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Spray Drying of Griseofulvin Solution Forming Its Solvate[1)]

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A spray drying process was introduced into our method of particle size reduction by "solvation and desolvation" for the purpose of producing spherical particles with a large effective surface area. By solvate formation and successive desolvation in a single process of spray drying, preparation of spherical particles, which consist of primary fines, was achieved.

Keywords——griseofulvin; spray drying; solvate formation; chloroformate; particle size reduction

In a series of studies on particle size reduction by "solvation and desolvation," the chloroformate of griseofulvin was first identified, and its thermal properties and the mechanism involved in the method were investigated to find suitable conditions for size reduction.[2)] Ultra-fine powders of griseofulvin and other medicinal compounds were successfully prepared.

In the present study, a spray drying process was introduced into our method of size reduction for the purpose of producing spherical particles with a large effective surface area. For this purpose, a solute–solvent system which forms a solvate was selected and the products were investigated by differential scanning calorimetry, thermogravimetry, X-ray powder diffractometry and scanning electron microscopy. The specific surface areas of the powders obtained were measured by a gas adsorption (BET) method.

Experimental

Materials——Griseofulvin: Recrystallized from acetone. Chloroform ($CHCl_3$): The reagent-grade product was distilled.

Spray Drying——A bench-top spray dryer, MINI SPRAY HO (IRA) provided by Yamato Scientific Co., Ltd., was used. A $CHCl_3$ solution of griseofulvin was atomized into a drying chamber through a peristaltic pump.

Differential Scanning Calorimetry (DSC)——An SSC/580-DSC 20 differential scanning calorimeter (Seiko Instruments & Electronics) was used. A sample amount of *ca.* 7 mg was used after precise weighing with a semimicrobalance. The heating rate adopted was 5 or 10 °C/min, and N_2 gas was passed through the furnace.

Thermogravimetry (TG)——A TGS-1 thermobalance (Perkin-Elmer Corp.) was used. The sample container was an uncovered platinum pan. A sample weight was 3—4 mg, and a heating rate of 8 °C/min was adopted under nitrogen gas flow.

X-Ray Powder Diffractometry——The instrument used was a JEOL JDX-7F X-ray diffractometer (CuK_α radiation, $\lambda = 1.542$ Å, Ni filter).

Scanning Electron Microscopy (SEM)——An S-430 (Hitachi) scanning electron microscope was used.

Measurement of Specific Surface Area——A BET gas adsorption apparatus P-850 (Sibata Scientific Technology Ltd.) was used. The sample weight was 1.0—2.3 g, and the gas for adsorption was N_2.

Results and Discussion

Griseofulvin was spray-dried with $CHCl_3$, which forms a solvate either by recrystalli-

Table I. Spray-Drying Conditions

Solvent	$CHCl_3$	$CHCl_3$
Concentration of griseofulvin (%)	2.0	2.0
Feeding rate for atomization (ml/min)	5	5
Air pressure for atomization (kg/cm^2)	1	1
Drying temperature (°C)		
Inlet temperature	23±2	133±3
Outlet temperature	23±2	90±3
Degree of reduced pressure in the drying chamber (mmHg)	4	4

