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TABLETING POTENTIAL OF CO-PROCESSED STARCH, ALGINIC ACID AND POLYVINYL PYRROLIDONE AS DIRECTLY COMPRESSIBLE EXCIPIENT

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ABSTRACT

The goal of the study was to evaluate the functionality of co-processed material containing starch, alginic acid and polyvinyl pyrrolidone in tableting. This was achieved by co-processing maize starch with alginic acid and polyvinyl pyrrolidone in an optimized ratio to develop a robust excipient with multifunctional properties. A systematic approach was applied to optimize the composition of the co-processed excipient by determining the proportion by percentage weight of each of the materials used in the co-processing. The optimized formula for preparing the co-processed excipient with multifunctional properties was found to be maize starch (82%), alginic acid (8%) and polyvinyl pyrrolidone (10%) respectively. Solid state characterization of the co-processed excipient revealed an increase in size of the particles, with spherical shape and rough surfaces. The flowability and compression properties of the co-processed excipient were found to be superior to that of maize starch, alginic acid and polyvinyl pyrrolidone, and the excipients were found to be compatible with one another when co-processed together and also compatible with the drug of choice for the study. The tablets produced using the co-processed excipient by direct compression conformed to the official specification for desirable immediate release tablets and compared well with the commercially available co-processed excipient, Ludipress®.

Keywords: Alginic acid, Co-processed excipients, Direct Compression, Maize starch, Polyvinyl pyrrolidone, Tablet

INTRODUCTION

The use of natural excipients for pharmaceutical formulations is currently gaining global interest compared to the synthetic ones because of their properties of being nontoxic, biocompatible, less expensive and widely available (Ameen *et al.*, 2021). Oral route remains the most preferred route of administration of therapeutic agents due to its accurate dosage, low-cost therapy, self-medication, non-invasive, ease of administration and high level of patient compliance (Arindam *et al.*, 2013). The choice of the excipients to be used is very important since they also offer add-on characteristic properties as integrity, uniformity, stability, solubility, and patient compliance to those intrinsic properties exhibited by the active pharmaceutical ingredients (Ameen *et al.*, 2021). With the progress in the development of novel drug delivery systems, more sophisticated

excipients are needed to impart certain properties into the final product.

The term 'multifunctional excipients' refer to excipients that fulfil multiple roles in a dosage form or drug delivery system, for example, a directly compressible filler material that also functions as a binder and/or disintegrant (Van der Merwe *et al.*, 2020). In recent years, pharmaceutical industry focuses on the search for multifunctional directly compressible excipients for tablet's production especially with the availability of high-speed compression machines. The need for such excipients has increased because of the simplicity and cost effectiveness of direct compression process. On the other hand, adequate physicochemical properties of pharmaceutical products are not in most cases achieved by utilizing single functional excipient with the active pharmaceutical ingredient in the formulation. Therefore, in response to these requirements, drug formulation scientists have now relied on newly developed materials obtained by coprocessing the existing excipients used by manufacturers in the commercial market (Benabbas *et al.*, 2021).

Particle engineering with co-processing provides a promising way to obtain excipients with improved properties that may be used successfully in tableting as directly compressible materials (Li *et al.*, 2017). Co-processing can be defined as a combination of two or more established excipients by an appropriate manufacturing process and it provides a synergistic modification of functional and physicochemical properties of individual excipients in a manner not achievable by simple physical mixture (Benabbas *et al.*, 2021). Co-processing is the widely adopted method of preparation of multifunctional excipients. Some of the methods used for preparing co-processed excipients are spray drying, agglomeration, melt granulation, wet granulation, co-fusion and co-precipitation (Benabbas *et al.*, 2021; Swami *et al.*, 2021). None of the single excipient currently available holds all the physicochemical characteristics necessary for the development of a drug formulation and so there is need to have modified excipients having more than one characteristic like enhanced flowability, decreased moisture sensitivity, enhanced compressibility and improved disintegration ability (Swami *et al.*, 2021). These improved properties can be achieved by co-processing two or more excipient mixtures (Benabbas *et al.*, 2021). Hence the need for combining maize starch, which is a popular diluent, binder and disintegrant in tableting with alginic acid which has high disintegration ability and with polyvinyl pyrrolidone to adhere the materials together and to confer better mechanical strength to the tablets formed using the co-processed excipient.

