# Effects of starch pre-gelatinization on the physicochemical and tableting properties of a co-processed excipient for direct compression

Sylvester O. Eraga[1], Olubunmi J. Olayemi[2], Onyinyechi P. Obidiro[3], Onyinye L. Osemeke[1], Magnus A. Iwuagwu[1]

[1]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Benin City, Nigeria
[2]Department of Pharmaceutical Technology and Raw Materials Development, National Institute for Pharmaceutical Research and Development, Abuja, Nigeria.
[3]Department of Pharmaceutical Sciences, College of Pharmacy, Howard University, Washington, DC 20059, USA

Corresponding author: Sylvester O. Eraga
Email: eragaso@uniben.edu
Telephone: +2348030884928

**ABSTRACT**

**Background:** Development of new molecules as excipients is costly and time consuming, hence a shift towards modifying already existing excipient via co-processing.

**Objective:** The study aimed to evaluate the effects of starch pre-gelatinization on co-processed *Ipomoea batatas* starch in directly compressed diclofenac and paracetamol tablet formulations.

**Methods:** Starch from *Ipomoea batatas* was extracted following standard procedure. Co-processing was carried out by co-dispersion of native starch (Excipient X) or pre-gelatinized starch (Excipient Y) with lactose and polyvinylpyrrolidone. The resulting excipients were subjected to physicochemical evaluation and interaction studies using Fourier transform infrared (FTIR). Tablet formulations of diclofenac and paracetamol were prepared by direct compression and evaluated for mechanical and in vitro dissolution properties.

**Results:** Excipients X and Y exhibited excellent flow properties. Swelling and hydration capacities (9.10 mL and 5.98 g/g, respectively) were significantly higher in Excipient Y than in Excipient X (9.10 mL and 5.98 g/g, respectively) but the moisture content of Excipient X was more than two times (17.52%) that of Excipient Y (7.94%). FTIR revealed no interaction between the co-processed excipients and the drugs. Excipient Y impacted better mechanical properties on the tablets and superior disintegration properties in both tablet formulations. In vitro drug release was faster from tablets produced with Excipient Y than those produced with Excipient X.

**Conclusion:** Co-processed pre-gelatinized *Ipomoea batatas* starch elicited superior mechanical, disintegration and drug release properties over its native counterpart in directly compressed diclofenac and paracetamol tablets.

**Keywords:** Co-processing, direct compression, excipients, *Ipomoea batatas*, starch, tablets

# Effets de la prégélatinisation de l'amidon sur les propriétés physico-chimiques et de compression/ compaction d'un excipient co-traité pour compression directe

Sylvester O. Eraga[1], Olubunmi J. Olayemi[2], Onyinyechi P. Obidiro[3], Onyinye L. Osemeke[1] et Magnus A. Iwuagwu[1]

[1]Département de pharmacie et de technologie pharmaceutique, Faculté de pharmacie, Université du Bénin, Benin City, Nigéria
[2]Département de technologie pharmaceutique et de développement des matières premières, Institut national de recherche et de développement pharmaceutiques, Abuja, Nigéria.
[3]Département des sciences pharmaceutiques, Faculté de pharmacie, Université Howard, Washington, DC 20059, États-Unis

Auteur correspondant: Sylvester O. Eraga
Courriel: eragaso@uniben.edu
Téléphone: +2348030884928

**RÉSUMÉ**

**Contexte:** Le développement de nouvelles molécules comme excipients est coûteux et prend du temps, d'où le passage à la modification d'excipients déjà existants par le biais du co-traitement.

**Objectif:** L'étude visait à évaluer les effets de la pré-gélatinisation de l'amidon sur l'amidon d'Ipomoea batatas co-traité dans des formulations de comprimés de diclofénac et de paracétamol directement comprimés.

**Méthodes:** L'amidon d' Ipomoea batatas a été extrait selon la procédure standard. Le co-traitement a été effectué par co-dispersion d'amidon natif (excipient X) ou d'amidon prégélatinisé (excipient Y) avec du lactose et de la polyvinylpyrrolidone. Les excipients obtenus ont été soumis à une évaluation physicochimique et à des études d'interaction par infrarouge à transformée de Fourier (FTIR). Des formulations de comprimés de diclofénac et de paracétamol ont été préparées par compression directe et évaluées pour leurs propriétés mécaniques et de dissolution in vitro.

**Résultats:** Les excipients X et Y ont présenté d'excellentes propriétés d'écoulement. Les capacités de gonflement et d'hydratation (respectivement 9,10 mL et 5,98 g/g) étaient significativement plus élevées dans l'excipient Y que dans l'excipient X (respectivement 9,10 mL et 5,98 g/g) mais la teneur en humidité de l'excipient X était plus de deux fois supérieure (17,52 %) à celle de l'excipient Y (7,94 %). La FTIR n'a révélé aucune interaction entre les excipients co-traités et les médicaments. L'excipient Y a eu de meilleures propriétés mécaniques sur les comprimés et des propriétés de désintégration supérieures dans les deux formulations de comprimés. La libération in vitro du médicament était plus rapide à partir des comprimés produits avec l'excipient Y que ceux produits avec l'excipient X.

**Conclusion:** L'amidon d'Ipomoea batatas pré-gélatinisé co-traité a présenté des propriétés mécaniques, de désintégration et de libération de médicament supérieures à celles de son homologue natif dans les comprimés de diclofénac et de paracétamol directement comprimés.

