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Physicochemical Characterization of Spray-Dried Phenylbutazone Polymorphs

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Abstract □ A spray-drying method was applied to the recrystallization of phenylbutazone, and the resulting samples were examined by X-ray powder diffractometry, differential thermal analysis, IR spectrophotometry, scanning electron microscopy, and hot-stage photomicroscopy. Three different crystalline forms (δ, β, and ϵ) could be prepared from methylene chloride solution by varying the drying temperature of sprayed droplets from 120°C to 30°C. Form ϵ, the fifth polymorph of phenylbutazone, was confirmed as a novel crystalline form which could not be prepared by recrystallization techniques. In this spray-drying system the composition of spray-dried samples was shown to be a function of the drying temperature. While the stable form δ was obtained at higher drying temperatures, form ϵ was obtained only under conditions affording a slower evaporation rate of the solvent. The dissolution properties of the pure modifications prepared by recrystallization techniques and the spray-dried samples were evaluated in simulated intestinal fluid. Form ϵ showed excellent *in vitro* availability and much higher solubility than any other of the forms.

Keyphrases □ Phenylbutazone—recrystallized polymorphs, spray-drying technique, physicochemical characterization □ Spray-drying—recrystallized polymorphs of phenylbutazone, physicochemical characterization □ Recrystallization—polymorphs of phenylbutazone, spray-drying technique, physicochemical characterization

The physicochemical properties of solid drug substances are of considerable importance in preformulation studies, because they are related to both the production of dosage forms and bioavailability. The nature of the crystalline forms affects bioavailability through the effect of crystal properties on dissolution rate. In a particular polymorphic form, many solids may be prepared *via* appropriate modification of the conditions of crystallization. Some important factors relating to the resulting crystalline forms when obtaining polymorphs by recrystallization techniques are the nature of solvent (its polarity and solvent power), temperature, and rate of cooling. The latter two factors can take part in the crystallization velocity. Although precise control of the recrystallization velocity is difficult for ordinary recrystallization techniques, a spray-drying method may enable one to produce different crystallization velocities by varying the drying conditions of the sprayed droplets.

While several papers dealing with the polymorphism of spray-dried drug substances have been published (1–5), little information is available on the relationship between the operating factors and the resulting crystalline forms. An interesting polymorphism of phenylbutazone was found using a spray-drying method (6). This paper describes a further investigation to provide basic physicochemical information on the polymorphic forms.

BACKGROUND

There have been several reports describing the polymorphism of phenylbutazone, including our previous communication (Table I). Matsunaga *et al.* (7) found that phenylbutazone gave three polymorphs, *i.e.*, forms I, II, and III, among which the former two polymorphs (available commercially) were considered to be a stable form and one of the metastable forms, respectively. The mutual transformation among them by heating or through grinding and compression has been investigated. Ibrahim *et al.* (8) independently reporting on the polymorphism and feasibility of crystalline structural changes under tableting conditions, found the presence of four forms (I, II, III, and IV). Müller (9) showed later that forms I and II were pseudopolymorphs resulting from solvation. This was also confirmed by our differential thermal analysis–thermogravimetry analysis (DTA–TG). While Müller suggested the existence of a fourth polymorph (form γ) other than forms α, β, and δ (which had been already identified), he could not isolate it, despite describing its thermogram. In the same year Chauvet *et al.* (10) reported the thermal behavior of three polymorphs, *i.e.*, forms I, II, and III, obtained by different methods, all of which were identical to those already found. They considered that form II was identical to that reported by Matsunaga; however, based on the results of thermomicroscopy and thermal analysis, we estimated that the form II should actually be identical to the form γ designated by Müller (9). In a previous publication, it was shown that a fifth crystalline form (form ϵ) is formed together with forms β and δ in a spray-drying system. In this system forms α and γ

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Table I—Crystalline Modifications of Phenylbutazone and Their Melting Points by Differential Scanning Calorimetry

Investigator	Modifications (Melting Points, °C)						
Matsunaga *et al.* (7)	I (103)	II (93, 103)	III (93)				
Ibrahim *et al.* (8)	IV (105)	III (93)				II (90)[a]	I (80)[a]
Müller (9)	δ (107.5)	α (93.5)	β (95.1)	γ (106.0)			
Chauvet *et al.* (10)	I (106)		III (96)	II (104)			
Matsuda *et al.* (6)	δ (103)[b]		β (91)[b]		ε (95)[b]		

[a] Solvates. [b] DTA data.

