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A method for predicting the amount of water required for wet granulation using NIR

Akio Miwa [a,*], Kouji Makado [b]

[a] Product Quality Assurance Division, Quality Assurance Head Office, Taisho Pharmaceutical Co., Ltd., 24-1, Takada 3-chome, Toshima-ku, Tokyo 170-8633, Japan
[b] Pharmaceutical Technology Laboratories, Taisho Pharmaceutical Co., Ltd., 403, Yoshino-cho 1-chome, Kita-ku, Saitama-shi, Saitama 331-9530, Japan

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ABSTRACT

The purpose of this study is to optimize the amount of water to be added as a binder solution in wet granulation. In our previous studies, we introduced a method to predict the suitable amount of water added to multi-component formulations by summing corresponding values of the components estimated by an NIR sensor prior to granulation. But in this theory, water added to a formulation is assumed to be evenly distributed to each excipient. To guarantee this theory, we used two-component mixtures as a simplified model to estimate the water distribution to each component using an NIR sensor. In cases in which the volume of water added was comparatively small, water was evenly distributed to each excipient; however, when the water added was increased it was not evenly distributed. To interpret this phenomenon, a new concept was introduced, taking the migration of water between each excipient into consideration. By introducing the concept, it turned out to be possible to predict the suitable amount of water to be added in the two-component model by summing the corresponding values of each component even in a range in which there was an uneven distribution.

1. Introduction

In our previous study, we estimated the suitable amount of water added for various excipients in granulation based on water distribution model to the powder internal/surface using an NIR sensor (Miwa et al., 2000). These corresponding values of excipients could be applied to estimate the suitable amount of water of formulations, which was calculated by summing the lower-limit or upper-limit of suitable amount of water for each component (excipient). These predicted values coincided well with the experimental ones for high-speed agitating and fluidized bed granulations (Miwa et al., 2000, 2008). If this phenomenon can be generally observed, the suitable amount of water added to various formulations could be predicted by simply calculating the suitable value of each excipient in advance.

But, in this method, water added to the excipients is assumed to be evenly distributed. Hence, it is important to verify the water distribution of each excipient and clarify whether the sum of the optimum water volumes of each excipient is actually equivalent to the volume of the formulation. However, no such study has been conducted till date.

In this study, we focused on the fact that a reflective NIR sensor detects only water on the powder surface in relation to granulation (Shimada and Nishii, 1990; Watano, 1996). Mixtures (1:1) of the two excipients were prepared as simplified models to determine whether water was evenly distributed to each excipient by comparing the NIR outputs of the mixtures and each excipient using various volumes of water added. We verified that the suitable amount of water in a formulation could be estimated by summing its upper and lower limits in each excipient.

2. Materials and methods

2.1. Materials

Four kinds of excipient powders were used: lactose (Borculo), cornstarch (Nippon Cornstarch), microcrystalline cellulose (Asahi Chemical Industry), and carboxymethyl-cellulose calcium (CMC-Ca, Nichirin Chemical).

2.2. Equipment

The water content on the powder surface was measured by a reflective NIR (WET EYE, Dalton). The detection wavelength was 1.94 μm and the contrast wavelengths were 1.8 μm and 2.1 μm (Shimada and Nishii, 1990; Watano, 1996). Purge air was not used during the measurements.

* Corresponding author at: Product Quality Assurance Division, Quality Assurance Head Office, Taisho Pharmaceutical Co., Ltd., 24-1, Takada 3-chome, Toshima-ku, Tokyo 170-8633, Japan. Tel.: +81 3 3985 1248; fax: +81 3 5951 0156.
E-mail address: akio.miwa@po.rd.taisho.co.jp (A. Miwa).

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2.3. Wet granulation of each excipient

Five grams of each component or a 1:1 mixture was placed in a mortar, and purified water (e.g., 0.125 ml) was added to the powder with a pipette. The mixture was kneaded with a mortar and pestle for approximately 2 min. The detecting element of the prove-type reflective NIR sensor was brought to the mixture without actually contacting the mixture and the output value of the NIR sensor was measured. Following the measurement, the mixture was voided. A new batch of the powder (5 g) was used for the next trial. A greater amount of purified water (e.g., 0.25 ml) was added to powder in the same manner, and the output value was measured once again. This process was repeated by increasing the amount of water, until excess granulation clearly occurred with gradual addition of water. We also measured 5 g of each component or a 1:1 mixture without addition of water.

