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RESEARCH PAPER

Effects of Oily Drug Rheology on Content Uniformity in Granules Obtained by Wet Granulation with a High-Shear Mixer

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ABSTRACT

The purpose of the present work was to elucidate the effects of viscosity on the content uniformity of an oily drug in granules obtained by wet granulation with a high-shear mixer. For this purpose, we used d-α-tocopheryl acetate diluted with a medium chain fatty acid triglyceride having viscosities in the range from 26.0 to 726.0 mPas. It was found that independent of viscosity, nuclei rich in the oily drug were formed in the process of mixing with powder and that those nuclei prevented uniform distribution of the drug throughout the granules. To achieve content uniformity, it is necessary for the nuclei formed before granulation to be fragmented and for the oily drug to be distributed uniformly throughout granules. Tensile strength of the nuclei was attributed to the viscosity of the oily drug, according to a model for tensile strength of a granule under dynamic conditions. When viscosity of the oily drug increased, tensile strength of the nuclei increased and the extent of the drug demixing in granules was large and constant independent of granulation time. On the other hand, when viscosity of the oily drug decreased, tensile strength of the nuclei decreased. The extent of the drug demixing was small with lower viscosity but increased with a prolonged granulation time. In the case of the oily drug, we found that a decrease in its viscosity led to the improvement of the content uniformity in granules. The viscosity of the oily drug significantly affects its content uniformity in granules by a high-shear mixer granulation.

Key Words: Oily drug; d-α-tocopheryl acetate; Content uniformity; Demixing; Viscosity of oily drug; Tensile strength.

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INTRODUCTION

In pharmaceutical preparations, uniformity of drug content is very important to assure the therapeutic effect and to minimize 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.

The mechanisms of granulation with a high-shear mixer were reported that during high-shear granulation, there were different phases: nucleation, fragmentation, densification, exponential growth due to coalescence, and break-up.[1–3] The nucleation starts with one droplet of binder solution when the droplet reaches the moving powder bed. The agglomerate formation and growth depend on the distribution of the binder solution, which is facilitated by low viscosity. In the case of coalescence, the subsequent agglomerate formation and growth by coalescence is affected and promoted by a higher binder viscosity.[4,5] However, there have been few studies of drug content uniformity with the granulation. 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, the demixing of a drug during high-shear granulation is reported.[6–8] Selkirk[6] related solubility of the drug substance or diluent with intragranular drug migration during drying. He suggested that fluid and the solute were drawn to the surface of the granule as drying proceeds, which resulted in a solute-enriched granule. Recently, Dries and Vromans[9] related demixing of the drug substance with granule growth mechanisms. Inhomogeneity of the granule was attributed to a difference in primary particle size between drug substance and diluent. However, there had been no previous studies about content uniformity in the granules in the case of oily drugs, prior to our work.

In a previous paper, 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.[10] These VE-rich nuclei prevented uniform distribution of VE throughout granules, and marked variation in the content of VE 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. But the effect of oily drug viscosity on its content uniformity in granules has been open to question until now.

The purpose of the present work was to elucidate effects of oily drug viscosity on its content uniformity in granules obtained by wet granulation using a high-shear mixer.

MATERIALS AND METHODS

Materials

d-α-Tocopheryl acetate (VE; 99.8% purity, Tama Biochemical Co., Ltd., Japan) was chosen as a marker substance of oily drug. Medium chain fatty acid triglyceride (ODO; The Nisshin Oil Mills, Ltd., Japan) was used as a diluent of VE to vary the viscosity of VE. Light anhydrous silicic acid (Aerosil 200; Nippon Aerosil Co., Ltd., Japan) was used as an adsorbent for oily drug, α-lactose (Pharmatose 200 mesh; DMV, The Netherlands) was used as a diluent, and corn starch (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.

Determination of the Diluted VE Viscosity

The VE was diluted with ODO to the concentration of 25%, 50%, or 75% w/w of VE. The viscosities of the diluted or nondiluted VE were determined at 20, 30, 40, and 50°C by a rotation viscosimeter, Rheometer Rheostress RS150 (Haake, Germany), with a Cone-Plate sensor system and TC80 peltier temperature control system.

