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# Application of principal component analysis enables to effectively find important physical variables for optimization of fluid bed granulator conditions

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ABSTRACT

Principal component analysis was applied to effectively optimize the operational conditions of a fluidized bed granulator for preparing granules with excellent compaction and tablet physical properties. The crucial variables that affect the properties of the granules, their compactability and the resulting tablet properties were determined through analysis of a series of granulation and tabletting experiments. Granulation was performed while the flow rate and concentration of the binder were changed as independent operational variables, according to a two-factor central composite design. Thirteen physicochemical properties of granules and tablets were examined: powder properties (particle size, size distribution width, Carr's index, Hausner ratio and aspect ratio), compactability properties (pressure transmission ratio, die wall force and ejection force) and tablet properties (tensile strength, friability, disintegration time, weight variation and drug content uniformity). Principal component analysis showed that the pressure transmission ratio, die wall force and Carr's index were the most important variables in granule preparation. Multiple regression analysis also confirmed these results. Furthermore, optimized operational conditions obtained from the multiple regression analysis enabled the production of granules with desirable properties for tabletting. This study presents the first use of principle component analysis for identifying and successfully predicting the most important variables in the process of granulation and tabletting.


## 1. Introduction

Granulation is a critical process for enlarging the size of fine drug particles and additives in order to manufacture granules with good compressibility and resulting tablet properties such as a suitable hardness and disintegration. Larger granules have better flowability, resulting in several advantages such as a decrease in adhesion of the powder to the die wall, and an increase in uniform mixing of the active ingredient in the manufacturing process. The methods for granulation are generally categorized into wet and dry processes. Wet granulation generally produces granules with high porosity; therefore, this process is useful in making tablets with desirable properties (Wikberg and Alderborn, 1991). Fluidized bed granulation is one of the most common techniques for wet granulation. It has several advantages, such as one-step mixing, continuous granulation and drying, and producing granules with better compressibility rather than that prepared by other wet granulation methods such as extrusion and rotogranulation. Until now, numerous studies using fluidized bed granulators have investigated the relationship between the operational conditions and the particle properties of granules, between the particle properties of granules and their compaction properties in the tabletting process, and between the compaction properties of the granules and the properties of the final tablets.

For instance, since the water content in a container generally affects the properties of granules during granulation process, Kokubo et al. (1995) previously demonstrated that the concentration and viscosity of binder solutions significantly affected the particle size and hardness of granules. Other researchers found that the droplet size of the binder solutions, which depends on the air pressure of the spray, was also an important factor in the particle enlargement process (Schaafsma et al., 2000; Lin and Peck, 1995). Additionally, by means of multiple linear regression analysis, relationships between operational conditions and granule's properties have also been investigated (Dacanal and Menegalli, 2010; Ehlers et al., 2009; Rambali et al., 2001). Furthermore, various powder properties such as particle size, size distribution width, flowability, and density were also found to affect compression and tablet properties (Charinpanitkul et al., 2008; De Jong, 1991; Fichtner et al., 2005; Johansson et al., 1995). At first glance, it would appear that this information could be used to prepare granules with optimal properties for tabletting. However, because these studies were performed using different types of machines, and different types of formulations and granules, no consistent information about the operational conditions for fluidized bed granulators has yet been

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published. In order to optimize the operational conditions for fluidized bed granulators for producing granules with good flowability and compaction properties for tablets, it would be desirable to perform a series of experiments using granules prepared on the same machine. A comprehensive analysis of granulation conditions, the particle properties of granules, their compactability and tablet properties could then be performed.

Previously, Merkku et al. (1994) examined the effect of process conditions, such as the inlet air temperature, atomizing air pressure and the amount of binder solution in the fluidized bed granulator, on the flowability of granules and the tablet properties. However, the results were incomplete because only limited data, such as flowability, angle of repose, friability and disintegration time, were collected in the study. Again, because there are numerous parameters remained to analyze, we first must clarify what properties are important when optimizing the operational conditions in a fluidized bed granulator.

Against this background, we used principal component analysis to find the most important variables in the process for manufacturing granules. Principle component analysis is a method of reducing the dimensionality of a data set which contains a large number of interrelated variables, while retaining the variation present in the data set. This is achieved by transforming to a new set of variables, called principal components, which are uncorrelated, and which are ordered so that the first few retain most of the variation present in all of the original variables (Jolliffe, 2002). In the present study, we first performed granulation by independently varying the flow rate and concentration of the binder solution because these operational factors have a large effect on the properties of the granules. The following powder properties of the granules were examined: the median diameter, relative size distribution width, Carr's index, Hausner ratio and aspect ratio. Subsequently, compaction experiments were performed on the granules, using a single punch tabletting machine. The compaction properties, comprising pressure transmission ratio, die wall force and ejection force, and also tablet properties such as tensile strength, friability, disintegration time, weight variation and drug content uniformity were also examined. After that, principle component analysis was performed on all 13 properties obtained in the series of experiments. Furthermore, to verify the principle component analysis results, we investigated the relationships between the granulation conditions and all 13 properties by means of multiple linear regression analysis. Process optimization was finally performed to establish granulation conditions for the manufacture of tablets with optimal compaction and tablet properties.

## 2. Materials and methods

### 2.1. Materials

Acetaminophen (APAP) was kindly provided by Iwaki Pharmaceutical Co., Ltd. (Shizuoka, Japan). Lactose monohydrate (listed in the Japanese Pharmacopeia Fifteen Edition (JP 15th), DMV Japan Co., Ltd., Tokyo, Japan) and corn starch (listed in JP 15th, Nihon Shokuhin Kakou Co., Ltd., Tokyo, Japan) were used as fillers, and an aqueous solution of hydroxypropylcellulose (HPC-L, listed in JP 15th, Nippon Soda Co., Ltd., Tokyo, Japan) was used as a binder. Magnesium stearate (abbreviated as Mg-St, listed in JP 15th) was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan).

