Evaluation of Weight Variation in Mini-Tablets Manufactured by a Multiple-Tip Tool

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Recently, owing to their pharmaceutical and clinical utility, mini-tablets have been well studied by researchers. Mini-tablets are usually manufactured by compression molding using a multiple-tip tool in a rotary tableting machine. Owing to their special structure, ensuring uniformity is a very important challenge in the manufacturability of mini-tablets using the multiple-tip tool. In this study, we aimed to evaluate the weight variation in mini-tablets produced by a multiple-tip tool, which is considered to be the root cause affecting the uniformity, and to investigate the physical properties of drug granules and tableting conditions in a rotary tableting machine that could reduce this weight variation. In addition, the relationship between these factors and response was visualized using response surface analysis. It was shown that the weight variation in mini-tablets produced by a multiple-tip tool was reduced when using a forced feeder compared with an open feeder. Furthermore, in the case of an open feeder, the optimal range of the average particle size diameter of drug granules and the rotational speed of the rotating disc in the rotary tableting machine were determined from response surface analysis. It was suggested that it is possible to reduce the weight variation in the mini-tablets by selecting drug granules with an average particle size diameter of 100–150 µm and using tableting conditions with a rotational speed of 40–60 rpm. This study elucidated the factors that affect uniformity and determined their optimal range for the manufacture of mini-tablets.

Key words: mini-tablet; weight variation; multiple-tip tool; granulated mannitol; granulated lactose; powder flowability

Introduction

Recently, the miniaturization of tablets has emerged as a focus of pharmaceutical research.¹,² Mini-tablets, defined by WHO as tablets with a diameter of ≤4 mm,³ have attracted attention as a new dosage form to improve adherence, and their pharmaceutical and clinical suitability has been investigated.⁴,⁵ Many pharmaceutical aspects have been studied, including the development of mini-tablets with a diameter of 1–2 mm to increase miniaturization, enhance dissolution control, and the improvement of absorption by modification of the tablet surfaces.⁶–⁸ Many studies of mini-tablets have been performed, investigating not only oral formulations, but also long-term sustained-release topical formulations that can be inserted into the conjunctival sac.⁹,¹⁰ In contrast, from a clinical perspective, tablets with a diameter of 2 mm can be administrated 2 d after birth, and tablets with a diameter of 3 mm can be taken by half of all children at the age of 2 years and by most children at the age of 5 years. Furthermore, mini-tablets were shown to be more acceptable than solutions, powders, and conventional tablets.¹¹,¹²

Mini-tablets are usually manufactured by compression molding using a special punch with multiple punch heads called a multiple-tip tool¹³ (Fig. 1A). A multiple-tip tool is fixed in place within a rotary tableting machine. Advanced technology is required for the manufacture of mini-tablets.¹,¹³ In particular, ensuring uniformity is one of the most important challenges in manufacturing of mini-tablets. Although several papers have reported the manufacturability and uniformity of mini-tablets,¹³–¹⁸ there have been no reports describe the weight variation in mini-tablets produced by a multiple-tip tool at the microscopic level. We believe that verifying and controlling the weight variation in mini-tablets produced by a multiple-tip tool are very important to ensure uniformity, because the weight variation is ultimately thought to affect uniformity in manufacturing.

The physical properties of granules (types of excipients and particle size distribution) are considered as major factors affecting the weight variation in mini-tablets produced by a multiple-tip tool.¹⁵–¹⁷ Lactose and mannitol are common excipients used in granules.¹⁸,¹⁹ Mannitol is a sugar alcohol with high crystallinity, low hygroscopicity, and low reactivity with drugs; it has moderate sweetness and coolness, and has excellent palatability.¹⁰ Therefore, mannitol has been used widely in recent years for the development of orally disintegrating tablets.²¹

In this study, we aimed to evaluate the weight variation in mini-tablets produced by a multiple-tip tool and to investigate physical properties of drug granules and tableting conditions that can reduce the weight variation in these mini-tablets. Mitiglinide calcium hydrate, a fast-acting insulin secretagogue developed by Kissei Pharmaceutical Co., Ltd. (Japan), was selected as the model drug. Granulated mannitol or granulated lactose with different particle size distributions were selected, and the influence of the physical properties of mitiglinide granules on the weight variation in mini-tablets produced by the multiple-tip tool was evaluated. In addition, as other po-

