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Prediction of suitable amount of water addition for wet granulation

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Abstract

The purpose of this study was to predict the amounts of water addition suitable for pharmaceutical formulations in wet granulation, using a high-speed mixer or a fluidized bed granulator, before granulation trials. In order to determine the suitable amount of water addition, each excipient was first subjected to kneading with water in a mortar and a refractive near-infrared moisture sensor (IR sensor) measured the amount of water at the powder surface. Further by analysis the plot (output value of the IR sensor vs. amount of added water) for each excipient, the amount of water addition for granulation was determined for it. As a second step, two model formulations were designed and suitable amounts of water for granulation were predicted by summation of the obtained excipient values. The predicted value was compared with the experimental value for high-speed mixer granulation. The predicted and experimental amounts of water addition corresponded for the two model formulations, suggesting that the above method is useful for estimating suitable amounts of addition of water for formulations before granulation trials.

Keywords: Infrared sensor; Wet granulation; Water; Suitable amount; Prediction; Excipient

1. Introduction

In wet granulation processes using a high-speed mixer or a fluidized bed granulator, the amount of water added to powders is one of the most important questions, since particle growth has been found to occur by liquid bridging of powders (Newitt and Conway-Jones, 1958). However, in actual operation, amounts of added water have been determined based on the experience and judgment of expert operators because of the difficulty of quantitative analysis of powder properties and behaviors.

Theoretical reports on the fluidized bed granulation process using the refractive near-infrared moisture sensor (IR sensor), which can measure the water content on powder surfaces have recently increased. Monitoring of moisture content

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can be used to regulate particle growth. The relationships between moisture content and powder properties such as particle size have been investigated. In granulation systems at steady moisture content state, a correlation exists between particle size and moisture content, and suitable moisture content for formulations can thereby be determined (Schæfer and Wørts, 1978; Watano et al., 1991, 1994, 1995).

However, in the above cases, no method for determining suitable moisture content, before granulation trials has been described. Further, since suitable moisture content varies with the pharmaceutical formulation, due to powder properties (e.g. water-absorbing potential, coherent strength) (Watano et al., 1996a), predicting the suitable amount of water is difficult. If the amount of water addition can be predicted before granulation trials, many advantages will accrue in handling and scale-up of the granulation process. Only a few studies have considered the prediction of amount of added water using theoretical approaches (Jover et al., 1996).

In order to determine suitable amounts of water for pharmaceutical formulations before granulation trials, we ensured that granulation occurred by liquid bridging of powder (Newitt and Conway-Jones, 1958) and that the IR sensor could measure only the water content of the powder surface related to granulation (Shimada and Nishii, 1990; Watano, 1996b). With use of the IR sensor, we presumed that the water behavior of the liquid bridge state (pendular and funicular state) could be grasped. Firstly, for each excipient of formulation components, we attempted in this study to determine the suitable amount of water addition, by analysis of the output value of IR sensor against amount of added water. As a second step, the suitable amounts of water for two pharmaceutical formulation models were predicted by summation of each excipient value. As a final step, the predicted values for pharmaceutical formulations, were compared with experimental values obtained by high-speed mixer granulation and tabletting.

2. Materials and methods

2.1. Materials

The powders used were lactose (NCZ), D-mannitol (Towa Chemical Industry), cornstarch (Nippon Cornstarch), microcrystalline cellulose (Avicel PH101, Asahi Chemical Industry), carboxymethyl-cellulose calcium (CMC-Ca, Nichirin Chemical), low-substituted hydroxypropyl cellulose (L-HPC LH21, Shin-Etsu Chemical), hydroxypropyl cellulose (HPC-L, Nippon Soda), and magnesium stearate (Taihei Chemical).

2.2. Equipment

The water content on powder surfaces was measured by a refractive near-infrared moisture (IR) sensor (WET-EYE, Fuji Paudal). The detection wavelength was 1.94 μm and the contrast wavelengths were 1.8 and 2.1 μm (Shimada and Nishii, 1990; Watano, 1996b). The purge air was not used during measuring.

2.3. Wet granulation of each excipient

In the case of lactose, 10 g were placed in a mortar. Purified water (0.2 ml) was added to the powder using a pipette. The mixture was kneaded by a pestle in the mortar. The detecting element of the IR sensor was brought to the mixture in non-contacting condition, and the output value of the IR sensor was then measured. After measurement, the mixture was voided. New lactose (10 g) was used for the next trial. A larger amount of purified water (0.4 ml) was added to lactose in the same manner, and the output value was measured again. This process was repeated with increasing amounts of water, until excess granulation clearly occurred with gradual addition of water. The other excipients were tested in a similar fashion for each excipient, with $n = 3$.

2.4. Analysis of plots

The output value of the IR sensor was plotted against amount of water addition (100 WA/(WA + WB), where, WA, weight of water; WB,

weight of powder). The suitable amount of added water was determined by comparing the inflection point of the graph with optical microscopic observations (Microphoto-FX, Nikon) and the 840 μm aperture-passed yields of wet granulation.

