Scale-Up Studies on High Shear Wet Granulation Process from Mini-Scale to Commercial Scale

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A newly developed mini-scale high shear granulator was used for scale-up study of wet granulation process from 0.2 to 200 L scales. Under various operation conditions and granulation bowl sizes, powder mixture composed of anhydrous caffeine, D-mannitol, dibasic calcium phosphate, pregelatinized starch and corn starch was granulated by adding water. The granules were tabletted, and disintegration time and hardness of the tablets were evaluated to seek correlations of granulation conditions and tablet properties. As the granulation proceeded, disintegration time was prolonged and hardness decreased. When granulation processes were operated under the condition that agitator tip speed was the same, similar relationship between granulation time and tablet properties, such as disintegration time and hardness, between 0.2 L and 11 L scales were observed. Likewise, between 11 L and 200 L scales similar relationship was observed when operated under the condition that the force to the granulation mass was the same. From the above results, the mini-scale high shear granulator should be useful tool to predict operation conditions of large-scale granulation from its mini-scale operation conditions, where similar tablet properties should be obtained.

Key words scale-up; high shear granulation; mini-scale granulator; agitator tip speed; force to granulation mass

Recently the importance of QbD (Quality by design) in International Conference on Harmonisation (ICH) Q8 has been highlighted,[1)] and scientific levels of formulation designing and manufacturing designing are more and more emphasized. In addition, there is pressure on the pharmaceutical industry in shortening the development time of new products. Further, considering current situation that there are cases where levels of formulation study and scale-up study, prerequisites of validation, are not sufficient, it is tended to be interpreted that conventional validation is not final verification of validity of acceptable manufacturing conditions, but one of processes of the cycle oriented to Continuous Improvement of quality through Product Life Cycle.[1,2)]

From the viewpoint of QbD, in the unit operations of formulation manufacturing, granulation process is a process which has a significant impact on quality of final products, and should be considered mostly to be studied. Therefore scale-up of high shear granulation has been approached in several ways.[3—7)] But in wet granulation, for example, there are numerous combinations of process parameters such as agitation speed, irrigation speed of binder solution, *etc.* and current situation is that generalized solution, covering from a small production scale to a commercial production scale, is not obtained.

The concept of Design Space introduced in ICH Q8 defines the appropriate operation space of respective operation parameter in a commercial production scale, and vast experiments should be needed to establish multidimensional operation space of these variation factors. In the case of investigational drugs, however, there is a situation that ample drug substance can not be available, and this situation being considered, it is a critical requisite to establish experiment system of a small scale where by using small quantity of drug substance extrapolation to commercial production is intended as a means of realizing the concept of ICH Q8. But few studies report scale-up from a mini-scale to pilot scale.[5)]

In this study, experiments and analyses were performed by using a newly developed 0.2 L mini-scale high shear mixer where extremely small amount of drug substance is used, in order to seek possibilities to establish Design Space which can extrapolate manufacturing conditions from a small scale to pilot scale (investigational new drug production scale), finally to a commercial scale.

Experimental

Materials Anhydrous caffeine (Shiratori Seiyaku Co., Ltd.) was used as model drug. The following inactive ingredients were purchased from commercial sources: D-mannitol (Toa Kaseikogyo Co., Ltd.) and dibasic calcium phosphate (Kyowa Kagaku Co., Ltd.) as fillers, pregelatinized starch (Matsutani Kagakukogyo Co., Ltd.) as a binder, corn starch (Nihonshokuhin-Kako Co., Ltd.) as a disintegrant, magnesium stearate (Taihei Kagaku Sangyo Co., Ltd.) as a lubricant for the preparation of the tablets. Purified water was used as the granulation liquid.