**Mots clés:** Co-traitement, compression directe, excipients, Ipomoea batatas , amidon, comprimés

## INTRODUCTION

The discovery or development of newer drug excipient products is a time consuming and costly process.[1] There is a shift of attention towards modifying already existing excipients to achieve new molecules with improved properties. In line with this new focus, novel drug delivery systems using co-processed materials, non-traditional polymers and materials of natural origin as excipients are also gaining more attention among drug formulator and researchers.[2-5]

Starch is a natural, renewable and biodegradable polymer with structural and functional characteristics that makes it suitable for a variety of applications.[6] I*pomoea batatas*, one of the varied sources of starch is a plant native to tropical regions of the Americas but has spread into Africa, Asia, Europe and East Indies.[7] It's a source of raw materials such as starch, liquid glucose, monosodium glutamate, ethanol and citric acid.[8]

Various modifications (physical, chemical, and enzymatic) of starch have been reported to alter and improve its functional properties, facilitating its use as pharmaceutical excipients.[9] Excipients were formerly known as inactive ingredients, however, studies have shown that they are pivotal to the release of the active pharmaceutical ingredients and are indispensable in dosage form performance.[2,4,10] Excipients used for tablet formulations should remain physically and chemically stable throughout the shelf life of the drug product. They must be readily and commercially available and must be manufactured according to pharmaceutical standards. Two or more established excipients could be combined by an appropriate process to yield a co-processed excipient.[3,4]

Co-processing is the interaction of two or more excipients at the sub-particle level to provide synergy in functionality and reduce drawbacks of individual excipients.[11] This process was initially used by food industries to improve stability, solubility, and wettability, and also to enhance the gelling properties of food ingredients. More recently, co-processing is one of the ways pharmaceutical industries develop new excipients.[12] Conventional grades of excipients cannot handle the technologically advanced high-speed rotary tablet presses requiring powders with excellent flow, good compressibility, compatibility, particle size distribution and homogeneity, hence the need for co-processed excipients.[13] The primary materials that are selected to be co-processed complement the functionality of one another by providing the desirable property where either of them is deficient. This study investigated the effect of co-processing *Ipomoea batatas* starch and polyvinylpyrrolidone as an excipient for direct compression, on the tablet properties of diclofenac potassium and paracetamol formulations.

## MATERIALS AND METHODS

### Materials

Diclofenac potassium and paracetamol powders were gift samples from Edo Pharmaceuticals, Benin City, Edo State, Nigeria. Lactose powder (Sigma Chemicals, St. Louis, USA), povidone USP K-90 (polyvinylpyrrolidone), sodium hypochlorite (Reckitt and Coleman Nig. Ltd). Double-distilled water was prepared in the laboratory of the Department of Pharmaceutics and Pharmaceutical Technology, University of Benin. Freshly harvested *Ipomoea batatas* tubers were purchased locally and processed into starch powders in the Department of Pharmaceutics and Pharmaceutical Technology, University of Benin.

### Starch extraction

Starch from the tubers of *Ipomoea batatas* was extracted using an earlier published method.[14] About 5.0 kg of tubers were washed thoroughly and peeled. The peeled tubers were sliced into pieces and washed again before been wet milled with an electric blender (Moulinex, France). The resulting slurry was dispersed in 1.0 L of distilled water containing 30 ml of 3.5 %w/v sodium hypochlorite and left to stand overnight. The dispersion was filtered using a muslin cloth and the filtrate allowed to stand for 6 h. The supernatant was carefully decanted, the starch sediment was re-suspended in excess water and allowed to stand for 4 h before decanting. This procedure was repeated several times with the supernatant tested with a litmus paper until the supernatant gave a neutral pH. The wet starch sediment was air-dried for 72 h and further dried in a hot air oven (Gallenkamp, United Kingdom) at 60$^{o}$C for 1 h. The dried starch was pulverized into powder, passed through a sieve of 250 µm mesh sieve and stored in an airtight container.

### Preliminary evaluation of extracted starch

### Organoleptic properties

The taste, odour and colour of the starch were assessed by three individuals using the sensory organs and their unanimous perceptions recorded.

**Solubility**

About 100 mg of the extracted native starch was placed in 10.0 mL of water in a test tube at room temperature and shaken. The dispersion was left standing for 30 min and then filtered. The filter paper with the residue was air-dried to a constant weight. The difference in weight between the filter paper alone and with the residue was used as a measure of the extent of solubility of the starch powder.

**Chemical test**

A 5.0 mL aliquot from a 10.0 %w/v starch suspension was introduced into a test tube and a few drops of 0.01 M iodine solution were added. The resulting colour change was recorded.

**Preparation of excipients**

Exactly 400 g quantity of the extracted native starch powder and 100 g of lactose was transferred into a 1.0 L stainless steel jar. Exactly 500 mL quantity of distilled water was added and stirred thoroughly with a steel rod. Eight grams (8.0 g) of polyvinylpyrrolidone, equivalent to 2.0 %w/w of the native starch was added to the freshly prepared starch-lactose dispersion and mixed. The mixture was transferred to a shear mixer and homogenized for 30.0 min at 1500 rpm (Silverson, UK). The resultant paste of uniform consistency was air-dried, pulverized and sieved with a 250 µm size mesh. The prepared excipient powder was labelled "Excipient X" and then sealed in an airtight bottle.

Similarly, using the same procedures and quantities of starch, lactose and polyvinylpyrrolidone, "Excipient Y" was prepared with the only difference of heating the starch-lactose dispersion up to the starch pre-gelatinization temperature of 65$^{o}$C before mixing with polyvinylpyrrolidone and homogenizing.

**Characterization of excipients**

The powdered excipients prepared were subjected to the following evaluation;

***Bulk and tapped densities***

Excipient powder weighing about 6.0 g was poured into a 100 mL glass measuring cylinder and the volume occupied was recorded. The bulk density was calculated by dividing the weight of the powder with the recorded volume. The same measuring cylinder containing the powder was tapped gently 100 times on a flat wooden surface and the new volume occupied was recorded. The tapped density was then calculated by dividing the mass of the powder with the volume obtained after tapping.