2.5. Wet granulation and tabletting of formulations

The formulations are listed in Table 1. Excipients other than magnesium stearate were granulated with purified water using a 25-L high-speed type mixer (Vertical Granulator 25L, Powrex). The mixed powder (formulation A, 4500 g, formulation B, 3500 g) was charged in and sprayed with water during agitation. Four levels, beneath the lower limit, lower limit, upper limit, and above the upper limit of the predicted suitable amount, were set as spray amounts. The mixture was granulated for 5 min in total and dried with a fluidized bed dryer (FD-3S, Powrex). The dried granules were screened through a 500 μm aperture mesh. Magnesium stearate was then blended with the granules.

The obtained granules were tabletted on a rotary tablet press (Correct 12 HU, Kikusui) fitted with 12 standard concave punches (diameter 8 mm). For each compression, 200 mg of granules were used. The press speed was maintained at 360 tablets/min, with the compression force set from 0.6 to 1.4 ton/punch stepwise at 0.2 ton/punch.

2.6. Evaluation of granules and tablets

A laser diffraction method with a He-Ne laser beam (Microtrack USP, Nikkiso) was used to measure a granule particle size. The air pressure to disperse particles is 2 kgf/cm^2 in dry method. The median diameter was determined for three measurements. Bulk density (loose, tap) was measured using a powder property tester (Powder Tester, Hosokawa micron). Tablet hardness was determined using a tablet hardness tester with a pressure attachment (WHT-1, Pharma-Test). Tablet disintegration time was determined using a disintegrating apparatus (NT-2HS, Toyama) with plastic disks for formulation A, but without plastic disks for formulation B. The average hardness of 20 tablets and the disintegration time of six tablets were also used for evaluation.

Table 1
Test formulations

	A	B
Lactose	35	60
Microcrystalline cellulose	39	14
Cornstarch	10	10
CMC-Ca	10	10
HPC-L	6	6
Total	100	100

3. Results and discussion

3.1. Estimate of suitable amount of water addition for each excipient

Water added to powder was assumed to distribute inside of, or on the surface of powder. Fig. 1 shows various plot patterns of amount of added water versus. output value. If the inside/surface distribution is constant during addition of increas-

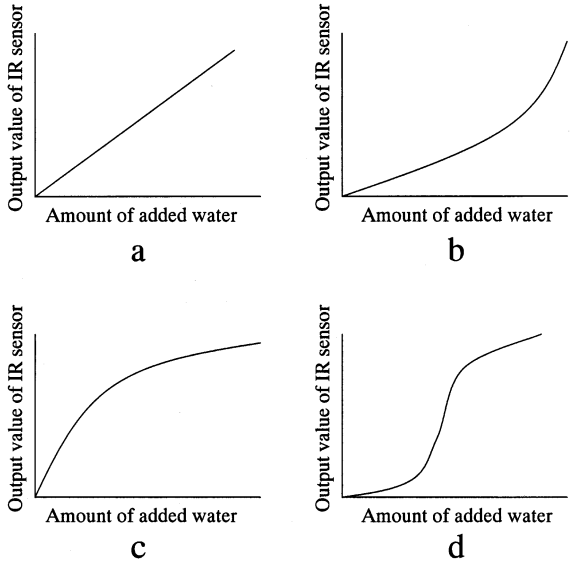

Fig. 1. Plot patterns of added water versus. output value of IR sensor.

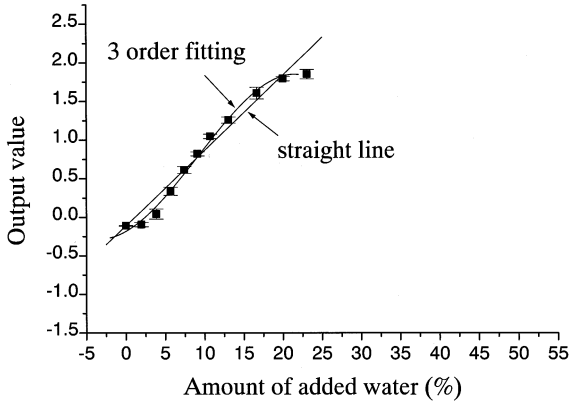

Fig. 2. Change in output values for lactose. *X*-axis shows 100 WA/(WA + WB); WA, weight of water; WB, weight of powder.

ing amounts of water, it seems reasonable to think that the output values of IR sensor against amount of added water, increase regularly (Fig. 1a). If the distribution changes during addition of increasing amounts of water, it seems reasonable to think that the output values increase or decrease irregularly. Fig. 1b shows the case of constant inside/surface-distribution below an amount of added water, but increasing surface ratio because of saturation absorption capacity above the amount of added water. On the contrary, Fig. 1c shows the case of decreasing surface ratio above an amount of added water. In addition, Fig. 1d shows the case of increasing surface ratio abruptly after at the beginning of adding water because of the very low absorption capacity of powder, and shows the case of the levering, off the top of output value.

