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Improvement of Content Uniformity of d-α-Tocopheryl Acetate as an Oily Drug in Granules by Emulsification

Yoshiteru Kato
Formulation Research Laboratories, Eisai Co., Ltd, Takehaya, Kakamigahara, Gifu, Japan

Masaki Takeno
Analytical Research Laboratories, Eisai Co., Ltd, Honjo, Saitama, Japan

ABSTRACT To elucidate the effects of an oily drug emulsification on its content uniformity in granules obtained by wet granulation with a high-shear mixer, d-α-tocopheryl acetate (VE) was emulsified with hydroxypropylcellulose (HPC-L) solution (mean diameter of the VE droplets was 1.3 μm). When VE was added to the mixing powder as the emulsion, nuclei rich in VE were not formed and then the content of VE was fairly uniform throughout the granules even at 2 min granulation. We found that the oily drug poor content uniformity could be improved significantly by adding an emulsified drug to the powder in granulation process.

KEYWORDS Oily drug, d-α-Tocopheryl acetate, Content uniformity, Emulsion, Wet granulation, High-shear mixer

INTRODUCTION

In pharmaceutical preparations, uniformity of drug content is very important to assure the therapeutic effect and to minimize the side effects. To assure 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 tabletting operations. The wet granulation process is often preferred to enhance flowability, to increase compressibility, to alter physical appearance, and to assure drug content uniformity in pharmaceutical manufacturing.

Although granulation is intended to yield a homogeneous product, there are indications that this is certainly not always the case. In the case of solid drug particles, variation in drug content during high-shear granulation is reported (Selkirk, 1976; Warren et al., 1977; Vromans et al., 1999; Dries & Vromans, 2002; Loggia et al., 2002). However, there had been no previous studies about content uniformity in the granules in the case of oily drugs prior to our works (Kato et al., 2001, 2004).

In previous papers, we reported that nuclei rich in oily drug were formed in the process of mixing oily drug with powder using d-α-tocopheryl acetate (VE) as a model oily drug. These nuclei rich in VE prevented uniform distribution of VE throughout granules and marked variation in the content of VE, poor content uniformity was indicated in comparison with solid drugs. By regulating the amount of binder solution, it was possible to achieve content uniformity of VE in granules

Address correspondence to Yoshiteru Kato, Formulation Research Laboratories, Eisai Co., Ltd., Takehaya, Kakamigahara, Gifu 501-6195, Japan; E-mail: y3-kato@hhc.eisai.co.jp

(Kato et al., 2001). We also found that the extent of the drug poor content uniformity depended significantly on viscosity of the drug (Kato et al., 2004). When viscosity of the drug was high, the drug poor content uniformity in granules was large and was constant independent of a granulation time. On the other hand, when viscosity of the drug was low, the drug poor content uniformity was small with a short granulation time but became large with a prolonged granulation. According to a model for tensile strength of a granule under dynamic conditions, these phenomena could be explained by the tensile strength of nuclei attributed to the viscosity of the oily drug.

From our previous studies, prevention of nuclei formation or fragmentation of the nuclei during granulation might be necessary to achieve content uniformity for oily drugs. It was expected that when an oily drug is added to the powder as the fine droplets by emulsification, the formation of nuclei during granulation would be avoided and that it would be possible to achieve content uniformity in granule. The purpose of the present work was to elucidate effects of size reduction of an oily drug by emulsification on its content uniformity during granulation.