Preparation of Granules All materials listed in Table 1, except magnesium stearate, were sieved through 30 mesh metal screen. The powder mixture was loaded into granulation bowl and mixed for 3 to 5 min. The top drive high shear type granulators with the removable transparent grass bowl size of 0.2 L (model IMC-1855, Imoto Seisakusho Co., Ltd., Japan), referred to as "mini-scale" hereafter, and the bottom drive high shear type granulator with the bowl size of 11 L and 200 L (model FSGS5JD and FSGS100J, respectively, Fukae-Kogyo Co., Ltd.), referred to as "pilot scale and commercial scale, respectively" hereafter, were used for the mixing and granulation. The granulation operations were conducted under the conditions shown in Table 2. The 20% (w/w) amount of water to the powder was added from a nozzle into bowl for wet granulation in all scale batches. The irrigation time

Table 1. Unit Formula of Tablets

Component	Amount (mg/tablet)	Function
Anhydrous caffeine	10	Active ingredient
Dibasic calcium phosphate	120	Filler
D-Mannitol	40	Filler
Pregelatinized starch	4	Binder
Corn starch	30	Disintegrant
Magnesium stearate	1	Lubricant
Total weight (mg)	205	

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Table 2. Operation Parameters of High Shear Granulator

	Bowl size (L)		
	0.2 L	11 L	200 L
Amount of powder (g)	30	1000	46000
Radius of agitator blade (m)	0.0385	0.15	0.45
Agitator rotation speed (rpm)	300—1150	300	130 (170)[a)]
Chopper speed (rpm)	—	2500	1500
Granulation time (min)	1.3—40	5—20	10—25 (2.9)[a)]
Irrigation time (min)[b)]	0.25,[c)] 1, 2	1	5.5

a) The numbers described in parentheses are calculated based on the Option 1. *b*) The amount of 20% (w/w) granulation water was added to the powder during irrigation time. *c*) Granulation water was added in 0.25 min for the agitator rotation speed of 1150 rpm condition.

was set for each scale batch so as not to generate locally over-wet portion in the irrigation period. The obtained granules were dried with ventilated dryer for mini-scale batches and fluidized bed dryer for large-scale batches. The dried granules were sized by manual sieving with 16 mesh metal screen and pulverizer (model Power-mill P-3, Showa-Giken Kogyo Co., Ltd.) for mini-scale and large-scale batches, respectively. The particle size distribution of the sized granules was measured by sieve analysis. The fractions of 16 mesh-passed granules were used for tabletting for all scales.

Preparation of Tablets The granules were lubricated by mixing with 0.5% (w/w) magnesium stearate in plastic bag for 30 s and in a V-shape blender for 2 min for mini-scale and large-scale batches, respectively. The lubricated granules were tabletted to obtain weight of 205 mg tablets (Table 1) by compression at approximately 3.2 kN (2.8—3.6 kN) with using two 9.25-mm long and 5.55-mm wide oblong shape punches and dice. ABM-200S (JT Tohshi Co., Ltd.) and LIBRA-836K-ACZ (Kikusui Seisakusho Ltd.), tabletting machines, were used for mini-scale and large-scale batches, respectively. The lubrication was conducted under appropriate condition in all batches since there observed no sticking in tableting process and no clear prolongation of disintegration time of tablets due to insufficient lubrication and over-lubrication, respectively.

Scanning Electron Microscopy (SEM) and Electron Probe Micro Analysis (EPMA) To evaluate formation of granules visually and microscopically, granules were withdrawn before lubrication. Scanning electron micrographs and electron Probe Micro Analysis images of the granules were taken by using an electron scanning microscope (JSM-6390LV, JEOL DATUM Ltd.), and electron probe micrograph which is equipped with electron scanning microscope. Samples were fixed on an aluminum stub with conductive double sided adhesive tape and SEM pictures were taken under 2.0 kV accelerating voltage condition. Calcium was an EPMA target element to examine the disposition and distribution of ingredients in the granules.

Tablet Hardness Erweka tablet hardness tester (TBH200, Nihon Siber-Hegner Co., Ltd.) was used. Each of four and ten tablets was used for tablet hardness testing for mini-scale batches and for larger scale batches, respectively.

Disintegration Test Disintegration time of tablets was measured by using a disintegration tester (NT-40H, Toyama Sangyo) without disk. The test fluid was 900 ml of distilled water maintained at 37 °C. The frequency of the basket-rack movement was 30 cpm. Disintegration test was conducted using six tablets for each batch.

