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RESEARCH PAPER

Further Observation of Content Uniformity of d-α-Tocopheryl Acetate as an Oily Drug in Granules Obtained by Wet Granulation with a High-Shear Mixer

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ABSTRACT

Using d-α-tocopheryl acetate (VE) as a model drug, we investigated the effects of the amount of binder solution on content uniformity of oily drugs in granules obtained by wet granulation with a high-shear mixer. When the amount of binder solution was below the water volume for the plastic limit, the content of VE was less than 50% in the fractionated fine granules, but was more than 200% in the fractionated large granules. Large variations were seen in the contents of VE even if the granulation time was extended up to 30 min. This large variation was not decreased by the milling process. On the other hand, when the amount of binder solution was at or above the water volume for the plastic limit, less variation was observed in the content of VE throughout the granules, and the content of VE was fairly uniform. Nuclei rich in VE were formed when VE was adsorbed with the powder before granulation. When the amount of binder solution was below the water volume for the plastic limit, the shearing force of mixer blades to the granules was low, so that the nuclei rich in VE were not fragmented. This led to the nonuniformity of VE content throughout the granules. On the other hand, when amount of binder solution was at or above the water volume for the plastic limit, the shearing force of mixer blades against the granules increased and

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became sufficient to fragment the nuclei. This led to the uniformity of VE content throughout the granules. This study showed that content uniformity of VE in the granules can be achieved by controlling the physical shearing force of mixer blades by regulating the amount of binder solution.
Key Words: *Content uniformity; Granulation; Oily drug; d = α =Tocopheryl acetate*

INTRODUCTION

In pharmaceutical preparations, uniformity of drug content is very important to ensure the therapeutic effect and to minimize side effects. To ensure the content uniformity of a finished batch of tablets or capsules, it is necessary to validate content uniformity of intermediate products such as powder mixes or granules prior to capsule filling or tableting operations.

Many investigators (1–4) have studied the content uniformity of drug-excipient blends, especially in the case of low drug doses, and it has been shown statistically or experimentally that nonuniformity of drug could not be resolved by mixing and that larger drug particles had to be reduced in size before attempting to make a homogeneous blend. However, these studies only dealt with cases of mixing of drug particles with excipient.

In pharmaceutical manufacturing, the wet granulation process is often preferred to enhance flowability, to increase compressibility, to alter physical appearance, and to ensure drug content uniformity. However, there have been few studies of drug content uniformity with granulation even in the cases of solid drug particles (5–7). Especially, there have been no previous studies in the case of oily drugs.

In this study, using d-α-tocopheryl acetate as a model drug, we investigated the effects of amount of binder solution on the content uniformity of an oily drug in granules obtained by wet granulation with a high-shear mixer.

EXPERIMENTAL

Materials

d-α-Tocopheryl acetate (VE; 99.8% purity, Tama Biochemical Co., Ltd., Japan) was chosen as a model oily drug. Light anhydrous silicic acid (Aerosil 200; Nippon Aerosil Co., Ltd., Japan) was used as an adsorbent for VE; α-lactose (Pharmatose 200 mesh; DMV, The Netherlands) was used as a diluent; cornstarch (Nihon Shokuhin Kakou Co., Ltd., Japan) and low substituted hydroxypropylcellulose (L-HPC LH-31; Sinetsu-Kagaku Co., Ltd., Japan) were used as disintegrators. Hydroxypropylcellulose with an average molecular weight of 105,000 (HPC-L; Nippon Soda Co., Ltd., Japan) was used as a binder. Tocopherol nicotinate, which was used as an internal standard for VE, was synthesized at Eisai Kawashima Factory (Eisai Co., Ltd., Japan). All other chemicals were analytical grade.