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

The Carr's index of the excipient powder was calculated by dividing the difference between the tapped and bulk densities with the tapped density value and the ratio gotten expressed as a percentage. The Hausner's ratio value was calculated by simply dividing the tapped density with the bulk density.

**Flow rate and angle of repose**

About 10.0 g of the excipient powder was allowed to flow under gravity through a funnel with an orifice diameter of 0.85 cm and clamped about 5.0 cm from a flat horizontal platform. The time taken for the whole powder mass to flow through the orifice was recorded. The ratio of the powder weight to the time of flow was calculated as the flow rate while the height and base diameter of the heap of powder made on the flat horizontal platform were measured and used in calculating the angle of repose with Equation 1.

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

Where h is the height of the heap of granules and r is the radius of the circular base

**Particle density**

Liquid paraffin was carefully poured into a glass pycnometer (specific gravity bottle) of 25 mL capacity until full and then weighed (a). It was emptied and rinsed of any residual paraffin with acetone before been dried. A 1.0 g quantity of the excipient powder (b) was introduced into the bottle, filled with liquid paraffin and weighed (c). The different weights recorded were used to calculate the particle (true) density of the excipient using Equation 2.

$$\rho = b / [(a+b) - c] S \quad .... \quad (2)$$

Where ρ = particle density of the excipient, a = weight of the bottle + liquid paraffin, b = weight of the excipient, c = weight of the bottle + liquid paraffin + excipient and S = specific gravity of liquid paraffin

**Moisture content**

Using a moisture content analysis balance (Ohaus Corp., USA), a crucible containing about 1.0 g of the excipient was placed on the balance and weighed before being transferred to a hot air oven operated at 105$^{o}$C, until a constant weight was obtained. The difference between the starting and final weights of the crucible content was calculated as the moisture content.

**Swelling index/capacity**

A 1.0 g quantity of the excipient powder with a tapped 100 times in a 50 mL measuring cylinder and the tapped volume obtained was recorded. A dispersion of the powder was formed in the cylinder with a mixture of 1.0 ml of 96 % ethanol and 25 mL distilled water. The dispersion was made up to volume with more distilled water, the tube was closed firmly and shaken vigorously at 10 min intervals for 1.0 h. The dispersion was allowed to stand for 3.0 h and the volume of the sediment recorded. The swelling capacity was calculated as the difference between the sediment and tapped volumes of the excipient powder.

***Hydration capacity***

About 1.0 g of the excipient powder was introduced into each of four 15 mL centrifuge tubes and 10 mL of water was also added to each tube to form a dispersion. The tubes were covered and shaken for about 2.0 min, allowed to settle for 10 min and centrifuged at 1000 rpm for 10 min with a bench centrifuge. The resulting supernatant was decanted and the sediment weighed. The hydration capacity was calculated from the ratio of the sediment and dry excipient weights.

**Fourier transform infrared (FTIR) characterization**

FTIR characterization was carried out on the co-processed excipients and a physical mixture of the ingredients used in the co-processing (FTIR-4100 Spectrophotometer, Shimadzu Co. Japan). Five milligrams of the sample were blended with potassium bromide to give a 200 mg weight powder. The blended powder was compressed using a press into a tablet, and then placed in the sample compartment of the spectrophotometer and scanned at a range of 4000 - 1000 cm-1.

**Tablet formulation by double compression**

Eight (8) batches of powder blends consisting of four batches each for diclofenac potassium (A-D) and paracetamol (E-H) were prepared using the formula in Table 1. The calculated ingredients to prepare 80 tablets per batch were dry mixed in a mixer for 5 min in ascending order of weights and compressed directly into slugs with a heavy-duty tableting machine (Koln, Germany). The slugs were broken down into granules with a mortar and pestle, screened through a 1.0 mm mesh size sieve and then compressed directly into tablets with a single punch tableting machine (F-3 Manesty Machines, UK) at compression pressure of 35 kilonewtons. Die volume was adjusted based on the batches for uniformity of weights amongst the batches of tablets of diclofenac and those of paracetamol. The formulated tablets were kept in a desiccator with silica until use.

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

| Ingredients (mg) | Batches | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **A** | **B** | **C** | **D** | **E** | **F** | **G** | **H** |
| Diclofenac potassium | 100 | 100 | 100 | 100 | - | - | - | - |
| Paracetamol | - | - | - | - | 500 | 500 | 500 | 500 |
| Excipient X | 200 | 300 | - | - | 200 | 300 | - | - |
| Excipient Y | - | - | 200 | 300 | - | - | 200 | 300 |
| Lactose | 100 | - | 100 | - | 100 | - | 100 | - |
| **Total** | **400** | **400** | **400** | **400** | **800** | **800** | **800** | **800** |

**Drug-excipient interaction studies**

Drug-excipients interaction studies were carried out on the granules prepared from the slugs in order to determine any interactions between diclofenac or paracetamol with the test excipients using FTIR analysis. A 5.0 mg quantity of granules containing diclofenac and Excipient X and paracetamol with Excipient Y were used for the analysis.

**Tablet evaluations**

***Tablet weight***

The weight of individual twenty (20) tablet from each batch was measured with an electronic weighing balance (MT-200, Metler, Switzerland). The average weight and its standard deviation were calculated and recorded.

***Hardness test***

Ten tablets from each batch were subjected to diametric compression with an electronic tablet hardness tester (Campbell Electronics, Model HT-30/50, India). The average force causing the tablet to crack or break and its standard deviation were calculated and recorded as the hardness of the tablet.

