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Effect of batch size on the granule properties in planetary centrifugal granulation

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A granulation method using a planetary centrifugal mixer, called planetary centrifugal granulation, has been developed for small-scale production, such as extemporaneous preparation in pharmacies. Although the impact of its operational parameters on granulation is described, the scale effect has not been investigated. Therefore, we aimed to reveal the effects of vessel size and vessel filling rate on granule properties. In this study, ibuprofen 20% granules consisting of lactose, cornstarch, sodium carmellose, and talc were used as model granules. Granulation was performed using geometrically similar containers, 6–58 mL, with a filling rate of 20–70%. After granulation, we monitored the granule properties, for example, median diameter (d50), span of particle size distribution, and sphericity. At filling rates of 40% and 50% in the 58-mL vessel, the granules grew larger in diameter, and at a rate of 30%, the granules showed a higher sphericity. When the filling rate was 30%, d50 became larger and the span decreased as the vessel size increased. The yields of the granules were higher than 95% when using the 12–58 mL vessel. Lastly, the drug content uniformity and drug dissolution behavior of the granules produced in different vessel size were examined. The granules showed similar drug consistencies and drug dissolution profiles. In conclusion, the quality of the products was not affected by changes in vessel size. Thus, pharmacists could prepare and compound the granule formulations with high yield and appropriate quality using an adequate vessel in the same manner.

1. Introduction

When there is no commercial medicine that meets the needs of a patient, pharmaceutical compounding is a useful tool for preparing an appropriate formulation. Pharmacies use limited dispensing equipment to prepare a wide variety of compounded medicines. Because of space and time constraints, equipment should be able to sit on a tabletop, compounding methods should be simple, and preparation should be quick. To meet these requirements, we developed a small-scale spherical granulation method using a planetary centrifugal dispensing mixer (Eda et al. 2020). The powders were placed in a polypropylene ointment container, water was added, and the powders were agitated in a dispensing mixer for easy granulation with a high yield. The granules can be prepared using this method with approximately 1 min of granulation time and 4 h of drying time. As models, dantrolene (Miyazaki et al. 2020) and rifampicin granules (Miyazaki et al. 2021) were prepared. Drug loss at the time of dispensing and dosing was greatly improved by converting the highly dispersible and adherent powder from the capsule into granules.

However, when dispensing according to patient needs, the amount to be prepared differs each time. Therefore, it is necessary to change the granulation container and the filling rate for granulation, thus giving rise to the question as to whether the formulation characteristics of the granules remain unchanged during this process. In this study, we investigated the effect of container size and filling rate on granule properties using the same model formulation (20% ibuprofen (IBP) granules) as in a previous report (Eda et al. 2020).

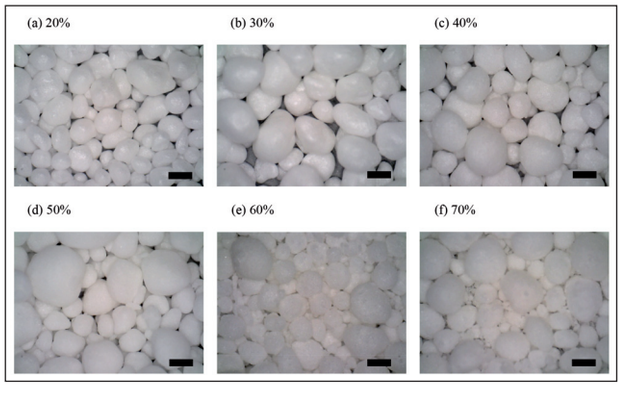

Fig. 1: Photos of granules prepared at the filling rates of 20% (a), 30% (b), 40% (c), 50% (d), 60% (e), and 70% (f). Photographs were taken at 50× magnification under a microscope. The black bars indicate 1 mm in length.