### 2.2. Experimental design

A two-factor central composite design was used to analyze the relationship between the powder properties of the granules, their compaction properties and the resulting tablet physical properties.

**Table 1**
Experimental design.

| Batch no. | $X_1$ | Flow rate (g/min) | $X_2$ | Binder concentration (%) |
|---|---|---|---|---|
| 1 | $\sqrt{2}$ | 4.0 | 0 | 5.0 |
| 2 | $-\sqrt{2}$ | 2.0 | 0 | 5.0 |
| 3 | 0 | 3.0 | $\sqrt{2}$ | 7.0 |
| 4 | 0 | 3.0 | $-\sqrt{2}$ | 3.0 |
| 5 | 1 | 3.7 | 1 | 6.4 |
| 6 | 1 | 3.7 | −1 | 3.6 |
| 7 | −1 | 2.3 | 1 | 6.4 |
| 8 | −1 | 2.3 | −1 | 3.6 |
| 9 | 0 | 3.0 | 0 | 5.0 |
| 10 | 0 | 3.0 | 0 | 5.0 |
| 11 | 0 | 3.0 | 0 | 5.0 |

The flow rate of the binder ($X_1$) and the concentration of binder solution ($X_2$) were used as independent variables. The normalized factor levels of the independent variables and the conditions for each batch are listed in Table 1.

### 2.3. Granulation

Before granulation, 45 g of APAP, 73.5 g of lactose and 31.5 g of corn starch were sieved through a 297 μm sieve. The binder liquid used was an aqueous solution of HPC-L. The binder concentration was varied according to the conditions of the experimental design. The granulation was performed with a top-spray desktop fluid bed granulator (FLOW COATER FL-MINI, Freund Corporation, Tokyo, Japan). In each experiment, a batch of 150 g of solids was granulated with 150 g of binder solution. The atomizing air pressure and inlet air temperature just before distributor plate were maintained at 0.05 MPa and 70 °C. After the addition of binder solution, the granules were air-dried at 80 °C until the outlet air temperature increased 5 °C.

### 2.4. Characterization of granules

#### 2.4.1. Particle size distribution

The particle size distribution was obtained by sieve analysis of approximately 10 g of granules using testing sieves (Tokyo Screen Co., Ltd., Japan) with aperture sizes from 75 to 1000 μm. The median diameter, $d_{50}$, was obtained from these data, and the relative size distribution width, RW, was defined as follows:

$$\mathrm{RW} = \frac{d_{90} - d_{10}}{d_{50}}.$$

Here, $d_{10}$, $d_{50}$ and $d_{90}$ are the particle sizes at the 10th, 50th and 90th percentiles of the cumulative undersize distribution, respectively. The fraction of granules with sizes larger than 1000 μm was removed as lumps.

#### 2.4.2. Carr's flowability index

The flow properties of the granules were determined by Carr's method (Carr, 1965). The following four tests were performed: (1) compressibility, (2) angle of repose, (3) angle of spatula and (4) uniformity coefficient. The uniformity coefficient was obtained by sieve analysis of the granules. Other properties were measured on a powder characteristics tester (Powder Tester, Hosokawa Micron Co., Ltd., Japan).

(1) For the determination of compressibility, a 100 mL cylinder container was filled with an accurately weighed granule sample, and the top of the sample was leveled off. The initial bulk density ($\rho_{\mathrm{initial}}$) was calculated as the ratio of the mass to the volume of the sample. Next, after the sample was then added to

the top container which had been mounted on the bottom container, the two containers were fixed with a vibrator and then shaken up and down for 3 min. The tapped bulk density ($\rho_{tapped}$) was calculated by the mass and volume after this operation had been performed. The compressibility was calculated using the values of $\rho_{initial}$ and $\rho_{tapped}$ according to the following equation:

$$\text{Compressibility}\,[\%] = \frac{\rho_{tapped} - \rho_{initial}}{\rho_{initial}} \times 100.$$

(2) The angle of repose was measured with a protractor. The heap of granules was formed by passing the sample through a funnel.
(3) The angle of spatula was measured using a protractor and a steel spatula with a $5 \times 7/8$ in. blade. The spatula was inserted into the bottom of a carefully built heap. The spatula was then withdrawn vertically, and the angle of the spatula formed with the heap was measured.
(4) The uniformity coefficient was calculated as follows:

$$\text{Uniformity coefficient} = \frac{d_{60}}{d_{10}}.$$

Here, $d_{10}$ and $d_{60}$ are the particle sizes at the 10th and 60th percentiles of the cumulative undersize distribution, respectively.

The flowability index was then calculated using the point scores out of 100 as previously described (Carr, 1965). As a score standard, the point "90–100" represents "excellent" flowability, "80–89" represents "good", "70–79" represents "fair", "60–69" represents "passable", "40–59" represents "poor", "20–39" represents "very poor", and "0–19" represents "very, very poor".

#### 2.4.3. Hausner ratio

The tapping density test was performed in the same manner described in Section 2.4.2, and the ratio of the tapped bulk density, $\rho_{tapped}$, to its initial bulk density, $\rho_{initial}$, provides the Hausner ratio (HF):

$$\text{HF} = \frac{\rho_{tapped}}{\rho_{initial}}.$$

A lower Hausner ratio indicates better packing.

