A Novel Blending Method for Dispensing Powdered Medicine

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We introduced the application of a planetary centrifugal mixer to dispensing powdered medicines to prevent from individual variation in the skills of pharmacists with a manual blending. The blending performance of the mixer was explored in terms of four operational variables, namely, operation speed (400–1000 rpm), operation time (10–60 s), charging rate in vessel (20–50%), and size of vessel (35, 58, 125, 550 mL), using colored lactose and crystalline lactose as the principle model medicine and diluent, respectively. The blending degree was assessed by image analysis, so the extent of uniformity was expressed as the relative standard deviation of the color difference signal Cb value of YCrCb color space. Application of the mixer to blending three commercial medicines with diluents was carried out. Sufficient blending was achieved at 10 s using a 20% charging rate and 35 mL vessel irrespective of operation speed. As the charging rate was increased, a higher operation speed was needed to obtain uniform blending. A larger sized vessel also required a higher operation speed. Uniform blending was achieved in all of the mixtures of colored lactose and crystalline lactose at the weight ratio of 1:9–9:1. In the application studies using Adona®, Anginal® and Neophylline® powder, the blending performance of the mixer was equivalent to that of the manual blending method, showing relative standard deviations of 2.2–3.3% and 1.8–3.8%, respectively. These results revealed that the planetary centrifugal mixer was suitable for blending powdered medicine.

Key words  dispensation; powdered medicine; planetary centrifugal mixer; blending powder; color difference signal

Blend uniformity is one of the most important requirements in dispensing powdered medicines. A lot of studies using a pestle and mortar have been conducted to examine the factors affecting the degree of blending.1–3 In the manual blending method, however, the degree of blending was greatly influenced by individual variation in the skills of pharmacists.4 It is possible that the quality of the dispensed medicines differed among the pharmacists. Therefore, we have proposed the application of a mechanical method using a planetary centrifugal mixer to blending powdered medicine.

The planetary centrifugal mixer is a type of container mixer without any agitators.5 The closed container rotates while it revolves in the mixer, resulting in powerful twisting mixing (Fig. 1).

The planetary centrifugal mixer is widely used in pharmacies to mix ointments.5 However, this is the first report in which the planetary centrifugal mixer has been used to blend powdered medicines.

In this study, we examined the planetary centrifugal mixer for uniformed blending of a model powdered medicine, namely, crystalline lactose colored by iron oxide. In general, the blending degree is greatly affected by the physical properties of the powdered medicines, including particle size, density, and flowability.6,7 In order to negate these factors, we investigated the blending degree of mixtures between colored lactose and crystalline lactose as the principal agent and diluent, respectively. These were made of the same crystalline lactose, so they were expected to have similar powder properties.3 This permitted us examine the mechanical conditions of the mixer.

During the course of our study, moreover, we developed an evaluating method for the degree of blending using digital image processing.5 In brief, digital color image is composed of three color planes: red, green, and blue (R, G, and B). The combination of RGB color planes gives ability to devices to represent a color in digital environment. Each color plane is quantized into discrete levels. Generally 256 (8 bits per color plane) quantization levels are used for each plane, for instance white is represented by (R, G, B)=(255, 255, 255) and black is represented by (R, G, B)=(0, 0, 0). RGB values obtained from digital photos were converted into YCrCb color space, and then the color difference signal Cb value was used as an indicator. YCrCb color space was designed for digital algorithms in handling television information and has become a widely used model in digital video systems. Y is the luma component, which represents the luminance and is computed as the weighted sum of RGB values. Cb is the difference between blue and luma component and Cr is the difference between red and luma component. This is expressed as follows:

\[ Y = 0.299R + 0.587G + 0.114B \]
\[ Cr = R - Y \]
\[ Cb = B - Y \]

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We used the image analysis method to evaluate the degree of blending in this study, because the method was direct, non-destructive, and a convenient tool for quantitative assessment of blending degree. An additional reason was that the colored lactose was selected as a model powder.

In this study, we investigated the effects of the operational variables operation speed, operation time, charging rate in vessel, and size of vessel, on the blending degree of the mixtures, and then carried out the dispensation of various commercial medicines and made comparisons with the manual method using a mortar and pestle.

**Experimental**

**Materials** Crystalline lactose, powdered lactose, and corn starch (Mylan Seiyaku Co., Ltd., Tokyo, Japan) were selected as diluents because they are generally used for dispensation. Iron oxide(III) was obtained from Wako Pure Chemical Industries, Ltd. (Osaka, Japan) and used as a pigment. Adona® powder 10% (carbazochrome sodium sulfonate hydrate, Mitsubishi Tanabe Pharma Co.), Anginal® powder 12.5% (dipyridamole, Choseido Pharmaceutical Co., Ltd.), and Neophylline® powder (aminophylline, Esai Co., Ltd.) were obtained for usage as model powdered medicines.

