*Malaysian Journal of Pharmaceutical Sciences*
*Vol. 21, No. 1, 107–122 (2023)*

# DIRECT COMPRESSION PROPERTIES OF CO-PROCESSED EXCIPIENT CONTAINING COW BONE POWDER, KHAYA GUM AND MAIZE STARCH

**YOHANAH DAUDA YERIMA[1], ADAMU BABAH ISAH[1], AVOSUAHI RUKAYAT OYI[1], ALIYU MUHAMMAD MUSA[2] AND YONNI ESHOVO APEJI[1*]**

[1]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Nigeria

[2]Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Nigeria

**Published online:** 25 May 2023
**To cite this article:** YERIMA, Y. D., ISAH, A. B., OYI, A. R., MUSA, A. M. & APEJI, Y. E. (2023) Direct compression properties of co-processed excipient containing cow bone powder, Khaya gum and maize starch, *Malaysian Journal of Pharmaceutical Sciences*, 21(1): 107–122, https://doi.org/10.21315/mjps2023.21.1.7
**To link to this article:** https://doi.org/10.21315/ mjps2023.21.1.7

## ABSTRACT

*The aim of this study was to evaluate the direct compression properties of a novel co-processed excipient (CPE) generated by processing cow bone powder (CBP), maize starch (MS) and Khaya gum (KG) together to form a single composite excipient. Design of experiments (DoE) was employed to optimise the formulation of CPE. CPE was prepared by wet granulation using the optimised formulation of CBP (40%), MS (40%) and KG (20%) as recommended by DoE. Assessment of the organoleptic properties of CPE revealed an odourless, tasteless and coarse texture with a neutral pH of 7.3. CPE was found to be partly crystalline and partly amorphous and demonstrated compatibility between the three components of the formulation. The material in terms of flowability compared well with the flow parameters of StarLac, a reference co-processed excipient. Tablets of diclofenac produced by direct compression using CPE as the directly compressible excipient compared well with the hardness and disintegration time of tablets made using StarLac® as the directly compressible excipient. The study's outcome shows that CPE can be used as a direct compression excipient in the formulation of tablets by direct compression.*

***Keywords:*** Co-processing, Excipient, Direct compression, Tablets

[*]Corresponding author: yehonathanapeji@gmail.com

## INTRODUCTION

Excipients are highly recommended in the preparation and formulation of any dosage form. They contribute to the stability, safety, processability, acceptability and sometimes bioavailability of oral dosage forms (Siew 2016; Madhav *et al*. 2017). In the formulation of oral solid dosage forms e.g., tablets, excipients are indispensable because they contribute significantly to the manufacturability and performance of the final dosage form. Tablets can be prepared by granulation or direct compression (DC) methods (Patel, Kaushal and Bansal 2006).

Currently, there is a growing preference for direct compression among pharmaceutical manufacturers because it is a method that is simple, cost-effective and particularly useful for drugs that are moisture or heat sensitive (Franc *et al*. 2018; Chattoraj and Sun 2018; Benabbas *et al*. 2021). However, not every single component excipient available can meet the requirements of the direct compression process, hence the need for novel excipients with DC properties. To address this challenge, many pharmaceutical scientists have embraced co-processing technology to generate novel excipients with improved properties.

The process of co-processing involves combining two or more excipients using an acceptable method to generate a single composite excipient that synergises the strengths of the interacting excipients while minimising their limitations i.e. poor binding and disintegrating properties, generating a product with enhanced properties (Gupta, Nachaegari and Bansal 2006; Marwaha, Sandhu and Marwaha 2010). This process is a particle engineering technique that modifies the particle structure thereby altering the physical properties without affecting the chemical integrity of the material to the barest minimum. The outcome of this process has led to the development of high functionality excipients e.g. Prosolv®, StarLac®, Ludipress® etc. that have addressed the challenges encountered by manufacturers when using single component excipients. Some of the benefits recorded with co-processed excipients (CPEs) includes improved flowability, compressibility, low lubricant sensitivity, enhanced disintegration efficiency and better dilution potential (Nachaegari and Bansal 2004).

Generally, single component excipients can be derived from plant sources such as starches, gums, and celluloses; animal sources such as gelatin, chitin and alginic acid and mineral sources such as dicalcium phosphate, calcium carbonate and kaolin. One of such excipients that is being explored in tablet formulation is the cow bone powder (CBP). CBP is derived from cow bone, a rigid tissue that performs mechanical, biological and chemical functions. The bone serves as a metabolic reservoir for calcium, phosphorous and other minerals (Emenike *et al*. 2016). A study carried out discovered that when cow bone is heated to high temperatures of about 1000°C in a furnace, it produces a by-product that is purely hydroxyapatite (calcium phosphate) which can be used as an excipient in tablet formulation (Emenike *et al*. 2016; Akindoyo *et al*. 2019).

CBP has been evaluated as a diluent in the formulation of tablets by direct compression. However, the functionality of CBP as a DC excipient is relatively poor when compared to other existing excipients used in direct compression. Hence, this study aims to develop a CPE containing CBP and evaluate its material properties to determine its suitability for direct compression. Design of Experiments (DoE) was employed to optimise the formulation of CPE containing CBP, maize starch (MS) and Khaya gum (KG). MS and KG will serve as disintegrant and binder, respectively, in the new CPE to achieve a balance of the mechanical and disintegration properties of the DC excipient. This study is yet to be reported in literature.

## METHODS

### Materials

Cow bone was sourced from fresh femur and tibia from the Zaria Abattoir (Zaria, Kaduna State), KG (*Khaya senegalensis,* Family: Meliaceae) was obtained from the environs of Ahmadu Bello University, Zaria, Kaduna State, MS (Quality Starch and Chemicals, Private Ltd, Tamil Nadu, India).

