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Prediction of suitable amounts of water in fluidized bed granulation of pharmaceutical formulations using corresponding values of components

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Abstract

This study describes application of a newly developed method to the fluidized bed granulation. The method is based on predicting suitable amounts of water to be added to multi-component formulations using the corresponding values of components prior to granulation trials. The range of appropriate amount of water for each component in a model formulation was estimated in our previous studies with a refractive near-infrared (NIR) moisture sensor. Using those values, we calculated the range of suitable amount of water to add for the model pharmaceutical formulation. In this study, we examined the relationship between the amount of water added to the model formulation and the NIR sensor output value. Then, we performed fluidized bed granulation of the model formulation at steady-state moisture content levels under monitoring with NIR sensor, within and beyond the suitable range of added water that was calculated from the corresponding range of each component. For the model formulation, we found that the predicted values for suitable amounts of added water well corresponded to those in the granulation trials, suggesting that this predictive method may be useful in estimating suitable amounts of water to be added to formulations before fluidized bed granulation trials.

Keywords: NIR; Moisture content; Pharmaceutical formulation; Fluidized bed granulation; Liquid bridge

1. Introduction

The recently issued Q8 guidelines of the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) on pharmaceutical development discuss the importance of "design space" or the idea of "quality by design". The amount of water added for wet granulation in the tablet manufacturing process can often serve as a crucial parameter in drug product quality and characteristics. When the effects of amounts of water added or optimal water amounts on powder and tablet properties are examined for a multi-component formulation, it is difficult to set experimental design parameters (specifically, average or range of added water) before granulation trials in general.

One of our previous studies (Miwa et al., 2000) showed that the suitable amount of water for each excipient in granulation can be determined with a refractive near-infrared (NIR) moisture sensor, based on the internal/surface distribution model. The study also showed that we could predict suitable water amounts for pharmaceutical formulations in high-speed mixer granulation by summing the lower-limit or upper-limit of each excipient, based on the mixing ratio of the excipient before wet granulation trials. Once we obtain the suitable amount of water to be added for each excipient or each active pharmaceutical ingredient (API), we can formulate suitable water amounts for various formulations before wet granulation trials, even for new formulations, by applying our method.

The studies reported so far have examined the relationship between moisture content and powder properties for fluidized bed granulation (Schæfer and Wørts, 1978; Watano et al., 1991) from a theoretical perspective, showing a reliable relationship between moisture content and mean particle diameter for granules obtained by tumbling fluidized bed granulation (Watano et al., 1994). More recently, the process of fluidized bed granulation has been analyzed using NIR moisture measurement combined with temperature and humidity monitoring (Rantanen et al., 2001). However, these studies did not focus on predicting suitable amounts of water for formulations before granulation

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Table 1
Test formulation

	Wt%
Lactose	60
Microcrystalline cellulose	14
Cornstarch	10
CMC-Ca	10
HPC-L	6
Total	100

trial. Since suitable moisture content varies with formulations depending on the properties of formulated powders (e.g., water-absorbing potential, coherent strength) (Watano et al., 1996), predicting suitable water amounts for each formulation before granulation trials has been difficult.

In this study, we evaluated the newly developed method (Miwa et al., 2000) for predicting the suitable amount of water to add in fluidized bed granulation. Two kinds of fluidized bed granulators were used in this study. One was a commercially available apparatus (FD-3S, Powrex). The other, which was newly developed for scale-up experiments, has the same height as a conventional product scale apparatus but is very narrow relative to width (APPARATUS A, Powrex).

2. Materials and methods

2.1. Materials

The powders used were lactose (DMV, Borculo), cornstarch (Nippon Cornstarch), microcrystalline cellulose (Avicel PH101, Asahi Chemical Industry), carboxymethyl-cellulose calcium (CMC-Ca, Nichirin Chemical), hydroxypropyl cellulose (HPC-L, Nippon Soda), and magnesium stearate (Taihei Chemical).