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tential factors that affect the weight variation in mini-tablets, including formulation, tabletting conditions (e.g., feeder types and rotational speed of the rotating disc) in the rotary tableting machine were considered. Two feeder types were considered, open feeder (Fig. 1B) and forced feeder (Fig. 1C), and the feeder selection is based on powder characteristics. Further, as the rotational speed of the rotating disc in the rotary tableting machine is an important parameter directly related to the manufacturing capacity of mini-tablets, optimization of this parameter according to powder characteristics is required. Therefore, in this study, the effects of feeder type and the rotational speed of the rotating disc in the rotary tableting machine on the

![Multiple-tip tool with 12 tips in a punch. The open feeder or forced feeder was set in the position (indicated by an arrow) in the rotary tableting machine.](image1)

**Fig. 1. Appearance of the Multiple-Tip Tool (A), Open Feeder (B), and Forced Feeder (C) with Two Paddles (D) in the Rotary Tableting Machine**

| Formulation (%) | M1 | M2 | M3 | M4 | M5 | M6 | M7 | L1 | L2 | L3 | L4 | L5 | L6 | L7 |
|-----------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Mitiglinide calcium hydrate | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Granulated mannitol | | | | | | | | | | | | | |
| Pearitol 100 SD | 65.5 | — | — | — | — | — | — | — | — | — | — | — | — |
| Pearitol 200 SD | — | 65.5 | — | — | — | — | — | — | — | — | — | — | — |
| Pearitol 300 DC | — | — | 65.5 | — | — | — | — | — | — | — | — | — | — |
| Granutol F | — | — | — | 65.5 | — | — | — | — | — | — | — | — | — |
| Granutol S | — | — | — | — | 65.5 | — | — | — | — | — | — | — | — |
| Granutol R | — | — | — | — | — | 65.5 | — | — | — | — | — | — | — |
| Mannit Q | — | — | — | — | — | — | 65.5 | — | — | — | — | — | — |
| Granulated lactose | | | | | | | | | | | | | |
| Dilactose F | — | — | — | — | — | — | — | — | — | 65.5 | — | — | — |
| Dilactose S | — | — | — | — | — | — | — | — | — | — | 65.5 | — | — |
| Dilactose R | — | — | — | — | — | — | — | — | — | — | — | 65.5 | — |
| Tabletose 80 | — | — | — | — | — | — | — | — | — | — | — | — | 65.5 |
| Lactose Fast Flo 316 | — | — | — | — | — | — | — | — | — | — | — | — | 65.5 |
| Super Tab 30 GR | — | — | — | — | — | — | — | — | — | — | — | — | 65.5 |
| Super Tab 24 AN | — | — | — | — | — | — | — | — | — | — | — | — | — | 65.5 |
| Cornstarch | 20.0 | 20.0 | 20.0 | 20.0 | 20.0 | 20.0 | 20.0 | 20.0 | 20.0 | 20.0 | 20.0 | 20.0 | 20.0 |
| Low-substituted hydroxypropyl cellulose | 10.0 | 10.0 | 10.0 | 10.0 | 10.0 | 10.0 | 10.0 | 10.0 | 10.0 | 10.0 | 10.0 | 10.0 | 10.0 |
| Hydroxypropyl cellulose | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 |
| Magnesium stearate | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 |
| Total | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
weight variation in mini-tablets produced by the multiple-tip tool were also evaluated. The relationship between these factors and response was visualized by using response surface analysis.

**Experimental**

**Materials** Mitiglinide calcium hydrate (average particle size diameter: 2.3 µm) was provided by Kissei Pharmaceutical Co., Ltd. Pearlitol 100 SD, Pearlitol 200 SD, and Pearlitol 300 DC (Roquette, France), Granulot F, Granulot S, and Granulot R (Freund, Japan), and Mannit Q (Mitsubishi Corporation Life Sciences, Japan) were the varieties of granulated mannitol. Dilactose F, Dilactose S, and Dilactose R (Freund), Tablettose 80 (MEGGLE, Germany), Lactose Fast Flo 316 (Foremost Farmas USA, U.S.A.), and Super Tab 30 GR and Super Tab 24 AN (DFE Pharma, Germany) were selected as the varieties of granulated lactose. Nishshoku cornstarch (Nihon Shokuhin Kako, Japan) was also used as an excipient. Low-substituted hydroxypropyl cellulose (L-HPC (LH-11), Shin-Etsu Chemical, Japan) was used as a disintegrant. Hydroxypropyl cellulose (HPC-L, Nippon Soda, Japan) was used as a binder. As a lubricant, magnesium stearate (Perteca LUB MST, Merck KGaA, Germany) was selected.