2.4. Analysis of plots

The output value of the NIR of each component or the 1:1 mixture was plotted against the amount of water added ($100a/W$), where a, water weight and W, powder weight.

3. Results and discussion

3.1. Prediction of suitable water amount in two-component model

Fig. 1 is a schematic representation of water distribution in the one-component excipient model. In general, the reflective NIR sensor detects the water adhered or retained on the powder surface (Shimada and Nishii, 1990; Watano, 1996). The ratio of the amount of water between the powder surface and the interior powder differs according to each excipient and changes depending on the volume of water added. In fact when "a" ml of water is added to W g of excipient, the output plot pattern of the NIR sensor against a/W or $a/(W+a)$ differs according to each excipient and a linear relationship is not observed even with a single excipient (Miwa et al., 2000). When "a" ml of water is added to W g of an excipient and the ratio of water detectable by NIR sensor is defined as α, the amount of water detected by the NIR sensor (NIR) can be written as Eq. (1):

$$\mathrm{NIR} = \alpha \cdot a/W \quad (1)$$

This theory can be expanded to the two-component model under the assumption that NIR detects the sum of water distributed on the powder surface of each excipient ($\mathrm{NIR_{A:B}}$). The following equation can be obtained, taking the weight ratio of each excipient into consideration (Fig. 2):

$$\mathrm{NIR_{A:B}} = W_A/(W_A+W_B)\alpha_A a_A/W_A + W_B/(W_A+W_B)\alpha_B a_B/W_B \quad (2)$$

where a_A and a_B denote the amount of water distributed to excipients A and B, α_A and α_B denote the ratio of amount of water detectable by the NIR sensor when a_A ml and a_B ml of water are distributed to W_A g of excipient A and W_B g of excipient B, respectively.

If the amount of water added ("a" ml) is distributed to excipients of the total weight; W_{total} ($W_{total} = W_A + W_B$) according to the weight ratios, as was assumed previously, then the amount of water distributed to each excipient are $aW_A/(W_A+W_B)$ (ml) and $aW_B/(W_A+W_B)$ (ml) for excipient A (Weight W_A) and excipient B (Weight W_B), respectively, because the weight ratios of excipients A and B are $W_A/(W_A+W_B)$ and $W_B/(W_A+W_B)$, respectively.

Therefore, the water distributed to excipient A in the two-component model, the ratio of water to the excipient weight (a_A/W_A) can be written as

$$a_A/W_A = (aW_A/[W_A+W_B]/[W_{total}W_A]/[W_A+W_B]) = a/W_{total} \quad (3)$$

Similarly, as for the one-component model of excipient A, the ratio of water to the excipient weight (a/W) becomes a/W_{total}. Namely, the ratio of the amount of water distributed to excipient A in the two-component model (a_A/W_A) is equivalent to that of the one-component model (a/W) as long as the amount of water added is distributed according to the weight ratios. Then, α_A in the two-component model becomes equal to α in case of only excipient A exists. It means that $\alpha_A a_A/W_A$ in the two-component model is equal to $\alpha a/W$ (=$\mathrm{NIR_{A\text{-}one}}$) of the NIR output value in the one-component model for excipient A. This finding is also adaptable to excipient B as well as excipient A, and the following equation can be obtained for the two-component model:

$$\mathrm{NIR_{A:B}} = (W_A/[W_A+W_B])\mathrm{NIR_{A\text{-}one}} + (W_A/[W_A+W_B])\mathrm{NIR_{B\text{-}one}} \quad (4)$$

Eq. (4) indicates the output value of a mixture that can be estimated by each excipient and its ratio. When each excipient is blended 1:1, $W_A = W_B$, and the output value is written as follows:

$$\mathrm{NIR_{A:B=1:1}} = (\mathrm{NIR_{A\text{-}one}} + \mathrm{NIR_{B\text{-}one}})/2 \quad (5)$$