Table 1: Formulation of granules prepared at various filling rates

Filling rate (%)	20	30	40	50	60	70
Ibuprofen (g)	1.32	1.98	2.64	3.31	3.97	4.63
Lactose monohydrate (g)	3.00	4.51	6.02	7.52	9.03	10.53
Cornstarch (g)	1.29	1.93	2.58	3.22	3.87	4.51
MCC (g)	0.33	0.50	0.66	0.83	0.99	1.16
CMC (g)	0.33	0.50	0.66	0.83	0.99	1.16
Talc (g)	0.33	0.50	0.66	0.83	0.99	1.16
Total (g)	6.61	9.92	13.22	16.53	19.84	23.14
Water added (mL)	1.85	2.70	3.55	4.40	5.20	6.20

MCC: Microcrystalline cellulose, CMC: Carboxymethyl cellulose

2. Investigation, results, and discussion

2.1. Observation of compounded granules

To investigate the effect of filling rate in the vessel on the granule characteristics, granulation using a 58–mL vessel was performed with a filling rate of 20–70%. When the filling rate was 80%, it was impossible to load the binder solution (pure water) in the vessel. Formulation of the granules is described in Table 1, and photographs are shown in Fig. 1. In all the cases, spherical granules with smooth surfaces were obtained.

2.2. Effect of filling rate of materials in the vessel on particle size distribution of granules

The particle size distribution of the granules obtained is shown in Fig. 2. The particle size increased with increasing filling rate. However, in the case of 60% and 70% filling rates, the amount of fraction with size less than 300 μm increased, indicating that the ungranulated fraction increased. In general, a higher filling rate prevents materials from moving freely, lading to less agglomeration (Terashita et al. 2002). The d50, span, and yield of the granules prepared with a filling rate of 20–70% are summarized in Table 2. At a filling rate of 40–50%, the produced granules had a larger d50 and a smaller span. The yield at a 20–40% filling rate was excellent, exceeding 99%.

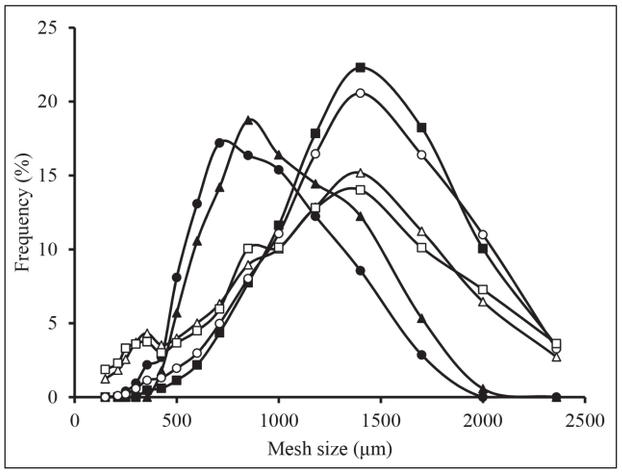

Fig. 2: Particle size distribution of granules prepared at various filling rates Keys: ●, 20%; ▲, 30%; ■, 40%; ○, 50%; Δ, 60%; □, 70%

2.3. Effect of filling rate of materials in the vessel on the sphericity of granules

In general, the sphericity and size of particles affect the flow properties (Fu et al. 2012). The sphericity of the granules is shown in Fig. 3. At a lower filing rate, 20–40%, higher sphericity was observed. When the granules were rolling on the wall of the vessel, the granules obtained high sphericity (Morin and Briens 2014). When the filling rate increased to 70 %, the sphericity of the granules decreased to 0.61. This was caused by inhibited motion of the granules due to the high load of the materials in the vessel. Based on the results, we considered that a filling rate of 30–40% was adequate to obtain high production efficiency and high sphericity of the granules.

