Preformulation Investigation II: Dissolution Kinetics and Thermodynamic Parameters of Polymorphs of an Experimental Antihypertensive

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Abstract □ Polymorph I of an experimental antihypertensive was obtained by recrystallization from methanol, water, or hydrochloric acid; Polymorph II was harvested from isopropanol, dimethylformamide, or dimethylacetamide. The dissolution rate and peak solubility of Polymorph II are three or four times greater than that of Polymorph I. After reaching the maximum concentration plateau, the dissolution rate of Polymorph II is exceeded by the nucleation rate and an apparent first-order decline in the drug concentration is observed. This is attributed to the *in situ* crystalline transformation of a less stable Polymorph II to a more stable Polymorph I. Although the nucleation process remains as first order within a 3-hr. period, the nucleation rate is changed at a specific time. The time at which the first-order nucleation rate changes is a function of the temperature: the lower the temperature, the slower the nucleation half-life and the longer the observed transition time of the nucleation process. The relation between the rate of first-order nucleation process and the degree of saturation of the system is derived and verified with the experimental data. Various thermodynamic parameters involved in this transformation are calculated. The enthalpy change, the free energy change, and the entropy change for the conversion of Polymorph II to Polymorph I were determined to be −2232 cal./mole, −172.4 cal./mole, and −6.6 e.s.u., respectively. Furthermore, the attainable peak solubilities and the first-order nucleation rates of Polymorph II obtained from different recrystallization solvents are different from each other. These findings may imply that the variation of absorption and therapeutic efficacy of a drug supplied in a dosage form by different firms could be caused not only by employing different polymorphs but also by using the same polymorph recrystallized from different solvents.

Keyphrases □ Dissolution kinetics—polymorphs of an experimental antihypertensive, effect of recrystallization from different solvents □ Bioavailability, polymorphs of an experimental antihypertensive—effect of recrystallization from different solvents on dissolution kinetics □ Polymorphism—effect of structure and recrystallization from different solvents on dissolution kinetics □ 1-(2,3-Dihydro-5-methoxybenzo[*b*]furan-2-ylmethyl)-4-(*o*-methoxyphenyl)piperazine hydrochloride polymorphs—dissolution kinetics, thermodynamic parameters

Particular substances are by no means restricted to specific crystalline forms or even to different forms in the same crystallographic system. Such multiplicity of forms with the same chemical properties is termed polymorphism. In general, the number of forms that a material assumes is relatively few, although in principle there is no limit. Two types of polymorphism are encountered in nature: reversible (enantiomorphism) and irreversible (monotropism). The familiar pair of rhombic and monoclinic sulfur is a common example of dimorphic enantiomorphism, while white and red phosphorus form a monotropic system.

The pharmaceutical applications of polymorphism were recently reviewed by Haleblian and McCrone (1). Three main reasons for studying polymorphism in the drug industry are: (*a*) to improve the physical and/or chemical stability of a drug in various dosage forms, (*b*) to enhance the tableting behavior of powders, and (*c*) to increase the dissolution rate and, ultimately, the absorption and therapeutic efficacy of a drug. Since the first patent on stable cortisone acetate suspension was granted to Macek (2) and the bioavailability of amorphous *versus* crystalline novobiocin acid was demonstrated by Mullins and Macek (3), the investigation of polymorphism has been increasing.

Generally speaking, two types of phase changes may take place during the dissolution or solubility study of a compound: polymorphic change and solvate formation. A number of pharmaceutical compounds undergoing phase reversions have been reported. These include: cortisone acetate (2), novobiocin acid (3), phenobarbital (4, 5), sulfathiazole (6, 7), methylprednisolone (7–10), prednisolone (11), glutethimide (12), theophylline (12), aspirin (13–16), ampicillin (17), aminoalicyclic penicillin (18), chloramphenicol palmitate and stearate (19–25), mefenamic acid (25), a potential antihypertensive (26) and antiviral (27) compound, chlordiazepoxide hydrochloride (28), cephaloglycin (29), and cephalexin (29).

In a previous paper (30), the relationship of salt forms and biological activity of a potential antihypertensive compound was reported. The present report focuses on the dissolution kinetics and thermodynamic parameters of polymorphs of this same compound, 1-(2,3-dihydro-5-methoxybenzo[*b*]furan-2-ylmethyl)-4-(*o*-methoxyphenyl)piperazine hydrochloride[1].

EXPERIMENTAL

Preparation of Polymorphs—The compound employed for this investigation was known to be crystallized from isopropanol–ethyl acetate (95:5). A series of solvents including methanol, isopropanol, isoamyl alcohol, acetone, dimethylacetamide, dimethylformamide, distilled water, and 0.1 *N* hydrochloric acid were employed as recrystallization solvents. An excess quantity of the compound was introduced into 500 ml. of solvent at 60°. The undissolved drug was filtered off, and the saturated solution was cooled overnight in a 6° refrigerator. The crystals were then harvested by filtration with a sintered-glass funnel and allowed to dry at 60° under high vacuum for 7 days. The crystals obtained from each solvent were subjected to the following tests: elemental analysis, melting-point determination, purity tests, IR spectra, and X-ray diffraction patterns. By using U. S. standard sieves, a fraction of 20–40-mesh particles was collected for use in the dissolution studies.

Determination of Dissolution Profiles—An excess of the drug beyond its equilibrium solubility was introduced into 100 ml. of 0.1 *N* hydrochloric acid maintained at 37°. The method employed was essentially that of Shefter and Higuchi (12). The drug and the dissolution medium were stirred by an overhead stirrer operating at 500 r.p.m. The three-blade stirrer, 2.3 cm. in diameter, was placed 2 cm. below the surface of the dissolution medium. At prescribed intervals, aliquot samples were withdrawn and replaced with the same volume of fresh medium kept at 37°. The samples were im-

[1] Su-17770B.