2.2. Equipment

Two kinds of fluidized bed granulators (FD-3S, Powrex and a custom apparatus called APPARATUS A, Powrex) were used in this study. APPARATUS A has the same height but is very narrow relative to width compared to a conventional product scale apparatus. A refractive NIR moisture sensor (WET EYE, Dalton) was attached to the FD-3S. A refractive NIR moisture sensor (WETRON, Kurabo) and a particle size measuring machine (PARTICLE VIEWER, Powrex) were attached to APPARATUS A. Both NIR sensors performed measurements using fixed wavelength detectors (1.94 or 1.95 μm as detected wavelengths and 1.8 and 2.1 μm as contrast wavelengths). Particle sizes after granulation were measured by laser diffraction using a He-Ne laser (Microtrac FRA, Nikkiso).

2.3. Relationship between added water and NIR output value

We placed 10 g of one model pharmaceutical formulation (Table 1) in a mortar, then added purified water (0.5 ml) to the powder with a pipette. The mixture was kneaded with a mortar and pestle. The detecting element of the IR sensor was brought to the mixture without actually contacting the mixture, and the output value of the IR sensor was then measured. Following measurement, the mixture was voided. A new batch of the same formulation (10 g) was used for the next trial. A greater amount of purified water (1.0 ml) was added to powder in the same manner, and the output value measured once again. This process was repeated with increasing amounts of water (1.5, 2.0, 2.5, 3.0 ml), and also the output value with amounts of water (0 ml) was measured.

2.4. Wet granulation and tableting of formulations

Excipients of the formulation (Table 1) were granulated with purified water using two types of fluidized bed granulators at steady-state moisture content values.

The mixed powder (3500 g for FD-3S, 4000 g for APPARATUS A) was charged in a fluidized bed granulator and sprayed with water during granulation. Four water levels – beneath the lower limit of the predicted suitable moisture content, at the lower limit, at the upper limit, and above the upper limit – were regulated by controlling spray speeds manually. The wet granules were dried after granulation. For granulation with APPARATUS A, moisture content and particle size were monitored by WETRON and PARTICLE VIEWER, respectively, while wet powder was observed with an optical microscope (Microphoto-FX, Nikon). The mixture was granulated until the total water amount was exhausted (2300 g for FD-3S, 2000 g for APPARATUS A), then dried. The dried granules were obtained by screening through a 500 or 710 μm aperture mesh, respectively, for the FD-3S and APPARATUS A. Fig. 1 and Tables 2 and 3 show an image of the manufacturing process and the corresponding conditions.

The granules obtained with the FD-3S were then blended with magnesium stearate (0.5 wt%) and tableted on a rotary tablet press (Correct 12 HU, Kikusui) fitted with 12 standard concave punches (6 mm diameter). For each compression 100 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 in increments of 0.2 ton/punch.

2.5. Evaluation of granules and tablets

We used laser diffraction (He-Ne laser; Microtrac FRA, Nikkiso) to measure dried granule sizes. The air pressure

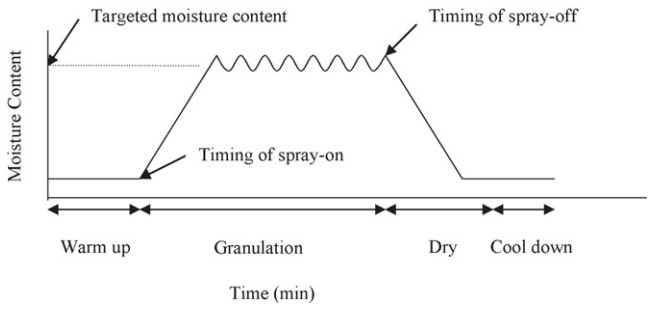


Fig. 1. Image of fluidized bed granulation.

Table 2
Manufacturing condition using fluidized bed granulator (FD-3S)

Parameter	Amount of water against powder				
	5%	10%	15%	20%	25%
Granulation apparatus	← FD-3S →				
Moisute content monitoring equipment	← WET EYE →				
Powder weight (Kg)	3.5	3.5	3.5	3.5	3.5
Inlet air temperature (°C)	70	70	70	70	70
Inlet air volume (m^3/min)	1.5	1.5	1.5	1.5	1.5
Exhausted total water weight (kg)	2.3	2.3	2.3	2.3	2.3
Granulation time (i.e. spray time) (min)	70	62	55	46	45
Out put value of WET EYE on granulation	0.4-0.45	0.7-0.75	0.95-1.0	1.25-1.3	1.35-1.4
Product temperature after drying (°C)	45	45	45	45	45