MATERIALS AND METHODS

Materials

Maize starch (extracted from Sammaz-17 maize variety obtained from IAR, ABU Zaria), Alginic acid, Diclofenac (Central Drug House P Ltd. New Delhi, India), Polyvinyl pyrrolidone (BDH Chemicals Ltd, England), Diclofenac, Ludipress® (BASF SE, Germany). All other materials and solvents used were of analytical grade.

Methods

Extraction of maize starch

A variety of maize grain (*Zea mays*) with a voucher number Sammaz-17 was obtained from the Institute of Agricultural Research (IAR), ABU Zaria, Nigeria. The extraction was carried out as described by Okpanachi *et al*. (2012) with slight modifications. Prior to the extraction, the grains were cleaned thoroughly with distilled water to remove

foreign matter and dried. A 5 kg quantity of the cleaned grains was weighed and then steeped in 10 L distilled water for 72 h. The steeped grains were washed with water 3 times and then milled using milling machine. About 10 L of distilled water was then added to the ground mixture and then sieved several times using a calico cloth to recover the starch. The starch mixture was allowed to settle for 24 h and the supernatant removed by decantation. The sediment was centrifuged for 10 min at 2500 rpm (Laboratory centrifuge Centra CL2, China). The starch was obtained by scooping off the upper brown layers. The tightly packed starch was then dried in an oven (Gallenkamp Oven BS, England) at 40 ºC for 2 h and milled to fine powder using a blender. The starch obtained was transferred into an air-tight container and stored at room temperature for further use.

Preparation of the co-processed excipient

The co-processed excipients containing maize starch (MS), alginic acid (AA) and polyvinyl pyrrolidone (PVP) were prepared by wet granulation method as carried out by Agrawal *et al*. (2011), using PVP as the binding agent at fixed concentration of 10%. Different combinations of MS, AA and PVP as listed out in Table II were prepared. The required proportion of MS was weighed and transferred into a clean mortar. The required amount of the AA was also weighed and added into the mortar containing the MS and mixed thoroughly. The required amount of PVP was weighed and dissolved in warm water. The dissolved PVP was poured into the mortar containing the MS and the AA, and massed thoroughly until a uniform dispersion within the system was obtained. The damp mass was passed through 1.6 mm sieve and the granules obtained were partially dried in an oven at 40 ºC for 20 min. The partially dried granules were then passed through 1 mm sieve to obtain nearly uniform sized granules. The granules were transferred to the oven again to completely dry at 40 ºC for 1 h and then packaged in air-tight containers for further use.

Preparation and screening of placebo tablets

Placebo tablets (300mg) were prepared for each formulation of the co-processed excipient by direct compression method using Single Punch Tablet Machine (Erweka, Germany). The tablets were kept for 24 h and then screened for friability, breaking force required to crush the tablets, and disintegration time to select the optimized composition for the study from the results.

Powder characterization

Angle of Repose

A clean glass funnel was clamped on a retort stand such that the perpendicular height of the tip of the funnel was 10 cm from the flat table surface with a clean sheet of paper. A 10 g quantity of each of the samples was poured into the funnel, with opening of the funnel blocked with a cotton wool. The cotton wool was then removed and a powdered heap was formed. The height was measured as *h* (cm), and the diameter of the circumference of the heap was divided to obtain the radius, *r* (cm). The angle of repose was obtained using the equation below:

$$Tan\,\theta = \frac{h}{r}$$ --- Eq. 1

Where θ = angle of repose, h = height of the powder heap and r = radius of heap base

Bulk and Tapped densities, Hausner's ratio, Carr's index

A 10 g (W) quantity of each of the powder samples was placed into a clean 100 mL measuring cylinder and the volume, V_o (bulk

volume), occupied by each of the samples without tapping was noted. The cylinder was tapped 100 times on a hard table top and tapped volume (V_{100}) was recorded. The experiment was repeated in triplicates. The bulk and tapped densities were calculated as the ratio of mass (W) to volume (V_o and V_{100}) respectively. Hausner's ratio was calculated as the ratio of the tapped density to the bulk density, while Carr's index was the percentage difference between the values of the two densities to that of the tapped density.

