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Importance of evaluating the consolidation of granules manufactured by high shear mixer

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Abstract

The effects of the process parameters of high shear wet granulation on the granule properties and dissolution properties of mefenamic acid from tablets have been studied, and the importance of evaluating the consolidation of granules has been considered. The process parameters selected for investigation were the amount of water added, the impeller rotation speed and the kneading time. Increases in the amount of water and the kneading time led to increases in the particle diameter of the granules and to decreases in the mean pore diameter. The mean pore diameter decreased with increases in the impeller rotation speed, while the particle diameters were independent of the impeller rotation speed. The process parameters affected the surface morphology and the internal morphology of the granules. The mean particle diameter and the mean pore diameter of the granules basically correlated with the dissolution properties of the tablets. The contribution of the mean pore diameter to this correlation was higher than that of mean particle diameter. Therefore, it was concluded that evaluation of the granule consolidated state, such as the mean pore diameter, was important in order to assure the dissolution properties of drug products.

Keywords: High shear granulation; Process parameter; dataNESIA; Dissolution; X-ray computed tomography; Pore size

1. Introduction

Wet granulation using a high shear mixer is one of the most common granulation methods because the manufacturing time is relatively short and the granules exhibit high density and good flowability for filling capsules or dies in the tableting process.

A great number of papers on high shear granulation have been published, focusing mainly on three types of research fields, the first of which is the mechanism of granule growth in the high shear wet granulation process. Granule growth starts with the formation of large primary nuclei, and proceeds continuously by the formation of small nuclei due to the repeated breakage and coalescence of the granules (Vonk et al., 1997; Knight et al., 1998; Mackaplow et al., 2000; Johansen and Schæfer, 2001a,b; Schæfer, 2001; van den Dries and Vromans, 2002; van den Dries et al., 2003). The second field of study concerns the scaling-up of the high shear granulation process. An equal Froude number has resulted in a comparable process with regard to temperature and particle size distribution (Horsthuis et al., 1993). On the other hand, the impeller tip speed and water content of the mixture have been selected and investigated as the critical process parameters in the case of kneading process scaling-up (Ameye et al., 2002). Monitoring of the impeller power consumption has been successful in the scale-up of this process (Faure et al., 1999; Sirois and Craig, 2000). These findings are important for the manufacture of drug products by pharmaceutical companies in order to achieve consistent performance of the drug products. The final area of investigation has been the effect of the process parameters on granule properties. The process parameters in high shear granulation have been seen to affect the particle size distribution, specific surface area and porosity of the granules, and their influence on the compression process has also been investigated (Badawy et al., 2000).

For investigating the process parameters of the kneading process of solid dosage forms including water-insoluble active pharmaceutical ingredients (API), it is important to investigate

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Table 1
Compositions in formulation

Mefenamic acid	25.0%
Lactose monohydrate	49.5%
Low-substituted hydroxypropylcellulose	15.0%
Microcrystalline cellulose	5.0%
Hydroxypropylcellulose	5.0%
Magnesium stearate	0.5%
Total	100.0%

Tablet weight: 100 mg/tablet.

not only the granule properties but also the dissolution properties of a drug product. However, there is little literature on the investigation of the effect of process parameters in the high shear granulation process on the dissolution properties of a drug product for immediate release.

In this study, the effects of the process parameters in wet granulation using a high shear mixer on the dissolution properties of mefenamic acid as water-insoluble API from tablets was investigated to explore the correlation between the granule properties and the dissolution properties of tablets. The amount of water added, the kneading time and the impeller rotation speed were identified as the critical process parameters affecting the granule properties. The importance of evaluating the consolidation of the granules is presented using X-ray computed tomography and mercury porosimetry.