Various characteristic excipients were examined to confirm the water behavior of powder surfaces. Lactose and D-mannitol as representatives of water-soluble excipients, cornstarch as poorly water-soluble excipient, carboxymethyl-cellulose calcium and low-substituted hydroxypropyl cellulose as disintegrates, microcrystalline cellulose as weak disintegrate, and hydroxypropyl cellulose as a binder, were examined.

Figs. 2–9 show the relationship between amount of added water and output value of the

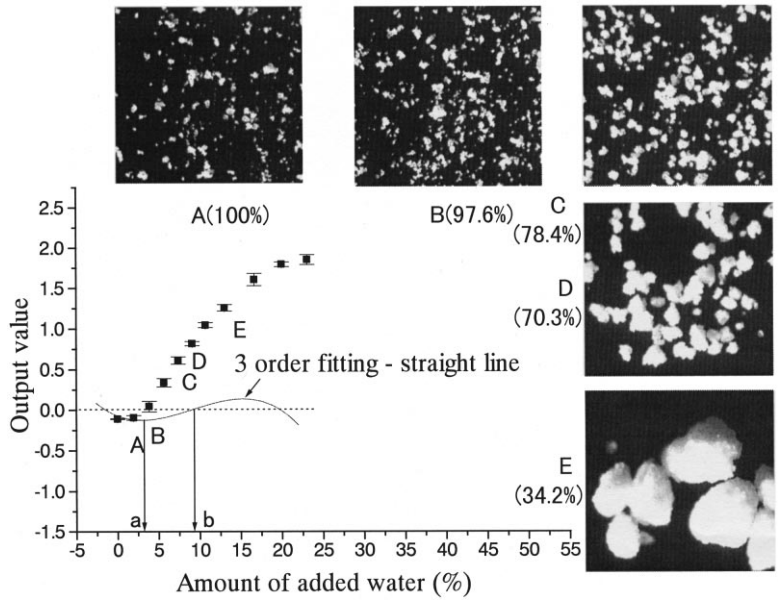

Fig. 3. Change in output values for lactose. *X*-axis shows 100 WA/(WA + WB); WA, weight of water; WB, weight of powder; a, point water began to adhere to the surface of powder; b, limit point at which water was present on the surface of powder. From a to b, suitable range of water addition. Pictures and percentages show wet granules and the 840 μm aperture-passed yields for each water amount, respectively. The length of one side of pictures shows 1500 μm.

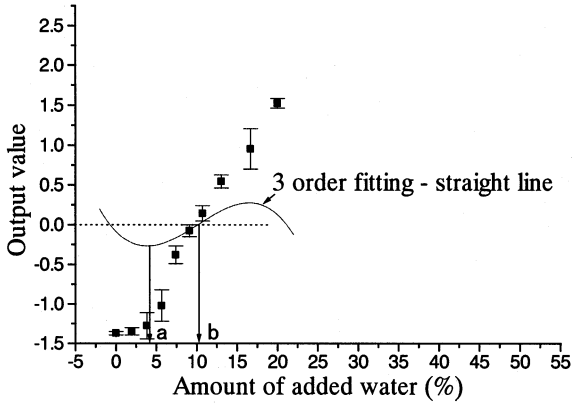

Fig. 4. Change in output values for D-mannitol. *X*-axis shows 100 WA/(WA + WB); WA, weight of water; WB, weight of powder; a, point water began to adhere to the surface of powder; b, limit point at which water was present on the surface of powder without dissolving the powder. From a to b, suitable range of water addition.

IR sensor. The obtained plot patterns were different for each excipient, and were classified into several patterns. Findings for each excipient were as follows:

3.1.1. Lactose, D-mannitol

For lactose, above about 2% water, the output value abruptly increased, while at about 20%, the output value began to level off the top (Fig. 2).

Below about 2%, added water appeared to be retained powder inside since the output value did not change, i.e. surface water did not increase. Above this point, water inside the powder appeared to saturate, water began to be present on the surface of the powder, and water on the surface of the powder increased since output value abruptly increased. Lactose may finally have begun to dissolve gradually due to its high solubility, resulting in the levering off the top of the output value. To confirm these hypotheses, we compared optical microscopic observations and measured the 840 μm-passed yields of wet granules.

