# Surface Transformation during Dissolution of Aspirin

R. V. GRIFFITHS* and A. G. MITCHELL

**Abstract** □ A dissolution pattern that indicates a solvent-mediated phase change is observed when aspirin crystals are dissolved in aqueous media. It is suggested that the phase change is caused by the crystallization of a less soluble form on the crystal surface during dissolution. The kinetic and thermodynamic parameters of the two forms were determined using a rotating disk method of dissolution. An isergonic relation was demonstrated for the phase transformations of aspirin and other pharmaceutical compounds reported in the literature.

**Keyphrases** □ Aspirin dissolution—surface transformation □ Dissolution, aspirin crystals—kinetic, thermodynamic parameters □ Phase change, solvent mediated—aspirin crystal dissolution □ Rotating disk—aspirin dissolution □ Attenuated total reflectance—aspirin crystals □ X-ray analysis—aspirin crystals

Variation in the intrinsic dissolution rates of commercial aspirin was reported previously (1), and polymorphism was suggested as a possible cause (2). Tawashi (3) isolated two polymorphs of aspirin and found a marked difference in the rates of gastrointestinal absorption (4). Attempts to obtain these polymorphs for further study have been unsuccessful so far. However, during the determination of solubility, a pattern of dissolution was observed that suggested that aspirin undergoes a phase change in aqueous media.

Higuchi *et al.* (5) developed a mathematical model for dissolution from a mixture of two polymorphs, and they extended the theory to explain the anomalous behavior of metastable methylprednisolone where a phase change to the stable form occurs during dissolution. Nogami *et al.* (6–10) also developed models for dissolution, including dissolution that involves a simultaneous phase change. The method of Nogami *et al.* (6–10) was used to investigate the nature of the phase change that occurs during the dissolution of aspirin.

## EXPERIMENTAL

**Aspirin**—Aspirin USP grade[1] was used. Melting point and heat of fusion, 131° and 37.9 cal./g., respectively, were determined using a Perkin-Elmer differential scanning calorimeter, DSC-1B, with effluent gas analyzer.

**Bulk Dissolution**—Excess aspirin (5–10 times the equilibrium solubility) was added to 250 ml. 0.1 *N* hydrochloric acid maintained at a constant temperature and stirred rapidly with a 3-cm. Teflon stirrer. Samples were removed at suitable time intervals, using a pipet fitted with a filter stick, diluted, and analyzed spectrophotometrically at 276 and 305 nm. for aspirin and salicylic acid, respectively. The total amount of aspirin dissolved was calculated using simultaneous equations (11).

**Rotating Disk Dissolution**—The rotating disk method of Nogami *et al.* (6) was used under the following conditions: 3-cm. diameter disks of aspirin compressed at 3 tons/cm.$^2$; 100 ml. of 0.1 *N* hydrochloric acid at 30, 37, 45, and 50°; and rotation velocities of 100, 200, 300, and 430 r.p.m. checked with an electronic stroboscope. Samples were removed at suitable time intervals and analyzed spectrophotometrically.

[1] British Drug Houses, London, England, Lot 27648, mesh size 40.

**IR Attenuated Total Reflectance (ATR)**—The ATR spectra (Beckman IR-10 spectrophotometer fitted with TR-9 attachment and a KRS-5 crystal) of the surfaces of aspirin disks were determined before and after exposure to the dissolution medium, using the method of Higuchi *et al.* (12).

**X-Ray Analysis**—X-ray powder patterns were determined using nickel-filtered copper radiation and a General Electric powder camera.

## RESULTS AND DISCUSSION

**Bulk Dissolution**—Some results of the bulk-dissolution experiments are shown in Fig. 1. The concentration in the bulk increases rapidly and shows an initial peak before the equilibrium solubility, $C_s$, is reached. Similar curves have been observed both for dissolution that involves polymorphic phase changes (13, 14) and for phase changes due to hydration (10, 13–17). The peak is due to an abrupt transfer of solute from the large surface area of a more soluble form. The bulk liquid becomes supersaturated with respect to the more stable crystalline form which crystallizes out on the surface of the solid.

In previous studies (*e.g.*, 10 and 14), it was possible to identify the nature of the phase change by examination of the solid remaining after equilibrium was attained. However, in the case of aspirin, examination by means of microscopical techniques, melting point, X-ray, ATR, and DSC (heat of fusion and effluent gas analysis for water of hydration) failed to reveal any difference between the final and the initial crystals. In addition, it was possible to reproduce the bulk-dissolution curve using the excess solid filtered from the reaction vessel after equilibrium had been reached; the curve was qualitatively the same whether the excess solid was used after drying under vacuum or as a moist slurry. It is suggested, therefore, that the phase change takes place on the surface of the crystals. The surface layer goes into solution in the initial mass transfer to expose the high solubility form of the remaining crystal, which then yields the usual dissolution pattern.

