingdom) at 40 ºC for 1.0 h. The extent of MES solubility was calculated as the difference between the weight of the filter paper with dried residue and the filter paper and reported as a qualitative index.

Test for presence of starch

A 5 mL aliquot of MES suspension (10.0%w/v) was introduced into a test tube, to this, few drops of 0.01M iodine solution were added and the resulting color change was observed and recorded.

Preparation of co-processed excipients of MES and povidone

A batch of the MES was pre-gelatinized by weighing 500 g of MES into a stainless jar and adding sufficient amount of water to make a slurry while stirring intermittently. The jar containing the slurry was heated over a water bath (Sharma Scientific Co., New Delhi, India) with continuous stirring until a temperature of 64 °C was achieved. An amount povidone (10.0 g) was incorporated into the prepared pre-gelatinized starch paste and mixed with the aid of a homogenizer (Silverson Machines Ltd, UK) for about 20 min to ensure complete homogenization. The resultant paste was air-dried at 40 °C for 4.0 h, pulverized, passed through a sieve of 750 µm mesh size, packaged and labelled as EXP-A and stored in a desiccator until further use.

The other batch of MES was gelatinized by mixing 500 g of MES with sufficient amount of water to make a slurry while stirring intermittently. The slurry was heated over a water bath (Sharma Scientific Co., New Delhi, Delhi) with continuous stirring until a temperature of 80 °C was achieved. Afterwards, 10.0 g of povidone was incorporated into the already prepared gelatinized starch, homogenized, dried, sieved, packaged and coded as EXP-B then stored in a desiccator until further use.

Characterization of the co-excipients

Determination of flow properties

Bulk and tapped densities

The bulk volume occupied by 3.0 g of each of the co-processed excipients in a measuring cylinder of 100 mL capacity was noted and bulk density was computed as the ratio of the sample weight to that of the bulk volume (g/mL). The measuring cylinder containing the sample was tapped 100 times, the volume of the sample after tapping was noted as tapped volume and tapped density was computed as the ratio of the sample weight to the tapped volume (g/mL).

Carr's index and Hausner's ratio

These were computed using data obtained from bulk density (Bd) and tapped density (Td) as:

$$CI = \frac{Td-Bd}{Td} x100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Eqn\ 1$$

$$HR = \frac{Td}{Bd} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Eqn\ 2$$

Flow rate

The time taken for 10.0 g of the co-processed excipient to flow under gravity through an orifice was recorded, flow rate (g/sec) was calculated as the ratio of the weight of sample to the flow time.

Angle of repose

Ten (10) grams of each of the co-processed excipients was poured through a funnel whose

orifice had been plugged. The height and diameter of the heap formed after unplugging the orifice of the funnel were determined and used to calculate the angle of repose using the following equation:

$$tan^{-1}\frac{height\ f\ heap}{radius\ of\ heap} \ldots\ldots\ldots\ldots\ldots\ldots Eqn\ 3$$

Determination of moisture content

The co-processed (1 g) was dried in the hot air oven for 4 h at 105 °C. The initial weight of the co-processed excipient (W_1) and weight of the excipient after drying (W_2) were used to calculate percentage moisture content (MC) using the following equation;

$$MC = \frac{W1 - W2}{W1} x100 \ldots\ldots\ldots\ldots\ldots Eqn\ 4$$

Determination of swelling index

The method described [14] was adopted with some modifications. One (1) gram of the co-processed excipient was placed into a measuring cylinder (50 mL), the cylinder was tapped and the volume noted (V_1). The powder was suspended in 96 % ethanol (1.0 mL) and distilled water (25 mL), the mixture was made up to volume with water, the cylinder was closed and mechanically shaken every 10 min for a period of 1.0 h. The suspension was allowed to stand in the cylinder for 3 h then the volume of the sediment was recorded as (V_2). Swelling index (SI) was expressed in percentage using the following equation:

$$SI = \frac{V2 - V1}{V1} x100 \ldots\ldots\ldots\ldots\ldots\ldots Eqn\ 5$$

Hydration capacity

An earlier described method [15] was adopted. Dispersions of the co-processed excipient (10 %w/v) in water was prepared in a pre-weighed centrifuge tube (15 mL), shaken intermittently for 10 min and allowed to stand for another 10 min at room temperature. The dispersion was centrifuged at 1000 rpm for 10 min in the centrifuge (800B, Jiangsu, China) and the weight of the sediment was determined. Hydration capacity (%) was calculated as the ratio between the weight of the sediment after centrifugation and weight of the dried sample used in preparation of the suspension expressed in percentage.