**Formulation of Mini-Tablets** The formulations used to prepare the mini-tablets are shown in Table 1. The mini-tablets contained 0.5% mitiglinide calcium hydrate, 65.5% granulated mannitol or granulated lactose, 20% cornstarch, 10% low-substituted hydroxypropyl cellulose, 2% hydroxypropyl cellulose, and 2% magnesium stearate.

**Manufacture of Mitiglinide Granules** Mitiglinide calcium hydrate (5 g) was dispersed in 4% hydroxypropyl cellulose solution (500 g). Granulated mannitol or granulated lactose (665 g), cornstarch (200 g) and low-substituted hydroxypropyl cellulose (100 g) were placed in a fluidized bed granulator (MP-01, Powrex, Japan) and granulated with an inlet air temperature of 80°C by spraying with hydroxypropyl cellulose solution in which mitiglinide was dispersed. After completion of spraying, the wet granules were dried until the outlet air temperature reached 40°C. These processes were repeated to manufacture two batches of granules, which were mixed in a vinyl bag. The granules were sized using a Comill (QC-197S, Powrex) with a screen punch diameter of 0.991 mm and a rotational speed of 1000 rpm to obtain mitiglinide granules.

**Evaluation of Particle Size Distribution of Mitiglinide Granules** The particle size distribution of mitiglinide granules was measured by using an automated sonic sieving particle size analyzer (Robot Shifter RPS-205, Seishin Enterprise, Japan). Approximately 1 g of mitiglinide granules was weighed and sieved successively through seven sieves (apertures: 45, 75, 106, 180, 300, 500, and 850 µm). The particle size of mitiglinide granules corresponding to the 10, 50, 60, and 90th percentiles (d10, d50, d60, and d90) were determined from the cumulative undersize curve.

**Evaluation of Powder Flowability of Mitiglinide Granules** The powder Tester Model PT-N (Hosokawa Micron, Japan) was used to measure properties of powder flowability: angle of repose, compressibility, angle of spatuula, and uniformity. The measurement conditions used were: (1) angle of repose: table diameter was 8 cm, (2) compressibility: cup volume was 100 cm³ and tapping number was 180, (3) angle of spatuula: spatula area was 8 × 2.2 cm², shockng number was 1, and height was 15 cm, (4) uniformity: the d50/d10 ratio was calculated using the results of particle size distribution measurement. Compressibility was calculated from the following formula:

\[
\text{Compressibility} = \left(\frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}}\right) \times 100
\]

Car's index was determined by calculating the index of each parameter using the powder flowability index table and summing those values.\(^{22,23}\)

**Evaluation of the Weight Variation in Mini-Tablets Produced by the Multiple-Tip Tool** At the time of 0 punches, 480 punches, and 960 punches during continuous tabletting, the rotary tabletting machine was stopped and 12 mini-tablets within a specific multiple-tip tool was sampled (Fig. 2). The weight of the mini-tablets sampled was measured individually by using an electronic balance and the weight ratio to the average within the multiple-tip tool was calculated. Furthermore, the relative standard deviation (R.S.D.) of the weight of mini-tablets within multiple-tip tool was calculated to provide an index of weight variation in the mini-tablets produced by multiple-tip tool.

