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Optimization Direct Compression's Co-Processed Excipient Microcrystalline Cellulose PH 102 and Povidone® K 30

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Abstract: *The objective of the present study was to develop filler-binder co-processed excipient (CPE) from MCC PH 102 and Povidone® K 30 combination. The mixture was varied and co-processed by spray drying technique. Optimum proportion was determined by testing the flow ability and compressibility expressed in Tapping Index (T.I) and hardness, respectively. The test result indicates that the flow ability was fluctuating in different CPE proportions, while compressibility improved with the increase in proportion of Povidone® K 30. Optimum proportion was reached at 71 % MCC PH 102 and 29 % Povidone® K 30, with the values of T.I and hardness of 16,22 ± 0,39 % and 7,61 ± 0,12 kg, respectively. Optimum CPE generates tablets of paracetamol model drug that meet the USP requirements of tablet dosage, which include hardness, friability, disintegration time, and dissolution.*

Keywords: *Co-processed excipient; spray drying; MCC PH 102, Povidone® K 30*

I. Introduction

Filler-binder is a kind of excipient of direct compression tableting method [1]. Filler-binder can overcome the weakness of the physical properties of the active ingredients to make them compressible with direct compression method. Filler-binder can be made, among others, by co-processing with spray drying technique. Spray drying will produce powder particles with good flow ability and compressibility [2, 3].

MCC PH 102 is one of additional materials for direct compression with good compressibility, in spite of bad flow ability [4-7]. Povidone® K 30 is a binder with less compressibility, yet it has excellent flow ability [8]. The combination of these two ingredients, conducted by spray drying process, is expected to produce powder with excellent flow ability and compressibility [9, 10].

The current study aims to determine the effect of co-processing with spray drying on the physical properties of MCC PH 102 and Povidone® K 30 mixtures as well as to determine their optimum proportion as filler-binder co-processed excipients (CPE). Subsequently, this CPE will be used as excipient in the production of paracetamol tablets, a well-known active ingredient for bad compressibility and flow ability [11, 12].

II. Methodology

2.1. Materials

The following materials were used: paracetamol (Hengshui Jiheng, China), Povidone® K 30 (Hangzhou Nanhang), magnesium stearate (Faci Asia Pacific), MCC PH 102 (Ceolus PH 102; Asahi Kasei Chemicals, Tokyo, Japan), hydrophilic pyrogenic silica (HDK® N20 Pharma, Wacker Germany), and croscarmellose sodium (DMV-Fonterra Excipients B.V, Foxhol, Holand). All other solvents were analytical grade.

2.2. Method of Preparation

MCC PH 102 and Povidone® K 30 mixture of 100 g were suspended in 1000 mL of water, and then spray dried, with proportion according to table 1. The spray dryer parameters were made constant. They include inlet and outlet temperatures of 120°C and 60°C, respectively; suction speed of 4 mL/min, 3 bar pump pressure, and a 1 mm nozzle [13]. Formed CPE materials were dried in an oven at 50°C for 24 h and sieved using a 12 sieve, and subsequently added with hydrophilic pyrogenic silica at 1% concentration.

Paracetamol was compressed with optimum CPE and other excipients according to table 2, weighting 800 g in total per tablet with diameter and thickness of 13 mm and 5,5 mm, respectively, with hardness of 6 kg at minimum.

2.3. Evaluation of CPE

Flow ability test of tapping technique was conducted by pouring the powder into a 25 mL measuring cup. The latter was then tapped until the volume of the powder constant without reduction. Tapped volume was recorded to determine the tapping index and its specific gravity [14].

Compressibility test was conducted by compressing 250 g powder into tablet of uniform thickness. The resulting tablet was measured for its hardness using Monsanto hardness tester.

Table 1. CPE Proportion

Formula	MCC PH 102 (g)	Povidone® K 30 (g)
I	100	0
II	75	25
III	50	50
IV	25	75
V	0	100

Table 2. Paracetamol Tablet Formulation

Material	Amount per Tablet (mg)
Paracetamol	500
CPE	280
Magnesium stearate	5
Hydrophilic pyrogenic silica	10
Croscarmellose Sodium	5
Total	800

Table 3. Compressibility and Flow Ability Test

MCC PH 102: Povidone® K30	Hardness (kg)		T.I (%)	
	PM	CPE	PM	CPE
100:0	5,04 ± 0,25	5,41 ± 0,19	24,67 ± 1,33	31,11 ± 2,69
75:25	4,90 ± 0,41	7,14 ± 1,24	21,78 ± 0,38	19,56 ± 2,04
50:50	6,26 ± 1,45	13,28 ± 0,93	20,22 ± 1,39	28,67 ± 2,40
25:75	7,29 ± 1,78	12,56 ± 2,19	17,78 ± 1,68	35,56 ± 1,92
0:100	9,08 ± 1,28	14,12 ± 2,07	16,44 ± 1,68	32,00 ± 0,67

