Development and Characterization of a Microcrystalline Cellulose-based co-Processed Excipient using Design of Experiment Approach

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ABSTRACT

The study aims to develop a co-processed excipient (CPE) containing microcrystalline cellulose (MCC) and crospovidone (CPV) using the wet massing technique. Preformulation studies were carried out on CPE to characterize its physicochemical properties. Optimization of the formulation of CPE was carried out using a mixture of experimental designs. The optimization study suggested a composite excipient containing MCC (99 %) and CPV (1 %). Solid state characterization of CPE revealed a material that is predominantly crystalline in nature. The particle size of CPE increased in comparison to starting material. FT-IR confirmed the compatibility of MCC and CPV when co-processed together to yield a single composite excipient. There was a decrease in moisture content and moisture sorption capacity of CPE when compared to MCC. Powder characterization revealed an improvement in bulk flow properties of CPE relative to MCC. In summary, the physicochemical properties obtained suggest that CPE will be a suitable tableting excipient in solid dosage formulation by direct compression.

Keywords: Microcrystalline cellulose, crospovidone, co-processing, optimization, particle engineering, tablet.

1. INTRODUCTION

Excipients are a necessary requirement in tablet formulations because of their diverse functionalities [1,2]. They are rightly called functional components of a formulation because they influence the performance of the dosage form, hence they are crucial in determining the success of the formulation. For most formulations, excipients constitute about 60 - 80 % by weight. Considering the impact that excipients have on solid dosage form development, it has become necessary to keep developing excipients with improved functionality and performance.

Over the years, co-processing as a particle engineering technique has been applied by many researchers to develop high-functionality excipients [3]. This process involves the combination of two or more excipients at sub particle level with the aim of synergizing the superior qualities of the component excipients in composite particles while minimizing the limitations of the component excipients [4,5]. The functional attributes acquired by the co-processed excipient have been linked to physical changes occurring at the particle level with little or no change occurring chemically [3]. Performance evaluation of co-processed excipients have shown improvements in flowability, compressibility, dilution potential, lubricant sensitivity, disintegration and dissolution when compared to the individual excipients and their physical mixtures [6]. Many of the co-processed excipients developed so far have been commercialized and integrated into the mainstream of pharmaceutical development e.g., Prosolv®, Ludipress®, StarLac®, etc.

A typical excipient that has been used in the tablet formulation is microcrystalline cellulose (MCC). MCC is a pure partially depolymerized cellulose synthesized from

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α-cellulose precursor (type Iβ), obtained as a pulp from fibrous plant material, with mineral acids, hydrochloric acid, used to reduce the degree of polymerization [7]. Since its introduction in late 1950s, MCC has been recognized as the single most important tablet excipient developed in modern times. Many studies have proven MCC to be a utility excipient and it remains the most widely used direct compression excipient serving as a dry binder, disintegrant, an absorbent, diluent, a lubricant, and anti-adherent [8]. MCC is commercially available in different particle sizes, density, and moisture grades that have different properties and applications. Among the most commonly used grades of MCC are Avicel PH 101 and Avicel PH 102 (FMC Corporation, USA). Avicel PH 101 is the original grade of MCC, while PH 102 is available as a partially agglomerated product with a larger particle size and slightly better flowability. However, both grades do not differ significantly in their compressibility. Currently, MCC is the most compressible of all direct compression fillers and has the highest dilution potential and capacity [9]. Nonetheless, MCC has been shown to exhibit poor disintegrating property when used in concentrations exceeding 20 % as a multifunctional excipient in direct compression formulations [10,11]. Disintegration facilitates the release of the drug from the tablet and makes it available for action. Thus, the performance of the tablet dosage form has been linked to its ability to disintegrate readily when it comes into contact with the gastrointestinal (GI) fluid. It is therefore imperative to improve the disintegration profile of MCC as a multifunctional excipient in direct compression formulations. Hence, the goal of this study was to develop an MCC-based co-processed excipient with improved capacity for disintegration when used as a direct compression excipient in tablet formulation. This study will focus on optimizing the formulation of the co-processed excipient containing MCC and CPV using the design of experiment (DoE) approach and characterizing its physicochemical properties. To the best of our ability, no co-processed excipient exists combining MCC and CPV alone in composite particles. The choice of both excipients was based on their material and functional properties: MCC is a direct compression binder and deforms by plastic deformation[12] while CPV is a super disintegrant that yields by brittle fracture under the effect of pressure [13,14].

2. General Experimental

2.1. Materials

Paracetamol (Burgoyne Burbidge's and Co. Laboratory Chemical Mumbai, India), Microcrystalline cellulose, PH. Eur. NF, JP (VIVAPUR® 102), Crospovidone (Viva Pharm® PVPP XL-10), (JRS Pharma, Rosenberg, Germany).

2.2. Experimental Design

Design of Experiment (DoE) was employed to optimize the composition of the CPE containing MCC and CPV. Multivariate experiments were generated using the Simplex Lattice Mixture Design (Design-Expert ver. 12, Stat-Ease, Inc., Minneapolis, MN 55413, US) to quantify the impact of varying the composition of CPE on tablet properties. The input variables of MCC and CPV ranged from 90 – 99 % and 1 – 10 % respectively. Ten (10) experimental formulations of CPE were prepared based on the composition of the mixture design experiments given in **Table 1.** Tablets were prepared by mixing 100 mg of paracetamol, 396 mg of CPE and 4 mg of magnesium stearate to obtain an approximate weight of 500 mg for each tablet. Tablet formulations were compressed directly on a Single Punch Tablet Press using 12 mm flat-faced punches at a compression load of 7 KN. The tablet properties of tensile strength and disintegration time were evaluated as response variables for the design and data obtained was fitted into regression models. Model fitting and analysis was done using analysis of variance (ANOVA) integrated in the Design Expert Software and mathematical equations were generated for each response to quantify the impact of each input variable on the response. Two component mixture plots were drawn for each response to determine the optimum level content for each component of the co-processed excipient.

