**Evaluation of Dantrolene Granules Extemporaneously Reformulated from Capsules in a Pharmacy**

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Dantrolene capsule, an effective therapeutic agent for the treatment of spasticity, is administered to children who cannot swallow the capsule after reformulation into a powder. The powdered drug can alter the specified dosage and it is also difficult to dispense the powdered formulation because of its bulky and sticky nature. To resolve these problems, we reformulated dantrolene capsules into granules using a centrifugal planetary mixer in the pharmacy. The granules containing lactose-cornstarch, d-mannitol, or microcrystalline cellulose as a diluent were examined to determine particle size distribution, flowability, drug content uniformity, and disintegration time. The granules with microcrystalline cellulose were superior to the other forms, owing to their smaller size, good drug content uniformity, and rapid disintegration. We further investigated the usability of the granules in the dispensing procedure (dividing and packing) and in the dosing process (retrieval from package) using the powders as controls. The deviation of the divided amount and loss on dosing were reduced relative to the powders. In addition, drug dissolution properties and storage stability for 12 months were the same as those of the powders. Therefore, we concluded that dantrolene granules are excellent alternatives as an extemporaneous preparation in pharmacies.

**Key words** extemporaneous preparation; sodium dantrolene; spherical granulation; planetary centrifugal mixer; reformulation

**Introduction**

The need for pediatric formulations of marketed drugs has garnered increased attention. However, clinical trials involving children are associated with unique ethical and practical issues such as patient recruitment and a need for a greater investment than similar studies in adult populations. As a result, the unlicensed (off-label) use of medicines in children is a daily reality due to the lack of alternatives. The problem not only exists in the licensing of marketed drugs for pediatric use, but also in the lack of age-appropriate formulations. For children, it is occasionally difficult to swallow the solid dosage forms of most marketed drugs. Moreover, as dosing is often based on body weight, division into the necessary proportion of a solid formulation becomes difficult.

One solution is the use of extemporaneously prepared formulations in pharmacies, which are powders in Japan and solutions or syrups in the U.S.A. or EU. Typically, pharmacists prepare formulations derived from solid dosage forms such as tablets and capsules. For solutions, some extemporaneous preparations have some issues regarding their limited chemical stability, microbial sterility, and storage conditions. On the other hand, for powders, pharmacists added several excipients to the preparations for ease of precise weighing and division to unit-dose packages. Therefore, the resultant powders are required to fulfill standard levels of content uniformity, flowability, and storage stability. However, some extemporaneously prepared powders could not meet the grade or not be tested.

To resolve these issues, we proposed granules as an extemporaneous preparation for pediatric patients. These granules are produced to enhance the uniformity of the active pharmaceutical ingredient (API), facilitate weighing or dividing compounding, reduce weight loss during dispensing, reduce toxic exposure, and improve the stability of the product. Previously, some pharmacists reported that the granules were superior to powders with respect to flowability and weight loss on dispensing. However, the manufacture of granules and assurance of their quality were difficult assignments for pharmacists in the hospital. In general, the granulation technique is broadly classified into two types: dry granulation and wet granulation, with wet granulation being the most widely used granulation technique. Currently available granulation technologies include roller compaction for dry granulation, spray drying, supercritical fluid, low/high shear mixing, fluid bed granulation, and extrusion/spheronization for wet granulation. These technologies require long processing durations until the products can be used for dispensing. Therefore, we developed a concise granulation method for extemporaneous preparation using a dispensing mixer. The mechanism of the machine is based on revolution-rotation motion, causing a convective force in the vessel. The added water is spread over the entire materials and then wet mass granulates via rolling in the vessel. In this method, the granulation process spends 15–90 s.

In this study, we used sodium dantrolene capsule, an effective therapeutic agent for the treatment of spasticity in children as a model medicine. However, only capsule formulations are commercially available. Therefore, pharmacists or patients reformulated this drug to solutions in the U.S.A. and EU or powders in Japan. Thus, it was selected as a

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model medicine for this reformulation study.

The purpose of the present study was to manufacture extemporaneous granules of sodium dantrolene that were free flowing, offering rapid disintegration and were stable for an appropriate storage period. Additionally, we evaluated the granules for usability in the dispensing and dosing processes through a dividing and packaging study and a passing through a nasogastric feeding tube study. In these studies, 5% sodium dantrolene powder generated of Dantrium® capsule content and powdered lactose was prepared and used as a control.