### Methods

*Synthesis of CBP*

The method of Emenike *et al*. (2016) was adopted with slight modifications to synthesise CBP. One kilogram of fresh cow femur and tibia bones were collected from the abattoir (Zaria, Kaduna State). They were cut into pieces with the aid of an axe and heated to about 100°C for 1 h to remove all traces of meat, fat and bone marrow before cleaning with hot water. The weight of the bone pieces was obtained using the Gallenkamp Mettler balance (type P163, CH-8606 Grefensee-Zurich, Switzerland), allowed to dry for about two days and weighed again after drying. The dried cow bone was heated in an industrial furnace (project F 442 No: 91-442, type CFR, Holland) at 800°C for 6 h and allowed to cool overnight to a room temperature of 37°C. It was milled and the powder passed through a sieve of 250 µm before taking the final weight and storing in a plastic container for further studies.

*Extraction of KG*

The dried gum exudate was purified using the method described by Odeku and Itiola (2002). Pulverisation of crude gum was performed using an electric laboratory blender. A small quantity of the pulverised crude gum (~1 kg) was soaked in 2.5 L of distilled water for 72 h to allow for gum dissolution. The dispersion (solution) was strained through a calico cloth and precipitated with acetone to separate the pure gum from the dispersion. The precipitate was air dried for 24 h to remove acetone by vapourisation and purified KG was recovered. The dried gum was micronised using a blender and passed through a sieve (250 µm) to obtain the finely powdered gum which was stored in an airtight open-mouthed screw capped glass bottle for further use.

*Preparation of Experimental Formulations of CPE*

DoE was employed to optimise the formulation of the CPE containing CBP, KG and MS. A simple centroid (mixture) experimental design was used to generate 14 trial formulations containing varying proportions of the constituent excipients (Table 1). The content of MS (factor-A) varied from 40%–59%, CBP (factor-B) varied from 40%–59% and KG (factor-C) varied from 1%–20%. Each formulation of CPE according to the design in Table 1 was prepared by wet granulation. Plain tablets of CPE weighing 500 mg were prepared by direct compression and the parameters of tensile strength and disintegration time were evaluated for each formulation The effect of these independent variables (Factor A–C) on dependent variables ($Y_1$: tensile strength of tablet and $Y_2$: disintegration time of tablet) was studied using Design Expert® software version 12.0 (stat-Ease Inc. USA) to generate a design space for the prediction of the optimised formulation of CPE.

**Table 1:** Percentage of composition of each formulation of CPE showing the varied levels of the constituent excipients and their corresponding quantities by weight for a 20 g formulation.

| Run | Composition (%) | | | Mass composition (20 g) | | |
|---|---|---|---|---|---|---|
| | MS | CBP | KG | MS | CBP | KG |
| 1 | 40.0 | 49.5 | 10.5 | 8.0 | 9.9 | 2.1 |
| 2 | 43.2 | 52.7 | 4.1 | 8.6 | 10.5 | 0.9 |
| 3 | 49.5 | 49.5 | 1.0 | 9.9 | 9.9 | 0.2 |
| 4 | 43.2 | 43.2 | 13.6 | 8.6 | 8.6 | 2.8 |
| 5 | 40.0 | 40.0 | 20.0 | 8.0 | 8.0 | 4.0 |
| 6 | 49.5 | 49.5 | 1.0 | 9.9 | 9.9 | 0.2 |
| 7 | 40.0 | 59.0 | 1.0 | 8.0 | 11.8 | 0.2 |
| 8 | 49.5 | 40.0 | 10.5 | 9.9 | 8.0 | 2.1 |
| 9 | 52.7 | 43.2 | 4.1 | 10.5 | 8.6 | 0.9 |
| 10 | 59.0 | 40.0 | 1.0 | 11.8 | 8.0 | 0.2 |
| 11 | 40.0 | 40.0 | 20.0 | 8.0 | 8.0 | 4.0 |
| 12 | 59.0 | 40.0 | 1.0 | 11.8 | 8.0 | 0.2 |
| 13 | 40.0 | 59.0 | 1.0 | 8.0 | 11.8 | 0.2 |
| 14 | 46.3 | 46.3 | 7.4 | 9.3 | 9.3 | 1.4 |

*Preparation of CPE using the Optimised Formula*

The CPE containing CBP, KG and MS was prepared by wet granulation using the optimised formula obtained from DoE study. Based on the DoE, the optimised proportion for each of the excipient was found to be MS (40% w/w), CBP (40% w/w) and KG (20% w/w). KG (20% w/w) was dissolved in 110 mL of distilled water with the aid of a stirring rod for 5 min. The MS (40% w/w) and CBP (40% w/w) powders were mixed and wetted with the binding solution (KG) until the powder mix had consistency of damp mass. The wet mass was screened through 1.6 mm mesh sieve to generate granules. The granules were air dried at 25°C for 24 h and placed in the oven to complete the drying at 60°C for 60 min. The granules were milled to smaller particles and passed through 180 µm to compare with the size of the standard (StarLac®). It was packed into a tight sealed container before storing in the desiccator for further studies.

*Assessment of Organoleptic Properties*

The organoleptic properties of odour, colour, taste and texture were assessed for CBP, KG, MS and CPE. The pH for each material was also determined using a method described by Apeji, Oyi and Musa (2011)

*Scanning Electron Microscopy (SEM)*

Particle shape and morphology of CBP, KG, MS and CPE were examined using a scanning electron microscope (Phenom ProX, The Netherlands). The samples were placed initially on a double adhesive which was placed on a sample stub and then sputter-coated with gold under vacuum in an argon atmosphere prior to observation. The SEM images of the samples were taken at an acceleration voltage of 20 kV at various magnifications.