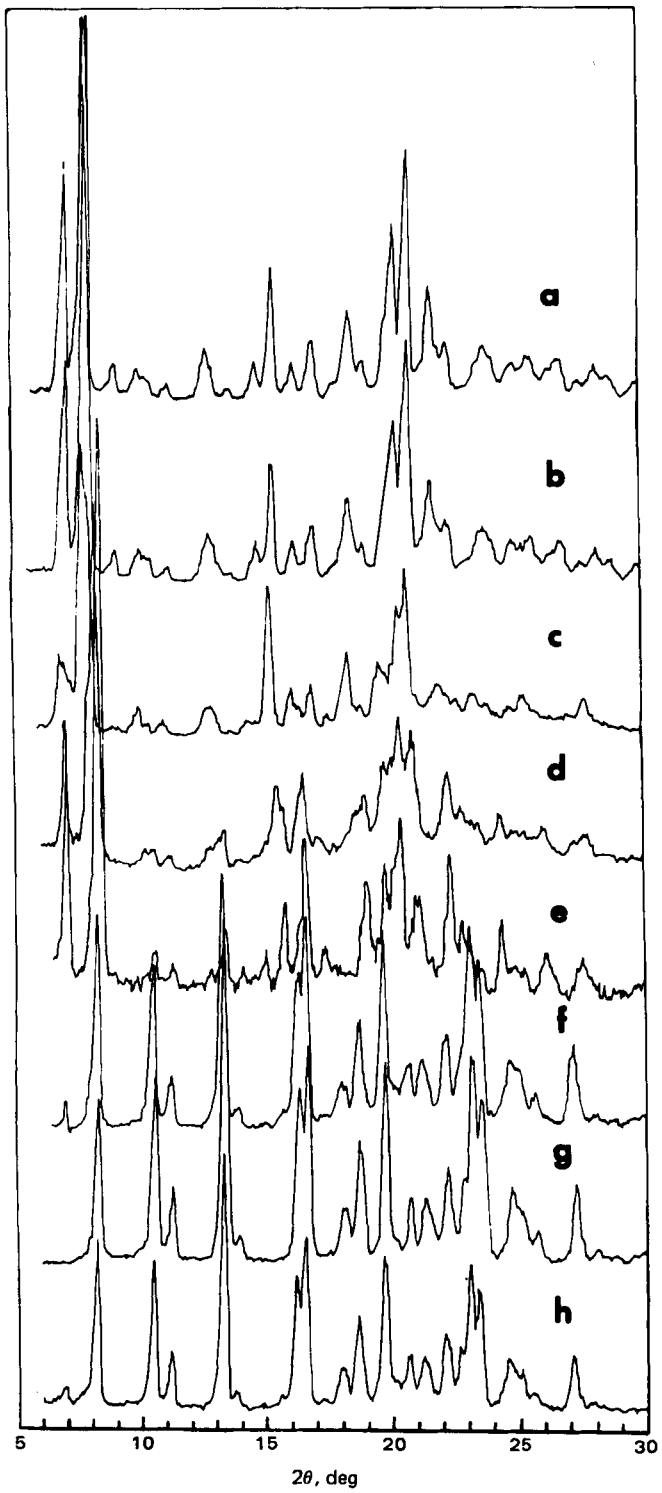

Figure 1—*X-ray powder diffraction patterns of form δ (a) and spray-dried samples prepared at drying temperatures of 120°C (b), 100°C (c), 80°C (d), 70°C (e), 60°C (f), 40°C (g), and 30°C (h).*

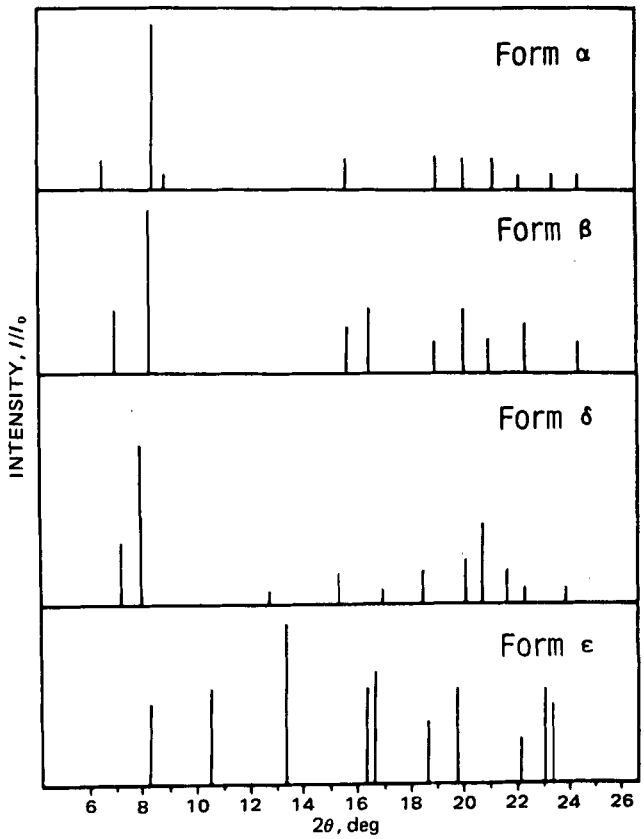

Figure 2—*Relative X-ray diffraction intensity patterns of forms α, β, and δ and the new form, ε.*

could not be obtained. The nomenclature of polymorphs in the present paper follows Müller's designations.

EXPERIMENTAL

Materials—A single batch of commercial phenylbutazone was used as received[1]. The drug was confirmed to be form δ (stable form) by X-ray powder diffraction analysis, differential thermal analysis (DTA), and IR spectroscopy. Form α was prepared by the method of Ibrahim (8); *i.e.*, water was added to a 2-propanol solution of form δ until it reached the cloud point, and Form β was prepared by pouring an ethanol solution of the same sample into cold water and stirring vigorously (9). These crystals were removed by filtration using a sintered-glass funnel and then dried under vacuum at room temperature. Methylene chloride was used as a solvent for spray drying. All the solvents were reagent grade and were used without further purification.

Spray Drying—Ten grams of phenylbutazone was dissolved in 200 mL of methylene chloride, and the solution was fed into a mini-spray drier[2] through a peristaltic pump at a flow rate of 20 mL/min. The temperature at the inlet of the drying chamber of the apparatus was varied in seven steps (120°C, 100°C, 80°C, 70°C, 60°C, 40°C, and 30°C) in seven runs; the temperature at the outlet varied from 64°C to 27°C, depending on the inlet temperature. Thus, seven samples (sample-120, -100, -80, -70, -60, -40, and -30, respectively) were prepared. The other operating

[1] Supplied by Ciba-Geigy (Japan) Ltd., lot no. 000978.
[2] Mini-Spray h_0; Yamato Kagaku Co., Tokyo, Japan.