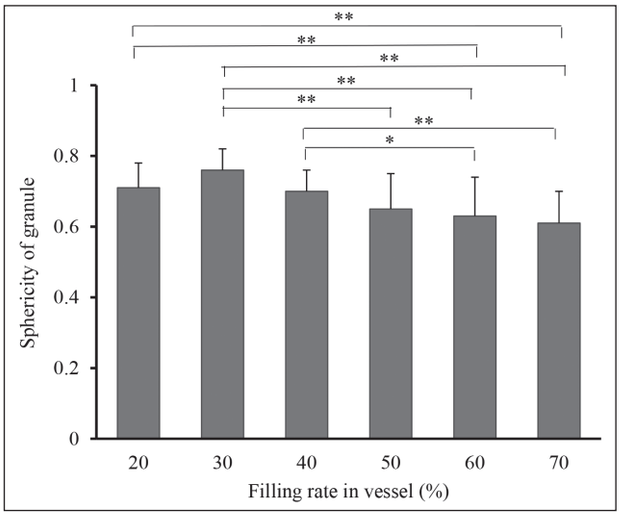

Fig. 3: Effect of filling rate of materials in the vessel on the sphericity of granules Each value represents the mean + SD of three batches of preparation. One-way ANOVA detected significant differences between groups ($F(5,174) = 13.21$, $p < 0.001$). Significant differences were observed (* $p < 0.05$, ** $p < 0.01$, Tukey's test).

2.4. Effect of vessel size on particle size distribution of granules

We performed granulation using vessels of 6, 12, 24, 35, and 58 mL, which had diameters of 31, 37, 45, 50, and 60 mm, respectively. The particle size distributions of the granules prepared according to Table 3 are shown in Fig.4. The filling rates were constant at 30% for all vessels. From the results shown in Fig. 4, the proportion of ungranulated fraction less than 300 μm increased with decreasing in the vessel size.

The d50, span, and yield values are listed in Table 4. As the size of the vessels increased, the d50 of the granules became larger and the span of the granule size distribution became smaller, indicating that the granulation state was more proceeded in a larger vessel. The moving force of the materials generated from the rotation and revolution of the vessel set in the mixer was influenced by the diameter of the vessel, because the diameter of the vessel is the maximum diameter of the rotating axis. The yields were higher than 95% when vessels of 12–58 mL were used.

Table 2: Yield and properties of granules prepared at various filling rates

Filling rate (%)	20	30	40	50	60	70
d50 (μm)	811.4 ± 92.04	893.7 ± 17.6	1250.4 ± 165.0	1249.5 ± 6.34	985.2 ± 99.56	976.3 ± 141.68
Span	0.83 ± 0.04	0.82 ± 0.06	0.62 ± 0.14	0.82 ± 0.02	1.29 ± 0.08	1.29 ± 0.21
Yield (%)	99.0 ± 0.89	99.5 ± 0.20	99.7 ± 0.17	95.4 ± 1.73	93.0 ± 0.50	89.2 ± 2.00

Values are represented as the mean ± S.D. of three batches of preparation.

Table 3: Formulation of granules prepared using vessels of different size

Vessel size (mL)	6	12	24	35	58
Ibuprofen (g)	0.21	0.41	0.82	1.20	1.98
Lactose monohydrate (g)	0.47	0.93	1.87	2.72	4.51
Cornstarch (g)	0.20	0.40	0.80	1.20	1.98
MCC (g)	0.05	0.10	0.21	0.30	0.50
CMC-Na (g)	0.05	0.10	0.21	0.30	0.50
Talc (g)	0.05	0.10	0.21	0.30	0.50
Total (g)	1.03	2.05	4.10	5.99	9.92
Water added (mL)	0.28	0.56	1.13	1.65	2.73

Table 4: Yield (%) and properties of granules prepared using vessels of different size

Vessel size	6-mL	12-mL	24-mL	35-mL	58-mL
d50 (μm)	545.8 ± 38.82	542.3 ± 49.24	665.1 ± 95.33	794.3 ± 37.11	893.7 ± 17.6
Span	1.69 ± 0.13	1.5 ± 0.08	1.2 ± 0.33	0.9 ± 0.05	0.8 ± 0.06
Yield (%)	89.8 ± 3.17	96.2 ± 2.93	98.7 ± 0.63	99.3 ± 0.21	99.5 ± 0.20

Values are represented as the mean±S.D. of three batches of preparation.