**Evaluation of the Drug Content of Mini-Tablets** The drug content of the mini-tablets was measured by using HPLC equipment (Shimadzu, Japan) fitted with a stainless steel column with an inside diameter of 4.6 mm and a length of 15 cm, packed with palmitoamidopropyl silylated silica gel (5 µm particle diameter). The column temperature was set at 35°C.
Table 2. Physical Properties of Mitiglinide Granules

| Formulation | Particle size distribution | Powder flowability |
|-------------|---------------------------|-------------------|
|              | $d_{10}$ (µm) | $d_{50}$ (µm) | $d_{90}$ (µm) | Angle of repose (degree) | Compressibility (%) | Angle of spatula (degree) | Uniformity (—) | Carr’s index | Flowability |
| M1          | 55.2          | 85.3          | 153.4         | 35.2                  | 15.4                | 51.6                  | 1.68           | 79.0         | Good       |
| M2          | 70.9          | 139.6         | 437.5         | 36.8                  | 13.2                | 48.4                  | 2.19           | 78.0         | Good       |
| M3          | 41.4          | 243.5         | 455.8         | 36.9                  | 10.0                | 50.8                  | 6.85           | 77.5         | Good       |
| M4          | 22.2          | 61.8          | 163.7         | 37.7                  | 19.6                | 60.3                  | 3.22           | 73.5         | Good       |
| M5          | 43.8          | 90.0          | 182.0         | 35.7                  | 16.1                | 51.9                  | 2.30           | 78.0         | Good       |
| M6          | 64.2          | 130.4         | 264.0         | 35.7                  | 13.9                | 41.3                  | 2.31           | 81.5         | Very good  |
| M7          | 30.7          | 61.1          | 157.8         | 38.6                  | 20.3                | 62.0                  | 2.24           | 70.5         | Good       |
| L1          | 35.2          | 71.6          | 168.7         | 38.8                  | 21.6                | 61.8                  | 2.37           | 69.0         | Passable   |
| L2          | 51.6          | 94.0          | 104.6         | 37.9                  | 20.3                | 55.4                  | 2.03           | 74.5         | Good       |
| L3          | 57.8          | 150.8         | 289.2         | 37.6                  | 16.0                | 43.1                  | 2.97           | 78.5         | Good       |
| L4          | 52.4          | 124.5         | 360.0         | 37.5                  | 18.7                | 50.8                  | 2.90           | 75.0         | Good       |
| L5          | 60.4          | 105.5         | 176.9         | 37.3                  | 18.5                | 53.7                  | 2.04           | 75.0         | Good       |
| L6          | 66.6          | 127.3         | 265.3         | 39.4                  | 18.4                | 51.1                  | 2.20           | 75.0         | Good       |
| L7          | 44.5          | 100.6         | 268.6         | 37.5                  | 17.1                | 54.9                  | 2.76           | 75.0         | Good       |

Flowability was based on the scores of Carr’s index. Carr’s index: extremely poor, 0–19; very poor, 20–39; poor, 40–59; passable, 60–69; good, 70–79; very good, 80–89; excellent, 90–100.

Fig. 3. Weight Variation (Relative Standard Deviation, R.S.D.) in Mini-Tablets Produced by the Multiple-Tip Tool

The combinations of granulated mannitol and open feeder (A), granulated mannitol and forced feeder (B), granulated lactose and open feeder (C), and granulated lactose and forced feeder (D) are shown. Each column represents the mean ± standard deviation (S.D.) of the weight variation of 12 mini-tablets sampled from each tip of the multiple-tip tool in three experiments (0 punches, 480 punches, and 960 punches).
One mini-tablet was added to exactly 10 mL of a mixture of water and acetonitrile (2:1). After the mini-tablet was dissolved, the sample solution was filtered through a 0.45-µm diameter membrane filter (Millex-LH, Millipore, France). The chromatographic separation was performed using the column and a mobile phase of a 62:37:1 mixture of water, acetonitrile, and n-amyl alcohol adjusted pH to 2 with phosphoric acid. The injection volume was 20 µL and the flow rate was 1.5 mL/min. The elution was monitored at 210 nm by using an ultraviolet detector.

Response Surface Analysis Analysis software dataNESIA (Azbil, Japan) was used to visualize the weight distribution of mini-tablets produced by multiple-tip tool and the relationship between the average particle size diameter of mitiglinide granules and the rotational speed of the rotating disc in the rotary tableting machine and the weight variation in mini-tablets produced by multiple-tip tool. The response surface was computed by using dataNESIA. By using the response surface method with multivariate spline interpolation, which is an interpolation method that can predict the nonlinearity of experimental data more accurately and stably, dataNESIA can create the response surface quickly, easily, and smoothly, even for complex objects. Therefore, dataNESIA makes it possible to visualize experimental data and efficiently perform optimal design. The “thin-plate double asterisk interpolation” method was used for dataNESIA analysis.