Determination of particle density

The liquid displacement technique was employed for this determination. A pycnometer was filled with liquid paraffin (25 mL), the bottle was wiped to remove residual liquid then weighed (W1). The bottle was emptied, rinsed with acetone and dried. The co-processed excipient; 1.0 g (Wp) was placed into the empty bottle, then filed with liquid paraffin, the bottle was wiped to remove spilled liquid and weighed (W2). Particle density (Pd) was expressed in percentage using the following equation where specific gravity of liquid paraffin is 0.865 g/mL:

$$Pd = \frac{Wp}{[(W1 + Wp) - W2]\ x\ SG} x100 \ldots\ldots\ldots\ldots Eqn\ 6$$

Preparation of diclofenac and paracetamol tablets

The direct compression technique of tablet manufacture was used to prepare 60 tablets of

each of the tablet formulations. Appropriate quantities of diclofenac were mixed with EXP-A or EXP-B and lactose to produce batches A1, A2, A3 and A4 with target weights of 400 mg according to the composition of ingredients in Table 1. Similarly, appropriate amounts of paracetamol were mixed with EXP-A and EXP-B and lactose to produce batches B1, B2, B3 and B4 with target weights of 800 mg as stated in Table 1. Separate batches (A5 and B5) containing physical mixtures of the active ingredients, cassava starch (MES) and povidone were prepared for comparison with the other batches. The powdered blends were compacted into tablets at compression pressure of 45 Newtons in a single punch tableting machine (Manesty Machines, U.K) using the 10 mm punch and die set. The tablets were kept for 24 h before evaluation to allow for elastic recovery.

Table 1: Composition of ingredients for formulation of diclofenac and paracetamol tablets

Ingredients (mg)	**Batches**									
	A1	**A2**	**A3**	**A4**	**A5**	**B1**	**B2**	**B3**	**B4**	**B5**
Diclofenac potassium	100	100	100	100	100	-	-	-	-	-
Paracetamol	-	-	-	-	-	500	500	500	500	500
EXP- A	200	300	-	-	-	200	300	-	-	-
EXP- B	-	-	200	300	-	-	-	200	300	-
Povidone	-	-	-	-	200	-	-	-	-	200
MES	-	-	-	-	100	-	-	-	-	100
Lactose	100	-	100	-	-	100	-	100	-	-
Total	**400**	**400**	**400**	**400**	**400**	**800**	**800**	**800**	**800**	**800**

Key: MES = starch extracted from tubers of Manihot esculenta, EXP-A = co-processed excipient prepared with pre-gelatinized MES and povidone, EXP-B = co-processed excipient prepared with gelatinized MES and povidone

Fourier Transform Infra-Red (FTIR) characterization

Possible interaction between the active ingredients and excipients was determined using the FTIR Spectrophotometer. The co-processed excipients; EXP-A and EXP-B, physical mixture of MES and povidone, tablet formulations of both drugs (A1 and B1) were triturated with potassium bromide powder to produce pellets (1.0 ton/cm^2). Infra-Red (IR) spectra of the samples were obtained between scanning ranges of 4000 and 1000 cm^{-1} from the FTIR-4100 Spectrophotometer (Shimadzu Co. Japan).

Evaluation of diclofenac and paracetamol tablet formulations

Determination of uniformity of tablet weight

Weight variation of the prepared tablets was determined by weighing 10 randomly selected tablets from each batch on the digital analytical balance (MT-200, Metler, Switzerland). Three (3) determinations were carried out, the average weight and standard deviation were computed.

Determination of Tablet hardness

Five (5) randomly selected tablets from each batch were crushed using the Monsanto Hardness tester (Gallenkemp, England), the mean and standard deviation were calculated for each batch.

Determination of Friability

Ten (10) tablets from each batch were randomly selected and collectively weighed (W_1) then they were placed in the drum of the Friabilator (Erweka Apparatebau, Germany) which was operated at 25 rpm for 4 min. Afterwards, the tablets were de-dusted, re-weighed (W_2) and friability (F) was calculated using the following equation;

$$F = \frac{W1 - W2}{W1} x100 \dots\dots\dots\dots\dots\dots\dots Eqn\ 7$$

Determination of disintegration time

Six (6) tablets from each batch were placed in each of the six (6) compartments of the disintegration tester (MK IV, Manesty machines, UK) containing distilled water (600 mL) maintained at 37 ± 0.5 ºC. The disintegration tester was operated and the time taken for all the fragments of the disintegrated tablets to pass through the compartment's mesh was noted and the average was computed as the disintegration time.

Crushing strength-Friability-Disintegration time ratio (CS/FR/DT)

This was computed as the ratio of tablet hardness; crushing strength (CS) to friability (FR) and disintegration time (DT).

Determination of calibration curve for diclofenac and paracetamol

Stock solution of diclofenac was prepared by dissolving diclofenac potassium (100 mg) in 100 mL of 0.1 N HCl. Graded concentrations were obtained by diluting the stock solution with appropriate portions of 0.1 N HCL to obtain concentrations of 0.01, 0.02, 0.04, 0.06, 0.08, 0.10 mg/mL. The wavelength of maximum absorption (λ max) was determined from the UV-Visible Spectrophotometer (T70 PG instrument Ltd) to be 241 nm. The values of absorbance and

corresponding concentrations were used to construct the calibration curve. Similarly, stock solution of paracetamol was prepared and diluted to obtain concentrations of 0.01, 0.02, 0.04, 0.06, 0.08, 0.10 mg/mL and the wavelength (λ max) was determined to be 245 nm. The calibration curve was also constructed.

