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Studies on Methods of Particle Size Reduction of Medicinal Compounds. VI.[1] Solvate Formation of Griseofulvin with Benzene and Dioxane[2]

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Solvate formation of griseofulvin with benzene and dioxane was confirmed by differential scanning calorimetry (DSC), thermogravimetric analysis (TG), and X-ray diffractometry. Combining ratios of the two solvates were determined by TG to be 1: 2 and 2: 1 with respect to griseofulvin and benzene, and griseofulvin and dioxane, respectively. From data by solubility measurements and by various thermal methods of analysis such as DSC, freezing point determination by cooling curve method, the phase diagrams of the systems between benzene and griseofulvin, and between dioxane and griseofulvin were constructed. Also, thermodynamic properties of these solvates were investigated. It was found that the transition temperatures and the overall heats of desolvation were 35° and 6.3±0.2 kcal/mole of solvent for the benzene solvate, and 80—85° and 6.0±0.5 kcal/mole for the dioxane solvate, respectively. Moreover, the possibilities of these solvates for applying to particle size reduction of griseofulvin were examined. As for the benzene solvate, the free griseofulvin obtained by desolvation has a specific surface area of 7 m^2/g, and a mean particle size of 0.58 μ. In the case of the dioxane solvate, the specific surface area after desolvation was reached to 4.8 m^2/g; however, the desolvated particles retained their original shapes. Surface structures of the two kinds of desolvated products were examined by scanning electron microscopy. As the results, it became clear that the desolvated particles from the dioxane solvate has a stout and very porous structure, though those from the benzene solvate are the laminar aggregates composed of very easily separable primary particles.

Among inherent factors affecting absorption or penetration of a solid drug from various dosage forms, the particle size is often found the most determining. It is usually recognized that the finer the size is, the higher bioavailability or efficacy of the drug can be obtained.[4] Therefore, particle size reduction to ultra-fine state becomes one of the most important processes in pharmaceutical manufacturing, and several mechanical techniques have been employed for this purpose. However, they are not always suitable for organic drug compounds because of difficulties such as fusion, adherence to mechanical parts, lack of uniformity in particle size, considerable increase in cost and danger of contamination by foreigh matters and microorganisms.

Such being the case, the authors reported a method of particle size reduction making use of the phase conversion from a solvate to the original drug compound and demonstrated experimentally that the new method could be applied easily and efficiently without problems

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[1] Part V: K. Sekiguchi, Y. Tsuda, and M. Kanke, *Chem. Pharm. Bull.* (Tokyo), 22, 2972 (1974). A word "Particle" is inserted in the previous title to represent more properly the contents of the authors investigation.

[2] Presented partly at the 95th Annual Meeting of the Pharmaceutical Society of Japan, Nishinomiya, 1975.

[3] Location: *9-1, Shirokane 5 chome, Minato-ku, Tokyo.*

[4] K.A. Lees, *J. Pharm. Pharmacol.*, **15**, 43 (1963); J.H. Fincher, *J. Pharm. Sci.*, **57**, 1825 (1968); J.D. Reinbold, F.J. Phillips, and H.F. Flippin, *Am. J. Med. Sci.*, **210**, 141 (1945); R.M. Atkinson, C.B. Bedford, K.J. Child, and E.G. Tomich, *Nature* **193**, 588 (1962); K. Sekiguchi, and N. Obi, *Chem. Pharm. Bull.* (Tokyo), **9**, 866 (1961); K. Sekiguchi, N. Obi, and Y. Ueda, *ibid.*, **12**, 134 (1964).

accompanied with mechanical milling procedures.[1,5,6] It was also suggested that solvates of drugs would be much more frequently formed than one believed, since modern drug compounds contain a variety of functional groups that have affinity to other molecules.

As examples of the above suggestion, the authors confirmed in this study the existence of benzene and dioxane solvates of griseofulvin that were hitherto unknown, and investigated physico-chemical and micromeritic properties of the two solvates and their desolvated products. Moreover, the application of these solvates for reducing particle size or increasing specific surface area of griseofulvin was discussed.

Experimental

Materials——Griseofulvin: Recrystallized from acetone. mp 220°.

Benzene: Analytical grade of benzene was treated with conc. H_2SO_4 and then purified by recrystallization and fractional distillation. fp 5.65°, bp 80.1°.

Dioxane: Reagent grade of dioxane was dehydrated and purified by recrystallization three times, refluxing over sodium and subsequent fractional distillation. fp 11.92°, bp. 101.5°.[7] The freezing points above were determined from plateaux in the cooling curves.[8]

Preparation of the Benzene and the Dioxane Solvates of Griseofulvin——Griseofulvin was dissolved in hot benzene or dioxane and the solution was held at about 20°. Since free griseofulvin was very easily separated out, seeding by the solvate crystals was necessary in each case for inducing crystallization.

Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TG)——DSC under semiclosed and closed conditions were done by the use of a Perkin-Elmer DSC-1B Differential Scanning Calorimeter. The sample weight was 5—15 mg and N_2 gas was passed through the furnace. For TG under constant rates of heating or at constant temperatures, a Perkin-Elmer TGS-1 Thermobalance was employed.

