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Application of Near-Infrared Spectrometry to Evaluate the Mechanism of Wet Granulation Using a High-Speed Mixer with Porous Calcium Silicate and Sugar Alcohols

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The current study examined the mechanism of wet granulation with a high-speed mixer using porous calcium silicate (PCS) as the excipient and low-molecular-weight sugar alcohols (erythritol, mannitol, maltitol, or xylitol) as the binder. Granules did not form when erythritol or mannitol was used as the binder. No major changes in X-ray powder diffraction data and near-infrared (NIR) spectroscopy spectra were noted when xylitol was used in granulation. Meanwhile, granules formed when xylitol was used as the binder. The NIR spectra of the obtained granules had a widened band near 5100 cm\(^{-1}\) due to hydroxyl groups. From the peak fitting near 4800 cm\(^{-1}\) using the Gaussian–Lorentzian product function, the contribution of hydrogen bonds in water species increased during granulation. The NIR spectra of these potential binders revealed a band of hydroxyl groups for intramolecular hydrogen bonds near 6900 cm\(^{-1}\) when maltitol or xylitol was used as the binder, whereas no band was observed for erythritol and mannitol. Changes in the NIR spectra assigned to water were useful in evaluating the progression of granulation as a process analytical technology. Moreover, X-ray powder diffraction illustrated that the peak due to xylitol crystals disappeared. Xylitol existed in an amorphous state in the granules, suggesting molecular interactions. Thus, hydroxyl groups in sugar alcohols facilitate hydrogen bonding between PCS (silanol groups) and molecules via water, and this is considered to be the mechanism by which granules are formed.

Key words xylitol; maltitol; erythritol; mannitol; porous calcium silicate; near-infrared spectroscopy

As tablets and capsules are the most common and convenient solid oral dosage forms, an optimally designed granulation technology can be a tremendous tool to minimize variability among batches and hence diminish the risk of poor-quality medicines. Wet granulation is the process of size enlargement in which small primary particles are joined using agitation and a liquid binder. Three main types of granulators are used in pharmaceutical manufacturing: tumbling, fluidized bed, and mixer granulators. High-shear wet granulation is one of the most widely used granulation methods. In this method, dry powders are placed in a mixing vessel usually containing an impeller, which revolves on a horizontal plane, and a chopper, which rotates in either the vertical or the horizontal plane. The dry powders are mixed by the rotating impeller before the liquid binder is poured or sprayed into the mixture. Agitation is maintained by the rotating impeller. As the liquid droplets disperse throughout the powder, they form granular nuclei. The granules grow until a predetermined optimum endpoint is reached. Snow et al. and Iveson et al. suggested that granule formation is controlled by a combination of wetting and nucleation, consolidation and growth, and breakage and attrition.

The binder plays a crucial role in granule formation, and it is considered a key component in high-shear granulation. The type and concentration of the binder solution influence the various physical attributes of tablets, such as hardness, dissolution time, disintegration time, compressibility, and content uniformity.

Porous calcium silicate (PCS), which has a structure of assembled petal-like flakes, is used to improve the drug solubility or dissolution properties of tablets. We previously reported a new approach to prepare granules with a high content of an extremely hygroscopic drug (Chinese medicine extract) using PCS. In that study, we did not use a binder, as the soluble starch and polysaccharides contained in the Chinese medicine extract may have acted as binders. PCS is an inorganic compound that is insoluble in water. Thus, the addition of a binder, such as starches, sugars, dextrins, and sugar alcohols, is needed to apply this method to other drugs. In addition, we previously reported the effect of saccharides as binders on the dissolution of nifedipine granules containing PCS. In that study, we identified xylitol as the best binder among seven saccharides used. However, the mechanism of wet granulation using a high-speed mixer granulator with PCS and sugar alcohols remains unclear.