Flow rate

Ten (10) g of each of the samples was passed through the Erweka flowability tester (Type: GDT, Germany). The time taken for the sample to flow out of the apparatus was recorded. The procedure was repeated three times and the average reading was recorded in gram per seconds (g/s).

Fourier transform infra-red (FTIR) spectroscopy

Fourier transform infrared scan was collected for the samples, MS, AA, PVP and the co-processed excipient at 400-4000 cm^{-1} using FTIR spectrophotometer (CARY-60 Agilent Technologies, California, 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 MicroLab PC software was used for data collection and Agilent Resolution Pro software was used to analyze the data.

Scanning electron microscopy (SEM)

The surface morphologies and sizes of the primary materials and the co-processed excipient were examined using scanning electron microscope (Phenom ProX by Phenom world Eindhoven, The Netherlands). During the experiment, the sample was placed on a double adhesive on a sample stub and then sputter-coated with gold under vacuum in an argon atmosphere prior to observation. The SEM images of the sample were taken at an acceleration voltage of 20 kV at various magnifications.

Tableting

Tablets containing diclofenac as an active ingredient were prepared by direct compression using the optimized co-processed excipient (CPE), Ludipress®, and physical mixture of the primary constituents of the CPE as stated in Table I.

Tablet characterization

The tablets formed were characterized by carrying out the following tests. Test for weight uniformity was conducted on 20 tablets according to the method described by the USP, while the tablet thickness was measured using digital Vernier caliper. The friability of 10 tablets was determined using friabilator (Type TA3R, Erweka, Germany) at a rotation speed of 25rpm for 4 minutes. The tablets were removed, dusted and the percentage of weight loss was determined. The crushing strength of the tablets from each formulation was determined using Monsanto hardness tester (Monsanto Chemical Co., USA).

The disintegration test was performed on six tablets using the disintegration tester (Type ZT3, Erweka, Germany) while the dissolution studies was conducted using dissolution apparatus (Type DT, Erweka, Germany). The dissolution medium used was phosphate buffer solution (pH 6.8), thermostatically maintained at 37±0.5°C.

Table I: Formula for diclofenac tablets incorporating PM LDP and CPE as direct compression excipient.

Ingredients	Tablet formulations					
	PM		LDP		CPE	
	× 1 tab	× 200 tabs	× 1 tab	× 200 tabs	× 1 tab	× 200 tabs
Diclofenac (33 %)	100	20	100	20	100	20
LDP/CPE (65 %)	195	39	195	39	195	39
MST (1 %)	3	0.6	3	0.6	3	0.6
Talc (1 %)	3	0.6	3	0.6	3	0.6
Total (mg, g)	**300**	**60**	**300**	**60**	**300**	**60**

Key: - LDP – Ludipress®**;** CPE – Co-processed excipient; PM – Physical Mixture; MST – Magnesium stearate

The dissolution basket containing the tablet was set to rotate at a speed of 100 rpm. A 10 mL sample was taken from the dissolution medium at different time intervals (5,10, 20, 30, 45, and 60 min) and each volume of the sample withdrawn was replaced with an equivalent volume of fresh dissolution medium maintained at the same temperature. The sample taken was filtered, diluted with the dissolution medium, and the absorbance of the resulting solution was determined using UV spectrophotometer at λ_{max} of 276 nm. The percentage of drug released at each time interval was determined using the equation obtained from standard calibration curve of the pure drug.