***Friability***

Ten tablets from each batch were weighed and then placed in the drum of a friabilator (Erweka Apparatebau, Germany). The apparatus was operated at 25 revolutions per minute (rpm) for 4 min. Afterwards, the tablets were brought out, dusted and reweighed. The percentage difference in weights of the tablets at the beginning and end of experiment was calculated and recorded.

***Disintegration time***

The disintegration times of six (6) tablets from each batch were determined in distilled water at 37 ± 0.5$^{o}$C using a BP disintegration test unit (MK IV, Manesty Machines, UK). The tablets were introduced into each of the six tubes suspended in a 1000 mL beaker containing distilled water and the tubes oscillated until all the fragments of the tablets passed through the mesh at the bottom of the tube. The times were recorded and the mean and standard deviation calculated.

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

The ratio was computed from the values of the tablet crushing strength (CS), friability (FR) and disintegration time (DT).

***Dissolution profiles***

Dissolution test for the tablets was carried out using the paddle method in a six station BP Dissolution Apparatus (ST7, G.B. Caleva Ltd, England). A 900 mL volume of 0.1 N HCl was introduced into the beakers of the dissolution apparatus and the temperature of the dissolution medium raised and maintained at 37.0 ± 0.5$^{o}$C. One tablet was placed in each of the six (6) beaker and the apparatus was operated at 100 rpm. A 5.0 mL volume of dissolution fluid was withdrawn at pre-determined intervals and replaced with same volume (5.0 mL) of fresh 0.1 N HCl solution each time. Each sample was diluted with fresh 0.1 N HCl solution and the absorbance of the resulting solution read at 241.0 nm for the diclofenac and at 245.0 nm for paracetamol using a UV-Spectrophotometer (T70 PG instrument Ltd). The concentration and percentage of drug released at the various time intervals were calculated with the equations generated from the calibration plots of pure diclofenac and paracetamol drug powders.

**Statistical analysis**

Descriptive statistics using Microsoft Excel (2007) was done for all data. 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**

**Starch powder properties**

The organoleptic evaluations of the extracted Ipomoea batatas native starch revealed a white, odourless, tasteless and smooth-in-texture powder which was partially soluble (0.25%) in water at ambient room temperature. The chemical reaction between the aqueous dispersion of the starch and iodine solution gave a blue black colouration, confirming the presence of the polysaccharide.

**Physicochemical characteristics of excipients**

Results from the characterizations of the prepared excipients are outlined in Table 2. The bulk powder properties of the prepared excipients exhibited a larger difference between the tapped and bulk densities of Excipient Y in comparison with Excipient X. These differences are reflected in their Carr's indices and Hausner's ratios which were lower for Excipient X. The flow rate and moisture content of Excipient X were two times higher than those of Excipient Y while the angle of repose, swelling index and hydration capacity of Excipient Y were higher in comparison to Excipient X.

**FTIR characteristics of excipients**

The FTIR spectra of the prepared Excipients X and Y as well as the physical mixture (Z) of the ingredients (native starch and povidone) used in their preparation are shown in Figure 1. Basic functional groups like alcohol, alkane and alkene were observed in the three spectra although some variations in intensity and broadness of the bands were observed in spectrum of Excipient Y.

**Table 2:** Powder properties of the prepared co-processed excipients

| Parameters | Co-processed excipient | |
|---|---|---|
| | X | Y |
| Bulk density (g/cm$^3$) | 0.6048 ± 0.0132 | 0.6314 ± 0.0132 |
| Tapped density(g/cm$^3$) | 0.6720 ± 0.0211 | 0.7976 ± 0.0132 |
| Carr's index (%) | 10.00 ± 0.32 | 20.00 ± 0.12 |
| Hausner's ratio | 1.11 ± 0.01 | 1.26 ± 0.03 |
| Flow rate (g/sec) | 4.75 ± 0.05 | 1.99 ± 0.14 |
| Angle of repose (°) | 17.60 ± 0.44 | 20.40 ± 1.06 |
| Particle density (g/cm$^3$) | 2.42 ± 0.11 | 2.66 ± 0.08 |
| Moisture content (%) | 17.52 ± 0.25 | 7.94 ± 0.43 |
| Swelling index (ml) | 0.70 ± 0.18 | 9.10 ± 0.02 |
| Hydration capacity (g/g) | 3.55 ± 0.42 | 5.98 ± 0.13 |

The FTIR spectrum of Excipient X (native starch) shows broad absorption bands around 3982 and 3380 cm-1 which indicates the presence of hydrogen-bonded hydroxyls on the starch molecules. These broad bands of -OH group was observed to be broader in spectrum of Excipient Y at 3381 cm-1 which could be indication of more intense vibration associated with ring hydrogen atoms.

Vibrations around absorption peaks of 2353 cm-1, which represent C-H stretch for the alkane group of compounds, were found to be similar for all the spectra. Small intensity peaks at about 1424 cm-1 assigned to C-H stretch was observed to be similar in spectrum of Excipient Z but was slightly broadened in spectrum of Excipient Y. Vibration bands about 852 - 533 cm-1 due to the skeletal stretching of starch were observed in similar wavenumbers in spectra of Excipient Y and Z.