Results and Discussion Physical Properties of Mitiglinide Granules The particle size distribution and powder flowability of mitiglinide granules were evaluated (Table 2). By changing the types of granulated mannitol or granulated lactose, mitiglinide granules with different particle size distribution and powder flowability were obtained. For mitiglinide granules manufactured with granulated mannitol, granules with an average particle size diameter of 61.1–243.5 µm and a Carr’s flowability index of 70.5 (good) to 81.5 (very good) were obtained. In contrast, for mitiglinide granules manufactured with granulated lactose, granules with an average particle size diameter of 71.6–150.8 µm and the Carr’s flowability index of 69.0 (passable) to 78.5 (good) were prepared.

Weight Variation in Mini-Tablets Produced by the Multiple-Tip Tool The weight variation in mini-tablets (R.S.D. of the weight of the mini-tablets) produced by a multiple-tip tool is shown in Fig. 3, and the weight distribution was visualized by using response surface analysis (Fig. 4: Formulations M1–M7; Fig. 5: Formulations L1–L7). The comparison of Fig. 3A with Fig. 3B and Fig. 3C with Fig. 3D revealed a
trend toward smaller weight variation in mini-tablets produced by the multiple-tip tool using the forced feeder compared with the open feeder for mitiglinide granules prepared with granulated mannitol and granulated lactose. It was also shown that the weight distribution was smaller with the forced feeder in Figs. 4 and 5. This is thought to have led to a reduction in the weight variation in the mini-tablets because the forced feeder forces the lubricant mixture into the die. Comparatively, in the open feeder, the weight variation in the mini-tablets appeared to be influenced by the physical properties of mitiglinide granules and the rotational speed of the rotating disc, as the lubricant mixture is filled into the die by gravity. These results suggest the usefulness of the forced feeder for the manufacture of mini-tablets.

For the mitiglinide granules prepared with granulated mannitol, M7 and M4 had smaller average particle size diameter and Carr's flowability index than other mitiglinide granules (Table 2). As a result of manufacturing mini-tablets with an open feeder using these formulations, the weight variation in mini-tablets produced by a multiple-tip tool was larger (Fig. 3A). Furthermore, the weight of mini-tablets prepared with tips located in the outer and forward direction relative to the rotating disc (e.g., tip position #11 and 12 in Fig. 2) was increased (Fig. 4). In contrast, the weight of mini-tablets prepared with tips located in opposite direction (e.g., tip position #6 and 7) were decreased. Furthermore, it became clear that
the weight variation in mini-tablets prepared by the multiple-tip tool increased as the rotational speed of the rotating disc in the rotary tableting machine was increased (Fig. 3A). This was thought to be owing to the fact that the poorer powder flowability of these granules required a longer die retention time to be densely packed in the die. The faster rotational speed resulted in heavier mini-tablets from the outer and forward tips (e.g., tip position #11 and 12) with a longer die retention time. In contrast, the inner and backward tips (e.g., tip position #6 and 7) with a shorter die retention time resulted in lighter of mini-tablets. Focusing on M3, it had larger average particle size diameter and Carr’s flowability index than other granules (Table 2). It was revealed that the weight variation in mini-tablets produced by the multiple-tip tool was larger, and the weight of the mini-tablets prepared with the tips located in the outer and forward direction relative to the rotating disc (e.g., tip position #11 and 12) was increased (Fig. 4). This phenomenon was similar to M7 and M4, which had smaller average particle size diameter and Carr’s flowability index. However, the weight variation in the mini-tablets was not affected by the rotational speed. The larger average particle size diameter and the larger centrifugal force applied to the particles, which resulted in heavier mini-tablets in the outer and forward tips (e.g., tip position #11 and 12). On the other hand, the inner and backward tips (e.g., tip position #6 and 7), experiencing a smaller centrifugal force, produced lighter mini-tablets. However, as the powder flowability was relatively superior, the weight variation in the mini-tablets was considered to be less affected by the rotational speed. Because, the die retention time sufficient for the most dense packing of the lubricant mixture in the die could be ensured, even at higher rotational speeds.