Experimental

Prescription Survey We surveyed the prescriptions for inpatients and outpatients at Shizuoka Children Hospital for one year, 2018. The number of recipes that requested the reformulation of the Dantrium® capsule into the powdered formulation and single dose amount for each patient were explored.

Materials Dantrium® capsules were purchased from Orphan Pacific Co. (Tokyo, Japan). Powdered lactose (Pfizer Co., Ltd., Tokyo, Japan), cornstarch (Pfizer Co., Ltd., Pharma Pacific Co. (Tokyo, Japan), powdered lactose (Pfizer Co., Ltd., Osaka, Japan) were used as the diluents. Sodium dantrolene was obtained from FUJIFILM Wako Pure Chemical Corporation. Powdered lactose was prepared and used as a control.

Sodium carboxymethylcellulose (CMC, FUJIFILM Wako Pure Chemical Corporation) and talc (Kenei Chemical Co., Ltd., Osaka, Japan) were used as binders and lubricants, respectively. Sodium dantrolene was obtained from FUJIFILM Wako Pure Chemical Corporation. Ultrapure water was generated by an arium™-mini Plus (Sartorius Co., Ltd., Tokyo, Japan) and used. All other chemicals were of analytical grade and used as received.

Preparation of 5% Sodium Dantrolene Powder and Granules The formulations of 5% sodium dantrolene powder and 5% sodium dantrolene granules are listed in Table 1.

To prepare 5% sodium dantrolene powder, the contents of twenty Dantrium® capsules (4.66 g) and 5.34 g of lactose were obtained from FUJIFILM Wako Pure Chemical Corporation and used. All other chemicals were of analytical grade and used as received.

Preparation of 5% Sodium Dantrolene Powder and Granules

| Ingredient          | Powder | Granule (L/S) | Granule (D-Mannitol) | Granule (MCC) |
|---------------------|--------|---------------|----------------------|---------------|
| Dantrium® capsule   | 20 cap | 20 cap        | 20 cap               | 20 cap        |
| (Capsule content)   | (4.66 g) | (4.66 g)     | (4.66 g)             | (4.66 g)      |
| Lactose             | 5.34 g | —             | —                    | —             |
| L/S                 | —      | 4.34 g        | —                    | —             |
| D-Mannitol          | —      | —             | 4.34 g               | 4.34 g        |
| MCC                 | —      | —             | —                    | 4.34 g        |
| CMC                 | —      | 0.50 g        | 0.50 g               | 0.50 g        |
| Talc                | —      | 0.50 g        | 0.50 g               | 0.50 g        |
| Total amount        | 10 g   | 10 g          | 10 g                 | 10 g          |
fractions. The granules were divided into six fractions: granule (L/S): < 500, 500–710, 710–1000, 1000–1400, 1400–1700, and 1700–2000 µm, granule (o-mannitol): < 710, 710–1000, 1000–1400, 1400–1700, 1700–2000, and 2000–2360 µm, granule (MCC): < 150, 150–300, 300–500, 500–710, 710–1000, and 1000–1400 µm. The frequency (%) and drug content of each fraction were determined. Approximately 100 mg of sample was dissolved in 100 mL of a mixture of water and methanol (4:6) and analyzed by HPLC as described in Section “Determination of Sodium Dantrolene by HPLC.” All experiments were performed in triplicate.

Disintegration Test The disintegration test was carried out according to a prior report.23 The granules, each containing 50 mg of sodium dantrolene, were mixed with 20 mL of distilled water in a 20-mL catheter syringe (Nipro Co., Ltd., Osaka, Japan) by revolving the syringe end-to-end fifteen times per 60 s. The revolution was repeated until all granules were disintegrated, and the time needed for disintegration was recorded.

In Vitro Dissolution Profiles Dissolution profiles were examined according to the dissolution test (paddle method) of the Japanese pharmacopeia 17th Ed.22 using a dissolution apparatus (NTR-6100 A, Toyama Sangyo Co., Ltd., Osaka, Japan). The dissolution medium (900 mL) was ultrapure water, and the temperature was maintained at 37 ± 0.5 °C. The paddle speed was set to 50 rpm. Sodium dantrolene granules (0.5 g) or powder (0.5 g) were added to the dissolution medium. The sample medium was collected at 15, 30, 45, 60, and 90 min and then filtered through a 0.45-µm filter (Minisart RC15, Sartorius Japan K. K., Tokyo, Japan) prior to analysis. The amount of dissolved drug was analyzed using HPLC as described below. All experiments were performed in triplicate.