Freezing-point Determination——A Beckmann freezing-point apparatus was used to determine freezing points of pure solvents and eutectic temperatures of solute-solvent mixtures. Temperatures were taken every 15 seconds near inflection points in the cooling curve.

Visual Determination of Peritectic Temperature——A thin thermometer was inserted into a small test tube packed with about 1 g of the solvate crystals. The tube was heated at a rate of 1°/min in a water or liquid paraffin bath which was stirred by a magnetic stirrer. Since at the peritectic point the solvate is decomposed into the desolvated solid and its solution, the temperature where the content of the test tube became just partially liquid was read visually.

Solubility Measurements——In an ampule, a certain amount of free griseofulvin or its solvates was sealed with 10 ml of benzene or dioxane. Seven to twelve ampules thus prepared were immersed in a thermostated bath and were then shaken mechanically. After certain period from 1 to 150 hours, shaking was stopped and the sample solution was taken from one ampule by a syringe and filtered through a 0.2 μ membrane filter. The dissolved amount of griseofulvin was determined gravimetrically by evaporating the solvent and subsequent drying in a desiccator. Thus, the time-concentration curves at various constant temperatures were obtained, and the solubilities of griseofulvin in benzene and dioxane were decided from equilibrium plateaux in the curves as shown in Table I.

Measurement of the Weight Loss from the Benzene Solvate at a Constant Temperature——About 1 g of the freshly prepared solvate which was adhered some amount of liquid benzene was placed on the pan of a chemical balance maintained at 45±1°. The weight change was read at certain intervals. From the time-weight curve thus obtained, the amount of combined benzene was determined.

Infrared Spectroscopy (IR)——A Jasco IRA-1 Grating Infrared Spectrophotometer was used.

1) Spectra of the Solvates: By nujol mull method. In the case of the benzene solvate, it was first pulverized with liquid benzene. Immediately after removing the extra solvent by placing the wet powder between filter papers, it was mixed with liquid paraffin on the NaCl cell plate. For the dioxane solvate, the ordinary procedure was followed.

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5) K. Sekiguchi, K. Ito, E. Owada, and K. Ueno, *Chem. Pharm. Bull.* (Tokyo), **12**, 1192 (1964); K. Sekiguchi, I. Horikoshi, and I. Himuro, *ibid.*, **16**, 2495 (1968).

6) I. Himuro, Y. Tsuda, K. Sekiguchi, I. Horikoshi, and M. Kanke, *Chem. Pharm. Bull.* (Tokyo), **19**, 1034 (1971); K. Sekiguchi, *Yakkyoku* (J. Pract. Pharm.), **16**, 9 (1965); K. Sekiguchi, *Zairyo* (J. Soc. Material Sci.), **21**, 502 (1972).

7) The authors confirmed experimentally that the freezing point of dioxane and the eutectic temperature of the mixture of griseofulvin and dioxane lowered considerably in the presence of a minute amount of water.

8) The fps in the above represent the end of freezing; therefore, they are equal to the thaw point.

Table I. Solubility Data for Griseofulvin in Benzene and in Dioxane at Various Temperatures

Temp (°C)	Solubilities of griseofulvin (w/w %)	
	in benzene	in dioxane
22.0	1.18	—
25.0	1.33	2.92
30.0	—	3.27
31.1	1.67	—
35.0	1.72	—
37.2	—	3.85
40.0	1.82	4.25
45.0	1.85	4.80
50.0	—	5.51

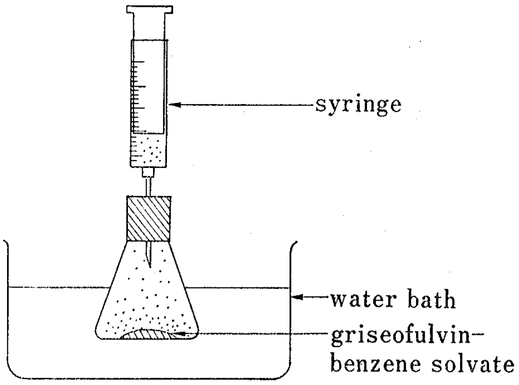

Fig. 1. Schematic Diagram of the Apparatus used for collecting the Vapor Mixture of Benzene and CCl_4

2) Detection of Combined Benzene in the Benzene Solvate: Freshly prepared crystals of the solvate were washed several times with CCl_4 and then placed in a flask equipped with an injection syringe (Fig. 1). On heating the flask, desolvation of the solvate was occurred and the syringe was filled with expanded benzene and CCl_4 vapor. The vapor mixture was then introduced into an IR gas cell and the spectrum was taken.

X-Ray Powder Diffractometry——A X-ray Diffraction Analyzer Type-7F of the Japan Electron Optics Laboratory Co., Ltd. was used (Ni filter, Cu–Kα ray $\lambda = 1.542$ Å). In the case of the benzene solvate, measurements were done with and without cooling by dry ice. Also, changes of the relative intensity of the X-ray peak of a 2θ value at 8.8° were monitored.

