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Solubility of a New Polymorph of Phenobarbital obtained by Crystallization in the Presence of Phenytoin[1)]

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Physicochemical properties of some polymorphs of phenobarbital were studied. A new polymorph, form III-Ph, with a slightly changed crystal habit was obtained by addition of phenytoin at the time of recrystallization.

The transition temperature and the heat of transition between form III-Ph and form III, and between form III and form II were determined to be 46°C and 0.201 kcal/mol, and 77°C and 0.404 kcal/mol, respectively, by solubility measurement. As the dissolution rates of form III-Ph and form III were higher than that of form II, they are expected to show better bioavailability than form II.

Keywords——phenobarbital; polymorph; phenytoin; allobarbital; recrystallization; dissolution behavior; heat of transition; heat of solution

Many pharmaceuticals can exist in different polymorphic forms and the differences in molecular arrangements can affect the physicochemical properties and bioavailability. One method to alter the properties of a crystal is to change the crystal habit of an original compound by recrystallizing it in the presence of a small amount of a compound which is structurally very similar to the base material.[2–4)]

In the case of phenobarbital, more than thirteen different polymorphic forms have been reported.[5–7)] In the present study, phenobarbital was recrystallized in the presence of a similar compound. As a result, form III-Ph was obtained by addition of 6% phenytoin, and this form showed a higher dissolution rate than forms II and III. The dissolution behavior

and thermal properties of the three polymorphs (form II, form III and form III-Ph) were studied in this work.

Experimental

Materials——1) Form II: Phenobarbital of JP grade (Hoei Yakuko Co., Ltd.) was dissolved in acetone and recrystallized.

2) Form III: 30 g of phenobarbital of JP grade was dissolved in 120 ml of acetonitrile and recrystallized. It was also obtained by addition of 2.1 g of allobarbital (Tokyo Kasei Kogyo Co., Ltd.) at the time of recrystallization.

3) Form III-Ph: 30 g of phenobarbital of JP grade was dissolved in 120 ml of acetonirile and 1.8 g of phenytoin (Sanko Seiyaku Kogyo Co., Ltd.) was added. The mixture was maintained for three days at room temperature. The quantity of phenytoin in form III-Ph was about 1% as determined by high performance liquid chromatography.[8]

Elemental analysis data are shown in Table I.

Table I. Elemental Analysis Data for the Three Forms of Phenobarbital

	Elemental analysis (%)		
	C	H	N
Calcd	62.06	5.21	12.06
Form II	62.03	5.19	12.01
Form III	62.10	5.22	12.04
Form III-Ph	62.02	5.16	12.04

Characterization of Crystal Forms——Crystal forms were characterized by infrared (IR) spectrophotometry (JASCO IRA-1 grating infrared spectrophotometer), X-ray diffraction (Rigaku Denki Geigerflex 2012, Ni-filter, Cu-Kα radiation, 35 kV, 15 mA), and differential scanning calorimetry (DSC, Rigaku Denki, CN. 80, 85-DI).

Solubility Determination[9]——Distilled water (400 ml) in a 600 ml beaker was maintained at constant temperature (20, 25 and 30°C), 210—250 μm of a sample powder, approximately twice the saturated concentration, was added, and the mixture was stirred at 200 rpm. A 1 ml sample was taken at appropriate intervals using a cotton-filtered whole pipette, and after dilution with borate buffer at pH 9.5,[10] the concentration of phenobarbital was determined at λ_1=260 nm and λ_2=238 nm using a dual-wavelength spectrophotometer (Hitachi 356).

Results and Discussion

Effects of the Addition of Phenytoin and Allobarbital

Generally, in order to alter the crystal habit, it is most effective if a compound similar to the original one is used. Usually it is added at a level of 0.1—5%.[2] Form III is obtained by recrystallization of phenobarbital from acetonitrile, but some change can be seen in the X-ray diffraction pattern when recrystallization is carried out in the presence of a little phenytoin. In order to determine a suitable amount of phenytoin, it was added in amounts varying from 1 to 7.5% at the time of recrystallization, and the most remarkable change was seen in the presence of 6 or 7% phenytoin. This crystal form was designated form III-Ph. Form III-Ph was transformed to form III with the passage of time, but this transition was found to be delayed by leaving the crystals in the solvent. Consequently, to obtain form III-Ph, the crystals had to be kept for three days at room temperature in the solvent after the addition of 6% phenytoin. The form III-Ph thus obtained was stable for three months. No change was found in the X-ray diffraction pattern after addition of allobarbital.

Characterization of Crystal Forms by X-Ray Diffraction, DSC and IR

The X-ray diffraction patterns are shown in Fig. 1. Those of form II and form III agreed with those reported by Huang,[11] and a slight change was seen in the pattern of form

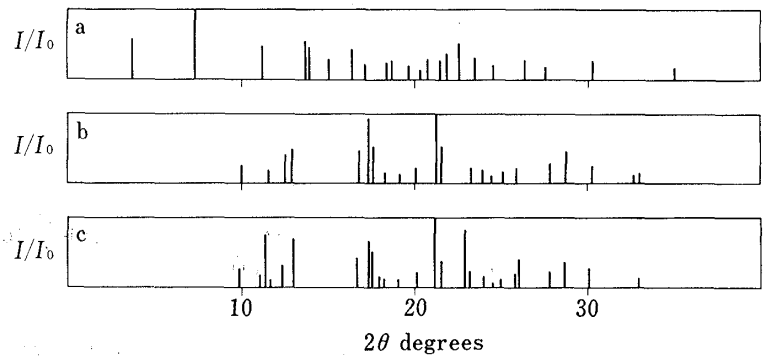

Fig. 1. X-Ray Diffraction Patterns of the Polymorphic Forms of Phenobarbital

a: form II, b: form III, or form III with addition of allobarbital, c: form III-Ph.