Determination of Sodium Dantrolene by HPLC The concentration of sodium dantrolene was analyzed using an HPLC system (Shimadzu Co., Kyoto, Japan) consisting of a pump (LC-10AS), a sample injector (SIL-10A), and a UV-Vis spectrophotometric detector (SPD-10A). A C18 column (TSK-gel ODS-100 V, 4.6 mm × 150 mm, Tosoh Co., Tokyo, Japan) was used for separation, and dantrolene was detected at 233 nm. The mobile phase was 25 mM phosphate buffer (pH 3.5) with methanol (50:50, v/v) and then filtered through a 0.45-µm filter (Minisart RC15, Sartorius Japan K. K., Tokyo, Japan) by revolving the syringe end-to-end fifteen times per 60 s. Therefore, weight-loss upon dosing was an important parameter, and was calculated using Eq. 7.

Dosing loss (%) = [1 – (amount of medicine taken out of package/ amount of medicine in unit-dose package)] × 100 (7)

Drug Recovery after Passing through a Nasogastric Feeding Tube The sample solution for the simple suspension method25 was prepared by adding 0.5 g of 5% sodium dantrolene granule or powder in an injector, aspirating 20 mL of hot water into the injector, and leaving this mixture for 10 min to prepare the suspension. Thereafter, the sample solution was passed through a nasogastric feeding tube (8Fr, 120 cm, Covidien Japan Co., Ltd., Tokyo, Japan), followed by flushing of the tube with 20 mL of distilled water and air. The solutions passed through the tube were collected in a 100-mL measuring flask and filled with methanol. Dantrolene concentration in the solution was determined using HPLC (see section “Determination of Sodium Dantrolene by HPLC”).

Storage Stability The formulations were protected from light, and kept under the environmental conditions of 25 ± 5 °C and 50 ± 5% relative humidity for a period of 12 months. The samples were withdrawn at 3-, 6-, and 12 months intervals and assayed for drug content using HPLC (see section “Determination of Sodium Dantrolene by HPLC”).

Statistical Analysis A comparison of the mean values of the properties of granules was performed by one-way ANOVA followed by Tukey’s test for multiple comparisons. Comparison between granules (MCC) and the powder formulation was conducted using Student’s t-test. Differences between groups were considered significant when the p value was less than 0.05.

Results Prescription Survey The 31 prescriptions ordered to transform the Dantrium® capsule to a powder formulation was derived from Shizuoka Children’s Hospital. The dose ingested by patients was varied from 0.17 to 0.75 capsules, and the median value was 0.49 capsules. Therefore, we decided that the drug containing the percent of reformulated preparations was 5%; this is because the median amount of product in one unit-dose package should be 0.245 g. Further, 0.2–1.0 g was considered to be an appropriate amount in a package.

Characteristics of the Granules The 5% sodium dantrolene granules and powder were prepared according to Table 1. Optical images of the granules and powder are shown in Fig. 1. The 5% powder showed clear orange color derived from sodium dantrolene despite the dilution with excipients. Dantrium® capsule contains lactose, cornstarch, talc, magnesium stearate, and sodium dantrolene.26 The granules were almost spherical in shape and had a smooth surface with slightly
were observed relate to the powder (*; p nitol) Fig. 1. Images of the Powder and Granules Captured with a Microscope (30×).
(a) Powder, (b) Granule (L/S), (c) Granule (α-mannitol), and (d) Granule (MCC) black bars indicate 2000 μm. (Color figure can be accessed in the online version.)

Table 2. Characterization of the 5% Sodium Dantrolene Granules Prepared with Different Diluents

| Sample                  | d10 (μm) | d50 (μm) | d90 (μm) | Span (μm) | Yield (%) |
|-------------------------|----------|----------|----------|-----------|-----------|
| Granule (L/S)           | 449±190  | 1042±215 | 1437±220 | 0.98±0.21 | 94.1±1.2  |
| Granule (α-Mannitol)    | 704±265  | 1461±242 | 1937±142 | 0.89±0.26 | 95.6±1.0  |
| Granule (MCC)           | 153±61   | 488±59*  | 763±49*  | 1.28±0.27 | 94.1±4.3  |

Values represent the mean ± standard deviation (S.D.) of three preparations. A significant difference was observed between the granule (α-mannitol) and granule (MCC) (*p < 0.05, Tukey’s test). Significant differences were observed between all combinations (*p < 0.05, Tukey’s test).