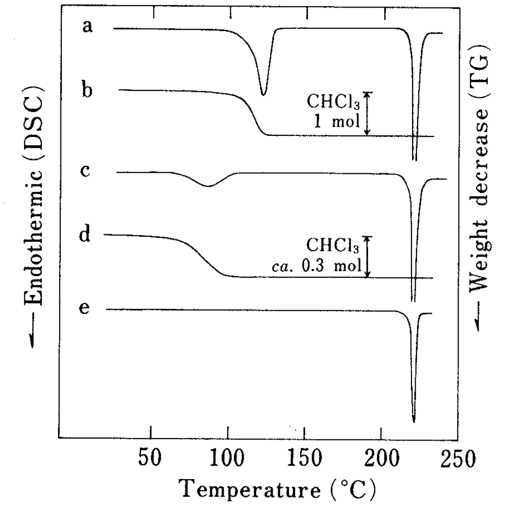

Fig. 1. DSC and TG Curves of Spray-Dried Product and Griseofulvin Chloroformate

(a) DSC curve of the ordinary crystalline chloroformate of griseofulvin (open conditions): sample weight, 7.044 mg; heating rate, 10 °C/min. (b) TG curve of the ordinary crystalline chloroformate of griseofulvin (open conditions): sample weight, 3.821 mg; heating rate, 8 °C/min. (c) DSC curve of the spray-dried product obtained at the inlet drying temperature of 23±2 °C (open conditions): sample weight, 6.950 mg; heating rate, 10 °C/min. (d) TG curve of the spray-dried product obtained at the inlet drying temperature of 23±2 °C (open conditions): sample weight, 2.885 mg; heating rate, 8 °C/min. (e) DSC curve of the spray-dried product obtained at the inlet drying temperature of 133±3 °C (open conditions): sample weight, 7.022 mg; heating rate, 5 °C/min.

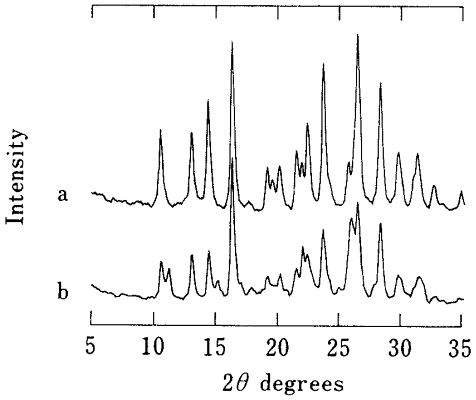

Fig. 2. X-Ray Diffraction Patterns of Griseofulvin and the Spray-Dried Product (2θ Scan Speed: 4 °/min)

(a) Griseofulvin. (b) Spray-dried product (inlet temperature of 23±2 °C).

zation from $CHCl_3$ or by gas sorption with a combining ratio of 1 : 1 (griseofulvin : $CHCl_3$). The conditions used for spray drying are listed in Table I. Since the precise temperature of the sample material itself in the process of spray drying was difficult to determine, we tentatively chose two inlet temperatures, 23±2 °C and 133±3 °C.

Griseofulvin–Chloroform System

Figure 1(c) shows the DSC curve of the spray-dried product obtained at the lower inlet temperature (23±2 °C). The appearance of an endothermic peak between 70 and 100 °C attributable to desolvation of chloroformate (solid-gas phase transition) indicates the formation of griseofulvin solvate during the spray drying. Moreover, the position of the endotherm is at a significantly lower temperature range in comparison with that of the ordinary crystalline chloroformate (Fig. 1(a)). This phenomenon can be ascribed to the larger surface area of the product than that of the ordinary solvate (less than 1 m^2/g), as will be discussed later. The results of TG and X-ray diffractometry (weight decrease (Fig. 1(d)) and the new diffraction peaks (2θ: 11.3, 15.2, 25.0°; Fig. 2(b))) indicated that the product was a mixture of free griseofulvin and the solvate (content of chloroformate; *ca.* 30%), and hence the solvate obtained by spray drying would have been partially desolvated. On the other hand, at the higher inlet temperature (133 ± 3 °C) the spray-dried product was found to be free griseofulvin, as shown in Fig. 1(e).

TABLE II. Specific Surface Area of Spray-Dried Griseofulvin

Conditions		Specific surface area (m^2/g)
Solvent	Drying temp. (inlet, °C)	
$CHCl_3$	23 ± 2	3.0→5.5[a]
	133 ± 3	4.7

[a] The product was a mixture of free griseofulvin and the solvate (contents of chloroformate; *ca.* 30%). The latter value is that obtained after heat treatment for desolvation.