The output values of the IR sensor were plotted against the amounts of added water for granulation of lactose (Fig. 2), and could be fitted by a 3-order curve. Further, a straight line which was connected to two points of added water 0% and largest slope of the 3-order curve, could be considered as an imaginary-line in the case of con-

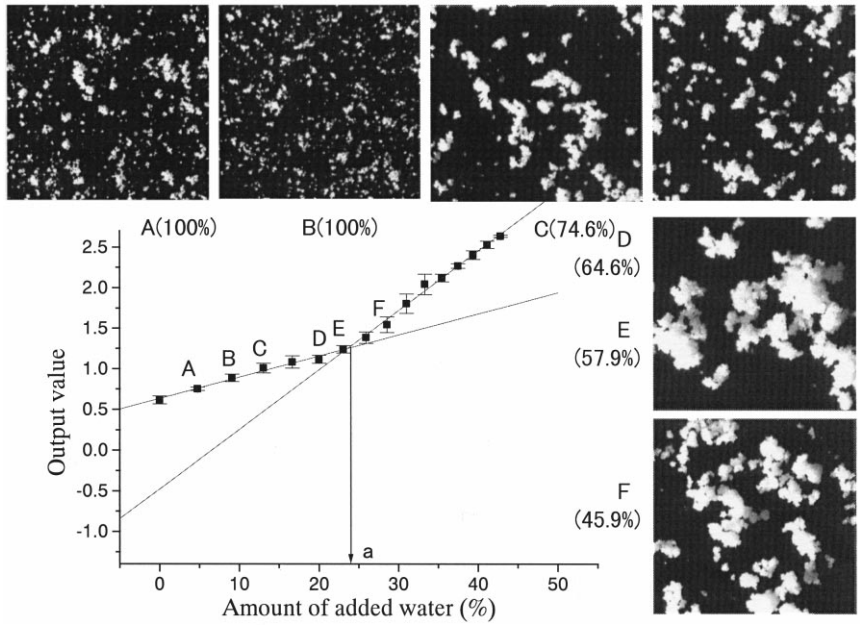

Fig. 5. Change in output values for cornstarch. *X*-axis shows 100WA/(WA + WB); WA, weight of water; WB, weight of powder; a, upper limit of suitable range of water addition.

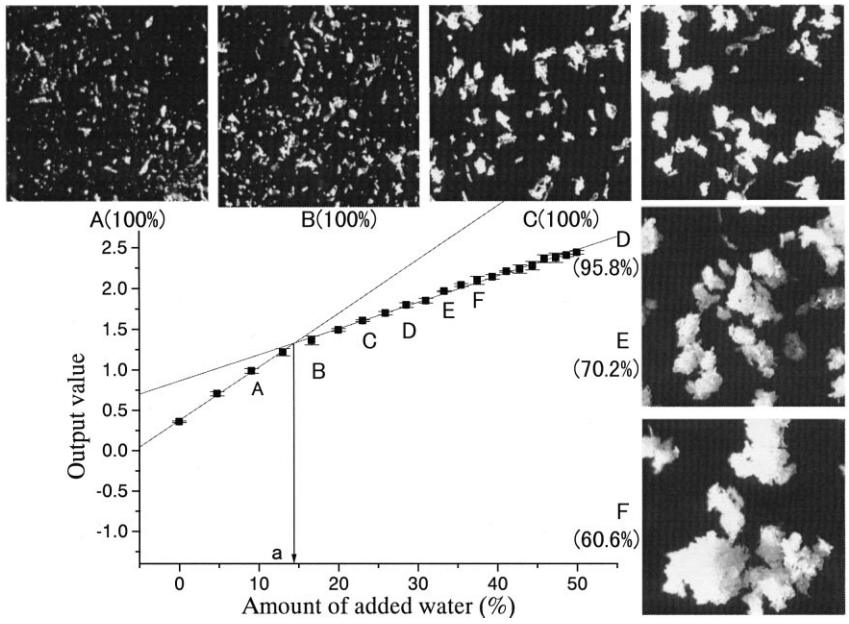

Fig. 6. Change in output values for CMC-Ca. *X*-axis shows l00 WA/(WA + WB); WA, weight of water; WB, weight of powder; a, lower limit of suitable range of water addition.

stant inside/surface distribution, during addition of increasing amounts of water. The point of largest slope of the 3-order curve means the change point of surface water increase ratio. Surface water appeared to increase abruptly below this point, but above this point, increasing of surface water become dull, since the change of slope turns from + to − in the boundary of this point. This point is a top point of 2-order curve, obtained by differentiating the 3-order curve.

Below added water amounts of the intersection of the straight line and 3-order curve, inside ratio of water is high, comparing with the case of constant inside/surface distribution, since the output values of 3-order curve are smaller than that of the straight line as the imaginary-line. On the other hand, surface ratio is considered to be high above the added water amounts of intersection, since the output values of 3-order curve are larger than that of the straight line. In order to determine the suitable amount of water of lactose, a new curve was obtained by subtracting the straight line from the 3-order curve (Fig. 3).