The mean of triplicate readings was determined for each of the procedures conducted, and the comparison of results was carried out using one-way ANOVA at 95% confidence interval.

RESULTS AND DISCUSSION

The percentage yield of starch extracted from the maize grains was found to be 35.2 %. A systematic approach was used to produce the co-processed excipients containing MS, AA and PVP. Since the amount of PVP was fixed at 10 % for all the formulations, and the same compaction force was used throughout the compression of the placebo tablets, the variation in the properties of the tablets observed was as a result of the differences in the proportion of MS and AA. The formulations F-3 and F-8 (table II) produced tablets with the most appealing properties in terms of friability, crushing strength and disintegration time. Formulation F-1 which contained higher concentration of AA was expected to produce harder tablets, but produced tablets that were rather softer than F-2 and F-3. This could be due to elastic recovery of the tablets when higher concentration of alginic acid was used (Benabbas *et al.*, 2021). Formulations containing lower amounts of alginic acid produced tablets that were very soft even though they also contain 10% of PVP. This could possibly be as a result of the compression pressure used was not sufficient to produce sufficiently hard tablets when the amount of alginic acid was reduced successively and for the sake of comparison, uniform compression pressure was maintained for all the formulations.

During the second phase of the screening which involved F-3 and F-8 (table III), the tablets produced in both the formulations

were hard and not very friable. Formulation F-3 with higher AA content was able to disintegrate within a shorter period of time compared to F-8. This could be due to the disintegration ability of AA which is correlated to its high-water absorption capacity, and high swelling capacity in water which promote fast penetration of water into the tablet matrix, thereby creating a pressure on the tablet surface which breaks the tablets (Benabbas *et al.*, 2021; Sanchez-Ballester *et al*., 2021).

Table II: Screening of placebo tablets containing co-processed excipients

Formulation	Proportion	Friability (%)	Hardness (Kgf)	Disintegration time (min)
F-1	80:10:10	6.15	4.0 ± 00	13 ± 1.58
F-2	81:9:10	1.20	7.7 ± 0.84	23.2 ± 2.17
F-3	82:8:10	1.18	7.7 ± 1.48	23.4 ± 2.70
F-4	83:7:10	3.21	3.6 ± 0.22	24.8 ± 3.11
F-5	84:6:10	1.95	3.6 ± 0.55	22.8 ± 2.17
F-6	85:5:10	1.15	4.4 ± 0.74	22.8 ± 5.31
F-7	86:4:10	1.95	4.5 ± 0.50	21.0 ± 3.00
F-8	87:3:10	0.40	7.9 ± 0.89	26.8 ± 1.64
F-9	88:2:10	2.44	6.2 ± 0.27	23 ± 2.74
F-10	89:1:10	87.34	2.6 ±0.22	22.2 ± 3.35
F-11	90:0:10	100	1.7 ± 0.27	21.0 ± 2.74

Table III: Screening of diclofenac tablets containing F-3 And F-8 as directly compressible materials

Formulation	Friability (%)	Hardness (Kgf)	Thickness (mm)	Tensile Strength (MN/m^2)	Disintegration time (min.)
F-3	0.66	8.50 ± 0.65	4.91 ± 0.04	0.90 ± 0.01	17.50 ± 1.52
F-8	0.66	8.60 ± 0.42	4.90 ± 0.02	0.91 ± 0.02	28.50 ± 1.64

The flowability of the materials was assessed using flowability indictors which include AoR, CI, HR and FR. Good powder flow is very important in tableting in order to ensure weight and content uniformity of the tablets. The powder flow behavior is governed by a number of factors which include particle size, size distribution,

density, shape and surface properties (Guo and Wu, 2017). The result of the physicochemical properties revealed that the CPE has superior flow properties in terms AoR, CI and HR over the primary materials. This was confirmed from the results of the dynamic flow properties obtained using powder flow rate meter (FR). The improvement in the flow could be as a result of agglomeration of the particles together when the materials were co-processed together. In comparison with LDP however, the results revealed that LDP had better flowability than CPE even though the mean particle size of CPE was higher (table IV). This could be due to the smoother surface texture of the LDP over CPE (Burnett et al., 2011).