Table 3
Manufacturing condition using fluidized bed granulator (APPARATUS A)

Parameter	Amount of water against powder			
	5%	10%	20%	25%
Granulation apparatus	← APPARATUS A →			
Moisute content monitoring equipment	← WETRON →			
Particle size monitoring equipment	← PARTICLE VIEWER →			
Powder weight (Kg)	4.0	4.0	4.0	4.0
Inlet air temperature (°C)	70	70	70	70
Inlet air volume (m^3/min)	1.0	1.0	1.0	1.0
Exhausted total water weight (kg)	2.0	2.0	2.0	2.0
Granulation time (i.e. spray time) (min)	101	91	70	46
Out put value of WETRON on granulation	ca. 0.03	ca. 0.07	ca. 0.15	ca. 0.19
Product temperature after drying (°C)	45	45	45	45

used to disperse particles was 2 kgf/cm^2 for the dry method. Median diameters were 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 (WHT-1, Pharma-Test); tablet disintegration time in water was determined using a disintegrating apparatus (NT-2HS, Toyama) without plastic disks. We based evaluations on the average hardness of 20 tablets and disintegration time for six tablets.

3. Results and discussion

3.1. Estimates of suitable water amounts in model formulation

One of our previous studies (Miwa et al., 2000) gives the values shown in Table 4 for the suitable amounts of water for each excipient. As shown in our earlier study (Miwa et al., 2000), we calculated suitable amounts of added water for one model formulation by summing the lower and upper limits of each

Table 4
Suitable range of water addition for each excipient[a]

Excipient	Lower–upper limit	
	$100W_A/(W_A + W_B)$	$100W_A/W_B$
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] W_A, water weight; W_B, powder weight.
[b] The value was estimated based only on microscopic observations.

Table 5
Mixing ratio and suitable range of water addition for this formulation[a]

	Mixing ratio	Suitable range
Lactose	60	(1.8–6.0)
Microcrystalline cellulose	14	(3.8–7.1)
Cornstarch	10	(1.5–3.1)
CMC-Ca	10	(1.7–5.0)
HPC-L	6	(0–0)
Total	100	(8.8–21.2)

[a] Values in the parenthesis are suitable range of water addition based on mixing ratio for each excipient water amount shows by $100W_A/W_B$: W_A, water weight; W_B, powder weight.

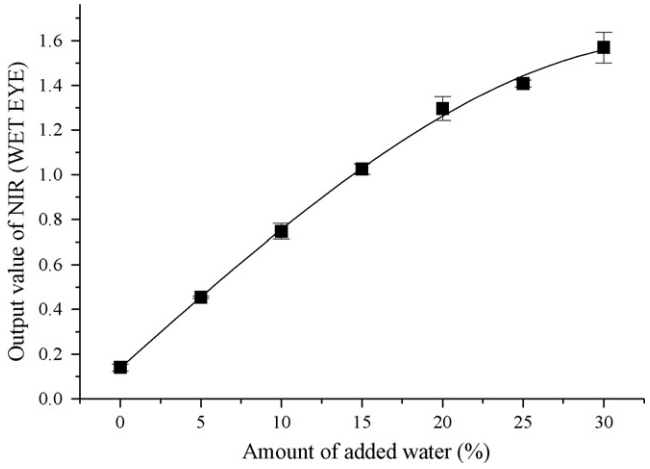


Fig. 2. Plotted patterns for water added vs. NIR sensor output values (WET EYE). *X*-axis shows $100W_A/W_B$: W_A, water weight; W_B, powder weight.

excipient while considering the mixing ratio of the excipients. The resulting estimates against powder weight for suitable water amounts for the formulation were 9–21% (Table 5).

3.2. Relationship between added water and output value of NIR

To correlate the amount of water added to the formulation to moisture content (i.e., output value of the refractive NIR moisture sensor), we plotted output values for the NIR sensor (WET EYE) against the amounts of water added (Fig. 2). This showed that adding 5%, 10%, 15%, 20%, 25%, and 30% water against powder corresponded, respectively, to ca. 0.45, ca. 0.75, ca. 1.0, ca. 1.3, ca. 1.4, and ca. 1.6 as NIR sensor output values. When we used WETRON as the NIR sensor, the values 5%, 10%, 15%, 20%, and 25% for added water amounts corresponded to ca. 0.03, ca. 0.07, ca. 0.11, ca. 0.15, and ca. 0.19 for NIR sensor output values.