In contrast, for the mitiglinide granules prepared with granulated lactose, L1 had the smallest average particle size diameter and Carr’s flowability index than other mitiglinide granules (Table 2). As a result of manufacturing mini-tablets with an open feeder using this formulation, the weight variation in mini-tablets produced by a multiple-tip tool was larger (Fig. 3C). However, the weight variation in the mini-tablets was not as large as for mini-tablets prepared with granulated mannitol. Furthermore, the weight distribution of L1 at a rotational speed of 20 rpm showed the opposite tendency to M7 and M4 (Fig. 5). This difference may be due to the difference in adhesiveness depending on the type of excipient.

Drug Content of Mini-Tablets The correlation between the mini-tablet weight and drug content of the mini-tablet was evaluated (Fig. 6). The result of the formulation of M1 produced with the open feeder was selected as a representative because it showed an acceptable average weight variation (R.S.D. was approximately 1% in Fig. 3A). There was a positive correlation between the mini-tablet weight and drug content of the mini-tablets. This suggested that results of the weight variation in mini-tablets produced by the multiple-tip tool obtained this study could be utilized for the prediction of drug content variation in mini-tablets. Furthermore, it was suggested that the drug content of mini-tablets could be adjusted arbitrarily by adjusting the weight of the mini-tablets.

Response Surface Analysis of the Effects of Physical Properties of Mitiglinide Granules and Tableting Conditions on the Weight Variation in Mini-Tablets Produced by the Multiple-Tip Tool The average particle size diameter and rotational speed were selected as the physical properties to control mitiglinide granules and the tableting conditions in the rotary tableting machine, and the effects of these properties on the weight variation in mini-tablets produced by the multiple-tip tool were visualized by using response surface analysis for each feeder type (Fig. 7). The response surface analysis showed that there was an optimal range to reduce the weight variation in mini-tablets produced by a multiple-tip tool using an open feeder. Both granules prepared with granulated mannitol and with granulated lactose may have smaller weight variation when mitiglinide granules with an average particle size diameter of 100–150 µm and tableting conditions with a rotational speed of 40–60 rpm were selected in an open feeder. An increase in the suction force in the die is considered to be the reason why the weight variation in the mini-tablets produced by the multiple-tip tool was reduced when the rotational speed of the rotating disc in the rotary tableting machine was higher in the optimal range. These results were consistent with the reports of Cho et al.

In contrast, with the forced feeder, a robust response surface was obtained that was not easily affected by the average particle size diameter and the rotational speed. However, in the case of mitiglinide granules prepared with granulated mannitol, when the average particle size diameter exceeded 200 µm, there was an increased risk of the weight variation in mini-tablets produced by the multiple-tip tool. Using a model die filling system, Schiano et al. reported with greater particle size and powder flowability, better filling properties were obtained in the die. Therefore, our results are considered to illustrate one of the characteristic phenomena encountered in the manufacturing of mini-tablets produced by a multiple-tip tool using a forced feeder in a rotary tableting machine. We believe that these characteristic phenomena should be recognized and more attention should be paid to the manufacturing of mini-tablets produced by a multiple-tip tool with a forced feeder in a rotary tableting machine.

Conclusion In this study, we aimed to evaluate the weight variation in mini-tablets produced by a multiple-tip tool, which is considered to be the root cause affecting the uniformity of mini-tablets, and to investigate the physical properties of drug granules and the tableting conditions in the rotary tableting machine that can lead to a reduction in the weight variation in mini-tablets produced by a multiple-tip tool. It was clearly shown that the weight variation in the mini-tablets was reduced by the use of a forced feeder compared with an open feeder. Furthermore, in the case of the open feeder, the optimal range of the average particle size diameter of drug granules and the rotational speed of the rotating disc in the rotary tableting machine could be determined by using response surface analysis. This study elucidated the factors that affected uniformity and their optimal range for the manufacturability of mini-tablets. We believe that the findings of this study provide important and critical insights to support systematic improvements in the manufacture of mini-tablets.