2. Materials and methods

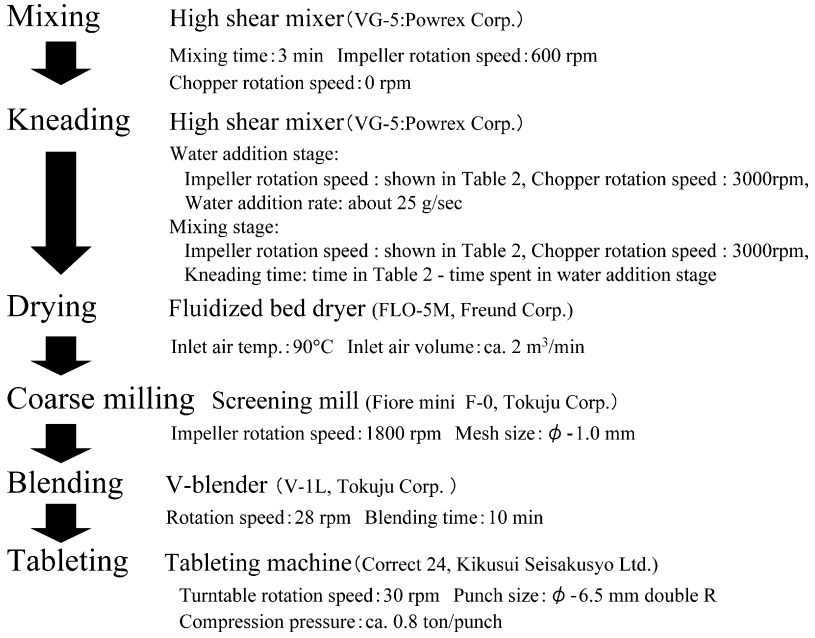
2.1. Materials

Table 1 shows the formulations used in this study. All ingredients met the Japanese Pharmacopoeia (JP) 14th grade. Mefenamic acid (Sankyo Organic Chemicals Co. Ltd., Japan) was used as an API. The excipients used were lactose monohydrate (Lactochem®, Friesland Foods Domo, Netherlands) and microcrystalline cellulose (Ceolus® PH-101, Asahi Kasei Chemicals, Japan) as fillers, low-substituted hydroxypropylcellulose (L-HPC® (LH22), Shin-Etsu Chemical Co. Ltd., Japan) as a disintegrant, hydroxypropylcellulose (HPC-L®, Nippon Soda Co. Ltd., Japan) as a binder and magnesium stearate (NOF Corp., Japan) as a lubricant.

2.2. Manufacturing process

The granules were manufactured as follows (Scheme 1) with a manufacturing scale of 1 kg.

Mefenamic acid, lactose monohydrate, low-substituted hydroxypropylcellulose, hydroxypropylcellulose and microcrystalline cellulose were weighed and poured into a high shear mixer (VG-5, Powrex Corp., Japan). The mixing process was conducted under conditions of 600 rpm for the impeller rotation speed, 0 rpm for the chopper rotation speed and 3 min for the mixing time. The kneading process had two steps: the water addition step and the mixing step after the complete addition of the water. In the water addition step, the impeller rotation speed was set as shown in Table 2, the chopper rotation speed was 3000 rpm and the water addition rate was about 25 g/s. After the water addition step, the mixing step was conducted continuously after the complete addition of the water with the same impeller and chopper rotation speed. The kneading time shown in Table 2 is the total time, including the time when the water was added as well as the mixing time after the water was added. After kneading, the wet mass was dried with a fluidized bed dryer (Flow coater multi-FLO-5M, Freund Corp., Japan) up to 60 °C for the exhaust air temperature under conditions of 90 °C for the inlet air temperature and ca. 2 m^3/min for the inlet air volume. The coarse milling of the dried granules was performed using a screening



Scheme 1. Manufacturing procedures and conditions.

Table 2
Granulation conditions of manufacturing parameters

Batch number	Amount of water added (%)	Impeller rotation speed (rpm)	Kneading time (min)
1	40	600	6
2	50	600	6
3	30	600	6
4	40	300	6
5	40	900	6
6	40	600	3
7	40	600	9
8	40	100	6
9	40	1130	6
10	40	600	1
11	40	600	18

mill (Fiore mini type F-0, Tokuju Corp., Japan) with an open mesh screen of 1.0 mm in diameter and an impeller speed of 1800 rpm. The screened granules and magnesium stearate were mixed for 10 min with a 1 L V-shaped blender (Tokuju Corp., Japan) at 28 rpm. The tableting process was conducted with the lubricated granules using a round-shaped tool with double radii, 6.5 mm in diameter. The tableting process was conducted under conditions of ca. 0.8 tonnes per punch and a turntable rotation speed of 30 rpm (tableting machine: Correct 24, Kikusui Seisakusho Ltd., Japan).

The parameters of the kneading process used in this study are shown in Table 2. The process parameter variables selected for evaluation were the amount of water added, the kneading time and the impeller rotation speed. In this study, we focused on the differences in the dissolution behavior of drug products when the drug products manufactured using granules showed different properties. Therefore, a statistical design was not adopted, but a one-factor-at-a-time approach was employed because of its simplicity.