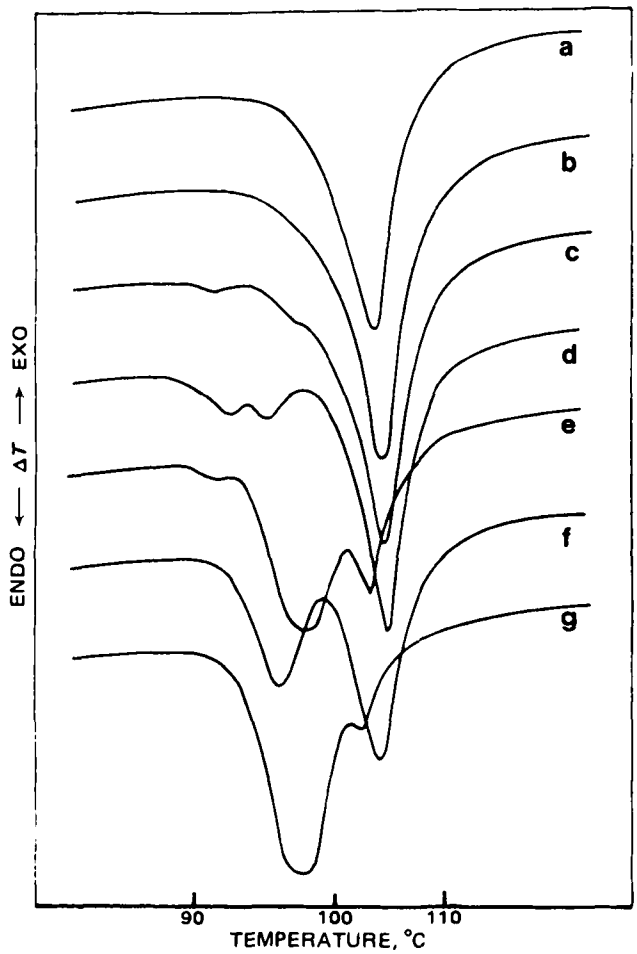

Figure 3—*DTA thermograms of spray-dried samples prepared at drying temperatures of 120°C (a), 100°C (b), 80°C (c), 70°C (d), 60°C (e), 40°C (f), and 30°C (g).*

conditions were: air pressure for atomizing, 2 kg/cm^2; flow rate of compressed air, 20 L/min; degree of reduced pressure in the drying chamber, 60–80 mm H_2O.

Characterization of Polymorphs—*X-ray Powder Diffraction Analysis*—X-ray diffraction patterns were recorded on a X-ray diffractometer[3] with Ni-filtered Cu-K_α radiation. The diffractometer was set at 35 kV–7 mA, 1° beam slit, and 0.2° detector slit with a count range of 2000 cps, a scanning speed of 1°/min, and a chart speed of 10 mm/min.

Differential Thermal Analysis—The thermograms of spray-dried samples and crystalline modifications prepared by the recrystallization method were recorded on a thermal analyzer[4] in an open-pan system; dry nitrogen at a constant flow rate was used as the carrier gas. α-Alumina served as a standard material. The rate of heating was 10°C/min unless otherwise stated. Thermogravimetry (TG) was also carried out for spray-dried samples to investigate the feasibility of the formation of solvates.

Infrared Spectroscopy—The IR spectra of forms δ and ϵ were recorded on a double-beam spectrophotometer[5] using the potassium bromide disk technique. No polymorphic changes in form ϵ were induced by grinding or compressing for sample preparation.

Scanning Electron Microscopy—The scanning electron photomicrographs of samples-120, -80, -60, and -30 were taken using a microscope[6] at magnifications ranging from 1000 to 3000×.

Photomicroscopy by the Hot-Stage Method—A photomicroscope equipped with a hot-stage was employed, and appearance changes during polymorphic transformation were observed for forms α and β and sample-30. The heating rate was 2°C/min.

Measurements of Solubility and Dissolution Rate—The solubilities

[3] Geigerflex 2011; Rigaku Denki Co., Tokyo, Japan.
[4] Model DTA-30; Shimadzu Co., Kyoto, Japan.
[5] Model 295; Hitachi Co., Tokyo, Japan.
[6] Model JSM-U3; Jeol Ltd., Tokyo, Japan.

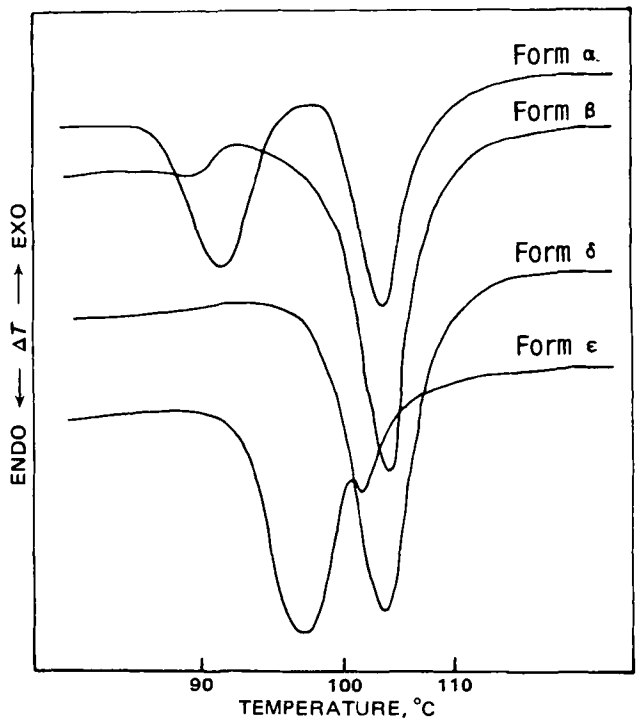

Figure 4—*DTA thermograms of forms α, β, δ, and ϵ.*

of different spray-dried samples were determined in simulated intestinal fluid (USP XIX), pH 7.5. An excess amount of powdered sample and 100 mL of the dissolution medium were placed in a 200-mL Erlenmeyer flask with a glass stopper. The flasks were fixed on the sample holder in a thermostatic water bath maintained at 37°C and mechanically shaken at a fixed rate of 60 strokes/min. Aliquots (2 mL) of the solution were withdrawn at designated intervals with a pipet fitted with a sintered-glass filter and suitably diluted with the dissolution medium. The concentrations of drugs were determined by measurement of the absorbance at 264 nm using a UV spectrophotometer. The resultant loss in volume was compensated for by adding dissolution medium maintained at the same temperature.