Table IV: Physicochemical properties of MS, AA, PVP, CPE and LDP

	MS	AA	PVP	CPE	LDP
BD (g/*mL*)	0.46±0.02	0.27±0.02	0.45±0.01	0.46±0.02	0.52±0.01
TD (g/*mL*)	0.63±0.00	0.44±0.01	0.56±0.01	0.52±0.02	0.59±0.00
HR	1.36±0.05	1.64±0.06	1.22±0.03	1.13±0.04	1.13±0.02
CI (%)	26.40±2.77	39.45±2.04	18.18±1.56	12.14±2.65	11.28±1.28
MPS (µm)	225.8±0.00	180.55±0.00	82.07±0.00	325.6±0.00	156.47±0.00
AoR (°)	43.48±0.70	45.93±0.23	37.22±0.49	26.81±0.77	20.44±1.28
FR (g/sec)	2.10±0.02	0.52±0.04	4.60±0.22	5.47 ±0.36	9.47±0.75

Key: - MS – Ma**ize s**tarch; AA – Alginic acid; PVP – Polyvinyl pyrrolidone; LDP – Ludipress®**;** CPE – Co-processed excipient

FT-IR spectroscopy was conducted to determine whether there was any chemical interaction when the materials were co-processed together. FTIR is an important spectroscopic analysis that is used in pharmaceutical characterizations, quality control, and sample detection (Song *et al.*, 2020). The FT-IR spectra revealed that there was no chemical interaction between the primary materials when they were co-processed together because the characteristic absorption bands observed in the IR spectra of MS, AA and PVP were still maintained in the absorption spectrum of the CPE. This in an indication that the improved functionality observed in the CPE could be attributed to physical modification that occurred within the particles of the materials (Apeji, 2016). The overlay plot confirmed the drug-excipient compatibility as no evidence of the formation of new functional group was observed in the spectrum of the mixture. To further confirm the drug-excipient compatibility, FT-IR of the CPE granules (figure III) was collected, and the overlay plot confirmed that there was no chemical interaction between the CPE and the drug even after granulation where water (which was thought to serve as medium for chemical reaction) was introduced since the principal absorption bands for each spectrum was reflected in the final spectrum of the mixture.