MATERIALS AND METHODS

Materials

d-α-Tocopheryl acetate (VE; 99.8% purity, Tama Biochemical Co., Ltd., Tokyo, Japan) was chosen as an oily drug. Colloidal silicon dioxide, anhydrous (Aerosil 200; Nippon Aerosil Co., Ltd., Yokkaichi, Japan) was used not only as a stabilizer for emulsion but also an adsorbent for the oily drug. α-Lactose (Pharmatose 200mesh; DMV, Veghel, The Netherlands) was used as a diluent; corn starch (Nihon Shokuhin Kakou Co., Ltd., Tokyo, Japan) and low substituted hydroxypropylcellulose (L-HPC LH-31; Sinetsu-Kagaku Co. Ltd., Tokyo, Japan) were used as a disintegrator. Hydroxypropylcellulose (HPC-L) with an average molecular weight of 105,000 (HPC-L; Nippon Soda Co., Ltd., Tokyo, Japan) was used as not only a binder but also an emulsifier. Di-n-octyl-phthalate (Wako Pure Chemical Industries, Ltd., Osaka, Japan) was used as an internal standard for VE. All other chemicals were analytical grade.

Preparation of VE Emulsion

d-α-Tocopheryl acetate (VE) emulsion was prepared according to a direct emulsification process by an application of a homogenizer (Robomics, Tokushu Kika Kogyo Co., Ltd., Tokyo, Japan). Hydroxypropylcellulose (HPC-L; 21g) was dissolved in 500 mL of purified water. d-α-Tocopheryl acetate (VE) (70g) and colloidal silicon dioxide, anhydrous (5g) were added to the solution and homogenized with the homogenizer for 20 min at 9000 rpm and the VE emulsion was obtained.

Granulation

The high-shear mixer (SMV-20; Kawata Mfg. CO., Ltd., Osaka, Japan) described in a previous paper (Kato et al., 2001), was employed in the experiment. The temperature of the mixer heating jacket was set to 40°C in the experiment. Colloidal silicon dioxide, anhydrous (51 g), low substituted HPC-L (189 g), α-lactose (1050 g), and corn starch (104 g) were mixed in the mixer for 3 min at a blades speed of 750 rpm. The mixture was kneaded for 10 min under the same conditions after addition of the VE emulsion as binder solution containing the drug, and the wet granules (approximately 50 g) were sampled every 2 min. During the 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 distribution of VE in the granules.

Determination of VE Droplet Size Distributions in Emulsion

d-α-Tocopheryl acetate (VE) droplet size distributions in the emulsion were observed with an optical microscope and mean diameter of the fine droplets was determined by a laser light scattering technique (N4 PLUS Submicron Particle Size Analyzer, Beckman Coulter, Krefeld, Germany). The angle and temperature of the determination conditions were 90 degrees and 20°C, respectively.

Determination of VE Content in Granules

Contents of VE in the granules were determined using high performance liquid chromatography

(HPLC). Each type of granule fractionated with sieves was milled gently using an agate mortar. Approximately 210 mg of the milled granules were accurately weighed and transferred to 50 mL glass volumetric flasks. After addition of 40 mL of ethanol to the flasks, samples were sonicated for 10 min (Tokyo Chouonpa Co., Ltd., Tokyo, Japan), adjusted to 50 mL by ethanol after cooling at room temperature, and then centrifuged at 3,500 rpm for 5 min. Two mL of ethanol containing di-n-octyl-phthalate as an internal standard were added to each accurate 10 mL of the supernatant and mixed. The mixed solution was analyzed by HPLC with an LC-10A apparatus (Shimadzu Co., Kyoto, Japan) and both VE and di-n-octyl-phthalate were detected using a spectrophotometer at 280 nm. The column used was a YMC ODS-A312 (6 mm i.d. × 150 mm l., 5 μm, YMC Inc., Kyoto, Japan). The mobile phase was methanol and the flow rate was 1.5 mL/min. d-α-Tocopheryl acetate (VE) content in the granule was shown as a relative percentage against the theoretical VE concentration.