Table 1. Composition of Mixture Design Experiments

	Components	
Formulation	**MCC (%)**	**CPV (%)**
1	96	4
2	93	7
3	99	1
4	92.25	7.75
5	96.75	3.25
6	90	10
7	99	1
8	90	10
9	99	1
10	94.5	5.5

MCC – Microcrystalline cellulose, CPV – Crospovidone

2.3. Preparation of CPE

About 100 g of CPE was prepared by wet massing technique as described by Goyanes et al [15] with modifications. The quantities of MCC and CPV were calculated based on the optimized composition, weighed out on an electronic balance (Mettler, Philip Harris Ltd, England) and mixed for 5 min using a mortar and pestle. The powder blend was further massed with 20 mL of distilled water and the wet mass was screened through a 0.5 mm sieve to achieve uniformity in particle size. The co-processed material was then allowed to dry in an oven (Gallenkamp Oven BS size 3, England) at 40 ^{0}C for 1 h and kept in an airtight container for further studies.

2.3.1. Particle Size Analysis

Particle size analysis was carried out by optical microscopy using a light microscope (Fisher Scientific Company, Kent, UK). A minimum of 100 particles were counted for each sample using a calibrated eyepiece micrometer for measurement and the parameter of d_{50} was determined for each sample.

2.3.2. Scanning Electron Microscopy (SEM)

Particle shape and morphology of MCC, CPV 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.

2.3.3. Powder X-ray Diffraction

X-ray diffraction analysis was carried out on MCC, CPV 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 º on a 2θ scale, measuring the angle between the emitted ray and the reflected ray. The raw data obtained were analysed with DIFFRAC plus EVA, version 9.0 (Bruker, AXS, Karlsruhe, Germany) diffraction software.

2.3.4. Differential Scanning Calorimetry (DSC)

DSC thermograms of MCC, CPV, and CPE were collected using a DSC Q2000 (TA Instruments, Delware, USA). Samples weighing 5 mg were deposited in standard aluminium pans with perforated lid and heated at a rate of 10 ºC/min from 25 ºC to 200 ºC. Data acquisition was performed under an inert atmosphere of nitrogen at a flow rate of 50 mL/min. The DSC cell was previously calibrated with high-purity indium as metallic standard. Analysis of scan was carried out using the Universal Analysis software, version 4.5A (TA Instruments, New Castle, DE, USA).

2.3.5. Fourier-Transformed Infra-red (FT-IR) Spectroscopy

IR scans of MCC, CPV, and CPE were collected over a range 4000 – 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 MicroLab PC software was used for data collection and SpectraGryph 1.2 - spectroscopy software was used to analyse the data.

2.3.6. Angle of Repose, Bulk and Tapped Densities

Angle of repose of MCC, CPV and CPE was measured

using the fixed funnel method [16]. 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 Eq. 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.

$$Tan\ \theta\ = \frac{2h}{d} \ldots\ldots\ldots\ldots Eq.1$$

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

Bulk and tapped volumes of the powders were determined according to the method were specified by USP [17] and the densities calculated using Eq. 2 & 3 respectively. The parameters of Carr's index (CI) and Hausner's ratio (HR) were computed using Eq. 4 & 5 respectively. A mean of three replicates with standard deviation was recorded for each parameter.

$$Bulk\ Density\ (BD) = \frac{weight}{Bulk\ volume\ (V_B)} \ldots\ldots\ldots\ldots \text{Eq. 2}$$

$$Tapped\ density\ (TD) = \frac{weight}{Tapped\ volume\ (V_T)} \ldots\ldots\ldots\ldots \text{Eq. 3}$$

$$CI = \frac{TD - BD}{TD} \times 100\ \% \ldots\ldots\ldots \text{Eq. 4}$$

$$HR = \frac{TD}{BD} \ldots\ldots\ldots\ldots\ldots \text{Eq. 5}$$

2.3.7. Swelling Capacity

To measure swelling capacities of MCC, CPV and CPE, 1 g sample of each material was poured into respective 100 mL measuring cylinders and the tapped volume occupied by each sample was noted as V_1. Water was added to the various samples to the 100 mL mark in the measuring cylinder. After 24 h of standing, the final volume of the sediment was recorded as V_2 and swelling capacity was calculated using the equation below:

$$S = \frac{V_2 - V_1}{V_1} \times 100 \ldots\ldots\ldots\ldots \text{Eq. 6}$$

Moisture content and Moisture sorption capacity

The residual moisture present in the samples of MCC, CPV and CPE was determined by gravimetric analysis. Each powder sample (1 g) was dried to constant weight at 105 °C. Moisture content was calculated using Eq. 7 and expressed as the percentage weight loss.

$$\frac{Initial\ weight - Final\ weight}{Initial\ weigt} \times 100 \ldots\ldots\ldots \text{Eq. 7}$$

Moisture sorption capacity for each material was determined using a 1 g sample. Each sample was exposed to a RH=75 % in a desiccator containing saturated solution of NaCl in its reservoir. The samples were kept at room temperature (25 ± 2 °C) in this controlled environment for a period of five days and the amount of moisture sorbed over this period was calculated as the weight gain expressed in percentage.

