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Thermal Analysis of Griseofulvin-Chloroform System by High Pressure Differential Scanning Calorimetry[1]

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Thermal analysis of the griseofulvin–chloroform system was done by differential scanning calorimetry with special pressure-resistant sample containers. Thus, the complete phase diagram in a condensed state could be constructed successfully. From the diagram, it was confirmed that a single one-to-one solvate having an incongruent melting point of 147°C was formed between the two components.

Keywords——griseofulvin; chloroform; phase diagram; differential scanning calorimetry; pressure-resistant sample container

In the earlier studies on particle size reduction by solvation and desolvation,[2] the chloroform ($CHCl_3$) solvate of griseofulvin was first identified, and its thermal properties were investigated to find suitable conditions for desolvation. At that time, it was considered that the system of griseofulvin and $CHCl_3$ belonged to the one forming a compound with an incongruent melting point.

In order to confirm the supposition, it was necessary to construct the phase diagram in a condensed state; however, in spite of repeated trials, a successful result could not be obtained with the instruments then available. For example, when differential scanning calorimetry (DSC) was done by sealing the sample mixture in an ordinary liquid container, a complete DSC curve could not be obtained because of rupturing of the container due to increased vapor pressure.

Fortunately, a new sample container for DSC has recently been developed in Japan.[3] This container withstands a pressure of about 50 atm, and suffices the above requirement. By the use of this high pressure-resistant container, the pending problem to construct the phase diagram of griseofulvin–chloroform as a condensed system could be solved at long last.

Experimental

Materials——1. Griseofulvin: Recrystallized from acetone, mp 220°C.

2. $CHCl_3$: The reagent-grade product was twice distilled, and the fraction distilling between 61—62°C was used.

3. Griseofulvin Chloroformate: Prepared by crystallization from $CHCl_3$ solution or by sorption of $CHCl_3$ vapor.

Differential Scanning Calorimetry——Thermoflexes DSC and TG -DSC (Rigaku Denki Co., Ltd.), which permit thermal analysis between -150—250°C, were used. At various heating rates and under a nitrogen gas flow of 30 ml/min, measurements were done with or without simultaneous thermogravimetry for detecting possible leakage of $CHCl_3$ vapor.

Sampling in the High Pressure Sample Container——Free griseofulvin or its chloroformate was weighed precisely in the container. Then, an appropriate amount of $CHCl_3$ was dropped in with a micro-syringe. An aluminum cover was mounted horizontally in the appropriate position, and the container was hermetically sealed by caulking with a special caulker. Thus, about 5—15 mg of samples with various compositions was prepared.[3]

Determination of the Eutectic, Peritectic and Melting Temperatures——In accord with the ICTA recommendations[4], the eutectic and the peritectic temperatures were determined from he extrapolated onset of the lower one or two endothermic peaks in the DSC curve, while the maximum of the highest peak was taken as the melting point.

Results and Discussion

When the high pressure container was used, none of the sample mixtures showed leakage of $CHCl_3$, irrespective of their composition, and two or three peaks generally appeared in each DSC curve (Fig. 1).