The minimum point (a) of the new curve was considered to be the point at which water began to adhere to the powder surface, since the output value began to abruptly increase at the point (a) and the 840 μm-passed yield (97.6%) of point B was lower than that (100%) of point A. On the other hand, at point E, lactose appeared to begin to dissolve completely, based on the picture and

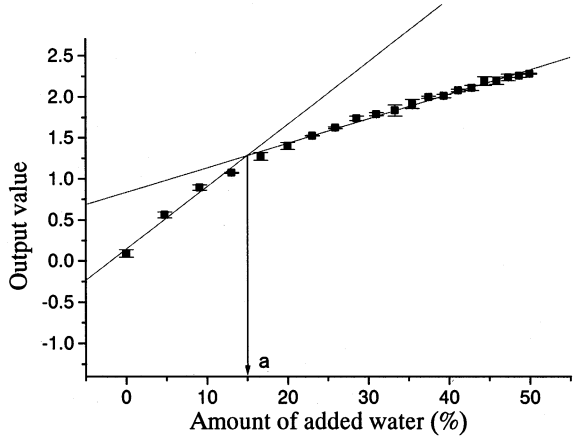

Fig. 7. Change in output values for L-HPC. *X*-axis shows 100 WA/(WA + WB); WA, weight of water; WB, weight of powder; a, lower limit of suitable range of water addition.

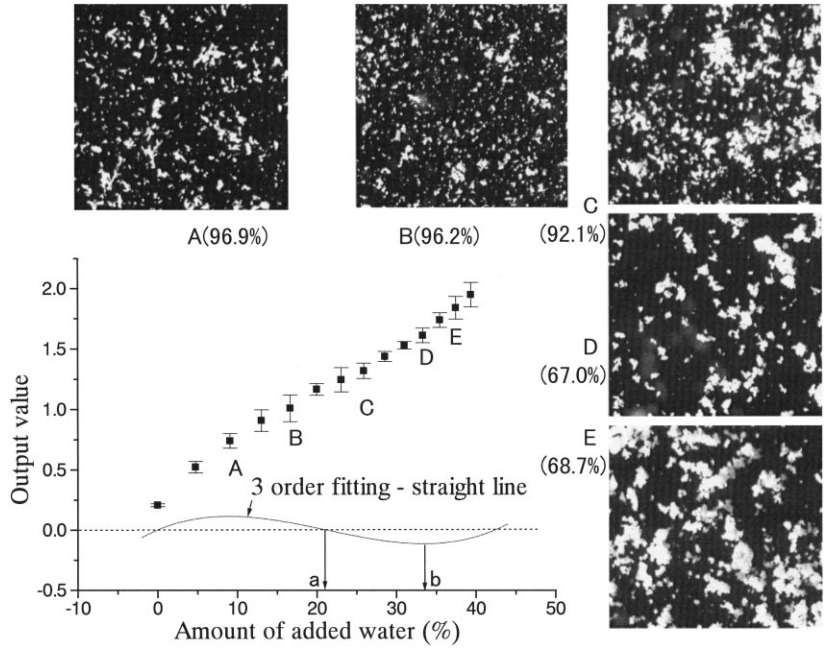

Fig. 8. Change in output values for microcrystalline cellulose. *X*-axis shows 100 WA/(WA + WB); WA, weight of water; WB, weight of powder; a, point water began to adhere to the surface of powder; b, limit point at which water was retained on the surface of powder without excessive granulation. From a to b, suitable range of water addition.

the 840 μm-passed yield (34.2%) of wet granules. While the 840 μm-passed yields (78.4 and 70.3%) at points C and D, were markedly higher than that (34.2%) at point E. For this reason, the intersection of the 3-order curve and the straight line was considered to be the limiting point (b), where powder could retain water on its surface. The amount of water between points (a) (3.0%) and (b) (9.0%) was defined as the amount of water suitable for granulation of lactose.

For D-mannitol, the 3-ordered-fitted curve pattern was similar to that for lactose (Fig. 4). The suitable amount for granulation was determined, ranging from 3.9 to 10.2% in the same fashion as lactose. It appeared that the similarities in patterns of the two excipients were due to their high water solubility.

3.1.2. Cornstarch

There was an inflection point (water amount 23.6%) in the plot (Fig. 5). The inflection point was defined as the upper limit of the suitable range for granulation, based on optical microscopic observations and the 840 μm-passed yield of wet granules. This curve was examined as follows:

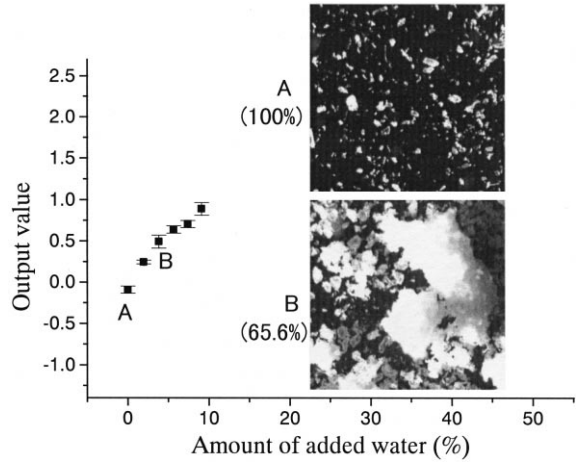

Fig. 9. Change in output values for HPC-L. *X*-axis shows 100 WA/(WA + WB); WA, weight of water; WB, weight of powder.