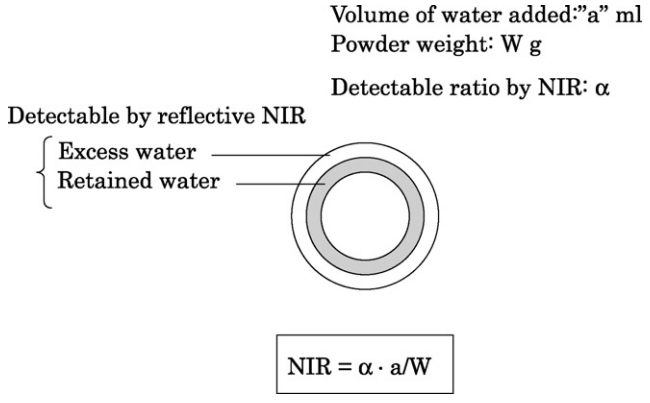

Fig. 1. Schematic representation of water distribution in the one-component model. When "a" ml of water is added to W g of an excipient and the ratio of water detectable by an NIR sensor is defined as α the amount of water detected by the NIR sensor (NIR) can be written as $\mathrm{NIR} = \alpha \cdot a/W$.

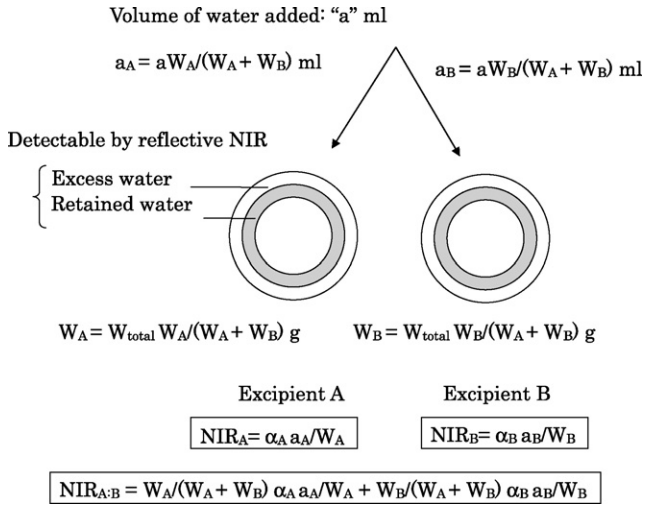

Fig. 2. Schematic representation of water distribution in the two-component model. When "a" ml of water is added to W_{total} g of powder, including excipients A and B, a_A ml and a_B ml of water is distributed to W_A g of excipient A and W_B g of excipient B according to the weight ratio. When α_A and α_B denote the ratios of water detectable by an NIR sensor for excipient A and B, the amounts of water of excipient A and B detected by the NIR sensor can be written as $\mathrm{NIR_A} = \alpha_A a_A/W_A$ and $\mathrm{NIR_B} = \alpha_B a_B/W_B$, respectively. The total can also be written as the sum of $\mathrm{NIR_A}$ and $\mathrm{NIR_B}$.

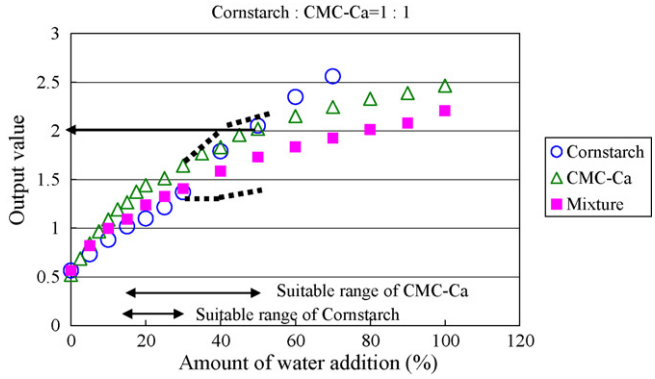

Fig. 3. Change in NIR output values for cornstarch, CMC-Ca, and the 1:1 mixture. The *X*-axis shows $100a/W$; *a*, weight of water; *W*, weight of powder. The ranges of arrows (↔) show the suitable amount of water added from the lower limit to the upper limit of each excipient. The dotted lines show the predicted NIR output values of each excipient in the mixture in amounts of water added above the upper limit of one excipient with the lower water retention potential (cornstarch in this case). The value "2.0" shown by the arrow (←) indicates the NIR output value when water was added to the upper limit of one excipient with the higher water retention potential (CMC-Ca in this case). This interpretation is also adaptable for Figs. 4–8, which show the change in the NIR output values for the 1:1 mixture and its components. Dotted lines are not shown because the upper limit of CMC-Ca (50%) and that of microcrystalline cellulose (51%) are similar to Fig. 8.

Eq. (5) shows the NIR output value of mixture ($NIR_{A:B=1:1}$), which is the average of each excipient's value as long as the amount of water added is distributed according to the weight ratios.