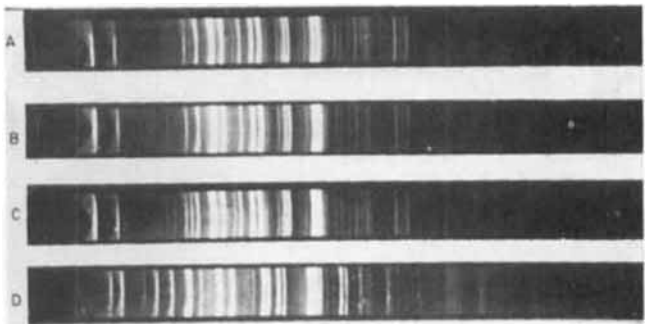

Figure 1—*X-ray patterns of an experimental antihypertensive before recrystallization study (Pattern A, Polymorph II) and after recrystallization from methanol (Pattern D, Polymorph I), isopropanol (Pattern B, Polymorph II), and isoamyl alcohol (Pattern C, mixed Polymorphs I and II but predominantly Polymorph II).*

mediately filtered through a Millipore filter assembly using filter paper having a pore size of 0.45 μ. The filtrates were properly diluted and assayed spectrophotometrically at 282 nm. using a spectrophotometer (Hitachi).

Determination of Intrinsic Dissolution Rate—Approximately 250 mg. of powder was compressed into a disk in a die-punch assembly attached to the Carver press. A compression force of about 2000 p.s.i. was employed, with a 0.8-cm. (0.33-in.) punch. By using the dissolution apparatus of Wood *et al.* (31), the intrinsic dissolution rate of the compound was investigated in 600 ml. of 0.1 *N* hydrochloric acid at 37°. The solution was stirred with a three-blade stirrer, 4.3 cm. in diameter, at 60 r.p.m. At prescribed time intervals, aliquot samples were withdrawn and assayed as already indicated.

RESULTS AND DISCUSSION

Elemental analysis and various purity tests for samples recrystallized from methanol, isopropanol, and isoamyl alcohol are shown in Table I. Residual recrystallization solvents were not discernible, and the purity tests further substantiated the analytical purity of these samples. The representative X-ray diffraction patterns are depicted in Fig. 1. The original sample before recrystallization is designated as Polymorph II and is shown as Pattern A in Fig. 1. The original sample was transformed to Polymorph I after the material was recrystallized from methanol. As indicated by Pattern B of Fig. 1, the original sample remains as Polymorph II if isopropanol is employed as the recrystallization solvent. However, the material transforms to Polymorph I upon contact with methanol. The X-ray diffraction pattern of Polymorph I is depicted as Pattern D in Fig. 1. If isoamyl alcohol is used, mixed Polymorphs I and II are obtained with Polymorph II as the predominant constituent. This is depicted in Pattern C of Fig. 1. The IR spectra of Polymorphs I and II are illustrated in Fig. 2. Distinct differences in IR and X-ray profiles are evident and offer a rapid method of polymorph identification.

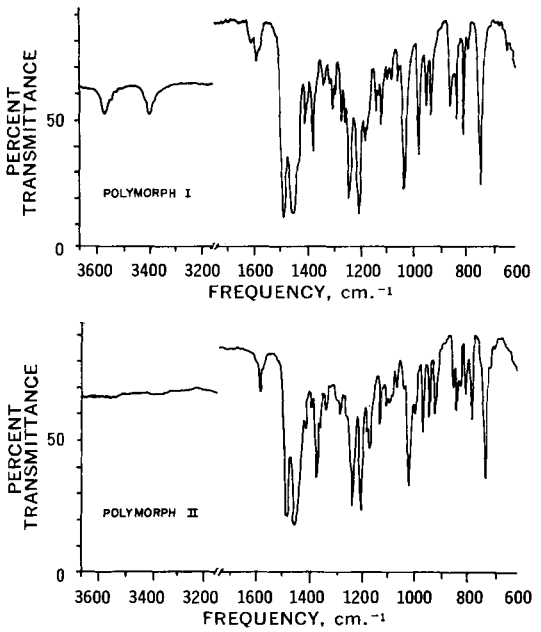

Figure 2—*IR spectra of an experimental antihypertensive recrystallized from methanol (Polymorph I, upper spectra) and isopropanol (Polymorph II, lower spectra).*

The dissolution behavior of Polymorph I (recrystallized from methanol) in 0.1 *N* hydrochloric acid is shown in Fig. 3. The curves were obtained at 15, 27, and 37°. As expected, the initial dissolution rate is increased as the temperature of the dissolution medium is increased. It can be seen that the concentration of drug in solution approaches the equilibrium solubility very rapidly and remains essentially constant. The remaining materials from the dissolution study of Polymorph I were isolated and dried under vacuum. The X-ray diffraction patterns, IR spectra, and melting points of these materials were found to be identical to those of Polymorph I before commencing the dissolution profile determination.

The dissolution profiles of Polymorph II (recrystallized from isopropanol) at 10, 27, and 37° as a function of time are shown in Fig. 4. It is evident from these curves that after an apparently rapid dissolution and attainment of peak drug concentration, there is a decline of drug in solution with time. A dissolution profile of this type can be properly characterized by the following five parameters: (*a*) the magnitude of initial dissolution rate, (*b*) the peak solubility attained at pseudosteady state, (*c*) the time the apparent nucleation process commences, (*d*) the kinetic order and rate of nucleation and

Table I—Elemental Analysis and Purity Tests for the Samples of the Antihypertensive Recrystallized from Methanol, Isopropanol, and Isoamyl Alcohol

Recrystallization Solvent[a]	Elemental Analysis—Theory	Elemental Analysis—Found	Purity Tests—Titrimetry[b]	Water Content[c]	TLC[d]	Residual Solvent[e]	Polymorph Assigned[f]	Melting Point[g]
Methanol	C 64.52 H 6.96 Cl 9.01 N 7.13	64.54 6.97 9.48 7.05	99.8 ± 0.5	<0.2%	Trace impurity at R_f 0.75	None	I	224°
Isopropanol	C 64.52 H 6.96 Cl 9.01 N 7.13	64.71 7.11 9.75 7.16	100.2 ± 0.5	<0.2%	Trace impurity at R_f 0.75	None	II	219°
Isoamyl alcohol	C 64.52 H 6.96 Cl 9.01 N 7.13	64.67 7.04 9.68 7.21	99.7 ± 0.5	<0.2%	Trace impurity at R_f 0.75	None	I + II (II ≫ I)	—

[a] See text for sample treatment. [b] Nonaqueous potentiometric titration with perchloric acid in the presence of mercuric acetate. [c] As determined by Karl Fischer titrimetric method. [d] Major spot has R_f of 0.90 when developed by ethyl acetate–isopropanol–methanol (80:18:2) on silica gel HA_{254}. [e] As determined by GLC for determining the residual solvent employed for recrystallization study. [f] As assigned by IR and X-ray results. [g] Corrected values as determined with the Thomas–Hoover capillary melting-point apparatus.