Near-infrared (NIR) spectroscopy is becoming increasingly popular as a nondestructive and noninvasive analytical method. It has been used to study pharmaceutical raw materials, packaging materials, particle size, polymorphism, optical isomers, moisture, and quantitative and qualitative variables of dosage forms. NIR spectroscopy could be an interesting tool to monitor wet granulation because it provides both chemical and physical information about the sample. In the NIR region, the most intense absorption bands of pure water are found around 6900 and 5100 cm\(^{-1}\). The band near 5100 cm\(^{-1}\) is caused by a combination of OH stretching and bending vibrations, and that near 6900 cm\(^{-1}\) is attributable to the first overtone OH stretching vibrations of water molecules. It is well established that the states of water molecules mainly depend on their hydrogen-bonding ability. Thus, NIR spectrometry is useful as a process analytical technology (PAT) to evaluate wet granulation processes using water. The advantage

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of PAT is based on science and engineering principles to evaluate and diminish risks related to process quality. Therefore, PAT can be utilized to enhance pharmaceutical development, manufacturing processes, and formulation design.

PCS can absorb 4-fold more liquid than other compounds such as crystalline cellulose, silicon dioxide, magnesium aluminate silicate, and this characteristic means that approximately 50% more water can be added to it as an excipient in granulation compared to powder. Thus, the NIR spectra of granulation samples are water spectra, allowing direct discernment of changes in the state of water during granulation. The objectives of this study were to reveal changes in water’s behavior due to the excipient and binder when granules are formed and consequently to evaluate the mechanism of wet granulation using a high-speed mixer granulator with PCS and sugar alcohols. Furthermore, X-ray diffraction was applied to elucidate the mechanism of this granulation. In this study, four sugar alcohols (erythritol, mannitol, maltitol, and xylitol) were selected as binders, and their structure–function relationships were evaluated.

Experimental

Materials

PCS was purchased from Tomita Pharmaceutical Co., Ltd. (Tokushima, Japan). Xylitol, maltitol, and mannitol were obtained from Towa Chemical Industry Co., Ltd. (Osaka, Japan). Erythritol was purchased from Mitsubishi Chemical Foods Corporation (Tokyo, Japan). Other reagents were of analytical grade and were used without further purification.

Preparation of Granules

Wet granulation was conducted using a high-speed mixer (EARTHTECHNICA Co., Ltd., Tokyo, Japan). In total, 122.2 g of water was added to 61.1 g of PCS and mixed for 5 min at 200 rpm using an agitator and at 3000 rpm using a chopper. Then, 87.2 g of the binder was added to the PCS–water mixture, which was then stirred under the aforementioned conditions. When erythritol was used as the binder, samples were withdrawn 1, 15, 60, 65, and 70 min after addition. When xylitol was used as the binder, samples were withdrawn 1, 5, 15, 18, and 20 min after addition. These samples were used to measure the NIR spectra. After drying (New HD-60, Nagano Scientific Equipment MFG. Co., Ltd., Japan) at 70°C for 12 h, bulk density measurements and X-ray diffractometry were performed. The particle size distributions of the obtained granules were measured via laser diffraction and the scattering method using a dry module (LS 13 320, Beckman Coulter, Tokyo, Japan). The bulk densities of granules were measured according to method 1 (measurement in a graduated cylinder) of the determination of bulk and tapped densities in Japanese Pharmacopoeia 17.

Powder X-Ray Diffraction (PXRD)

PXRD was performed using Cu K-ALPHA1 radiation, a voltage of 40kV, and a current of 200 mA (RINT-2000, Rigaku Corporation, Tokyo, Japan). Patterns were obtained by scanning the 2θ range from 5 to 70° using a step size of 0.02° and a step speed of 5°/min.

Fourier-Transformed Near-Infrared (FT-NIR)

FT-NIR measurements were performed using an FT-IR/NIR spectrometer (PerkinElmer Frontier, PerkinElmer Japan Ltd., Japan) with an InGaAs detector. The samples were directly measured using a reflectance accessory. Each sample reading averaged 32 individual spectra at a resolution of 4 cm⁻¹, and scanned over the wave number region of 10000–4000 cm⁻¹. Curve fitting was performed using GRAMS/32 software (Grams/32, version 4.04, Galactic Industries Corp., Salem, NH, U.S.A.).

Results and Discussion

Because of its features, including water insolubility, numerous pores, and special petal structure, granules cannot be prepared with PCS using water as the binder. Therefore, a binder must be added to PCS to achieve granulation. A wet granulation method using a high-speed mixer granulator and four binders was used in this study. The properties of the obtained granules are presented in Table 1. The vessel temperature of the high-speed mixer granulator was gradually decreased after the addition of the binder. This may represent the dissolution process of the binder in water held within PCS. From the particle size distribution, heavy granules formed when maltitol or xylitol was used as the binder, whereas fine granules formed when erythritol or mannitol was used even if granulation was continued for 70 min. These results suggested that maltitol and xylitol are more suitable binders than erythritol and mannitol for PCS-based granules.