Furthermore, this theory can be expanded to the multi-component model and the following equation can be obtained:

$$NIR_{Multi} = \alpha NIR_{A\text{-one}} + \beta NIR_{B\text{-one}} + \gamma NIR_{C\text{-one}} + \cdots$$
$$(\alpha + \beta + \gamma + \cdots = 1) \quad (6)$$

where NIR_{Multi} denotes the NIR output value in the multi-component model and α, β, and γ are the weight ratios of each excipient.

3.2. Relationship between NIR sensor output value and amount of water added in the two-component model

The relationship between NIR output values and the amount of water added to cornstarch:CMC-Ca (1:1 mixture) and cornstarch:microcrystalline cellulose (1:1 mixture), as well as the output values of each excipient as references is shown in Figs. 3 and 4, respectively. The suitable ranges of water to add for each excipient are also shown in Table 1 (Miwa et al., 2000). As shown in Fig. 3, in the area where comparatively small amount of water was added (i.e. until approximately 31%, amount of water added/powder weight × 100), the NIR values of the 1:1 mixture were equal to the average of each excipient's value. The amount of water (31%) coincided with the upper limit for cornstarch. If >31% water was added, the value of the mixture drastically deviated from the average of each excipient.

Similarly, for the 1:1 mixtures with cornstarch, microcrystalline cellulose, and CMC-Ca to lactose, the values of the mixtures were equal to the averages of each excipient until approximately 10% water addition, which is the value equivalent to the upper limit for lactose. If >10% water was added, the values of the mixture drastically deviated from the averages of each excipient (Figs. 5–7).

The output value of the microcrystalline cellulose:CMC-Ca (1:1 mixture) also indicated the average of each excipient until approximately 51% water was added, which is the value equivalent to the upper limit for microcrystalline cellulose. If >51% water was added, the value of the mixture drastically deviated from the average of each excipient (Fig. 8).

Table 1
Suitable range of water addition for each excipient[a].

Excipient	Lower–upper limit	
	$100a/(a+W)$	$100a/W$
Lactose	3.0–9.0	3–10
D-mannitol	3.9–10.2	4–11
Cornstarch	13[b]–23.6	15–31
CMC-Ca	14.5–33[b]	17–50
L-HPC	15.0–33[b]	18–50
Microcrystalline cellulose	21.2–33.8	27–51
HPC-L	0–0	0–0

[a] *a*, water weight; *W*, powder weight.
[b] The value was estimated based only on microscopic observations.

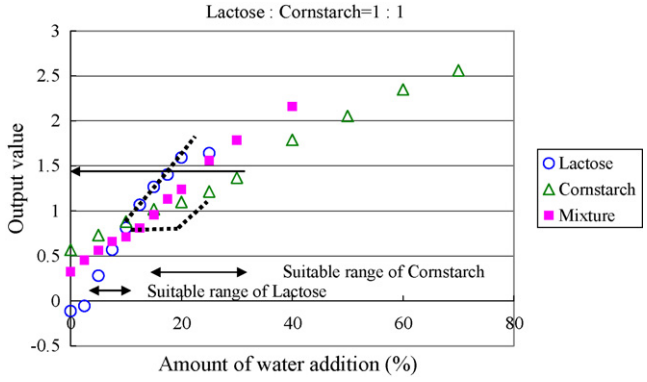

Fig. 5. Change in NIR output values for lactose, cornstarch, and the 1:1 mixture.

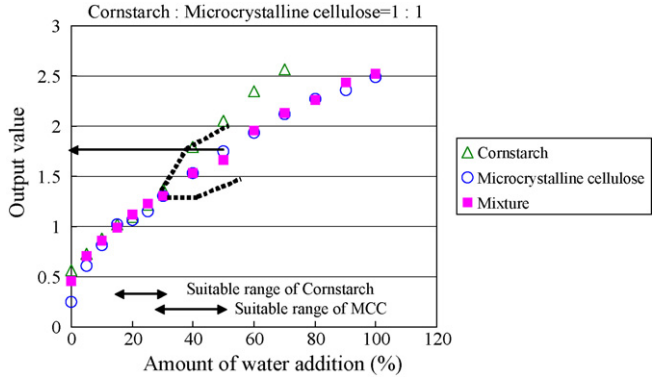

Fig. 4. Change in NIR output values for cornstarch, microcrystalline cellulose, and the 1:1 mixture.

