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Research Article

Optimization of Microcrystalline Cellulose PH 101, Lactose, and Kollidon® K 30 To Obtain Co-Processed Excipient Through Spray Drying

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ABSTRACT

The most efficient tablet processing method is direct compression. For this method, the filler-binder can be made by co-processing via spray drying method. The purpose of this study was to investigate the effect of spray dried co-processing on microcrystalline cellulose (MCC) PH 101, lactose and Kollidon® K 30 as well as to define the optimum proportions. Spray dried MCC PH 101, lactose, and Kollidon® K 30 were varied in 13 different mixture design proportions to obtain compact, free-flowing filler-binder co-processed excipients (CPE). Compactibility and flow properties became the key parameters to determine the optimum proportions of CPE that would be compared to their physical mixtures. The result showed that the optimum proportion of CPE had better compactibility and flow properties than the physical mixtures. The optimum CPE, consisting of only MCC PH 101 and Kollidon® K 30 without lactose, that were characterized using infrared spectrophotometer, differential scanning calorimetry (DSC), X-ray diffraction (XRD), and scanning electron microscope (SEM) indicated no chemical change therein. Therefore, this study showed that spray dried MCC PH 101, lactose and Kollidon® K 30 could be one of the filler-binder alternatives for direct compression process.

Keywords: Co-processed excipients, Spray drying, Mixture design, MCC PH 101, Lactose, Kollidon® K30.

INTRODUCTION

Direct compression tablet manufacturing is strongly influenced by the excipients, especially the filler binder[1]. Filler binder is an excipient that has been modified to improve its flowability and compressibility[2].

MCC PH 101 is one of the direct compression excipients, which has good compactibility[3,4], while lactose is a filler commonly used in tablets. In addition, Kollidon® K 30 is a binder with bad compactibility in dry form but possesses excellent compactibility when activated with water[5]. The combination of these materials carried by a spray drying process is expected to result in acceptable compactibility and flowability for direct compression tablet manufacturing[6].

Accordingly, this research aims to determine the effect of co-processing with spray drying on the physical properties of a mixture of MCC PH 101, Lactose and Kollidon® K 30 as well as to determine the optimum proportions using a mixture design model. When the optimum proportions are obtained, a characterization is conducted using Fourier Transform Infrared (FTIR), Differential Scanning Calorimetry (DSC), Thermal Gravimetric Analysis (TGA), X-Ray Diffraction (XRD) and Scanning Electron Microscopy (SEM) to identify the process of excipient's character changes[7].

MATERIAL AND METHODS

Materials

Microcrystalline cellulose (MCC PH 101/Ceolus PH 101) was produced by Asahi Kasei Chemicals, Japan, lactose was the product of Hillmar Ingredients Inc., and Kollidon® K 30 was manufactured by Hangzhou Nanhang. Meanwhile, all other solvents were of analytical grades.

Methods

Determination of Mixture Proportion

The proportions of MCC PH 101, Lactose and Kollidon® K 30 were determined using the mixture design from Design Expert® 9 software and presented in Table 3.

Formulation of CPE

The suspension of 10% w/v co-processed excipient was made by suspending 100 g mixture of MCC PH 101, lactose and Kollidon® K 30 in 1000 mL of water. The suspension was then sucked into the spray dryer with 1 mm nozzle. The spray drying parameters were made constant, which consisted of inlet temperature (120°C), suction speed (4 mL/min), and pump pressure (3 Bar). Next, the powder was dried for 24 hours in an oven at 50°C[8,9].

Evaluation of Physical Properties

To evaluate the powder flow, 25 grams of powder was poured into funnel flow apparatus. Next, to define the particle size,a sieving method was conducted for 25 grams of powder for 30 minutes. Then, for the tapping test, the powder mass was poured into a 25 mL measuring cup and tapped until it reached a constant powder volume and did not decrease. As for the test of weight and size uniformity, 500 mg powder mass was compressed at equal volume and

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Table 1: Mixture Proportion.

Run	MCC PH 101 (%)	Lactose (%)	Kollidon® K 30 (%)
1	90	0	10
2	50	0	50
3	0	90	10
4	70	0	30
5	17.5	52.5	30
6	0	50	50
7	30	30	40
8	0	70	30
9	90	0	10
10	45	45	10
11	46.67	16.67	36.67
12	17.5	52.5	30
13	45	45	10

pressure and then tested for the hardness using a hardness tester[10].