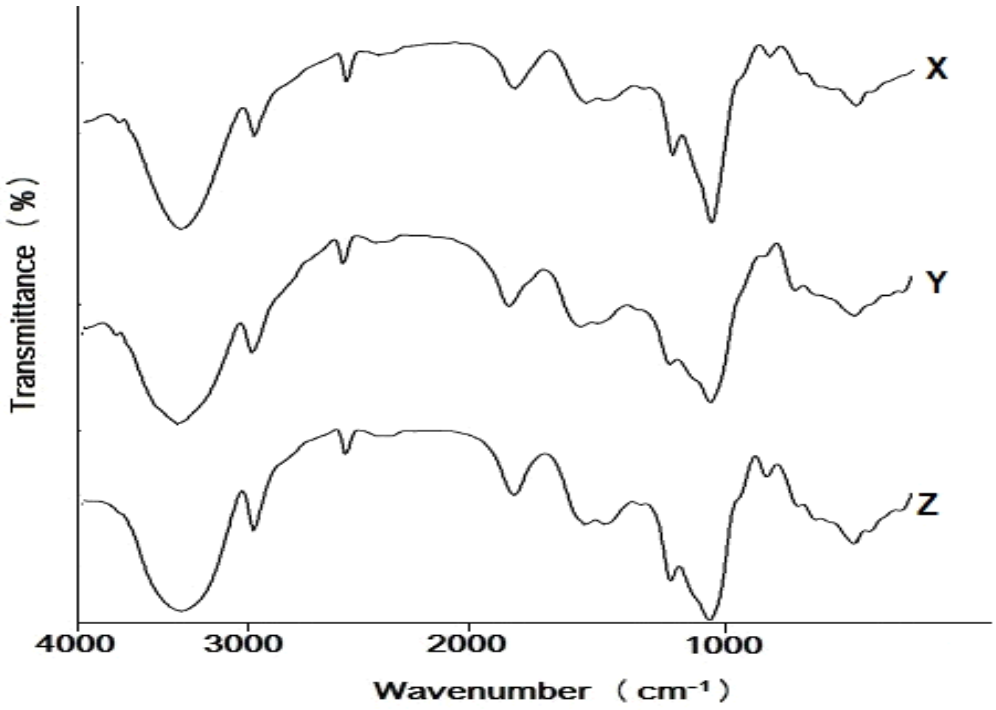


**Figure 1:** FT-IR spectra of Excipient X, Y and physical mixture of the native starch and povidone (Z)

Post-compression parameters

Results from the tablet evaluations are shown in Table 3. The tablet weight values showed that the mean weights of the various batches were within acceptable limits while their hardness tests revealed crushing strength values ranging from 4.0 - 8.6 kp, with diclofenac tablets formulated with co-processed Excipient Y (Batches C and D) having higher values. Generally, an increase in the amounts of the co-processed excipients in all the batches of tablets resulted in increased tablet hardness. Similarly, only tablet batches prepared with co-processed Excipient Y had friability values less than 1.0 % and the diclofenac batches of tablets also had the lowest values. However, increase in the amounts of the co-processed excipients in the tablets also resulted in increased friability. Both diclofenac and paracetamol batches of tablets prepared with Excipient Y (Batches C, D, G and H) exhibited shorter disintegration times of 1.0 - 3.50 min as against the 6.0 - 11.60 min of tablet batches prepared with Excipient X (Batches A, B, E and F).

The crushing strength/friability/disintegration time ratio (CS/FR/DT) of the various batches of tablets was between 0.14 and 12.29, with tablets formulated with co-processed Excipient Y having higher values amongst the diclofenac (Batches C and D) and paracetamol (Batches G and H) tablet formulations. Comparatively, the diclofenac tablet batches showed higher CS/FR/DT values over their paracetamol counterpart batches, with respect to the type and quantity of excipient used in their formulation.

**Table 3:** Properties of the formulated diclofenac and paracetamol tablets

| Batch | Weight (mg) | Hardness (kp) | Friability (%) | Disintegration time (min) | CS/FR/DT |
|---|---|---|---|---|---|
| A | 401 ± 0.05 | 4.5 ± 0.85 | 1.23 ± 0.85 | 10.30 ± 0.85 | 0.36 |
| B | 400 ± 0.11 | 5.0 ± 0.85 | 1.85 ± 0.85 | 11.60 ± 0.85 | 0.23 |
| C | 398 ± 1.45 | 7.0 ± 0.85 | 0.45 ± 0.85 | 1.40 ± 0.85 | 11.11 |
| D | 400 ± 0.15 | 8.6 ± 0.85 | 0.70 ± 0.85 | 1.00 ± 0.85 | 12.29 |
| E | 804 ± 0.12 | 4.0 ± 0.85 | 2.37 ± 0.85 | 6.00 ± 0.85 | 0.28 |
| F | 800 ± 1.22 | 4.2 ± 0.85 | 3.47 ± 0.85 | 8.40 ± 0.85 | 0.14 |
| G | 802 ± 0.45 | 6.0 ± 0.85 | 0.80 ± 0.85 | 3.50 ± 0.85 | 2.14 |
| H | 801 ± 0.85 | 7.9 ± 0.85 | 0.95 ± 0.85 | 2.00 ± 0.85 | 4.18 |

The dissolution profiles of the various batches of tablets as shown in Figure 1 revealed variable drug release over 60 min of testing. Data showed that the batches of tablets prepared with Excipient X achieved a maximum drug release in the range of 72.9 - 84.6% as against the 90.8 - 100% of tablets formulated with Excipient Y. Also, only the Excipient Y batches of tablets released up to 70% of their drug content within 40 min except the batch A tablets.

