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ORIGINAL ARTICLE

Improving rheological characteristics of hydrophilic ointment base by treatment with a high-pressure wet-type jet mill

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Background: A high-pressure wet-type jet mill is a powerful equipment used for the dispersion and emulsification of substances. In this study, we investigated its usefulness in the preparation of skin cream formulations. *Method*: We prepared a hydrophilic ointment base as a typical skin cream base, and then treated it with the wet-type jet mill under different conditions. Controllable factors of the wet-type jet mill included processing pressure, treatment cycle, and temperature of the treatment. *Result*: Treatment with the wet-type jet mill had a great impact on the rheological characteristics of the hydrophilic ointment base. The hysteresis areas and yield values of the treated ointments were significantly increased by increasing the processing pressure and temperature during the treatment. From scanning electron microscopic observations, the oil droplet size of the hydrophilic ointments decreased after treatment with the wet-type jet mill, suggesting that a decrease in oil droplet size mediates changes in the rheological characteristics. *Conclusion*: Because we can expect the wet-type jet mill to control the rheological characteristics of the ointment, it is a promising tool for the preparation of skin cream formulations.

Key words: *High-pressure wet-type jet mill; hydrophilic ointment base; oil droplet size; thixotropy; viscosity*

Introduction

Today, emulsions are widely used in many commercial products including medicines, cosmetic products, food products, and paints. In most cases, decreasing the oil droplet size is an exciting challenge to improve the performance of these products. Although high-speed mixers and high-pressure homogenizers are well known as machines used for emulsification[1–6], they have some limitations. For example, the circumferential velocity of the high-speed mixer is weak by nature and it is difficult to obtain submicron-sized emulsions. High-pressure homogenizers possess sufficient capacity to prepare submicron-sized emulsions; however, scaling-up is a problem because of their small capacity and this limits their use in industrial manufacturing[7–9].

A high-pressure wet-type jet mill is a promising tool for improving dispersion and emulsification processes. The internal arrangement of the high-pressure wet-type jet mill is shown in Figure 1. Once fluids (e.g., slurry and emulsion) are fed into the mill, they are pressurized by a hydraulic plunger pump. The pressure can be increased to a maximum of 245 MPa. The pressurized fluids are supplied to a chamber by passing through two branched channels where they collide at extremely high speed in the center of the chamber. Because of turbulent forces and cavitations caused by passing the pressurized fluids through the orifice, along with counter collision, excellent dispersion and emulsification processes can be achieved[7–11]. Furthermore, several other benefits can be achieved by using the wet-type jet mill. These include preventing the risk of contamination and shortening the treatment time. In addition, because the wet-type jet mill can deal with a lot of fluid in a short time and can be easily integrated into one-pass operations, it is applicable for industrial manufacturing. To date, this mill has been applied to decreasing sizes of various