Determination of the Optimum Proportion of CPE

Intersection was implemented to determine the optimum proportion of co-processed excipients for all of the parameters generated from the mixture design model.

Characterization Test

FTIR Analysis

Nicolet Avatar 360 FTIR was used in this study by mixing the powder with Potassium Bromide (1%w/w) and compressing it into a thin pellet followed by putting it into the equipment. Using spectral resolution of 4 cm^{-1}, the samples were scannedin the range of 4000-400 cm^{-1}.

DSC Analysis

The thermal characteristics were measured using Shimadzu DSC-60 Plus. Samples were weighed as much as 5 mg powder in an aluminium pan, and an empty aluminium pan was used as a reference. The heating rate was 10^0/minute while the temperature ranged from 35^0 to 300^0C.

TGA Analysis

The analysis used Perkin Elmer Instruments Thermogravimetric Analyzer SII. The reference samples used aluminium oxide. These samples were put into a sample cup as much as 7 mg then heated with a temperature of 30°C to 600°C and 5°C/minute heating rate.

XRD Analysis

The X-ray diffraction used Shimadzu X-ray Diffractometer Anode 6000 with Cu radiation and graphite monochromator. The power intensity was 30 mA and 40 kV with 2θ angular range, varying from 5° to 60° with a size range of 0.02° and scan speed of 3°/minute.

SEM Analysis

The morphology of the powder was analyzed using SEM to take micrograph pictures[11].

RESULTS AND DISCUSSION

Physical Evaluation of CPE

In this study, the flowability was determined by measuring the tapping index (TI). However, the flow speed and angle of repose were not calculated because the CPE powder did not flow in this test.

The tapping index (TI) equation derived from the Design Expert software was (Eq. 1):

Equation 1. TI = 0.47697(A) + 0.59768(B) + 1.68311(C) – 0.010452(A)(B) – 0.026389 (A)(C) – 0.027505 (B)(C) + 0,000762 (A)(B)(C)

in which A was the fraction of MCC PH 101, B was the fraction of lactose, and C was the fraction of Kollidon® K 30.

Equation 1 shows that the interaction among MCC PH 101, lactose, and Kollidon® K 30 is influential in increasing the value of TI, which also means worsen flowability. Yet, the interaction between lactose and Kollidon® K 30 has the greatest influence on improving the flowability. In addition, the spray drying process has led to the development of granules where, at a certain proportion, the size of the formed granules is the most optimal to improve the flowability[12,13].

Then, the compactibility was obtained from the hardness (hardness test). The interaction between MCC PH 101, lactose, and Kollidon® K 30 was found through Equation 2.

Equation. 2. Hardness = 0.076756 (A) + 0.012334 (B) – 0.033446 (C) + 0.000165 (A)(B) + 0.001087 (A)(C) + 0.001866 (B)(C) + 0.000036 (A)(B)(C)

where A was the fraction of MCC PH 101, B was the fraction of lactose, and C was the fraction of Kollidon® K 30.

Table 2: Physical Evaluation of CPE.

Run	Yield (%)	Moisture Content (%)	TI (%)	Hardness (kg)
1	64.257	4.106 ± 0.41	32	7.39 ± 0.02
2	51.437	5.416 ± 0.18	46	4.94 ± 0.61
3	37.049	4.215 ± 0.35	44	2.43 ± 0.25
4	46.839	4.960 ± 0.52	24	6.69 ± 0.67
5	35.007	5.159 ± 0.34	44	3.73 ± 0.34
6	34.046	5.287 ± 0.20	42	3.54 ± 0.20
7	49.480	5.084 ± 0.34	52	3.95 ± 0.89
8	39.100	4.433 ± 1.11	38	3.83 ± 0.47
9	68.165	4.431 ± 0.23	36	7.73 ± 0.28
10	46.061	3.311 ± 1.00	40	5.03 ± 0.62
11	52.940	4.293 ± 0.30	44	4.38 ± 0.49
12	39.429	4.837 ± 0.60	48	3.61 ± 0.49
13	38.160	3.111 ± 0.12	34	4.43 ± 0.28