#### 2.4.4. Image analysis

The shapes of granules were determined by image analysis of the size fraction from 106 to 700 μm using WinROOF image analysis software (version 5.5, Mitani Co., Ltd., Japan). The aspect ratio was measured for 40 randomly chosen granules, and is defined as follows:

$$\text{Aspect ratio} = \frac{\text{Length of major axis}}{\text{Length of minor axis}}.$$

### 2.5. Tablet preparation and determination of compactability

The granule samples were mixed with 0.5% Mg-St. The tablets were prepared using a tabletting process analyzer (TabAll; Okada Seiko Co., Ltd., Tokyo, Japan) with flat-faced punches of 8 mm in diameter, and each tablet weighed 200 mg. The tabletting speed was 10 tablets/min for all samples. The applied compression pressure was 10 kN unless otherwise stated. Various force profiles were measured using TabAll, and were recorded on a tabletting pressure recording system (Daatsu 3, Okada Seiko Co., Ltd., Tokyo, Japan). The pressure transmission ratio (PTR) was calculated by the following formula:

$$\text{PTR}\,[\%] = \frac{P_L}{P_U} \times 100.$$

Here, $P_L$ is the maximum pressure of the lower punch and $P_U$ is the maximum pressure of the upper punch in the tabletting process. Therefore, if the value of PTR is larger, it suggests that the better compaction could be performed and the powder samples have good compactability. The ejection force applied to the lower punch during tablet ejection was measured by a load cell, and the die wall force was the maximum force applied to the die wall during compression. In general, die wall force is commensurate with the friction force ($F_D$) between powder and die wall; therefore, if the value of die wall force is smaller, the powder is considered to have better compactability. In addition, if $F_D$ value decreases, the value of ejection force decreases, suggesting that the samples have better compactability.

### 2.6. Determination of tablet properties

#### 2.6.1. Tensile strength

For the tensile strength measurements, six tablets were selected at random from a batch of tablets. The tensile strength of the tablets was determined by diametrical compression tests, which were performed on a desktop checker (DC-50, Okada Seiko Co., Ltd., Tokyo, Japan) to measure accurately the maximal diameter crushing force ($F$). The diameter and thickness of the tablets were measured with a micrometer having precision of 0.01 mm (500-302 CD-20, Mitsutoyo Corporation, Kanagawa, Japan). The tensile strength (TS) was calculated by the following formula as previously described (Fell and Newton, 1970):

$$\text{TS} = \frac{2F}{\pi DT},$$

where $D$ and $T$ are the diameter and the thickness of tablets, respectively.

#### 2.6.2. Friability

The friability tests were performed according to the JP 15th friability test. Ten tablets from each batch were sampled at random and rotated with a constant frequency of 25 rpm for 4 min using a friabilator (TFT-120, Toyama Sangyo Co., Ltd., Osaka, Japan). The total weight of the tablets was recorded before and after rotation, and the friability was expressed as the percentage loss due to abrasion or fracture.

#### 2.6.3. Disintegration time

The disintegration time was measured using six tablets chosen at random, according to JP 15th, using a disintegration tester (NT-1HM, Toyama Sangyo Co., Ltd., Osaka, Japan). Distilled water at $37 \pm 0.5\,^{\circ}\text{C}$ was used as a medium. The arithmetic mean represents the characteristic disintegration time of the tablets of each batch.

#### 2.6.4. Weight variation

Thirty tablets were weighed on an electronic balance, and the standard deviation of the weight variation of the tablets was determined.

#### 2.6.5. Content uniformity

Three tablets chosen at random were put in 200 mL diluted water, and dissolved for 2 h at 37 °C. After the drug was completely dissolved, the solution was withdrawn and samples were filtered through a membrane filter (0.45 μm). The amount of APAP released into the medium was quantitatively determined as a proportion of the total APAP contained in a tablet by UV spectroscopy (wavelength: 243 nm; UV-mini 1240, Shimadzu Corp., Tokyo, Japan). The

standard deviation of the amount of APAP per tablet was taken as an index of drug content uniformity.

### 2.7. Statistical analysis

Principle component analysis was performed using free software (MLVAR95. EXE) developed by Kimio Kanda to classify differences between the results, detect different trends, define outliers, and to gain an overview of the data. Shiino et al. (2010) also reported that this software MLVAR95. EXE could give enough usability and validation for this analysis. Additionally, the multiple linear regression analysis and optimization was performed using the software packages ALCORA and OPTIM, which were developed by Kozo Takayama (Hoshi University), in Windows XP. A linear regression was performed on the data for each characteristic as a function of the two process parameters and their interactions. The response surfaces were constructed using Maple 13 (Waterloo Maple Inc., Canada).

## 3. Results and discussion

### 3.1. Characterization of granules and the resulting compactability and tablet properties

Table 2 shows the characterization of granules (particle size, relative size distribution width, Carr's index, Hausner ratio and aspect ratio) of all 11 batches. Table 3 shows the compactability properties (pressure transmission ratio, die wall force and ejection force), and the following tablet properties are also shown: tensile strength, friability, disintegration time, weight variation and drug content uniformity. Principle component analysis and multiple linear regression analysis were then performed on these data.

### 3.2. Principal component analysis

Firstly, principle component analysis was performed to examine the relationship of all 13 properties obtained from the series of experiments. Principle component analysis has been reported to be a useful method for investigating the relationship between large numbers of variables. It allows the results to be simplified into latent variables (principal components) that explain the main variance in the data (Haware et al., 2009). Loading plots of the first two principal components are shown in Fig. 1. The first component (PC1) was responsible for 28.1% of the total variance in the data set, and the second (PC2) was responsible for a further 22.8%; thus, the cumulative contribution ratio was about 50%. In general, it is considered that variables near each other are positively correlated, while those on opposite sides of the origin are negatively correlated in loading plots. With regard to the variables for compactability, the pressure transmission ratio and ejection force were plotted on opposite sides of the origin, and the ejection force and die wall force were plotted in similar positions. Therefore, pressure transmission ratio was found to be negatively correlated with ejection force, and ejection force was positively correlated with die wall force. This result implies that if the compactability of the granules is improved, the pressure transmission ratio will increase, while ejection force and die wall force will decrease. This result is consistent with previous reports (Doelker and Massurelle, 2004). Therefore, this PCA result was also considered to be reasonable, although the cumulative contribution ratio of PC1 and PC2 was only 50%. In addition, particle size and the pressure transmission ratio were positively correlated, as were the relative size distribution width and ejection force. Furthermore, among the granule powder property and tablet property variables, Carr's index and the aspect ratio were positively correlated with tensile strength and disintegration time, and Hausner ratio was positively correlated with friability. This indicates