**Measurement of Physical Properties** Mean diameter, apparent bulk density, and angle of repose were determined according to Japanese Pharmacopeia XVI. In brief, mean diameter was calculated from the cumulative amount curve remaining on the sieves with openings of 53, 75, 100, 150, 250, and 355 μm. Apparent bulk density was measured with a measurable cylinder (25 mL) using 10 g of powder. Angle of repose was determined from circular conic formed on a cylinder of 20 mm in diameter.

**Colored Diluents Preparation** Crystalline lactose or corn starch mixed with iron oxide were mixed using a mortar and pestle at a mass ratio of 1:19, until it became homogeneous.

**Preparation of Mixtures with Planetary Centrifugal Mixer** Blending of principal medicine and diluents was carried out using a planetary centrifugal mixer (NR-500, Thinky Co., Ltd., Tokyo, Japan) at the weight ratio of 1:1, except especially mentioned. Weighted powders were poured into the vessel (ointment container, UG35mL, UG58mL, UG125mL, Umano Chemical Container Co., and 550mL, Thinky Co., Ltd.) without any agitators, and the vessel was closed with a lid. Subsequently, the vessel was set in the mixer with a fitting adaptor. The mixer was operated according to the experimental schedule stated in the results section. The experiments were repeated three times.

The operational variables were operation speed, operation time, charging rate in vessel, and size of vessel. The ratio of rotation and revolution speed was fixed at 1:1. The capable variety and operational variables used in this study are summarized in Table 1.

**Manual Blending** Manual blending was performed with a mortar and pestle according to the Japanese Guidelines for Dispensation. That is, the mortar (10 cm in diameter and 5 cm in depth) was held and rotated by the left hand, and the pestle was rotated by the right hand spirally in the direction opposite to that of the rotation of the mortar. Thereafter, 10 clockwise rotations followed by 10 anticlockwise rotations were repeated three times, the mortar thus being rotated 60 times. In some cases, an additional 20 rotations may be performed. It has been reported that uniform mixing is achieved after 60–80 rotations in the case of the preparation of 5.0–30.0 g of powdered medicines. Manual blending was conducted by just one pharmacist with 20 years of dispensing experience to exclude inter-individual variation. The experiments were repeated three times.

**Results**

**Effect of Operation Speed on the Blending Degree** Mixtures of colored lactose and crystalline lactose at a weight ratio of 1:1 were used in the former part of this study. We examined the influence of operation speed of the mixer on the blending degree at a 20% charging rate in a 35 mL vessel. The operation time was stepped in increments of 10 s. The relative standard deviation was plotted as a function of operation time, as shown in Fig. 2.

The relative standard deviation values decreased to lower than 6.08% until 10 s irrespective of operation speed. The results indicated a sufficient blending degree was achieved. Thereafter, the values seem to decrease gradually along with operation time. However, no significant difference in the relative standard deviation was observed among operation time points at each operation speed. This indicated that the degree of blending reached a plateau as early as 10 s, and prolongation of operation time did not improve the degree of blending. In addition, operation speed plays a minor role in the degree of blending at a 20% charging rate in a 35 mL vessel.

### Table 1. Operational Variables of the Planetary Centrifugal Mixer

| Variable              | Examined value | Potential value |
|-----------------------|----------------|-----------------|
| Time (s)              | 10, 20, 30, 40, 50, 60 | 1–1800         |
| Speed (rpm)           | 400, 700, 1000 | 400–1000        |
| Charging rate (%)     | 20, 30, 40, 50  | 1–80            |
| Vessel size (mL)      | 35, 58, 125, 550 | 10–750          |

Statistical Analysis To compare the blending ratio, data were subjected to statistical ANOVA followed by Tukey’s multiple range test. The significance of the differences between the results obtained from the planetary centrifugal mixer and manual blending method was determined using Student’s *t*-test. The statistical significance was considered to be at the level of *p*<0.05.

Digital Image Processing Digital photos of mixtures were taken with a microscope (M3, Scalar Co., Ltd., Tokyo, Japan) equipped with a lens (30N, magnification of thirty times), and obtained as Microsoft Bitmap files (VGA). Pixel analysis was performed by ImageJ (ver.6, National Institute of Health, Washington, D.C., U.S.A.). Subsequently, the color element values of RGB were converted to YCrCb color space (ITU-R BT.601, International Telecommunication Union). The color difference signal, Cb, was used as an indicator of the blending degree of the mixtures.