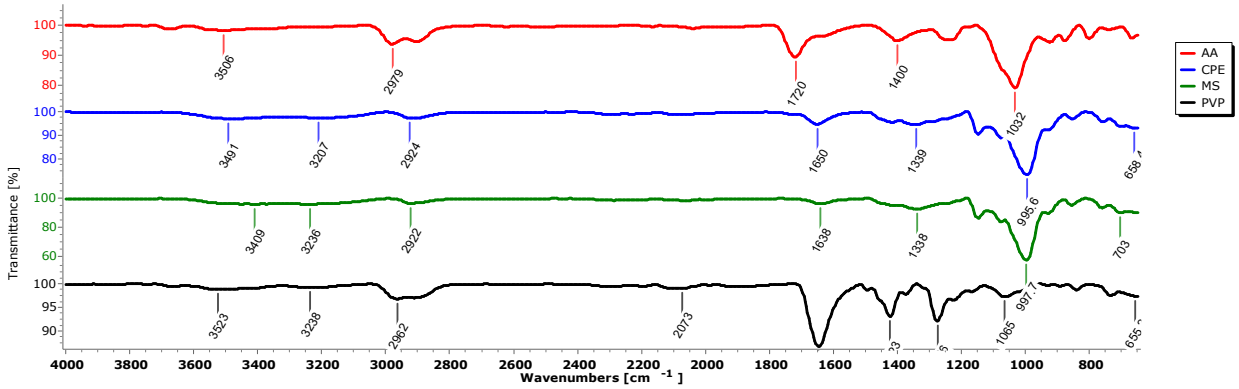

Figure I: FTIR spectra for MS, AA, PVP, and CPE

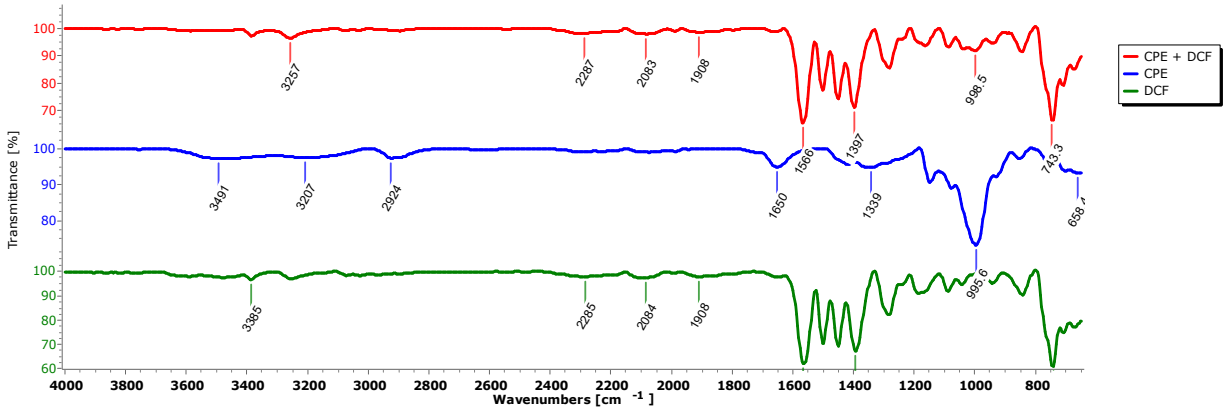

Figure II: FTIR spectra for diclofenac (DCF), CPE and CPE + DCF

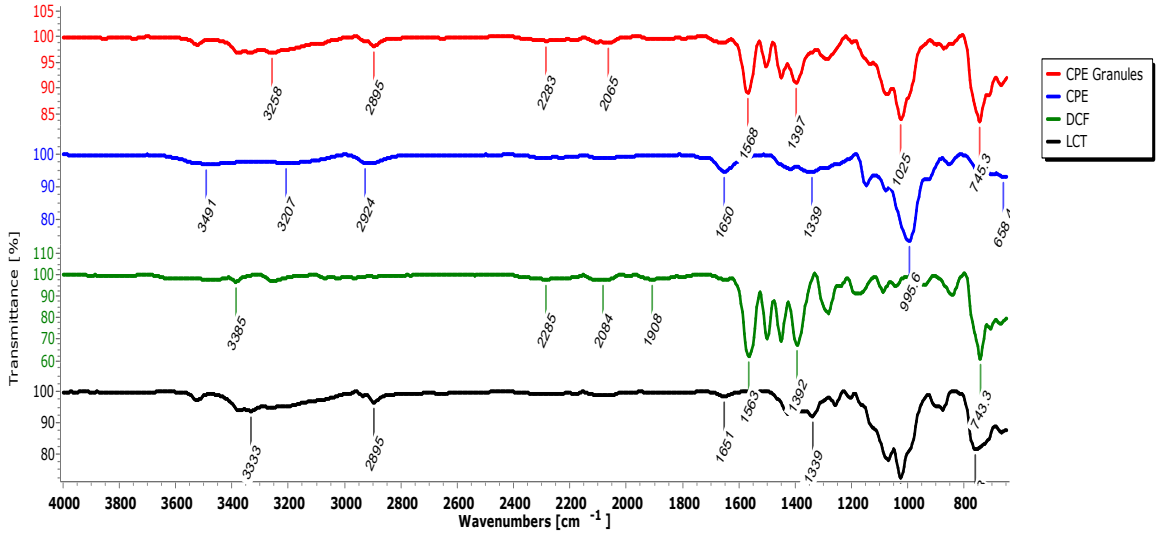

Figure III: FTIR spectra for CPE, lactose, diclofenac and CPE granules

Scanning Electron Microscopy (SEM) was used for identification of the surface morphology and surface topography of the materials. The SEM image of MS revealed