*Powder X-Ray Diffraction (PXRD)*

X-ray diffraction analysis was carried out on CBP, KG, MS and CPE using a Rigaku Miniflex 300 II Benchtop X-Ray diffractometer (Rigaku Corporation, Tokyo, Japan). The samples were positioned in the holding tray of the machine and scanned from 5° to 90° on a 2θ scale, measuring the angle between the emitted ray and the reflected ray. The raw data obtained was analysed with Smart Lab Studio-II software.

*Fourier Transform Infra-Red Spectroscopy (FT-IR)*

FT-IR scans for CBP, KG, MS and CPE were generated over a range of 4,000 $cm^{-1}$ to 650 $cm^{-1}$ using a Cary 630 FT-IR Spectrometer (Agilent Technologies, USA). Each sample was subjected to an average of 32 scans at a nominal resolution of 8 $cm^{-1}$, employing background spectrum of gold. The Cary 630 Micro Lab PC software was used for data collection and SpectraGryph 1.2—spectroscopy software was used to analyse the data.

*Characterisation of Flow Properties*

The flow properties of CPE and StarLac® were characterised by measuring the angle of repose (AoR) using the fixed funnel method (Pilpel 1965). Each powder sample weighing 20 g was poured through a fixed funnel suspended at a height 8 cm above the bench surface. The height and diameter of the conical heap of powder formed was measured and Equation 1 was used to calculate the angle of repose. A mean of three replicates was recorded as the final angle of repose for each sample.

$$Tan\theta = \frac{2h}{d} \qquad \text{Equation 1}$$

where $h$ is the height of heap of powder cone (cm), $d$ is diameter of the cone base (cm) and is the angle of repose.

Bulk and tapped densities of the powders were also determined according to the method specified by the United States Pharmacopoeial (2012) and the densities were used to compute the parameters of Carr's index (CI) and Hausner's ratio (HR) using Equations 2 and 3, respectively. A mean of three replicates with standard deviation was recorded for each parameter.

$$CI = \frac{TD - BD}{TD} \times 100\% \qquad \text{Equation 2}$$

$$HR = \frac{TD}{BD} \qquad \text{Equation 3}$$

where BD and TD are bulk and tapped densities, respectively.

*Tablet Formulation by Direct Compression*

Tablets containing diclofenac (100 mg) were prepared by direct compression using CPE as DC excipient in comparison to StarLac® as the reference standard. The formulation of the drug and excipients were mixed together and compressed on a single punch tablet press into tablets weighing ~200 mg. The tablets were kept for 24 h to allow for elastic recovery before tablet parameters were evaluated.

## RESULTS

The effect of varying the formulation of CPE containing CBP, MS and KG on tablet properties was evaluated. The results are presented in Table 2.

**Table 2:** Design formulations and their corresponding tablet properties.

| Run | MS (%) | CBP (%) | KG (%) | TS (MPa) | DT (min) |
|---|---|---|---|---|---|
| 1 | 40.0 | 49.5 | 10.5 | 0.53 ± 0.16 | 2.41 ± 0.07 |
| 2 | 43.2 | 52.7 | 4.1 | 0.23 ± 0.09 | 0.92 ± 0.28 |
| 3 | 49.5 | 49.5 | 1.0 | 0.34 ± 0.13 | 0.58 ± 0.22 |
| 4 | 43.2 | 43.2 | 13.6 | 0.88 ± 0.08 | 3.17 ± 0.18 |
| 5 | 40.0 | 40.0 | 20.0 | 0.75 ± 0.08 | 6.5 ± 0.65 |
| 6 | 49.5 | 49.5 | 1.0 | 0.44 ± 0.12 | 0.69 ± 0.09 |
| 7 | 40.0 | 59.0 | 1.0 | 0.59 ± 0.07 | 0.57 ± 0.07 |
| 8 | 49.5 | 40.0 | 10.5 | 0.59 ± 0.04 | 3.88 ± 0.16 |
| 9 | 52.7 | 43.2 | 4.1 | 0.59 ± 0.08 | 1.52 ± 0.36 |
| 10 | 59.0 | 40.0 | 1.0 | 0.48 ± 0.06 | 0.79 ± 0.17 |
| 11 | 40.0 | 40.0 | 20.0 | 1.29 ± 0.04 | 12.29 ± 1.04 |
| 12 | 59.0 | 40.0 | 1.0 | 0.32 ± 0.01 | 0.85 ± 0.39 |
| 13 | 40.0 | 59.9 | 1.0 | 0.79 ± 0.21 | 0.69 ± 0.08 |
| 14 | 46.3 | 46.3 | 7.4 | 1.02 ± 0.12 | 2.44 ± 0.42 |

The tensile strength (TS) of tablets ranged from 0.23 MPa to 12.9 MPa while the disintegration time (DT) of tablets ranged from 0.57 min to 12.29 min. Tablets of higher TS were produced from formulations containing higher concentration of KG (Runs 5, 11 and 14) and this was reflected in the DT as harder tablets generally take a longer time to disintegrate. Also, it was observed that formulations containing higher concentration of MS produced tablets that disintegrated in less than 1 min (Runs 3, 10 and 12) when compared to other formulations. The corresponding TS of tablets of these formulations was relatively lower when compared to other formulations. For formulations containing higher proportion of CBP (Runs 7 and 13), the TS of tablets was relatively higher when compared to other formulations containing a lower proportion of CBP (Runs 10 and 12). Overall, variation in the formulation of CPE affected the properties of tablets that were generated.

The tablet properties of TS and DT which represent the responses (dependent variables) for the design were fitted into models by the Design Expert software (version 12.0) and the results of the analysis is presented in Table 3.