Measurements of Specific Surface Area——A BET gas adsorption apparatus (Model 600-P, Shibata Chemical Apparatus Co., Ltd.) was used. The sample amount was 5—10 g, and the gas for adsorption was N_2 (The cross-sectional area of the N_2 molecule was taken as 1.62×10^{-20} m^2). For calculation of the mean particle size, the density of griseofulvin was determined to be 1.47 from the weight and volume of a disk made by compressing dry griseofulvin powder under pressure of 5 tons/cm^2 in a vacuum.

Scanning Electron Microscopy——Electron micrographs of the surfaces of desolvated products were taken by a scanning electron microscope (MINI-SEM model MSM-4, Hitachi-Akashi Co., Ltd.) with an accelerating voltage of 1.5 kV.

Microscopic Measurement of Particle Size——After the aggregates of the desolvated products of the benzene solvate were pressed lightly to separate into primary particles, microphotographs of the distributed powder were taken by a microscope (Microscope model-FHF-Tr-IV, Olympus Optical Co., Ltd.), and the Green diameters of about 250—350 particles were measured. The mean diameters and the particle size distributions were determined statistically.

Results and Discussion

Solvate Formation of Griseofulvin with Benzene and Dioxane

It is well known that griseofulvin is usually crystallized out as rhombs, octahydra or spheroidal assemblies of slender needles. However, the authors found that different crystal forms of griseofulvin were sometimes isolated when the benzene and the dioxane solutions were supercooled to room temperature. The crystals from benzene were monoclinic plates, while those from dioxane were characteristic polyhydra. It was also observed that both kinds of crystals lost their transparency on standing. From these findings, solvate formation was thought to be quite probable. Accordingly, crystals obtained from benzene and dioxane solutions were examined by DSC, TG, IR, and X-ray diffraction analysis, and the solvates of griseofulvin formed with these solvents was confirmed.

1) **DSC Curves under Semiclosed and Closed Conditions**——As shown in Fig. 2, two or three endothermic peaks appear at two different temperature ranges in the DSC curves of the crystals prepared by procedures described in the experimental part. The peak at about 220° corresponds to the melting point of griseofulvin, while pairs of peaks at lower temperatures can be attributed to peritectic decomposition of the solvates and to evaporation or boiling of the molten liquid, respectively. Under semiclosed condition the DSC curve of crystals from

dioxane, shows only one peak at lower temperature, as seen in Fig. 2 (a). Probably, the fact will be ascribed to overlapping of the heat effects above, since the peak appears at nearly the same temperature as the first peak in Fig. 2 (b) due to peritectic decomposition under closed condition. In other words, peak separation under closed condition will be the result of vapor pressure increase in the system.

2) **TG Curves**——Corresponding to the DSC peaks caused by desolvation, distinct weight changes are observed in the TG curves. Therefore, existence of the benzene and the dioxane solvate will be certain.

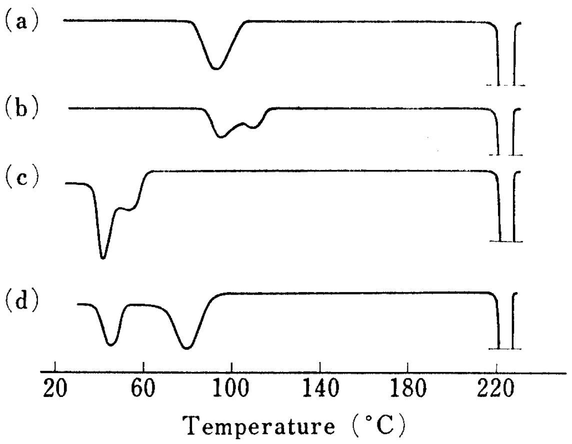

Fig. 2. DSC Curves of Dioxane and Benzene Solvates of Griseofulvin under Semiclosed and Closed Conditions

(a): griseofulvin-dioxane solvate under semiclosed condition, sample weight 9.22 mg, heating rate 16°/min, range 8 mcal/sec
(b): griseofulvin-dioxane solvate under closed condition, sample weight 4.03 mg, heating rate 16°/min, range 4 mcal/sec
(c): griseofulvin-benzene solvate under semiclosed condition, sample weight 3.89 mg, heating rate 16°/min, range 8 mcal/sec
(d): griseofulvin-benzene solvate under closed condition, sample weight 5.88 mg, heating rate 16°/min, range 8 mcal/sec

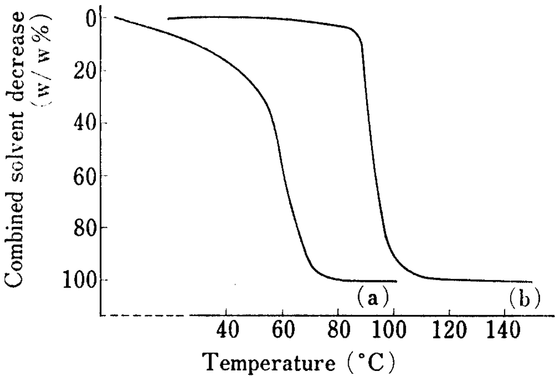

Fig. 3. TG Curves of Dioxane and Benzene Solvates of Griseofulvin

(a): griseofulvin-benzene solvate (4.753mg→3.427mg)
(b): griseofulvin-dioxane solvate (5.102mg→4.518mg)