Granulation

The high-shear mixer (SMV-20; Kawata Mfg. Co., Ltd., Japan) described in a previous paper,[10] was employed in the experiments. The temperature of the heating jacket was set to 40°C in all the experiments. Light anhydrous silicic acid (56 g) and low substituted hydroxy-propylcellulose (189 g) were mixed in the mixer for 3 min at a blade speed of 750 rpm. The powder was mixed for 5 min under the same conditions

after adding 70 g each of the diluted or nondiluted VE warmed at 40°C and then mixed again for 3 min after addition of α-lactose (1050 g), corn starch (104 g), and hydroxypropylcellulose (21 g). The mixture was kneaded for 10 min under the same conditions after the addition of 500 mL of purified water as binder solution, 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 hr and then fractionated with sieves to determine distribution of VE in the granules.

Determination of VE 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 the addition of 20 mL of ethanol to the tubes, samples 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, which were then inverted and centrifuged at 3000 rpm for 5 min. The supernatant solution was analyzed by high performance liquid chromatography with an LC-10A 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 i.d. × 150 mm l., GL Sciences Inc., Japan). The mobile phase was methanol and the flow rate was 1.0 mL/min. The VE content in the granule was shown as a relative percentage against the theoretical VE concentration and was equal to the content of oily drug (mixture of VE and ODO) in granules.

RESULTS

Rheological Properties of Diluted VE with ODO

A well-known low viscous oil, ODO is well-miscible with VE. In this study, VE diluted with ODO to concentrations of 25%, 50%, 75%, and 100% (nondiluted) w/w were used to elucidate the effects of oily drug viscosity on the drug content uniformity in granules obtained by wet granulation with a high-shear mixer. Figure 1 shows the effect of temperature on viscosities of the diluted or nondiluted VE with ODO. The viscosities of the diluted or nondiluted VE decreased as temperature increased and correlation between temperature and logarithm of the viscosity was found to be linear. It was reported that temperature of granules increased during wet granulation with a high-shear mixer.[11,12] Therefore, it was necessary to control the temperature of granules during granulation to elucidate the effects of oily drug viscosity on the drug content uniformity in granules with a high-shear mixer. In this study, temperature of the high-shear mixer heating jacket was set at 40°C and was controlled during granulation in all experiments. The viscosity of 25%, 50%, 70% or 100% VE at 40°C was 26.0, 56.2, 184.0, or 726.0 mPas, respectively.

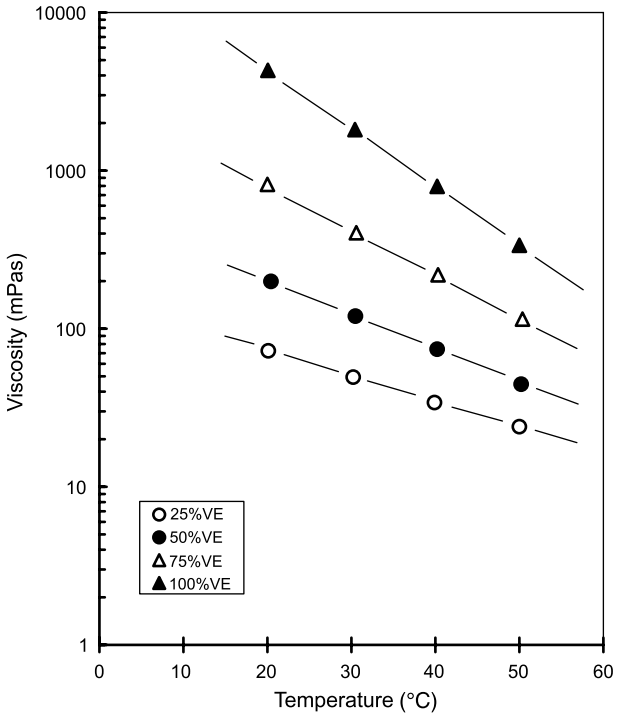

Figure 1. Relationship between temperature and viscosity of diluted VE with ODO.

Changes of Diluted or Nondiluted VE Distribution in Different Size Fractions of Granules in the Process of Granulation

Previously,[10] we reported that it was possible to achieve content uniformity of VE in granules by regulating the amount of binder solution and that the