**Table 3:** Model analysis for both responses.

| Responses | Model | *p*-value | Lack-of-fit *p*-value | $R^2$ |
|---|---|---|---|---|
| TS | Linear | 0.033 | 0.4252 | 0.4621 |
| DT | Linear | 0.0002 | 0.8300 | 0.7802 |

The outcome of the analysis shows that the linear model was selected for both responses on the basis of the *p*-value which was significant at $p < 0.05$. The lack-of-fit *p*-value was not significant at $p < 0.05$ implying that the model fitted the responses. The coefficient of fitness ($R^2$) obtained for both responses was 0.4621 and 0.7802 for TS and DT, respectively

implying that the model selected accounts for about 46% and 78% of the changes observed in the TS and DT values, respectively, as a result in variation in formulation.

The effect of varying the formulation of CPE on tablet properties of TS and DT was expressed mathematically in the equations below:

$$TS = 0.395*MS + 0.541*CBP + 0.993*KG \quad \text{Equation 4}$$

$$DT = 0.547*MS – 0.0187*CBP + 8.02*KG \quad \text{Equation 5}$$

The relationship above shows that all the components of CPE exert a positive effect on TS of tablets implying that an increase in concentration or proportion by weight of each component in the formulation of CPE will cause an increase in the TS of tablets. However, KG was found to exert a greater influence on TS when compared to other components on the basis of its coefficient term (0.993). So, the effect of each component on TS is ranked in the following order, KG > CBP > MS. All three components of CPE were found to exert a significant effect on the DT of tablets and were ranked in the following order, KG > MS > CBP with KG having a more prominent effect on KG due to its coefficient term of 8.02. It must be noted however that while the effect of KG and MS on DT of tablets was positive, that of CBP was negative implying that an increase in the proportion of CBP in the formulation of CPE relative to the other components will decrease the DT of tablets.

Based on the regression equations obtained for each response, a contour plot was generated for each response to illustrate graphically the effect of each component of CPE on the tablet property. The graphs are presented as Figures 1 and 2, respectively, for TS and DT. The contour plot for TS presented as Figure 1 shows that TS decreases when the proportions of MS and CBP move from lower concentration regions to higher concentration regions. However, the reverse is the case with KG as TS increases when the content of KG increases in the formulation of CPE. Increasing the concentration of KG from 1% to 20% led to an increase in TS from 0.5 MPa to 0.9 MPa (a shift from the sky blue to greenish yellow regions). This confirms that KG exercises a greater impact in defining the TS of tablets.

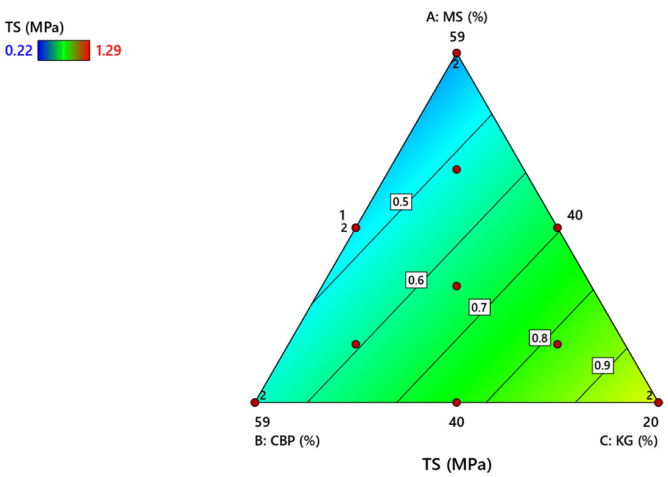


**Figure 1:** Contour plot showing the effect of the three excipients on TS.

The contour plot for DT presented as Figure 2 shows that increasing the content of MS from 40% to 59% does not significantly affect the reduction in DT of tablets. There, however, seems to be some reduction in the DT of tablets when the content of CBP rose from 40% to 59% in the formulation. Again, there was a significant increase in the DT of tablets when the content of KG rose from 1% to 20%. This further suggests that KG in the formulation of CPE is playing a prominent role in defining the outcome of the tableting properties of CPE under development. Hence, it will be critical to consider this component in the final stage of optimisation of the formulation of CPE.

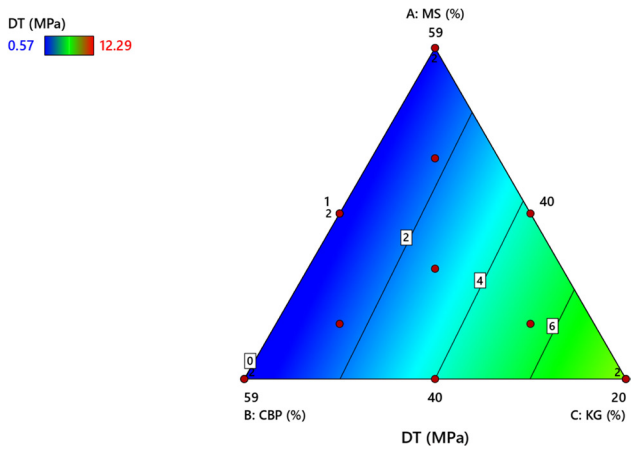


**Figure 2:** Contour plot showing the effect of the three excipients on DT.

Based on the analysis and assessment of the relationship between the formulation factors and tablet properties, optimisation of the formulation of CPE was conducted numerically using the design space to suggest a desirable formulation of CPE that will yield acceptable tablet properties. A set of criteria was defined for the factors and responses for the design as outlined in Table 4. A formulation of CPE containing MS (40%), CBP (40%) and KG (20%) will yield tablets having TS and DT of 0.993 MPa and 8.018 min, respectively, was predicted and confirmed. The DoE model was therefore accepted for the optimisation.