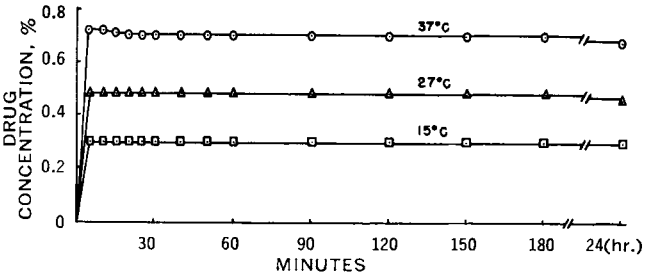

Figure 3—*Dissolution profiles of an experimental antihypertensive recrystallized from methanol (Polymorph I) in 0.1 N HCl at 15, 27, and 37°.*

whether or not the nucleation rate is changing as a function of time, and (*e*) the approximate equilibrium solubility.

It is apparent from a comparison of Figs. 3 and 4 that the initial dissolution rate and the peak solubility of Polymorph II are three or four times greater than those of Polymorph I. It took approximately 30–40 min. for Polymorph II to reach the pseudosteady phase or peak solubility. When the maximum concentration plateau is reached, the dissolution rate of Polymorph II is exceeded by the nucleation rate and an apparent first-order decline in the drug concentration is observed. This is attributed to the *in situ* crystalline transformation of a less stable Polymorph II to a more stable Polymorph I (26), as evidenced by the facts that: (*a*) the limiting value of this decline in drug concentration was found to approximate the equilibrium solubility of Polymorph I, and (*b*) the properties of the materials isolated from the dissolution study of Polymorph II were found to be identical to those of Polymorph I. Hence, the complete *in situ* crystalline reversion of Polymorph II to Polymorph I was clearly confirmed. Further evidence of the transformation was tested by the following two experiments:

1. During the course of determining the dissolution profile of Polymorph II, the precipitate retained on the filter paper was collected and dried under high vacuum at 40° for several hours. The X-ray diffraction patterns of the precipitate collected 30 min. postdissolution is shown as the middle photo of Fig. 5. The data clearly demonstrate that Polymorph II undergoes *in situ* crystalline transformation. The diffraction maxima at 2ϕ = 13.7, 14.8, and 17.5 are characteristic of Polymorph I, and these values are already clearly detectable with the sample of Polymorph II at 30 min. postdissolution.

2. The material harvested 24 hr. after the dissolution study of Polymorph II was collected in a medium-porosity sintered-glass funnel and divided into two portions. The first portion was immediately subjected to Karl Fisher determination and found to contain 14.8% water. The second portion was dried under vacuum at 40° for 24 hr., and the water content was found to be 0.27%. By using these "wet" and "dry" samples, the dissolution profiles in 0.1 *N* hydrochloric acid at 37° were redetermined and found to be identical to each other as well as superimposable to the dissolution profile of Polymorph I at 37°, as shown in the upper curve of Fig. 3.

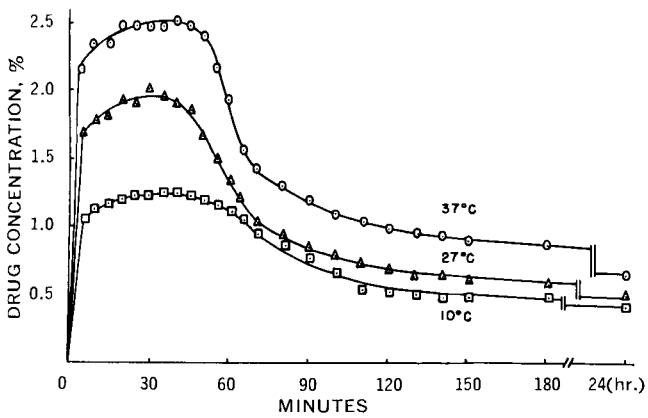

Figure 4—*Dissolution profiles of an experimental antihypertensive recrystallized from isopropanol (Polymorph II) in 0.1 N HCl at 10, 27, and 37°.*

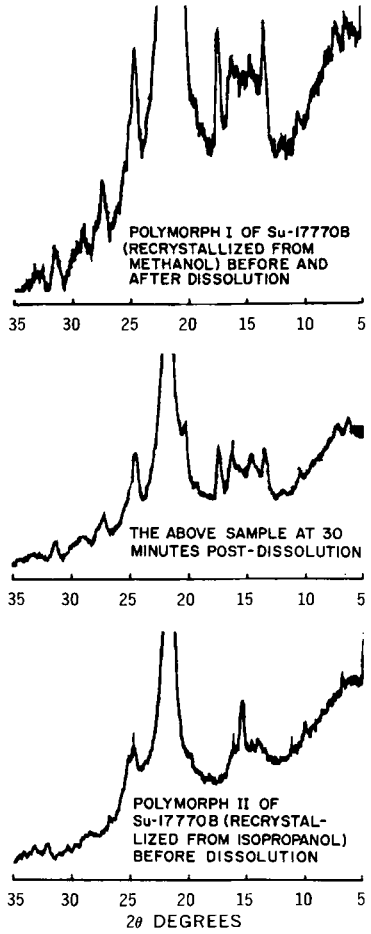

Figure 5—*X-ray diffraction patterns of Polymorph II of an experimental antihypertensive before dissolution (upper photo) and at 30 min. postdissolution (middle photo). Polymorph I is shown in lower photo.*

When isoamyl alcohol was employed as the recrystallization solvent, mixed Polymorphs I and II were harvested, with Polymorph II as the predominant component. From the dissolution profiles of Polymorphs I and II (Figs. 3 and 4, respectively), it was predicted