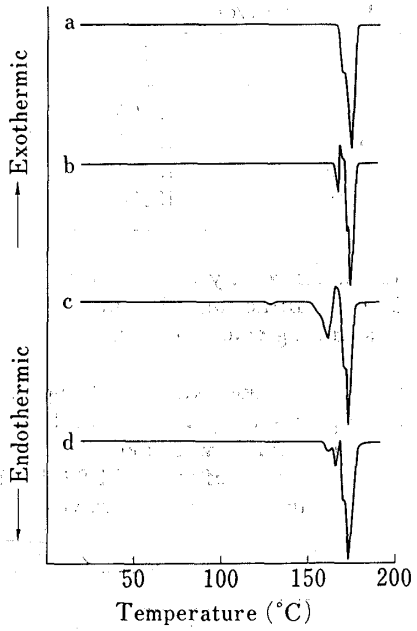

Fig. 2. Thermograms of the Polymorphic Forms of Phenobarbital by DSC (heating rate: 10 K/min)

a: form II, b: form III, c: form III with addition of allobarbital, d: form III-Ph.

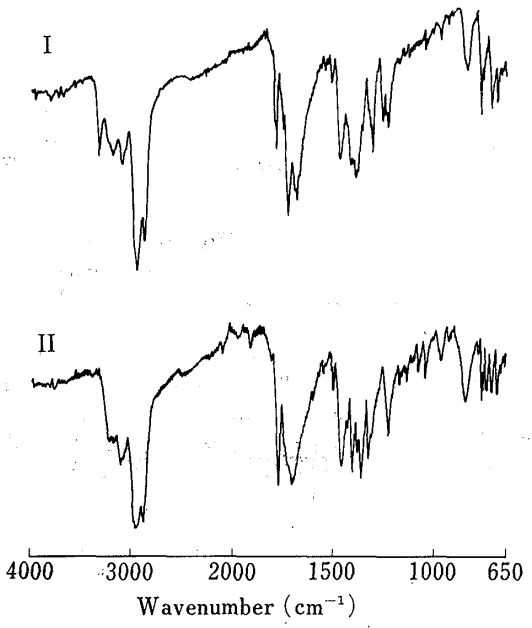

Fig. 3. IR Spectra of the Polymorphic Forms of Phenobarbital in Nujol

I: form II, II: form III, form III with addition of allobarbital, form III-Ph.

III-Ph compared with that of form III. As shown in Fig. 2, the DSC curve of form III-Ph exhibits a new endothermic peak before the endothermic peak of form III at about 165°C, and the exothermic peak which is seen with form III is not observed. IR spectra are shown in Fig. 3; there is no apparent difference between form III and form III-Ph.

Thus, it is considered that form III-Ph is a very similar crystal form to form III. Except in DSC, there was no difference between form III obtained by addition of allobarbital and that obtained in the absence of allobarbital.

Dissolution Behavior

Solubility values determined from the dissolution curves of phenobarbital polymorphs (form II, form III and form III-Ph) at different temperatures (20, 25, 30°C) are shown in Table II.

Table II. Solubilities for Form II, Form III and Form III-Ph of Phenobarbital at Various Temperatures

Temp. (°C)	Exptl. Soly., (mg/ml)		
	Form II	Form III	Form III-Ph
20	1.05	1.18	1.22
25	1.28	1.42	1.45
30	1.51	1.66	1.69

Table III. Thermodynamic Values calculated for Form II, Form III and Form III-Ph of Phenobarbital

Transition temperature (°C)		Heat of solution (kcal/mol)	Heat of transition (kcal/mol)
Form II		6.36	
	77		0.45
Form III		5.91	
	46		0.20
Form III-Ph		5.71	

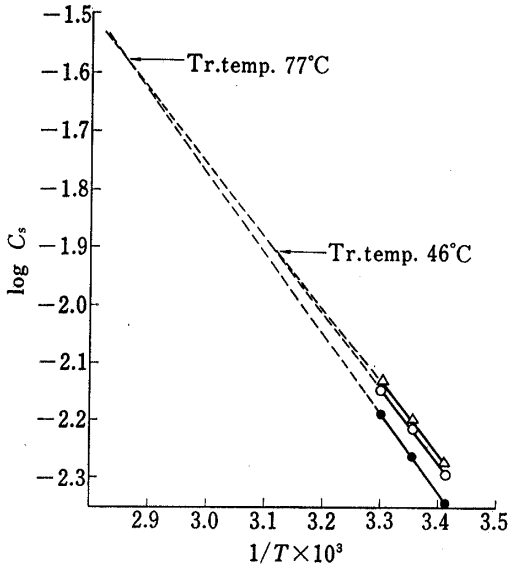

Fig. 4. The van't Hoff's Plots for Form II, Form III and Form III-Ph of Phenobarbital in Water

●—●: form II, ○—○: form III, △—△: form III-Ph.

The thermodynamic parameters[12] calculated from the van't Hoff's plots, from the solubility for form II, form III and form III-Ph are shown in Fig. 4 and Table III.

The solubility of form III-Ph obtained in the present study is very much higher than that of form II of JP grade. It should therefore show better absorption and bioavailability.

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