**Table 4:** Optimisation criteria for each variable of the design and the prediction.

| Factors | Criteria | Prediction |
|---|---|---|
| MS | Minimise (40%–59%) | 40% |
| CBP | Minimise (40%–59%) | 40% |
| KG | Maximise (1%–20%) | 20% |
| TS | Maximise (0.22 MPa–1.29 MPa) | 0.993 MPa |
| DT | In range (0.57 min–12.29 min) | 8.018 min |

Organoleptic properties of CPE in comparison to its component excipients were assessed and the results presented in Table 5. All the materials were found to be odourless and tasteless except for KG that had a mild-acidic taste owing to a pH of 3.6. The component excipients all varied in colour ranging from ash-white to white and this affected the final

colour of CPE which was light brown. Combination of the three component excipients in the formulation of CPE yielded a material that is coarse in texture while the pH of CPE was 7.3 implying a balance between the acidic and basic components of the formulation. The organoleptic properties of CPE obtained are consistent with the properties of commercial co-processed excipients that are used in the production of oral solid dosage forms.

**Table 5:** Organoleptic properties of CBP, KG, MS and CPE.

| Property | CBP | KG | MS | CPE |
|---|---|---|---|---|
| Odour | Odourless | Odourless | Odourless | Odourless |
| Colour | Ash-white | Light brown | White | Light brown |
| Taste | Tasteless | Mild acidic | Tasteless | Tasteless |
| Texture | Brittle | Coarse | Smooth | Coarse |
| pH | 9.1 | 3.6 | 5.4 | 7.3 |

SEM analysis of the component excipients and CPE was carried out to observe the particle structure, shape and surface morphology of the materials. The pictures as presented in Figure 3 shows MS (Figure 3A) characterised by polygonal shaped smooth-surface particles of various sizes while CBP (Figure 3B) also shares similar structure and shape with MS particles though having a higher proportion of small sized particles of varying diameters. The particles of KG (Figure 3C) appear granular making the surface rough while CPE particles (Figure 3D) appear irregular in shape showing a dispersion or mixture of the components with rough surfaces and enlarged particle size owing to co-processing. Examination of the particle structure and morphology of CPE shows that the three component excipients having been unified into a co-processed particle with properties derived from the component excipients.

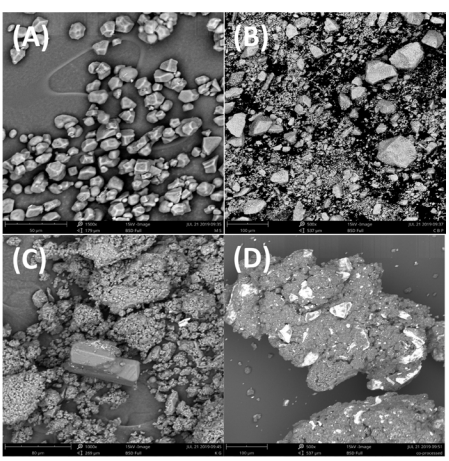


**Figure 3:** SEM pictures of (A) MS, (B) CBP, (C) KG and (D) CPE.

The PXRD patterns of the component materials and CPE are presented in Figure 4. The PXRD patterns of MS and KG are characterised by diffused and low intensity peaks indicating strongly that both materials are predominantly amorphous while CBP

displays sharp, distinct peaks implying the material is predominantly crystalline. These characteristics peaks as identified in the component materials were also prominent in the PXRD of CPE implying that the materials are compatible and can be processed together to form a co-processed excipient.

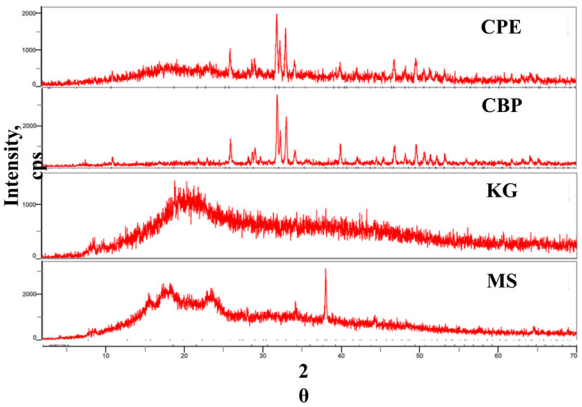


**Figure 4:** PXRD patterns of CPE, CBP, KG and MS.

Figure 5 presents the FT-IR spectra for MS, CBP, KG and CPE. The characteristic peaks reflected by each spectrum is a representation of the chemical composition of the material and as such differs from one material to another. However, the characteristic peaks of each spectrum of the component materials were reflected in the spectrum of CPE suggesting that chemical reaction between the materials was minimal during co-processing and so the chemical properties of CPE were not modified as a result of co-processing.