Assessment of Blending Degree Five photos were taken at different positions of the sample spread on the stage area. The blending degree of the mixture was assessed using the relative standard deviation of Cb value. In general, the blending degree proceeds with an increase in blending time, and then uniform blending is obtained. Therefore, a smaller relative standard deviation (% of Cb value means a higher uniformity of blending. A value less than 6.08% is recognized as sufficient blending.
fore, operation time was fixed at 50 s in further studies.

**The Effect of Charging Rate in Vessel on the Blending Degree** The blending degree changed along with variations in vessel size and operation speed. Blending was performed for 50 s. The results are displayed in Table 2.

When the charging rate rose to 30%, powders did not blend sufficiently at the operation speed of 400 rpm. At a 40% charging rate, sufficient blending did not occur even at an operation speed of 700 rpm. As the charging rate rose to 50%, powders could not be blended at any operation speed. These results indicated that a higher charging rate required a higher speed in order to achieve uniform blending. In general, high filling led to a decrease in motion of contents. While a lower charging rate is preferable for uniform blending, this study showed that the charging rate can be set up to 40%.

**Effect of Vessel Size on the Blending Degree** The influence of vessel size on the blending degree was examined using 58, 125, and 550 mL cylinder vessels with a diameter of 53, 53, and 88 mm, respectively. The charging rate in the vessels was fixed to 20%. The results are listed in Table 3.

When powders were blended in a 58 mL vessel, sufficient blending was obtained irrespective of operation speed. However, blending in a 125 mL vessel required a higher operation speed than 700 rpm. Moreover, blending in a 550 mL vessel required more than 1000 rpm of operation speed. At the same charging rate, the usage of a larger vessel requires a larger amount of powder. Therefore, the convective force needed for motion was increased. At the same time, the diameter of the vessels affected the blending degree because the powder in the vessel was moved by not only the revolution force but also the rotation force. Thus, the relative standard deviation of a 125 mL vessel at the speed of 1000 rpm was slightly higher than that of a 58 mL vessel due to the same diameter of these vessels.

**Uniformity at the Various Blending Ratios** The influence of blending ratio between colored lactose and crystalline lactose on the blending degree was investigated. The blending was carried out at a 500 rpm operation speed and 20% charging rate in a 35 mL vessel. Figure 3 illustrates the relative standard deviations of various blending mixtures at the weight ratios of 1:9, 3:7, 5:5, 7:3, and 9:1. Irrespective of blending ratio, the relative standard deviations were found to be of similar values, varying 1.02–1.94. There was no significant difference in the relative standard deviation among the blending ratios of 1:9–9:1. The results illustrated that uniform mixtures were obtained at a wide range of blending ratios.

**Application to the Dispensing of Various Commercial Medicines** We applied the blending method to dispensing powdered medicine using three kinds of diluents, lactose powder, crystalline lactose, and corn starch, and three commercial medicines, Adona® 10% powder, Anginal® 12.5% powder, and Neophylline® powder. Many factors influence the degree of blending. In general, powders with similar particle size and gravity tend to be blended homogeneously. Their physical properties are summarized in Table 4.

The mixtures of medicines and diluents were decided according to ordinary dispensing procedure in pharmacies. Corn starch is used as a pharmaceutical diluent for Neophylline® instead of lactose to prevent chemical incompatibility. Mixtures of Adona®-powdered lactose, Anginal®-crystalline lactose, and Neophylline®-corn starch were prepared at

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**Table 2. Effect of Charging Rate in Vessel on the Blending Degree**

| Charging rate | Operation speed |
|---------------|-----------------|
|               | 400 rpm | 700 rpm | 1000 rpm |
| 20%           | 0.885±0.60 | 0.640±0.31 | 0.696±0.40 |
| 30%           | × | 3.06±1.0 | 1.66±1.1 |
| 40%           | × | × | 3.28±1.6 |
| 50%           | — | × | × |

The relative standard deviation (%) of Cb value is presented as the mean±S.D. of three experiments. Symbols × and —, indicate uncompleted blending and untested, respectively.

**Table 3. Effect of Vessel Size on the Blending Degree**

| Vessel size | Operation speed |
|-------------|-----------------|
|             | 400 rpm | 700 rpm | 1000 rpm |
| 58 mL       | 1.64±1.2 | 1.50±0.48 | 1.24±0.45 |
| 125 mL      | × | 0.726±0.15 | 4.71±1.0 |
| 550 mL      | × | × | 1.57±1.4 |

The blending was conducted using 58, 125, and 550 mL vessels at a 500 rpm speed and 20% charging rate for 50 s. The relative standard deviation (%) of Cb value is presented as the mean±S.D. of three experiments. Symbol × indicates uncompleted blending.
a weight ratio of 1:1 using a planetary centrifugal mixer (500 rpm, 50 s), and compared with a traditional method using a mortar and pestle. The blending degree of the methods is presented using relative standard deviations as shown in Fig. 4.