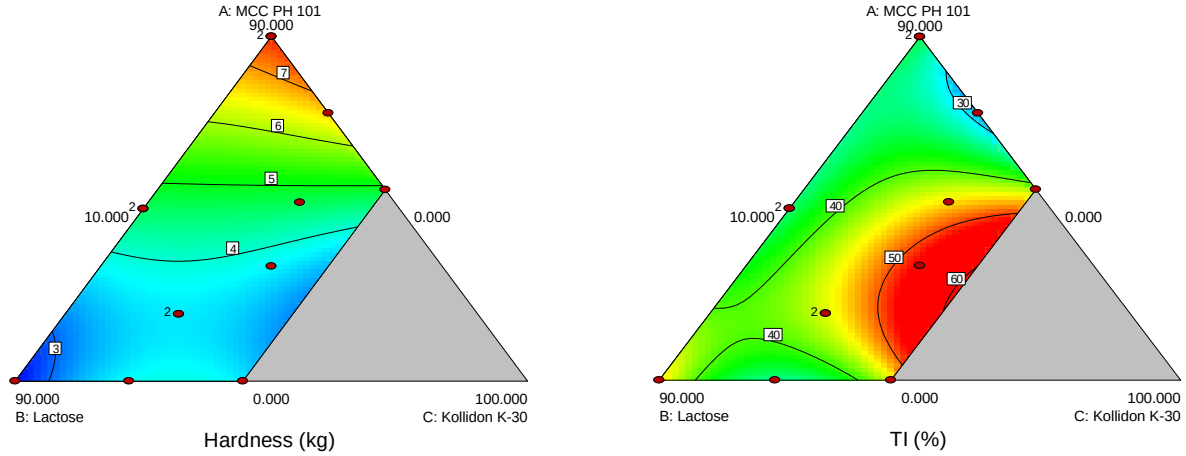

Figure 1: Contour Plot.

Table 3: Comparison of CPE.

Parameter	Prediction	Actual	Sig.
TI (%)	29.462	29.333 ± 1.155	0.865
Hardness (kg)	7.245	7.333 ± 0.040	0.051

The interactions among these three ingredients are important in increasing the hardnessvalue, which also means increasing compactibility. As a matter of fact, Kollidon® K 30 can individually decrease compactibility because it has poor compactibility in dry form, while the spray drying process can cause interactions among the three excipients, which can improve the material compactibility. In the spray drying process, water exposure can cause interactions among MCC PH 101, lactose and Kollidon®K 30, in which the structure will be disguised by Kollidon® K 30.

Other parameters including yield and moisture content were also determined in this test. The higher proportion of Kollidon® K 30, the lower yield resulted. This was due to hygroscopicity of this material. Moisture content were all being kept under 5% for all of formula.

Determination of the Optimum Proportion of CPE

The optimum proportion of CPE based on Design Expert Software was obtained by made intersection of TI and hardness as main parameters (Figure 1). The goal of TI were minimized and on the other hand the hardness were set to be maximized. The optimum proportion of MCC PH 101 and Kollidon® K 30 according to the Design Expert were 79.632% and 20.368% respectively. This optimum proportion of CPE was then formulated in triplicate and evaluated.

The evaluation of the predicted optimum formula was then compared with the actual optimum formula, and the result is presented in Table 2. In this table, the statistical analysis shows the significance between the predicted value and experimental value. This statistical analysis was considered valid because the predicted value and the experimental result were not significantly different.

Next, the optimum proportion of CPE was also compared with the physical mixture. In the physical mixture, the obtained TI value was 31.333 ± 1.15%, which was greater than that of CPE. Therefore, it can be said that spray dried CPE has better flowability than the physical mixture. The spray drying process can cause interaction between MCC PH101 and Kollidon® K 30, in which Kollidon® K 30 will envelop MCC PH 101 particle, so that the flowability of the mixture will improve. Additionally, the physical mixture's hardness reached 7.18 ± 0.01 kg, which was slightly lower than that of the CPE. This co-processing via spray drying resulted in plastic deformation, while the dry mixture exhibited elastic deformation[14,15]. Plastic deformation is more advantageous in terms of tablet compression because it will produce strong, sturdy tablets[16]. In contrast, plastic deformation is disadvantageous in tablet compression because it will cause the tablet-forming particles to return totheir individual, previous shapes after compression. As a result, the tablets have low hardness and become fragile[17].