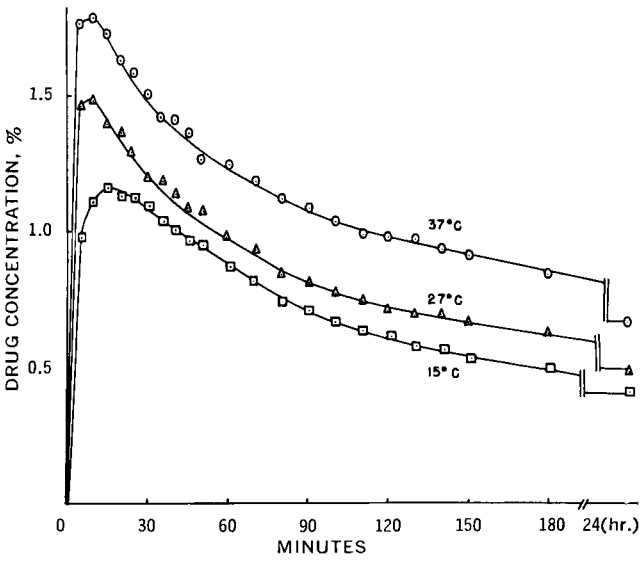

Figure 6—*Dissolution profiles of an experimental antihypertensive from isoamyl alcohol in 0.1 N HCl at 15, 27, and 37°.*

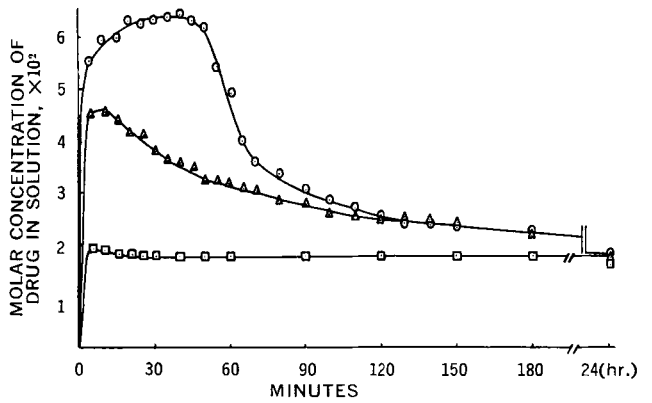

Figure 7—*Dissolution profiles of Polymorph I (from methanol, lower curve), Polymorph II (from isopropanol, upper curve), and mixed Polymorphs I and II (from isoamyl alcohol with II>>I, middle curve) of an experimental antihypertensive in 0.1* N *HCl at 37°.*

that the dissolution rate, peak solubility, time for commencing the nucleation process, and nucleation rate obtained with this sample would be intermediate between those of Polymorphs I and II but with closer resemblance to Polymorph II. This prediction is confirmed by the dissolution profiles shown in Fig. 6. As the drug begins to dissolve, the initial rate is dominated by the solubility of Polymorph II. Because of the reversion of Polymorph II to I, Polymorph I forms and crystallizes out into the dissolution medium. Therefore, upon reaching peak solubility and followed by the decrease of drug concentration in solution, the limiting solubility of this mixed polymorph was found to be the equilibrium solubility of Polymorph I. The complete transformation to Polymorph I was verified again by the various methods already mentioned.

Figure 7 provides the relative magnitude and characteristics of the dissolution profiles of the individual and mixed Polymorphs I and II in 0.1 *N* hydrochloric acid at 37°. The dissolution curve of Polymorph II (upper curve) merges together with that of the sample containing mixed polymorphs (middle curve) at about 2 hr. postdissolution. Nevertheless, complete conversion from Polymorph II to Polymorph I was seen to occur within 24 hr., as shown by the same equilibrium solubilities of these three samples at 24 hr. postdissolution. It is apparent from the comparison of these three curves that the initial dissolution rate of Polymorph II is decreased, the peak solubility is reduced from 6.45×10^{-2} to 4.55×10^{-2} *M*, the time needed for initiating the nucleation process is shortened from about 40 to 10 min., and the nucleation rate is suppressed approximately threefold when there is only about 5–10% of Polymorph I "contaminating" Polymorph II. The difference in the peak solubilities of Polymorphs II and I is about 3.5-fold. Therefore, in selecting the proper polymorph, the advantages of faster dissolution rate and higher peak solubility afforded by Polymorph II are certainly obvious from the *in vitro* standpoint.

Table II—Relationship of Initial and Intrinsic Dissolution Rates in 0.1 *N* Hydrochloric Acid at 37°

Recrystallization Solvent	Polymorph	Initial Dissolution Rate[a], mole/min.	Intrinsic Dissolution Rate[b], mg.-cm.²/min.
Methanol	I	0.0038	0.27
Isoamyl alcohol	I + II (II ≫ I)	0.0091	1.00
Isopropanol	II	0.0109	1.27

[a] Amount of drug in solution at 5 min. postdissolution as obtained from the dissolution profiles of Fig. 7. [b] Calculated from the slope of Fig. 8.

Intrinsic dissolution rates of these three samples were determined under conditions of constant agitation, constant surface, and constant thickness of diffusion layer. The result is depicted in Fig. 8. As expected from the dissolution profiles shown in Fig. 7, Polymorph II had a more rapid intrinsic dissolution rate (upper curve, Fig. 8) than Polymorph I (lower curve, Fig. 8). Although a straight-line relationship is observed for Polymorph I, the slope of the line for Polymorph II deviates from linearity after about 8 min. This deviation was also found for the sample recrystallized from isoamyl alcohol (middle curve of Fig. 8). The upper and middle curves of Fig. 8 strongly confirm the fact that Polymorph II is being transformed to Polymorph I during the dissolution process.