In vitro dissolution studies

The type II dissolution apparatus and 8-station dissolution tester (ST7, G.B. Caleva Ltd, England) was employed for this study. One (1) tablet was introduced into one of the dissolution vessels containing 0.1 N HCl (900 mL) that was maintained at 37.0 ± 0.5°C. The apparatus was set to operate at 100 rpm for 60 min. Aliquots of 5 mL were withdrawn from the vessel at pre-determined intervals (5, 10, 20, 30, 40, 50, 60 min) and replaced with equal volume of medium. The withdrawn samples were adequately diluted and absorbances were measured from the UV-Visible Spectrophotometer at 241 nm and the concentration of diclofenac released from the tablet formulations was determined from the constructed calibration curve. *In vitro* release of paracetamol from the tablet formulations was determined similarly, with the dissolution apparatus set at same operating conditions. Absorbance of withdrawn samples was determined at 245 nm and the content of paracetamol released was determined from the calibration curve.

Modeling of drug release profile

Kinetics of drug release was determined by fitting the data obtained from *in vitro* dissolution studies into the zero order, first order, Higuchi and Hixson-Crowell kinetic models while the mechanism of release was determined by the Korsmeyer-Peppas model [16]. The model with the highest coefficient correlation was selected to describe the best fit for the kinetics and mechanism of drug release.

Statistical analysis

Descriptive statistics using Microsoft Excel (2007) was applied to all the data obtained from this study. Mean and standard deviations of replicate determinations were computed and reported. Differences between mean was determined using one-way ANOVA while $p < 0.05$ was considered significant.

RESULTS

Physical properties of Manihot esculenta starch (MES)

The extracted *Manihot esculenta* starch (native) was white in color, odourless and smooth in texture. It was partially soluble in water at room temperature and gave a blue-black coloration upon addition of iodine solution.

Flow properties of co-processed excipients

The flow properties of the co-processed excipients (EXP-A and EXP-B) are shown in Table 2. EXP-A was found to have lower bulk density (0.469 g/mL) and higher tapped density (0.612 g/mL) than EXP-B (0.499 g/mL and 0.588 g/mL respectively). Correspondingly, the Hausner's ratio of EXP-B (1.18) was lower than that of EXP-A (1.31) and Carr's index was also lower (15 %) than that of EXP-A (23.43 %).

Angle of repose of EXP-A was found to be lower (15.25 °) than that of EXP-B (24.12 °) while flow rate was 4.56 g/sec and 1.46 g/sec respectively. Moisture content was higher for EXP-A (17.52 %) than EXP-B (7.94 %), swelling index and hydration capacity were found to be lower for EXP-A (0.7 and 3.5 %) than EXP-B (9.1 and 5.98 %). Both co-processed excipients were found to be partially soluble at room temperature. The particle density (2.42 and 2.66 respectively) was similar for both excipients.

Table 2: Physicochemical characterization of co-processed excipients

Parameters	EXP-A	EXP-B
Bulk density(g/mL)	0.469 ± 0.01	0.499 ± 0.02
Tapped density(g/mL)	0.612 ± 0.04	0.588 ± 0.06
Angle of repose (°)	15.25 ± 1.40	24.12 ± 0.92
Hausner's ratio	1.31 ± 0.01	1.18 ± 0.02
Carr's index (%)	23.43 ± 0.02	15.00 ± 0.01
Flow rate (g/sec)	4.56 ± 1.20	1.46 ± 1.12
Solubility (at room temperature)	Partially soluble	Partially soluble
Moisture content (%)	17.52 ± 0.82	7.94 ± 0.42
Swelling capacity/index (%)	0.7 ± 0.01	9.1 ± 0.50
Particle density (g/ml)	2.42 ± 0.06	2.66 ± 0.10
Hydration capacity (g)	3.55 ± 0.11	5.98 ± 0.14

Post-compression parameters

Table 3 shows that the average weights of diclofenac tablet formulations were between 396 and 402 mg while those of the paracetamol tablet formulations were between 798 and 804 mg. Diclofenac tablet formulations (A1-A5) were observed to be generally stronger than paracetamol tablet formulations (B1-B4) with hardness values ranging between 7.9 and 11 kp and 5 and 5.8 kp respectively and these were stronger than those containing physical mixtures of the native starch and povidone in both formulations (A5 and B5) with values of 5 and 4.5 kp respectively. Correspondingly, friability values of diclofenac tablet formulations were lower (0.45 - 1.10 %) than those of paracetamol tablets (1.27 - 4.02 %) while A5 and B5 had 1.33 and 3.20 %, respectively (Table 3). Disintegration time was between 1.70 and 12.77 for diclofenac tablet formulations and between 4.50 and 8.72 min for paracetamol tablets. Tablet formulations containing the native starch; A5 and B5 were found to disintegrate faster (1.55 and 1.45 respectively) than those containing the co-

processed excipients (Table 3). Generally, it was observed that increase in concentration of the co-processed excipients (EXP-A and EXP-B) in both tablet formulations led to increase tablet hardness with a corresponding decrease in friability and disintegration time.

The crushing strength (hardness)/friability/disintegration time ratio (CS/FR/DT) of both drug formulations was between 0.35 and 4.22 (Table 3), with diclofenac tablet formulations having higher values than the paracetamol formulations. In diclofenac tablet formulations, A1 containing EXP-A had the least value (0.80) while A4 had the highest value (4.22). Formulation B3 containing EXP-B in paracetamol tablet formulations had the least value (0.35) while B4 had the highest value (0.70). CS/FR/DT of A4 and A5 containing the physical mixture of native starch and povidone in both drug formulations were 2.45 and 0.79, respectively.