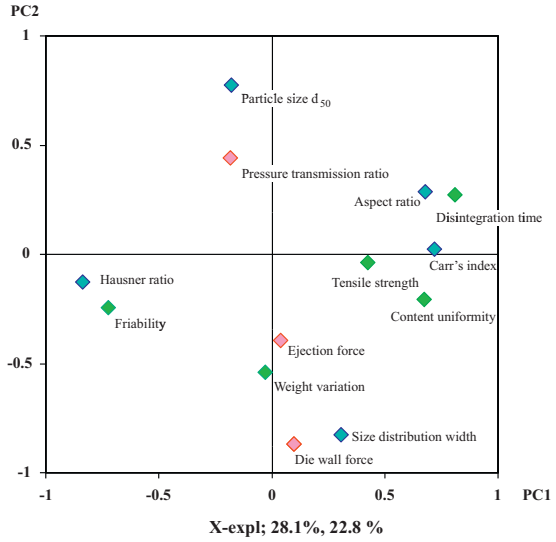


**Fig. 1.** Loading plot obtained by principal component analysis of granules' powder properties, compactabilities, and tablet properties. The two displayed principal component explain 28.1% and 22.8% of the data variance, respectively.

that these two groups of variables are negatively correlated. Since the granules generally show good flowability when Carr's index is larger and the Hausner ratio is smaller, if the flowability and packing properties of the granules can be improved, an increase in tablet hardness and a decrease in friability might be observed.

On the basis of this analysis, all 13 properties were classified into following four groups based on the origin; top, bottom, right and left. Considering the manufacturing process, compactability parameters are crucial important because they are related to tabletting problems; therefore, as a representative variable in each group plotted in top and bottom, pressure transmission ratio and die wall pressure are chosen as a predominant parameter. Additionally, when focusing on the right and left groups, which all were constructed of flowability and tablet properties, Carr's index is considered to be one of the crucial parameters because it strongly influences other powder properties and tablet properties. Therefore, we speculated that the compactability parameters die wall force and pressure transmission ratio and the flowability parameter Carr's index are the most important variables in the preparation of superior granules for tablets.

### 3.3. Multiple regression analysis

To confirm the validity of the principle component analysis results and further optimize the operational conditions of the fluidized bed granulator, multiple regression analysis was performed using the program ALCORA (Takayama et al., 1990). The significance of each operational factor and their effect on the powder properties of granules (Table 4), compactability properties (Table 5), and tablet physical properties (Tables 6 and 7) were determined. The relationships linking the main factors and their interactions with the results were determined, and are presented as quadratic equations of the general form:

$$Y = a_1X_1 + a_2X_2 + a_3X_1^2 + a_4X_2^2 + a_5X_1X_2,$$

where $a_1$, $a_2$, $a_3$, $a_4$, and $a_5$ were coefficients of each term. Since the coefficients were calculated using the coded values (Table 1), the various terms can be compared directly. Therefore, coefficients represent the positive or negative effects of two parameters and their interactions against the each final property. Each table contains the coefficients; the $p$-value obtained by $t$-test to assess the significance of each term; and the $R^2$ value (the coefficient of determination

**Table 2**
Characterization of granules.

| Batch no. | Particle size $d_{50}$ (μm) | Relative size distribution width (–) | Carr's index (point) | Hausner ratio (–) | Aspect ratio (–) |
|---|---|---|---|---|---|
| 1 | 381.36 | 1.49 | 76.5 | 1.20 | 1.23 |
| 2 | 145.45 | 2.79 | 77.0 | 1.19 | 1.25 |
| 3 | 206.82 | 2.59 | 74.5 | 1.20 | 1.27 |
| 4 | 223.18 | 1.84 | 68.5 | 1.26 | 1.20 |
| 5 | 332.27 | 1.56 | 75.0 | 1.20 | 1.19 |
| 6 | 197.73 | 3.00 | 73.0 | 1.24 | 1.21 |
| 7 | 205.00 | 2.68 | 75.5 | 1.20 | 1.23 |
| 8 | 113.18 | 2.80 | 75.0 | 1.22 | 1.18 |
| 9 | 256.67 | 1.77 | 74.5 | 1.23 | 1.22 |
| 10 | 327.27 | 1.70 | 75.0 | 1.23 | 1.23 |
| 11 | 210.00 | 1.65 | 73.0 | 1.24 | 1.24 |

**Table 3**
Compactability and tablet physical properties.

| Batch no. | Pressure transmission ratio (%) | Die wall force (kN) | Ejection force (kgf) | Tensile strength (–) | Friability (%) | Disintegration time (s) | Weight variation (mg) | Content uniformity (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | 90.29 | 2.78 | 8.08 | 1.80 | 0.16 | 143 | 2.66 | 3.51 |
| 2 | 89.70 | 4.47 | 4.45 | 3.60 | 0.17 | 253 | 2.45 | 4.69 |
| 3 | 92.21 | 2.87 | 7.94 | 3.21 | 0.17 | 343 | 3.81 | 2.49 |
| 4 | 91.51 | 3.53 | 3.53 | 1.88 | 0.39 | 78 | 2.45 | 1.91 |
| 5 | 91.10 | 1.57 | 9.11 | 3.75 | 0.54 | 239 | 2.20 | 0.23 |
| 6 | 90.90 | 3.95 | 7.38 | 2.70 | 0.67 | 73 | 3.91 | 0.49 |
| 7 | 91.83 | 3.23 | 3.07 | 3.48 | 0.24 | 297 | 1.39 | 1.11 |
| 8 | 90.38 | 4.07 | 12.6 | 3.44 | 0.54 | 95 | 2.99 | 1.15 |
| 9 | 90.69 | 3.03 | 4.73 | 2.76 | 0.38 | 90 | 1.39 | 1.44 |
| 10 | 91.51 | 2.89 | 1.24 | 3.06 | 0.65 | 114 | 2.39 | 0.32 |
| 11 | 91.39 | 2.26 | 6.08 | 3.69 | 0.18 | 204 | 1.97 | 0.93 |