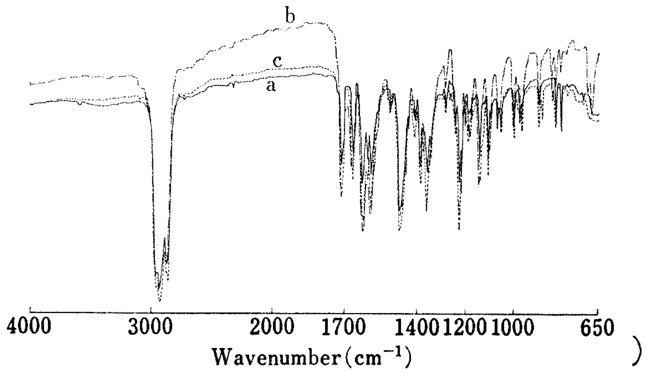

Fig. 4. IR Spectra of Griseofulvin and Its Solvates

—— (a): griseofulvin
---- (b): griseofulvin-benzene solvate
------ (c): griseofulvin-dioxane solvate

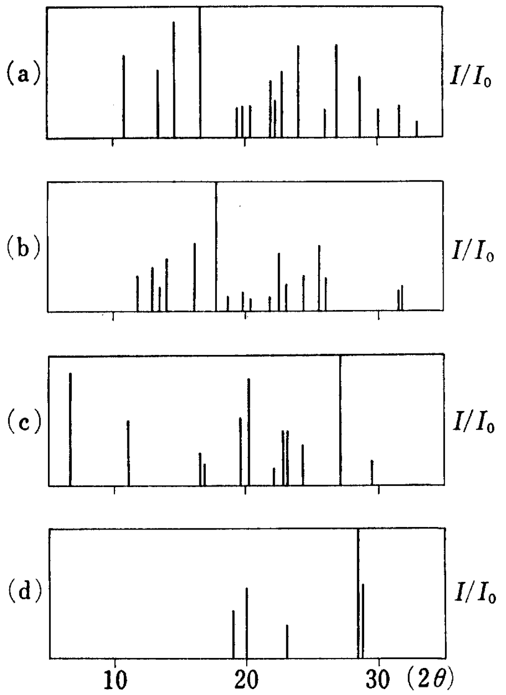

Fig. 5. X-Ray Powder Diffraction Patterns of Griseofulvin, its Dioxane and Benzene Solvates, and Benzene

(a): griseofulvin
(b): griseofulvin-dioxane solvate
(c): griseofulvin-benzene solvate cooled with dry ice
(d): benzene cooled with dry ice

3) IR Spectra——IR spectra of the benzene and dioxane solvates of griseofulvin are shown in Fig. 4. Different from the chloroform solvate reported in the previous paper,[5] neither appearance of new peaks nor shift of original peaks for griseofulvin and the two solvents were observed. However, in the case of the benzene solvate, the infrared gas analysis of the evolved vapor indicates the presence of the combined benzene.

4) X-Ray Powder Diffraction Patterns——Results of X-ray diffractometry of griseofulvin and its benzene and dioxane solvates are shown in Fig. 5. It is evident from these patterns that each of the solvates belongs to an independent molecular species. When measurements of the benzene solvate were done without cooling the sample powder, the X-ray pattern obtained in each run differs considerably. However, the patterns of the benzene solvate became fixed by cooling with dry ice. Therefore, it is certain that the solvate easily loses benzene molecule in air and is stable only at low temperature. On the other hand, the dioxane solvate was found to be much more stable. It is also considered that the X-ray pattern under cooling represents that of the pure benzene solvate of griseofulvin.

Combining Ratios of the Solvates

From the TG curve in Fig. 3, the combining ratio of the dioxane solvate was determined to be precisely 2: 1 with respect to griseofulvin and dioxane: however, the ratio of the benzene solvate is only estimated to be nearly 1: 2, since the solvate more or less decomposes during sampling for TG. For this reason, the weight change at a constant temperature was measured with larger amounts of the sample crystals wetted by mother liquor (Fig. 6). Thus, the above ratio of 1: 2 with regard to griseofulvin and benzene was definitely confirmed.