2.3. Particle size analysis

The particle size was measured by the sieve analysis method using a Gilsonic Auto Siever (GA-6, Seishin Enterprise Co. Ltd., Japan). After coarse milling, the granules were evaluated with 18, 30, 50, 70, 100, 150, 200 mesh (JP 14th) sieves. The particle size distribution was calculated by the ratio of the residual weight of the granules on each sieve to the granule weight before sieving. From these calculations, a particle size distribution curve was drawn and the median diameter (hereafter "50% particle diameter") was calculated.

2.4. Porosity measurement of granules

The intragranular porosity was measured by mercury porosimetry (Autopore 9420, Micromeritcs, USA). The mercury filling pressure used ranged from 3 psia to 60,000 psia. In this determination, the granules from 50 to 70 mesh sieved fractions (212–300 μm) were used to clarify the difference between the intergranular pore and the void space (intragranular pore). From the pore size distribution curve, the median diameter (hereafter "50% pore diameter") was calculated. There were some cases in the determination of the pore size distribution using mercury porosimetry that values over 10 μm were treated as void space (Badawy et al., 2006). This is because the typical pore size distribution profiles were bimodal or multimodal with the larger pore size distribution representing void space. Therefore, in this study, 10 μm was taken as the cut-off point between the pores and the void space.

2.5. Scanning electron microscopy (SEM)

The granules from the 50 to 70 mesh sieved fractions (212–300 μm) were observed by scanning electron microscopy (JSM-5310LV, JEOL Ltd., Japan).

2.6. X-ray computed tomography (X-ray CT)

The granules from 50 to 70 mesh fractions (212–300 μm) were observed by X-ray CT (XMS-BS90, Microscopic Scan Co. Ltd., Japan). The evaluation conditions were an X-ray tube voltage of 50 kV, an X-ray tube current of 0.06 mA, a slice width of 0.005 mm, a re-construction usable field of 1.0 mm, and a pixel size of 0.001 mm.

2.7. Dissolution test

A dissolution test of mefenamic acid from tablets was conducted using a dissolution tester (NTR-6000, Toyama Sangyo Co. Ltd., Japan) in compliance with method II (paddle method) in JP 14th. The dissolution medium used was 900 mL of phosphate buffer containing 2% sodium lauryl sulfate (pH 6.8). The paddle rotation speed was 50 rpm, and the dissolution properties of mefenamic acid were calculated from the proportion of the dissolved amount of mefenamic acid against the potency of the tablets. The dissolved amount of mefenamic acid was determined by UV–vis spectroscopy (UV-1600, Shimadzu Corp., Japan) using samples taken from the medium every 5 min up to 60 min. The detection wavelength of mefenamic acid using UV–vis spectroscopy was 285 nm, which showed the maximum value of the UV spectrum. The dissolution percent of the mefenamic acid was calculated by the ratio of the absorbance at each sampling time to the absorbance of completely dissolved dosed mefenamic acid. In this study, the dissolution percent after 15 min (hereafter "D15") was used for evaluation because the dissolution properties at this time point were the most discriminating.

2.8. Data analysis with dataNESIA

The computer program VisualNESIA in dataNESIA (Version 3.1, Yamatake Corp., Japan) was used to analyze the correlation between the 50% particle diameter, the 50% pore diameter and D15. This program is a tool used to characterize the correlation among multiparameters using response surface methodology by multispline interpolation.

In this study, to visually evaluate the effect of the two kinds of input variables (50% particle diameter and 50% pore diameter)

Table 3
Properties of granules manufactured under various conditions

Batch number	50% particle (μm)	Specific volume (loose) (mL/g)	Specific volume (tapped) (mL/g)
1	192.0	1.72	1.42
2	290.4	1.72	1.42
3	86.3	1.81	1.41
4	149.1	1.86	1.47
5	156.6	1.87	1.49
6	151.8	1.86	1.49
7	156.2	1.82	1.48
8	156.9	1.88	1.47
9	157.5	1.86	1.49
10	142.8	1.86	1.49
11	197.0	1.82	1.48

on the output variable (D15), analysis with this program was conducted with the raw data using the response surface method. Moreover, the contribution ratios of the above parameters to D15 could be calculated by dataNESIA automatically.

3. Results and discussion

3.1. Effect of process parameters on granule properties

The process parameter variables selected for investigation were the amount of water added, the kneading time and the impeller rotation speed. After a preliminary investigation, 30%, 40% and 50% of the amount of water added to the powder were chosen.