Table 3: Physico-mechanical properties of tablet formulations

Batch	Weight (mg)	Hardness (kp)	Friability (%)	Disintegration time (min)	CS/FR/Dt
A1	401 ± 0.005	9.2 ± 0.05	0.90 ± 0.10	12.77 ± 1.20	0.80
A2	400 ± 0.004	11.0 ± 0.10	0.45 ± 0.02	7.60 ± 0.60	3.22
A3	396 ± 0.002	6.0 ± 0.15	1.02 ± 0.30	4.08 ± 0.42	1.45
A4	402 ± 0.002	7.9 ± 0.02	1.10 ± 0.42	1.70 ± 0.44	4.22
A5	398 ± 0.005	5.0 ± 0.12	1.33 ± 0.23	1.55 ± 0.22	2.43
B1	798 ± 0.001	5.0 ± 0.50	1.40 ± 0.12	8.72 ± 1.00	0.41
B2	803 ± 0.003	7.0 ± 0.25	1.27 ± 0.22	8.20 ± 0.80	0.67
B3	801 ± 0.001	7.6 ± 0.20	3.20 ± 0.40	6.70 ± 0.12	0.35
B4	804 ± 0.002	8.8 ± 0.04	2.80 ± 0.04	4.50 ± 0.30	0.70
B5	800 ± 0.004	4.5 ± 0.13	4.02 ± 0.42	1.45 ± 0.20	0.79

Dissolution profiles

In vitro dissolution profile of diclofenac and paracetamol tablet formulations is displayed in Figures 1 and 2, respectively. Drug release from diclofenac tablet formulations containing the co-processed excipients (EXP-A and EXP-B) was observed to be between 59 and 62 % (Figure 1) at the end of 60 min while it ranged from 66 to 75 % for paracetamol tablet formulations (Figure 2). However, formulations A5 and B5 containing the physical mixture of native starch and povidone in diclofenac and paracetamol tablet formulations respectively showed the highest drug release with 71.4 and 82 % respectively.

Model-fitting for drug release

The release kinetics of the formulated tablets was determined by the zero-order, first-order, Higuchi and Hixson-Crowell models while the mechanism of release was determined by the Korsmeyer-Peppas model. The correlation coefficient (r^2) of the various models and the diffusion coefficient (n) are shown in Table 4. The best linearity fit of dissolution data for tablet formulation A1 was achieved by the Hixson-Crowell model with r^2 of 0.9881 while for A2 and A3, it was the First order model with r^2 of 0.9932 and 0.9394 respectively. Formulation A4 was found to fit the Higuchi model with r^2 of 0.9484. All the formulations of paracetamol tablets were found to best fit the Higuchi model with r^2 values between 0.9527 and 0.9862. on the other hand, formulations A5 and B5 were found to follow the Zero order and First order models respectively. The mechanism of drug release for all the tablet formulations as assessed by the Korsmeyer-Peppas model was found to be the Case II transport (Table 4).

Table 4: Kinetics and mechanism of drug release from formulated tablets

Batch	Model					
	Zero Order	First Order	Hixson-Crowell	Higuchi	Korsmeyer-Peppas	
	r^2	r^2	r^2	r^2	r^2	N
A1	0.9872	0.9799	0.9881	0.9607	0.9212	5.1382
A2	0.9919	0.9932	0.9875	0.9752	0.9269	5.0959
A3	0.8846	0.9394	0.8052	0.9380	0.9522	6.5689
A4	0.8688	0.9226	0.8146	0.9484	0.9683	2.5651
A5	0.9941	0.9849	0.9939	0.9678	0.9224	5.3698
B1	0.9025	0.9312	0.8797	0.9527	0.9659	2.8615
B2	0.9293	0.9625	0.9105	0.9693	0.9672	3.0642
B3	0.9610	0.9791	0.9343	0.9862	0.9866	2.4914
B4	0.9529	0.9701	0.9293	0.9814	0.9866	2.5520

B5	0.8894	0.9628	0.8569	0.9566	0.9671	2.9114

Drug-excipient interaction

The spectra of the physical mixture of the unmodified starch and povidone, EXP-A and EXP-B are displayed as Figures 3A, 3B and 3C respectively. Figures 3A and 3B were found to have some more intensified peaks than Figure 3A. The spectra of pure diclofenac sodium and paracetamol pure powder are displayed as Figure 4A and 4C respectively while the spectra of diclofenac and paracetamol tablet formulations are displayed as Figures 4B and 4D respectively. Variations to the intensity and broadness of the absorption peaks and bands were observed in the different spectra displayed as Figure 4.

DISCUSSION

Flow characteristics is an important factor in the tableting process, it is required that materials flow easily and uniformly into the tablet dies to ensure uniform tablet weights and production of tablets with consistent and reproducible properties. The angle of repose of a powder provides an insight into the magnitude of the cohesiveness of the powder and hence its flowability. Limits set for this measurement indicate that that materials with values < 30 ° possess excellent flow, those with values between 31° and 35 ° indicate good flow while those between 36 ° and 40 ° possess fair flow and values > 40 ° signify poor flow [17,18]. Our results as presented in Table 2 shows that EXP-A and EXP-B possess excellent flow. This can be attributed to the inherent characteristic of the co-processing technique which improves flow of materials [19].