**Table 4**
Multiple regression analysis of characteristics of granules.

| Term | Particle size $d_{50}$ | | Relative size distribution width | | Carr's index | | Hausner ratio | | Aspect ratio | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Coefficient | *t*-Test | Coefficient | *t*-Test | Coefficient | *t*-Test | Coefficient | *t*-Test | Coefficient | *t*-Test |
| $X_1$ | 68.2 | <0.05 | −0.346 | <0.05 | – | – | 0.00288 | N.S. | – | – |
| $X_2$ | 25.4 | N.S. | – | – | 1.37 | <0.05 | −0.0172 | <0.05 | 0.0171 | <0.05 |
| ${X_1}^2$ | – | – | 0.299 | N.S. | 1.42 | <0.05 | −0.0184 | <0.05 | – | – |
| ${X_2}^2$ | −29.4 | N.S. | 0.336 | N.S. | −1.21 | <0.05 | – | – | – | – |
| $X_1 \times X_2$ | – | – | −0.332 | N.S. | – | – | −0.00530 | <0.05 | −0.0171 | N.S. |
| Constant | 258 | <0.05 | 1.71 | <0.05 | 74.2 | <0.05 | 1.23 | <0.05 | 1.22 | <0.05 |
| | $R^2 = 0.494$ | | $R^2 = 0.225$ | | $R^2 = 0.678$ | | $R^2 = 0.951$ | | $R^2 = 0.233$ | |

which was doubly adjusted with degrees of freedom), which is an indicator of the fit of each linear regression equation.

### 3.3.1. Powder properties of granules

As shown in Table 4, the flow rate of the binder ($X_1$) has a positive effect on particle size, and a negative effect on the relative size distribution width, whereas the binder concentration ($X_2$) did not show a large effect. In addition, the effect of the variables on the response of particle size was evaluated by response surface plots for particle size (Fig. 2). It is apparent that an increase in $X_1$ strongly contributed to an increase in particle size, whereas $X_2$ did not show an effect. This phenomenon might be explained by the droplet size of the binder solution: as the flow rate of the binder increases, the droplet size of the binder increases, and a stronger solid bridge forms between the granules. This may promote adhesion and agglomeration, which in turn increases particle size. Conversely, the negative correlation between flow rate and the relative size distribution width may mean that the shortening of the granulation time with the increase in flow rate could improve the uniformity of the granule size.

**Table 5**
Multiple regression analysis of compactability.

| Term | Pressure transmission ratio | | Die wall force | | Ejection force | |
|---|---|---|---|---|---|---|
| | Coefficient | *t*-Test | Coefficient | *t*-Test | Coefficient | *t*-Test |
| $X_1$ | – | – | −0.523 | <0.05 | 0.858 | N.S. |
| $X_2$ | 0.328 | <0.05 | −0.519 | <0.05 | – | – |
| ${X_1}^2$ | −0.619 | <0.05 | 0.343 | N.S. | 1.63 | <0.05 |
| ${X_2}^2$ | 0.314 | N.S. | – | – | – | – |
| $X_1 \times X_2$ | −0.313 | N.S. | −0.384 | N.S. | – | – |
| Constant | 91.3 | <0.05 | 2.90 | <0.05 | 2.00 | <0.05 |
| | $R^2 = 0.679$ | | $R^2 = 0.581$ | | $R^2 = 0.430$ | |

**Table 6**
Multiple regression analysis of tablet properties (compaction pressure: 10 kN).

| Term | Tensile strength | | Friability | | Disintegration time | | Weight variation | | Content uniformity | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Coefficient | *t*-Test | Coefficient | *t*-Test | Coefficient | *t*-Test | Coefficient | *t*-Test | Coefficient | *t*-Test |
| $X_1$ | −0.377 | N.S. | – | – | −29.5 | <0.05 | 0.252 | N.S. | – | – |
| $X_2$ | 0.371 | N.S. | −0.0942 | N.S. | 93.0 | <0.05 | – | – | – | – |
| ${X_1}^2$ | – | – | – | – | 24.2 | N.S. | 0.264 | N.S. | 0.985 | N.S. |
| ${X_2}^2$ | – | – | – | – | 30.2 | N.S. | 0.552 | N.S. | – | – |
| $X_1 \times X_2$ | – | – | – | – | – | – | – | – | – | – |
| Constant | 3.03 | <0.05 | 0.373 | <0.05 | 136 | <0.05 | 1.91 | <0.05 | 0.944 | N.S. |
| | $R^2 = 0.236$ | | $R^2 = 0.00672$ | | $R^2 = 0.764$ | | $R^2 = -0.186$ | | $R^2 = 0.162$ | |

**Table 7**
Multiple regression analysis of tablet properties (compaction pressure: 5 kN).

| Term | Tensile strength | | Friability | | Disintegration time | | Weight variation | | Content uniformity | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Coefficient | *t*-Test | Coefficient | *t*-Test | Coefficient | *t*-Test | Coefficient | *t*-Test | Coefficient | *t*-Test |
| $X_1$ | −0.223 | <0.05 | – | – | −10.6 | <0.05 | – | – | −0.379 | <0.05 |
| $X_2$ | 0.318 | <0.05 | −0.0810 | <0.05 | 58.7 | <0.05 | – | – | −0.191 | N.S. |
| ${X_1}^2$ | 0.209 | <0.05 | – | – | – | – | −0.344 | N.S. | 0.206 | N.S. |
| ${X_2}^2$ | – | – | 0.0649 | <0.05 | 31.4 | <0.05 | −0.524 | <0.05 | – | – |
| $X_1 \times X_2$ | – | – | −0.0972 | <0.05 | −13.0 | N.S. | – | – | 0.599 | <0.05 |
| Constant | 1.70 | <0.05 | 0.167 | <0.05 | 94.2 | <0.05 | 2.64 | <0.05 | 0.645 | <0.05 |
| | $R^2 = 0.712$ | | $R^2 = 0.806$ | | $R^2 = 0.933$ | | $R^2 = -0.295$ | | $R^2 = 0.704$ | |