3.1.1. Effect of process parameters on 50% particle diameter and specific volume

The 50% particle diameter and the specific volume of granules manufactured under various conditions are shown in Table 3. The effects of the process parameters on the 50% particle diameter are shown in Fig. 1. The 50% particle diameters were significantly different in the case of changing the amount of water added (batch numbers 1, 2 and 3). In the case of the kneading time, the 50% particle diameters were slightly increased in proportion to the increases in kneading time (batch numbers 1, 6, 7, 10 and 11). However, there was little change in the 50% particle diameters in the case of the impeller rotation speed (batch numbers 1, 4, 5, 8 and 9). The specific volume of each batch was not significantly affected. With regard to the 50% particle diameter, the most significant process parameter of the three investigated in this study was the amount of water added.

3.1.2. Effect of process parameters on surface morphology of granules

Fig. 2 shows the scanning electron microphotographs of the granules sieved from 212 to 300 μm. As seen in the photos of batches 1, 2 and 3, the amount of water added had no effect of on the surface morphology of the granules. On the other hand, the photos of batches 1, 10 and 11 show that the kneading time significantly affected the surface morphology of the granules. From the photos of batches 1, 8 and 9, it can be seen that the impeller rotation speed significantly affected the surface morphology of the granules. In the case of a low total revolution number of granules (impeller rotation speed × kneading time) in the mixer, the granule was formed by adhesion to maintain the intact shape of the ingredients. However, in the case of a high total revolution number of granules, the surface morphology of the granule was smooth, which suggested that the ingredients were consolidated by the shear from the impeller or chopper and by collision among the granules and between the granules and the wall of the high shear mixer.

3.1.3. Effect of process parameters on internal morphology of granules

The internal morphology of the granules was investigated using X-ray computed tomography (X-ray CT). X-ray CT has been widely used in the medical field, as well as in the field of pharmaceutical science. This technology has been applied to observe tablet shape and dimension, coating thickness, and the distribution of components in tablets or capsules (Hancock and Mullarney, 2005). The porosity in granules or tablets has also been observed and determined quantitatively (Farbera et al., 2003; Sinka et al., 2004). Bouwman et al. observed a cross-section of microcrystalline cellulose granules with this technology and determined the porosity quantitatively by image analysis. They revealed that the porosity of granules kneaded for a long time was obviously lower compared with those kneaded for a short time, both visually and quantitatively (Bouwmann et al., 2005).

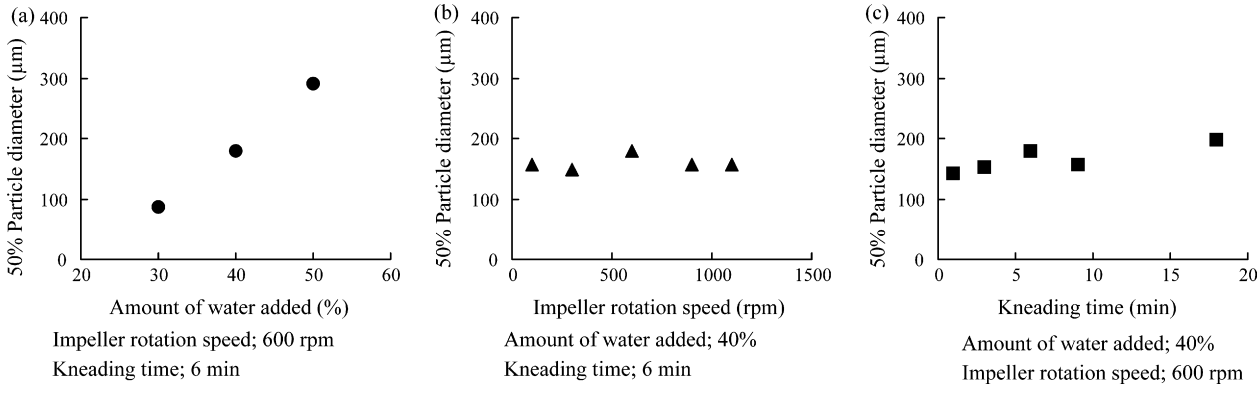


Fig. 1. Effects of process parameters on 50% particle diameter. (a) Amount of water added, (b) impeller rotation speed and (c) kneading time.