Characterization Test

FTIR Analysis

The results of IR spectra analysis in the wavelength range of 4000-400 cm^{-1}(Figure 2) showed that at 3455.59 cm^{-1}spectra of Kollidon® K 30 water molecules appeared in the sample due to the highly hydrophilic nature of Kollidon® K 30. A prior research suggested that the spectra of Kollidon® K 30 possessed a widened peak of functional groups that characterized the hydrogen bonding at wave number 3450 cm^{-1}. This was also evidenced by the widening endothermic phase in DSC analysis on Kollidon® K-30 due to its hygroscopic nature[18].

In addition, the results of co-processed excipient analysis at 3442.08 cm^{-1}were similar to the peak in the physical mixtures (3457.36 cm^{-1}) and MCC PH 101 (3451.86 cm^{-1}), while the peak at 2902.53 cm^{-1} had similarities to the peak in MCC PH 101 (2902.38 cm^{-1}). These CPE's spectra were actually combined from several peaks in MCC PH 101 and in Kollidon® K-30. However, the shape more resembled MCC PH 101's spectra because of the dominant composition compared to Kollidon® K 30. Meanwhile, the spectra of CPE were nearly the same as that of the physical mixtures. It showed that no chemical changes occurred during the spray drying process of CPE.

DSC Analysis

The result of DSC test on Kollidon® K 30 (Figure 3) showed wide endothermic graphs at around 50-150^{0}C due

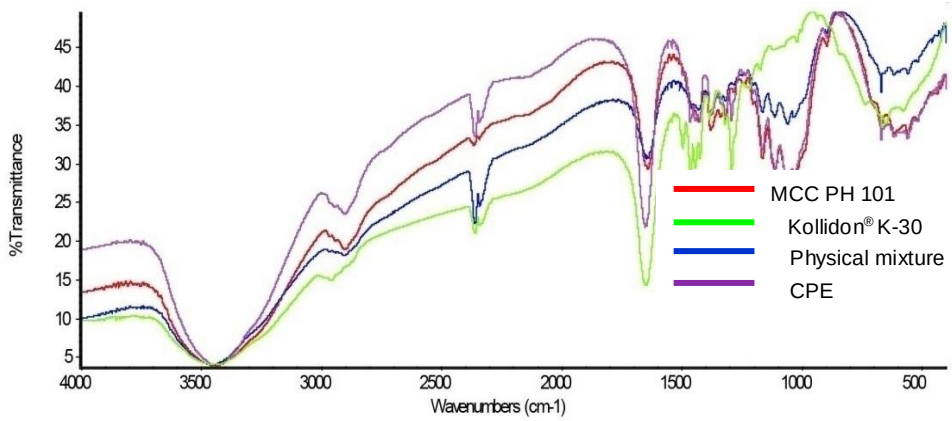

Figure 2**:** FTIR spectra.

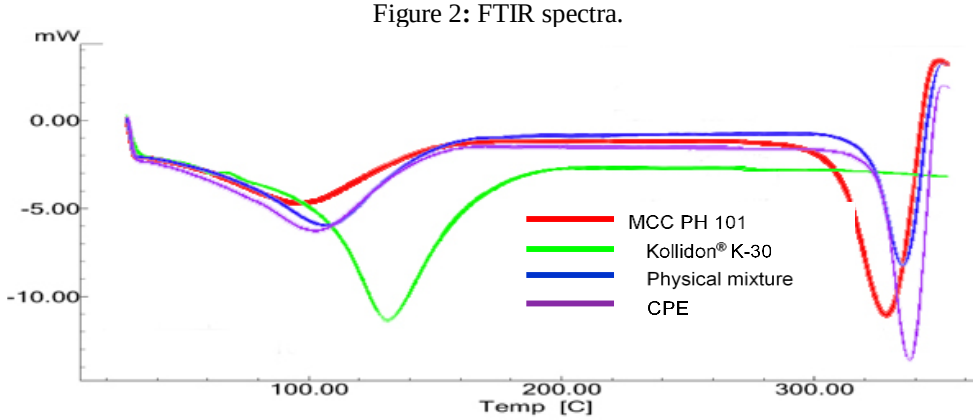

Figure 3: DSC spectra.