The bulk and the tapped densities of powdered materials depend largely on the particle shape and size distribution, and these reflect the inter particulate interaction between the powders. Data obtained from these determinations were used to compute the Carr's compressibility index (CI) which defines the ability of a material to deform under pressure. Limits set for this measurement indicate that materials with values ≤ 10 % possess excellent flow, those between 11 and 15 % have good flow, values between 16 and 20 % are representative of fair flow and values > 25 % indicate poor flow. Hausner's ratio (HR) on the other hand, is a measurement of the cohesiveness of a powdered material which describes its degree of densification. Materials with values ≤ 1.11 are said to be cohesive, and those with values between 1.12 and 1.20 are less cohesive [20]. The CI and HR values from our results show that both excipients are not cohesive however, EXP-B possess better propensity to be compacted and deformed under pressure than EXP-A. The technique of co-processing has been reported to reduce the cohesivity of powders which translates to greater tendency for improved powder flow [21].

Particle density of EXP-B was slightly higher but not significantly different than that of EXP-A; this implies that both excipients have the

capability of promoting even packing when compacted [13]. Modification of starch by gelatinization leads to disruption of starch granules which creates voids within the particles thereby reducing the friction between them. This allows for better flow and consequently, impacts the packing behavior of the starch granules.

Moisture content plays an important role in stability of tablet formulations. The presence of moisture beyond acceptable limits influences flow of powders negatively, leads to loss of tablet strength and encourages growth of microbial contaminants in tablet formulations [22]. Table 2 shows that EXP-A had higher amount of moisture than EXP-B which was outside the acceptable limit of 15 % specified for materials intended for pharmaceutical uses [23]. High water content in a powder increases the adhesion force between particles which can cause poor flow rate [24]. This implies that co-processed excipient prepared with pre-gelatinized starch (EXP-A) may cause poor flow when incorporated into other ingredients.

Swelling is an important parameter that reveals the ability of starch granules to absorb water and our results show that EXP-B has significantly higher swelling index than EXP-A. This can be attributed to the fact that gelatinization increases the swelling factor and water absorption index of starch [25] while pre-gelatinization (annealing) decreases the swelling factor [26]. Hydration capacity (HC), on the other hand, is a parameter that signifies the total amount of water that is retained by starch gel under heat [27]. As observed with the swelling index, hydration capacity of EXP-B was found to be appreciably higher than that of EXP-A. The process of gelatinization is observed to cause attraction of more water molecules leading to greater swelling [28]. It is therefore assumed that EXP-B may serve as a better tablet disintegrant than EXP-A since they will absorb more water and swell which is one of the mechanisms of action of starch as a disintegrant [29].

The drug-excipient interaction studies determined by FT-IR spectra shows that a strong, broad band broad bands in Figure 3B and 3C spectra at about 3800 cm^{-1} and 3000 cm^{-1} which corresponds to the O-H stretch but was not observed in Figure 3A. This may be ascribed to the presence of intra-and intermolecular hydrogen bonds in the starch granules as a result of modification. A weak absorption band at 2354 cm^{-1} in Figure 3A representing C-H stretch for alkane was observed to be weakly intensified at 2359 cm^{-1} in Figure 3B but greatly intensified at 2369.72 cm^{-1} in Figure 3C. The presence of wavenumber between 856.21 - 587.82 cm^{-1} for the co-processed excipients and the physical mixture of the same was found to be indicative of the vibration of the glycosidic linkage and the fingerprint of the individual excipients. Figure 4A exhibited distinctive peak at 3245 cm^{-1} corresponding to NH stretching of the secondary amine, the peak at 1571 cm^{-1} corresponds to C=O stretching of the carboxyl ion while those observed at 1498.89 and 746 cm^{-1} corresponds to the C = C ring stretching and C-Cl stretching

respectively all characteristic features of diclofenac sodium [30, 31]. Figure 4B shows characteristic vibrational peaks at 3320 and 3316 cm-^{1} indicating O-H and CH_3 stretching respectively. The peak at 1651 cm-^{1} corresponds to C=O stretching while the bend at 1559.37 cm-^{1} corresponds to N-H amide. The lower-intensity peak at 1507 cm-^{1} (Figure 4C) indicates the presence of asymmetrical bending in C-H bond while the peak at 1435.33 cm-^{1} indicates C-C stretching. The absorption peaks at 1373.19 - 1326.73 cm-^{1} and 1239 cm-^{1} are indicative of symmetrical bending in C-H and C-N (aryl) stretching and those at 1113 and 973.13 cm-^{1} corresponds to C-O stretching and C-N (amide) stretching, respectively. Vibrational peaks between 802.06 and 502.04 cm-^{1} (Figure 4C) are indicative of para-di-substituted aromatic ring and out of plane ring deformation of phenyl ring, respectively [32]. FT-IR spectrum of diclofenac tablet formulation (A1) as displayed in Figure 4B shows a sharper peak at the C=O stretching of the carboxyl ion (1576 cm-^{1}). The spectrum of paracetamol tablet formulation; B1 (Figure 4D) shows that N-H amide bending was sharper at a slightly higher wavenumber of 1561.45 cm -^{1} than that of pure paracetamol powder (Figure 4C). Similarly, more intense vibrations were observed at 1652.91 and 1240.30 cm-^{1} compared to Figure 4C. The change in intensity of absorption peaks as shown in this study may be indicative of increase in the amount of the functional group associated with the molecular bond which is suggestive of strong bonds between the drugs and co-processed excipients. Intensity changes in absorption band stretches have also been attributed to the change in the amylose and amylopectin content of starch molecules as a result of modification [33]. Our study shows that all the characteristic peaks observed in the pure drugs were also retained in the tablet formulations (Figures 4A and 4C) and no new peaks or formation of new functional groups were observed. Therefore, it can be said that there is no chemical interaction or complex formation between the drugs and excipients.