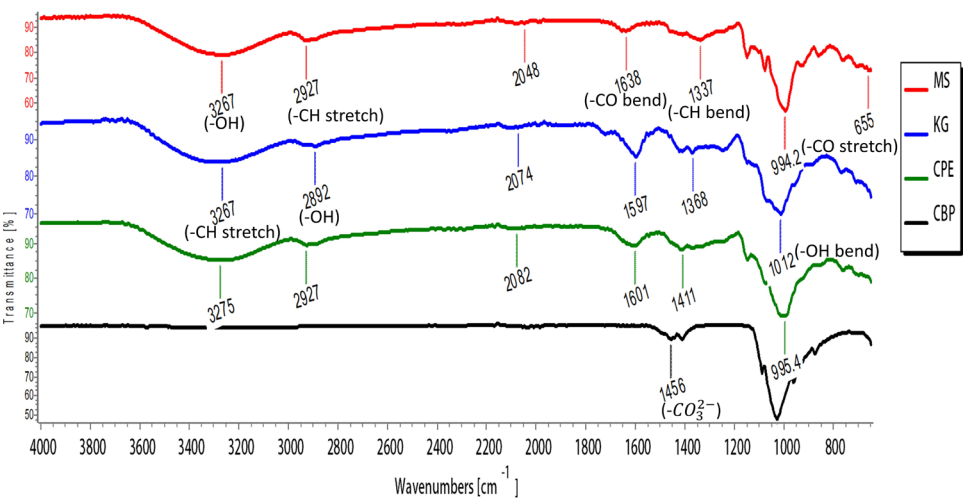


**Figure 5:** FT-IR of CBP, KG, MS and CPE.

This was further confirmed when the FT-IR spectra of CPE and a physical mixture of the three components in their stated proportions were compared in Figure 6. The two spectra did not differ significantly implying that co-processing did not cause a chemical change to occur and thus the materials can be processed together while maintaining their chemical integrity.

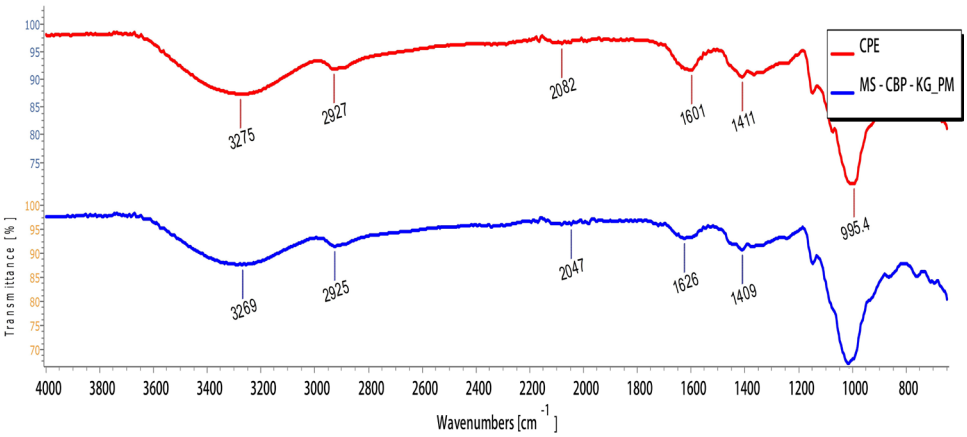


**Figure 6:** FT-IR of CPE and MS-CBP-KG_PM.

The flow properties of CPE were compared to a reference co-processed excipient (StarLac®) by evaluating flow parameters like angle of repose, CI and Hausner's ratio (HR). The result of the analysis is presented in Table 6. Both materials reported values of angle of repose < 30° suggesting that they possess excellent flow properties. This outcome was confirmed by CI and HR which had values less than 20% and 1.2, respectively. Generally, materials having CI < 20% and HR < 1.2 tend to flow freely and is characteristic of pharmaceutical excipients used in the formulation of tablets by direct compression.

**Table 6:** Flow parameters for CPE and StarLac®**.**

| | Materials | |
|---|---|---|
| **Parameters** | **CPE** | **StarLac®** |
| Angle of repose (°) | 24.70 (0.47) | 26.90 (0.87) |
| Bulk density (g/mL) | 0.78 (0.02) | 0.58 (0.00) |
| Tapped density (g/mL) | 0.91 (0.00) | 0.65 (0.00) |
| HR | 1.16 (0.02) | 1.19 (0.01) |
| CI (%) | 13.56 (0.68) | 15.60 (0.54) |

The results of the tablet properties are presented in Table 7. Evaluation of tablet parameters shows that there was no significant difference in tablet properties at $p < 0.05$ when comparing the tablet parameters of the two different formulations except for the disintegration time of tablets that differed significantly. The drug-release profile of the two formulations presented in Figure 7 shows that 100% of diclofenac was released in 60 min.

**Table 7:** Tablet properties.

| | Diclofenac tablets | |
|---|---|---|
| **Properties** | **CPE** | **STD** |
| Mean weight (mg) | 203 ± 8.23 | 199 ± 8.76 |
| Thickness (mm) | 2.73 ± 0.05 | 2.68 ± 0.05 |
| Crushing strength (kgf) | 5.08 ± 0.38 | 4.93 ± 0.38 |
| Disintegration time (min) | 5.97 ± 1.11 | 3.61 ± 0.71 |
| Friability (%) | 0.99 | 0.50 |

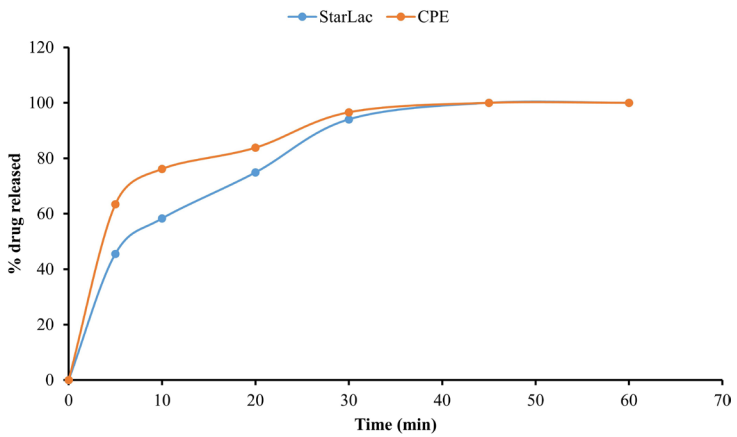


**Figure 7:** Drug-release profile of CPE and StarLac®.

## DISCUSSION

This study aimed to characterise the material properties of a novel excipient generated by co-processing CBP, MS and KG in optimal proportions. The concept of co-processing as a particle engineering technique has been used by pharmaceutical scientists to generate excipients for the pharmaceutical industry. In order to maximise the functionality of CPE in tableting, it was necessary to optimise the formulation of CPE. Design of Experiments (DoE) was therefore applied to optimise the formulation of CPE.