The relative standard deviations of all systems are less than 6.08%. These results indicated sufficient blending was achieved. No significant differences (p<0.05) between the planetary centrifugal mixer and the manual method were detected. Therefore, the planetary centrifugal mixer is an alternative blending method to dispense powdered medicines. Despite the usage of different diluents, powdered lactose, crystalline lactose, and corn starch, all of the mixtures were blended sufficiently in both methods.

**Discussion**

This is the first ever reported application of a planetary centrifugal mixer to powder blending. In this study, we confirmed that a planetary centrifugal mixer was a useful tool for dispensing powdered medicine. Sufficient blending mixtures were obtained at a 500 rpm operation speed, 50 s operation time, and 20% charging rate (Figs. 3, 4). A rapid and concise method for the blending of powdered medicines in dispensing has been developed. It is worth noting that uniform blending was achieved at the very early time of 10 s (Fig. 2). This will be time-saving and convenient for pharmacists. In addition, the results shown in Table 3 demonstrated the possibility of moving up to a 550 mL vessel from 35 mL, meaning 7–110 mL of practical volume at a 20% charging rate. This range will cover the requirements of pharmacies because about 5–50 g of powders is mixed at once with a mortar and pestle. Overall, this method was found to be suitable for dispensing in pharmacies.

A lot of studies on blending powdered medicine were performed using a mortar and pestle. The effects of various factors on blending degree have been discussed. However, the findings of the studies were affected by individual variation in the skills of pharmacists. In contrast, the present method overcame the variation in individual skills, and will contribute to uniform dispensation in all pharmacies.

Presently, the planetary centrifugal mixer is used for mixing of ointments in pharmacies. The mechanism of mixing of ointments is thought to powerful twisting mixing caused by rotational and centrifugal forces. In the same way, powders in the vessel move along the twist flow from center to outer and also from bottom to top. Thus, strong convective and shear forces are generated in the vessel, and act on the blending of the powders. However, a detailed mechanism of powder blending was not elucidated.

Further studies will be needed to establish a versatile standard method for powder blending using a planetary centrifugal mixer. At the same time, however, this study has resulted in the development of many important and promising technologies that can be used for the powder industry.

**References**

1) Nakamura H., Higo K., Suzuki A., Fujinuma Y., Tanaka Y., Ohtani M., Kotani H., Iga T., *Jpn. J. Hosp. Pharm.*, 23, 305–311 (1997).
2) Nakamura H., Yanagihara Y., Sekiguchi H., Komada F., Kawabata H., Ohtani M., Saitoh Y., Kariya S., Suzuki H., Uchino K., Iga T., *Yakugaku Zasshi*, 124, 127–134 (2004).
3) Nakamura H., Yanagihara Y., Sekiguchi H., Ohtani M., Kariya S., Uchino K., Iga T., *Yakugaku Zasshi*, 124, 135–139 (2004).
4) Nakamura H., Fujinuma Y., Matsumoto M., Ohtani M., Kotaki H., Uchino K., Iga T., *Jpn. J. Pharm. Health Care Sci.*, 27, 491–494 (2001).
5) Miyamatsu H., Sekine Y., Soeda H., Matsuzawa K., Uezaki S., Akashi T., *Jpn. J. Soc. Hosp. Pharm.*, 40, 395–399 (2004).
6) Okada J., Matsuda Y., Morita S., Wada Y., Ohnishi H., *Yakugaku Zasshi*, 88, 827–831 (1968).
7) Okada J., Matsuda Y., *Yakugaku Zasshi*, 89, 1562–1565 (1969).
8) Miyazaki Y., Miyawaki K., Uchino T., Kagawa Y., *J. Pharm. Sci. Tech.*, 73, 402–409 (2013).
9) Japan Pharmaceutical Association, “The Japanese Guidelines for Dispensation,” 12th ed., Yakujinippou-sha, Tokyo, Japan, 2008.
10) Tanno K., Ikeda M., Sasaki Y., *Jpn. J. Pharm. Health Care Sci.*, 5, 73–79 (1979).
11) Ushijima K., Usuijima I., To H., Higuchi S., *Kyushu Yakugakkai Kaiho*, 40, 47–51 (2006).
12) Sakurai Y., Fuji S., Ito S., *J. Pharm. Sci. Tech.*, 16, 7–12 (1956).