($\bar{x}$ ± SD ; n = 3)

2.4. Optimum Proportion Determination

Proportion of optimum CPE is determined using Design-Expert® by referring to the intersection of flow ability and compressibility parameters

2.5. Evaluation of Paracetamol Tablet

Six tablets were randomly tested for hardness using Stokes hardness tester. Ten tablets were randomly tested for brittleness, dust-freed, weighed on analytical balance, and subsequently tested for brittleness on an abrasive tester. They were then dust-freed and weighed for the second time, as well as calculated for their weight loss percentage [14]. Disintegration time test was performed randomly for 6 tablets on a disintegration tester. The liquid used was distilled water of 36-38 °C, with the instruments speeding up and down by 30 times per minute. A tablet was declared destroyed when no part of it left on the screen. The time required for the tablet to disintegrate was recorded [14].

Dissolution test was carried out on the medium of 900.0 mL phosphate buffer (pH 5.8). Samples obtained from the test were measured for their absorbance using UV spectrophotometer at maximum wavelength. The obtained absorbance value was put into a standard curve to determine the level. The level obtained was included in the linear regression equation to obtain the dissolution rate [14].

III. Results And Discussion

The flow ability of powder is critical in the tablet manufacturing process and affect the weight and content uniformity [15, 16]. Flow ability is evaluated by determining the tapping index (T.I). Flow rate and repose angle were not calculated because not all of the powder can flow in this test.

In dry mixture, the higher the proportion of Povidone® K 30, the better is its flow ability (and the lower the T.I value). It is consistent with the CI equation for mixture obtained using Design-Expert® (Fig.1; equation 1):

$$T.I = 0{,}2440\ A + 0{,}1551\ B \quad (1)$$

The equation indicates that MCC PH 102 provides greater contribution to the higher value of T.I (increasingly poorer flow ability) than that of Povidone® K 30. This is because the flow ability of MCC PH 102 is indeed poorer than that of Povidone® K 30. In CPE obtained from spray drying, the flow ability was, in

general, no better than that of the dry mixture. T.I. value in CPE (equation 2) is also not forming a straight line of linear pattern as in the dry mixture.

T.I = 0,3090 A + 0,3179 B – 0,0016 AB – 0,0001 AB(A–B) (2)

The lowest T.I. value in dry mixture proportion of 100 % Povidone® K 30 was not found in the T.I. of CPE, which is high. T.I. value on CPE is shown to be low in the proportion of 75 % MCC PH 102 : 25% Povidone® K 30, outside the proportion, T.I. tend to be high. Spray drying process of both mixture have caused the development of granules where in such a proportion the size of formed granules is probably the most optimal to support the flow ability [17].

Compressibility is expressed as the hardness, the load required to disintegrate the tablet made of powder compression; the harder, the better is the compressibility [18, 19]. In compressibility testing, the higher the concentration of Povidone® K 30, the higher is the compressibility. In spray drying process, water exposure may activate Povidone® K 30 as a binder [20]. Although water is revaporized in that process, the residue remains in the powder and this affects the improved compressibility of the powder. For dry mixture, the compressibility is lower than that of spray drying. Povidone® K 30 that only dry-mixed without water will only results in less compact mixture compared to that of spray drying powder.

The results of powder compressibility testing are listed in table 3. For dry mixtures, the higher the proportion of Povidone® K 30, the higher was the hardness of the tablet. In this case, hydrophilic pyrogenic silica contributes the impact of hardness improvement of the tablet on Povidone® K 30 in 100% proportion. The lowest hardness value was found in a dominant proportion of MCC PH 102 (equation 3).

Hardness = 0,049237 A + 0,091148 B – 0,00043810 AB (3)

The equation indicates that the Povidone® K 30 proportion strongly affect the increased hardness, while its interaction with MCC PH 102 decreases the hardness.

The CPE tablet hardness was expressed in plot 1/hardness (equation 4). This reverse transformation was performed to refine the model fit where the normal model has a significant lack of fit [21].

1/Hardness = 0,00188607 A + 0,000735862 B – 0,0000158434 AB (4)

Powder compressibility was increasingly higher (1/hardness is increasingly smaller) with an increasingly higher proportion of Povidone® K 30. Povidone® K 30 hydrated by suspension in spray drying process is estimated to greatly contribute to the high value of hardness.