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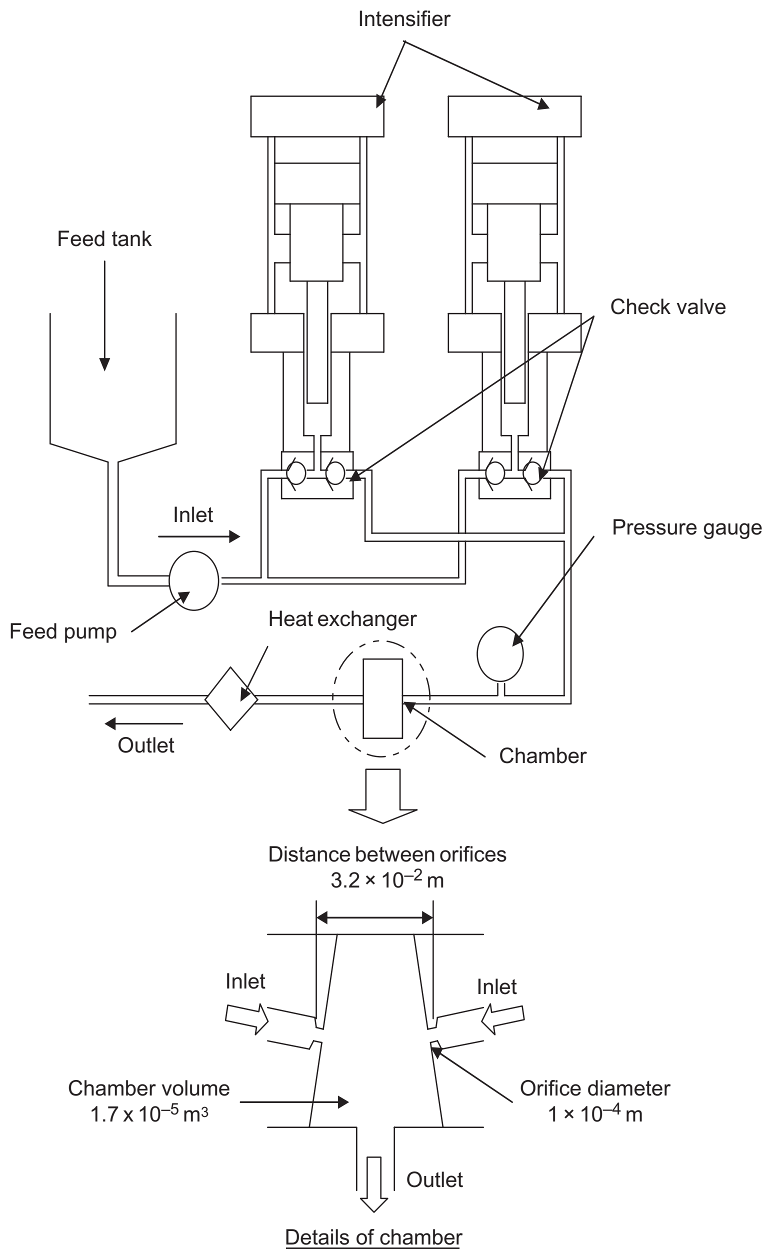

Figure 1. A schematic diagram of high-pressure wet-type jet mill.

materials[7–11]. Several studies have reported that treatment with the wet-type jet mill results in fine and uniform oil droplets within emulsions[7–10].

Hydrophilic ointment base is one of the most popular oil–water (O/W)-type emulsions used in pharmaceuticals. Skin cream formulations made from this base exhibit an interesting rheological characteristic called thixotropy. Thixotropy is a property of some non-Newtonian pseudoplastic fluids that show a time-dependent change in viscosity; that is, the longer shear stress the fluid undergoes, the lower the viscosity. The thixotropic nature of skin cream formulations contributes to their usefulness[12].

We think that the high-pressure wet-type jet mill can bring about great benefits for the preparation of skin cream formulations. The oil droplet size of the hydrophilic ointment base is thought to be decreased by treatment with a high-pressure wet-type jet mill. Because the size of oil droplets in an emulsion exerts a predominant influence on its rheological characteristics[13–16], a significant alteration of rheological characteristics in an emulsion can be observed by treatment with a high-pressure wet-type jet mill. We think it is possible to obtain skin cream formulations that have much more suitable properties by manipulating the processes of the wet-type jet mill.

The aim of this study was to evaluate the usefulness of the wet-type jet mill in the preparation of the skin cream formulations. A hydrophilic ointment base was treated under various conditions. Processing pressure, treatment cycles, and temperature during treatment were selected as process variables of the wet-type jet mill. The rheological characteristics of hydrophilic ointment bases obtained, such as viscosity, hysteresis area, and yield value, were examined. In addition, microscopic observations of the oil droplets were conducted using a scanning electron microscope (SEM).

Materials and methods

Materials

White petrolatum, stearyl alcohol, propylene glycol, monostearate glyceride, methyl parahydroxybenzoate, and propyl parahydrobenzoate were purchased form Wako Pure Chemical Industries (Osaka, Japan). Poly-(ethylene glycol)-60 (PEG-60) hydrogenated castor oil was purchased form Nikko Chemicals Co. Ltd. (Tokyo, Japan). All other reagents were of chemical grade.