3. RESULTS AND DISCUSSION

3.1 Optimization studies

Several formulations of CPE were prepared and screened to optimize the composition of CPE. A summary of the tablet responses obtained for each experimental formulation is presented in **Table 2**. Tensile strength values ranged from 0.24 – 1.1 MPa and was found to be higher in formulations containing higher concentrations of MCC. Tablets also disintegrated in less than a minute across all the investigated formulations with rapid disintegration times recorded with formulations containing higher concentrations of CPV. Hence, increasing the concentration of MCC produced stronger tablets with relatively longer disintegration times while the reverse was the case when the concentration of CPV increased. This increase in tensile strength has been attributed to the excellent binding characteristics of MCC as a direct compression excipient [7,18]. The mechanical properties of MCC demonstrates a high degree of plasticity during

compression giving rise to tablets with higher tensile strength that takes a longer time to disintegrate [19]. This has been attributed to extensive hydrogen bonding during plastic deformation leading to an increase in bonding surface area and bond strength [7]. This agrees with the findings of Apeji et al [20] who studied the impact of several binders including MCC on the tableting properties of co-processed excipient developed using these binders. The co-processed excipient containing MCC performed better in terms of tensile strength as a result of plastic deformation characterized by a lower yield pressure.

The overall effect of CPV on tensile strength and disintegration of CPE has been attributed to its super disintegrating properties. The effect on tensile strength may be due to the micronized particle size of CPV as observed during particle size analysis (**Table 4**), where the particle size ranged from 10 -120 μm. Due to its relatively small particle size, CPV may have been adsorbed onto the surface of MCC during co-processing thereby lowering the bonding surface area and bonding strength of MCC particles resulting in a reduction in tensile strength of tablets. The corresponding effect on disintegration time has been associated with a reduction in tensile strength of tablets. Tablets of lower tensile strength are expected to disintegrate faster due to the relatively weak interparticulate bonding matrix and increased porosity of the tablet. The rapid disintegration time observed with increasing concentrations of CPV may be linked to its cross-linked structure [21]. CPV is a water insoluble synthetic cross-linked polyvinylpyrrolidone that exerts its disintegration effect primarily by strain recovery and to a lesser extent by wicking and secondary swelling [22]. Kaur et al [23] repo super disintegrant concentration of super disintegrant is above a critical level of 5 %, the disintegration time remains almost constant. This explains why formulations of CPE containing higher concentrations of CPV exceeding 5 % maintained a constant disintegration time between 10 - 20 s at higher concentrations.

Table 2. Response Results of Tensile Strength and Disintegration time of the Mixture Design Experiments

	Responses	
Formulation	**TS (MPa)**	**DT (min)**
1	0.63±0.08	0.23±0.02
2	0.46±0.06	0.1±0.04
3	1.09±0.13	0.84±0.3
4	0.4±0.04	0.11±0.01
5	0.69±0.25	0.28±0.17
6	0.24±0.05	0.13±0.01
7	1.1±0.14	0.78±0.38
8	0.27±0.07	0.13±0.03
9	1.09±0.27	0.93±0.7
10	0.51±0.08	0.20±0.09

3.2. Summary Statistics for the Model

Summary statistics for the models selected for each response variable is given in Table 3. Each model was significant for the corresponding response variable at $p < 0.05$, justifying their selection. The goodness of fit of the model denoted by R^2 was high for both responses indicating a high degree of correlation between the experimental and predicted responses. The Pred R^2 was in reasonable agreement with the Adj R^2 as their difference did not exceed 0.2. This implies therefore that the model selected for each response was reliable. The lack-of-fit statistic was found to be insignificant at $p < 0.05$ for both responses implying that the model selected fits the design. An adequate precision greater than 4 was obtained for both responses implying that the models selected had adequate signal to navigate the design space for the purpose of searching for optimum solutions.

The models for both responses were transformed by inverse Sqrt as recommended to improve the fitness of the model to the design.

Table 3. Model Summary Statistics

Response	Source	Std dev	R^2	Adj R^2	Pred R^2	Adeq. Precision	Seq. *p*-value	Lack of fit *p* value
TS	Linear	0.167	0.837	0.816	0.768	12.07	0.0002	0.198
DT	Quadratic	0.375	0.837	0.790	0.700	8.56	0.0187	0.115

The coded equations in terms of pseudo-components for tensile strength (TS) and disintegration time (DT) is given below in Eq. 8 & 9:

$$1/Sqrt\ (TS)\ = +1.09 * A\ + 1.93 * B \ldots\ldots\ldots\ldots. \ Eq. 8$$

$$1/\ Sqrt\ (DT)\ = +1.26 * A\ + 2.76 * B\ + 3.37 * AB \ldots\ldots\ldots\ldots. \ Eq. 9$$

Where A and B represents the relative proportions of MCC and CPV respectively in the co-processed excipient.

The coded equations given above was useful in identifying the relative impact of each factor variable on the response by comparing the factor coefficients. The two-component mix plots based on the equations above for both responses are given in Figures 1 & 2.

Figure 1 is a two-component mix plot illustrating the effect of each factor variable on tensile strength (TS). The plot shows that TS increases with increase in the proportion of MCC and decreases with increase in the proportion of CPV.