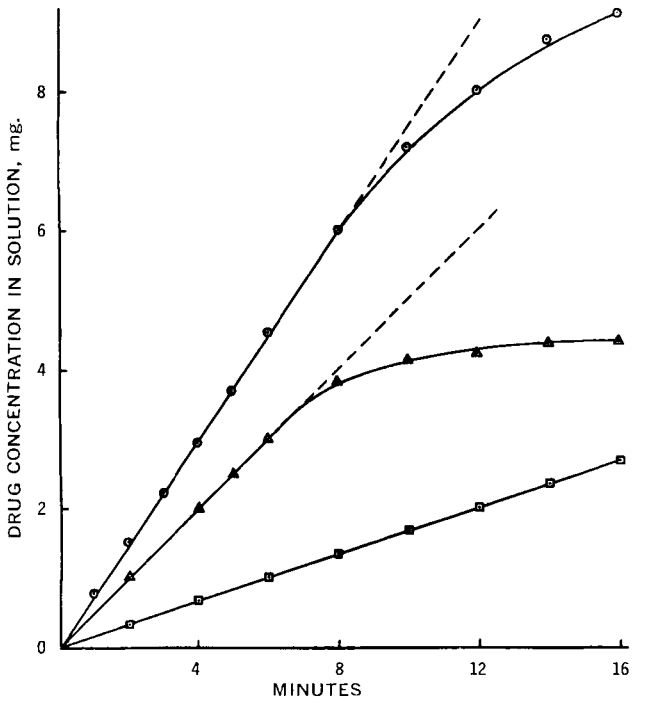

Figure 8—*Plots illustrating the intrinsic dissolution behaviors of Polymorph II recrystallized from isopropanol (upper curve), Polymorph I recrystallized from methanol (lower curve), and sample containing mixed Polymorphs I and II as harvested from isoamyl alcohol (middle curve).*

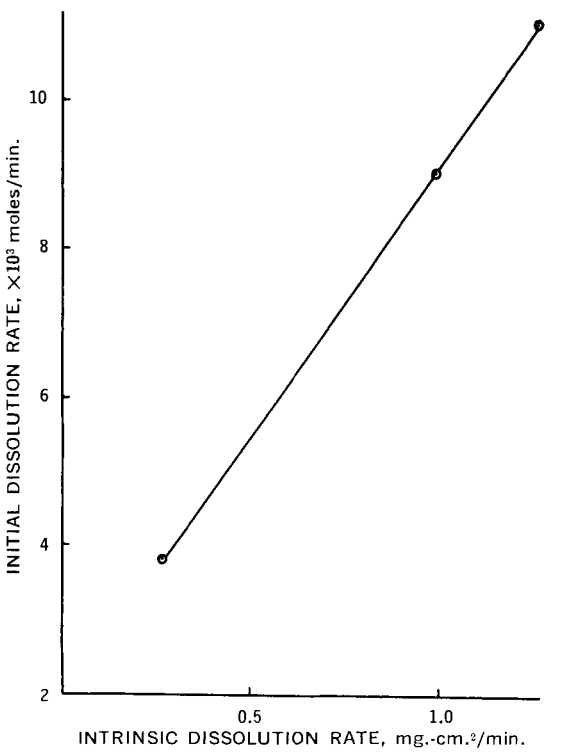

Figure 9—*Correlation of initial dissolution rate and intrinsic dissolution rate of an experimental antihypertensive. See Table II for details.*

Table III—Characteristics of Dissolution Profiles in 0.1 *N* Hydrochloric Acid

Recrystallization Solvent[a]	Polymorph	Peak Solubility, molar, $\times 10^2$	Nucleation Characteristics: Time Nucleation Starts, min.	First-Order Nucleation Process: $t_{1/2}^{I}$, min.	$t_{1/2}^{II}$, min.	Transition Time, min.[b]	Equilibrium Solubility,[c] molar, $\times 10^2$
Methanol	I	1.92 (37°)	<5	—	—	—	1.71
		1.23 (27°)	—	—	—	—	1.20
		0.82 (15°)	—	—	—	—	0.79
Isopropanol	II	6.45 (37°)	40	35	265	90	1.69
		5.12 (27°)	35	39	280	100	1.23
		3.20 (10°)	40	54	295	114	1.02
Isoamyl alcohol	I + II (II ≫ I)	4.55 (37°)	10	89	260	72	1.71
		3.79 (27°)	10	90	235	87	1.23
		2.99 (15°)	15	105	186	118	1.07

[a] See text for sample treatment. [b] Time at which first-order nucleation rate is changed. [c] Drug concentration in solution at 24 hr. postdissolution was taken as approximated equilibrium solubility.

Table II demonstrates the relationship between the intrinsic dissolution rate and the initial dissolution rate. The intrinsic dissolution rate was calculated from the slope of the individual curve shown in Fig. 8, whereas the initial dissolution rate was obtained from the drug concentration in solution at 5 min. postdissolution from the dissolution profiles illustrated in Fig. 7. It is shown that the compound with the higher dissolution rate goes into solution rapidly regardless of the rotating speed and the method employed. The correlation of intrinsic and initial dissolution rates is clearly illustrated by Fig. 9.

As mentioned previously and as shown in Figs. 4 and 6, the concentration of drug in solution starts to decline after reaching the pseudosteady phase. Although the order of the decline in drug concentration was reported to be first order by several authors (11, 17, 25), definitive analysis of the data was not performed. For this reason, the dissolution data presented in Figs. 4 and 6 are transformed into logarithmic plots as demonstrated in Fig. 10. These curves show that the nucleation characteristics during the dissolution profile determination in 0.1 *N* hydrochloric acid are first order in nature. The upper three curves are obtained with Polymorph II recrystallized from isopropanol, whereas the lower three curves are obtained with the sample recrystallized from isoamyl alcohol. Although the nucleation process remains as first order within a 3-hr. period, the nucleation rate is changed at a specific time for each curve. The time at which the first-order nucleation rate changes is found to be a function of the temperature of the dissolution medium: the lower the temperature, the slower the nucleation half-life and the longer the observed transition time of the nucleation process. The nucleation characteristics obtained at various temperatures are summarized in Table III. For example, the first-order nucleation process of Polymorph II at 37° starts at about 40 min. postdissolution with a nucleation half-life of 35 min.; at about 90 min. postdissolution, the half-life is 265 min. until the equilibrium solubility is reached.