Preparation of hydrophilic ointment base

The hydrophilic ointment base was prepared according to JP XIV (Table 1). Briefly, white petrolatum, stearyl alcohol, PEG-60 hydrogenated castor oil, and monostearate glyceride were fused in a water bath at 75°C and the mixture was stirred until it became homogeneous. This liquid was used as the oil phase. For the aqueous phase, propylene glycol, methyl parahydroxybenzoate, and propyl parahydrobenzoate were added to water and then stirred in a water bath at 75°C. The two phases were then mixed in a water bath at 75°C and formed an O/W-type emulsion. The emulsion was stirred gently until it was cooled to room temperature. The water contents were fixed at 70%.

The prepared hydrophilic ointment base was then treated with a high-pressure wet-type jet mill (HJP25003; Sugino Machine Ltd., Toyama, Japan). The processing pressures (100, 150, 200, and 245 MPa), treatment cycles (1 and 2 cycles), and temperatures (25°C and 40°C) of the treatment were selected as process variables of the wet-type jet mill.

Table 1. Formulation of hydrophilic ointment based on JP XIV.

Component	(g)
White petrolatum	250
Stearyl alcohol	200
Propylene glycol	120
PEG-60 hydrogenated castor oil	40
Monostearate glyceride	10
Methyl parahydroxybenzoate	1
Propyl parahydroxybenzoate	1
Water	Adequate dose

Measurement of viscosity

Flow curves of shear rate against shear stress were obtained using a viscometer (TV-30; Toki Sangyo Co. Ltd., Tokyo, Japan). The temperature of the base plate was 25 ± 0.1°C. The shear rate was changed in the range of 3.83–191.5 s^{-1}. The hysteresis area was calculated as the area surrounded by the hysteresis loop using the trapezoidal method. The magnitudes of yield stress were determined using the Casson model[17,18].

$$\sqrt{S} = \sqrt{S_C} + \sqrt{aD},$$

where S is the shear stress, S_C is the Casson yield value, a is the Casson viscosity, and D is the shear rate.

SEM observation of oil droplets

The oil droplets of the hydrophilic ointment bases were observed using SEM (JSM-5600LV; Jeol Co. Ltd., Tokyo, Japan). Hydrophilic ointments (15 μL) were set in a wet SEM capsule (QX102-capsules; M&S Instruments Inc. Ltd., Osaka, Japan). The capsule contains an ultra-thin membrane that is transparent to the electron beam; however, it is impervious to water. The mechanical strength of the membrane is high enough to resist a one-atmosphere pressure difference; therefore, the sample contained in the capsule is completely isolated from the vacuum in the microscope chamber. The samples can be directly imaged in their native wet environment with SEM. The oil droplet size was measured as a Feret diameter and represented as the mean ± SD of 100 measurements.

Results and discussion

To evaluate the usefulness of the wet-type jet mill as a tool for the preparation of hydrophilic ointment bases, we investigated the effect of process variables on rheological characteristics. The viscosity, hysteresis area, and yield value of the hydrophilic ointment base were selected as rheological characteristics. Generally, thixotropic fluids form a three-dimensional structure in the system. Once a certain degree of shear stress is given to the fluids, their internal structure is destroyed. Although the destroyed structure can be reconstructed by removing the shear stress, a time lag is required

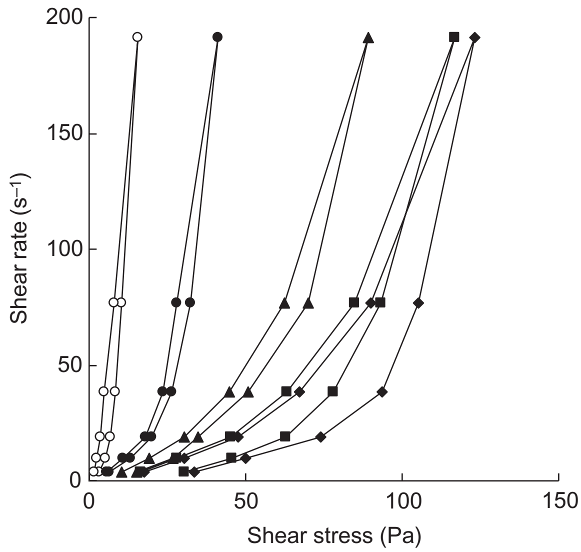

Figure 2. Flow curves of the hydrophilic ointment base after treatment with the wet-type jet mill as a function of processing pressures. Treatment with the wet-type jet mill was conducted at 25°C. (❍) Untreated hydrophilic ointment and hydrophilic ointments treated at (●) 100 MPa, (▲) 150 MPa, (■) 200 MPa, and (◆) 245 MPa.

before completion of the reconstruction. Therefore, viscosity values of the decreasing shear-rate curve of thixotropic fluids is lower than those of the increasing shear-rate curve, and the hysteresis area can be regarded as an index of the three-dimensional structures that were present in the sample before the measurement. The yield value is defined as the stress that must be applied before flow of the fluid will start. It is also used as a parameter representing the thixotropic properties of the fluid.