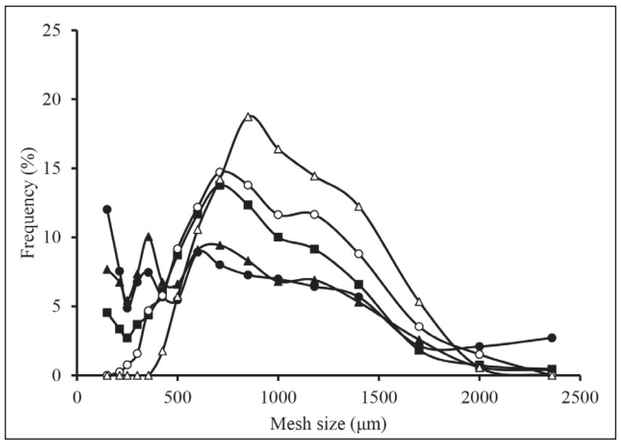

Fig. 4: Particle size distribution of granules prepared using the vessels with different size Keys: ●, 6-mL; ▲, 12-mL; ■, 24-mL; ○, 35-mL; Δ, 58-mL

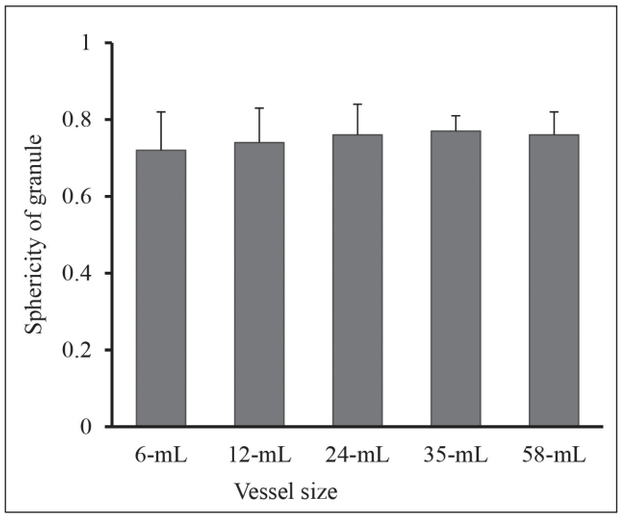

Fig. 5: Effect of vessel size on the sphericity of granules. Each value represents the mean+SD of three batches of preparation. There was no significant difference among them (Tukey's test).

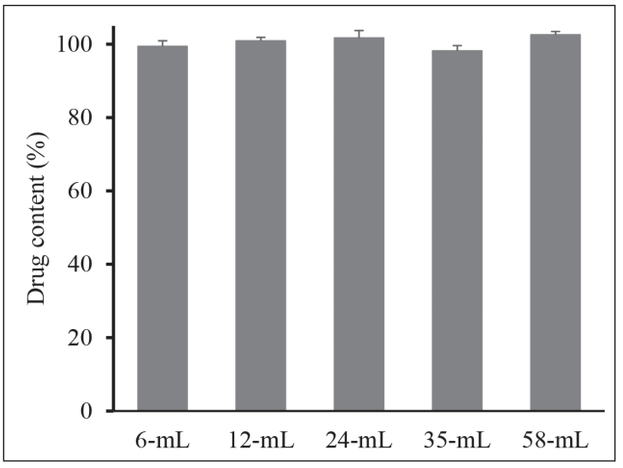

Fig. 6: Drug content of granules prepared using vessels of different size. Values represent drug content percent against theoretical content amount. Each value represents the mean±SD of three batches of preparation.