Figure 1 shows the NIR spectra of the binders used in this study. A hydroxyl group that participated in intramolecular hydrogen bonding was observed in the NIR spectra at 6970–6760 cm⁻¹ when erythritol or D-mannitol was used as the binder. Conversely, the hydroxyl group participating in intermolecular hydrogen bonding was observed for mixtures containing maltitol or xylitol at 6670–6270 cm⁻¹. The second derivatives of NIR spectra have often been monitored to investigate the wavelengths and intensities of peaks in detail, as they make peak detection easy and separate overlapped peaks from single peaks. To further understand the structural characteristics of the sugar alcohols, the second derivatives of the spectra were obtained. The expanded NIR spectra in the region of 7000–5800 cm⁻¹ are shown in Fig. 2. In the spectra for maltitol and xylitol, several peaks were observed in the regions corresponding to both inter- and intramolecular hydrogen bonds. Conversely, for erythritol and mannitol, several peaks were observed in the region corresponding to intramolecular hydrogen bonds, but not in the region corresponding to intermolecular hydrogen bonds. Moreover, Fig. 2 reveals that the intramolecular hydrogen bonds were weaker than the intermolecular hydrogen bonds because the peak of the intramolecular hydrogen bonds was blue-shifted compared with the intermolecular hydrogen bonds. Therefore, the intramolecular hydrogen bonds in xylitol and maltitol were considered to be cleaved to free-hydroxyl groups by the energy of stress using the agitation. On the contrary, the intermolecular hydrogen bonds of the hydroxyl groups in erythritol and mannitol may not be cleaved to free-hydroxyl groups. These results suggested that maltitol and xylitol interact more easily with PCS.

Table 1. Properties of PCS Granule Using Various Sugar Alcohols as a Binder

<table>
<thead>
<tr>
<th>Binder</th>
<th>Erythritol</th>
<th>D-Mannitol</th>
<th>Maltitol</th>
<th>Xylitol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulation time (min)</td>
<td>70</td>
<td>70</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Particle size distribution (µm)</td>
<td>D10</td>
<td>27.69</td>
<td>19.36</td>
<td>29.34</td>
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<tr>
<td></td>
<td>D50</td>
<td>133.5</td>
<td>64.29</td>
<td>346.0</td>
</tr>
<tr>
<td></td>
<td>D90</td>
<td>625.5</td>
<td>503.2</td>
<td>684.9</td>
</tr>
<tr>
<td>Bulk density (g/mL)</td>
<td>Start</td>
<td>0.25</td>
<td>0.24</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>0.26</td>
<td>0.25</td>
<td>0.36</td>
</tr>
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</table>
than do erythritol and mannitol. This difference in molecular interaction may reflect the differences in granule formation. As a result, xylitol and maltitol functioned as binders during granulation using PCS as the excipient.