Figure 2 represents the flow curves for hydrophilic ointment bases treated with the wet-type jet mill at various processing pressures. All flow curves showed a hysteresis loop, and their shapes were markedly changed by different processing pressures. The viscosity values of hydrophilic ointment bases at each measured shear rate are shown in Table 2. Treatment with the wet-type jet mill significantly raised the viscosity, and the values increased with increases in processing pressures (Table 2). In accordance with this, the hysteresis area and yield value significantly increased with increasing processing pressures (Figure 3). In addition, obvious differences in viscosity values for increasing and decreasing shear rate curves were observed, and higher values were obtained for increasing shear rate curves, especially at low-shear stresses (Table 2).

These findings were thought to be related to decreasing the oil droplet size of the hydrophilic ointment base by treatment with the wet-type jet mill. Decreasing the oil droplet size affects the rheological characteristics, such as viscosity, of emulsions[12–15] . Korhonen et al. investigated the relationship between oil droplet size and viscosity using an emulsion that dispersed caprylic triglyceride, isopropyl palmitate, glycerin, and cetostearyl alcohol in water. From their study, it was demonstrated that an emulsion with smaller oil droplets (1.7 μm maximum diameter) was much more viscous than an emulsion with larger oil droplets[13]. Rajinder also reported that the viscosity of an emulsion increased with decreases in oil droplet size using an emulsion composed of petroleum oil, Triton X-100, and water with a droplet size range of 5–18 μm[14,15]. When the oil droplet size decreases, interactions between oil droplets, such as Van der Waals forces, become stronger because of an increased packing density, and oil droplets can then interact with each other much more frequently. Interactions via the Van der Waals force are weak by nature, and the network is gradually broken by the shear stress of the measurement of viscosity. According to this mechanism, hydrophilic ointment bases become more

Table 2. Viscosities of hydrophilic ointments after treatment with wet-type jet mill as a function of processing pressure.

		Processing pressure of mill (MPa)				
Shear rate (s^{-1})	Direction of change in shear rate	0	100	150	200	245
3.8	Upward	0.83 ± 0.39	1.64 ± 0.30	4.01 ± 2.77	7.98 ± 2.54**	8.75 ± 1.04**
	Downward	0.45 ± 0.16	1.49 ± 0.08	2.76 ± 0.98*	4.25 ± 0.97**	4.60 ± 0.42**
9.6	Upward	0.55 ± 0.25	1.37 ± 0.28	2.80 ± 2.17*	3.87 ± 1.18**	5.24 ± 0.09**
	Downward	0.26 ± 0.10	1.14 ± 0.09	2.02 ± 0.80*	2.93 ± 0.61**	3.17 ± 0.17**
19.2	Upward	0.35 ± 0.14	1.05 ± 0.18	1.82 ± 0.70	4.29 ± 1.58**	3.86 ± 0.21**
	Downward	0.18 ± 0.06	0.95 ± 0.14	1.57 ± 0.50**	2.36 ± 0.32**	2.49 ± 0.22**
38.3	Upward	0.22 ± 0.07	0.69 ± 0.18	1.32 ± 0.46**	2.03 ± 0.11**	2.45 ± 0.24**
	Downward	0.13 ± 0.04	0.62 ± 0.21	1.18 ± 0.33**	1.65 ± 0.13**	1.75 ± 0.19**
76.6	Upward	0.14 ± 0.04	0.42 ± 0.14	0.85 ± 0.19**	1.22 ± 0.07**	1.37 ± 0.16**
	Downward	0.10 ± 0.03	0.37 ± 0.12	0.88 ± 0.21**	1.11 ± 0.07**	1.17 ± 0.13**
191.5	—	0.08 ± 0.02	0.22 ± 0.07	0.47 ± 0.05**	0.61 ± 0.07**	0.64 ± 0.10**

Treatment with the wet-type jet mill was conducted at 25°C. Each value represents the mean ± SD (n = 3). Significant differences when treated hydrophilic ointment was compared with the untreated hydrophilic ointment are indicated; *P < 0.05 and **P < 0.01.