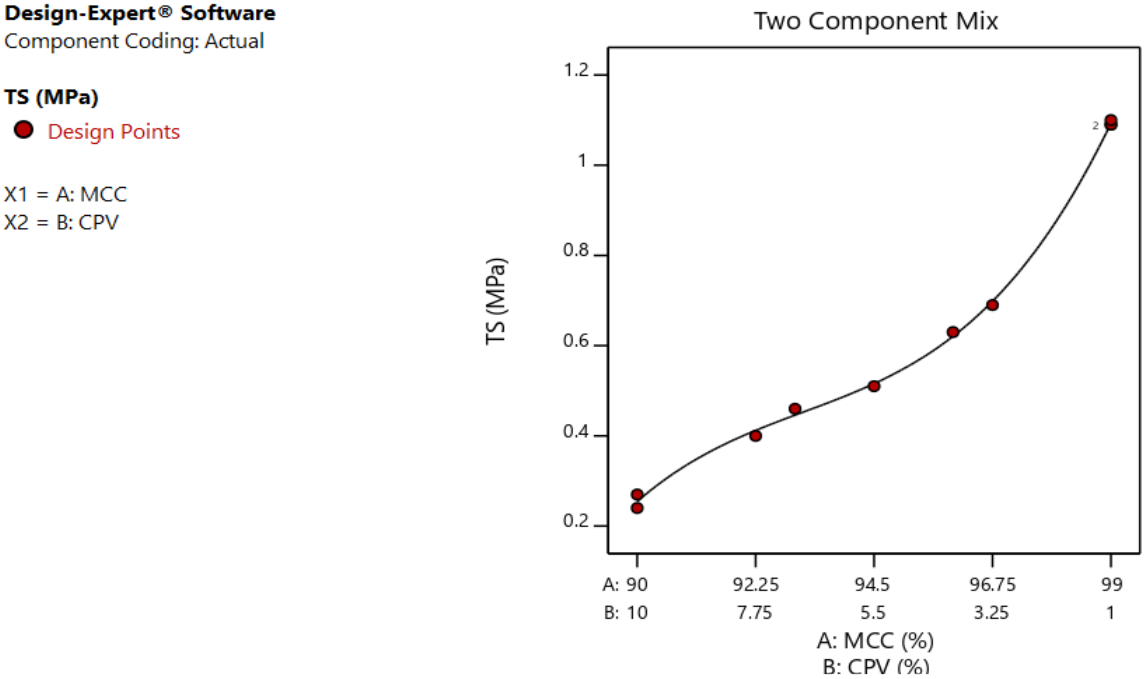

Figure 1. Two-component mix plot showing the effect of the factor variables, MCC and CPV, on tensile strength of tablets

Figure 2 is a two-component mix plot illustrating the effect of each factor variable on disintegration time (DT). The plot shows that DT increases with increase in the proportion of MCC and decreases with increase in the proportion of CPV.

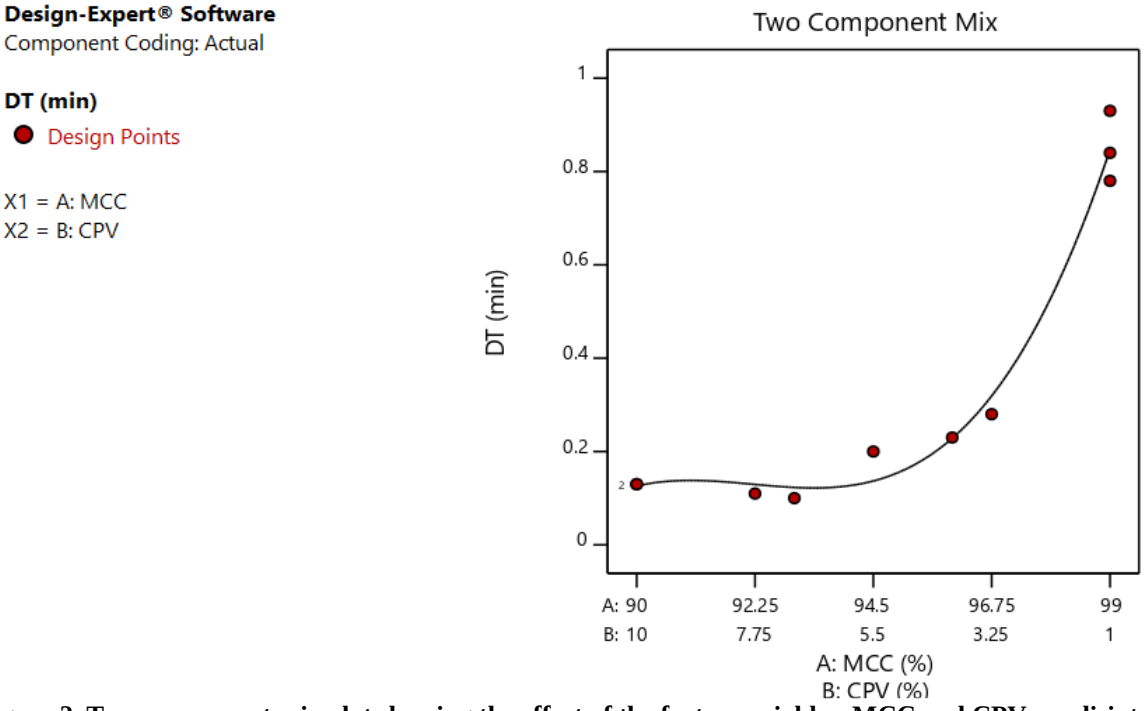

Figure 2. Two-component mix plot showing the effect of the factor variables, MCC and CPV, on disintegration time of tablets

Formulation Optimization and Validation

Numerical optimization was performed using statistical models to find the optimal formulation of the co-processed excipient (CPE). The tablet tensile strength was set to maximum, and the disintegration time minimized as criteria for selecting an optimum formulation of CPE. According to the statistical prediction, the optimal formulation was:

MCC – 99 %

CPV – 1 %

TS – 0.948 MPa

DT – 0.632 min

Desirability – 0.953

An experiment was performed using the selected mixture to validate the different response models. All the observed results of the measured responses were within the prediction intervals and in good agreement with the predicted results (Table 4).