Granulation

Light anhydrous silicic acid (56 g) and low substituted hydroxypropylcellulose (189 g) were mixed in a high-shear mixer (SMV-20, Kawata Mfg. Co., Ltd., Japan) for 3 min with the mixing blades at 750 rpm. The powder was mixed for 5 min under the same conditions after adding 70 g of VE warmed at 70°C and then mixed again for 3 min after addition of α-lactose (1050 g), cornstarch (104 g), and hydroxypropylcellulose (21 g). The mixture was kneaded for 10 min under the same conditions after addition of purified water as a binder solution, and the wet granules (approximately 50 g) were sampled every 2 min. When the mixture was kneaded for 30 min, the wet granules were sampled every 10 min. During kneading, amperes used by the mixer motor were monitored and multiplied by voltage (200 V) to calculate the power consumption of the mixer motor. The granules thus obtained were spread and dried in a tray dryer at 50°C for 12 h and then fractionated with sieves to determine both mean diameters of the granules and distribution of VE. After drying, the granules obtained after 10 min of kneading were milled using a screening mill (Power Mill, Showa Kagaku Kikai Kosakusho Co., Ltd., Japan) with a 14-mesh screen.

Particle Size Distribution

Diameters of the granules were measured by the sieving method. Mean diameters D_{50} were calculated with the Rosin-Rammler chart.

Determination of Water Volume for Plastic Limit

Samples of 10 g of the powder before kneading but containing VE were weighed on a glass plate and kneaded with a stainless steel spatula after stepwise addition of purified water. The point at which the powder resulted in a larger agglomerate mass was termed the *plastic limit* (8), and the volume of water at that point was termed the *water volume for plastic limit*.

Determination of d-α-Tocopheryl Acetate Content in Granules

Contents of VE in the granules were determined using high-performance liquid chromatography. Each type of granule fractionated with sieves was milled gently using an agate mortar. Samples of approximately 50 mg of the milled granules were accurately weighed and transferred to 50-ml glass centrifugal tubes. After addition of 20 ml of ethanol to the tubes, they were sonicated for 10 min (Tokyo Chouonpa Co., Ltd., Japan). Five ml of ethanol containing tocopherol nicotinate as an internal standard were added to each tube; the tubes were then inverted and centrifuged at 3000 rpm for 5 min. The supernatant solution was subjected to high- performance liquid chromatography with an LC-6A apparatus (Shimadzu Co., Japan), and both VE and tocopherol nicotinate were detected using a spectrophotometer at 240 nm. The column used was a Nucleosil 100 C18 (4.6 mm ID × 150 mm l, GL Sciences, Inc., Japan). The mobile phase was methanol, and the flow rate was 1.0 ml/min.

RESULTS AND DISCUSSION

Effects of Amount of Binder Solution on Granulation

Figure 1 shows granulation curves. Binder solution was purified water, and amount of binder solution was 500, 525, 550, 575, or 600 ml. In the case of wet granulation with a high-shear mixer, a greater amount of binder solution is associated with faster particle size increase (9). The effect of amount of binder solution on granule growth can be explained by the effect on the degree of liquid saturation of the granules during the granulation process (10). The water volume for plastic limit determined in this study is closely related to liquid saturation. We estimated the effects of amount of binder solution on granule growth from the viewpoint of water volume for plastic limit. The water volume for plastic limit with the formulation in this study was 3.79 ± 0.18 ml/10 g (mean ± SD, $n = 5$), and this was equal to 565 ml for the mass of 1470 g of the formulation.

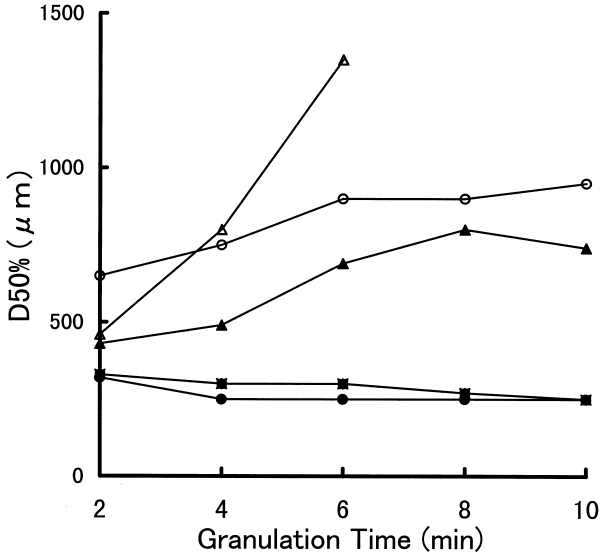

Figure 1. Granulation curves. Binder solution was purified water, and amount of binder solution was ■, 500 ml; ●, 525 ml; ▲, 550 ml; ○, 575 ml; or △, 600 ml.