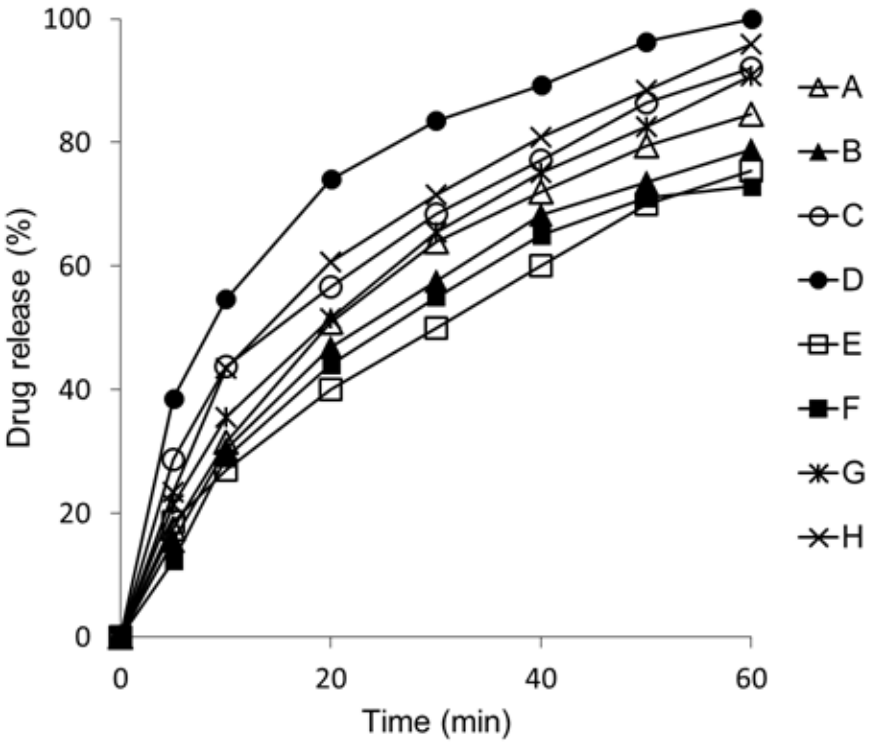


**Figure 2:** *In vitro* dissolution profiles of the diclofenac and paracetamol tablet formulations

**Drug-excipient interaction**

The spectra of pure diclofenac sodium powder and diclofenac granules prepared with Excipients X and Y are displayed as Figure 3(a), (b) and (c), respectively. The FT-IR spectrum of pure diclofenac sodium (Figure 3(a) 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.

Figure 3(d), (e) and (f) show the spectra of pure paracetamol powder and granule formulations of paracetamol with Excipients X and Y, respectively. FT-IR spectrum of paracetamol showed characteristic vibrational peaks at 3320 and 3316 cm-1 indicating O-H and CH3 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 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 are indicative of para-di-substituted aromatic ring and out of plane ring deformation of phenyl ring, respectively.

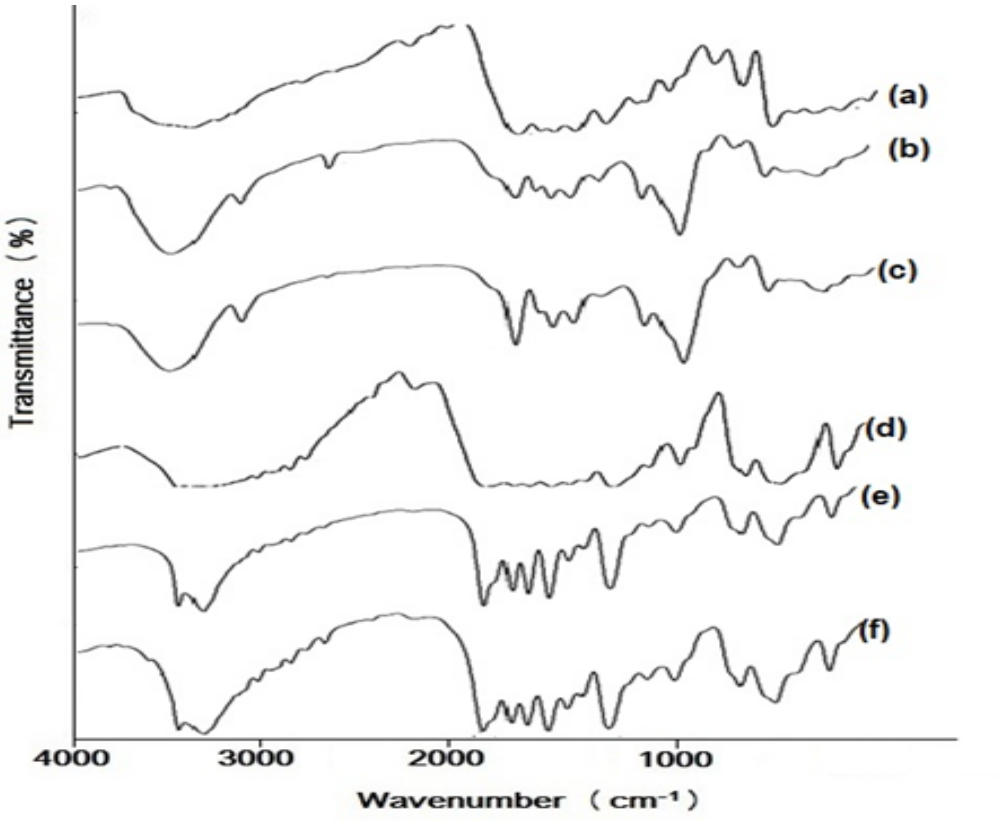


**Figure 3:** FT-IR spectra of diclofenac sodium powder (a), diclofenac granules prepared with Excipients X (b) and Y (c) and paracetamol powder (d), paracetamol granules prepared with Excipients X (e) and Y (f)

**DISCUSSION**

One of the easiest and most cost-effective methods of tablet manufacturing is direct compression because it involves only blending and compression of excipients.[15] The use of co-processed excipients in direct compression carries a plethora of benefits. The effect of co-processing on directly compressed paracetamol and diclofenac potassium tablets formulated with co-processed Ipomoea batatas starch and polyvinylpyrrolidone was investigated in this study.