that the particles of MS are spherical and polygonal in shape. This is consistent with result obtained in the study conducted by Odeku and Itiola (2007). The particle morphology of AA showed that its particles are elongated in shape with rough surfaces. This may have contributed to its poor flowing property (Guo and Wu, 2017). The particles of PVP are irregularly shaped, with shiny appearance and are closely bound together because of the adhesive nature of PVP. The particle morphology of CPE showed particles of MS blended with AA and bound together by PVP with shiny appearance which may have been conferred to them by the PVP.

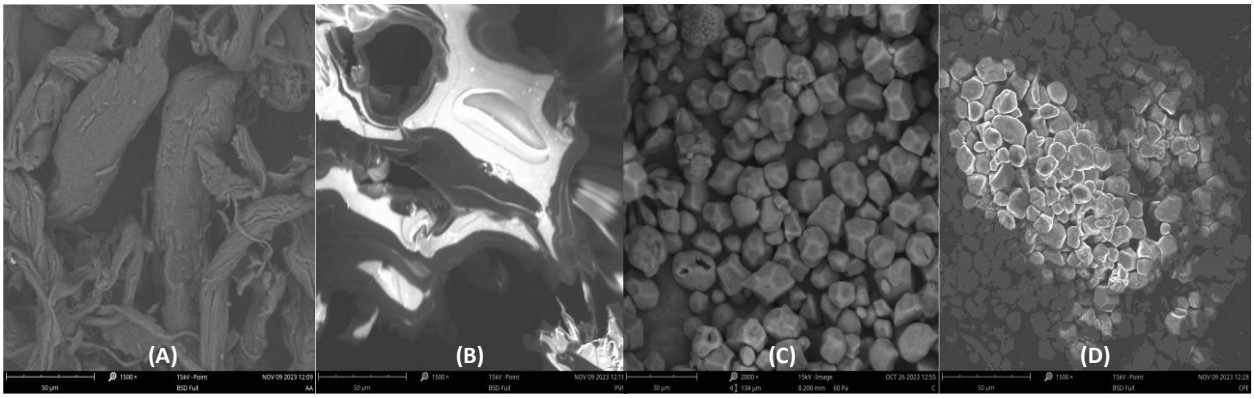

Plate I: SEM images of (A) AA, (B) PVP, (C) MS and (D) CPE

Compendial and non-compendial tests were carried out to validate the tablets as to whether they conform to the standard specifications or not. The test for the uniformity of weight is a simple way to assess the variation in content of drug dose, which makes the test useful as a quality control procedure during tablet production. The results of the mean tablet weight of diclofenac tablets showed that all the tablets have passed the specification for weight variation according to the USP/NF (2009). This is evidence that the materials used during the tableting had a uniform flow of the powder volumes from hopper into the die cavity (Apeji, 2016). Tablet friability is the measure of ability of the tablets to withstand stress during processing and transportation. According to USP/PF (2016), there should be no cracked, cleaved or broken tablets, or loss in weight greater than 1% after tumbling for a formulation to be considered as acceptable. From the results obtained, only CPE passed friability study, but LDP and PM failed. The reason for the failure of LDP in friability testing even though the tablets were hard could be due to capping of the tablets which was observed during the tableting. The friability failure of the CPE-PM could be due to lack of solid bridges which helps in joining two or more particles together (Stuart, et al., 2016).

Tablet hardness or crushing strength is an indicator of the strength of tablets (Okpanachi *et al.,* 2013). Materials that bond together well would form tablets with high crushing strength. Although, a tablet is expected to be hard, it is also expected to disintegrate and release the drug in it for absorption, thus a minimum requirement of 4 kgf crushing strength is said to be satisfactory (Oluwaseun *et al.*, 2017). From the results, all the tablet formulations have passed crushing strength except CPE-PM. The failure of CPE-PM could be due to lack of solid bridges which helps in joining two or more particles together to form a stable compact (Stuart *et al.*, 2016).