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Conflict of Interest  HK is an employee of Kissei Pharmaceutical Co., Ltd. NN serves as a consultant to Kissei Pharmaceutical Co., Ltd.

References
1) Aleksovski A., Dreu R., Gasperlin M., Planinsek O., Expert Opin. Drug Deliv., 12, 65–84 (2015).
2) Klingmann V., AAPS PharmSciTech, 18, 263–266 (2017).
3) World Health Organization Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series, 970, 197–216 (2012).
4) Kluk A., Sznitowska M., Brandt A., Szurkowski K., Plata-Nazar K., Mysliwiec M., Kaminska B., Kotlowska H., Int. J. Pharm., 485, 1–6 (2015).
5) Thompson S. A., Tuleu C., Wong I. C. K., Keady S., Pitt K. G., Sulkiffe A. G., Pediatrics, 123, 235–238 (2009).
6) Tissen C., Woertz K., Breitkreutz J., Kleinebudde P., Int. J. Pharm., 416, 164–170 (2011).
7) Lazzari A., Kleinebudde P., Knop K., Int. J. Pharm., 536, 440–449 (2018).
8) Vemula S. K., Venisetty R. K., Veerareddy P. R., J. Drug Deliv. Sci. Tec., 40, 66–72 (2017).
9) Refai H., Tag R., Drug Deliv., 18, 38–45 (2011).
10) Choonara Y. E., Pillay V., Carmichael T. R., Meyer L. C. R., Du Toit L. C., Naylor S., Wanblad C., J. Pharm. Sci., 100, 1819–1832 (2011).
11) Klingmann V., Linderskamp H., Meissner T., Mayatepek E., Moeltner A., Breitkreutz J., Bosse H. M., J. Pediatr., 201, 202–207.e1 (2018).
12) Hayakawa Y., Uchida S., Namiki N., Eur. J. Pharm. Sci., 84, 157–161 (2016).
13) Cho C.-H., Kim J.-Y., Park E.-S., Powder Technol., 362, 90–100 (2020).
14) Mitra B., Chang J., Wu S.-J., Wolfe C. N., Ternik R. L., Gunter T. Z., Victor M. C., Int. J. Pharm., 525, 149–159 (2017).
15) Blanco D., Antikainen O., Räikkönen H., Mah P. T., Healy A. M., Juppo A. M., Yli-rau J., Int. J. Pharm., 581, 119280 (2020).
16) Goh H. P., Heng P. W. S., Liew C. V., Int. J. Pharm., 534, 279–286 (2017).
17) Schiano S., Chen L., Wu C. Y., Powder Technol., 337, 78–83 (2018).
18) Goh H. P., Heng P. W. S., Liew C. V., J. Pharm. Sci., 108, 1161–1171 (2019).
19) Paul S., Chang S. Y., Dun J., Sun W. J., Wang K., Tajabri P., Boissier C., Sun C. C., Int. J. Pharm., 566, 24–31 (2019).
20) Matsui K., Takeuchi S., Haruna Y., Yamane M., Shimizu T., Hatsuma Y., Shimono N., Sunada M., Hayakawa M., Nishida I., Ito S., Ida M., Seno M., Sugihara S., Minagawa Y., Tachiki H., J. Drug Deliv. Sci. Tec., 57, 101728 (2020).
21) Takayama Y., Tomita T., Kuroda J., Kageyu A., Yonekura C., Hiramura Y., Tahara K., Takeuchi H., Int. J. Pharm., 547, 106–113 (2018).
22) Paul S., Chang S. Y., Dun J., Sun W. J., Wang K., Tajabri P., Boissier C., Sun C. C., Int. J. Pharm., 566, 24–31 (2019).
23) Carr H. L., Chem. Eng., 72, 163–168 (1965).
24) Hayashi Y., Tsuji T., Shiratori K., Oishi T., Kosugi A., Kumada S., Hirai D., Takayama K., Onuki Y., Int. J. Pharm., 532, 82–89 (2017).
25) Kurosaki T., Kishikawa R., Matsunoto M., Kodama Y., Hamamoto T., To H., Niidome T., Takayama K., Kitahara T., Sasaki H., J. Control. Release, 136, 213–219 (2009).