Results and Discussions

Effect of Granulation Time on Tablet Properties in Mini-Scale Batches Figure 1 shows the effect of agitator rotation speeds and granulation times on disintegration time and hardness of tablets prepared in 0.2 L granulation batch under various operation conditions. The effect of agitator rotation speeds was examined within 10 min granulation time and no clear relationship between agitator rotation speed and tablet properties was found. The effect of granulation times was examined at the agitator rotation speed of 600 rpm. As the granulation proceeded, disintegration time was prolonged and hardness decreased. Further, to study this phenomenon

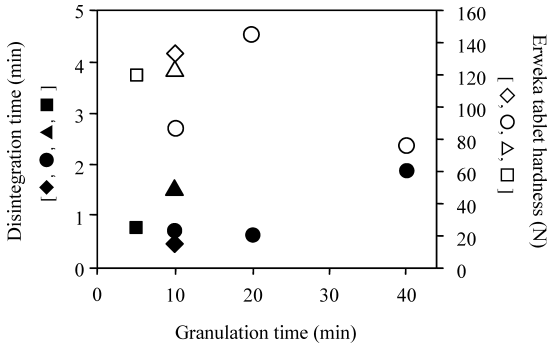

Fig. 1. The Effect of Agitation Speed and Granulation Time on the Disintegration Time and Hardness of Tablet in 0.2 L Scale

Closed symbols and open symbols represent disintegration time and hardness of the tablet, respectively. Agitator rotation speed: ◆, ◇: 300 rpm; ●, ○: 600 rpm; ▲, △: 900 rpm; ■, □: 1150 rpm.

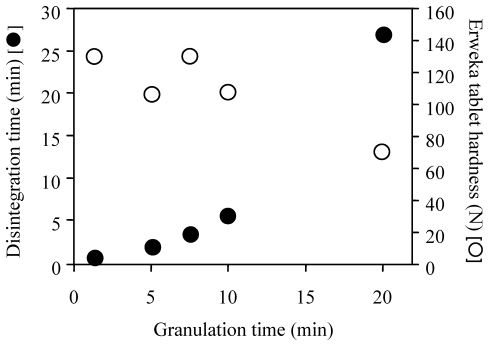

Fig. 2. The Effect of the Granulation Time on the Disintegration Time and Hardness of Tablet in 0.2 L Scale at Agitator Rotation Speed of 1150 rpm

●, disintegration time; ○, hardness of the tablet.

the effect of granulation time on tablet properties was examined at agitator rotation speed of 1150 rpm where granulation proceeded faster. Obvious prolongation of disintegration time and decrease of tablet hardness were observed even at 20 min granulation as shown in Fig. 2. To elucidate factors which caused these tablet property changes, morphological observation of the obtained granules was conducted. SEM and EPMA photographs of granules granulated for 1.3 and 20 min are shown in Figs. 3 and 4, respectively. The size of particles granulated for 20 min is larger than that of particles granulated for 1.3 min. The surface of particles granulated for 1.3 min is rough (Fig. 3b) and void spaces were observed inside (Fig. 3c), indicating that materials should just become massed together. On the other hand, the granule prepared by 20 min granulation has round and smooth surface (Fig. 4b) with dense structure inside of it. Morphological studies of granules were done by EPMA mapping with calcium as a target element on the cross section of granules, where the distribution of dibasic calcium phosphate was observed (Figs. 3d, 4d). It is found that dibasic calcium phosphate distributes not only inside of the granule but also in the outer surface of the granule like coating layer (Fig. 4d). Dibasic calcium phosphate is water insoluble component and was formulated at the concentration of 59% (w/w) in the tablet. The particle size of the granules grow larger and the surfaces of them were coated by dibasic calcium phosphate, a major component, to generate dense, hard and less compactable granules, as the granulation process proceeded. Conse-