3.3. Verifying estimated suitable water amounts in a model formulation by FD-3S

A model formulation was granulated at five moisture content levels: below the lower limit (0.4–0.45); at the lower limit (0.7–0.75); at the midrange of the limit (0.95–1.0); at the upper limit (1.25–1.3); and above the upper limit (1.35–1.4) of the estimated suitable amount as the output value of WET EYE by regulating spray speeds on a fluidized bed granulator (FD-3S).

We measured median particle size (D50), apparent powder density, tablet hardness, and disintegration time to evaluate the dried granules and tablets obtained with each water amount (Fig. 3).

The range estimated to represent suitable amounts of water (10–20%) did not result in significant differences in powder properties. The amount estimated to be below the lower limit (5%) was judged to exhibit inadequate granulation due to particle size and looseness of the granules. Granules obtained at 25% showed powder properties similar to those obtained at 20%, but with inadequate resulting powder flow in the fluidized bed granulator. Thus, 25% was deemed too high for granulation. The finding that particle size does not increase at 25% suggests that wet granules decay during the drying process due to inadequate

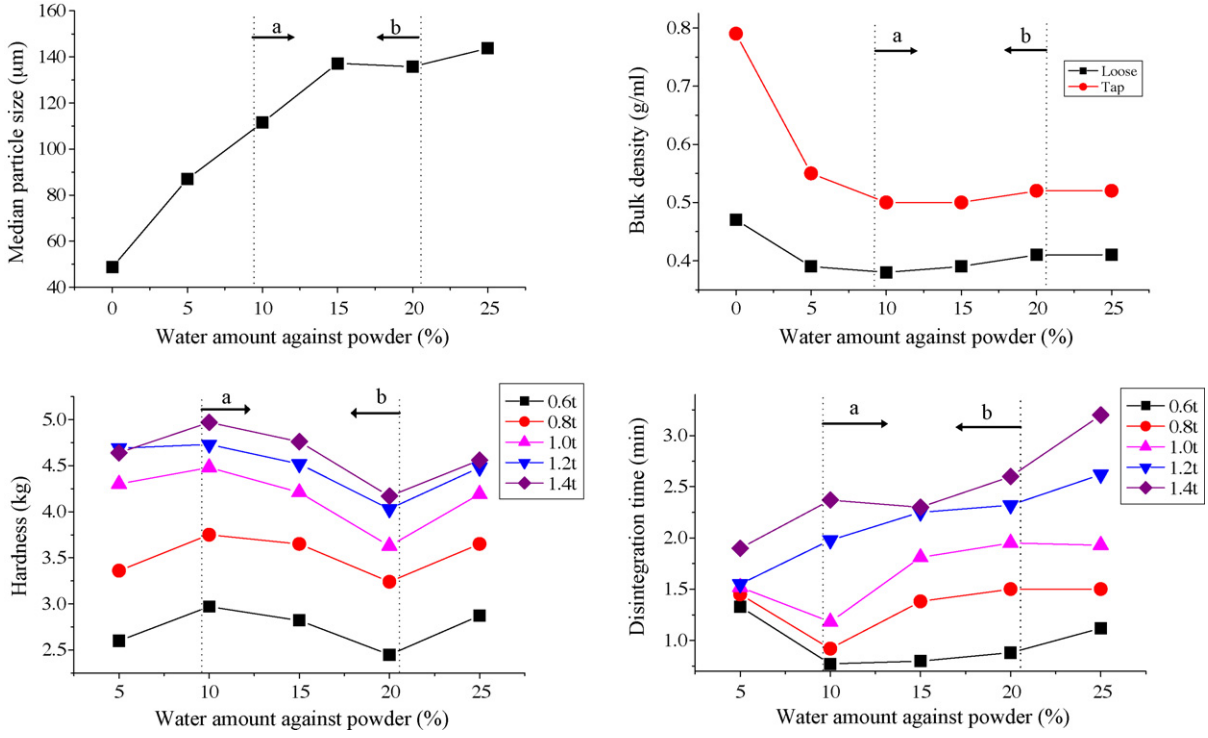


Fig. 3. Properties of granules and tablets manufactured by FD-3S in the formulation. *X*-axis shows $100W_A/W_B$: W_A, water weight; W_B, powder weight. From a to b: suitable range of added water for the formulation.