Flow parameters are the simplest and most popular methods of predicting the flowability of powders.[16] Angle of repose is one of the indirect measurements of powder flow parameters; specific values of this measurement portray the levels of flowability of powdered materials. Values < 30$^o$ indicate excellent flow, 31$^o$ and 35$^o$ indicate good flow, between 36$^o$ and 40$^o$ shows fair flow and > 40$^o$ imply poor flow.[17] Table 2 shows that both excipients X and Y possessed excellent flow. The Hausner's ratio and Carr's index were determined from the bulk and tapped densities data obtained from the excipients. Table 2 shows that Excipient X with Carr's index ≤ 10 % and Hausner's ratio ≤ 1.11 possessed excellent but cohesive flow while Excipient Y with Carr's index of 20 % and Hausner's ratio of 1.26 showed fair flow that is less cohesive. Since inter-particulate interactions are generally associated with cohesive powders, these interactions may be said to be more pronounced in Excipient X than in Excipient Y. Though there exist differences in flowability between the excipients, pre-gelatinization has been known to confer new functionality and value-added properties to starch powder.18 Pre-gelatinization causes changes in structure and crystallinity, and a plastic deformity that enhances the compressibility of starch powder.19 These properties coupled with high bulk and tapped densities of pre-gelatinized starch make it fit for use as fillers in capsule form and as excipients for tablet manufacturing.20

Furthermore, the FTIR characterization of the prepared excipients and the physical mixture of the ingredients used in their preparation revealed some salient features in their spectra (Figure 1). The broader -OH group band observed at 3381 cm-1 in the spectrum of Excipient Y may be attributed to possible changes in amylose:amylopectin ratio due to modification.21 Also, the similarity observed in all the spectra especially between vibration bands 852 - 533 cm-1 wavenumbers can be attributed to the skeletal stretching of starch21,22 These similarities depict a characteristic basic fingerprint

of the starch present in the excipients investigated, hence no new peak was observed in the spectra of Excipients X and Y when compared with the spectrum of the physical mixture.

Weight uniformity is an important parameter in tablet evaluation that gives an idea of even distribution of ingredients in the formulation and precludes issues of batch variability. Variation in the weight of individual tablets could be attributed to non-uniform powder or granule flow, resulting in uneven filling of the dies. Table 3 shows that all the tablet formulations were within the official limits for tablets weighing 400 and 800 mg and none of the tablets deviated from the average weights by more than 5.0 %. This shows the ingredients were adequately distributed in the tablets and also shows the ease of tablet production with the co-processed excipients.

Friability is related to the hardness and the tendency of tablets to fracture or chip at the surface which can negatively affect the aesthetics of the tablet in addition to giving inconsistent bioavailability. The official limit is set at < 1.0%[23] and our results show that all the tablets formulated with Excipient Y were within the limit set while those prepared with Excipient X were very friable and did not meet the official specification. It can be inferred that incorporation of pre-gelatinized Ipomoea batatas starch, co-processed with povidone and lactose can yield tablets that withstand mechanical stress encountered during packaging, transportation, handling and storage.

Tablet hardness is an indication of the mechanical strength of tablets and values between 4 and 10 kp are set as limits for uncoated tablets.[24] Generally, hardness was observed to increase with increase in amount of the co-processed excipients. Tablets prepared with Excipient Y were harder than those prepared with Excipient X across both tablet formulations. This corresponds with the results of friability testing which shows Excipient Y confers greater mechanical strength on the tablets than Excipient X.

Evaluation of disintegration time is related to the time it takes a tablet to break down into particles and release its active ingredient for absorption. Table 3 shows that all the tablets disintegrated within the official limit of < 15 min.24 However, we observed that tablets prepared with Excipient Y disintegrated faster than those prepared with Excipient X therefore, it can be said that Excipient Y possesses better disintegrating property than Excipient X. This can be attributed to higher swelling and hydration capacity of Excipient Y as a result of pre-gelatinization. Pre-gelatinization is known to disrupt the molecular orderliness of starch granules leading to higher granular swelling resulting in faster tablet disintegration.[25]

Crushing strength-friability-disintegration ratio is an overall measure of mechanical strength of a tablet.[26] It strikes a balance between tablet hardness, friability and disintegration time. Using this parameter, Table 3 shows that tablets prepared with Excipient Y in both drug formulations are stronger than those prepared with Excipient X. This suggests that Excipient Y has the ability to produce robust tablets with good balance between its binding ability and disintegration indices.

Figure 2 shows the dissolution profile of the tablet formulations and it can be seen that increasing the amount of any of the co-processed excipients increased the rate of drug release from the tablet formulations. However, Excipient Y elicited faster drug release in both tablet formulations. This is in tandem with fast disintegration time presented in Table 3. Disintegration is known to be a precursor to dissolution; it is expected that the faster the tablet breaks up the rate of drug release will be higher as observed in Figure 1. Higher dissolution rate implies higher drug bioavailability and faster therapeutic outcomes.

Lastly, the FTIR drug-excipient compatibility study revealed that the distinctive absorption bands of diclofenac and paracetamol seen in their individual spectrum were also observed unchanged in their granule formulations with Excipient X and Y, suggestive of no interaction between drugs and excipients.

**CONCLUSION**

Results from the study has shown that diclofenac and paracetamol tablets formulated with co-processed Ipomoea batatas starch and polyvinylpyrrolidone possessed peculiar properties depending on the physicochemical properties of the co-processed materials. The co-processed excipient prepared with pre-gelatinized Ipomoea batatas starch (Excipient Y) exhibited superior characteristics over Excipient X, co-processed with native Ipomoea batatas starch, possessing good flow and compressibility properties as well as producing tablets with minimal friability. It also imparted higher crushing strengths, shorter disintegration times as well as increased and faster drug release from its tablet formulations.