Table 4. Predicted and observed results of the optimized formulation (CPE)

Factors/Responses	Criteria	Predictions	Observations
MCC	In range (90 – 99 %)	99 %	99 %
CPV	In range (1 – 10 %)	1 %	1 %
TS	Maximize (0.24 – 1.09 MPa)	0.948 MPa	0.88 MPa
DT	Minimize (0.1 - 0.93 min)	0.632 min	0.76 min

3.4. Solid State Characterization

The SEM images for CPV, MCC and CPE are presented below in Figure 3. Particles of CPV are smaller in size, appearing as aggregates of primary particles. Particle morphology of MCC appears irregular and fibrous with some degree of roughness of the surface. CPE particles appeared to have the same surface morphology and shape of MCC possibly because MCC constitutes 99 % of CPE. Materials characterized by irregular shape and rough surfaces tend to bind more firmly and form solid compacts owing to the effect of mechanical interlocking [24]. Particle morphologies of MCC as examined by SEM showed that MCC is primarily composed of irregularly shaped particles with intercalated microfibrillar structure (**Figure 3**). Co-processing of MCC with CPV had little or no effect on the morphological appearance and shape of MCC which may be due to the relatively low proportion of CPV present in the co-processed excipient. The improvement in particle size and flow behaviour of CPE may therefore be attributed to the method of co-processing as a particle engineering technique rather than the presence of CPV in its particulate structure.

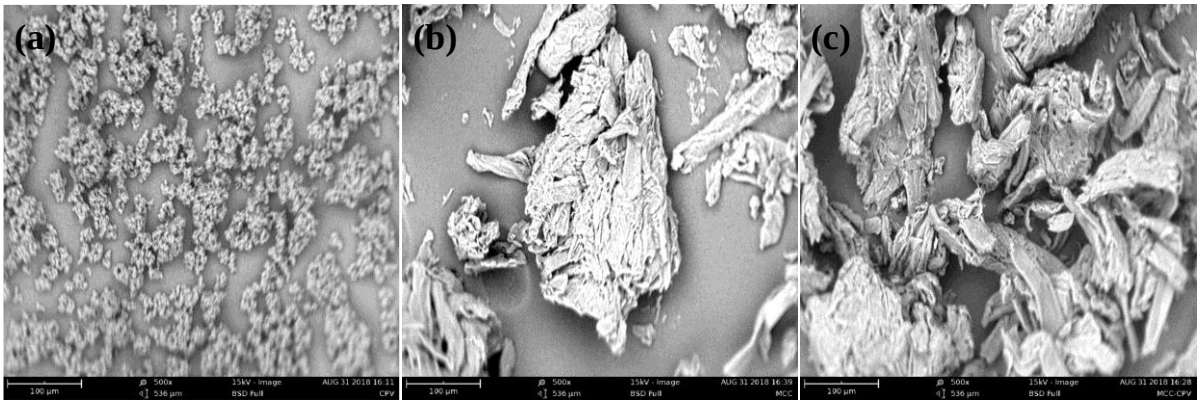

Figure 3. SEM images of (a) CPV, (b) MCC, and (c) CPE

The diffraction curves of CPE, MCC and CPV are presented in Figure 4. The diffraction patterns of CPE and MCC are characterized by three distinct peaks occurring at angles 15°, 16.4°, and 22.5° on the 2 Theta scale. The PXRD pattern obtained for MCC corresponds to that reported by Rojas et al.[26] confirming the crystalline nature of MCC. This implies that MCC crystallinity was maintained in CPE. Crystalline materials are characterised by prominent, sharp diffraction peaks which correlate with the degree of crystallinity of the material and is typical of most active pharmaceutical ingredients (API) that occur as crystals and some excipients like MCC. However, most excipients are classified as predominantly amorphous in nature and therefore do not produce sharp diffraction peaks when exposed to X-ray [27]. The diffraction curve of CPV shows a halo pattern suggesting that the material is amorphous. The diffraction peaks identified in MCC were maintained in CPE suggesting that CPV and MCC are compatible. Co-processing MCC with CPV did not alter the crystallinity of MCC implying that there was no modification of the molecular structure of MCC as a result of processing. Although CPV produced a diffraction halo pattern that corresponds to amorphous materials [28,29], it was not sufficient to cause a significant change in the crystallinity of MCC possibly because of the low proportion of CPV employed in co-processing. For tableting purposes, excipients that are largely amorphous are preferred because of their superior compressibility [30].