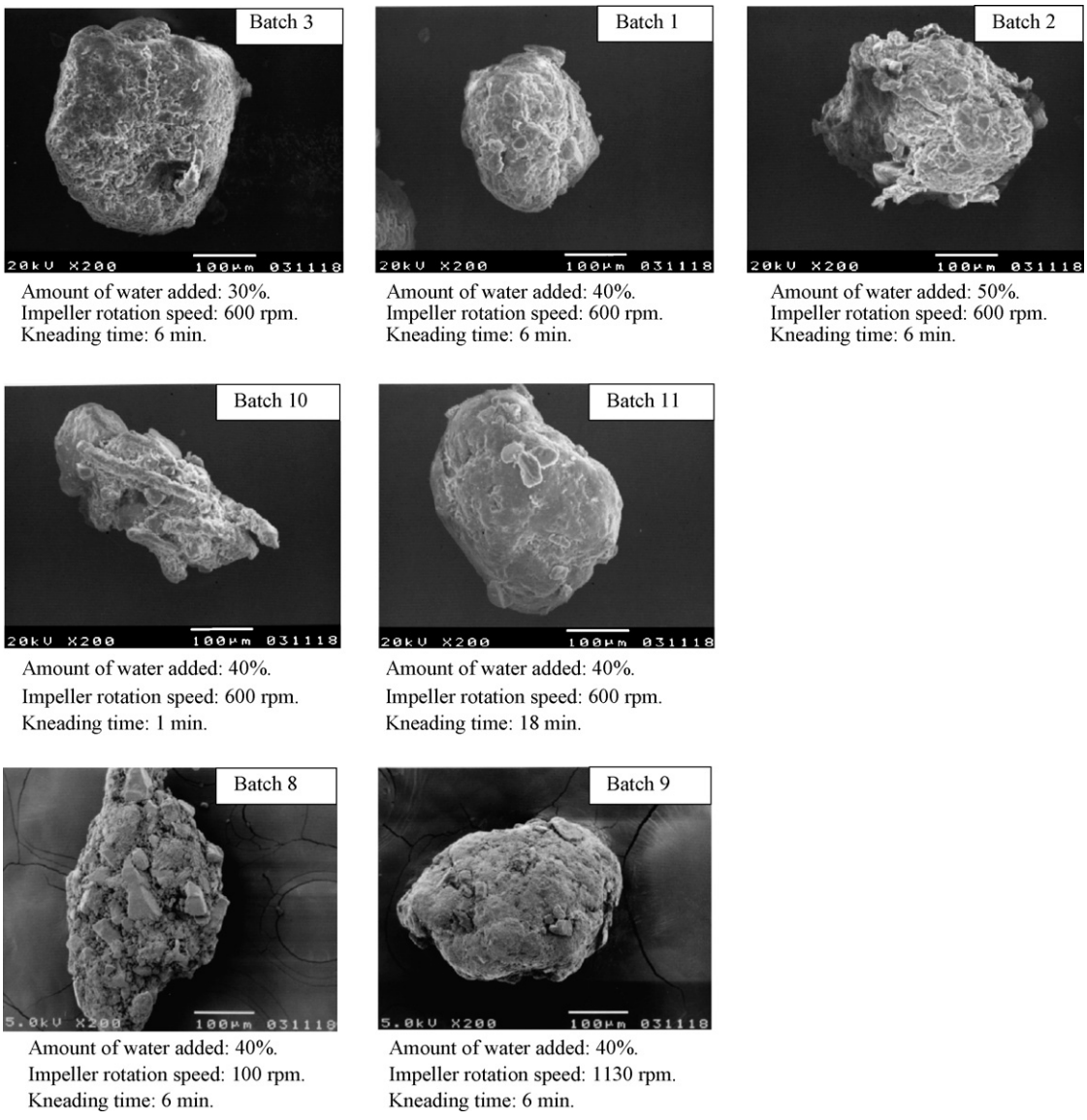


Fig. 2. Scanning electron micrographs of granules manufactured under various conditions.

X-ray CT imaging photos of granules manufactured under high and low impeller rotation speeds were obtained (Fig. 3). Visually, the porosity of granules manufactured with an impeller rotation speed of 1130 rpm was significantly lower than that of those produced with an impeller rotation speed of 100 rpm. From these images, the porosity in the granules was calculated by dividing the area of the pore (black area in granules) by the area of the granule (gray). The porosity in the granules was 41% for the impeller rotation speed of 100 rpm and 17% for that of 1130 rpm (average value, $n = 3$), indicating that the difference of impeller rotation speed affected the consolidation of the granules.

3.1.4. Effect of process parameters on 50% pore diameter of granules

The pore size distribution patterns of granules analyzed using mercury porosimetry are shown in Fig. 4. The pore size distribution curves showed a shift to a small pore size with increases in the amount of water added, the impeller rotation speed and the kneading time. In addition, the effects of the kneading process parameters on the 50% pore diameter are illustrated in Fig. 5. The 50% pore diameters decreased as the amount of water added, impeller rotation speed and kneading time were increased. Mercury porosimetry has been one of the methods used to evaluate the state of granule consolidation, where the porosity of the granules became smaller with the progress of kneading and the granules were consolidated (Badawy et al., 2000; Mehta et al., 2000; van den Dries and Vromans, 2002; Badawy et al., 2006). Therefore, consolidation of the granules could be observed by mercury porosimetry, and the 50% pore diameter was the parameter which indicated consolidation of the granules. It was considered that the pore diameter would be decreased for the following reasons: (1) lactose and HPC which dissolved in the added water might be immersed deeply into the granule and act as a binder to adhere with the nuclei and (2) air in the granule might be squeezed by high shearing.