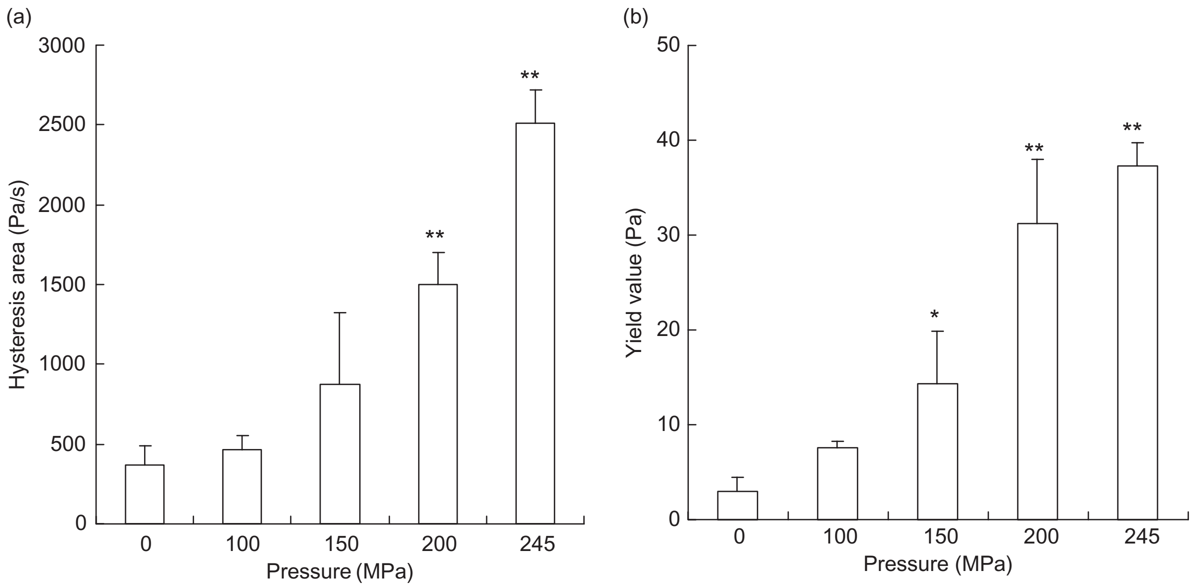

Figure 3. Effect of processing pressure on rheological characteristics of hydrophilic ointment bases. Treatment with the wet-type jet mill was conducted at 25°C. (a) Hysteresis area, (b) yield value. Each value represents the mean ± SD ($n = 3$). Significant differences between treated and untreated hydrophilic ointments for hysteresis area and yield value are indicated; $^*P < 0.05$ and $^{**}P < 0.01$.

viscous and thixotropic in nature by treatment with the wet-type jet mill. Furthermore, because the oil droplet size is thought to decrease with higher processing pressure, changes in the rheological characteristics proceed by increasing the processing pressure.

Subsequently, we investigated the effect of the treatment cycle on rheological characteristics. Hydrophilic ointment bases were treated at 150 MPa with one and two cycles. Their hysteresis loops were quite similar to each other (Figure 4). Changes in the hysteresis areas and yield values from one cycle to two cycles were 872.5 ± 454.1 to 853.3 ± 371.8 Pa/s and 14.3 ± 5.6 to 18.2 ± 3.42 Pa, respectively (data not shown). Thus, no effect of treatment cycle on rheological characteristics was observed in this study. In contrast, Seekkuarachchi et al. reported a significant effect of treatment cycles on oil droplet size[9]. They used an emulsion that dispersed kerosene and liquid paraffin in PEG solutions. Sodium dodecyl sulfate was used as a surfactant, and the water concentration was 90%. The oil droplet size of the emulsion was markedly decreased by repeating the treatment with the wet-type jet mill at 50 or 150 MPa. A possible explanation for this discrepancy in results is the different experimental conditions used, such as components of the formulation and water content. In this study, the system probably reached a steady state by the first treatment, and the second treatment was no longer able to provide the shear stress needed to affect its state.