In the case of both 500 ml and 525 ml of binder solution, both of which were below the water volume for plastic limit, particle size increased little with granulation time. In the case of both 550 ml and 575 ml, nearly equal to the water volume for plastic limit, particle size increased gradually. At 600 ml, which was above this volume, particle size increased rapidly. The granulation curves could be classified into three typical patterns in relation to the water volume for plastic limit and the granule growth.

Changes of d-α-Tocopheryl Acetate Distribution in Different Size Fractions of Granules in the Process of Granulation

With each typical pattern of the granulation curve, the change of VE distribution in different size fractions of the granules was determined during the process of granulation.

Figure 2 shows the distribution curves of VE with 525 ml of binder solution, which was below the water volume for plastic limit. Fig. 2A shows contents of VE in different size fractions of granules with granulation times from 2 min to 10 min. Regardless of the granulation time, the content of VE was more than 200% in the large granules (above 50-mesh sieve fraction). In contrast, the content of VE was less than 50% in the fine granules (below 83-mesh sieve fraction). The distribution curves of VE show antisigmoidal patterns. Even if the granulation time was extended to 30 min, these patterns did not change (Fig. 2B).

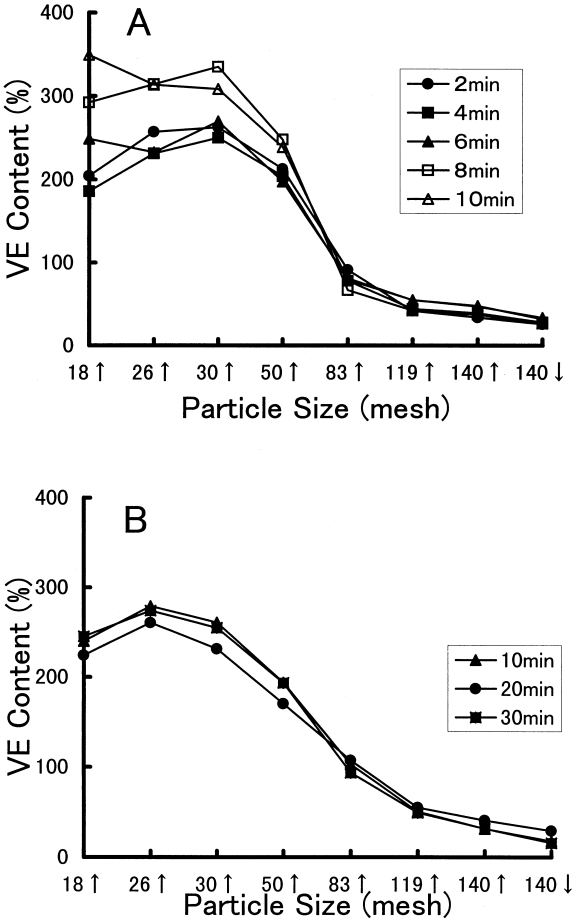

Figure 2. Distribution curves of VE with 525 ml binder solution. Fig. 2A shows the contents of VE with granulation times from 2 min to 10 min. Fig. 2B shows those when granulation time was extended to 30 min. The apertures of 18-, 26-, 30-, 50-, 83-, 119-, and 140-mesh sieves were 850, 600, 500, 300, 180, 125, and 106 μm, respectively. Numbers on the abscissa with either an upward or downward arrow indicate the fraction of granules on the numbered sieve or the fraction under the numbered sieve, respectively.