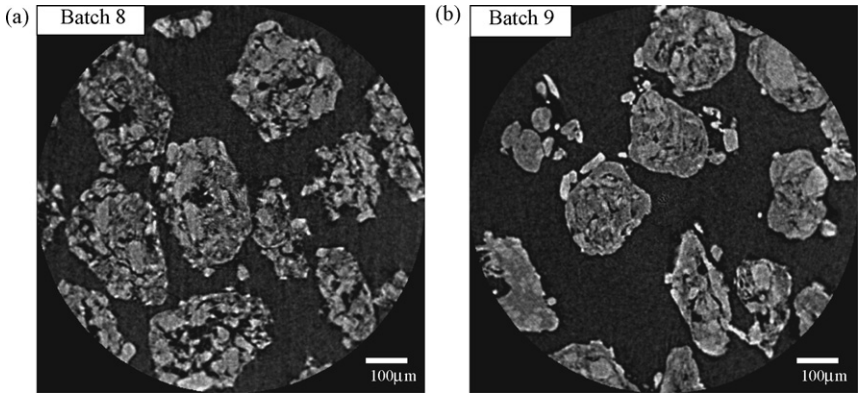


Fig. 3. Effects of impeller rotation speed on porosity of granules (X-ray CT observation). (a) Amount of water added, 40%; impeller rotation speed 100 rpm; kneading time, 6 min and (b) amount of water added, 40%; impeller rotation speed, 1130 rpm; kneading time, 6 min.

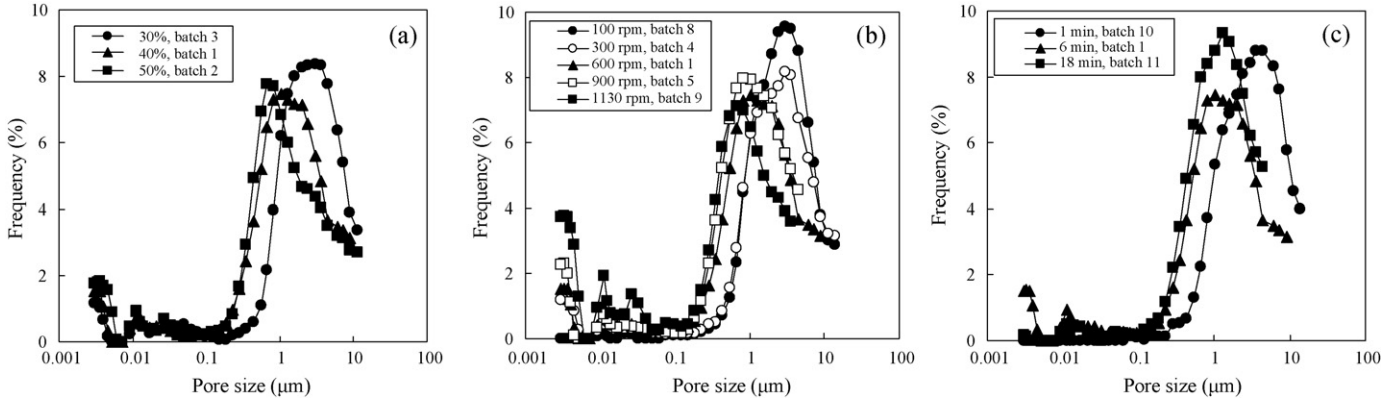


Fig. 4. Effects of process parameters on pore size distribution. (a) Amount of water added, (b) impeller rotation speed and (c) kneading time.

3.2. *Effects of process parameters on dissolution properties of mefenamic acid from tablets*

A dissolution test of the mefenamic acid from tablets consisting of granules manufactured under various conditions was conducted. Fig. 6 shows the dissolution profile of the mefenamic acid from tablets. Fig. 7 shows the effects of the process parameters on D15, which is the released percentage of mefenamic acid after 15 min. Significant differences were observed in the dissolution profiles and D15 among the tablets prepared using granules with 30%, 40% and 50% of water added. The effect of the impeller rotation speed and the kneading time on the dissolution profiles was less than that of the amount water added. However, an increase of all the process parameters led to a decrease of dissolution rate and D15. In this study, it was revealed that the pore diameter was decreased and consolidation was progressed in accordance with increases in the kneading parameters. From these results, it was considered that the reducing the pore diameter of the granules made the disintegration time of the granules increase. Therefore, it was observed that the dissolution rate of drug products using consolidated granules were decreased.