To study the mechanism of wet granulation using PCS, NIR spectroscopy was performed. In this study, erythritol and xylitol were selected as binders because they have approximately the same molecular weight. Figure 3 shows the NIR spectra at predetermined times after the addition of a binder to water-loaded PCS. Bands observed near 5100 and 6900 cm\(^{-1}\) correspond to H\(_2\)O bending vibration+stretching vibration and H\(_2\)O stretching vibration, respectively.\(^{24}\) The intensities of both peaks increased after the addition of erythritol (Fig. 3(a)). The peak intensity near 6900 cm\(^{-1}\) increased after the addition of xylitol (Fig. 3(b)), whereas that near 5100 cm\(^{-1}\) declined after 15 min. The peak areas were calculated to investigate the relationship between the granulation process and these peak intensities. Figure 4 shows the relationship between peak area and time after the addition of erythritol (Fig. 4(a)) and xylitol (Fig. 4(b)). For erythritol, the areas of both peaks gradually increased until 60 min before sharply increasing at later time points. On the contrary, for xylitol (Fig. 4(b)), although the area of the peak near 6900 cm\(^{-1}\) increased over time, that of the peak near 5100 cm\(^{-1}\) increased until 19 min and decreased thereafter. The increases in peak area at near 5100 cm\(^{-1}\) and near 6900 cm\(^{-1}\) on initial granulation may attribute to the increase in the aggregated state of PCS via water detected as a change of light scattering. This phenomenon may suggest the transition of the state of water from pendular to funicular on the granule growth mechanisms of the agitation granulation.\(^{25}\) In contrast, Takeuchi et al.\(^{26}\) reported that the contribution of hydrogen bonds in H\(_2\)O molecules is larger for the peak at 5155 cm\(^{-1}\) than that at 6897 cm\(^{-1}\). Moreover, Imoto et al.\(^{27}\) suggested that H\(_2\)O bending was more strongly dependent on the state of the hydrogen-bonded network than OH stretching. Therefore, the change of the band near 5100 cm\(^{-1}\) could depend on the state of the hydrogen-bonded network. Thus, the decrease in the area of the peak at 5100 cm\(^{-1}\) represents the transition of the hydrogen-bonded network, caused by crosslinking of PCS and xylitol via water, i.e., the change of xylitol from a liquid to a solid via increases in intramolecular hydrogen bonding between the hydroxyl groups of xylitol and silanol groups of PCS via water. This phenomenon may suggest the transition of the state of water from funicular to capillary.\(^{25}\) The gradual transition of the state of water during the granulation was believed to be caused by the strong water-holding property of PCS. Consequently, in this study, the required agitation granulation time was more than twice the time compared with the general case.

The relationship between the peak area and granulation time is illustrated in Fig. 5. It is considered that phase (1) represents dissolution of the binder in water trapped in PCS, phase (2) represents the interaction of the binder with PCS, and phase (3) represents the increase in granule formation. To assess these considerations, the particle size and temperature in the mixing vessel of a high-speed mixer were measured.
Table 2 shows the particle size distribution in each phase, and the temperatures in the mixing vessel are presented in Fig. 5. In phases (1) and (2), the particle size distribution and bulk densities did not change, indicating that granule formulation did not occur in these phases. The temperature decreased in phase (1), indicating that the binder dissolved in water trapped in PCS. In phase (3), the particle size distribution, bulk densities, and temperature increased with increasing granule formulation. These results strongly support our aforementioned considerations. Kuriyama et al.\textsuperscript{28} reported the same relationship between absorbance in the NIR spectra during the granulation process for hollow granules and the granulation time.

Maeda et al.\textsuperscript{29} suggested that the spectrum of water consists of at least five-components of the hydrogen-bonded molecules. In this study, curve fitting was performed using the Gaussian–Lorentzian product function for the 5100 cm\textsuperscript{-1} band as a three-component spectrum (Fig. 6). For the curve fitting, the baseline was approximated via a straight line between (a) Erythritol, (b) xylitol. Each line means the NIR spectra at the time after granulation start. (Color figure can be accessed in the online version.)
two points chosen on both sides (5460 and 4450 cm$^{-1}$) of the band envelope in the nonabsorbing region of the spectrum. In each component of the spectrum, the contribution of hydrogen bonds in water species may increase from P1 to P3; specifically, peak P1 is attributed to free water molecules, peak P2 to two water molecules with hydrogen bond, and peak P3 to water molecules with multiple hydrogen bonds. The ratio of each component area to the area of the 4900 cm$^{-1}$ band was calculated, as shown in Fig. 7. The ratio for P3 increased with

<table>
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<th>Table 2. Characterization of Sample on Each Phase</th>
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<tr>
<td>Phase</td>
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<tr>
<td>Granulation time (min)</td>
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<td>Particle size distribution (μm)</td>
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<tr>
<td>D10</td>
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<tr>
<td>D50</td>
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<tr>
<td>D90</td>
</tr>
<tr>
<td>Bulk density (g/mL)</td>
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Phase (1): dissolution of the binder in water trapped in PCS, Phase (2): the interaction of the binder with PCS, Phase (3): the increase in granule formation.

Fig. 4. Change of Peak Area Assigned to Water during Granulation Process
(a) Erythritol, (b) xylitol. (□) 6900 cm$^{-1}$, (■) 5100 cm$^{-1}$.

Fig. 5. Typical Changes of Peak Area Assigned to Water during Granulation Process
(□) Peak area, (○) temperature.