Peak solubility at the pseudosteady state of the dissolution profile in 0.1 *N* hydrochloric acid was considered to approximate true solubility of the polymorph (Polymorph II) before *in situ* crystalline conversion takes place, while the drug concentration in solution at 24 hr. postdissolution was taken as the equilibrium solubility of the polymorph after reversion (Polymorph I). Since the thermodynamic quantities involved in the crystalline transformation of the metastable polymorph to the stable one can be calculated from measurements made at several temperatures, the classical Van't Hoff plot was obtained (Fig. 11). A linear relationship exists between logarithmic molar solubility and inverse absolute temperature. The transition temperature for the reversion of Polymorph II to I was estimated to be about 124.7°. The values of the heat of solution for each crystal form were calculated from the slopes of Fig. 11 and were found to be 3058 and 826 cal./mole for Polymorphs I and II, respectively. Therefore, the enthalpy (ΔH) for the conversion to Polymorph I was determined to be −2232 cal./mole. This value is

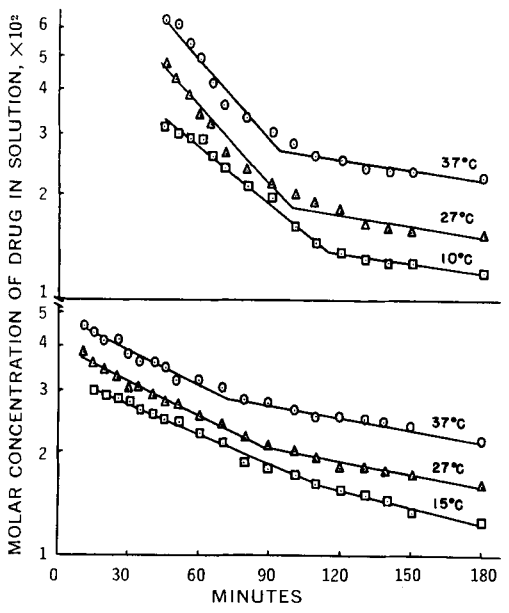

Figure 10—*Plots demonstrating the first-order nucleation characteristics of an experimental antihypertensive during the dissolution profile determinations in 0.1 N HCl. The upper three curves are for Polymorph II recrystallized from isopropanol; the lower three curves are the sample recrystallized from isoamyl alcohol containing mixed Polymorphs I and II.*

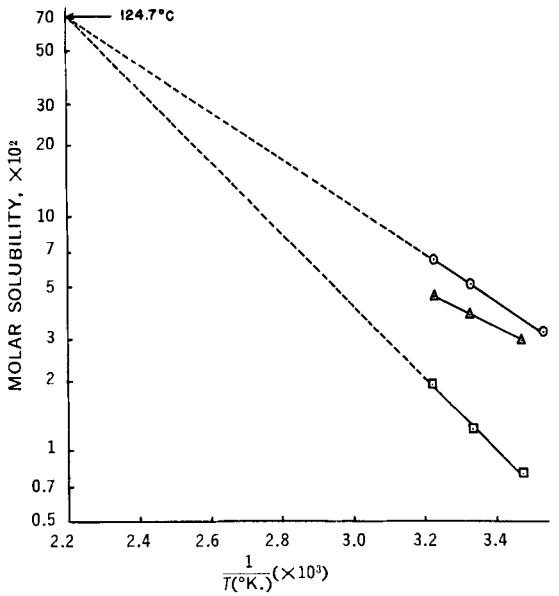

Figure 11—*The classical Van't Hoff plot for Polymorph I (□, recrystallized from methanol), Polymorph II (○, recrystallized from isopropanol), and mixed Polymorphs I and II (△, obtained from isoamyl alcohol) of an experimental antihypertensive.*

Table IV—Thermodynamic Properties of Polymorphs of the Antihypertensive Compound

Polymorph	ΔH_f, cal./mole[a]	ΔH, cal./mole[b]	$-\Delta G_T$, cal./mole[b] 310°K.	300°K.	ΔS_T, e.s.u.[b] 310°K.	300°K.	Transition T, °C.[a]	ΔS, e.s.u.
I	3058.2	—	—	—	—	—	—	—
II	826.1	−2232.1	−172.4	−248.7	−6.6	−6.6	124.7	−5.6

[a] Heat of solution was calculated from the slope of Fig. 11. [b] Calculated for the conversion to Polymorph I.

considerably less than that noted for the trihydrate–anhydrous system (17) of ampicillin (−6400 cal./mole) and for Polymorphs C to A (−4592 cal./mole) or B to A (−6352 cal./mole) systems of chloramphenicol palmitate (25). However, it is twice as large as that found for Polymorphs I and II of mefenamic acid.

The free energy difference, ΔG_t, between Polymorphs I and II at constant temperature and pressure was found to be −172.4 cal./mole at 37° and −248.7 cal./mole at 27°. The entropy change, ΔS_t, for the crystalline transformation was computed to be −6.6 e.s.u. The entropy change at the transition temperature of 124.7° was calculated to be −5.6 e.s.u. The thermodynamic parameters for Polymorphs I and II of the compound are summarized in Table IV.

The deposition or nucleation of a solid crystalline phase from liquid can only occur if some degree of supersaturation is first achieved in the system. The degree of supersaturation is the prime factor controlling the deposition process. Exactly how a crystal nucleus is formed is not known with a great degree of certainty. However, the phenomenon can be analyzed by considering the various energy requirements. Since the formation of a solid particle demands the expenditure of a certain quantity of energy in the creation of the solid surface, the total work (W_t) needed to form a stable crystal nucleus is equal to the sum of the work required to form the surface (W_s, a positive quantity) and the work required to form the bulk of the particle (W_p, a negative quantity). Thus:

$$W_t = W_s + (-W_p) \qquad \text{(Eq. 1)}$$

For the formation of a spherical particle, for instance, Eq. 1 can be expressed as:

$$W_t = A\delta - V \cdot \Delta p \qquad \text{(Eq. 2)}$$

where δ is the surface energy per unit area, Δp is the pressure difference within and without the covered surface, and A and V are the surface area and volume, respectively, of the particle formed. If the new particle is taken to be a sphere with the radius of r, then:

$$A = 4\pi r^2 \qquad \text{(Eq. 3)}$$

$$V = {}^4/_3\pi r^3 \qquad \text{(Eq. 4)}$$

and:

$$\Delta p = \frac{2\delta}{r} \qquad \text{(Eq. 5)}$$

Then, Eq. 2 can be written as:

$$W_t = 4\pi r^2 \delta - {}^4/_3\pi r^3 \cdot \frac{2\delta}{r} \qquad \text{(Eq. 6a)}$$