RESULTS AND DISCUSSION

VE Droplet Size Distributions in Emulsion

To clearly elucidate the effects of an oily drug emulsification on the content uniformity in granules with a high shear-mixer, the amount of purified water for preparation of the emulsion was fixed to 500 mL, which was below the water volume for the plastic limit (Toyoshima et al., 1971) for the formulation used in this study. d-α-Tocopheryl acetate (VE) emulsion was prepared by the application of the homogenizer and the VE droplet size distributions in the emulsion were observed by using an optical microscope. Figure 1 shows the representative optical photomicrograph with the emulsion at ×200 magnifications. Each scale in the photomicrograph shows 6 μm length. As shown in Fig. 1, VE was well-dispersed in the binder solution as fine droplets of which diameters were below 6 μm but there were some large droplets (diameters of the droplets were about 30 μm). The mean diameter of the VE droplets in the emulsion determined by using the Submicron Particle Size Analyzer was 1.3 μm. The low droplet size and the standard deviation were 0.19 μm and 0.62 μm, respectively. The high droplet size was over the determination range (more over 3 μm).

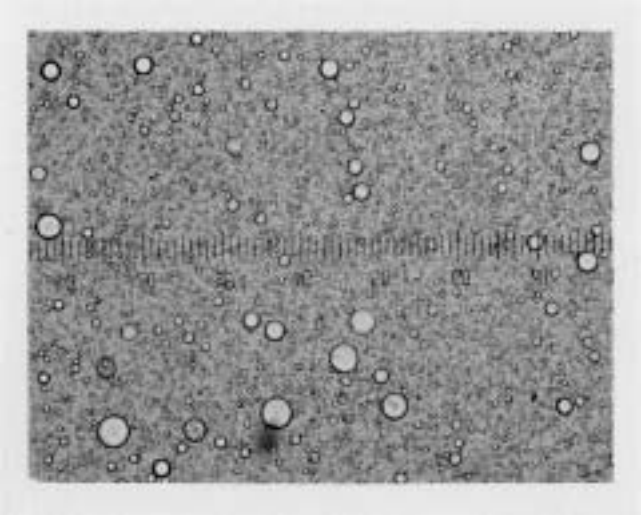

FIGURE 1 Photograph of an Optical Microscope of the VE Emulsion (×200). Each Scale in the Photograph Shows 6 μm.

These were similar to the results from the observation with Fig. 1. Hydroxypropylcellulose (HPC-L) was not only a binder but also an emulsifier and it was confirmed that VE was emulsifiable with HPC-L aqueous solution and was dispersed as fine droplets in the binder solution.

VE Distribution in Different Size Fractions of Granules in the Process of Granulation

Figure 2-A shows distribution curves of VE with granulation time from 2 min to 10 min when the emulsified VE was added to the powder. Figure 2-B shows distribution curves of VE when non-emulsified VE was added to the powder as a comparison [the data were already reported previously (Kato et al., 2004)]. When the emulsified VE was added, the content of VE was fairly uniform throughout the granules regardless of the granulation time from 2 min to 10 min. On the contrary, when the non-emulsified VE was added, the content of VE was more than 200% in large granules (above 50-mesh sieve fractions) and less than 60% in fine granules (below 119-mesh sieve fractions). The contents showed marked variations, "poor content uniformity".

Figure 3 shows particle size distribution curves with granulation time from 2 min to 10 min when the emulsified VE (Fig. 3A) or non-emulsified VE (Fig. 3B) was added to the powder. The particle size distributions