In Table 4, the terms $X_2$, ${X_1}^2$ and ${X_2}^2$ were significant in Carr's index, the terms $X_2$, ${X_1}^2$ and $X_1 \times X_2$ were significant in the Hausner ratio and the term $X_2$ was significant in the aspect ratio. Carr's index and the Hausner ratio were ultimately affected by both operational factors $X_1$ and $X_2$, as shown in the response surface plots (Fig. 3). This phenomenon could be explained by particle size and size distribution width. Generally, adhesion force and gravity are significant forces that are thought to act directly on granules during packing. Adhesion force is proportional to the square of particle size, and gravity is proportional to cube of particle size. This means that as the particle size of granules increases, the influence of the gravity becomes greater than that of adhesion force, and consequently dense packing becomes easy and flowability further increases. On the other hand, the relative size distribution width has also been reported to affect the packing properties. Furnas (1931) demonstrated that bulk porosity decreases as the ratio of

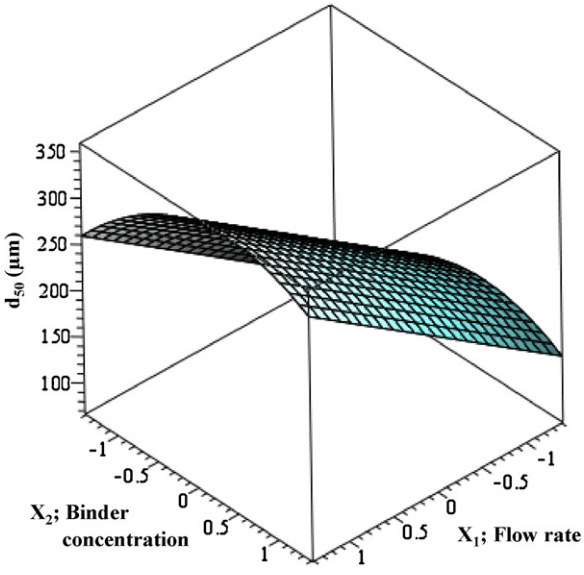


**Fig. 2.** Response surface plots of particle size $d_{50}$ as a function of flow rate ($X_1$) and concentration ($X_2$) of the binder.

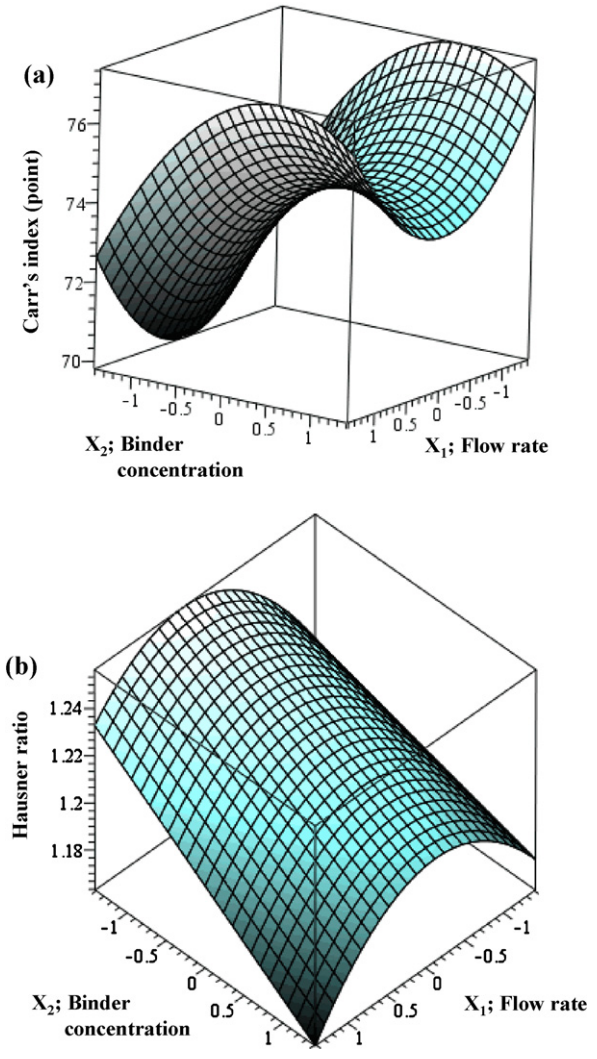


**Fig. 3.** Response surface plots of Carr's index (a) and Hausner ratio (b) as a function of flow rate ($X_1$) and concentration ($X_2$) of the binder.

fine particles to large particles slightly increases, indicating that the wide relative size distribution width tends to make granules pack densely. As shown in Fig. 3, as the flow rate of the binder ($X_1$) decreased from 0 to $-\sqrt{2}$, Carr's index increased and the Hausner ratio decreased. This might depend on the effect of wide relative size distribution because the particles in this range were enough small (Fig. 2 and Table 4), resulting in an improvement of the flowability. On the other hand, although the distribution width was narrow enough as the $X_1$ increased from 0 to $\sqrt{2}$ (Table 4), the effect of particle size might become predominant, resulting in an improvement of the flowability. In addition, flowability was improved with an increase in $X_2$. This phenomenon might be attributed to an increase in aspect ratio as the particles become more ellipsoidal. It was reported that if ellipsoidal instead of spherical particles were used, an increase in the density of randomly poured particles was obtained (Donev et al., 2004). Therefore, the flowability could be improved by changing the particle shape from spherical to ellipsoid, because of the increase in the binder concentration ($X_2$).