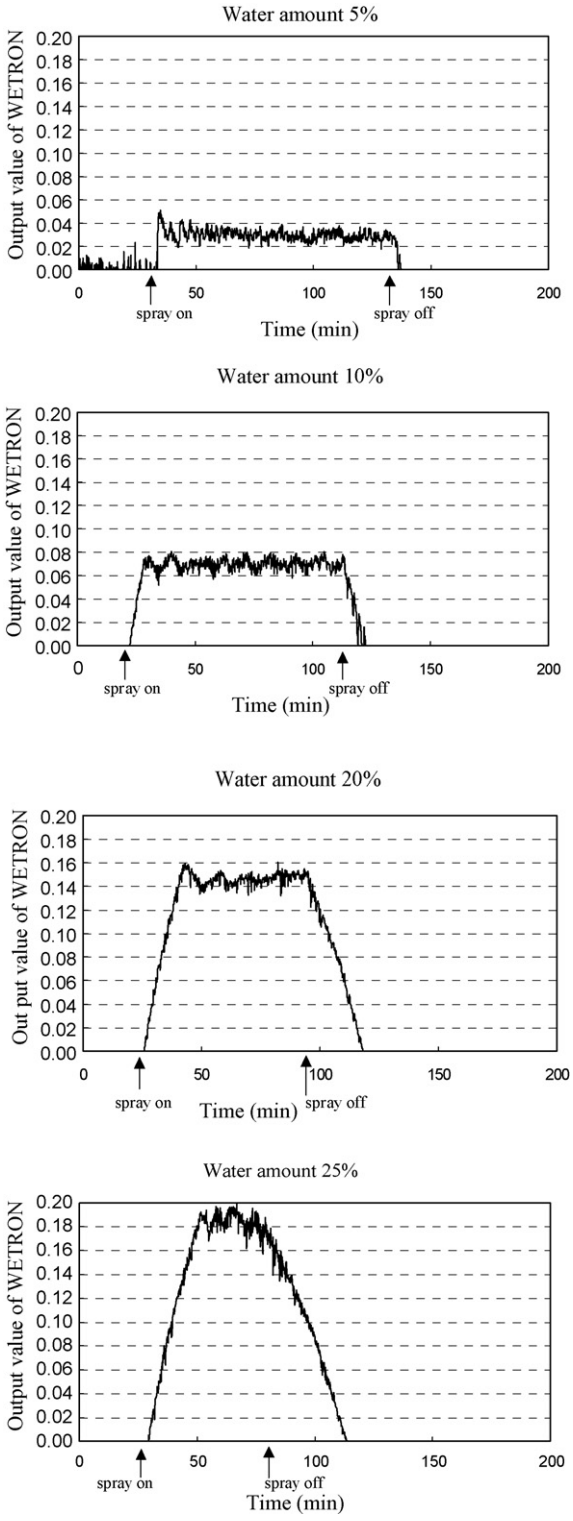


Fig. 4. Moisture contents monitoring in APPARATUS A with WETRON attached.

binding forces created by low binder content relative to volume of water added. The lower and upper limits predicted appeared suitable for the granulations, based on measurements of physical parameters (e.g., particle size).

For this model formulation, the estimated suitable amounts of water added and experimental values corresponded. From this finding, we deduce that the estimated suitable amount of each excipient is adequate and proceed to derive a summation rule based on excipient mixing ratios, which in turn are based on the values obtained for each excipient.

This formulation was also examined in a previous report (Miwa et al., 2000) for high-speed mixer granulation (vertical granulator 25L, Powrex). The bulk density and tapped density of the granules obtained by fluidized bed granulation were less than those obtained with high-speed mixer granulation. The variability in particle size resulting from the different amounts of water added in fluidized bed granulation is less than with high-speed granulation.