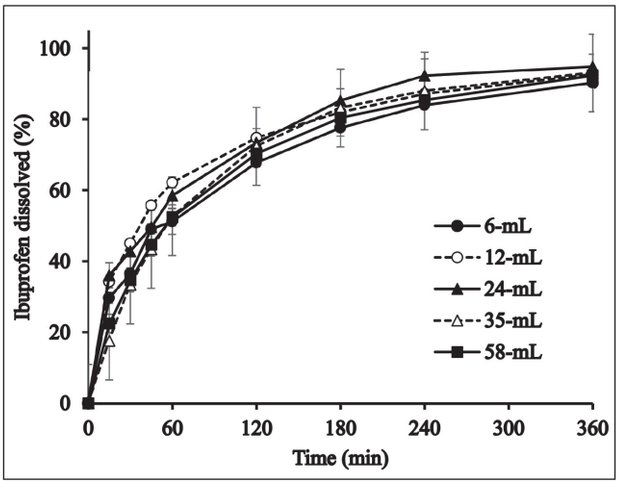

Fig. 7: Dissolution profiles of ibuprofen from granules prepared using vessels of different size Each point represents the mean±SD of three batches of preparation.

2.5. Effect of vessel size on sphericity of granules

The sphericity of the granules prepared using vessels of different sizes is shown in Fig. 5. All granules showed high sphericity, with a value larger than 0.7. There were no significant differences among them. The sphericity was maintained because the filling rate was equal even though the size changed, thus ensuring the same percentage of voids and allowing the contents to move sufficiently.

2.6. Drug content uniformity and drug dissolution profiles

Finally, we conducted formulation testing, particularly testing of drug content uniformity and drug dissolution. Figure 6 shows the results of the drug content uniformity. In all types of vessels, the percentage of drug content was within 95–105%. The vessel size did not affect drug content uniformity.

Figure 7 shows the drug dissolution profiles of the granules prepared using vessels of various sizes. Drug dissolution from the granules increased rapidly during the first 60 min, and then reached a constant rate in the later phase. All dissolution curves were almost superimposed, indicating that the vessel size did not affect drug dissolution. These results demonstrate that changing the container size to match the dispensing volume does not affect the quality of the formulation.

2.7. Conclusion

In the planetary centrifugal granulation method, when the container filling rate was set at 30%, granules of the same quality were obtained, regardless of the container used (6 to 58 mL). The granulation batch size can be changed based on patient demand.

This effective granulation method could benefit pharmacists by allowing for extemporaneous compounding of dosages for personalized therapy.

3. Experimental

3.1. Materials

Lactose monohydrate and cornstarch were purchased from Pfizer Co., Ltd. (Tokyo, Japan) and their mixture at a ratio of 7:3 (w/w) was used as a pharmacopeial diluent because the mixture is generally used for standard formulations (Kato et al. 2005). Microcrystalline cellulose (MCC) and sodium carboxymethyl cellulose (CMC) were obtained from Fujifilm Wako Pure Chemicals Co., Ltd. (Kyoto, Japan) and used as diluents and binders, respectively. Talc purchased from KENEI Pharmaceutical Co., Ltd. (Tokyo, Japan) was used as a lubricant. Ibuprofen 50® (IBP) was supplied by BASF Co., Ltd. (Tokyo, Japan) and was used as an active pharmaceutical ingredient (API). Ultrapure water (Arium mini plus, Sartorius Japan Co., Ltd., Tokyo, Japan) was used as the wetting agent. HPLC grade methanol and acetonitrile were purchased from Fujifilm Wako Pure Chemicals Co., Ltd. (Kyoto, Japan). All other reagents were of reagent grade.

3.2. Granulation experiments

Twenty percent IBP granules were prepared as a model formulation, which was composed of 20% IBP, 65% lactose-cornstarch (7:3) mixture, 5% MCC, 5% CMC, and 5% talc. Granulation was conducted as described in our previous study (Eda et al. 2020). In brief, a predetermined amount of each ingredient was weighed into a plastic container and blended at 1,200 rpm for 45 s in a dispensing mixer (MW-N300DS-1, Beat Sensing Co., Ltd., Shizuoka, Japan). Water, equivalent to 67.5% of the plastic limit value of the materials, was added, and then the mixture was granulated at 1,200 rpm for 45 s in the dispensing mixer. Calculations of the plastic limit value were performed in the same way as in our previous study (Eda et al. 2020). The granules were dried on a shelf at 50 °C, for 4 h.