The ability of compressed tablets to release drug is measured by the disintegration test which is the time it takes for a dosage form to break into primary particles upon exposure to a suitable medium with occasional mild agitation. For a conventional immediate release (uncoated) tablets, disintegration should not exceed 15 min. The study revealed that all the tablet formulations conformed to the official specification for tablet disintegration. The length of the disintegration time is in the order of CPE>LDP>CPE-PM.

Table V: Properties of diclofenac tablets containing CPE, LDP and PM as directly compressible materials

Formulation	Weight Variation (mg)	Friability (%)	Crushing Strength (kgf)	Thickness (mm)	Disintegration time (min)
CPE	305±5.27	0.77	7.9±0.85	4.66±0.04	13.60±1.30
LDP	291±7.38	1.16	7.6±0.82	4.59±0.02	9.47±1.37
PM	298±7.89	100	0.88±0.11	5.79±0.14	8.70±1.47

Key: - LDP – Ludipress®**;** CPE – Co-processed excipient; PM – Physical Mixture

Drug dissolution is the process by which drug molecules are liberated from a dosage form and go into solution. This is an important process because only drugs in solution are absorbed into the body to produce the desired pharmacological effect. Dissolution rate of the drug molecule is a critical factor to drug absorption and for many drug formulations, it is the rate limiting step. According to BP (2002), 75% of the drug should be released within 45 min. The study revealed that all the batches of the tablets have passed dissolution test as more than 75 % of diclofenac was released within 45 min in all the tablet formulations.

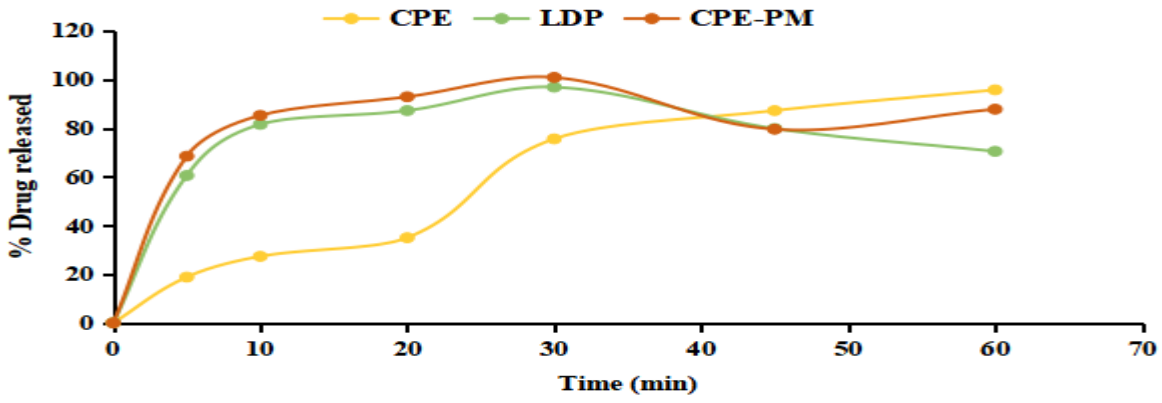

Figure IV: *In-vitro* Drug Release Profile of Diclofenac Tablets Containing CPE, LDP and CPE-PM as Directly Compressible Excipients

CONCLUSION

From the studies conducted, it was observed that the co-processed excipient developed exhibited better flow properties compared to

the native starch, alginic acid and PVP, and the excipients used for the co-processing were compatible with one another and with the drug used in the formulation. It also revealed that the co-processed excipient exhibited desirable characteristics required for tableting by direct compression method, and compared well with the Ludipress® counterpart ($p < 0.05$). The developed co-processed excipient can therefore serve as an alternative to the existing commercial excipients in the formulation of tablets by direct compression.

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