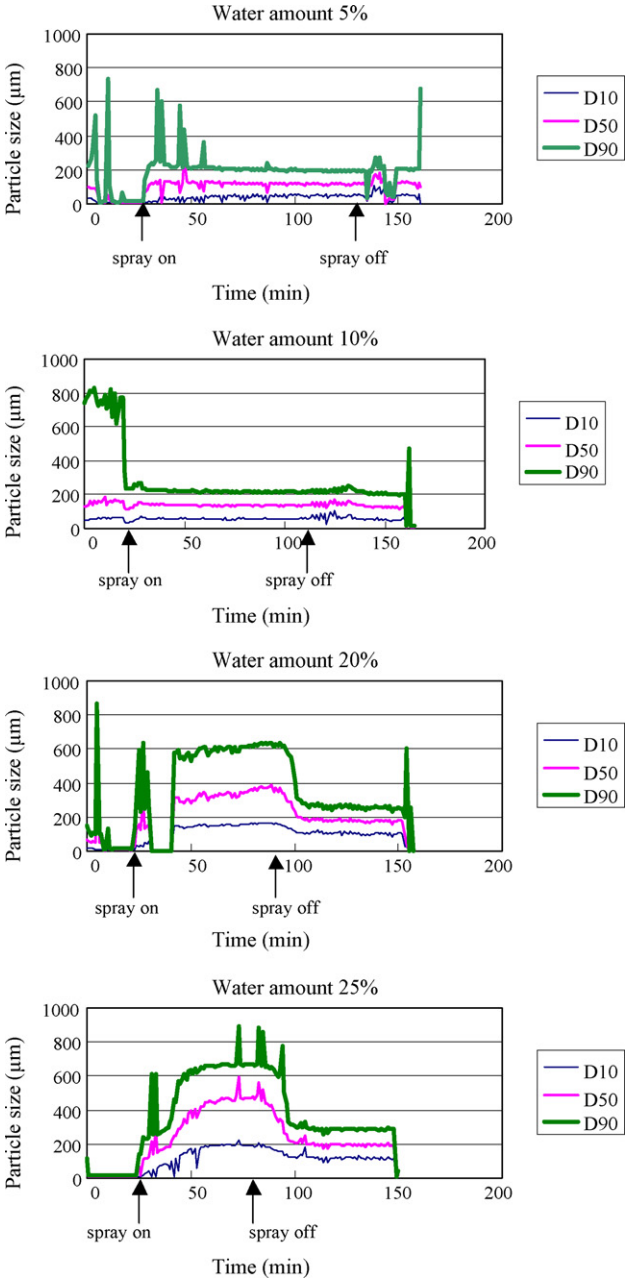


Fig. 5. Particle size monitoring in APPARATUS A with PARTICLE VIEWER attached.

3.4. Verification of estimated suitable water amounts in model formulations with APPARATUS A

In observations with the FD-3S, we showed we could estimate the amount of water needed to obtain a suitable liquid bridge state for formulations before granulation trials. However, as mentioned in an earlier paper (Miwa et al., 2000), it falls beyond the scope of this method to estimate physical properties such as granule size. In the wet state, even with a suitable liquid bridge state, physical properties such as granule size are believed to vary during the drying process due to differences in interparticle binding force, which is affected by the amount of binder and equipment operating conditions. If we can monitor particle size during the granulation process in the wet state – which better reflects the liquid bridge situation – we would most likely be able to obtain more useful information regarding suitable amounts of water. For this reason, we sought to monitor the particle size of wet granules during granulation using the fluidized bed granulator (APPARATUS A) and attached particle size monitoring equipment (PARTICLE VIEWER). Before granulation, just as with the FD-3S, we examined the correlation between water added to the model formulation and output values of the NIR sensor (WETRON), using a mortar. We performed granulation of the model formulation by regulating moisture content at four steady-state levels (below the lower limit, at the lower limit, at the upper limit, and above the upper limit of the estimated suitable amount) as WETRON output values (Fig. 4).

We monitored D10, D50, and D90 as the accumulated particle size of wet granules using the PARTICLE VIEWER for the four moisture content levels, as shown in Fig. 5. Fig. 6 shows a summary of particle sizes and optical microscopic observations of wet granules during granulation and dry granules after the drying process. Pictures of wet granules are at the endpoint of the wet granulation process (i.e., before drying).