Figure 3 shows the distribution curves of VE with 575 ml of binder solution, which was nearly equal to the water volume for plastic limit. Similar to the case with 525 ml of binder solution, the distribution curves of VE were antisigmoidal. However, the variations in the content of VE with 575 ml of binder solution were further reduced compared to those with 525 ml. At 2 min of granulation, the content of VE in the 26-mesh sieve fraction was about 180%. However, longer granulation was associated with less variation in the content of VE throughout the granules. After 6 min of granulation, the content of VE was fairly uniform throughout the granules.

Figure 4 shows the distribution curves of VE with 600 ml of binder solution, which was above the water volume for plastic limit. The content of VE was fairly uniform throughout the granules.

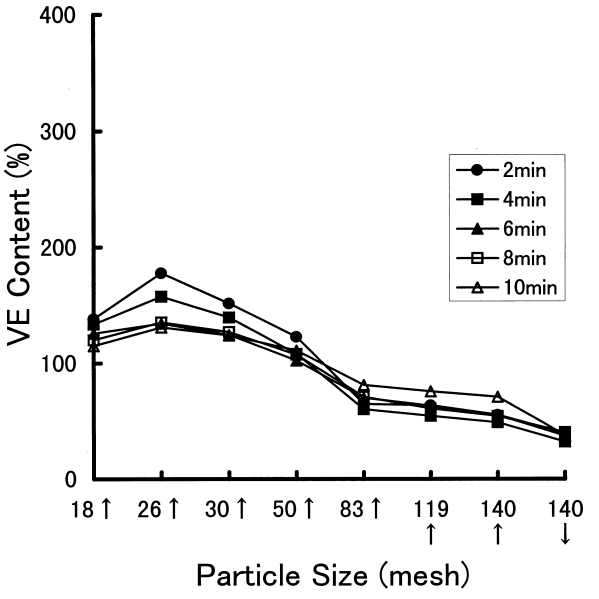

Figure 3. Distribution curves of VE with 575 ml binder solution. The numbers on the abscissa are the same as those in Fig. 2.

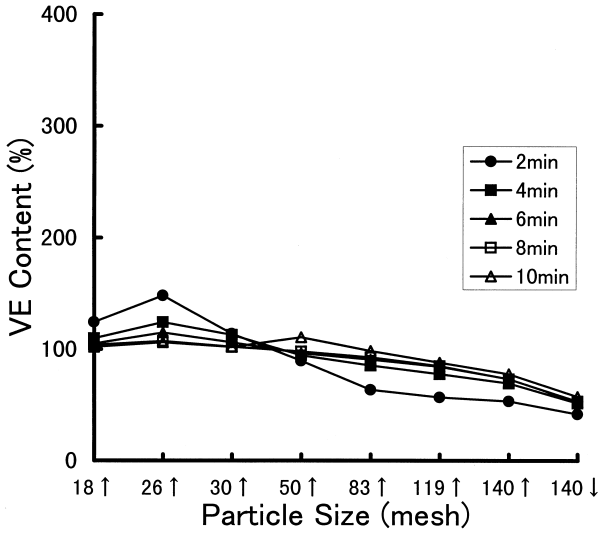

Figure 4. Distribution curves of VE with 600 ml binder solution. The numbers on the abscissa are the same as those in Fig. 2.

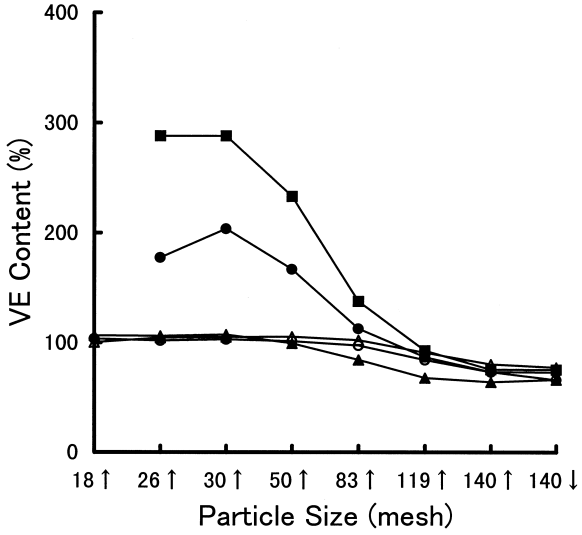

Figure 5. Distribution of VE in different size fractions of milled granules. Amount of binder solution was ■, 500 ml; ●, 525 ml; ▲, 550 ml; ○, 575 ml; or △, 600 ml. When the amount of the binder solution was either 500 or 525 ml, few granules were presented on the 18-mesh sieve. The numbers on the abscissa are the same as those in Fig. 2.