Below the inflection point, it appeared that the inside/surface distribution of water was constant, since the output value increased constantly.

On the other hand, since the slope of the graph abruptly increased above the inflection point, it appeared that the ratio of penetration into the powder was decreased, and added water laminated the powder surface more than penetrating into the powder, resulting in excessive granulation. The inflection point was defined as the upper limit of the suitable range of granulation based on comparison of the 840 μm-passed yields (57.9 and 45.9%) at point E and F with that (64.6%) at point D.

Furthermore, no lower limit could be found in the graph. However, the lower limit of the suitable range of granulation of cornstarch was determined to be about 13%, since the 840 μm-passed yield of wet granules decreased abruptly from 100% at point B to 74.6% at point C. The difference of particle size between point B and C, was also confirmed by optical microscopic observations.

3.1.3. Carboxymethyl-cellulose calcium, low-substituted hydroxypropyl cellulose

These plots were similar in pattern, each with an inflection point (Figs. 6 and 7). Compared with the cornstarch pattern, these patterns were similar in having one inflection point each, but their slopes decreased above their inflection points.

For Carboxymethyl-cellulose calcium (CMC-Ca), we speculate that the amount of water on the powder surface gradually increased below the inflection point, given the constant increase in the output value of the IR sensor. It thus appeared that the powder did not swell, since water did not sufficiently penetrate it. On the other hand, above the inflection point, since the slope became gentle, we speculate that a part of added water penetrated powder, the increase ratio of water on powder surface became dull. Above this point, the powder was considered to swell by absorbing water. The inflection point (14.5%) was defined as the lower limit of the suitable range for granulation, based on optical microscopic observations and the 840 μm-passed yield (100%) of point B.

On the other hand, the upper limit of the suitable range for granulation could not be found in the graph. The value of CMC-Ca was therefore, determined to be about 33%, based on the 840 μm-passed yield (95.8%) of point D and that (70.2%) of point E. The difference of particle size between point D and E was also confirmed by optical microscopic observations.

For low-substituted hydroxypropyl cellulose (L-HPC), of similar pattern to CMC-Ca, the lower and upper limits of suitable range for granulation were in the same fashion determined to be 15 and about 33%, respectively. It appeared that the similar behaviors of these two excipients were due to the characteristics of disintegrates (swelling excipients).

3.1.4. Microcrystalline cellulose

The plots appeared to combine the patterns of cornstarch and disintegrate such as CMC-Ca (Fig. 8). That is to say, the pattern is disintegrate-like, with addition of small amount of water and cornstarch-like at higher amounts. It is reasonable to suppose that at higher amounts of water, the water absorption capacity of microcrystalline cellulose was lower than that of disintegrates such as CMC-Ca, and microcrystalline cellulose could not absorb water like cornstarch, because of saturation of the capacity. The characteristics of microcrystalline cellulose corresponded to those of 'week disintegrate'. We analyzed the plot as follows:

The plots of microcrystalline cellulose could be fitted by a 3-order curve. Furthermore, a straight line which was connected the point of added water 0% and smallest slope of the 3-order curve could be considered as an imaginary-line in the case of constant inside/surface distribution, during addition of increasing amounts of water. The intersection was considered the converting point of inside/surface distribution of water (below the intersection, high inside-ratio, and above it, high surface-ratio). By subtracting the straight line from the 3-order curve, a new curve was obtained.

In the new curve, point (a) was the amount of added water at the intersection of the 3-order curve and straight line. Point (a) was defined as the lower limit of the suitable range, since the

Table 2
Suitable range of water addition for each excipient[a]

Excipient	Lower-upper limit	
	100WA/(WA+WB)	100WA/WB
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] WA, weight of water; WB, weight of powder.
[b] The value was estimated based only on microscopic observations.

change in 840 μm-passed yield between point B (96.2%) and C (92.1%) is larger than the change between point A (96.9%) and B (96.2%).

On the other hand, the minimum point (b) of the curve, was considered the upper limit of the suitable range, since output value increase above point (b) and the 840 μm-passed yield of wet granules changed between point C (92.1%) and D (67.0%). Regarding the reason that point (b) is the upper limit of suitable range, in spite of the little change of the 840 μm-passed yield between point D and E, it was suggested that the yield of the point E did not decrease comparing with the expected value, since microcrystalline cellulose has weak binding force due to its insoluble property. It is reasonable to suppose that the ratio of penetration into the powder was decreased, and that added water laminated the powder surface more than penetrating the powder, resulting in excessive granulation above point (b).

The range of amount of water added between point a (21.2%) and b (33.8%) was considered suitable for granulation.