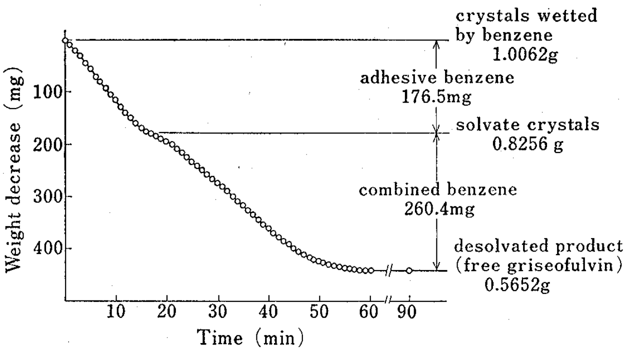

Fig. 6. Isothermal Desolvation Curve of Griseofulvin-Benzene Solvate at 45°

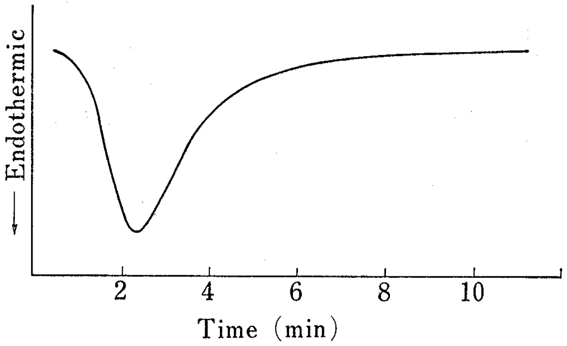

Fig. 7. Isothermal DSC Curve of Griseofulvin-Dioxane Solvate at 70°

From the heating and the isothermal DSC curves in Fig. 2 (a) and (c), and Fig. 7, the overall heats of desolvation of the benzene and the dioxane solvates were determined to be 6.3±0.2 and 6.0±0.5 kcal/mole of solvent, respectively. The heat of transition or peritectic reaction of the benzene solvate is also estimated to be 2.1±0.1 kcal/mole of benzene from the first peak of the DSC curve in Fig. 2 (d), since the two peaks are separated without overlapping and the second one is regarded as the heat of evaporation or boiling from the solution formed by peritectic reaction. In this connection, the instability of this solvate will be explained by the small value of the heat of transition.

Previously, the authors suggested that griseofulvin and chloroform are combined to form a solvate either by hydrogen bonding or by some dipole-induced dipole interaction force.[5,6] The combining mechanisms of the benzene and the dioxane solvates are yet uncertain; however, since IR spectra showed no peak shift, it can at least be said that the forces in these solvates differ from that in the chloroform solvate. At present, the authors presume intuitively that both solvates belong to inclusion compounds, but the types of interaction involved will differ each other, since distinct differences in appearance and mechanical strength are observed between desolvated products of the two solvate (Fig. 16).

Phase Diagrams of the Solvates

For constructing the phase diagram of a system that contains a liquid component, combination of data by various methods is necessary, because none of the methods are sufficient for the purpose by itself. Accordingly, the authors employed several methods as in the following.

1) Melting Point Determination[9] : Solubility measurement and visual observation on heating.

2) Eutectic Point Determination : Cooling curve method using a Beckmann thermometer and visual observation on heating.

3) Peritectic Point Determination : DSC and visual observation on heating.

The cooling curve method was found unsuitable for measuring melting points[9] of griseofulvin-benzene mixture as is illustrated in Fig. 8, although the eutectic temperatures of them could be determined with high accuracy. Data by visual observation of the change on heating were apt to be somewhat higher than those by other methods. Similarly, the peritectic point determined by DSC gave a little higher values than the one by solubility measurements.

The phase diagram of the benzene and griseofulvin system is shown in Fig. 9. It represents the type forming a compound with an incongruent melting point. The solubility data by Elworthy and Lipscomb[10] are also plotted in the figure. Since two melting point curves exist between compositions at E and E′ in Fig. 9, the portion E–E′ of the curve a-E–E′ will belong to the metastable liquidus. Also, the fact that the curve a-E–E′ and the extension of the stable liquidus c–P meet at a point E′ on the solidus d-E′-e at 4.50° will indicate that E′ is the metastable eutectic point. Accordingly, the point E which is the intersection of the stable liquidus of a-E and P–E must be the stable eutectic point, though it could not be determined experimentally. Values of the peritectic temperature obtained from the phase diagram, by DSC, and by visual observation were 35°, 38°, and 39°, respectively. Good agreement among these values will prove the validity of the diagram. The points A and B each determined by the authors and by Elworthy and Lipscomb[10] represent the metastable solubilities,

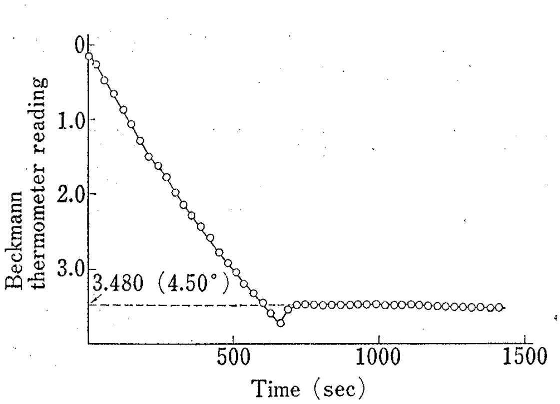

Fig. 8. Cooling Curve of Griseofulvin-Benzene System (Griseofulvin 0.8 w/w %)