Selkirk (5) reported that content of borax, a water-soluble drug, decreased to about 80% in fine granules and increased to about 110% in large granules when a planetary mixer was used to prepare granules of 2% borax in lactose, and that the variation in borax concentration throughout the granule batch increased with amount of binder solution. Nishimura and Yui (6,7) studied the effects of binder solution on the distribution of components in different size fractions of granules using both yellow No. 5, a water-soluble dye powder, and its aluminum lake, a water-insoluble dye powder, and reported similar results as those described by Selkirk. They suggested that solvent migration could account for the reported results.

In the case of VE, an oily drug, marked variation in the content of VE was indicated when the amount of binder solution was below the water volume for plastic limit and when particle size increased little. The content of VE was low in the fine granules, but was high in the large granules. This was similar to the hydrophilic or hydrophobic powder components reported previously (5–7), but the variation in the content of VE (from 50% to 300%) was greater than that (from 80% to 110%) reported in the hydrophilic or hydrophobic powder components.

VE contents showed marked variation. In addition, in contrast to the hydrophilic or hydrophobic powder components, when amount of binder solution was increased to or above the water volume for plastic limit, the variation in the content of VE throughout the granules decreased with granulation time, and the content of VE became fairly uniform. These findings indicated that we are able to achieve content uniformity of VE in the granules by regulating amount of binder solution, and that the discrepancies between VE and the hydrophilic or hydrophobic powder components might be due to differences in the mechanisms of distribution in the granules.

d-α-Tocopheryl Acetate Distribution in Different Size Fractions of Milled Granules

In pharmaceutical manufacturing, granules prepared by wet granulation are often milled after drying to break particles or agglomerates into smaller pieces prior to capsule filling or tableting operations. We studied the effects of the milling process on the content uniformity of VE in granules. Fig. 5 shows the distribution of VE in different size fractions of the milled granules. D_{50} values of the milled granules prepared with 500, 525, 550, 575, or 600 ml of binder solution were 150, 180, 430, 540,

and 550 μm, respectively. When amount of binder solution was at or above the water volume for plastic limit (above 550 ml), the content of VE throughout the milled granules was fairly uniform. However, in the cases of both 500 and 525 ml of binder solution, the marked variation in the content of VE seen before milling (data shown in Fig. 2) was not decreased by the milling procedure. These observations indicated that, in the case of VE, an oily drug, it is necessary to produce granules with uniform VE content in the granulation process to ensure the content uniformity of VE in the granules.

d-α-Tocopheryl Acetate Distribution in the Powder Before Granulation

There are different phases during high-shear granulation: nucleation, fragmentation, densification, exponential growth due to coalescence, and break-up (9). Nucleation starts with one droplet of binder solution. At the moment a droplet reaches the moving powder bed in the mixer, a nucleus is formed. In the case of VE, an oily drug, it was assumed that, similar to the binder solution, nuclei rich in VE would be formed in the process of mixing with the powder.

Figure 6 shows the distribution of VE in different size fractions of the powder before granulation. The content of VE was above 600% in the large fractions (above 50-mesh sieve fraction) and was about 400% even in the 83-mesh sieve fraction. The weight percentage of the fraction below 140-mesh sieve comprised about 80% of the powder mass, but the content of VE in the fraction below 140-mesh sieve was only 40%. A very large degree of variation in the content of VE was seen in the powder before granulation. Nuclei rich in VE were formed in the process of mixing of VE with powder. These nuclei, which were rich in VE, would prevent uniform distribution of VE throughout the granules.