Using 500 mL of the dissolution medium, the dissolution rate was determined by a stationary disk method similar to that described by Wood

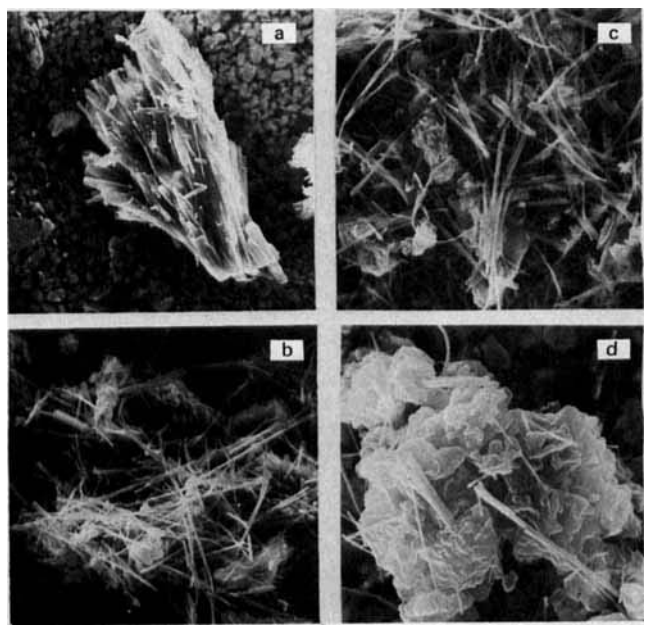

Figure 5—*Scanning electron microphotographs of spray-dried samples prepared at drying temperatures of 120°C (a), 80°C (b), 60°C (c), and 30°C (d). Original magnification for a, b, and c was 1000×; for d it was 3000×.*

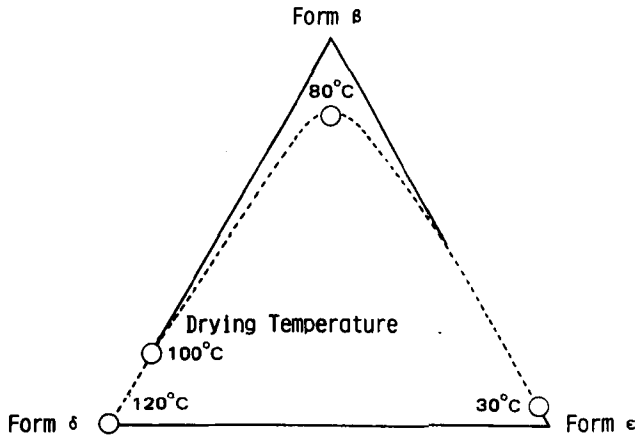

Figure 6—*Schematic phase diagram of spray-drying system of phenylbutazone.*

et al. (11) and Matsunaga *et al.* (7). A 100-mg portion of each sample was compressed in an 8-mm i.d. stainless steel die under the compression force of 1000 kg, using an accurate compression/tension-testing machine[7]. No polymorphic changes occurred during the compression for any of the samples. The rotation velocity of the stirring blade was maintained at 150 rpm during the experiment. The sampling procedures were the same as those described above; the rate was determined four times for each sample.

RESULTS AND DISCUSSION

Polymorphic Behavior—A wide range of drying temperature was applicable in this study; the spray drying could be performed successfully even at 120°C, which was much higher than the melting point of the stable form δ (103.0°C), because the surface temperature of recrystallizing crystals dropped below the melting point due to the evaporation heat of the solvent. Another extreme temperature (30°C) was applied to the present operating condition, although the boiling point of solvent was 40.1°C under atmospheric pressure.

Figure 1 shows the X-ray powder diffraction patterns of spray-dried phenylbutazone samples prepared at different drying temperatures together with a pure modification, form δ. The diffraction pattern of the sample-120 was quite similar to that of form δ. Within the range of 120–100°C the diffraction intensities decreased with a lowering in drying temperature, and the diffraction peak at 14.9° disappeared and new peaks appeared at 19.0° and 27.4°. This suggests that the sample-100 is not composed of only a single crystalline form. At the drying temperature of 80°C, although some of diffraction peaks attributable to the sample-120 still existed, the position of the maximum intensity peak at 8.0° (which was characteristic to form δ, sample-120, and sample-100) shifted to slightly higher diffraction angles, and the diffraction pattern was converted to one differing from that of the sample-120. At the temperature of 70°C new diffraction peaks appeared at 13.2°, 16.6°, 19.6°, and 23.1°, suggesting the presence of a third crystalline form in sample-70. Below 60°C the diffractograms showed quite different patterns from any of those obtained at temperatures above 70°C; they were no longer affected by drying temperature.

Figure 2 shows the relative X-ray diffraction intensity patterns of forms α, β, and δ [prepared by the recrystallization methods (8, 9)] and a new crystal form ε, obtained at 30°C. Distinct differences in the profiles were evident especially for form ε. Based on the collation of the diffraction patterns in Fig. 1 with those of pure crystal modifications, sample-120 was identified as form δ. However, sample-100 most likely consisted of a mixture of forms δ and β. Samples-80 and -70 seemed to be composed of mixtures of forms δ, β, and ε.