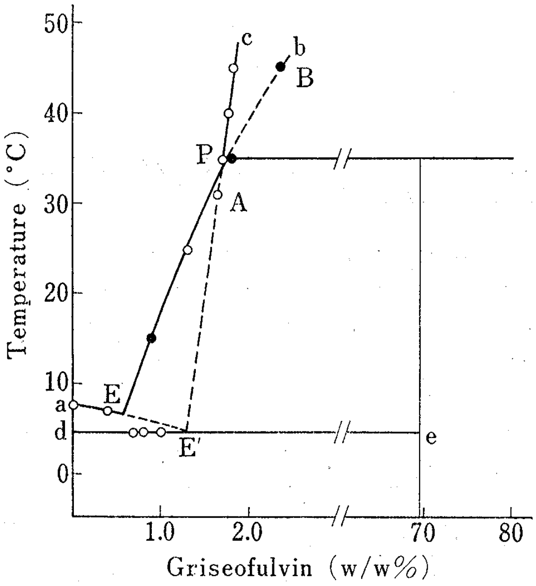

Fig. 9. Phase Diagram of Griseofulvin-Benzene System

values obtained by the authors (○) and by Elworthy, *et al.* (●)

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9) The melting point is defined here as the temperature at the end of melting on the beginning of freezing.

10) P.H. Elworthy and F.J. Lipscomb, *J. Pharm. Pharmacol.*, **20**, 790 (1968).

since they lie on the extensions of the stable liquidus curves. Relating to this fact, the latter authors mentioned nothing about the solvate formed between griseofulvin and benzene; on the contrary, they suggested that strong interactions between them are unlikely.

As shown in Fig. 10, the phase diagram of the dioxane and griseofulvin system is rather incomplete by difficulties of measurements employed. Therefore, it does not offer so much informations as that of the benzene and griseofulvin system. However, the liquidus and solidus curves are thought to be the stable ones, since the points on the curve b-E were obtained by solubility determination after equilibrium concentration was completely attained in the presence of the solvate crystals. Although the peritectic temperature of 80—85° was determined only by DSC, it is supposed that the system will also be the one forming a compound with an incongruent melting point.

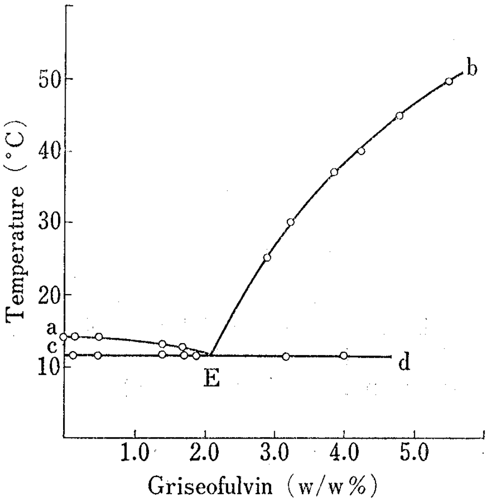

Fig. 10. Phase Diagram of Griseofulvin-Dioxane System

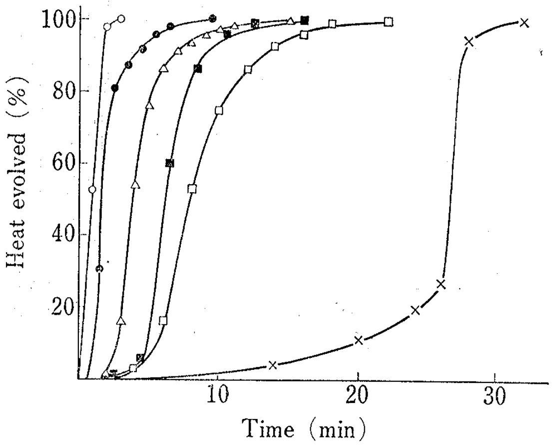

Fig. 11. Effects of Particle Size and Temperature on Desolvation Time of Griseofulvin-Dioxane Solvate

○: 80°, 1.5 mm crystals; ●: 70°, 0.1—0.5 mm crystals; △: 70°, 1.5 mm crystals; ■: 60°, 0.1—0.5 mm crystals; □: 60°, 1.5 mm crystals; ×: 50°, 0.1—0.5 mm crystals

Particle Size Reduction by Desolvation

Prior to micromeritic analysis, influence of particle size of the dioxane solvate and of its desolvating temperature upon the time required for complete desolvation was investigated by DSC. For this purpose, classified crystals of the solvate were put in a solid pan without crimping and the heat effect accompanied with desolvation was measured at constant furnace temperatures. From curves in Fig. 11, it is evident that the finer the solvate crystals and the higher the temperature, the more rapid desolvation is occurred. Probably, these effects will be related both to molecular hysteresis of the solvate crystals and to hindered diffusion of dioxane vapor through the desolvated layer.

Table II. Desolvation Conditions and Results of Particle Size Reduction of Griseofulvin Solvates

Solvate	Desolvation conditions		Recovered griseofulvin	
	Temp (°C)	Pressure	Specific surface area	Mean diameter[a]
Griseofulvin–Benzene	25	atmospheric	7 m^2/g	0.58μ
Griseofulvin–Dioxane	25	atmospheric	4.8 m^2/g	0.85μ

[a] $d=6/\rho\cdot S$
d=mean diameter $\rho=1.47$ S=specific surface area

Results of particle size reduction *via* desolvation of the solvates and the conditions adopted are summarized in Table II. The microphotograph of the particles obtained by desolvating the benzene solvate and their size distribution are also shown in Fig. 12 and 13. The fact that a somewhat larger diameter was measured by microscopic analysis of the product from the benzene solvate will be due to partial agglomeration of primary particles.