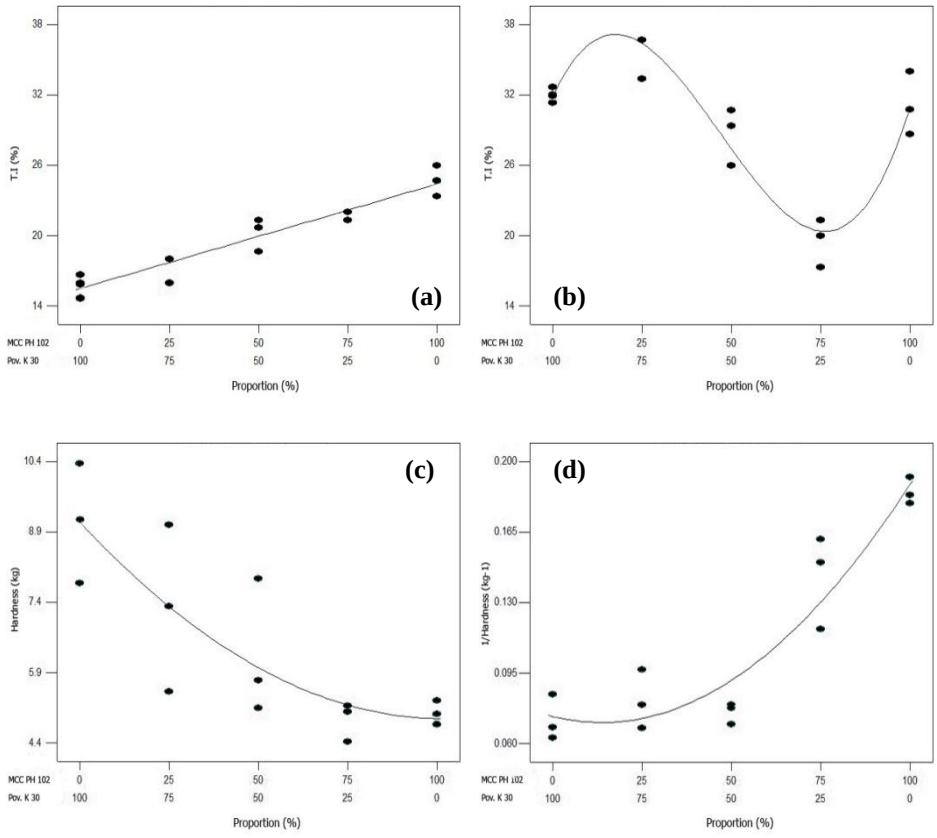

Figure 1. Flow Ability and Compressibility Value (a. T.I Dry Mixture; b. T.I CPE; c. Hardness Dry Mixture; d. 1/Hardness CPE)

Flow ability and compressibility have become the parameters following the drug dose used to determine the tablet compression method: whether direct compression or granulation [16]. Theoretical predictive values for T.I. and hardness at optimum proportion are 20,77 % and 8,20 kg, respectively.

Optimized CPE proportions (71 % MCC PH 102 : 29 % Povidone® K 30) were replicated 3 times with the same parameter as in optimizing process. The results of characterization are included in Table 4.

Statistical testing indicates that both T.I and hardness are significantly different from their theoretical predictive values. Limited number of replications made the differences possible [22]. The validity of statistical test will improve with the increasing number of sample. In addition, the model fit obtained from the mixed design was possibly differ from its real value. Wide disparity between the values of the model might reduce their validity. Figure 1 indicates that T.I and hardness values were not uniform, despite equal proportion. Variation in spray dried powder was very likely to be caused by such differences. The real values obtained from T.I tests, albeit different from the predicted ones, turned out to be indicating better results, while the hardness values tend to be lower than the predicted ones.

Table 4. Optimum CPE Characteristics

Parameter	Predicted	Observed
T.I (%)	20,77	16,22 ± 0,39
Hardness (kg)	8,20	7,61 ± 0,12

Physical evaluation of paracetamol tablet including hardness, friability, disintegration time and dissolution were within the recommended limit according to USP 32 requirements (Table 5).

Table 5. Paracetamol Tablet Characteristics

Parameter	Replication I	Replication II	Replication III	Criteria
Hardness (kgf)	10,82	7,23	8,56	4-10
Friability (%)	0,49	0,80	0,91	<1
Weight Variation Deviation (%)	>5	>5	>5	<5
Disintegration (minute)	2'43"	1'12"	1'08"	<15'
Dissoluted Paracetamol in 30 minutes (%)	92,77	97,52	97,63	≥ 85

IV. Conclusion

The present study showed that combination of MCC PH 102 and Povidone® K 30 can be developed as filler binder co-processed excipient (CPE). It was found that mixture of MCC PH 102 and Povidone® K 30 generates fluctuating CPE in terms of flow ability, while the compressibility increased with the additional proportion of Povidone® K 30. Optimum CPE proportion is generated at 71 % : 29 % (MCC PH 102 : Povidone® K 30).

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