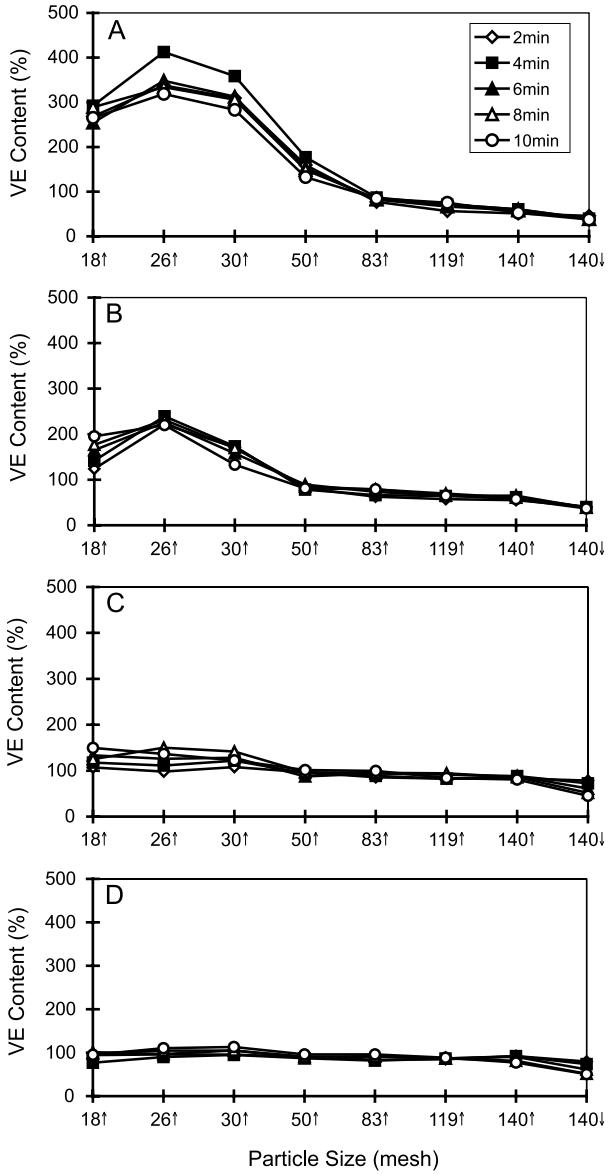

Figure 2. Distribution curves of 100% (A), 75% (B), 50% (C), and 25% (D) VE. The apertures of 18-, 26-, 30-, 50-, 83-, 119-, and 140-mesh sieves were 850, 600, 500, 300, 180, 125, and 106 μm, respectively. Numbers on the abscissa with either an upward or downward arrow indicate the fraction of granules on the numbered sieve or the fraction under the numbered sieve, respectively.

amount of binder solution was equal to or above water volume for the plastic limit. The water volume for the plastic limit is the point at which powder results in a larger agglomerate mass when the powder is kneaded with a stainless steel spatula with stepwise addition of purified water. The water volume is equal to 565 mL for the mass of 1470 kg for the formulation used in this study. To clearly elucidate the effects of oily drug viscosity on the content uniformity in granules with a high shear-mixer, the amount of binder solution was fixed to 500 mL, which was below the water volume for plastic limit. Figure 2 shows distribution curves of VE with granulation time from 2 min to 10 min. Figure 2A shows the contents of VE in different size fractions of granules when 100% VE was used. Regardless of the granulation time, the content of VE was more than 200% in large granules (above 50-mesh sieve fractions) and, on the contrary, less than 60% in fine granules (below 119-mesh sieve fractions). In the case of 100% VE, the contents showed marked variations, ''demixing,'' as reported previously.[10] However, these marked variations in VE content decreased and the content of VE became fairly uniform throughout the granules as concentration of VE decreased from 100% (Fig. 2A) to 25% (Fig. 2D). This improvement in VE content uniformity was attributed to the decrease in the drug viscosity from 726.0 mPas (100% VE) to 26.0 mPas (25% VE). Since VE is well-miscible with ODO, the content of VE in different size fractions of granules is equal to the content of the oily drug in granules. In this study, the viscosity of oily drug significantly affects the content uniformity in granules by a high-shear mixer.

Diluted or Nondiluted VE Distribution in Powder Before Granulation

In the case of VE, we showed that nuclei rich in VE were formed in the process of mixing VE with

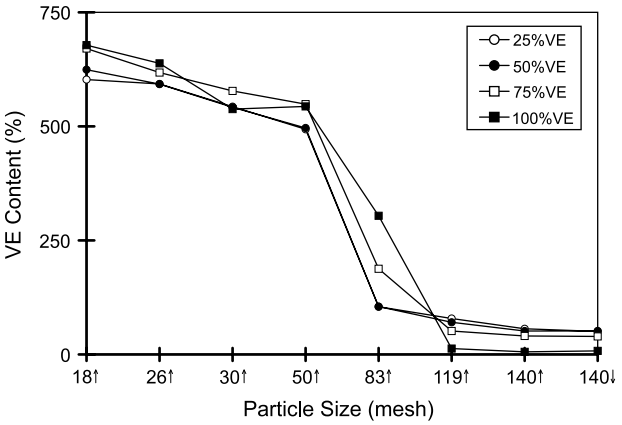

Figure 3. Distribution of diluted VE in different size fractions of powder before granulation. The numbers on the abscissa are the same as those in Fig. 2.