Treatment with the wet-type jet mill was conducted at 40°C and changes in the thixotropic properties of the

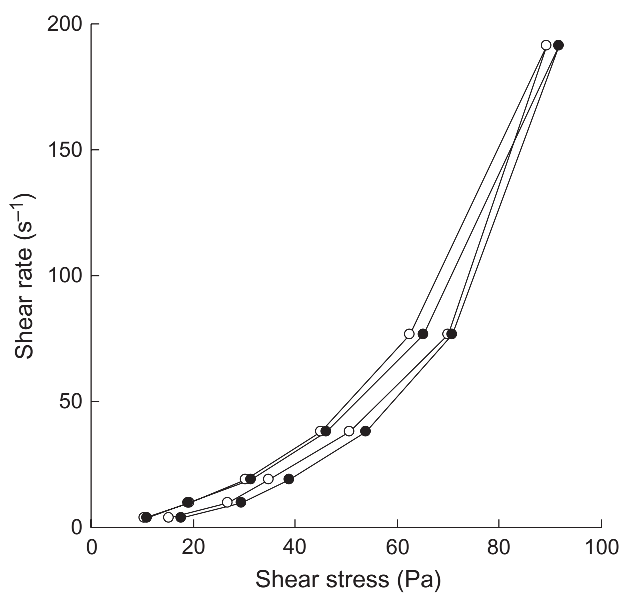

Figure 4. Flow curves for hydrophilic ointment base after treatment with a wet-type jet mill as a function of treatment cycles. Treatment with the wet-type jet mill was conducted at 150 MPa at 25°C. (❍) One cycle, (●) two cycles.

hydrophilic ointment base were investigated. As shown in Figure 5, hysteresis area and yield values after treatment at 40°C tended to be higher than those at 25°C. The viscosity of the colliding fluids was decreased by increasing the temperature inside the chamber. We think this is what made the oil droplet size decrease and induced more obvious changes in the rheological

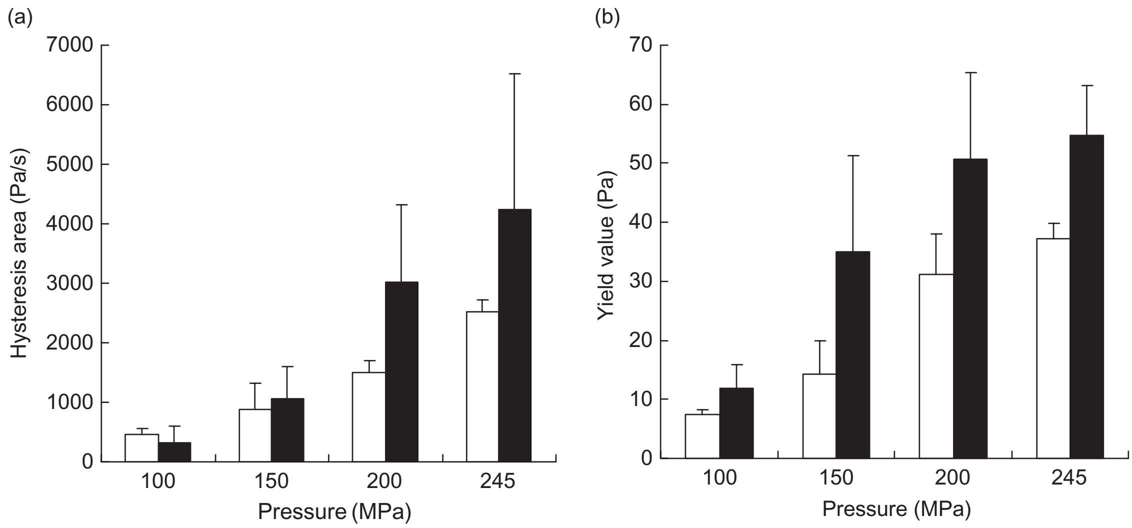

Figure 5. Effect of temperature on the rheological characteristics of hydrophilic ointment bases. Treatment with the wet-type jet mill was conducted at 150 MPa at (□) 25°C or (■) 40°C. (a) Hysteresis area, (b) yield value. Each value represents the mean ± SD (n = 3).