3.1.5. Hydroxypropyl cellulose

No inflection point was present in the plot. Since the powder began to adhere and solidify at the beginning of water addition, it appeared that the range of suitable amount for granulation was very small (0% < lower-limit < upper-limit < 1%). Both the lower and upper-limits were therefore, determined to be near 0%.

As a result, the excipients were classified into the following five types, by water behavior and graph patterns. The suitable range of water addition could be determined for each excipient. The results for all excipients are combined in Table 2.

1. Soluble type (e.g. lactose, D-mannitol).
2. Non soluble and non swelling type (e.g. cornstarch).
3. Swelling type (disintegrating type) (e.g. CMC-Ca, L-HPC).
4. (2)/(3) combined type (weak swelling type) (e.g. microcrystalline cellulose).
5. Adhering and solidifying type (binder type) (e.g. HPC).

Each pattern corresponded to the water behavior of each excipient. For example, lactose and D-mannitol had the same pattern (Fig. 1d), as did CMC-Ca and L-HPC (Fig. 1c). Cornstarch exhibited a reasonable pattern of non soluble and non swelling type (Fig. 1b). Microcrystalline cellulose, of weak swelling type, exhibit a pattern like that of disintegrate and cornstarch at small and large amount of water added, respectively (Fig. 1c and b). The classification of patterns, thus, appeared to reflect powder properties.

The water inside/surface distribution hypotheses based on IR output value were useful to explain water behavior in various type excipients. Our findings suggest that the IR sensor is useful, not only for regulating the moisture content in the fluidized bed granulation process, but also for determining the water behavior at the powder surface. We then tested each exicipient value in actual granulation trials.

3.2. Estimates of suitable water amounts in model formulations

Suitable amounts of added water in two model formulations were calculated, by summation of the lower-limit or upper-limit of each excipient considering the mixing ratio of excipients. This method of calculation was used since we assumed that added water spread through the powder uniformly. As a result, suitable water amounts for formulations A and B were estimated to be respectively 15–32 and 9–21% against powder weight (Table 3).

3.3. Verificanon of estimated suitable water amounts in model formulations

The two model formulations were granulated with four amounts of water, below the lower-limit, lower-limit, upper-limit, and above the upper-limit of estimated suitable amount. By measuring median particle size, apparent powder density, tablet hardness, and disintegration time, the granules and tablets obtained with each water amount were evaluated (Fig. 10).

For formulation A, 6%, estimated to be below the lower limit, was judged too small an amount for granulation, since median particle size remained the same as that of the powder mixture prior to granulation. However, 16%, estimated to be the near the lower limit, was judged appropriately for granulation, since the particle size increased and tapped density decreased, compared with those for manufacture at 6%. In addition, 40% was judged too large an amount for granulation, since tablet hardness was decreased, and disintegration time increased compared with those for manufacture at 30% of the near upper-limit, even though particle size did not increase. Adhesion of wet granules on the inner wall of the granulation apparatus was also observed at 40%. The finding that particle size did not increase at 40% suggests that wet granules decay during the drying process because of low content of binder compared with volume of water added.

For formulation B, which had a narrow range of suitable water amounts, similar findings were observed. It appeared that the predicted lower and upper limits were appropriate for granulation, based on the results of physical property measurement (particle size etc.), but adhesion of powder to the inner wall was observed at 30%, above the estimated upper limit.

The hardness decreased in excess water for formulation A, even when bulk density did not change, while the hardness did not decrease in excess water for formulation B. The difference in the hardness behavior between formulations A and B seems to relating the ratio of lactose/microcrystalline cellulose. Microcrystalline cellulose might lose compressibility in excess water, since decrease in hardness was clearly greater for formulation A than for formulation B.

The estimated suitable amounts of water addition and experimental values, thus corresponded for both two-model formulations. It follows from this that the estimated suitable amount of each excipient is adequate and the summation rule based on mixing ratio, using the obtained value of each excipients, comes into existence.

In this study, we showed that the amount of water needed to obtain a suitable liquid bridge state, could be estimated for formulations before granulation trials. However, it is beyond the scope of this method to estimate the physical properties such as particle size of granules. In the wet condition, even with a suitable liquid bridge state, during drying process, physical properties such as particle size of granules depend on the amount of binder and operating conditions of the apparatus because of the difference of binding force among

Table 3
Mixing ratio and suitable range of water addition for these formulations[a]

	A formulation		B formulation	
Lactose	35	(1.1–3.5)	60	(1.8–6.0)
Microcrystalline cellulose	39	(10.5–19.9)	14	(3.8–7.1)
Cornstarch	10	(1.5–3.1)	10	(1.5–3.1)
CMC-Ca	10	(1.7–5.0)	10	(1.7–5.0)
HPC-L	6	(0–0)	6	(0–0)
Total	100	14.8–31.5	100	8.8–21.2

[a] ( ), Suitable range of water addition based on mixing ratio for each excipient. Water amount shows by 100WA/WB; WA, weight of water; WB, weight of powder.