Uniformity of tablet weight is an important process evaluation parameter; it establishes that all ingredients in the tablet are evenly distributed thus, preventing issues of inconsistencies in tablet doses and possible problems in bioavailability of the active medicament. Tablet weight is influenced by factors which include flow characteristics of the material. Our results show that the average weight of all the tablet formulations was within the specified limits for weight deviation.

This shows that all the ingredients were adequately distributed in the tablets, it also shows that incorporation of the co-processed excipients can produce tablets with uniform weights.

Tablet hardness is a criterion that indicate the mechanical strength of a tablet in relation to manufacturing, transportation, storage and handling [34]. The limit for hardness of uncoated tablets is set at approximately 4.5 kp although this may vary depending on the excipients incorporated into the formulation. It is however

necessary to formulate tablets with optimum strength because very hard tablets may not disintegrate readily while soft tablets may not withstand the pressure of handling. Table 3 shows that increasing the concentration of EXP-A and EXP-B in both tablet formulations produced a corresponding increase in tablet hardness. This can be attributed to the formation of more particle to particle contact between the excipient and drug leading to the creation of stronger bridges and stronger tablets [35]. Several factors including compression force, use of co-processed excipient, amount of binder and method of granulation have been reported to impact tablet hardness to varying degrees [36]. On the other hand, tablets containing either of the co-processed excipients in both tablet formulations were observed to be stronger than those containing the physical mixture of the native starch and povidone, this could be attributed to increased adhesiveness of the co-processed excipients.

Friability is closely related to tablet hardness; it measures the strength of a tablet in relation to its resistance to fracture and abrasion. The official specification for tablet friability is set at ≤ 1 % and our results show that only formulations A1 and A2 met this specification. This corresponds to the result of hardness presented earlier, these batches with the highest hardness values among all the other tablet formulations were less prone to abrasion and fracture. All other tablet formulations were observed to fall outside the friability limit (≤ 1 %) implying that further research may be needed to optimize the tablet processes and formulation to obtain less friable tablets. However, tablet formulations containing the physical mixture of native starch and povidone were observed to be more friable than the corresponding co-processed mixture; this shows that co-processing improved the compressibility of the materials [37].

Tablet disintegration time is the time required for a tablet to break up into particles in a liquid medium thus releasing the active drug for absorption. Disintegration is a precursor to dissolution which in turn is a precursor to drug bioavailability and therapeutic response. An optimum disintegration time ensures requisite bioavailability, it may be influenced by the presence/absence of disintegrant, type and concentration of disintegrant incorporated in the tablet formulation. However, this dissolution-disintegration theory may not always be attained depending on the type of ingredients in the formulation and the intent of the formulation. Our results show that increasing the concentration of co-processed excipients decreased the disintegration time of tablets in both formulations. However, the effect of increasing the concentration of the co-processed excipient was more pronounced with EXP-B than with EXP-A. In addition, the presence of EXP-B was observed to elicit faster disintegration than EXP-A and this can be attributed to the higher swelling and hydration capacities of EXP-B which led to the generation of higher swelling force and the promotion of active disintegration mechanism in the tablets [38]. Nevertheless, the disintegration

times of tablets containing physical mixture of the native starch and povidone in both drug formulations were observed to be significantly lower than those containing either of the co-processed excipients. Overall, all the tablet formulated disintegrated within the official specification of ≤ 15 min for immediate release tablet formulations [39].

The hardness/friability/disintegration time ratio (CS/FR/DT) has been suggested as a better index in assessing the mechanical strength of tablets and high values of this ratio indicate a better balance between the binding and disintegrating properties of the materials [40, 41]. Table 2 shows that tablets containing higher amount of EXP-B (A4 and B4) had highest values in both drug formulations followed by formulations A3 and B3 respectively. This implies that incorporation of EXP-B produces tablets with better mechanical strength than EXP-A. Tablets containing physical mixtures of the native starch and povidone had the least CS/FR/DT ratio imply low strength and weak balance between their binding and disintegration ability.