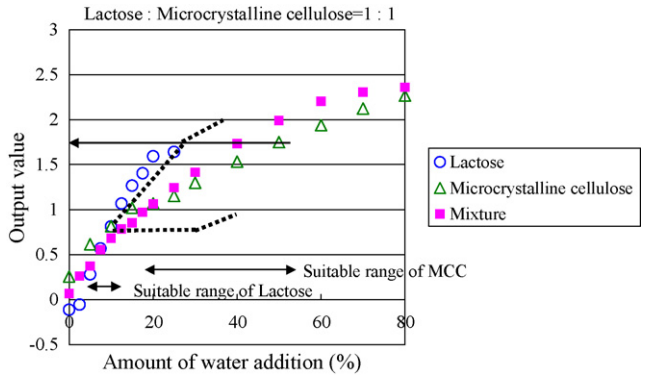

Fig. 6. Change in NIR output values for lactose, microcrystalline cellulose, and the 1:1 mixture.

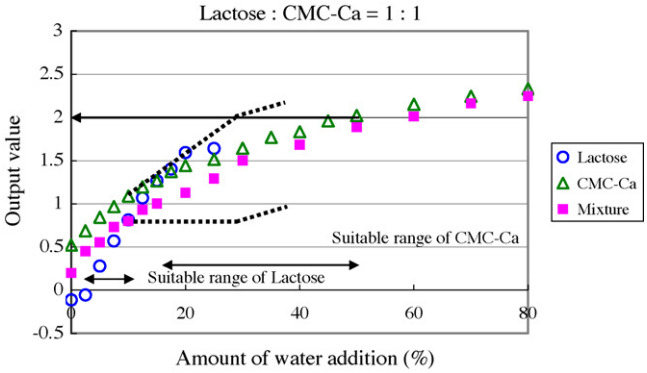

Fig. 7. Change in NIR output values for lactose, CMC-Ca, and the 1:1 mixture.

In every combination of the two-component model, the area with comparatively smaller amounts of water added, in other words, the area smaller than the approximate upper limit of suitable water addition for an excipient with lower water retention among two components, the NIR values of a 1:1 mixture were equal to the averages of each excipient, whereas the value of the mixture deviated from the average of each excipient if the volume added was higher than the upper limit.

From the above-mentioned reasons, Eq. (5) can be applied for the area with comparatively smaller amounts of water added, where the water added is evenly distributed to each excipient.

3.3. Assumption of water distribution in two-component model of excipients

To elucidate the NIR output patterns as shown in Section 3.2, we divided the water distribution in the two-component model into three steps. Fig. 9 shows the schematic representation of the concept, where excipient A was defined as the excipient with a lower capability for water retention. If the amount of water added is less than the upper limit of the suitable amount for excipient A, the water is evenly distributed to excipients A and B (Step 1). However, if the amount of water added surpasses the upper limit of the suitable amount for excipient A, the excess amount of water for excipient A is distributed to excipient B that has a higher capacity for water retention (Step 2). This tendency continues until the amount of water added reaches the upper limit of the suitable amount of water added for excipient B. If the amount of water added is higher than the upper limit of excipient B, then the excess is accumulated onto the surfaces of A and B (Step 3).

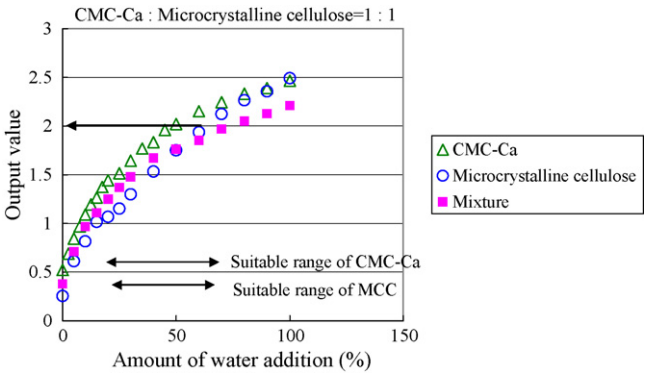

Fig. 8. Change in NIR output values for CMC-Ca, microcrystalline cellulose, and the 1:1 mixture.