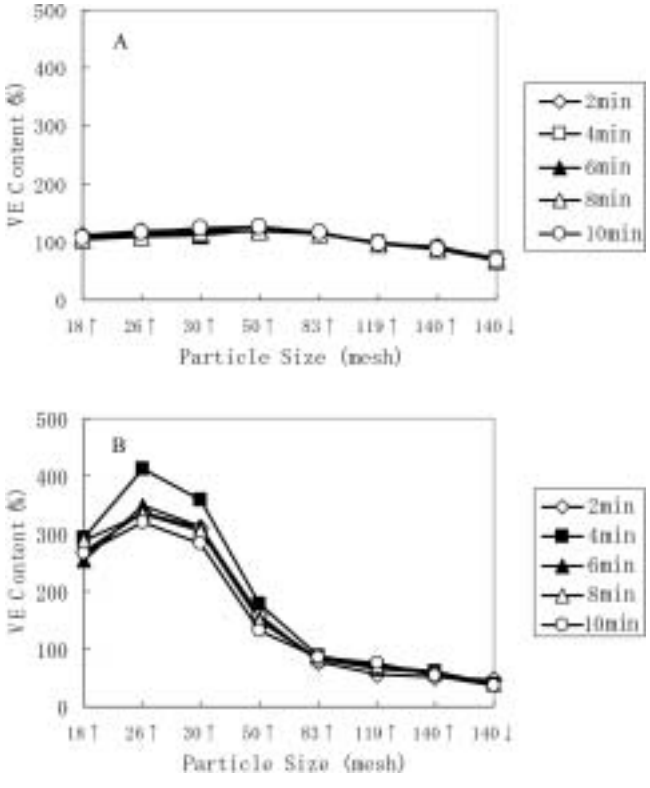

FIGURE 2 **Distribution Curves of VE when Emulsified (A) or Non-emulsified VE (B) Was Used. The Apertures of 18, 26, 30, 50, 83, 119, and 140 Mesh Sieves Were 850, 600, 500, 300, 180, 125, and 106 μm, Respectively. Numbers on the Abscissa with Either an Upward or Downward Arrow Indicate the Fraction of Granules on the Numbered Sieve or the Fraction Under the Numbered Sieve, Respectively.**

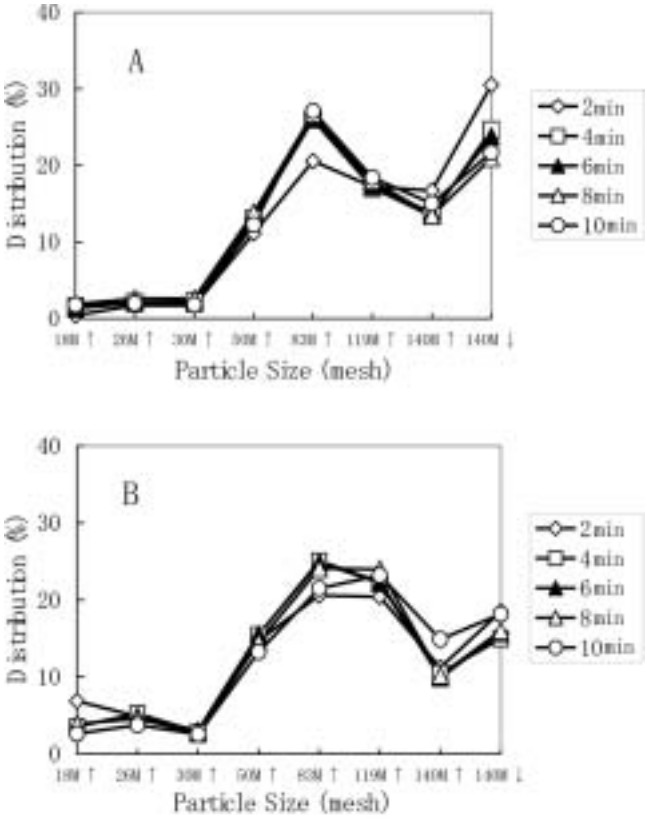

FIGURE 3 **Particle Size Distribution when Emulsified (A) or Non-emulsified (B) Was Used. The Apertures of 18, 26, 30, 50, 83, 119, and 140 Mesh Sieves Were 850, 600, 500, 300, 180, 125, and 106 μm, Respectively. Numbers on the Abscissa with Either an Upward or Downward Arrow Indicate the Fraction of Granules on the Numbered Sieve or the Fraction Under the Numbered Sieve, Respectively.**

were similar to each other and did not change during the granulation periods. The percentage of the powder below 119-mesh sieve fraction was about 35% and then the poor content uniformity shown in Fig. 2B was significant.