In vitro drug release profile from tablet formulations as displayed in Figures 1 and 2 shows that drug release increased with increase in concentration of the co-processed excipients irrespective of the drug formulation. The release profile from tablet formulations as displayed in Figures 1 and 2 shows tablets formulated with the physical mixture of native starch and povidone released the highest amount of drugs (diclofenac or paracetamol) at the end of the dissolution process followed by those formulated with EXP-A and then those formulated with EXP-B. The difference in drug release from these tablet formulations was observed to be significant at $p < 0.05$ in both tablet formulations. The observation is attributed to the fact that gelatinized starches exhibited more closed microstructure when compared to non-gelatinized starches as a result of agglomerated network which occurred during gelatinization [42]. It can be seen that even though tablets containing EXP-B disintegrated faster than EXP-A, the disintegration-dissolution theory is not followed here. This can be explained to be due to possible formation of a gelatinous layer around which contributed to retardation of drug release [43]. Overall, we observed that the co-processed excipients may not be suitable for use as tablet disintegrants but may be employed as binders in modified-release tablet formulations.

The model-fitting for drug release is a factor that enables prediction of release pattern of drugs from dosage forms [44]. The model with the highest correlation coefficient (r^2) was used to describe the predominate dissolution profile fitting and the possible kinetics of drug release. Results from this study shows that the kinetics of release varied depending on the type of excipient and drug used in the formulation.

The best fit for formulation A1 was the Hixson-Crowell model which assumes that the rate of drug release is based on the change in surface area and diameter of the particles in the tablets and suggests that drug release is not by diffusion but

by dissolution of tablet particles [45]. On the other hand, the kinetics of drug release for formulations A2 and A3 favored the First order model indicating that the rate of drug release was directly dependent of the concentration of drug within the tablet. Drug release from formulation A4 was found to favor the Higuchi model implying that drug release was achieved by diffusion from a porous matrix system as a result of the contact of the tablets with the dissolution medium. Meanwhile, formulation A5 was found to favor the Zero order kinetics which indicates continuous drug release which was dependent on time and independent of the dissolved drug concentration in the release medium. A different trend was observed with the release kinetics in paracetamol tablets; formulations B1, B2, B3 and B4 favored the Higuchi model indicating that drug release was by diffusion at a constant rate out of the drug concentration-rich tablet matrix into the surrounding fluid. Formulation B5 on the other hand, favored the first order release model which is different from that of A5. Our results show that drug release from the diclofenac tablet formulations A1, A2 and A3 were by dissolution while A4 and paracetamol tablet formulations containing the co-processed excipients (B1-B4) was basically by diffusion.

Drug transport through a polymeric matrix as assessed by the Korsmeyer-Peppas model describes the mechanism of drug release using the value of release coefficient (n) in various ways [46]. When the value of 'n' is 0.45, it indicates that drug release is controlled by diffusion of the drug from the matrix known as Fickian diffusion. Values of 'n' $\geq$ 0.89 indicate that drug release is swelling-controlled also called Super Case II transport while between 0.45 and 0.89 shows that drug release was achieved by the imposition of diffusion and swelling-controlled mechanisms also known as Anomalous or Non-Fickian diffusion. Our results show that drug transport from all the tablet formulations was controlled by swelling of the tablet matrix, relaxation, erosion of the matrix and subsequent drug release.

CONCLUSION

This study has shown that co-processing *Manihot esculenta* starch and povidone produced diclofenac and paracetamol tablet formulations with unique properties. The tablets were more robust with better mechanical strength than those tablets formulated with the physical mixture of native *Manihot esculenta* starch and povidone. However, formulations containing the physical mixture of native *Manihot esculenta* starch and povidone showed more rapid disintegration than those containing the co-processed excipients. Incorporation of the co-processed excipients in these tablet formulations show some form of modified drug release and may therefore be applicable for preparation of modified drug release tablet formulations.

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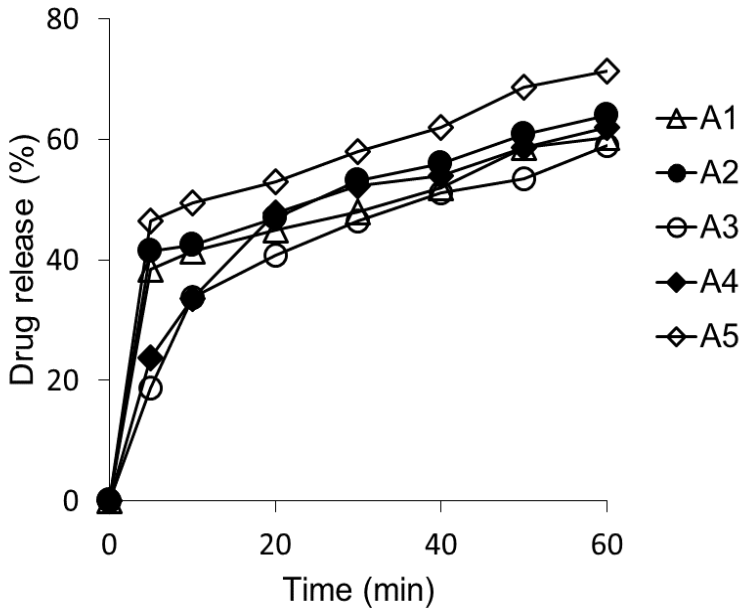