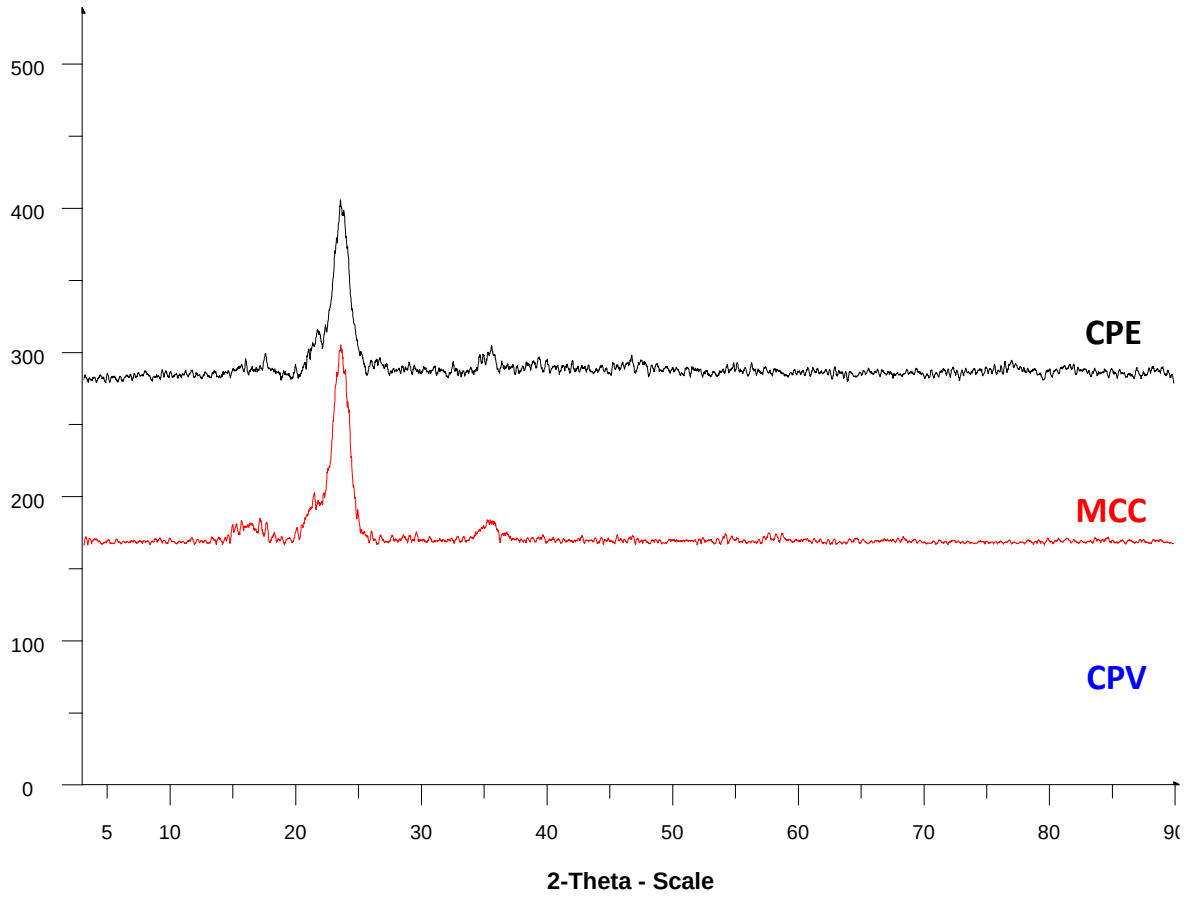

Figure 4. PXRD patterns of CPV, MCC and CPE

Overlay plots of the DSC thermograms of CPE, CPV, and MCC is presented in Figure 5. All three materials showed an endothermic transition corresponding to loss of moisture occurring between 50 – 100 ° C. A greater degree of moisture loss was observed with MCC owing to its higher moisture content (14 %) (**Table 5**). Moisture loss possibly occurred as a result of dehydration during heating of the sample [31]. The DSC scans of MCC and CPE were not characterized by a melting phase transition because of the strength of intermolecular interaction between polymeric strands and the high molecular weight of MCC which results in thermal degradation rather than melting at elevated temperatures [7]. This is consistent with the findings of PXRD as shown above in **Figure 4**. However, the absence of a melting peak for CPV corresponds to its amorphous nature.