The shearing force of mixer blades on granules is a very important factor for content uniformity of an oily drug (Kato et al., 2001) and power consumption by the mixer motor is closely related to the shearing force. When the emulsified VE was added, the amperage from the mixer motor during granulation was from 9.2 to 9.7 A, from which power consumption during the granulation was calculated as 1.8 to 1.9 kW and was equal to that when the non-emulsified VE was added (Kato et al., 2004). The shearing forces of mixer blades on granules were almost the same whether VE was emulsified or not emulsified. In the case of VE, nuclei rich in VE were formed in the process of mixing with the powder and the nuclei prevented uniform distribution of VE throughout the granules (Kato et al., 2001). The improvement of content uniformity when the emulsified VE was added was not led to by any changes in shearing force of the mixer blades but by the size reduction of VE by the emulsification. VE was emulsified using the homogenizer and then before the granulation VE had become fine droplets of which mean diameter was 1.3 μm. In this study, it became clear that when the emulsified VE was added to the powder, nuclei rich in VE might not be formed in the granulation process and that VE was distributed uniformly so that the content of VE was fairly uniform throughout the granules even at 2 min granulation.

The ΔVE content shown in Fig. 4 is the extent of poor content uniformity of VE and is calculated to evaluate the poor content uniformity process of VE in granules.

$$\Delta\text{VE content} = C_{max} - C_{min} \quad (1)$$

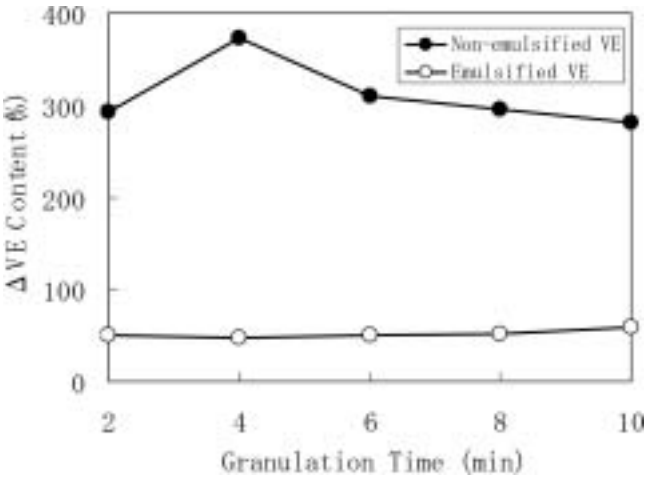

FIGURE 4 **Extent of Demixing Process when Emulsified or Non-emulsified VE Was Used.**

where Cmax and Cmin are the highest and lowest content, respectively, of VE in different size fractions of the granules at each granulation time in Fig. 2. When the emulsified VE was added to the powder, ΔVE content was much smaller than that when non-emulsified VE was added and was constant independent of the granulation time.

There had been two ways to improve VE content uniformity in granules. One was to regulate the amount of binder solution more than water volume for the plastic limit so that the physical shearing force of the mixer blades on the granules was sufficient to fragment the nuclei (Kato et al., 2001). Another was to decrease drug viscosity because tensile strength of the nuclei is closely related to the drug viscosity (Kato et al., 2004). In addition, this study showed that it was possible to achieve content of VE in granules fairly uniform when VE was added to the powder as the fine droplets by emulsification.

CONCLUSION

In the process of mixing an oily drug with powder, nuclei rich in the oily drug are formed. These nuclei prevent uniform distribution of the oily drug throughout granules and marked variation in the content of the drug is indicated in comparison with solid drugs.

d-α-Tocopheryl acetate (VE) was emulsified with HPC-L solution and the mean diameter of the VE droplets in the emulsion was 1.3 μm. When VE was added to the mixing powder as the emulsion, nuclei rich in VE were not formed and then the content of VE was fairly uniform throughout the granules. In this study, we found that in the case of an oily drug, the drug poor content uniformity could be improved significantly by adding an emulsified drug to the powder in granulation process.

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