powder and that those nuclei prevented uniform distribution of VE throughout the granules.[10] To clarify the effect of oily drug viscosity on the distribution, the diluted or nondiluted VE distribution in powder before granulation was investigated, and the results are shown in Fig. 3. As the viscosity of the oily drug decreased from 726.0 mPas (100%) to 26.0 mPas (25%), VE contents in the fine fractions (below 119-mesh sieve fraction) increased gradually. However, independent of viscosity, nuclei rich in VE (above 500% VE content) were formed in the process of mixing VE with powder in all cases and prevented uniform distribution of VE throughout the granules.

DISCUSSION

Previously,[10] we reported that it was possible to achieve content uniformity of VE in granules by regulating the amount of binder solution. However, the effects of oily drug viscosity on content uniformity in granules were not clear. In this study, we evaluated the effects of drug viscosity on the content uniformity in granules obtained by wet granulation with high-shear mixing using VE diluted with ODO to obtain viscosities in the range from 26.0 to 726.0 mPas.

Recently, Dries and Vromans[9] related demixing of a solid drug substance with granule growth mechanism. They reported that during high-shear wet granulation, inhomogeneity of a granule was attributed to a difference in primary particle size between the drug substance (micronized estradiol) and the diluent (lactose). They also found that at prolonged granulation, demixing was observed. One important parameter influencing drug distribution in granules was wet granule strength, and a second was the primary particle size difference between the drug and the diluent. The reason why a large difference in primary particle size of estradiol and lactose stimulated demixing was that the smaller particles in a powder mixture were the first to form granules that were strong enough to resist forces in the process and that the largest granule particles would consist of the smallest primary particles (estradiol). As the granulation process proceeded, granule strength increased through densification of the granules. The granules were then strong enough to withstand forces in the high-shear mixer, which resulted in unexpected demixing with a prolonged granulation. Loggia et al.[13] also reported a similar unexpected demixing process with a prolonged granulation using polyethylene oxide as a drug substance and xylitol as a diluent.

However, in the case of an oily drug, we found that the decrease in viscosity of oily drug led to the improvement of content uniformity in granules as shown in Fig. 2, and that viscosity of oily drug significantly affected its content uniformity in granules produced by a high-shear mixer. We attempted to evaluate the relationship between these demixing processes of oily drugs in granules and viscosities of the oily drugs using ''ΔVE content'' in Fig. 4. The ΔVE content shows the extent of demixing of the oily drug and is calculated:

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

Where, C_{max} and C_{min} are the highest and lowest content, respectively, of VE in different size fractions of the granules at each granulation time in Fig. 2. As shown in Fig. 4, it was found that the demixing processes of oily drugs were remarkably affected by their viscosities and that two typical patterns in relation to the viscosity could be classified. That is to say, there was a critical viscosity value in the demixing process between 56.0 mPas and 184.0 mPas and that the lower the viscosity, the smaller the extent of demixing of the drug in granules. The most viscous sample (726.0 mPas, 100% VE) in this study showed the biggest ΔVE content, about 300%, and when viscosity was decreased to 184.0 mPas, (75% VE), the ΔVE content decreased to about 200%. In both cases, these ΔVE contents did not change throughout the granulation time. On the contrary, in the case of the least viscous sample (26.0 mPas, 25% VE), fairly uniform VE content in the granule (ΔVE content was 16%) was obtained with a short granulation

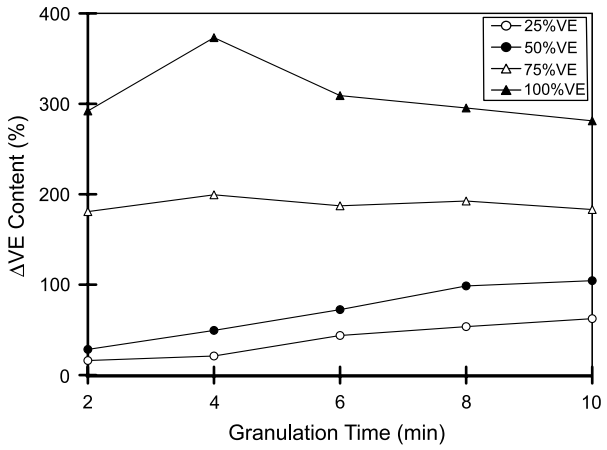

Figure 4. Relationship between demixing processes of diluted VE and the viscosities. ΔVE content was calculated by Eq. 1.