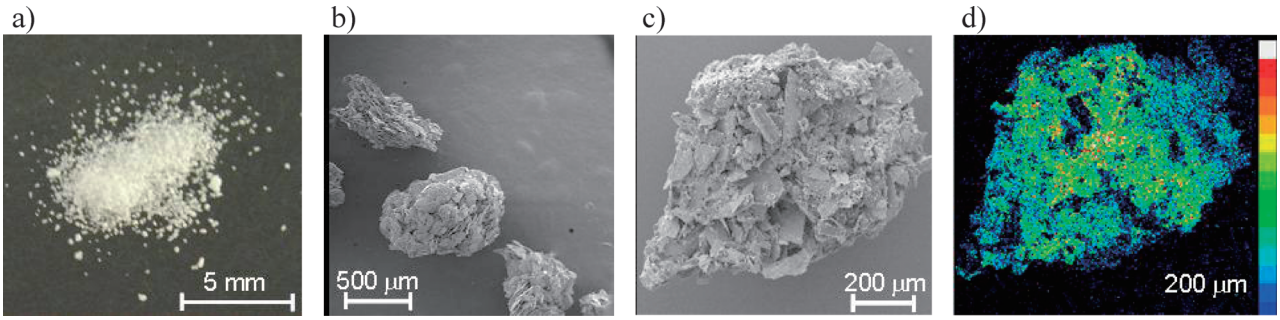

Fig. 3. Photos of Granules Prepared by Mini-Scale (0.2 L) Granulator with 1150 rpm Agitator Rotation Speed and 1.3 min Granulation Time
(a) Appearance, (b) and (c) SEM micrographs ×30 and ×240 (cross section), (d) EPMA micrograph ×240 (cross section, Ca mapping).

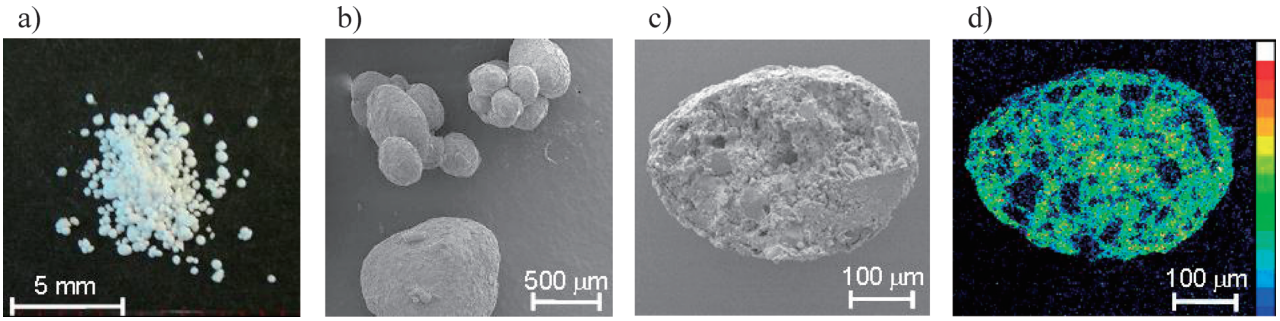

Fig. 4. Photos of Granules Prepared by Mini-Scale (0.2 L) Granulator with 1150 rpm Agitator Rotation Speed and 20 min Granulation Time
(a) Appearance, (b) and (c) SEM micrographs ×30 and ×240 (cross section), (d) EPMA micrograph ×240 (cross section, Ca mapping).

quently, it is thought that the tablet prepared from the obtained granules exhibited delay in disintegration time and decrease in hardness.

Thus the factors which influence on the properties of tablets were identified. Further, there found potential risk to cause serious troubles regarding quality of tablet in this formulation. From these findings obtained from 0.2 L batch scale studies, it is necessary to optimize the granulation process parameters in the scale-up study.