$$= {}^4/_3\pi r^2 \delta \qquad \text{(Eq. 6b)}$$

The total work of nucleation is thus one-third the work of forming its own surface. As a measure of the supersaturation, S, of the system as its size decreases, estimation is done from the well-known Gibbs–Thomson formula, which may be written in a general form as:

$$\ln S = \frac{2M\delta}{RTdr} \qquad \text{(Eq. 7)}$$

where d is the density, M is the molecular weight, R is the gas constant, and T is the absolute temperature. When the value of r in Eq. 7 is substituted in Eq. 6, one gets:

$$W_t = \frac{16\pi M^2 \delta^3}{3(RTd \ln S)^2} \qquad \text{(Eq. 8)}$$

This expression gives a measure of the work of nucleation in terms of the degree of supersaturation of the system. This equation is extremely important. It can be seen, for example, that when the system has just reached saturation ($S = 1$ or $\ln S = 0$), the amount of energy required for nucleation is infinite and, therefore, a saturated solution cannot nucleate spontaneously. However, the very same equation also suggests that any supersaturated solution can nucleate spontaneously because there is some finite work requirement associated with the process—it is merely a question of supplying the required amount of energy to the system.

The rate of nucleation, N, means the number of nuclei formed per unit time per unit volume. Kinetically, N can be expressed in the form of the Arrhenius reaction velocity equation:

$$N = A \cdot \exp\left(-\frac{\Delta G}{RT}\right) \qquad \text{(Eq. 9)}$$

where A is a frequency factor, and ΔG is the overall excess free energy of the particle, *i.e.*, the work of nucleation, W_t. From Eqs. 8 and 9, one gets:

$$N = A \cdot \exp\left(-\frac{16\pi M^2 \delta^3}{3R^3T^3 d^2(\ln S)^2}\right) \qquad \text{(Eq. 10)}$$

This equation indicates that three main variables govern the rate of nucleation: temperature (T), degree of saturation (S), and interfacial tension (δ).

For a first-order nucleation process, the rate of nucleation can be

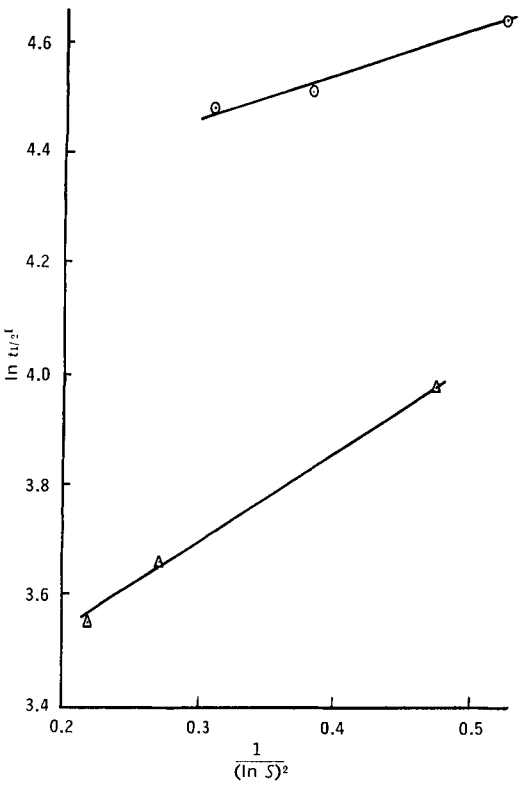

Figure 12—*Test of Eq. 12 for the relationship between the rate of the first-order nucleation process and the degree of saturation of the system for the polymorphs obtained from isopropanol (lower curve) and isoamyl alcohol (upper curve).*

Table V—Characteristics of Dissolution Profiles in 0.1 *N* Hydrochloric Acid at 37°

Recrystallization Solvent[a]	Polymorph	Peak Solubility, molar, $\times 10^2$	Nucleation Characteristics: Time Nucleation Starts, min.	First-Order Nucleation Process: $t_{1/2}^{I}$, min.	First-Order Nucleation Process: $t_{1/2}^{II}$, min.	First-Order Nucleation Process: Transition Time, min.[b]	Equilibrium Solubility[c], molar, $\times 10^2$
Isopropanol	II	6.45	40	35	265	90	1.69
Dimethylformamide	II	5.94	30	49	320	92	1.69
Dimethylacetamide	II	5.37	28	78	600	140	1.67
Methanol	I	1.92	<5	—	—	—	1.71
Water	I	1.71	<5	—	—	—	1.69
0.1 *N* HCl	I	1.74	<5	—	—	—	1.71
Isoamyl alcohol	I + II (II ≫ I)	4.55	10	89	260	72	1.71
Acetone	I + II (II > I)	3.56	12	180	540	45	1.73

[a] See text for sample treatment. [b] Time at which first-order nucleation rate is changed. [c] Drug concentration in solution at 24 hr. postdissolution was taken as approximated equilibrium solubility.

expressed kinetically as:

$$N = \frac{0.693}{t_{1/2}} \qquad \text{(Eq. 11)}$$

The value of $t_{1/2}$ is based upon a change in particle generation and is reflected by the drug concentration in solution. Combining Eqs. 10 and 11, one obtains:

$$\ln t_{1/2} = \ln \frac{0.693}{A} + \frac{16\pi M^2 \delta^3}{3R^3T^3 d^2} \cdot \frac{1}{(\ln S)^2} \qquad \text{(Eq. 12)}$$

Therefore, a linear relationship is expected when $\ln t_{1/2}$ is plotted as a function of the reciprocal values of $(\ln S)^2$. As shown in Fig. 12, a fairly good linear relationship between the rate of the first-order nucleation process and the degree of saturation of the system is established for the Polymorph II (lower curve) and the mixed Polymorphs I and II (upper curve).