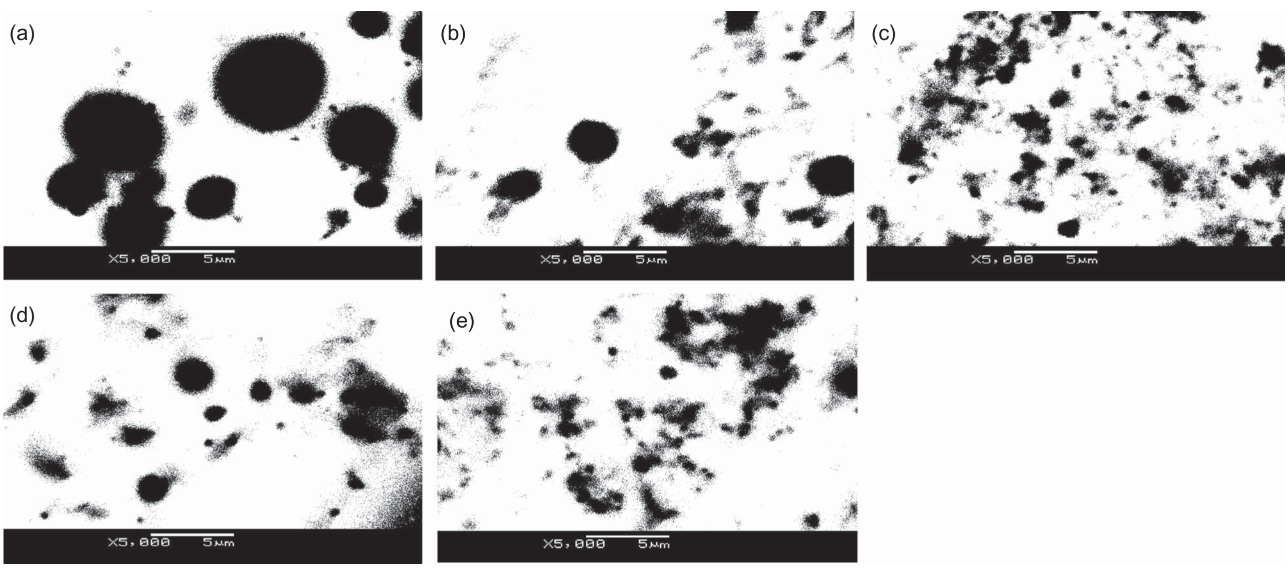

Figure 6. SEM micrographs of hydrophilic ointment bases after treatment with the wet-type jet mill. (a) Untreated hydrophilic ointment. Processing pressures: (b and d) 150 MPa, (c and e) 245 MPa. Temperature of the treatment: (b, c, and d) 25°C, (e) 40°C. Treatment cycle: (b, c, and e) one cycle; (d) two cycles.

characteristics. Seekkuarachchi and Kumazawa reported that the oil droplet size of an emulsion decreased by using a low-viscosity-dispersing phase[10]. This evidence strongly supports our findings.

We found that treatment with the wet-type jet mill had a large impact on the rheological characteristics of the hydrophilic ointment base. This effect is assumed to be mediated by decreasing the oil droplet size. To clarify this issue, we conducted microscopic observations of the hydrophilic ointment base using SEM. On average, the oil droplet size of the untreated hydrophilic ointment base was about 3.01 ± 1.58 μm (mean ± SD) (Figure 6a), whereas the oil droplet sizes after treatment with the wet-type jet mill were much smaller (Figure 6b–e). The oil droplet size was reduced from 1.27 ± 0.64 to 0.78 ± 0.28 μm by increasing the processing pressure from 150 to 245 MPa. An effect of temperature during treatment was also observed, and the oil droplet size reduced to 0.65 ± 0.22 μm by treatment at 40°C (Figure 6e). No difference was observed between hydrophilic ointments treated with one and two cycles (Figure 6b and d). SEM observations were coincident with changes in the rheological characteristics.