Table 3. Flowability of the 5% Sodium Dantrolene Granules Prepared with Different Diluents

| Sample                  | Bulk density | Tapped density | Hausner ratio |
|-------------------------|--------------|----------------|---------------|
| Powder                  | 7.32±0.102   | 4.86±0.114     | 1.51±0.033    |
| Granule (L/S)           | 5.26±0.085   | 4.67±0.024     | 1.13±0.018*   |
| Granule (α-Mannitol)    | 5.35±0.068   | 4.80±0.041     | 1.12±0.008*   |
| Granule (MCC)           | 6.71±0.099   | 5.78±0.021     | 1.16±0.015*   |

Values represent the mean ± S.D. of three determinations. Significant differences were observed relate to the powder (*; p < 0.05, Tukey’s test).

Table 4. Drug Content of Each Size Fraction of the Granule (L/S)

| Particle size fraction (μm) | Frequency (%) | Content (%) |
|-----------------------------|---------------|-------------|
| 1700–2360                   | 18.9±10.9     | 85.5±4.1    |
| 1400–1700                   | 15.0±5.1      | 100.3±7.6   |
| 1000–1400                   | 25.4±3.4      | 96.7±4.4    |
| 710–1000                    | 19.6±5.5      | 97.6±8.7    |
| 500–710                     | 12.4±7.5      | 97.2±10.6   |
| < 500                       | 8.7±6.6       | 88.3±4.8    |

Values represent the mean ± S.D. of three preparations.

Table 6. Drug Content of Each Size Fraction of the Granule (MCC)

| Particle size fraction (μm) | Frequency (%) | Content (%) |
|-----------------------------|---------------|-------------|
| 1000–1400                   | 10.2±1.9      | 100.7±5.7   |
| 710–1000                    | 23.1±3.7      | 102.6±6.8   |
| 500–710                     | 22.6±4.4      | 103.6±8.7   |
| 300–500                     | 23.9±2.1      | 101.1±6.1   |
| 150–300                     | 17.1±6.9      | 103.9±4.6   |
| < 150                       | 3.1±2.3       | n.d.        |

Values represent the mean ± S.D. of three preparations. n.d.; this could not be determined as the sample amounts were too small to assay the API content.

Table 7. Disintegration Time of the 5% Sodium Dantrolene Granules Prepared with Different Diluents

| Sample                  | Disintegration time (min) |
|-------------------------|---------------------------|
| Granule (L/S)           | 8.3±0.5*                  |
| Granule (α-Mannitol)    | 8.0±0.8*                  |
| Granule (MCC)           | 5.3±0.5                   |

Values represent the mean ± S.D. of three determinations. Significant differences were found compared with the granule (MCC) (*; p < 0.05, Tukey’s test).

The size of the granules (L/S) and granules (α-mannitol) were relatively large and in general, these diluents made the wet mass higher plasticity, leading to easy coalescence between granules. Thus, the d50 of granules (MCC) was significantly small among the three types of granules. Granules containing MCC were reported to shrink during drying. Therefore, the resultant granules became fine particles. The span value of the granule (MCC) was slightly large, indicating its inconsistent granule growth. However, the yields of the granules were similar with high recovery.

The flowability of the products was evaluated using the orange color. However, differences in size were noted.

Table 5. Drug Content of Each Size Fraction of the Granule (α-Mannitol)

| Particle size fraction (μm) | Frequency (%) | Content (%) |
|-----------------------------|---------------|-------------|
| 2000–2360                   | 19.2±7.7      | 98.0±11.3   |
| 1700–2000                   | 18.9±8.5      | 98.2±11.2   |
| 1400–1700                   | 20.6±3.5      | 100.0±3.8   |
| 1000–1400                   | 23.9±3.4      | 90.8±10.8   |
| 710–1000                    | 11.2±8.7      | 87.5±5.9    |
| < 710                       | 6.2±8.7       | n.d.        |

Values represent the mean ± S.D. of three preparations. n.d.; this could not be determined as the sample amounts were too small to assay the API content.
Hausner ratio listed in Table 3.

All granules showed good flowability against the sodium dantrolene powder. However, there was no significant difference among the granules. Overall, the granule formulations were well prepared from the capsule content by the present granulation method and demonstrated good flowability.