### 3.3.2. Compactability

Table 5 shows that the compactability parameters pressure transmission ratio, die wall force and ejection force were significantly affected by both process factors in granulation. Pressure transmission ratio had a large ${X_1}^2$ coefficient, and $X_1$ showed quadric behavior with an upward curvature (Fig. 4a). This is because $X_1$ affected particle size and the relative size distribution width, as mentioned in Section 3.3.1. This was in agreement with the principle component analysis results as shown in Fig. 1. In addition, the term ${X_1}^2$ only significantly affected the ejection force and pressure transmission ratio. However, die wall force exhibited different behaviors from the pressure transmission ratio and the ejection force; the terms $X_1$ and $X_2$ showed a monotonic decrease (Fig. 4b). The die wall force may be affected by the particle size. This in turn depends on the relative size distribution width which varies with flow rate ($X_1$), as well as the flowability and the particle morphology, which are dependent on binder concentration ($X_2$).

### 3.3.3. Tablet physical properties

As shown in Table 6, the two operational factors had little influence on the tablet properties of tensile strength, friability, weight variation and content uniformity. This is probably because the changes in these variables are small (Table 3). Disintegration time was the only variable affected by the two operational factors, possibly because the numerical changes of disintegration time were higher than that of other variables. It was found that disintegration time increased as $X_1$ decreased and $X_2$ increased.

Therefore, to investigate the influence of the two operational factors on tablet properties, the compaction pressure was reduced from 10 kN to 5 kN, and an additional multiple regression analysis was performed (Table 7). As a result, higher multiple correlation coefficients ($R^2$-value), as well as significant correlations between process conditions and tablet properties, were obtained for all tablet properties. This means lower compaction pressure could show the variation in tablet properties better than higher compaction pressure. Tensile strength increased as $X_1$ decreased and $X_2$ increased, which is a similar result to that of disintegration time under a compaction pressure of 10 kN (Table 6). In addition, the terms $X_2$ and ${X_1}^2$ were significant for tensile strength, and this behavior was similar to the multiple regression analysis of Carr's index (Table 4) and the principle component analysis (Fig. 1). In contrast, friability was strongly affected by binder concentration ($X_2$) and exhibited behavior similar to the Hausner ratio. This result was also agreed with the principle component analysis results (Fig. 1). Therefore, a lower compaction pressure better revealed differences in tablet properties, and these results were consistent with the principle component analysis results.

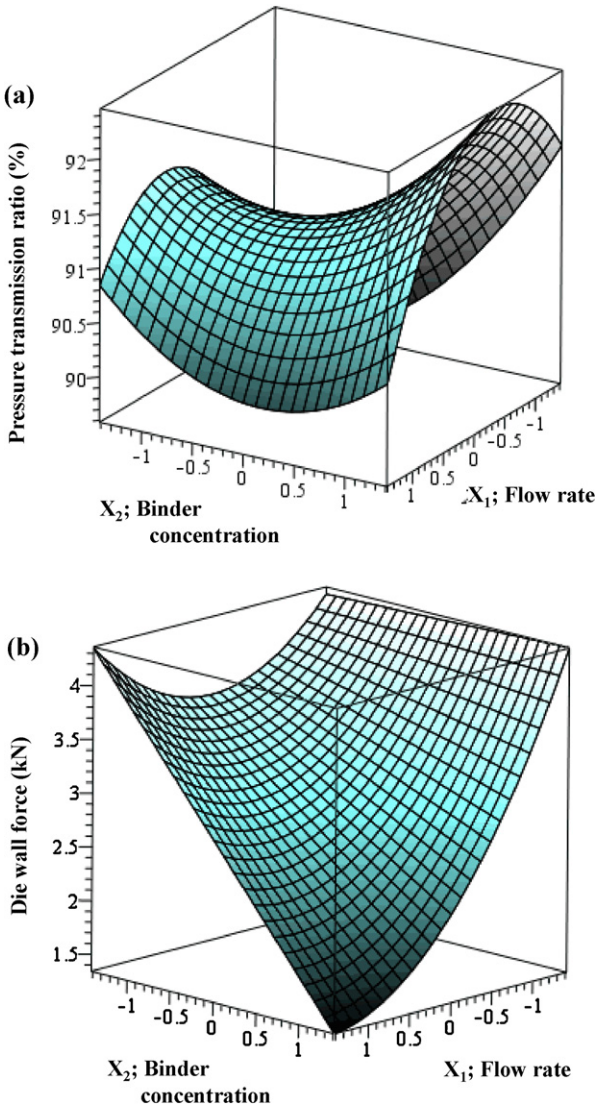


**Fig. 4.** Response surface plots of pressure transmission ratio (a) and die wall force (b) as a function of flow rate ($X_1$) and concentration ($X_2$) of the binder.

### 3.4. Process optimization

The results of principle component analysis and multiple regression analysis show that among the many variables involved in preparing granules and their tablets, compactability parameters such as pressure transmission ratio and die wall force and flowability parameters such as Carr's index were found to be crucially important. Carr's index was chosen as one of the parameters for optimization, since it had significant effects on all tablet properties, including hardness, friability and disintegration time. In addition, compactability parameters are important because they are related to problems in tabletting. In this study, it was found that pressure transmission ratio and ejection force showed similar behavior whereas die wall force had disparate properties as mentioned in Section 3.3.3. Takeuchi et al. (2004) reported that the profile of the die wall force was closely related to problems with tabletting, such as capping and sticking. The maximum die wall force was also found to be a useful parameter for powder compaction properties, as well as the pressure transmission ratio (Takeuchi et al., 2004).

**Table 8**
Process optimization.

| | Predicted | Experimental | Criterion |
|---|---|---|---|
| Pressure transmission ratio (%) | 90.1 | 90.7 | >90.0 |
| Die wall force (kN) | 4.25 | 2.04 | <4.00 |
| Carr's index (point) | 77.5 | 73.0 | >70.0 |

Other properties; tensile strength: 3.25, friability: 0.0413%, disintegration time: 208 s.