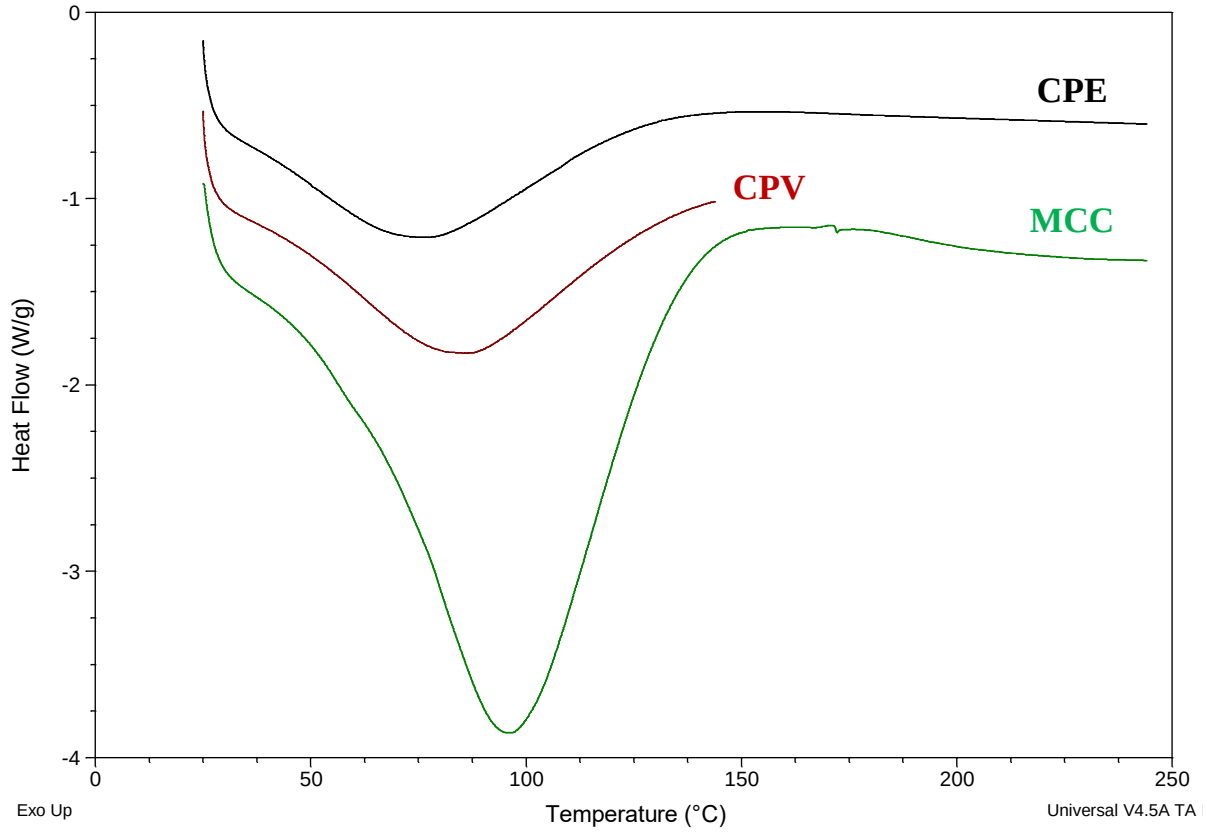

Figure 5. DSC thermograms of CPV, MCC and CPE

FT-IR spectra for MCC, CPV and CPE is displayed as **Figure 6**. The IR spectrum of MCC showed absorption bands occurring at the following frequencies: 3331 cm^{-1} (O-H stretching), 2894 cm^{-1} (C-H stretching), 2322 cm^{-1} (O=C=O stretching), 1636 cm^{-1} (C=C stretching), and 1314 cm^{-1} (O-H bending). This finding was consistent with that reported by Ciolacu et al [32]. The IR spectrum of CPV was characterized by absorption bands appearing at the following frequencies: 3391 cm^{-1} (N-H stretching), 2324 cm^{-1} (O=C=O stretching), 1648 cm^{-1} (C=O stretching), 1423 cm^{-1} (C-H bending), 1283 cm^{-1} (C-N stretching), 842.8 (C=C bending). These absorption bands were replicated in CPE implying that co-processing MCC and CPV did not result in any significant chemical reaction. This agrees with some findings in literature reporting the absence of chemical change during co-processing [33,34]. The absorption bands of MCC predominated in the IR spectrum of CPE owing to its higher proportion (99 %) in the co-processed excipient (CPE). There was no shift in position, or the appearance/disappearance of peaks as observed in the FTIR spectrum of CPE, revealing that there was no chemical interaction or modification of the interacting excipients during coprocessing. Excipient-Excipient compatibility was therefore established by FT-IR.

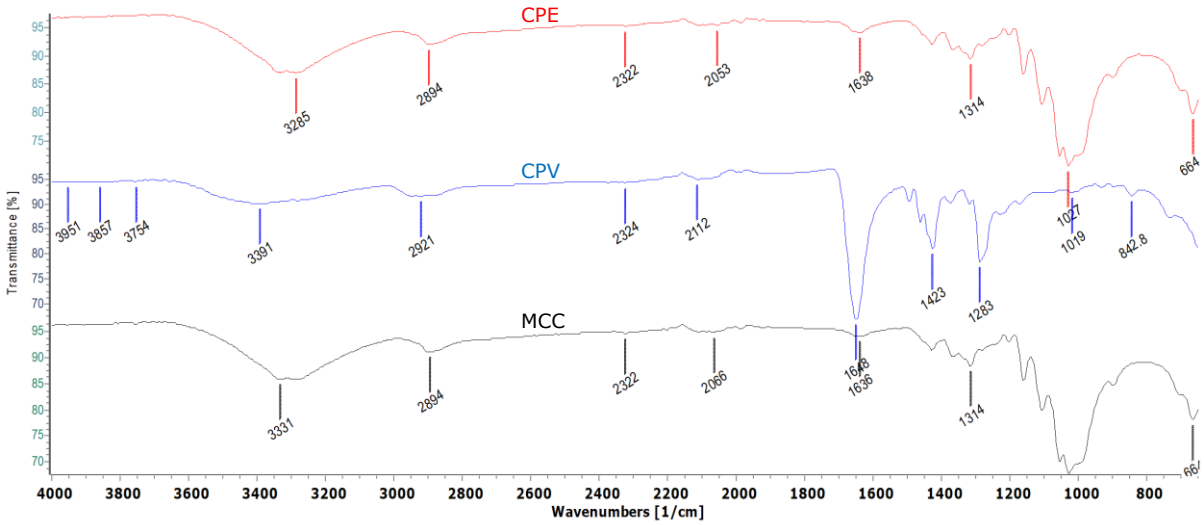

Figure 6. FT-IR spectra of CPV, MCC and CPE

3.5. Powder Properties

Powder properties of MCC, CPV and CPE are presented in **Table 5** showing the mean and standard deviation values in parenthesis. Based on the median diameter (d_{50}), CPE had the largest particle size while CPV had the smallest particle size. Particle size increased as a result of co-processing. This is consistent with the findings of other studies carried out involving co-processing where the co-processed excipient developed had a larger particle size relative to the constituent excipients [35,36]. The angle of repose values was ranked in the following order, CPE<MCC<CPV, with CPE having a value of 18.23 º and CPV having a value of 43.90 º. As a general rule, values of angle of repose < 30 º corresponds to free-flowing powders [37]. The flow properties of MCC were improved as a result of co-processing giving rise to CPE with an angle of repose < 30 º (**Table 5**). Particle size enlargement of CPE translated to an improvement in the flow behaviour of CPE as reported in **Table 5**. This can be attributed to a reduction in interparticulate friction and cohesion between particles that normally hinders free flow of powders [38]. Many studies have reported a correlation between particle size and flow characteristics of the powder with an increase in particle size leading to enhanced flowability [39]. The flow behaviour of a co-processed excipient designed for direct compression is a critical material attribute that is required for the robust formation of tablets by direct compression [3]. The improved flow of CPE will most likely impart flowability to the powder mix giving rise to uniformly sized tablets in weight and drug content.

Higher porosity values were obtained for MCC and CPE in comparison to CPV indicating that MCC and CPE had a greater degree of porosity compared to CPV. This corresponds well with the swelling capacity of all three materials as highly porous MCC gave rise to a greater degree of swelling (MCC>CPE>CPV) as seen in **Table 5**. The ability of a material to swell in the presence of water is a function of its hydrophilicity, wetting and hydration potential [40,41].