In this study, a series of ointment containers made of polypropylene (UG series, Umano Kagaku Youki Co., Ltd., Osaka, Japan) were used as granulation vessels. The vessels of 6–58 mL had a geometrically similar figure with different sizes. To investigate the effect of filling rate (20–70%), the a 58-mL vessel was employed. The filling rate of the vessels was fixed at approximately 30 % to investigate the effect of vessel size (6–58 mL). In this study, we produced three batches for all the experiments.

3.3. Determination of granulation efficiency and particle size distribution

Dry granules were passed through a 2800-μm sieve followed by a 150-μm sieve to remove any oversized agglomerates and fines. The remaining spherical granules were weighed, and the yield (%) was calculated using Eq. (1):

$$\text{Yield (\%)} = \text{remaining granules of size } 150\text{–}2800\ \mu\text{m (g)}/\text{loading powders (g)} \times 100 \quad (1)$$

The particle size distributions of the granules were measured using a series of standard sieves including 150, 250, 355, 425, 500, 600, 710, 850, 1000, 1180, 1400, 1700, 2000, 2360, and 2800 μm. The individual sieves were weighed after shifting. The particle size distribution and median particle size (d50) were evaluated using a log-normal distribution. The span was defined using Eq. (2).

$$\text{Span} = (d90 - d10)/d50 \quad (2)$$

where d10 and d90 are the diameters of the 10th and 90th percentiles of the cumulative oversize distribution, respectively.

3.4. Calculation of sphericity

The granules were observed using a microscope (M3, Schalar Co., Ltd., Tokyo Japan) equipped with a 30× lens (30N, Schalar Co., Ltd., Tokyo Japan). Sphericity was estimated using the circularity of the projected image of the granules. The images obtained were analyzed using the ImageJ software (ver. 1.51, National Institutes of Health, USA) for circularity (Eq. 3).

$$\text{Sphericity} = 4\pi \times (\text{area}/\text{perimeter}^2) \quad (3)$$

A sphericity value of 1.0 indicates a perfect sphere. An irregular shape will have a value of less than 1. The data are presented as the mean±S.D. of 30 granules.

3.5. Assay of content uniformity

A content uniformity analysis was performed to evaluate the distribution of the API in the final granules. Approximately 100 mg of the sample was dissolved in 100 mL of pure water and analyzed by HPLC as described in Section 3.7. All experiments were performed in triplicate.

3.6. Dissolution test

Dissolution was performed according to the dissolution test (paddle method) of the Japanese pharmacopeia 17th Ed (2016) using a dissolution apparatus (NTR-6100A, Toyama Sangyo Co., Ltd., Osaka, Japan). The dissolution medium (900 mL) was phosphate-citrate buffer (pH 5.5), and the temperature was maintained at 37±0.5 °C. The paddle speed was set to 50 rpm. Granules (1 g) of 710–1,400 μm in diameter were added to the dissolution medium. The sample medium was collected at 15, 30, 45, 60, 120, 180, 240, and 360 min, and then filtered through a 0.45-μm filter (TORAST Disc, Shimadzu Co., Kyoto, Japan) prior to analysis. The amount of dissolved drug was analyzed using HPLC, as described in Section 3.7. All experiments were performed in triplicate.

3.7. Determination of IBP concentration by HPLC

The concentration of IBP was analyzed using an HPLC system (Shimadzu Co., Kyoto, Japan) that consisted of a pump (LC-10AS), a sample injector (SIL-10A), and a UV-Vis spectrophotometric detector (SPD-10A). A C18 column (Shim-pack GWS, 5 μm, 4.6 × 150 mm, Shimadzu GLC Ltd., Tokyo, Japan) was used for separation, and IBP was detected at 264 nm. The mobile phase was 50 mM phosphate buffer (pH 2.6) with acetonitrile (40:60, v/v) (Japanese Orange Book, 2007).

3.8. Data analysis

All data are presented as the mean±standard deviation (S.D.). Statistical analysis of the data was performed with Tukey's test using SPSS software (Ver.23, SPSS Inc., Chicago, USA).

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Conflicts of interest: The authors declare no conflicts of interest.

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