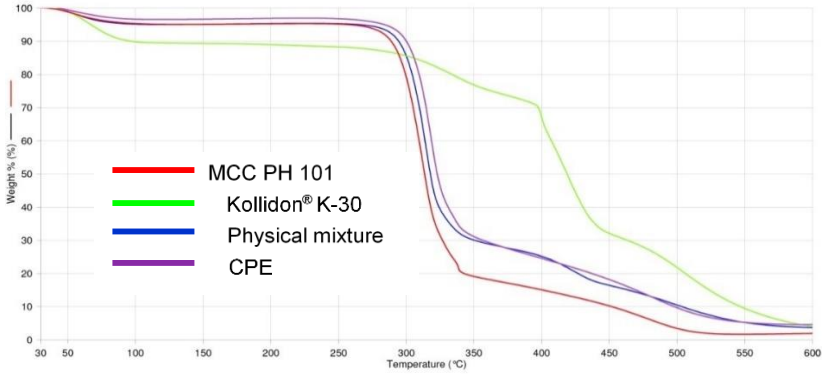

Figure 4**:** TGA spectra

to its hygroscopicity[18,19]. Meanwhile, the DSC test on CPE resulted in 336.42^{0}C peak value; this was not much different from that of the physical mixture of MCC PH 101 and Kollidon® K 30, which reached 334.33^{0}C. This means that the co-processed excipient made by spray drying method had the same characteristics as its physical mixture; although a physical modification occurred, the chemical properties, one of which is the melting point, did not change[20]. In addition, the ΔH of co-processed excipient was -129.22 J/g, which was lower than that of the single-constituent material. It shows that two interacting compounds will require less energy to melt[18].

TGA Analysis

The thermograms of physical mixture and co-processed excipient were similar (Figure 4). It proved that in spray drying process the co-processed excipient did not have a change in its chemical nature. Additionally, the thermograms of both CPE and physical mixture resembledthat of MCC PH 101 as the most dominant component. In TGA analysis, the co-processed excipients experienceda significant weight changeover a temperature range of about 275-350^{0}C. It corresponded to the DSC data, in whichthe CPE's peak at 336,42^{0}C indicated the occurrence of phase change at that temperature. Therefore, both data show that at the temperature range of 275-350^{0}C an endothermic reaction and chemical decomposition of material can occur.

XRD Analysis

The diffractograms of CPE and physical mixture were almost identical, and both resembled MCC PH 101 as the most dominant component although the intensity was different (Figure 5). The three of them had sharp peaks indicating crystalline packing of molecules[21]. In contrast, Kollidon® K 30 experienced amorphous deformation that

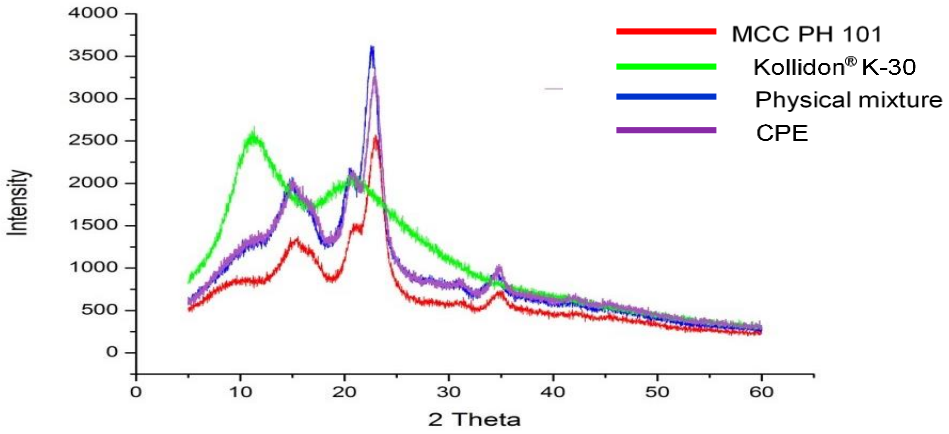

Figure 5: XRD diffractogram.