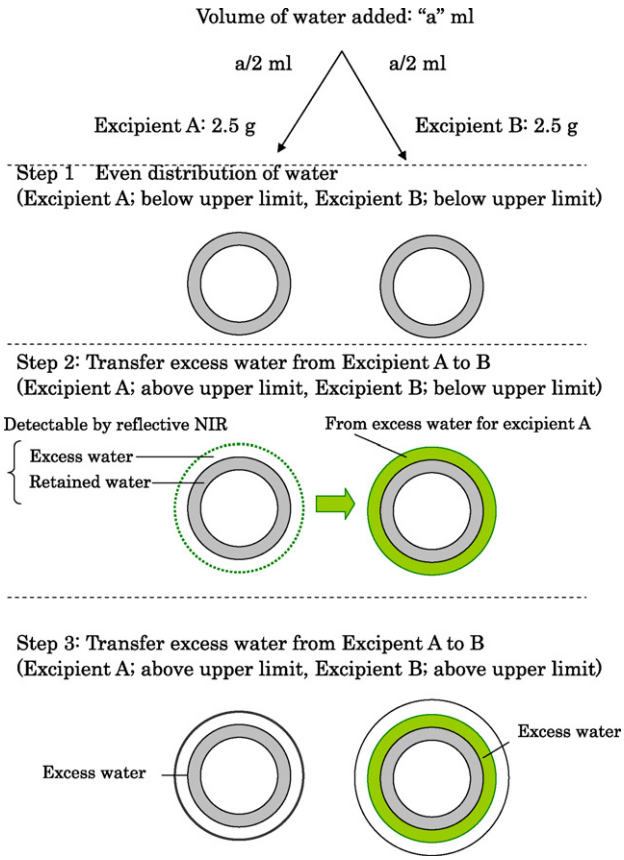

Fig. 9. Concept of three-step water distribution in the two-component model. Excipient A was defined as the one with the lower capacity for water retention.

3.4. Method to determine the suitable amount of water in the two-component model of excipients

3.4.1. The lower limit of the suitable amount of water added for a mixture

As described in Sections 3.1 and 3.2, the range in which the output value of the mixture is equal to the average of each excipient, water is evenly distributed to each excipient, so that the lower limit of the suitable amount of water added for a mixture can simply be determined as the average of the lower limit of the suitable amount for each excipient, under the conditions that the lower limit of each excipient is in this range.

In case of cornstarch–CMC-Ca, cornstarch–microcrystalline cellulose, and microcrystalline cellulose–CMC-Ca mixtures, the lower limit of each excipient (cornstarch 15%, CMC-Ca 17%, microcrystalline cellulose 27%) is in the range where water is evenly distributed (i.e., Step 1 shown in Fig. 9), so that the lower limit of the suitable amount of water added for the mixture is considered to be the average for each excipient (Figs. 3, 4 and 8).

In case of lactose–cornstarch and lactose–CMC-Ca mixtures, the lower limit of cornstarch or CMC-Ca is higher than the range where water is evenly distributed as shown in Figs. 5 and 7; but, because the average of the lower limit of the suitable amount of water added for lactose and cornstarch or CMC-Ca is within the range where water is evenly distributed, the lower limit of the suitable amount of water added for the mixture is also considered to be the average for the combined excipients.

In case of the lactose–microcrystalline cellulose mixture, the suitable range for each excipient does not overlap and the average of the lower limit for each excipient is out of range where water is evenly distributed, as shown in Fig. 6. In this case, microcrys-

talline cellulose, which has a higher capacity for water retention, takes up the excess water from lactose at the volume of the average of the lower limit of the suitable amount of water added for each excipient. Then, the actual lower limit of suitable water for the mixture is considered to be lower than the average for each excipient. However, this phenomenon is only observed when the lower limit of the suitable amount of water added for each excipient is drastically different from each other and the upper limit of the suitable amount of water added for an excipient with a lower capacity for water retention such as lactose is smaller than the lower limit of an excipient with a higher capacity for water retention such as microcrystalline cellulose. In a multi-component formulation, the probability of using excipients with overlapping the suitable range is very high, therefore, these kinds of phenomena may seldom occur.

3.4.2. The upper limit of the suitable amount of water added for a mixture

The upper limit of the suitable amount of water added for a mixture is the point where both excipients reach the upper limit of the suitable amount of water added, or the point at which Step 2 proceeds to Step 3 in Fig. 9. In case of the cornstarch–CMC-Ca mixture because cornstarch cannot retain >31% water (the upper limit of suitable amount of water added), the excess water will be transferred to CMC-Ca. If >31% water is added, the NIR output of cornstarch in the mixture will be constant against the amount of water added as shown by the dotted line in Fig. 3. In contrast, the dotted line for the NIR output of a CMC-Ca in the mixture can be plotted under the assumption that the output value of the mixture is the average of each excipient.