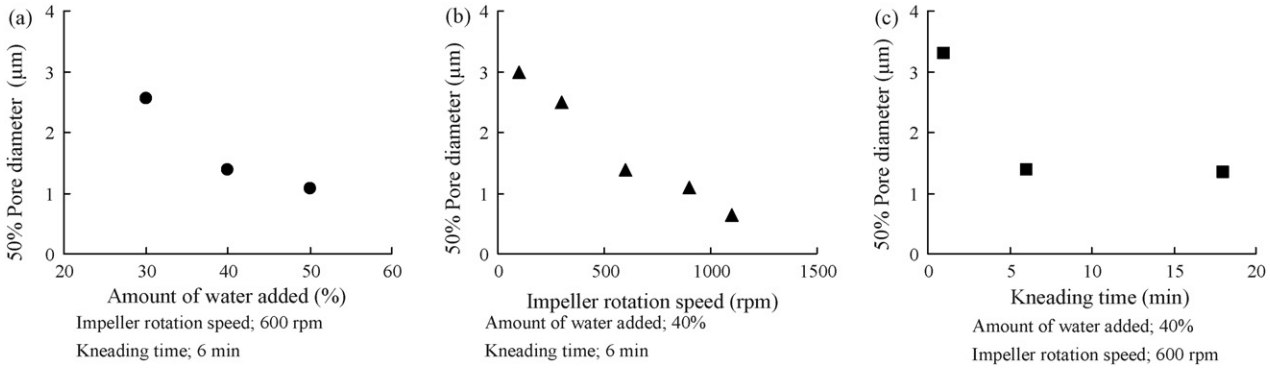


Fig. 5. Effects of process parameters on 50% pore diameter. (a) Amount of water added, (b) impeller rotation speed and (c) kneading time.

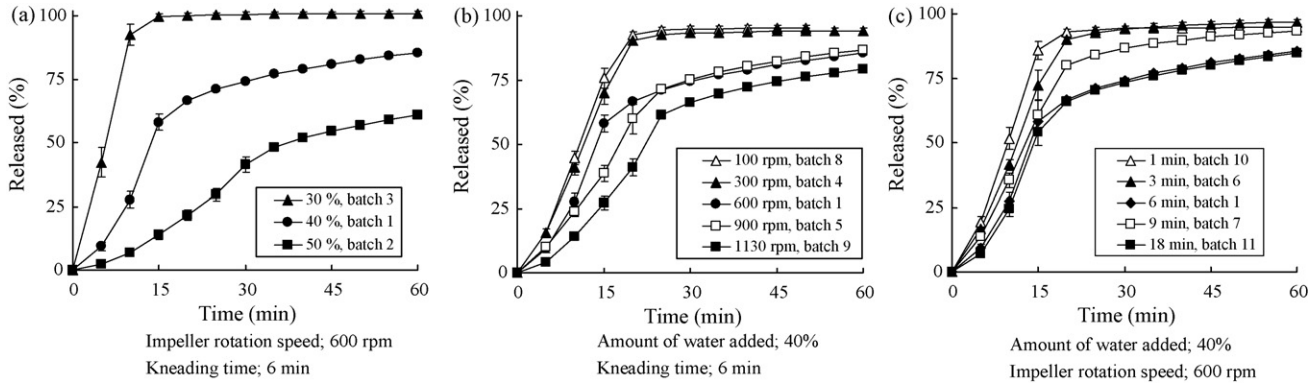


Fig. 6. Effects of process parameters on dissolution profiles of mefenamic acid in tablets. (a) Amount of water added, (b) impeller rotation speed and (c) kneading time.