Table 5. Powder Properties of MCC, CPV and CPE

Parameters	**MCC**			**CPV**			**CPE**		
	D_{10}	**D_{50}**	**D_{90}**	**D_{10}**	**D_{50}**	**D_{90}**	**D_{10}**	**D_{50}**	**D_{90}**
Particle size (µ)	70	100	170	20	40	70	90	180	280
Angle of Repose (°)	28.07 (2.30)			43.90 (4.65)			18.23 (1.70)		
Bulk Density (g/mL)	0.32(0.004)			0.60 (0.01)			0.34 (0.01)		
Tapped Density (g/mL)	0.40 (0.01)			0.78 (0.01)			0.45 (0.004)		
Carr's Index (%)	19.42 (1.77)			23.83 (1.75)			23.65 (0.93)		
Hausner's Ratio	1.24 (0.03)			1.31 (0.03)			1.31 (0.03)		
Porosity (%)	78.25 (0.73)			51.88 (0.78)			76.78 (0.28)		
Swelling capacity (%)	25			11.11			16.67		
Moisture Content (%)	14			8			3		
pH	7.5			7.6			7.5		

MCC – Microcrystalline cellulose, CPV – Crospovidone, CPE – Co-processed excipient

There appeared also to be a link between porosity and moisture sorption capacity as shown in **Figure 7** where highly porous MCC had the highest moisture retaining capacity. This implies that MCC has a higher degree of hygroscopicity compared to CPE. Moisture content was found to be higher for MCC (14 %) when compared to that of CPV (8 %) and CPE (3 %).

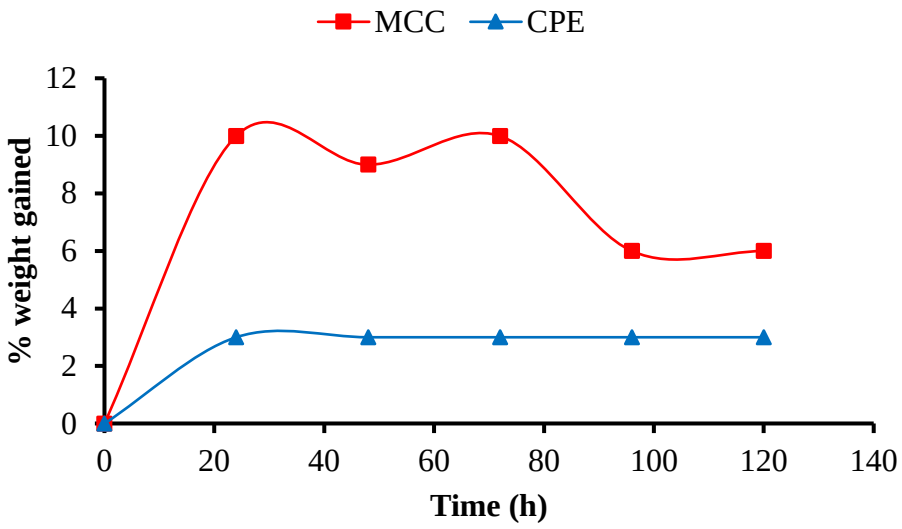

Figure 7. Moisture sorption capacity of MCC and CPE

The reduction in moisture content of CPE suggests that co-processing MCC with CPV lowered its capacity to adsorb or retain moisture as evidenced by the moisture sorption capacity (**Figure 7**). The improvement in flow property of CPE may also be attributed to its low moisture content considering the impact moisture content has on bulk powder properties like flowability and compressibility [42,43]. For the purpose of maintaining the stability of a formulation or product, it is necessary to use excipients that are less hygroscopic or non-hygroscopic to guide against instability during development and storage. A similar study involving the co-processing of mannitol and crospovidone was carried out by Katsuno et al [44] and yielded a product with good stability profile, rapid disintegration and increased hardness of the tablets. Other studies have also reported that co-processing with crospovidone yielded a product with good flowability and low hygroscopicity [45].

4. CONCLUSION

The goal of the study was to optimize the formulation of a co-processed excipient containing MCC and CPV and characterize the physicochemical properties to determine its suitability for tableting in direct compression formulations. The formulation of the co-processed excipient (CPE) was optimized to yield a composition of MCC (99 %) and CPV (1 %). Solid state characterization of CPE confirmed its semi-crystalline/amorphous nature and the absence of a chemical change occurring during co-processing. Assessment of the powder properties revealed an improvement in the flow behaviour of CPE. These properties obtained suggest that CPE will be a suitable tableting material in solid dosage formulation by direct compression.

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تطوير وتوصيف السليلوز الميكروستالين القائم على الخلايا الهضمية المعالجة المشتركة في الإكسبت باستخدام تصميم نهج التجربة

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ملخص

كان الهدف من هذه الدراسة هو تطوير مادة نامية (CPE) تمت معالجتها بشكل مشترك تحتوي على السليلوز المتبلور الدقيق (MCC) والكروسبوفيدون (CPV) باستخدام تقنية التكتلة الرطبة. وأجريت دراسات تمهيدية على CPE لتوصيف خصائصه الفيزيائية الكيميائية. وقد تم تحسين صياغة CPE باستخدام تصميم تجريبي خليط. واقترحت دراسة التحسين وجود سرعة مركبة تحتوي على مؤسسة تحدي الألفية (99٪) كشف توصيف الحالة الصلبة ل CPE عن مادة ذات طبيعة بلورية في الغالب. زاد حجم الجسيمات من CPE بالمقارنة مع المواد الأولية. أكدت FT-IR توافق MCC وCPV عند المعالجة المشتركة معا لتحقيق سرعة مركبة واحدة. كان هناك انخفاض في محتوى الرطوبة وقدرة الطورب الرطوبة من CPE بالمقارنة مع مؤسسة تحدي الألفية. وكشف توصيف المسحوق عن تحسن في خصائص التدفق السائب ل CPE بالنسبة إلى مؤسسة تحدي الألفية. باختصار الخصائص الفيزيائية الكيميائية التي تم الحصول عليها تشير إلى أن CPE سوف يكون منتقاة أقراص مناسبة في صياغة الجرعة الصلبة عن طريق الضغط المباشر.

الكلمات الدالة: السليلوز الميكروستالين، كروسبوفيدون، المعالجة المشتركة، التحسين، هندسة الجسيمات، الكمبيوتر اللوحي.

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