**Drug Content of Each Size Fraction** An important quality of granules is the consistency in the drug content of each size fraction. We examined the fractional drug content after separation by size using a series of standard sieves. The drug contents of each size fraction, with frequency, are summarized in Tables 4–6.

In Table 4, the drug content of the largest fraction (1700–2360 µm) was 85.5%, despite the high frequency of 18.9%. In Table 5, the drug content of the lower fractions, 710–1000 µm, showed a low value of 87.5%. These results indicate that granules (L/S) and granules (D-mannitol) were low uniformity for clinical use. In the agitation granulation, fractional drug content does not tend to be uniform. However, in Table 6, the granule (MCC) showed good consistency in the fractional drug content (95–105%) and sufficient for clinical use. This was because MCC led to rapid agglomeration before the segregation of excipients.

**Disintegration Test** In clinical settings, the formulation is suspended in water before being administered through a nasogastric tube. It is necessary to disintegrate it over a short time. Therefore, we investigated the disintegration of granules in water. The time required for complete disintegration is listed in Table 7.

The granules (MCC) spent a significantly shorter time than the other formulations. In general, MCC works as a disintegration agent due to its highly hygroscopic nature. Thus, granules (MCC) was recognized to be superior to granules (L/S) and granules (D-mannitol) for disintegration.

**Dissolution Behavior** The drug dissolution behaviors from the granules and powder were investigated for bioequivalence. Figure 2 shows the dissolution profiles of sodium dantrolene from the formulation.

During the first 15 min, all granules disintegrated and released almost 100% of the dissolved drug. Such finding indicated that the granules would be bioequivalent to the powder used in the present study.

**Usability on Dispensing** Based on the above results, we decided that the granules (MCC) were appropriate formulations for clinical use and sought to compare the granules (MCC) to the powder.

The usability upon dispensing was evaluated using weight loss in the dispensing process and variation of the amount of medicine retrieved from the unit-dose package. The results are presented in Table 8.

The weight loss (%) of granules (MCC) was significantly lower than that of the powder. CV% showed a low value in both formulations. In general, weight loss was caused by dispersion and adherence to the dividing and packing machine. Such finding indicates that granules (MCC) were hard to scatter and adhere to the apparatus during the dispensing process.

**Usability on Dosing** The usability upon dosing was evaluated using weight loss in the dosing process and variation in the amount of medicine retrieved from the unit-dose package (Table 9).

The weight loss (%) of granules (MCC) was significantly lower than that of the powder. Further, the CV% of the dosing amount showed a similar value in both formulations. The powder tended to adhere to the package. However, the gran-
The findings of this study shed light on methods that can be used to obtain an alternative formulation to powders or liquids for pediatric patients. In powders, issues of cross-contamination and weight loss are unavoidable while in solutions or syrups, drug stability and bacterial contamination are major hurdles for long drug-taking intervals.10 Conversely, granules could resolve those issues relatively with ease. The granules are also superior to the formulations owing to their usability for dispensing and dosing. Furthermore, high patient acceptability was recognized for multiparticulates such as small pellets and beads.13 Thus, the granules were recommended when the powders and liquids were inappropriate for extemporaneous prepartations.

Previously, granules were prepared as hospital formulations.10 However, this is rarely performed in pharmacies as the granulation method is time-consuming and labor intensive. The present methodology is different from ordinary granulation methods. First, less than 5 h, including a long procedure, was required to obtain the final products. Using this preparation method, pharmacists who accept the doctor’s receipt could prepare granules on demand on the same day.

This study had several limitations. First, sodium dantrolene was the only model medicine. However, three excipients such as L/S, -mannitol, and MCC, were employed as fillers to prepare granules with good properties in this study. Overall, MCC was found to be effective for achieving product consistency in the drug content (Table 6) and rapid disintegration of the granules (Table 7). Therefore, many attempts at granulation can be carried out by selecting adequate excipients for the candidate medicine. Nevertheless, there remains some discussions regarding its use for moisture-sensitive drugs or high drug loading. Generally, during formulation development, each drug substance poses a unique challenge that must be considered at the process selection stage by formulation development scientists.

In conclusion, the present methodology will allow pharmacists to select granule formulation as an extemporaneous preparation for pediatric patients who are unable to swallow capsules.

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Conflict of Interest The authors declare no conflict of interest.

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