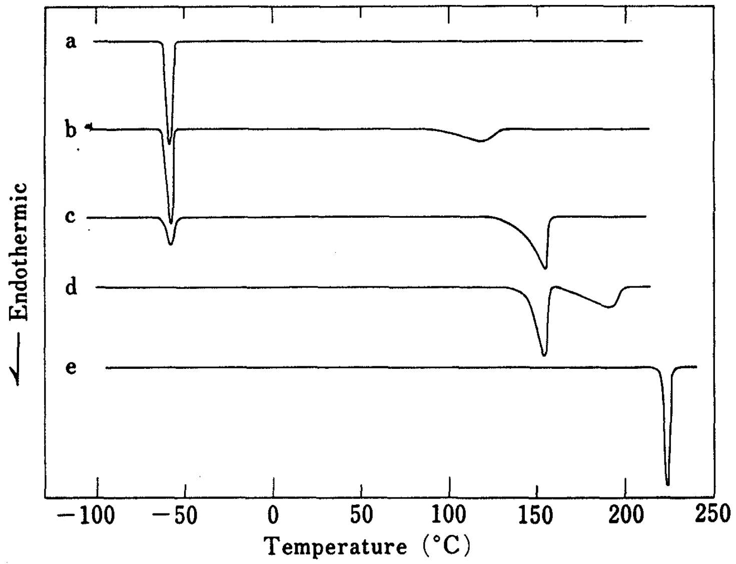

Fig. 1. DSC Curves of the Griseofulvin–Chloroform System

(a) Griseofulvin 0.0% (total sample amount 14.93 mg), (b) 19.4% (16.48 mg), (c) 55.2% (5.31 mg), (d) 77.0% (5.21 mg), (e) 100.0% (14.80 mg). Heating rate: 10°C/min.

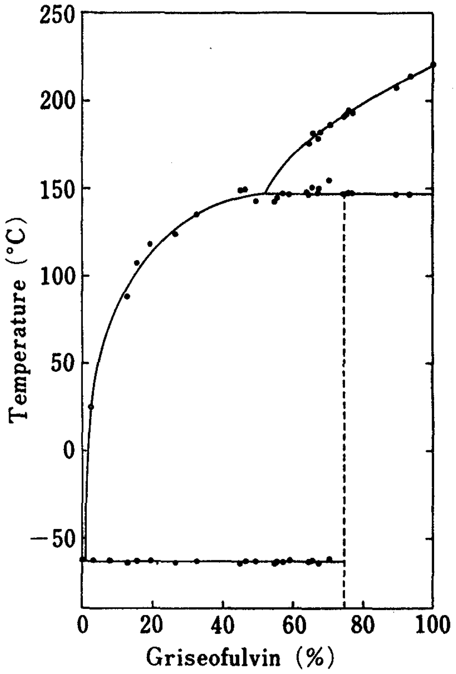

Fig. 2. Phase Diagram of the Griseofulvin–Chloroform System

The lower one or two peaks are assigned to the eutectic and/or peritectic fusion, while the higher one is attributable to melting of solid $CHCl_3$, the solvate or griseofulvin, depending on the composition of the sample. The measured temperatures of the three phase reactions were found to be almost constant (within ±1.0°C) at different heating rates between 1° and 10°C/min. It was also confirmed that metastable melting as a result of suspended peritectic reaction[5] did not occur at all. Thus, the phase diagram of the condensed system of griseofulvin and $CHCl_3$[6,7] was successfully constructed as shown in Fig. 2 by connecting the points for each phase reaction.

From these results, the following conclusions can be drawn regarding solvate formation and the size reduction of griseofulvin *via* the solvate.

(1) A single one-to-one solvate was formed between griseofulvin and $CHCl_3$ having an incongruent melting point of 147°C.

(2) The fact that very effective particle size reduction of griseofulvin could be accomplished by the solvation and desolvation method appears to be due both to the relatively high peritectic temperature of the solvate and to the strong escaping tendency of the $CHCl_3$ component upon heating, since these properties are favorable for solid phase decomposition.

References and Notes

1) This paper forms Part XX of the series entitled "Studies on Methods of Particle Size Reduction of Medicinal Compounds." Part XIX: K. Shirotani, E. Suzuki, and K. Sekiguchi, *Chem. Pharm. Bull.*, **31**, 2085 (1983).

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

3) Containers meeting this specification are obtainable from Daini-Seikosha Co., Ltd. and Rigaku Denki Co., Ltd.

4) G. Lombardi, "For Better Thermal Analysis," 2nd ed., International Confederation for Thermal Analysis, Rome, 1980.

5) K. Sekiguchi, K. Ito, and Y. Nakamori, *Chem. Pharm. Bull.*, **11**, 1123 (1963).

6) The pressure in the DSC container would not be constant during measurement of each sample mixture; however, in a condensed system, the effect of pressure on the phase transition temperatures will usually be very small, unless the pressure difference is extremely large. Therefore, the phase diagram of griseofulvin and $CHCl_3$ can reasonably be considered as an isobaric one.

7) The second peak of the sample containing a few percent griseofulvin was so shallow that the melting point could not be determined by DSC. For this reason, the value represented by an open circle in the liquidus curve of the phase diagram (Fig. 2) is that obtained from the solubility study in the previous paper.[2a)]