The X-ray diffraction analysis is not always able to distinguish a mixture of crystalline forms in a sample. The thermal behavior of a sample can be utilized as a supporting method for the identification and analysis of various forms in a mixture. The DTA curves of the samples in Fig. 1 and those of pure crystal modifications, together with sample-30, are illustrated in Figs. 3 and 4, respectively. The DTA curves for samples-120 and -100 showed a single endotherm at about 103°C corresponding to that of form δ despite of the differences in the X-ray diffraction patterns as seen in Fig. 1. The DTA curve for sample-80 showed an endothermic peak at 91°C, followed by a small exotherm characterizing transformation to form δ at ~93°C, a slight hollow at 95°C, and then a melting endotherm at 103°C. At the drying temperature of 70°C another small endothermic peak was observed at 95°C in addition to the peak at 92°C. Below 60°C such an endothermic change became more remarkable, showing another phase with thermodynamic instability. Conversely the endothermic peak at 91–92°C began to disappear as the drying temperature dropped. The possibility of the formation of solvate in the lower ranges of drying temperature was denied by the TG results and elemental analyses of these samples.

[7] Model IS-5000; Shimadzu Co., Kyoto, Japan.

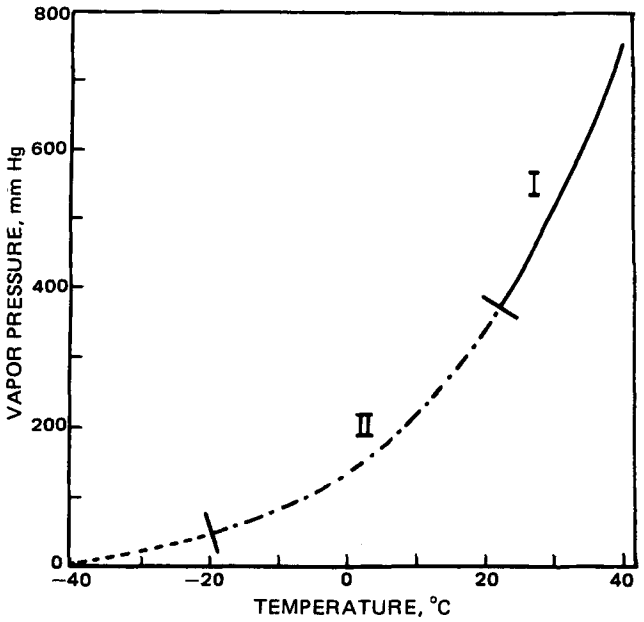

Figure 7—*Vapor pressure curve of methylene chloride and the resultant crystalline forms by the evaporation method. Key: (—) form δ; (·-·) mixture of forms δ and β; (- - -) not determined.*

Figure 5 shows the scanning electron photomicrographs of samples-120, -80, -60, and -30. As already pointed out by Müller (9), form δ did not differ essentially from form β in shape. Nevertheless, the shape of form δ in sample-120 was obviously a needle with round ends at higher magnifications, the individual single "crystal" being cluster of polycrystals. In the case of the sample-80 each crystal was entangled at random, but the crystals of forms δ and β were distinguishable from one another at higher magnifications. Simultaneously, the formation of form ε having a stony coral shape which was quite different from that of the other crystal modifications was detected. Although the amount of form ε obtained increased with a lowering in drying temperatures <60°C, form ε was not composed of a pure modification; a trace amount of form β existed even in sample-30.

The interpretation of X-ray diffractograms, thermograms, and scanning electron photomicrographs proved that sample-100 was composed of forms δ and β, and that sample-80 consisted of a mixture of forms δ, β, and ε, among which form β was the most abundant. The spray-drying system used in this investigation may qualitatively be summarized by a schematic phase diagram shown in Fig. 6. Very rapid evaporation of the solvent at higher temperatures in this system seemed to allow the maximum freedom for molecular orientation, resulting in the formation of the most stable form (δ) in the subsequent crystallization.

The evaporation rate of a single solvent is controlled by various factors including the vapor pressure of the solvent at a given temperature, the rate at which the heat is supplied, thermal conductivity and specific heat of the solvent, latent heat of evaporation, and the rate at which the vapor in contact with the solvent is removed. The transportation phenomena of vapor from a solution system, as in the case of this study, involve more complicated dynamic aspects. However, the major contributing factor in each case is the vapor pressure of the solvent. To simulate the evaporation of solvent from the sprayed droplets, the same solution was evaporated in a rotary evaporator at different temperatures under reduced pressure (15 mm Hg). The vapor pressure curve of methylene chloride and the forms of the resultant crystals are illustrated in Fig. 7. In this graph, while region I at higher temperatures gave only form δ, region II gave a mixture of forms δ and β. Though form ε could not be