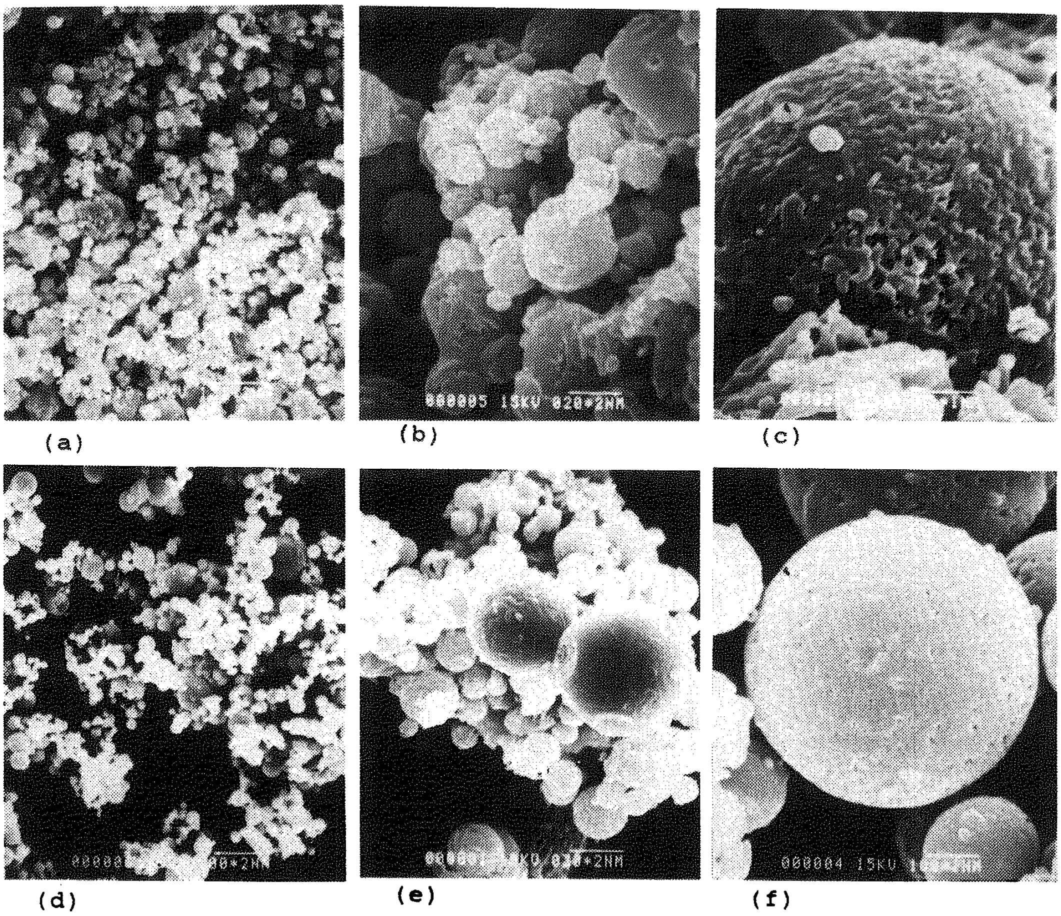
(a) (b) (c)
(d) (e) (f)

Fig. 3. Scanning Electron Micrographs of Spray-Dried Griseofulvin

(a), (b) and (c) Obtained from $CHCl_3$ solution at the inlet drying temperature of 23 ± 2 °C, then heated for desolvation (55, then 90 °C for several hours under reduced pressure). 1200 ×, 7400 ×, 11000 ×. (d), (e) and (f) Obtained from $CHCl_3$ solution at the inlet drying temperature of 133 ± 3 °C. 1600 ×, 4900 ×, 16000 ×.

Specific Surface Area and Surface Appearance of Spray-Dried Products

The specific surface area results are shown in Table II. Each of these values is larger than that of the product obtained simply *via* the solvate crystals.[2a,c] The spray-dried product at lower drying temperature, in which 30% of chloroformate remained (partially desolvated), significantly increased its specific surface area after conventional heat treatment (55, then 90 °C for several hours under reduced pressure) for desolvation. In the SEM photographs of the recovered griseofulvin, many spherical particles consisting of primary fines were observed (Fig. 3 (a), (b) and (c)). On the other hand, the spray-dried product prepared at higher drying temperature showed a similar surface appearance (Fig. 3 (d), (e) and (f)). This finding supports the view that solvate formation and successive desolvation of the solvate occurred efficiently in the single process of spray drying in the latter case.

Conclusion

The present study was a trial aimed at applying a spray drying technique in our method of particle size reduction by phase conversion. The process involved is solvate formation and successive desolvation in the dynamic process of spray drying. The result of spray drying at the inlet temperature of 23 ± 2 °C confirmed the occurrence of solvate formation. Spherical particles which consisted of primary fines were effectively produced by particle size reduction through "solvation and desolvation" and spherization by spray drying.

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References and Notes

1) This paper forms Part XXV of the series entitled "Studies on Methods of Particle Size Reduction of Medicinal Compounds." The preceding paper, Part XXIV: Y. Tsuda, E. Suzuki and K. Sekiguchi, *Chem. Pharm. Bull.*, **35**, 769 (1987).

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