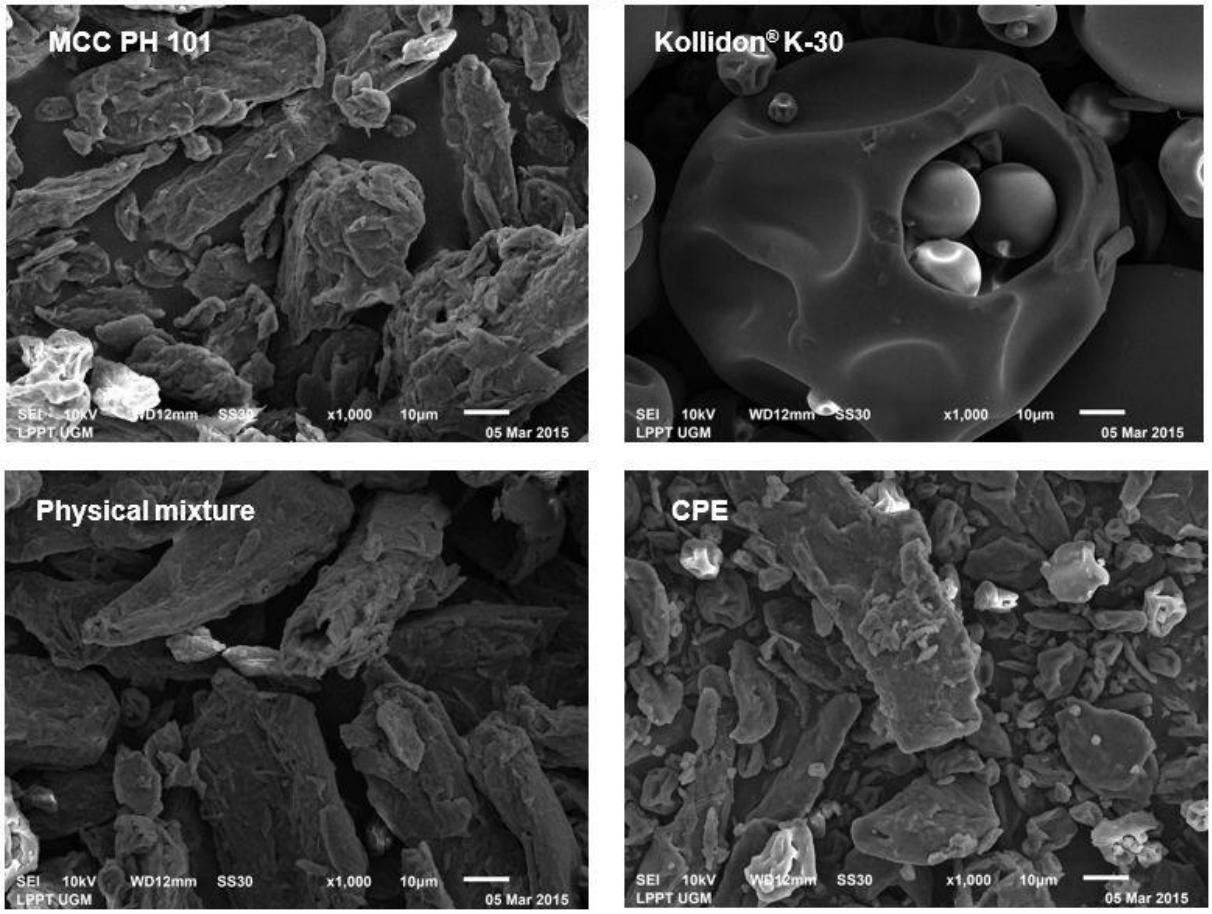

Figure 6: SEM images.

was indicated bythe blunt peak of diffractogram. All of these diffractogramsshowed that during the making of CPE there were no changes in the chemical properties of the component. A modification happened only to the physical properties of the substances[22].

SEM analysis

The morphology of MCC PH 101 and Kollidon® K 30 changed after the spray drying process to be co-processed excipient (Figure 6). The initial form of MCC PH 101 was longish and fairly uniform in size, while Kollidon® K-30 was round with various sizes. Both turned slightly oval with a smoother surface after the spray drying process. Kollidon® K 30 seemed to envelop and stick to MCC PH 101 particle, making it more bulky and round to obtain improvement in the flowability of the mixture[12]. This enveloping did not happen to the physical mixture where the two particles were only mixed in dry form. The morphological changes indicated that a physical modification occurred in the process of CPE making, and such changes might affect the physical properties.

CONCLUSION

This study showed that MCC PH 101 and Kollidon® K 30-based CPE could be used as direct compression filler binder. The next experiment aims to improve the flowability of CPE by optimizing the spray drying process.

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