CMC-Ca will receive excess water from cornstarch until the water added reaches 50% (the upper limit of the suitable amount of water added for CMC-Ca) or the output value of 2.0 (the output value at the upper limit of water added for CMC-Ca) in the mixture. In the range where water transfers from cornstarch to CMC-Ca (Step 2), CMC-Ca will receive all added water so that half of the water added will be sufficient to reach the upper limit of the suitable amount of water added for CMC-Ca in the mixture.

When the upper limits of cornstarch and CMC-Ca are defined as a% (i.e., 31%) and b% (i.e., 50%), respectively, Step 2 can be written as $(b-a)/2$%. By adding the upper limit of cornstarch (a%) to this value, the upper limit for CMC-Ca after cornstarch reaches its upper limit in the mixture or the upper limit of the mixture can be calculated as

$$\text{Upper limit of mixture } (\%) = a + (b-a)/2 = (a+b)/2 \quad (7)$$

The suitable amount of water added to a mixture is the average of each excipient, i.e., the amount of water in which Step 2 proceeds to Step 3 is expressed as $(a+b)/2$%.

The same analyses were conducted for each two-component model and the results are shown in Figs. 4–8. In cases of the cornstarch–microcrystalline cellulose and lactose–microcrystalline cellulose mixtures, microcrystalline cellulose, which has a higher capacity for water retention, received the excess water not retained by another excipient up to the output value of 1.8 (the output value at the upper limit of water addition for microcrystalline cellulose). In case of the lactose–cornstarch mixtures, cornstarch which has a higher capacity for water retention, received the excess water not retained by lactose up to the output value of 1.4 (the output value at the upper limit of water addition for cornstarch). In case of the microcrystalline cellulose–CMC-Ca and lactose–CMC-Ca mixtures, CMC-Ca, which has a higher capacity for water retention, received the excess water not retained by another excipient. The upper limits of the suitable amount of water added to these mixtures could also be estimated from the average of the upper limit of each excipient.

The relationship between the amount of water added and water distribution phenomena to excipients for a 1:1 mixture model has been discussed. Water added to a mixture was evenly distributed to each excipient until the water added reached the upper limit of the suitable amount of water added for the excipient with the lower capacity for water retention, but when the water exceeded this level, water was unevenly distributed to each excipient. However by introducing the concept of water transfer, the method to estimate the upper (lower) limit of the suitable amount of water to added for the formulation by summing the upper (lower) limit for each excipient was considered to be applicable, even in the range where water is unevenly distributed to each excipient. This calculation method applies not only for a 1:1 mixture but also for multi-component formulations.

Furthermore, except for CMC-Ca, which has the highest water retention capability among the excipients used in this study, the upper limit of the suitable amount of water added for the excipient with the lower capacity of water retention coincided with the point at which the NIR output value of the mixture began to deviate from the average of the value for each excipient. This finding indicates the correctness of the upper limits of each excipient, which were obtained in previous study (Table 1; Miwa et al., 2000).

Most excipients are basically hydrophilic so that the difference in wettability for each excipient does not influence the attractive force of water, because in the range where the amount of water added is comparatively small (smaller than or equal to the upper limit of the suitable amount of water added for the excipient with the lower capacity of water retention), water was evenly distributed in each excipient.

4. Conclusion

In a 1:1 mixture of excipients, the suitability of assumption in relation to water distribution and the prediction of the suitable amount of water added in the formulation were verified and the following findings could be obtained:

1. The range of water addition where the water is evenly or unevenly distributed to each excipient was determined. The amount of water that was necessary to add changed from an even distribution of each excipient to an uneven distribution coincided with the upper limit of the suitable amount of water added for the excipient with the lower capacity for water retention.
2. The method to determine the upper (lower) limit of the suitable amount of water to add for formulation by summing the upper (lower) limit of each excipient was considered to be applicable. Especially, upper limit of suitable amount of water added to formulations was determined by introducing the concept that excess water generated from the excipient with the lower capacity of water retention transfers to the excipient with the higher capability of water retention in the range where water is unevenly distributed to each excipient, These findings indicate that this method can be applied for a wide range of water addition situations and can be applied to multi-component formulations.

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