Analysis of the design as presented in the Results section shows that each component of CPE is a contributor to the final quality of CPE in terms of functionality and the contribution of each component is based on its inherent functionality as a tableting excipient. Tablets of higher TS were generated by formulations of CPE containing a higher proportion of KG because this material is used as a binder in tablet formulations (Odeku and Itiola 2002; Adenuga *et al*. 2008). Hence, the more binder in a formulation, the higher the compressibility and corresponding tensile strength of the formulation. However, for formulations containing a higher proportion of MS, tablets produced were found to have lower TS values primarily because MS acts as a disintegrant in tablet formulation (Olayemi, Oyi and Allagh 2008; Zámostný, Petrů and Majerová 2012) and therefore opposes the action of the binder in a formulation. When compared to the contribution in the formulation

of CPE, CBP acts principally as a diluent in tablet formulation and possesses weak binding and disintegrating properties making it a poor candidate for direct compression tableting (Emenike *et al.* 2016). Hence, the inclusion of MS and KG into the particle structure of CBP is more likely to improve the direct compression properties of CBP.

Particle shape and surface characterisation of CPE particles as revealed by SEM analysis shows that there was a transformation in the particle structure and morphology of the individual components of CPE after co-processing. Single composite particles of CPE were generated having fused together all three components in their various proportions into one homogeneous entity. The change in shape and structure of CPE particles can be attributed not only to the variation in shape and structure of the individual components but also to the method of co-processing. Co-processing by spray drying method generally produces particles that are spherical in shape thereby contributing to the enhanced flowability of co-processed excipients (Chauhan *et al*. 2017; Rathod *et al*. 2019; Dong *et al*. 2018).

PXRD characterisation of CPE particles revealed a material that is partly crystalline and partly amorphous owing to the processing together of materials that are principally amorphous (MS and KG) and principally crystalline (CBP) to form a co-processed excipient. The analysis also demonstrates compatibility between the three excipients as the diffraction integrity of each excipient was maintained in the newly formed excipient, CPE. FT-IR analysis also demonstrated a high degree of compatibility between the three excipients confirming the absence of chemical change occurring during co-processing. The goal of co-processing using any method has always been to engineer the particle structure thereby altering physical properties without affecting the chemical integrity of the material (Sharma, Modi, and Bansal 2015; Devanshu, Gupta and Kumar 2019).

Flowability is a critical process to the success of tablet formation by direct compression and because the flowability of a tablet formulation of DC is largely dependent on the flowability of the DC excipient, it was necessary to evaluate the flow behaviour of CPE. The flowability of CPE as assessed by characterising the AoR, CI and HR show that it compares well with StarLac. StarLac is a lactose-based CPE containing MS (15%) and prepared by spray drying. Similarity in flow properties suggests that CPE can be used as an alternative to StarLac as a DC excipient in tablet formation by DC.

The tablets produced by direct compression using CPE as DC excipient met the requirements for tablets of acceptable quality. The tablets were sufficiently hard and within the limits of acceptable friability. This implies that CPE is sufficiently compressible and compactable to produce tablets by direct compression without prior processing by granulation. The longer disintegration time observed with the tablets formulated with CPE in comparison to those of StarLac® may be attributed to the presence of KG in the composition of CPE where it acts as a binder. Binders generally give rise to harder tablets which corresponds to longer disintegration time (Batra *et al*. 2021). However, the extended disintegration time of CPE tablets did not exceed the limit permitted for immediate release tablets which is 15 min. Hence, both formulations passed the test for disintegration time and this led to a robust dissolution of the tablet formulations leading to a maximal release of the drug in 60 min.

## CONCLUSION

The material properties of CPE were characterised following the optimisation of the formulation of CPE using DoE. Organoleptic properties revealed a material that is odourless, tasteless, light brown and coarse in texture having a pH of 7.3 which is neutral. The material was found to be partly crystalline and partly amorphous with no change in the

chemical integrity of the material after co-processing. Flow properties of CPE were similar to those of StarLac, a reference standard. The tablets produced by direct compression were acceptable based on the recommended quality for immediate release tablets Hence, this study has confirmed the suitability of CPE as a direct compression excipient in the formulation of diclofenac tablets by direct compression and can therefore be used as an alternative to StarLac® in tablet formulation if the need arises.

## ACKNOWLEDGEMENTS

We sincerely appreciate the contributions of the Multi-user Science Laboratory, Ahmadu Bello University, Zaria for assisting with some of analysis carried out for the study. This work was self-funded.

## REFERENCES

ADENUGA, Y. A., ODEKU, O. A., ADEGBOYE, T. A. & ITIOLA, O. A. (2008) Comparative evaluation of the binding properties of two species of khaya gum polymer in a paracetamol tablet formulation, *Pharmaceutical Development and Technology*, 13(6): 473–480. https://doi.org/10.1080/10837450802179338

AKINDOYO, J. O., GHAZALI, S., BEG, M. D. H. & JEYARATNAM, N. (2019) Characterization and elemental quantification of natural hydroxyapatite produced from cow bone, *Chemical Engineering & Technology*, 42(9): 1805–1815. https://doi.org/10.1002/ceat.201800636

APEJI, Y., OYI, A. R. & MUSA, H. (2011) Formulation and evaluation of ascorbic acid tablets by direct compression using microcrystalline starch as a direct compression excipient, *International Journal of Health Research*, 4(3): 113–118.