This discussion is centered around the polymorphs recrystallized from methanol, isopropanol, and isoamyl alcohol. The characteristics of the dissolution profiles for the samples, recrystallized from other aqueous and nonaqueous solvents, in 0.1 *N* hydrochloric acid at 37° are summarized in Table V. As indicated in the first and second columns of Table V, the type of polymorph obtained is strongly dependent upon the solvent used in the recrystallization process. Polymorph II is obtained by employing isopropanol, dimethylformamide, or dimethylacetamide as the recrystallization solvent; Polymorph I is harvested from methanol, distilled water, or 0.1 *N* hydrochloric acid. However, if acetone or isoamyl alcohol is employed, samples containing mixed Polymorphs I and II with Polymorph II as the major component are obtained. Although the equilibrium solubilities of these eight samples, as listed in the last column of Table V, are practically identical regardless of the crystallization solvent employed, the peak solubilities attained by each sample are different from each other. There is almost a fourfold difference in peak solubilities at 37° between the samples obtained from isopropanol and the crystals harvested from water. Furthermore, the peak solubilities of Polymorph II obtained from different recrystallization solvents are different from each other. For example, Polymorph II harvested from dimethylacetamide attains a peak solubility of 5.37×10^{-2} *M*, which is approximately 10 and 20% lower than that reached by Polymorph II obtained from dimethylformamide and isopropanol, respectively. Since the samples employed for dissolution profile determination are fractions of 20–40-mesh particles, particle-size effect on the dissolution behavior (32) as a contributing factor to this difference in peak solubility could be ruled out. However, one should bear in mind that the surface characteristics of the solid particles recrystallized from different solvents could be different even if they were in the same particle-size range. Another plausible explanation is that a very minute amount of Polymorph I contained in Polymorph II recrystallized from dimethylacetamide or dimethylformamide was not detectable by the IR and X-ray techniques, thus lowering the peak solubilities for these two samples as compared to Polymorph II prepared from isopropanol.

The nucleation characteristics of the dissolution profiles in 0.1 *N* hydrochloric acid at 37° are also presented in Table V. The first-order nucleation rate differs among various Polymorph II's recrystallized from different solvents. For example, the first-order nucleation process of Polymorph II obtained from isopropanol had a half-life of 35 min. ($t_{1/2}^{I}$, fast nucleation step), which was changed at about 90 min. postdissolution to a half-life of 265 min. ($t_{1/2}^{II}$, slow nucleation step, and possibly crystal growth is involved). The same Polymorph II harvested from dimethylformamide and dimethylacetamide had a $t_{1/2}^{I}$ of 49 and 78 min. which changed to a $t_{1/2}^{II}$ of 320 and 600 min. at about 92 and 140 min. postdissolution, respectively. By assuming that the same formulation, manufacturing processes, and equipment are employed by different firms in production of the solid dosage form containing Polymorph II, the implication of these findings are significant since different dissolution patterns and, consequently, different bioavailabilities could be found if the Polymorph II employed was not harvested from the same recrystallization solvent. It is apparent that the proper choice of the most suitable crystalline modification can often significantly enhance the absorption and therapeutic efficacy of a given drug. Since modification of a crystalline habit of this type could be readily studied in a relatively short period of time, this approach may often provide the answer for those potential therapeutic agents that show poor availability *in vivo* because of slow rates of dissolution.

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Use of Adsorbents in Enhancement of Drug Dissolution I

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Abstract □ A new approach is described for increasing the dissolution rates of relatively insoluble powders. It is based on the concept of increasing the surface available for contact with dissolution media. This is accomplished by equilibration of the drug in an organic solvent (*e.g.*, acetone) on an insoluble excipient with an extensive surface (*e.g.*, fumed silicon dioxide). The drugs studied included indomethacin, aspirin, sulfaethidole, griseofulvin, reserpine, chloramphenicol, oxolinic acid, probucol, and hydrochlorothiazide. The effects of pH, wetting agents, and agitation intensity were investigated in some systems. An increased rate of release from the minuscular drug delivery system was observed in all instances.

Keyphrases □ Adsorbents—used to increase the dissolution rates of relatively insoluble drug powders □ Dissolution rates—micronized (minuscular) drug dispersed on microparticulate adsorbents □ Drug delivery system—micronized (minuscular) drug dispersed on microparticulate adsorbents

The poor dissolution characteristics of relatively insoluble drugs has long been a problem to the pharmaceutical industry. If one accepts the premise that the absorption of such drugs is rate limited by the dissolution process, then the physicochemical factors controlling the dissolution rate may be described by the Noyes–Whitney and Nernst equations (1, 2). The terms in these equations can be modified and the dissolution rate altered through the use of soluble salts, polymorphs, hydrates or solvates, molecular complexes, eutectics, and solid solutions. These approaches to altering the dissolution rate will now be considered in detail.

As a rule, a pharmaceutical salt exhibits a higher dissolution rate than the corresponding nonelectrolyte at an equal pH, although the salt and nonelectrolyte may have the same equilibrium solubility. Thus, under the conditions that favor conversion of the salt to the nonelectrolyte, faster dissolution of the salt occurs, but the nonelectrolyte precipitates as fine particles which then have the required characteristics for proper redissolution (3). If rapid dissolution of a nonelectrolyte is desired, it can be achieved by incorporation of a buffer substance into the formulation. Such a buffer effectively alters the pH of the diffusion layer, enhancing dissolution by *in situ* salt formation (4).

The concept of employing a suitable ligand to complex with a drug substrate in the formation of a more soluble entity is not new (5), but it has not been widely exploited until recently. One such application was made with the caffeine–ergotamine combination (6).

The successful utilization of a polymorph of significantly greater thermodynamic activity (*i.e.*, solubility) than the stable modification may provide, in some instances, therapeutic blood levels from otherwise physiologically inactive drugs. The use of such metastable compounds may lead to crystal reversions on standing, and these stability aspects must be considered (7). The use of solvates and hydrates has also enjoyed limited use, although the anhydrous forms of semisynthetic penicillins have been used to give blood serum levels consistently earlier and significantly higher than those observed after administration of similar formulations containing the hydrated material (8).

Reduction of particle size remains the accepted method for increasing dissolution rates. However, upon micronization, hydrophobic drugs have a tendency to clump when exposed to the dissolution medium (9). An apparent solution to this problem was provided by Sekiguchi and Obi (10). They proposed that the incorporation of a microcrystalline or molecular dispersion of a poorly soluble drug in a solid matrix of water-soluble carrier would increase the dissolution rate and absorption of the drug. Since then, modifications of the technique have been suggested under a variety of names, including solid solutions (11), eutectics (10), coprecipitates (12), and fast-release solid dispersions (13). The exact physical nature of these compositions is not exactly clear, but it is believed that the insoluble drug is