time (2 min). Additionally, the ΔVE content increased linearly with a prolonged granulation time and was 62% at 10 min. The long granulation time produced inhomogenous granules in VE content, which was unexpected. In the case of 56.2 mPas (50% VE), ΔVE contents were higher than those in the case of 26.0 mPas (25% VE) and also increased linearly with a prolonged granulation time. These unexpected increases in ΔVE content with prolonged granulation time were found when the viscosity of the drug was below the critical viscosity value.

There are different phases during high-shear granulation: nucleation, fragmentation, densification, coalescence, and break-up.[1–3] The nucleation starts with one droplet of binder solution. At the moment the droplet reaches the moving powder bed in a mixer, a nucleus is formed. We reported that in the case of VE, nuclei rich in VE were formed in the process of mixing with the powder, similar to the case of binder solution and that the nuclei prevented uniform distribution of VE throughout the granules.[10] In this study, it was clarified that independent of the drug viscosity, nuclei rich in oily drug were formed in the process of mixing with powder and that the nuclei prevented uniform distribution of the drug throughout granules (Fig. 3). To achieve content uniformity of the oily drug, it is necessary for the nuclei rich in drug formed before granulation to be fragmented and then distributed uniformly throughout granules. This will ensure that neither the shearing force of mixer blades on granules nor the tensile strength of the nuclei will significantly effect the drug distribution. Power consumption by the mixer motor is closely related to the shearing force of mixer blades on granules. In this study, the amperage from the mixer motor was monitored throughout granulation and the shearing force of mixer blades on granules was estimated. In all cases studied, the amperage from the mixer motor during granulation were from 9.2 to 9.7 A, from which power consumption during the granulation were calculated as 1.8 to 1.9 kW. The shearing forces of mixer blades on granules were almost the same for all experiments in this study, thus the extent of oily drug demixing shown in Figs. 2 and 4 were caused not by the differences in the shearing forces of mixer blades but by the differences in tensile strength of nuclei of oily drugs. Drier and Vromans[9] derived tensile strength of a granule under dynamic conditions (σv) from Rumpf's equation:[14]

$$\sigma v = 9/8 \times (1-\varepsilon)^2/\varepsilon^2 \times 9/16 \times \mu \times \nu/d \quad (2)$$

where ε, ν, d and μ=porosity, relative velocity of moving particles, surface mean diameter, and viscosity, respectively. This equation shows that tensile strength of a granule is proportional to the viscosity of a liquid and is inversely proportional to the mean diameter of granules. In the case of solid drug substance, Drier and Vromans[9] reported that tensile strength of the granule was attributed to the particle size and that demixing was observed. On the other hand, in the case of the oily drug, the strength of the VE-rich nuclei could also be represented by Eq. 2. When viscosity of the drug was high, the extent of the drug demixing in granules was large and constant independent of granulation time. On the other hand, when viscosity of the drug was low, the extent of drug demixing was small but increased with a prolonged granulation. In this study, tensile strength of the nuclei was attributed to viscosity of oily drug, and an increase in tensile strength resulted in increased demixing. That is to say, when viscosity of oily drug was high, the amount of nuclei having sufficient strength to withstand the shearing force applied in the mixer was increased. This made demixing of the oily drug in granules large, prevented an interaction of the nuclei, and then led to the large demixing constant during granulation. On the other hand, when viscosity of the oily drug was low, the strength of the nuclei decreased. This made demixing of the oily drug in granules low, promoted an interaction of the nuclei, and then led to the unexpected migration of the oily drug during a prolonged granulation. In this study, the critical viscosity value was between 56.2 mPas and 184.0 mPas, but this viscosity would depend on other variables, such as the blade speed and amount of binder solution.

CONCLUSION

In this study, we found that in the case of an oily drug, the extent of drug demixing depended significantly on the viscosity of the drug. The demixing process of an oily drug was classified into two typical patterns in relation to viscosity. When the viscosity of the drug was high, the extent of the drug demixing in granules was large and constant independent of granulation time. On the other hand, when viscosity of the drug was low, the extent of the drug demixing was small with a short granulation time but became large with 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.

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