Fig. 6. Curve Fitting for the 5460–4450 cm$^{-1}$ Region of NIR Spectra
with a Gaussian–Lorentzian Product Function
P1: free water molecules, P2: two water molecules with hydrogen bond, P3: water molecules with multiple hydrogen bonds.

Fig. 7. Change of Peak Area of the 5460–4450 cm$^{-1}$ Region of NIR Spectra Calculated by Gaussian–Lorentzian Product Function
(△) P1, (■) P2, (○) P3.
increasing time. However, the ratios for P1 and P2 increased until 19 min and decreased thereafter. From these results, it is considered that the contribution of hydrogen bonds in water species increased after 19 min. This suggests that granulation rapidly accelerates after 19 min. Moreover, the change of the NIR spectrum for this granulation was useful in determining the endpoint of granulation. The NIR spectrum of granulation using maltitol showed the same behavior using xylitol, and granulation using mannitol showed the same using erythritol (data not shown). Therefore, granulation conducted using PCS could be evaluated on the basis of changes of the NIR spectrum for water as the PAT.

To investigate the interaction between the binder and PCS, PXRD and NIR spectrometry were performed. Figures 8 and 9 show the NIR spectra and X-ray patterns of granules formed using erythritol and xylitol as the binder, respectively. In Figs. 8(a) and 9(a), no remarkable differences were observed between the granules and the physical mixture. These results...

Fig. 8. Effect of Erythritol or Xylitol on NIR Spectra of Granule
(a) Case of erythritol as a binder, (b) case of xylitol as a binder. (Color figure can be accessed in the online version.)
suggested that PCS and erythritol do not interact. Conversely, changes in the spectral pattern were noted for granulated xylitol compared to that of the physical mixture (Figs. 8(b) and 9(b)). As shown in Fig. 8(b), the NIR spectrum in the region of 6970–6270 cm\(^{-1}\) attributed to hydrogen-bonded hydroxyl groups specifically changed. Presumably, this can be viewed as an interaction between PCS and xylitol via hydrogen bonding. Thus, granulation continues due to the molecular interaction driven by hydrogen bonding via water between specific sites of PCS and the hydroxyl groups of the sugar alcohol. PCS is an inorganic compound consisting of silicon dioxide and calcium oxide, but the silanol groups of silicon dioxide may represent functional groups that could participate in intermolecular hydrogen bonding. In other words, molecular interactions between PCS and a sugar alcohol may occur via powerful hydrogen bonding between silanol groups and intramolecular hydrogen-bonded hydroxyl groups of the sugar alcohol. In Fig. 9(b), the diffraction pattern of the physical mixture exhibited characteristic peaks derived from xylitol, but the distinctive peak of xylitol was missing for the granules, indicating that the crystalline state of xylitol changed to an amorphous state after granulation.

From these results, the mechanism of granulation was speculated as follows. At the beginning of granulation, maltitol or xylitol, which was originally in a crystalline state, was dissolved in water held by PCS. As granulation progressed, dissolved xylitol solidified due to reduced solubility in the mixture induced by the stress of agitation in the high-speed mixer. During this process, intermolecular hydrogen bonding occurred between xylitol and PCS. Therefore, xylitol in these granules had an amorphous state. This amorphous xylitol included the bulky PCS, resulting in the formation of granules with large bulk densities.

**Conclusion**

Maltitol and xylitol possess intramolecular hydrogen-
bonded hydroxyl groups to cleaved to free-hydroxy groups by the stress of agitation, and they strongly interact with PCS, resulting in intermolecular hydrogen bonding and granulation. In addition, the NIR spectra of the obtained granules revealed changes in bands due to the hydroxyl groups in granules and permitted observation of intermolecular hydrogen bonding. Thus, molecular interactions between the silanol groups in PCS and the intramolecular hydrogen-bonded hydroxyl groups in the sugar alcohol via water is the mechanism of granulation when PCS is used as the excipient. X-Ray powder diffraction allowed discernment of these interactions and assessments of their intensity, substantiating the postulated mechanism of granulation. The results of this study indicated that the excipient and the binder interact during granule formation via hydrogen bonding. This study also indicated that the mechanism of granulation can be assessed by measuring the NIR spectra. Moreover, changes in the NIR spectrum assigned to water were useful as a PAT in evaluating the progress of granulation using PCS.

Conflict of Interest  The authors declare no conflict of interest.

References