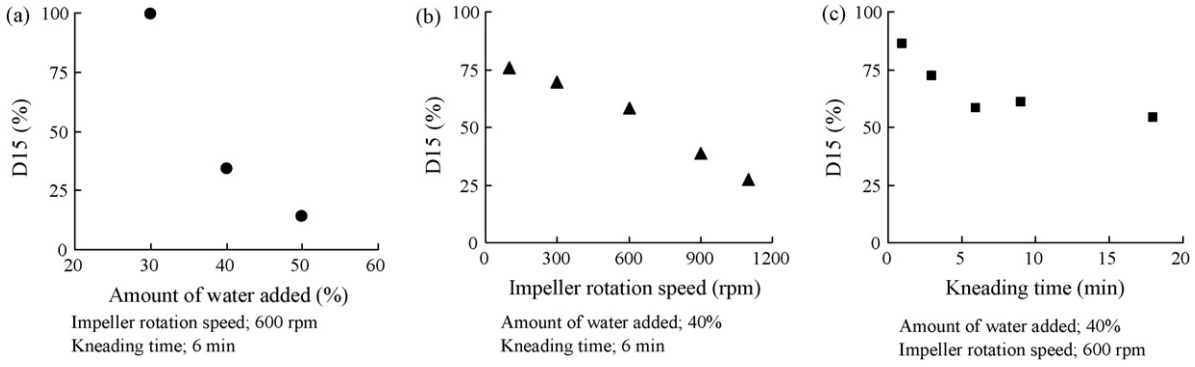


Fig. 7. Effects of process parameters on D15. (a) Amount of water added, (b) impeller rotation speed and (c) kneading time.

The response surface method with multispline interpolation has been employed to optimize the formulation of solid dosage forms and develop drug delivery systems (Surini et al., 2003; Onuki et al., 2004, 2005). In this study, this method was applied to evaluate the correlation among the 50% pore diameter of the granules, the 50% particle diameter and D15, and moreover, to detect the parameter most strongly correlated with D15. The computer program Visual NESIA in dataNESIA (Version 3.1, Yamatake Corp., Japan) was used. This program is a tool to characterize the correlation among multiparameters using the response surface methodology by multispline interpolation (Takayama, 2002, 2005; Takayama et al., 2004).

In this evaluation, the 50% particle diameter and the 50% pore diameter were used as the input variables and D15 was used as the output variable. The contribution ratios of the two above parameters to D15 could be calculated by dataNESIA automatically, and the result is illustrated in Fig. 8. Correlation between the 50% pore diameter of the granules, the 50% particle diameter and D15 could be visualized successfully by dataNESIA. It was clear that there was an increase in the 50% pore diameter and that a decrease in the 50% particle diameter led to D15 increase. However, the contribution ratios of the 50% pore diameter and the 50% particle diameter of the granules to D15 were different, and were calculated to be 72% and 28%, respectively. The 50% pore diameter affected D15 more strongly than the 50% particle diameter. Therefore, it was clear that an evaluation of the consolidation state, e.g. pore diameter, porosity, of the granules was important to assure the dissolution properties.

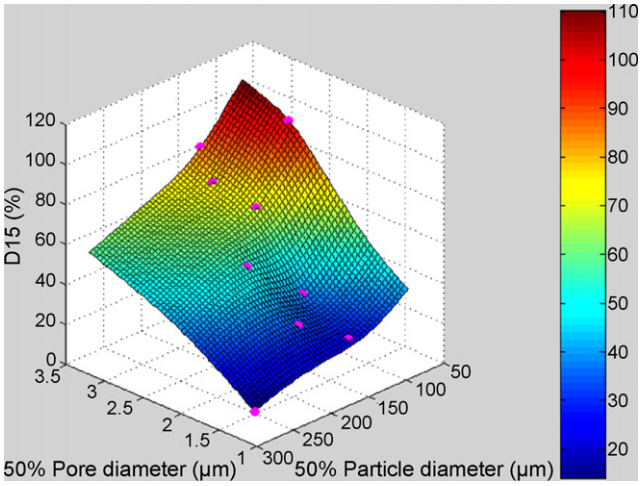


Fig. 8. Correlation between 50% pore diameter, 50% particle diameter and D15.

4. Conclusions

Using a high shear mixer, the effects of the process parameters on the dissolution properties of the mefenamic acid from tablets were investigated. The dataNESIA was successfully employed

to analyze the correlation among the 50% pore diameter, the 50% particle diameter and D15. This analysis could elucidate that both the 50% pore diameter and the 50% particle diameter had an influence on D15, but the contribution of the 50% pore diameter to this correlation was remarkably higher than that of the 50% particle diameter. The 50% pore diameter as an indicator of the consolidation of the granules, therefore, was a more influential parameter on dissolution behavior. Also, the difference of the consolidation state of the granules was observed by X-ray CT and consolidated granules with higher process parameters significantly showed less porosity.

From these findings, we conclude that not only the apparent properties of the granules, i.e. particle size, but also the internal properties of the granules, i.e. evaluation of consolidated state of the granules, are important to assure the dissolution properties of API from drug products.

Acknowledgement

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