Effects of Amount of Binder Solution on Power Consumption by the Mixer Motor

To achieve content uniformity of VE throughout the granules, it is necessary for the VE-rich nuclei formed before granulation to be fragmented and for VE to be distributed uniformly throughout the granules so that the physical shearing force of the mixer blades on the granules is significant. Measurement of either power consumption or torque is often used to determine the granulation end point or to monitor the granulation process (11,12). Both power consumption by the mixer motor and torque are closely related to the shearing force of mixer blades on the granules. In this study, the amount of amperes caused by the mixer motor was monitored throughout granulation to estimate the shearing force of mixer blades on the granules. After addition of the binder solution, the ampere increased rapidly and remained constant throughout granulation. We calculated the power consumption of the

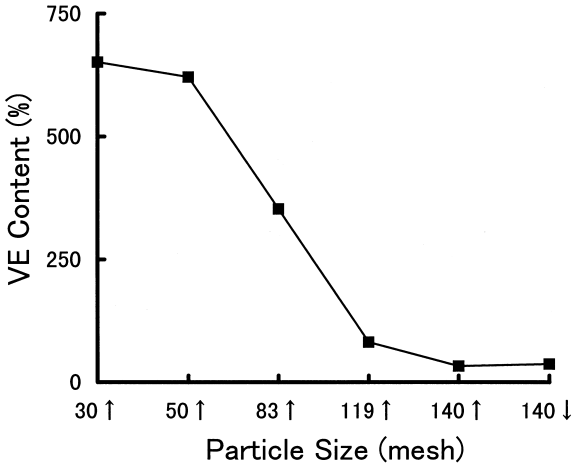

Figure 6. Distribution of VE in different size fractions of powder before granulation. The numbers on the abscissa are the same as those in Fig. 2.

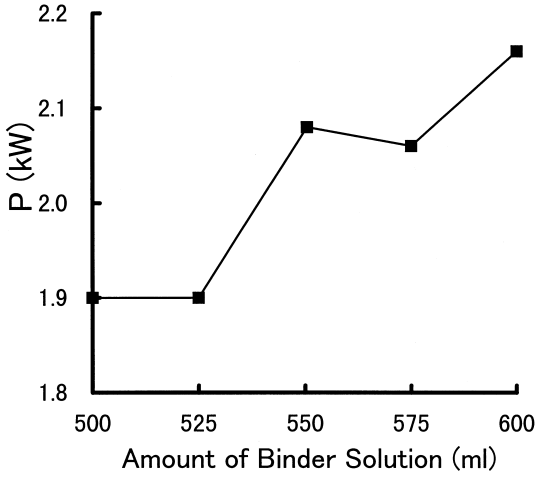

Figure 7. Relationship between power consumption and amount of binder solution.

mixer motor P (kW) with each amount of binder solution using the corresponding constant value.

Figure 7 shows the relationship between the power consumption by the mixer motor and amount of binder solution. The power consumption was 1.9 kW when the amount of binder solution was below the water volume for plastic limit. This was not sufficient to fragment the nuclei rich in VE, and this led to marked variation in the content of VE throughout the granules (Fig. 2). On the other hand, when the amount of binder solution was at or above the water volume for plastic limit, the power consumption increased to 2.1 kW or above. This was sufficient to fragment the VE-rich nuclei, and this led to the content uniformity of VE throughout the granules (Figs. 3, 4). This explained the marked variation in the content of VE when amount of binder solution was small and why the variation in content of VE decreased when amount of binder solution was increased to the water volume for plastic limit or above.

CONCLUSIONS

We showed that nuclei rich in VE were formed in the process of mixing of VE with the powder. When amount of binder solution was below the water volume for plastic limit, particle size increased little, and the shearing force of mixer blades on the granules was low. Under these conditions, the VE-rich nuclei were not fragmented, and there was marked variation in the content of VE throughout the granules. On the other hand, when amount of binder solution was at or above the water volume for plastic limit, particle size increased, and the shearing force of mixer blades on the granules increased. Shearing force became sufficient to fragment the VE-rich nuclei, and this led to content uniformity of VE throughout the granules.

This study showed that it is possible to achieve content uniformity of VE in granules by controlling the physical shearing force of mixer blades by regulating the amount of binder solution.

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