We observed deviations in particle size during the warm-up process, but the particle size (e.g., D50) of the wet granules remained constant during granulation at each steady-state level of moisture content (Fig. 5). This suggests the formation of a certain liquid bridge, depending on the moisture content.

Monitoring with PARTICLE VIEWER showed clear particle growth in the wet state with 20% and 25% water amounts compared to the particle sizes of the mixed powder before granulation and particle sizes of the dried granules after the drying process. On the other hand, particle sizes corresponding to 5% and 10% water amounts in the wet state were smaller than those for 20% and 25% water amounts (Fig. 5).

For moisture content levels corresponding to 5% water amounts (below the lower limit), D10 gradually increased during granulation with constant moisture content until spray-off. This was in contrast to D10s of 10%, 20% and 25% water, which resulted in constant particle size for wet granulation (Fig. 5). Thus, 5% water may be insufficient for granulation in terms of particle growth rates. That is, 5% water may be inadequate for shorter granulation times before the liquid bridge is completed. Additionally, microscopic observations of wet granules for 5% water showed a tendency toward particle growth but no significant differences compared to mixed powders without water (i.e., powder at 0% water content before granulation) and clearly less growth than for wet granules of above 10% water (Fig. 6). For this reason, particle growth was deemed inadequate at 5% water.

For moisture content levels corresponding to 10% water estimated to be the lower limit, monitoring with the PARTICLE VIEWER showed apparent wet particle size during granulation closer to sizes obtained with 5% than with 20% (Fig. 5). But microscopic observations of wet granules with 10% water appeared to show particle growth comparable to mixed powder before granulation or wet granules at 5% water levels (Fig. 6).

For moisture content corresponding to 25% of the water amount estimated above the upper limit, the D50 and D90 of

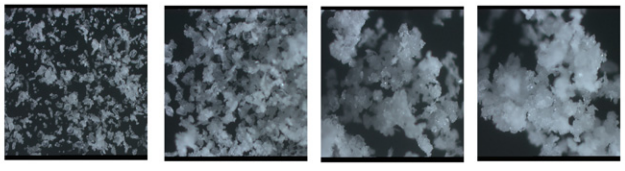
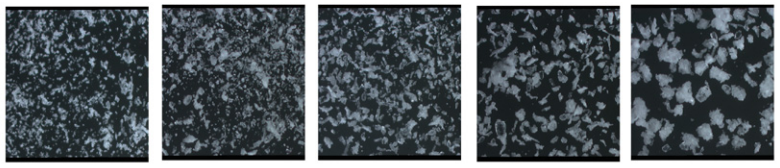
	Water amount against powder (%)				
	0%	5%	10%	20%	25%
Median Particle size (μm)					
(Wet granule)[a]	-	120	140	350	470
					
(dry granule)[a]	-	120	135	170	200
(dry granule)[b]	48	69	85	133	145
					

Fig. 6. Comparison of wet and dry granules manufactured by APPARATUS A. (a) Measured by PARTICLE VIEWER attached to fluidized bed granulator. (b) Measured by Microtrac after drying and screening though 710 μm aperture mesh. The pictures show wet or dry granules for each level of water added. The length of one side of the photographs corresponds to 2000 μm.

the wet granules were ca. 470 μm and ca. 650 μm. These were considered excessive given particle size (145 μm) after the drying process. Additionally, photographs of dry granules at 25% water showed large granules compared to granules below 20% water (Fig. 6). At 25% water, greater particle growth than necessary may result in problems including inadequate powder flow within the apparatus, a problem observed with the FD-3S at 25% water. This suggests that 25% water is too high for the creation of an optimal liquid bridge, despite the availability of dried powder.

Monitoring particle sizes during wet granulation appears to be a useful method for obtaining a better understanding of the liquid bridge state.

By applying our method, once we obtain the suitable amount of water to be added for each excipient or each active pharmaceutical ingredient (API), we can formulate suitable water amounts in terms of liquid bridge for various formulations in both fluidized bed and high-speed mixer granulation before wet granulation trials, even for new formulations.

4. Conclusions

We calculated suitable amounts of water for formulations based on various estimated water amounts for each excipient. The values estimated corresponded to experimental values obtained with fluidized bed granulation. The predictive method appears applicable to both fluidized bed and high-speed mixer granulators.

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