Therefore, the effect of the wet-type jet mill on the rheological characteristics of a hydrophilic ointment base is mostly caused by decreasing the oil droplet size.

Conclusions

We have demonstrated that the rheological characteristics of a hydrophilic ointment base were improved by treatment with the wet-type jet mill. From SEM observations, changes in the rheological characteristics can mostly be attributed to decreasing the oil droplet size. Because the wet-type jet mill possesses an excellent capacity for dispersion and emulsification, we believe it can extensively control the rheological characteristics of cream bases. From this study, we have successfully indicated the usefulness of the wet-type jet mill for the preparation of cream formulations.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

1. Floury J, Desrumaux A, Lardieres J. (2000). Effect of high-pressure homogenization on droplet size distributions and rheological properties of model oil-in-water emulsions. Innov. Food Sci Emerg, 1:127–34.
2. Cohen, D. (2005). High-shear mixing. Don't fall victim to common misconceptions. Chem Eng, 112:46–51.
3. Fradette L, Brocart B, Tanguy PA. (2007). Comparison of mixing technologies for the production of concentrated emulsions. Chem Eng Res Des, 85:1553–60.
4. Jafari SM, Assadpoor E, He Y, Bhandari B. (2008). Re-coalescence of emulsion droplets during high-energy emulsification. Food Hydrocolloid, 22:1191–202.
5. Silva CM, Ribeiro AJ, Figueiredo IV, Goncalves AR, Veiga F. (2006). Alginate microspheres prepared by internal gelation: Development and effect on insulin stability. Int J Pharm, 311:1–10.
6. Guerrero DQ, Esquivel DT, Quintanar AG, Allemann E, Doelker E. (2005). Adaptation and optimization of the emulsification-diffusion technique to prepare lipidic nanospheres. Eur J Pharm Sci, 26:211–8.
7. Tanaka K, Ibe H, Kumazawa H. (2003). Submicrometer size emulsification using a high pressure wet-type jet mill. Kagaku Kogaku Ronbunshu, 29:740–7.
8. Tanaka K, Muvuchi N, Kumazawa H. (2004). Effect of dispersed phase viscosity and volume fraction on submicrometer size oil-in-water emulsion formation using a high pressure wet-type jet mill. Kagaku Kogaku Ronbunshu, 30:186–93.
9. Seekkuarachchi IN, Tanaka K, Kumazawa H. (2006). Formation and characterization of submicrometer oil-in-water (o/w) emulsions, using high-energy emulsification. Ind Eng Chem Res, 45:372–90.
10. Seekkuarachchi IN, Kumazawa H. (2006). Production of submicrometer size o/w emulsions using a high-pressure wet-type jet mill. Chem Eng Comm, 193:501–25.
11. Seekkuarachchi IN, Tanaka K, Kumazawa H. (2008). Dispersion mechanism of nanoparticulate aggregates using a high pressure wet-type jet mill. Chem Eng Sci, 63:2341–66.
12. Barnes HA. (1994). Rheology of emulsions: A review. Colloid Surf A, 91:89–95.
13. Korhonen M, Niskanen H, Kiesvaara J, Yliruusi J. (2000). Determination of optimal combination of surfactants in creams using rheology measurements. Int J Pharm, 197:143–51.
14. Rajinder P. (1996). Effect of droplet size on the rheology of emulsions. AICHE J, 41:3181–90.
15. Rajinder P. (1998). A novel method to correlate emulsion viscosity data. Colloid Surf A, 137:275–86.
16. Levy G. (1962). Rheology of thixotropic montmorillonite dispersions. I. Changes on aging of plain and polysorbate 80 containing dispersions. J Pharm Sci, 51:947–51.
17. Demachi H, Matsui O, Abo H, Tatsu H. (2000). Simulation model based on non-Newtonian fluid mechanics applied to the evaluation of the embolic effect of emulsions iodized oil and anticancer drug. Cardiovasc Intervent Radiol, 23:285–90.
18. Kirsanov EA, Remizov SV. (1999). Application of the Casson model to thixotropic waxy crude oil. Rheol Acta, 38:172–6.