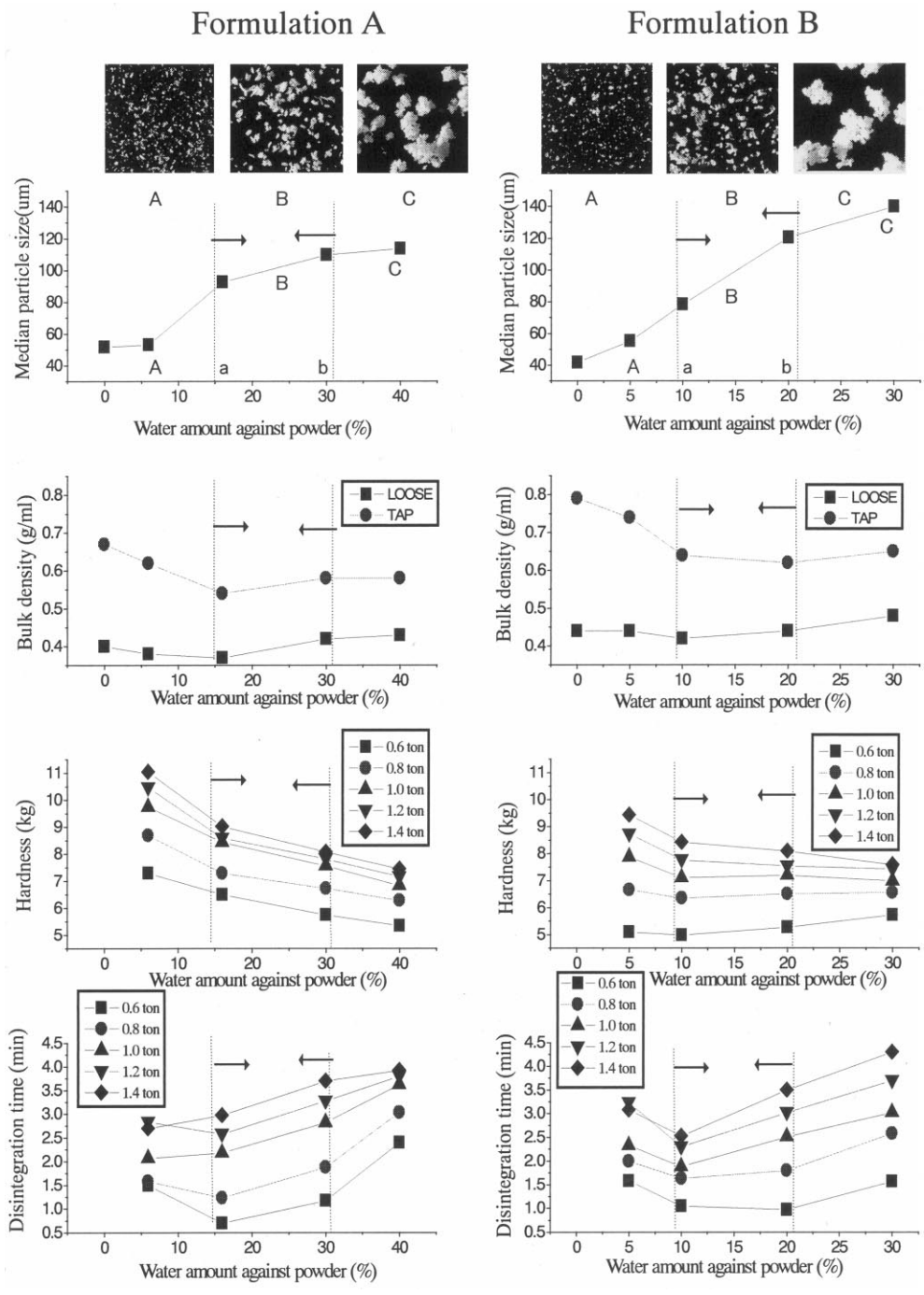

Fig. 10. The properties of each formulation. The left and right side show results for formulation A and B, respectively. *X*-axis shows 100 WA/WB; WA, weight of water; WB, weight of powder. From a to b, suitable range of water addition for each formulation. The pictures show 840 μm aperture-passed wet granules for each water addition. The length of one side of pictures shows 1500 μm.

particles The most important finding of this study is that with use of a refractive IR sensor, inside/surface distribution of water was grasped and suitable amount of surface water in wet condition was determined.

Our method can be used not only for high-speed mixers but also for fluidized bed granulation.

4. Conclusions

The results of our study using the IR sensor are as follows:

1. The examined excipients could be classified into five types based on water behavior at the powder surface, and the range of water addition suitable for granulation could be determined for each excipient.
2. With our method, the suitable amounts of added water calculated for two model formulations corresponded to experimental values.
3. Our findings suggest that amounts of water suitable for formulation can be estimated before granulation trials using our method.

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