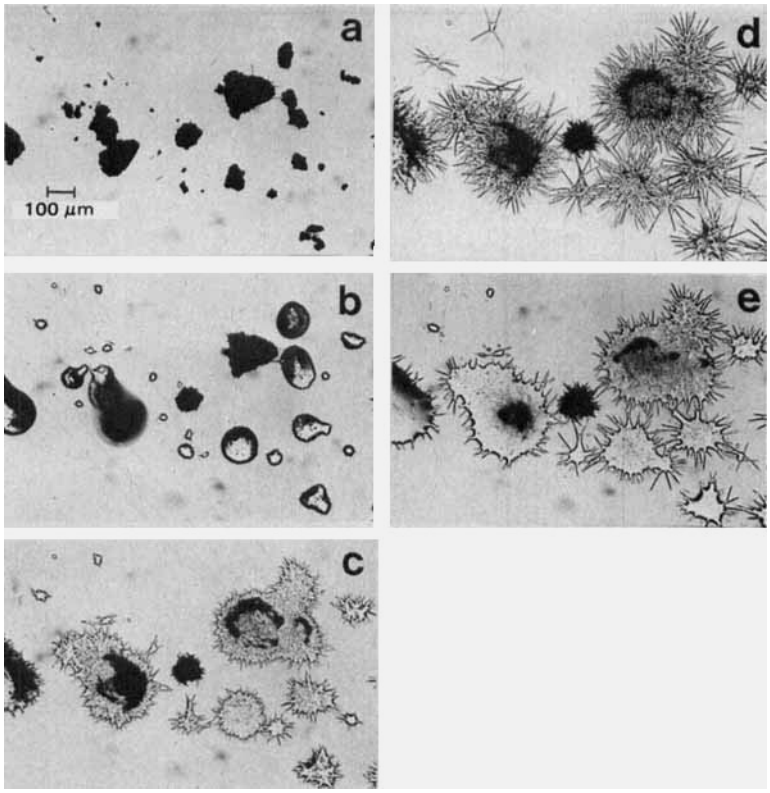

Figure 8—*Photomicrographs of form ϵ taken during the hot-stage microscopy study. Key: (a) 30°C; (b) 95°C; (c) 97°C; (d) 100°C; (e) 105°C.*

obtained within the range of the experimental condition, the result obtained in Fig. 7 may explain the present spray-drying system. From Figs. 6 and 7 form ϵ appears to be formed only at an extremely slow evaporation rate of the solvent.

Although form ϵ fused at its melting point and the liquid then recrystallized into form δ without generating a recrystallization exotherm under the ordinary analytical condition, the thermogram showed an exothermic peak at heating rates of <5°C/min. Such thermal behavior could also be