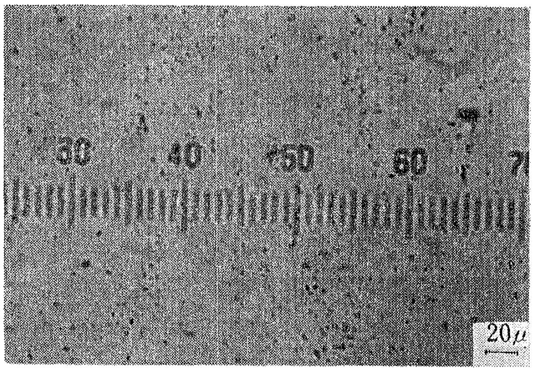

Fig. 12. Microphotograph of Griseofulvin Particles obtained by Desolvation of Griseofulvin-Benzene Solvate

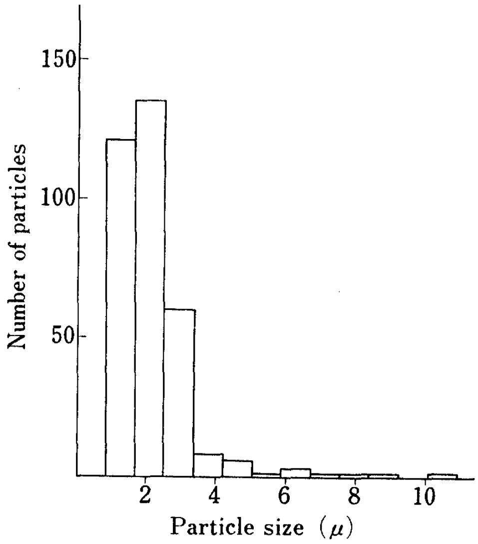

Fig. 13. Particle Size Distribution of Griseofulvin recovered by Desolvation of Griseofulvin-Benzene Solvate (mean particle size: 1.9815 μ)

In the case of the dioxane solvate, the desolvated product is comparatively stout and retains the shape of the original crystals. From the electron micrograph in Fig. 16 and the large specific surface area in Table II, it is clear that the product has a very porous structure. However, the stoutness retained even after desolvation was a peculiar experience for the authors, since all of the desolvated products previously investigated could be divided easily into fine primary particles. In this connection, the supposition that the solvate is likely to be an inclusion compound is partly based on this findings.

Since the benzene solvate of griseofulvin is not stable in environmental conditions, its X-ray patterns were measured periodically in order to find whether it is possible to obtain some information about the desolvation mechanism. As the result, appearance of a new peak at a 2θ value of 8.8° was confirmed as shown in Fig. 14. Because this peak is absent in both the X-ray patterns of the benzene solvate and of free griseofulvin, and because the peak intensity increases first and then decreases to zero before the end of desolvation (Fig. 15), it is certain that an intermediate structure is formed during the overall desolvation processes.

Surface Structures of the Desolvated Griseofulvin

The surface of griseofulvin particles after desolvation *via* the benzene solvate showed a stratified structure of tiny rods arranged in nearly one direction as shown in Fig. 16. Similar to the desolvated products of the chloroform solvate, these aggregates are easily separated into very fine primary particles.[5] On the other hand, the desolvated product of the dioxane solvate gave a scanning electron micrograph of stout aggregates. The mechanical rigidity is represented by the dense structure of their surfaces, though the surface roughness and the presence of many pores presumably due to evolved vapor are also observed clearly. Causes of such peculiar surface characteristics are at present unknown; however, it is conjectured that the type, the smaller ratio of dioxane molecule in the solvate, or even the capillary condensation during desolvation may have some relations to this result.

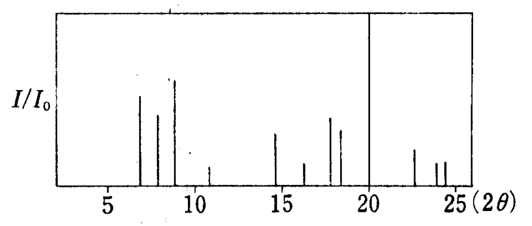

Fig. 14. X-Ray Powder Diffraction Pattern of Griseofulvin–Benzene Solvate, 11 Minutes after Desolvation.