Figure 1: *In vitro* dissolution profile of diclofenac tablet formulations

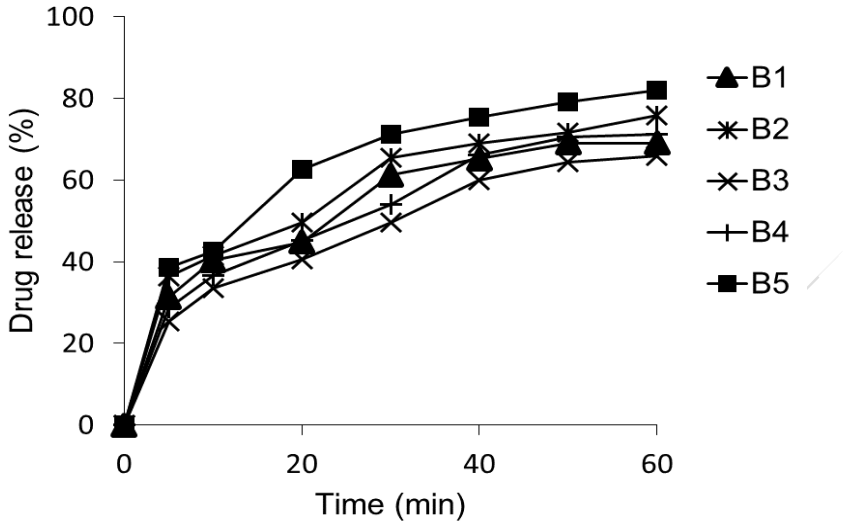

Figure 2: *In vitro* dissolution profile of paracetamol tablet formulations

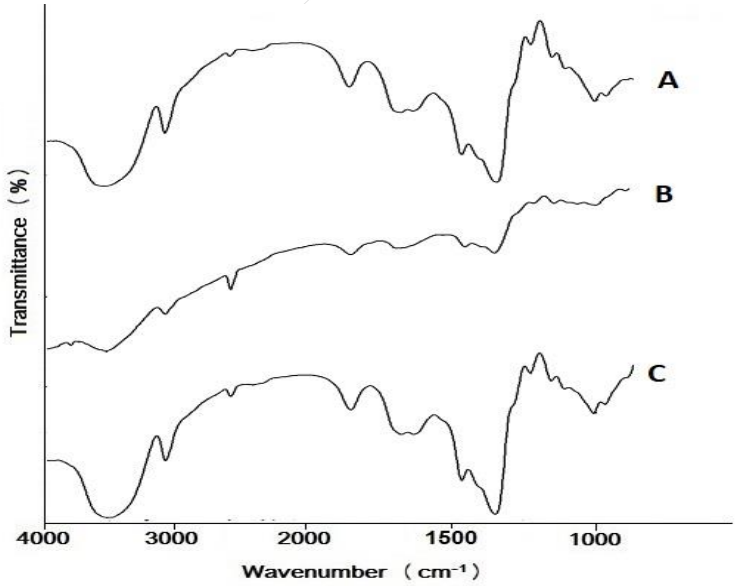

Figure 3: FT-IR spectra of EXP-A (A), EXP-B (B) and physical mixture of the native starch and povidone (C)

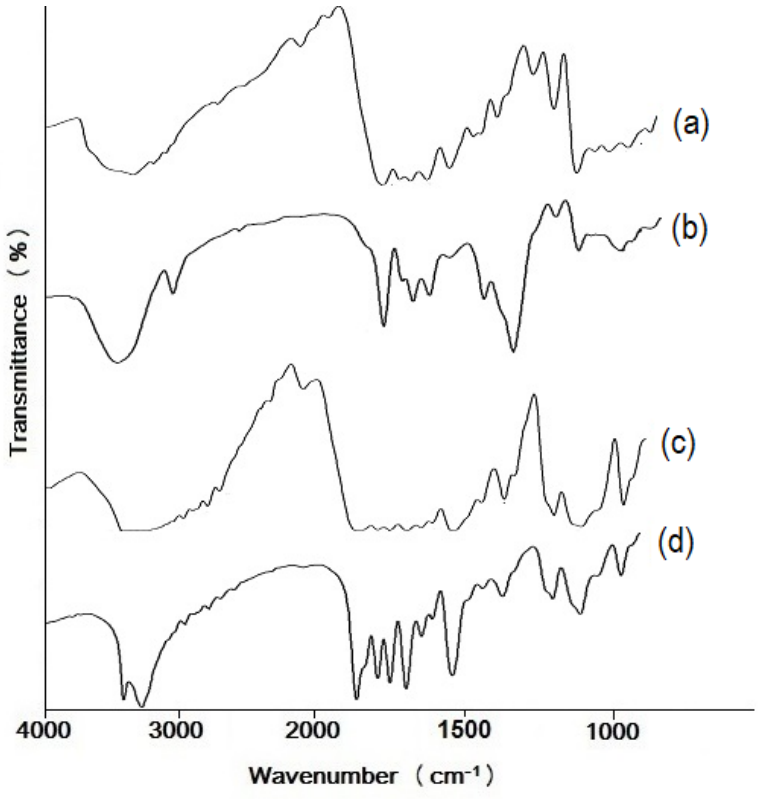

Figure 4: FT-IR spectra of pure diclofenac sodium powder (a), diclofenac tablet (b) pure paracetamol powder (c) and paracetamol tablet (d)

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