Effect of Granulation Time on Tablet Properties in Pilot Scale Batches A scale-up study from 0.2 to 11 L high shear granulator was conducted. The process operation parameters summarized in Table 3 were obtained by the calculation taking the following two independent options to establish operation parameters for different scale batches into consideration;

Option 1: matching the compaction force to the granulating mass between different scale batches, expressed as Eqs. 1 and 2.

$$R \cdot \omega \cdot t = \text{const.} \quad (1)$$

$$\{(m \cdot g)^2 + (m \cdot R \cdot \omega^2)^2\}^{0.5} = \text{const.} \quad (2)$$

Option 2: matching the agitator tip speed between different scale batches, expressed as Eqs. 3 and 4.

$$R \cdot \omega = \text{const.} \quad (3)$$

$$\omega \cdot t = \text{const.} \quad (4)$$

where R is radius of agitator blade, ω is agitator rotation speed, t is time, m is weight of powder and g is constant of gravity. Based on the compaction force matching rule (Option 1) proposed by Ashihara *et al.*,[8,9] agitator rotation speed

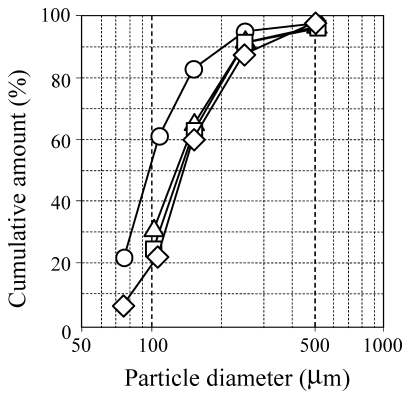

Fig. 5. Cumulative Particle Size Distribution of Sized Granules
□, 0.2 L scale batch (agitator speed 600 rpm, 10 min granulation), △, 0.2 L scale batch (1150 rpm, 1.3 min), ○, 11 L scale batch (300 rpm, 5 min), ◇, 200 L scale batch (130 rpm, 15 min).

600 rpm and 10 min granulation for 0.2 L batch scale is calculated to agitator rotation speed 300 rpm and 5 min granulation for 11 L batch scale. Likewise, based on the option 2 setting, agitator rotation speed 1150 rpm and 1.3 min granulation for 0.2 L batch scale is also calculated to agitator rotation speed 300 rpm and 5 min granulation for 11 L batch scale. A normal operation condition for 11 L scale granulator which is often used is obtained as a result from the calculation based on the experimental data on the 0.2 L scale granulator assuming both Options 1 and 2. The data on tablet hardness and disintegration time were obtained with small deviations as shown in Table 3, and these data indicate that tablets from these batches show sufficient hardness and fast disintegration. The cumulative particle size distributions of the sized granules are plotted in Fig. 5. Although there are slight

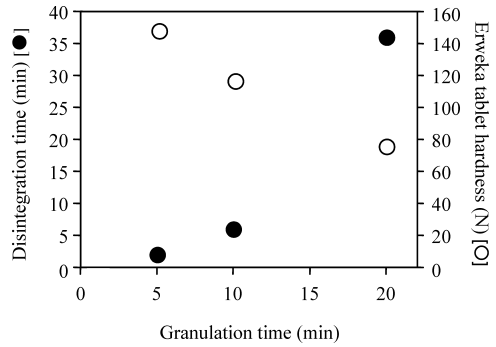

Fig. 6. The Effect of the Granulation Time on the Disintegration Time and Hardness of Tablet in 11 L Scale Batches

●, disintegration time, ○, hardness of the tablet.

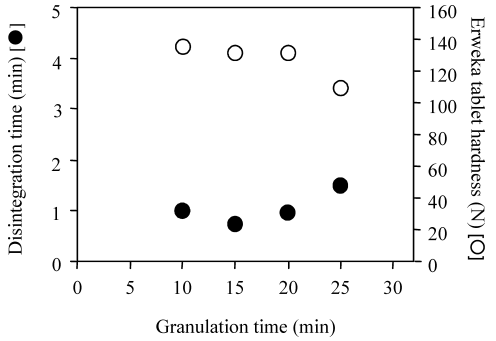

Fig. 7. The Effect of the Granulation Time on the Disintegration Time and Hardness of Tablet in 200 L Scale Batches

●, disintegration time, ○, hardness of the tablet.

