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

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Received: 19th Jan, 17; Revised 21st March, 17, Accepted: 12th June, 7; Available Online:25th June, 2017

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.

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

MATERIAL AND METHODS

Materials
The drying process has led to the interaction between MCC PH 101, lactose, and Kollidon® K 30. Sample temperature of 30°C to 600°C and 5°C/minute heating rate. These samples were put into a Thermogravimetric Analyzer SII. The reference samples were scanned in the range of 4000 cm⁻¹ to 4600 cm⁻¹ with a scan speed of 3°/minute. 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°/minute while the temperature ranged from 35°C to 300°C.

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

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):

\[ TI = 0.47697(A) + 0.59768(B) + 1.68311(C) - 0.010452(A)(B) - 0.026389(A)(C) - 0.027505(B)(C) + 0.000762(A)(B)(C) \]

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.

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

\[ TI = 0.076756 (A) + 0.012334 (B) - 0.033446 (C) + 0.000165 (A)(B) + 0.001087 (A)(C) + 0.001866 (B)(C) + 0.000363 (A)(B)(C) \]

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

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 scanned in the range of 4000-4000 cm⁻¹.

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 20 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.

Table 1: Mixture Proportion.

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

Table 2: Physical Evaluation of CPE.

<table>
<thead>
<tr>
<th>Run</th>
<th>Yield (%)</th>
<th>Moisture Content (%)</th>
<th>TI (%)</th>
<th>Hardness (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64.257</td>
<td>4.106 ± 0.41</td>
<td>32</td>
<td>7.39 ± 0.02</td>
</tr>
<tr>
<td>2</td>
<td>51.437</td>
<td>5.416 ± 0.18</td>
<td>46</td>
<td>4.94 ± 0.61</td>
</tr>
<tr>
<td>3</td>
<td>37.049</td>
<td>4.215 ± 0.35</td>
<td>44</td>
<td>2.43 ± 0.25</td>
</tr>
<tr>
<td>4</td>
<td>46.839</td>
<td>4.960 ± 0.52</td>
<td>24</td>
<td>6.69 ± 0.67</td>
</tr>
<tr>
<td>5</td>
<td>35.007</td>
<td>5.159 ± 0.34</td>
<td>44</td>
<td>3.73 ± 0.34</td>
</tr>
<tr>
<td>6</td>
<td>34.046</td>
<td>5.287 ± 0.20</td>
<td>42</td>
<td>3.54 ± 0.20</td>
</tr>
<tr>
<td>7</td>
<td>49.480</td>
<td>5.084 ± 0.34</td>
<td>52</td>
<td>3.95 ± 0.89</td>
</tr>
<tr>
<td>8</td>
<td>39.100</td>
<td>4.433 ± 1.11</td>
<td>38</td>
<td>3.83 ± 0.47</td>
</tr>
<tr>
<td>9</td>
<td>68.165</td>
<td>4.431 ± 0.23</td>
<td>36</td>
<td>7.73 ± 0.28</td>
</tr>
<tr>
<td>10</td>
<td>46.061</td>
<td>3.311 ± 1.00</td>
<td>40</td>
<td>5.03 ± 0.62</td>
</tr>
<tr>
<td>11</td>
<td>52.940</td>
<td>4.293 ± 0.30</td>
<td>44</td>
<td>4.38 ± 0.49</td>
</tr>
<tr>
<td>12</td>
<td>39.429</td>
<td>4.837 ± 0.60</td>
<td>48</td>
<td>3.61 ± 0.49</td>
</tr>
<tr>
<td>13</td>
<td>38.160</td>
<td>3.111 ± 0.12</td>
<td>34</td>
<td>4.43 ± 0.28</td>
</tr>
</tbody>
</table>
CPE has better flowability than the physical mixture. The spray drying process can cause interaction between MCC PH 101 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 deformation16,17. Plastic deformation is more advantageous in terms of tablet compression because it will produce strong, sturdy tablets16. In contrast, plastic deformation is disadvantageous in tablet compression because it will cause the tablet-forming particles to return to their individual, previous shapes after compression. As a result, the tablets have low hardness and become fragile17.

**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⁻¹spectra 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 nature18.

In addition, the results of co-processed excipient analysis at 3442.08 cm⁻¹were 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°C due
to its hygroscopicity\textsuperscript{18,19}. Meanwhile, the DSC test on CPE resulted in 336.42°C peak value; this was not much different from that of the physical mixture of MCC PH 101 and Kollidon\textsuperscript{®} K 30, which reached 334.33°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\textsuperscript{20}. In addition, the $\Delta H$ 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\textsuperscript{18}.

**TGA Analysis**

The thermograms of both CPE and physical mixture resembled that of MCC PH 101 as the most dominant component. In TGA analysis, the co-processed excipients experienced a significant weight change over a temperature range of about 275-350°C. It corresponded to the DSC data, in which the CPE’s peak at 336.42°C indicated the occurrence of phase change at that temperature. Therefore, both data show that at the temperature range of 275-350°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\textsuperscript{21}. In contrast, Kollidon\textsuperscript{®} K 30 experienced amorphous deformation that
was indicated by the blunt peak of diffractogram. All of these diffractograms showed 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 substances². 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 mixture¹². 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.
ACKNOWLEDGEMENT
The authors would like to thank Directorate of Research and Community Service of Universitas Islam Indonesia (DPPM UII) for supporting this work.

REFERENCES

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