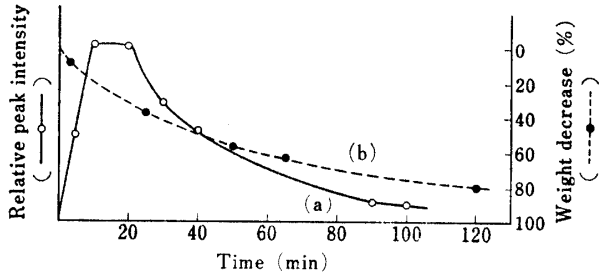

Fig. 15. Relative Peak Intensity Change in X-Ray Patterns of Griseofulvin–Benzene Solvate

(a): relative peak intensity change in X-ray patterns of griseofulvin–benzene solvate at 8.8° (2θ) (intermediate structure disappeared before completing desolvation)

(b): isothermal desolvation curve of griseofulvin–benzene solvate at 25°

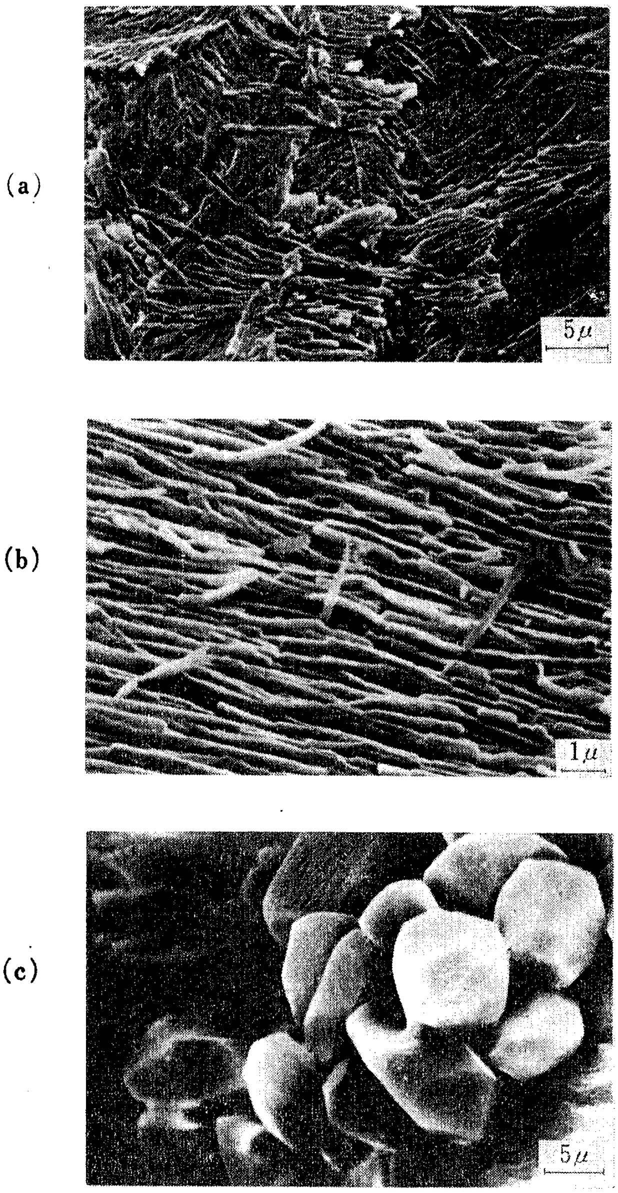

Fig. 16. Electron Micrographs of Desolvated Griseofulvin Surface

(a): *via* griseofulvin–benzene solvate, 2000x
(*b*): *via* griseofulvin–benzene solvate, 7000x
(*c*): *via* griseofulvin–dioxane solvate, 2000x

Conclusion

The benzene and dioxane solvates of griseofulvin which have hitherto been observed were recognized as real molecular species. However, it had been difficult to separate them in pure state before the procedures for isolation were established. Generally, on isolating any solvate of a drug compound which is thermodynamically stable in the experimental conditions, it often happens that either the metastable non-solvated compound or metastable solvate of lower order are actually obtained. These findings indicate us that the number of solvates is likely to be much more than now believed. For this reason, it can be said that the method of particle size reduction by way of desolvation of a solvate will have wider applicability.

It is also suggested from the above results that different kinds of bonding forces might be involved in solvates of a drug with different solvents. Accordingly, the stability of solvates differs considerably. When a solvate is very unstable in atmospheric conditions such as the benzene solvate of griseofulvin, its existence will not easily be confirmed unless various methods of identification are employed. On the contrary, in order to accomplish effective size reduction, the lower the stability of a solvate, the greater advantage would be expected.

Moreover, when a drug compound forms a number of solvates, it is thought possible to obtain size-reduced particles with various external shapes by selecting a particular solvent.

Although the anticipation is based on a few results of both ordinary and electron microscopy, further investigations will be required.

Lastly, the authors would like to emphasize the importance of the law of stages or of successive transformation formerly proposed by Wilhelm Ostwald.11) Surely, it is not a law but merely a generalization in strict sense, and is not known so well as other laws by this great pioneer of physical chemistry; nevertheless, it serves as a powerful guide for isolating various kinds of polymorphs, solvates and even molecular compounds, whether these physical forms are thermodynamically stable or metastable.

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11) A. Findlay, A.N. Campbell, and N.O. Smith, "The Phase Rule and Its Applications," 9th ed., Dover Publications, Inc., New York, 1951, pp. 54; K. Sekiguchi, "Iyakuhin Kaihatsu Koza: Physical Pharmacy (2)" Vol. 16, ed. by K. Tsuda and H. Nogami, Chijin-shokan, Inc., Tokyo, 1971, pp. 53.