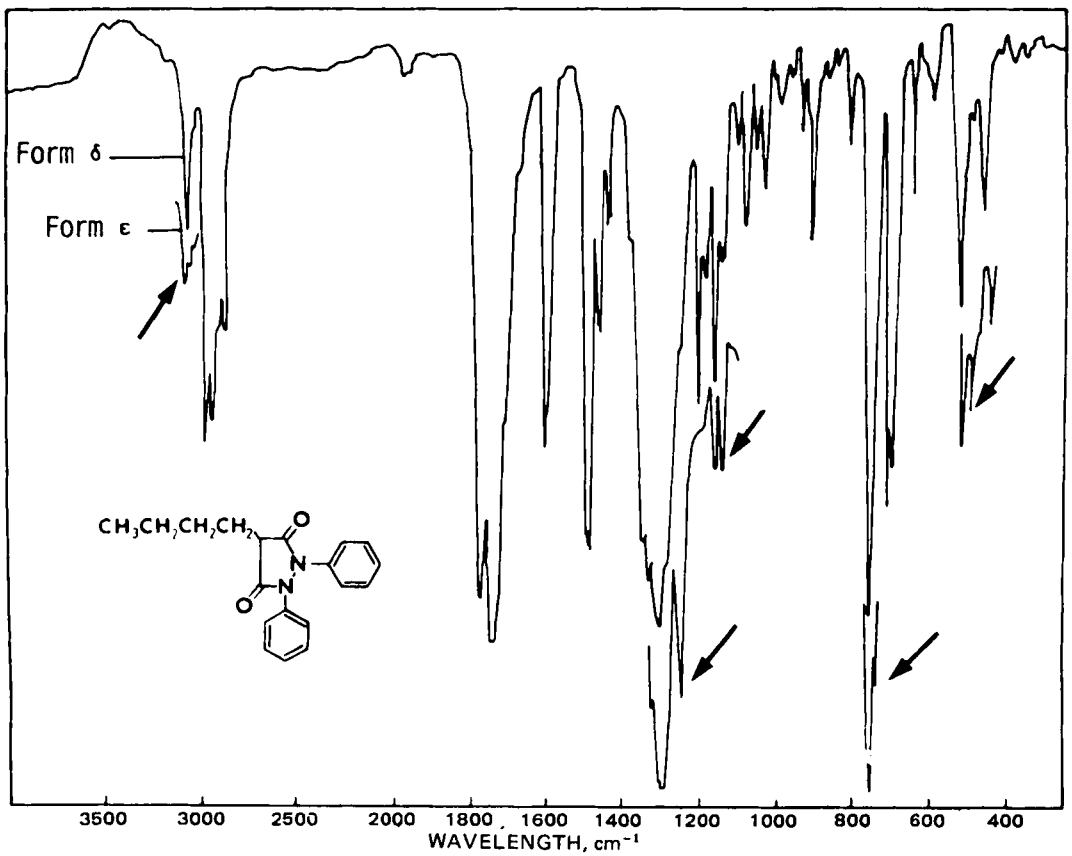

Figure 9—*IR spectra of forms δ and ϵ.*

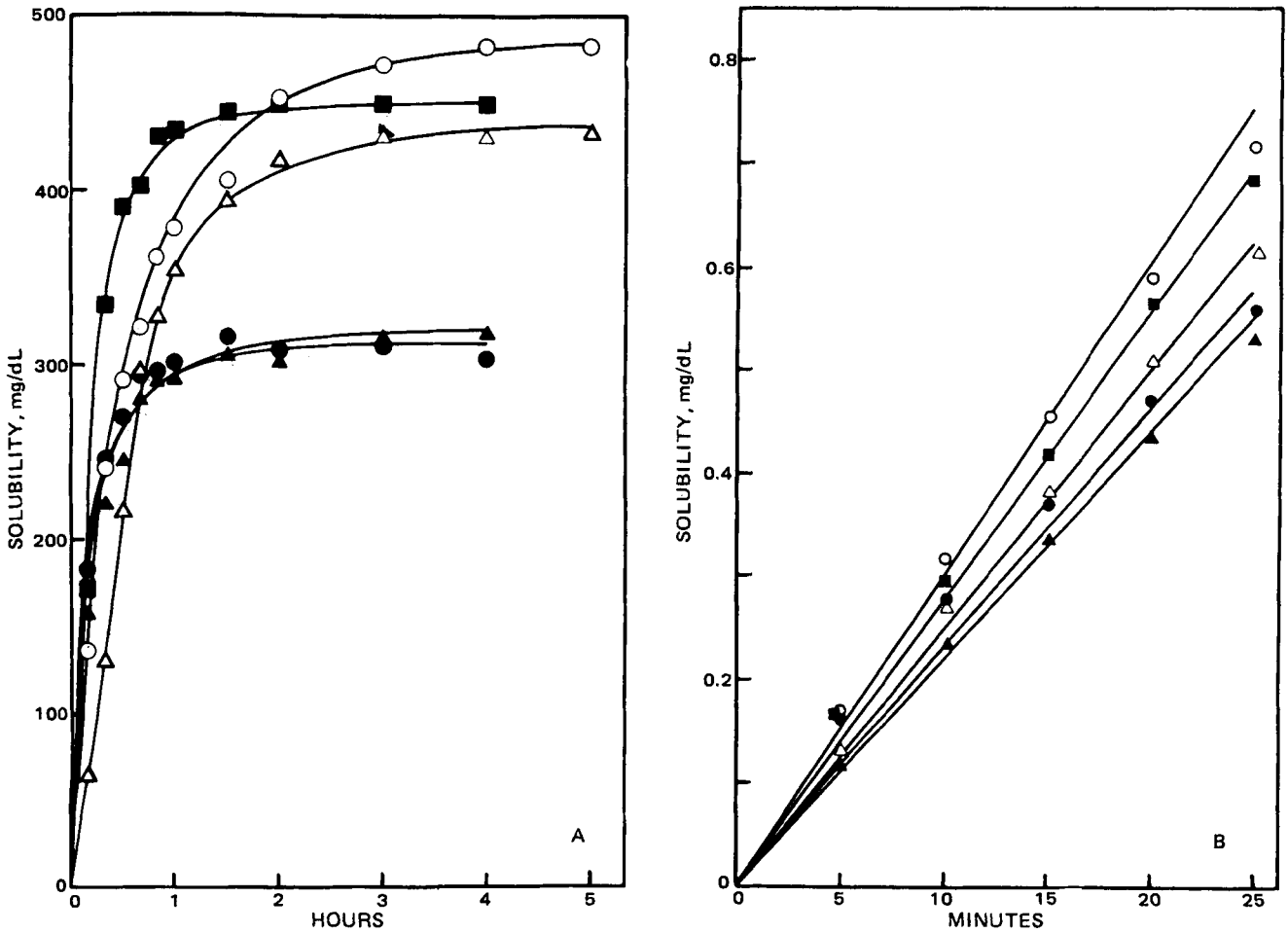

Figure 10—*Solubility profiles (A) and dissolution rates (B) of pure modifications and spray-dried samples prepared at different drying temperatures in simulated intestinal fluid at 37°C. Key: (●) form δ; (■) form β; (▲) sample at 120°C; (△) sample at 80°C; (○) sample at 30°C.*

evidenced by the hot-stage photomicroscopy. The result is shown in Fig. 8, visualizing the fusion of form ε at ~95°C and the polymorphic transformation to form δ in the range of 97–100°C.

Differing from the cases of forms α and β, grinding or compression did not induce the polymorphic transformation of form ε. Therefore, the IR spectrum of form ε was compared with that of form δ (Fig. 9). As indicated with arrows in Fig. 9, form ε was significantly different from form δ in five absorption bands (3050, 1293, 1130, 752, and 580 cm^{-1}). The differences for the C—N bonds between two nitrogen atoms and benzene rings and for the C—H bonds among individual benzene rings are attributable to the differences in crystalline structure.

Dissolution Properties—The dissolution behaviors of forms δ and β and of samples-120, -80, and -30 are depicted in Fig. 10A. Since the dissolution behavior of a mixture containing more than two polymorphs was hard to interpret even if the sample was of sufficient purity, only the three spray-dried samples in which one crystalline form was dominant were used in the dissolution study.

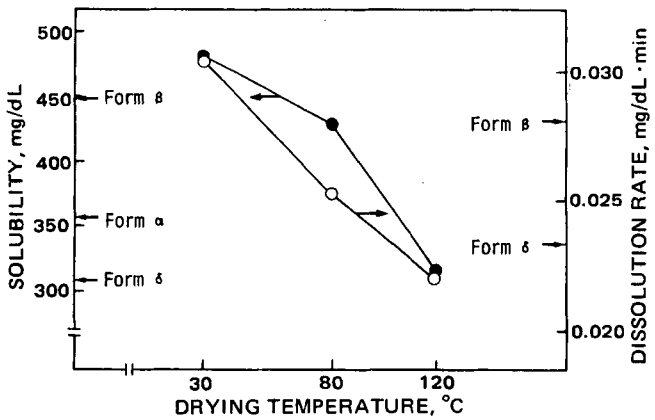

Figure 11—*Effect of drying temperature on the solubility (●) and dissolution rate (○) of spray-dried samples.*

The apparent equilibrium solubilities of forms β and ε were not affected by dissolution time, suggesting that they were not converted to form δ during the dissolution process. The dissolution rates of the samples in Fig. 10A are shown in Fig. 10B. Based on Müller's method (9), both the die and the punches were cooled with liquid nitrogen so as to prevent the polymorphic change during the disk preparation of sample-80. Good linear relationships were established for all the samples except for form δ, indicating that polymorphic transformation was also not induced during the dissolution measurement. The apparent dissolution rates calculated from the slopes of the regression lines, together with the solubilities in Fig. 10A, are given in Fig. 11 as functions of drying temperature. Both parameters increased with the increase in amount of form β in the sample, since the dissolution properties of form β were superior to those of form δ. As expected from the purity, the solubility of sample-80 reached nearly the same value as that of the pure modification β. However, the apparent dissolution rate was far smaller than that of form β. Below 80°C form ε contributed to both parameters more predominantly as the drying temperature dropped, and sample-30 gave a solubility ~1.56 times higher than that of form δ. Both the solubility and apparent dissolution rate of sample-30 were, of course, significantly higher than those of any of the other known crystalline forms including form α. The dependencies of these dissolution properties on the drying temperature were in good agreement, and the excellent *in vitro* availability of form ε was confirmed.