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**REFERENCES**

1. Yu YB, Taraban MB, Briggs KT, Brinson RG, Marino JP (2021). Excipient innovation through precompetitive research. *Pharmaceutical Research* 38, 2179-2184
2. Olayemi OJ, Nock-Anyebe S (2021). Evaluation of novel co-processed excipient for fast disintegration of aspirin tablet formulations. *Journal Pharmacy Bioresources* 18(1):1-11.
3. Ingle VB, Potdar SS, Mhetre RL, Kulkarni NS, Dhole SN (2021). Natural and modified excipients in novel drug delivery system: A review. *Research Journal Pharmaceutical Dosage Forms Technology.* 13(2):147-142.
4. Benabbas R, Sanchez-Ballester NM, Bataille B, Sharkawi T, Soulairol I (2021). Development and pharmaceutical performance of a novel co-processed excipient of alginic acid and microcrystalline cellulose. *Powder Technology.* 378:576-584,
5. Obidiro OP, Eraga SO, Iwuagwu MA (2022). Investigation of the tableting properties of modified *Dioscorea dumetorum* starch in direct compressed diclofenac tablet formulations. *Journal Basic Social Pharmacy Research.* 2(3):36-47.
6. Gamage A, Thiviya P, Mani S, Ponnusamy PG, Manamperi A, Evon P, Merah O, Madhujith T. (2022). Environmental properties and applications of biodegradable starch-based nanocomposites. *Polymers* 14(21):4578.
7. Nedunchezhiyan M, Byju G, Jata SK (2012). Sweet potato agronomy. *Fruit Vegetable Cereal Science Biotechnology.* 6 (1):1-10.
8. Garcia MA, Garcia CF, Gomes Faraco AA (2020). Pharmaceutical and biomedical applications of native and modified starch: A review. *Starch - Stärke* 72:1900270.
9. Truong VD, Avula RY, Pecota KV, Yencho GC (2018). Sweet potato production, processing, and nutritional quality. In: Siddiq M, Uebersax MA (eds). Handbook of Vegetables and Vegetable Processing. Vol. II, 2nd Edition. John Wiley & Sons Ltd, Hoboken, New Jersey, United States.
10. Bowles BJ, Dziemidowicz K, Lopez FL (2018). Co-processed excipients for dispersible tablets-part 1: Manufacturability. *AAPS Pharm Sci Tech* 19:2598-2609.
11. Parmar KP, Rao SG, Bansal AK (2021). Co-processing of small molecule excipients with polymers to improve functionality. *Expert Opinion Drug Delivery.* 18(7):907-928.
12. Bhatia V, Dhingra A, Chopra B, Guarve K (2022). Co-processed excipients: Recent advances and future perspective. *Journal Drug Delivery Science Technology.* 71:103316.
13. Rojas J, Buckner I, Kumar V (2012). Co-processed excipients with enhanced direct compression functionality for improved tableting performance. *Drug Development Industrial Pharmacy.* 38(10):1159-1170.
14. Eraga SO, Ndukwe JO, Iwuagwu MA (2017). An investigation of the direct compression properties of pre-gelatinised African bitter yam and cassava starches in acetylsalicylic acid tablet formulation. *Journal Applied Science Environmental Management.* 21(5):855-862.
15. Chen H, Aburub A, Sun CC (2019). Direct compression tablet containing 99% active ingredient - A tale of spherical crystallization. *Journal Pharmaceutical Science.* 108(4):1396-1400.
16. Kalman H (2021). Quantification of mechanisms governing the angle of repose, angle of tilting, and Hausner ratio to estimate the flowability of particulate materials. *Powder Technology.* 382:573-593.
17. Al-Hashemi HMB, Al-Amoudi OSB (2018). A review on the angle of repose of granular materials. *Powder Technology.* 330:397-417.
18. Ma H, Liu M, Liang Y, Zheng X, Sun L, Dang W, Li J, Li L, Liu C (2022). Research progress on properties of pre-gelatinized starch and its application in wheat flour products. *Grain & Oil Science Technology.* 5(2):87-97.
19. Kankate D, Panpalia SG, Kumar KJ, Kennedy JF (2020). Studies to predict the effect of pregelatinization on excipient property of maize and potato starch blends. *International Journal Biological Macromolecules.* 164:1206-1214.
20. Odeku OA, Schmid W, Picker-Freyer KM (2008). Material and tablet properties of pregelatinized (thermally modified) *Dioscorea starches*. *European Journal Pharmaceutics Biopharmaceutics.* 70(1):357-371.

21. Olayemi O, Adetunji O, Isimi C (2021). Physicochemical, structural characterization and pasting properties of pre-gelatinized Neorautanenia mitis starch. *Polimer Medicine.* 51(1):7-16.
22. Bakre LG, Olakunle O, Adedayo AM (2014). Influence of pregelatinization on the physicochemical and compressional characteristics of starches obtained from two local varieties of *Dioscorea rotundata*. *IOSR Journal Pharmacy.* 4(6):2319-4219.
23. United States Pharmacopoeia/National Formulary (2015). USP 38/NF 33, United States Pharmacopoeia Convention. Rockville, MD, USA.
24. Center for Drug Evaluation and Research (CDER) (2015). Guidance for industry: Size, shape, and other physical attributes of generic tablets and capsules. United States Food and Drug Administration. Silver Spring, Maryland.
25. Vanier NL, Pozzada dos SJ, Pinheiro BG, Zavareze ER (2020). Starches in foods and beverages. In: Meiselman H (ed). Handbook of Eating and Drinking. Springer, Cham. pp. 1-17.
26. Njega EK, Maru SM, Tripo LJ (2018). The binder effect of povidone on the mechanical properties of paracetamol containing tablets. *East Central African Journal Pharmaceutical Sciences.* 21(1-3):3-9.