BATRA, A., THONGSUKMAK, A., DESAI, D. & SERAJUDDIN, A. T. M. (2021). The effect of process variables and binder concentration on tabletability of metformin hydrochloride and acetaminophen granules produced by twin screw melt granulation with different polymeric binders, *AAPS PharmSciTech*, 22 (4): 1–17. https://doi.org/10.1208/s12249-021-02018-6

BENABBAS, R., SANCHEZ-BALLESTER, N. M., AUBERT, A., SHARKAWI, T., BATAILLE, B. & SOULAIROL, I. (2021) Performance evaluation of a novel biosourced co-processed excipient in direct compression and drug release, *Polymers*, 13: 988. https://doi.org/10.3390/polym13060988

CHATTORAJ, S. & SUN, C. C. (2018) Crystal and particle engineering strategies for improving powder compression and flow properties to enable continuous tablet manufacturing by direct compression, *Journal of Pharmaceutical Sciences*, 107(4): 968–974. https://doi.org/10.1016/j.xphs.2017.11.023

CHAUHAN, S. I., NATHWANI, S. V., SONIWALA, M. M. & CHAVDA. J. R. (2017) Development and characterization of multifunctional directly compressible co-processed excipient by spray drying method, *AAPS PharmSciTech*, 18(4): 1293–1301. https://doi.org/10.1208/s12249-016-0598-8

DEVANSHU, D., GUPTA, R. N. & KUMAR, K. J. (2019) Studies on effect of co-processing on palmyrah and maize starch mixtures using DOE approach, *International Journal of Biological Macromolecules*, 122: 417–424. https://doi.org/10.1016/j.ijbiomac.2018.10.079

DONG, Q. Q., ZHOU, M. M., LIN, X., SHEN, L. & FENG, Y. (2018) Differences in fundamental and functional properties of HPMC co-processed fillers prepared by fluid-bed coating and spray drying, *European Journal of Pharmaceutical Sciences*, 119: 147–158. https://doi.org/10.1016/j.ejps.2018.04.001

EMENIKE, I. V., TIMOTHY, S. Y., OKPANACHI, G. O. & MUSA, H. (2016) Tableting properties of thermally activated cow bone powder in high dose formulation, *International Journal of Pharmaceutical Development and Technology*, 6(2): 65–70.

FRANC, ALEŠ, VETCHÝ, D., VODÁČKOVÁ, P., KUBAĽÁK, R., JENDRYKOVÁ, L. & GONĚC, R. (2018) Co-processed excipients for direct compression of tablets, *Ces Slov Farm*, 67(5–6): 175–181.

GUPTA, P., NACHAEGARI, S. K. & BANSAL, A. K. (2006) Improved excipient functionality by coprocessing. IN: A. Katdare & M. V. Chaubal (Eds.). Excipient development for pharmaceutical, biotechnology, and drug delivery systems, pp.109–126 (New York: Informa Healthcare USA, Inc.). https://doi.org/10.1201/9781420004137.ch9

MADHAV, N., ABHJEET, O., SHUBHAMTY, A., VEDPRAKASH, G. & UPENDRA, R. (2017) Significance of pharmaceutical excipients: A review, *Innovat International Journal of Medical and Pharmaceutical Sciences*, 2(6): 1–12.

MARWAHA, M., SANDHU, D. & MARWAHA, R. K. (2010) Co-processing of excipients: A review on excipient development for improved tableting performance, *International Journal of Applied Pharmaceutics*, 2(3): 41–47.

NACHAEGARI, S. K. & BANSAL, A. K. (2004) Co-processed excipients for solid dosage forms, *Pharmaceutical Technology*, 28(1): 52–64.

ODEKU, O. A. & ITIOLA, O. A. (2002) Characterization of khaya gum as a binder in a paracetamol tablet formulation, *Drug Development and Industrial Pharmacy,* 28(3): 329–337. https://doi.org/10.1081/DDC-120002848

OLAYEMI, O., OYI, A. & ALLAGH, T. (2008) Comparative evaluation of maize, rice and wheat starch powders as pharmaceutical excipients, *Nigerian Journal of Pharmaceutical Sciences*, 7(1): 131–138.

PATEL, S., KAUSHAL, A. M. & BANSAL, A. K. (2006) Compression physics in the formulation development of tablets, *Critical Reviews in Therapeutic Drug Carrier Systems*, 23(1): 1–65. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v23.i1.10

PILPEL, N. (1965) Flow properties of non-cohesive powders, *Chemical and Process Engineering*, 46: 167.

RATHOD, P., MORI, D., PARMAR, R., SONIWALA, M. & CHAVDA, J. (2019) Co-processing of cefuroxime axetil by spray drying technique for improving compressibility and flow property, *Drug Development and Industrial Pharmacy*, 45(5): 767–774. https://doi.org/10.1080/03639045.2019.1569675

SHARMA, P., MODI, S. R. & BANSAL, A. K. (2015) Co-processing of hydroxypropylmethylcellulose (HPMC) for improved aqueous dispersibility, *International Journal of Pharmaceutics*, 485(1–2): 348–356.

SIEW, A. (2016) Excipients for formulation success, *Pharmaceutical Technology*, 40(10): 22–27.

UNITED STATES PHARMACOPOEIAL (USP) (2011) Bulk and tapped density for powders/physical tests, p. 258 (The United States Pharmacopeial Convention). https://www.drugfuture.com/Pharmacopoeia/usp35/PDF/0258-0265%20%5B621%5D%20CHROMATOGRAPHY.pdf

ZÁMOSTNÝ, P., PETRŮ, J. & MAJEROVÁ, D. (2012) Effect of maize starch excipient properties on drug release rate, *Procedia Engineering,* 42: 482–488. https://doi.org/10.1016/j.proeng.2012.07.439