In the present investigation the spray-drying technique could be applied to prepare different crystalline forms by varying the operating condition. More extensive research is necessary to examine the possibility of controlling the purity of the crystalline form.

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Expanded Solubility Parameter Approach I: Naphthalene and Benzoic Acid in Individual Solvents

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Received September 13, 1982, from the *Drug Dynamics Institute, College of Pharmacy, University of Texas, Austin, TX 78712 and the ‡Energy Center, University of California at San Diego, La Jolla, CA 92093. Accepted for publication November 17, 1982. §Present address: China Chemical and Pharmaceutical Co., Taipei, Taiwan.

Abstract □ An expanded solubility parameter system was tested in conjunction with the extended Hansen solubility approach and the UNIFAC method to calculate the solubilities of naphthalene and benzoic acid in polar and nonpolar solvents. The expanded parameter system is characterized by δ_d for the dispersion force, δ_p for dipolar forces, a basic or electron-donor parameter, δ_b, and an acidic or electron-acceptor parameter δ_a. The correlation between the calculated and observed solubilities of benzoic acid was increased by use of the four-parameter system. An indicator variable was required to bring the solubilities into line in strongly dipolar solvents such as *N*,*N*-dimethylformamide. For naphthalene, use of the four-parameter approach proved not to be an improvement over the three-parameter extended Hansen solubility approach. The UNIFAC method was not successful in calculating solubilities of benzoic acid in the 40 polar and nonpolar solvents. A triangular plot of the three Hansen parameters for benzoic acid, *p*-hydroxybenzoic acid, and methyl *p*-hydroxybenzoate illustrated the contributions of dispersion, dipolar, and Lewis acid–base (hydrogen bonding) interaction forces among the three benzoic acid compounds and the various classes of solvents. A multiple regression procedure for calculating the four partial solubility parameters of drug solutes was developed.

Keyphrases □ Solubility parameters, expanded—individual solvents, four-parameter extended Hansen approach, UNIFAC, naphthalene, benzoic acid □ Extended Hansen approach—solubility of naphthalene and benzoic acid in individual solvents, four-parameter system, UNIFAC □ Benzoic acid—model drug, solubility in individual solvents, four-parameter extended Hansen approach, UNIFAC

Recently (1) the solubility of naphthalene was investigated in individual solvents. A new technique, the extended Hansen solubility approach, was compared with the universal functional group activity coefficient (UNIFAC) method (2) and the extended Hildebrand solubility approach (3). The present study was undertaken to investigate the extended Hansen method in more detail and to expand the number of partial solubility parameters from three in the original Hansen approach to four to account for Lewis acid–base (electron acceptor and donor) properties.

Naphthalene was studied in 26 solvents at 40°C and benzoic acid in 40 solvents at 25°C. Naphthalene data were obtained from the literature (1), and benzoic acid data were generated in this laboratory. Both three- and four-parameter solubility systems were used to correlate the solubilities for naphthalene and benzoic acid.

THEORETICAL

Extended Hansen Solubility Approach—The extended Hansen method (1) was successful in predicting the solubilities of naphthalene in individual solvents. Naphthalene is a good model to begin the study of nonpolar compounds in single solvents; however, it is a poor prototype of a drug molecule. Although naphthalene provides π-electrons for solute–solvent interaction, its lack of functional groups and side chains makes it considerably less irregular than molecules typically encountered in the pharmaceutical sciences. Benzoic acid, with its behavior in water and other polar solvents, provides a considerably better model of a drug.

The extended Hansen solubility equation is written:

$$\log \frac{X_2^i}{X_2} = \log \alpha_2 = C_0A + C_1A(\delta_{1d} - \delta_{2d})^2 + C_2A(\delta_{1p} - \delta_{2p})^2 + C_3A(\delta_{1h} - \delta_{2h})^2 \quad \text{(Eq. 1)}$$

where X_2^i is the solute ideal mole fraction solubility, X_2 is the observed solute mole fraction solubility, α_2 is the activity coefficient of the solute, and C_i (where i = 0,1,2,3) are regression coefficients obtained from regression analysis. δ_{jd} is the partial solubility parameter representing London dispersion forces, δ_{jp} is the Keesom dipolar solubility parameter, and δ_{jh} is a term for generalized electron-transfer bonding which includes hydrogen bonding and other Lewis acid–base interactions; j is 1 for solvent and 2 for solute. These parameters are always taken at 25°C, regardless of use. A is a term from regular solution theory (4):

$$A = \frac{V_2\phi_1^2}{2.303RT} \quad \text{(Eq. 2)}$$

where V_2 is the molar volume of the solid solute taken as a hypothetical supercooled liquid at 25°C, ϕ_1 is the volume fraction of the solvent, R is the molar gas constant, and T is the absolute temperature. The volume fraction of the solvent is defined as:

$$\phi_1 = \frac{(1 - X_2)V_1}{(1 - X_2)V_1 + X_2V_2} \quad \text{(Eq. 3)}$$

where V_1 is the molar volume of the solvent.

The partial solubility parameters, δ_{1d}, δ_{1p} and δ_{1h} for the solvents are found in the literature (5). Solubility parameters for solid solutes are seldom reported because organic compounds may decompose near their melting points and because of the low vapor pressures of these compounds. The properties of the solid phase cannot be used since the state

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