differences in particle size distribution between batches, the properties of tablets obtained from 0.2 L batch scale (1150 rpm) are well agreed with that of 11 L batch scale (300 rpm). Further, in 11 L batch scale, the delay in disintegration time and decrease in tablet hardness with increase in granulation time, same as observed in 0.2 L batch scale, were observed (Fig. 6) when both granulation processes were operated under the same agitator tip speed conditions (Option 2). Since the weight of powder being granulated in both two batch scales are not so heavy to affect on the granulation process, agitator tip speed is supposed to be the major factor in the process. Therefore, the idea to use common agitator tip speed in different scales is considered to be valid in the scale-up study from 0.2 to 11 L.

Effect of Granulation Time on Tablet Properties in Commercial Scale Batches Following to 0.2 and 11 L scale batches, granulation study by using 200 L high shear granulator was conducted. Over processed granulation may cause a delay in disintegration and decrease in tablet hardness as observed in 0.2 and 11 L scale batches described above. At the same time, it is necessary to prepare sufficiently proceeded granule to prevent any troubles in compaction process since this formulation is readily to cause sticking. Therefore, to keep both compaction process operation and quality of tablet in desired status, much attention has to be paid to optimize the granulation time. Ashihara *et al.* reported that to use compaction force to the granulation mass as a common parameter to establish operation conditions for different scales (Option 1) is valid for the scale-up from small scale to commercial scale for high shear granulation process. Then operation parameters were calculated based on option 1 to obtain agitator rotation speed 170 rpm, 2.9 min granulation time (Table 1) for the initial stage of optimization. However, 2.9 min granulation time is too short for 200 L scale bath to complete granulation and achieve sufficient uniformity of granules. To date, universally applicable conversion rule on operation parameters for high shear granulation process is not established. Further, it is known from experience that optimal agitator rotation speed exists somewhere in between values calculated based on Option 1 and Option 2. Then the middle value calculated from Option 1 (170 rpm) and Option 2 (100 rpm), 130 rpm was used as agitator rotation speed for this formulation, and the effect of the granulation time on the properties of obtained tablet were examined. Although slight delay in disintegration time and slight decrease in tablet hardness was observed in tablet prepared by 25 min granulation, the properties of tablets kept excellent up to 20 min granulation as shown in Fig. 7. Thus this wide design space with the optimal granulation time of 15 min was established for commercial scale batch from the extrapolative experimental design based on the smaller scale batches. The cumulative particle size distribution of the sized granules and properties of tablet prepared by three granulation scale batches are shown in Fig. 5 and Table 3, respectively. Although there is a slight difference in particle size distribution of the granules, tablet hardness and disintegration time are agreed well between scales.

Table 3. Granulation Parameters and Properties of Tablets from Three Scale Batches

	Bowl size (L)			
	0.2 L	0.2 L	11 L	200 L
Agitator rotation speed (rpm)	600	1150	300	130
Granulation time (min)	10	1.3	5	15
Tablet hardness (N)	88.3±1.5	129.5±4.7	144.0±9.5	131.4±1.5
Disintegration time (s)	44.0±4.3	30.0±2.4	75.3±17.5	47.3±3.8

Conclusion

In the scale-up studies using model formulation, to use agitator tip speed as a common parameter to establish operation conditions for different scales was found to be valid in the study from mini-scale (0.2 L) to pilot scale (11 L). Likewise, to use compaction force to the granulation mass as a common parameter was found to be valid in the study from pilot scale (11 L) to commercial scale (200 L). The properties of powder to be granulated are different from formulation to formulation, and the wet granulation process parameters should be optimized for each relevant formulation with taking such properties into consideration. The mini-scale granulator provides more opportunities to conduct granulation studies to obtain useful information on the properties of powders from small amount of drug substance. This advantageous feature works well in the situation where the amount of drug is limited in the early stage of drug development.

It is suggested that the experimental design aimed for commercial scale can be planned in advance with small scale batches, and the establishment of progressive design space and risk-based approach for larger commercial scale can be

studied by using novel mini-scale granulator.

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