Therefore, both pressure transmission ratio and die wall force were also chosen as essential variables for optimization. Accordingly, operational conditions were optimized using the following criteria:

(1) The granules must possess a Carr's index greater than 70 points.
(2) The pressure transmission ratio must be greater than 90%.
(3) Die wall force must be greater than 4.0 kN.

The optimization was carried out using the OPTIM software package. Optimized operational conditions were obtained as follows: $X_1$ (flow rate of the binder) = 2.0 g/min and $X_2$ (binder concentration) = 5.2% (Table 8). As a result, each characteristic value was consistent with predicted values and complied with the desired product criteria. In addition, because the tablet properties of tensile strength, friability and disintegration time were 3.25, 0.0413% and 208 s, respectively, this optimization succeeded in preparing granules with good flowability and compactability for tablets.

## 4. Conclusions

Until now, numerous studies using fluidized bed granulators have investigated the relationships between the operational conditions and the particle properties of granules, between the particle properties and compaction properties in the tabletting process, and between the compaction and tablet properties. However, comprehensive analysis of these relationships using identical granules prepared on the same granulator machine has not been carried out. In order to identify the crucial variables that affect the granules' properties, principle component analysis was performed against 13 physicochemical properties. As a result, pressure transmission ratio, die wall force and Carr's flowability index were found to be crucial variables for manufacturing granules for tablets. In addition, the results of principle component analysis were verified by multiple regression analysis, and the optimized operational conditions produced the desired granules. Therefore, the present study demonstrates that principle component analysis is a useful method for determining the critical variables that affect the tabletting process and the properties of final tablets.

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## References

Carr, R.L., 1965. Evaluating flow properties of solids. Chem. Eng. 72, 163–168.
Charinpanitkul, T., Tanthapanichakoon, W., Kulvanich, P., Kim, K., 2008. Granulation and tabletization of pharmaceutical lactose granules prepared by a top-sprayed fluidized bed granulator. J. Ind. Eng. Chem. 14, 661–666.
Dacanal, G.C., Menegalli, F.C., 2010. Selection of operational parameters for the production of instant soy protein isolate by pulsed fluid bed agglomeration. Powder Technol. 203, 565–573.
De Jong, J.A.H., 1991. Tablet properties as a function of the properties of granules made in a fluidized bed process. Powder Technol. 65, 293–303.
Doelker, E., Massurelle, D., 2004. Benefits of die-wall instrumentation for research and development in tabletting. Eur. J. Pharm. Biopharm. 58, 427–444.
Donev, A., Cisse, I., Sachs, D., Variano, E.A., Stillinger, F.H., Connelly, R., Torquato, S., Chaikin, P.M., 2004. Improving the density of jammed disordered packings using ellipsoids. Science 303, 990–993.
Ehlers, H., Liu, A., Raikkonen, H., Hatara, J., Antikainen, O., Airaksinen, S., Heinamaki, J., Lou, H., Yliruusi, J., 2009. Granule size control and targeting in pulsed spray fluid bed granulation. Int. J. Pharm. 377, 9–15.
Fell, J.T., Newton, J.M., 1970. Determination of tablet strength by the diametral-compression test. J. Pharm. Sci. 59, 688–691.
Fichtner, F., Rasmuson, A., Alderborn, G., 2005. Particle size distribution and evolution in tablet structure during and after compaction. Int. J. Pharm. 292, 211–225.
Furnas, C.C., 1931. Grading aggregates. I. Mathematical relations for beds of broken solids of maximum density. Ind. Eng. Chem. 18, 1052–1058.
Haware, R.V., Tho, I., Bauer-Brandl, A., 2009. Application of multivariate methods to compression behavior evaluation of directly compressible materials. Eur. J. Pharm. Biopharm. 72, 148–155.
Johansson, B., Wikberg, M., Ek, R., Alderborn, G., 1995. Compression behaviour and compactability of microcrystalline cellulose pellets in relationship to their pore structure and mechanical properties. Int. J. Pharm. 117, 57–73.
Jolliffe, I.T., 2002. Principal Component Analysis. Springer Us, New York.
Kokubo, H., Nakamura, S., Sunada, H., 1995. Effect of several cellulosic binders on particle size distribution in fluidized bed granulation. Chem. Pharm. Bull. 43, 1402–1406.
Lin, K., Peck, G.E., 1995. Development of agglomerated talc. I. Evaluation of fluidized bed granulation parameters on the physical properties of agglomerated talc. Drug Dev. Ind. Pharm. 21, 447–460.
Merkku, P., Lindqvist, A.S., Leiviska, K., Yliruusi, J., 1994. Influence of granulation and compression process variables on flow rate of granules and on tablet properties, with special reference to weight variation. Int. J. Pharm. 102, 117–125.
Rambali, B., Baert, L., Massart, D.L., 2001. Using experimental design to optimize the process parameters in fluid bed granulation on a semi-full scale. Int. J. Pharm. 220, 149–160.
Schaafsma, S.H., Vonk, P., Kossen, N.W.F., 2000. Fluid bed agglomeration with a narrow droplet size distribution. Int. J. Pharm. 193, 175–187.
Shiino, K., Iwao, Y., Miyagishima, A., Itai, S., 2010. Optimization of a novel wax matrix system using aminoalkyl methacrylate copolymer E and ethylcellulose to suppress the bitter taste of acetaminophen. Int. J. Pharm. 395, 71–77.
Takayama, K., Okabe, H., Obata, Y., Nagai, T., 1990. Formulation design of indomethacin gel ointment containing d-limonene using computer optimization methodology. Int. J. Pharm. 61, 225–234.
Takeuchi, H., Nagira, S., Yamamoto, H., Kawashima, Y., 2004. Die wall pressure measurement for evaluation of compaction property of pharmaceutical materials. Int. J. Pharm. 274, 131–138.
Wikberg, M., Alderborn, G., 1991. Compression characteristics of granulated materials. IV. The effect of granule porosity on the fragmentation propensity and the compatibility of some granulations. Int. J. Pharm. 69, 239–253.