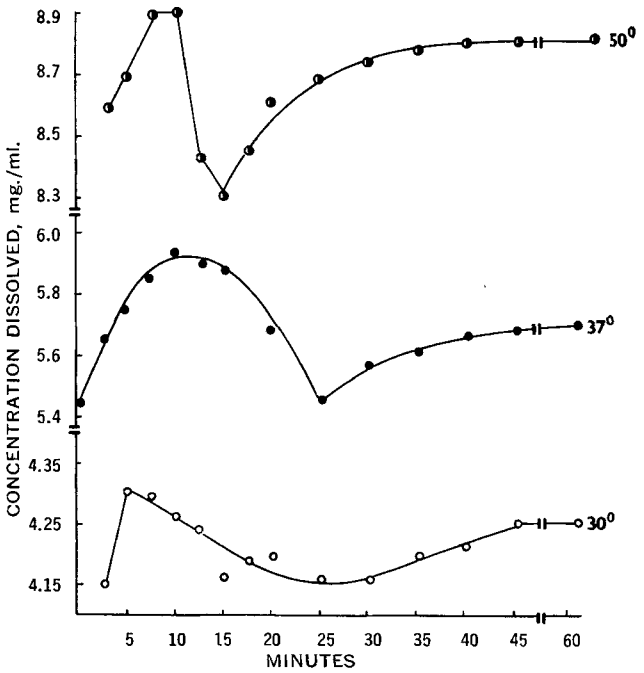


**Figure 1**—*Bulk dissolution of aspirin in 0.1* N *HCl.*

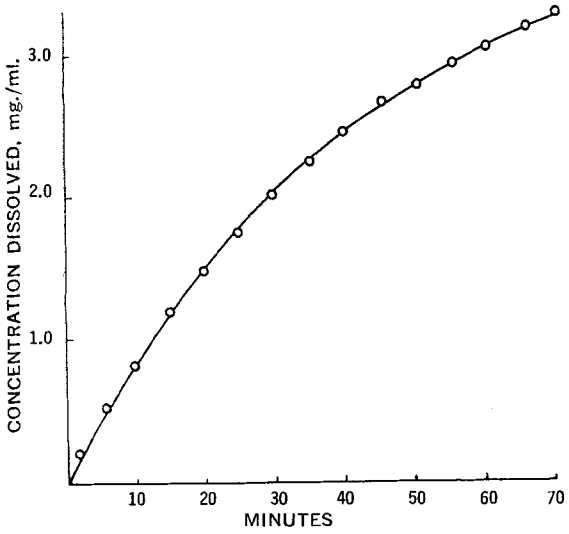


**Figure 2**—*Rotating disk dissolution of aspirin in 0.1* N *HCl at 30° and 430 r.p.m.*

**Rotating Disk Dissolution**—Figure 2 shows a typical dissolution curve made by taking samples up to about 80% of the solubility of aspirin. The dissolution curve was used to construct a finite differences diagram (Fig. 3) from which the saturated concentration, $C_0$, was estimated as described by Nogami *et al.* (6). The equilibrium solubilities, $C_s$, determined from bulk-dissolution experiments at various temperatures, are in good agreement with $C_0$ estimated kinetically from the finite differences diagram (Table I).

Figure 4 shows a concentration–time curve for the dissolution of aspirin over a short time interval. The linear curve is preceded by a steeper portion. Where dissolution is accompanied by a simultaneous phase change, Nogami *et al.* (10) showed that the final slope of the dissolution curve is related to the solubility of the stable form (*A*) by

$$\frac{dc}{dt} = k_t C_{sA} \qquad \text{(Eq. 1)}$$

**Table I**—Saturated Concentrations of Aspirin in 0.1 *N* HCl at Various Temperatures

| Temperature | $C_{sA}$, Bulk Dissolution Method, mg./ml. | $C_{0A}$, Finite Differences Method, mg./ml. | $C_{sB}$,[a] mg./ml. |
|---|---|---|---|
| 30° | 4.3 | 4.3 | 6.8 |
| 37° | 5.7 | 5.8 | 8.1 |
| 45° | 7.7 | 7.8 | 10.0 |
| 50° | 8.9 | 8.9 | 11.1 |

[a] Calculated from Eqs. 1 and 2.

**Table II**—Apparent Dissolution (Transport) Rate Constant, $k_t$, and Overall Rate Constant, $K_T$, for Dissolution of Aspirin in 0.1 *N* HCl at Various Temperatures and Rotation Rates

| Temperature | 100 r.p.m. | 200 r.p.m. | 300 r.p.m. | 430 r.p.m. |
|---|---|---|---|---|
| | | $k_t \times 10^2$, min.$^{-1}$ | | |
| 30° | 0.80 | 1.15 | 1.46 | 1.55 |
| 37° | 0.98 | 1.42 | 1.95 | 2.39 |
| 45° | 1.22 | 1.78 | 2.40 | 3.12 |
| 50° | 1.40 | 1.99 | 2.71 | 3.67 |
| | | $K_T \times 10$, cm. min.$^{-1}$ | | |
| 30° | 1.15 | 1.65 | 2.06 | 2.22 |
| 37° | 1.40 | 2.03 | 2.77 | 3.40 |
| 45° | 1.73 | 2.52 | 3.40 | 4.41 |
| 50° | 1.98 | 2.84 | 3.83 | 5.24 |

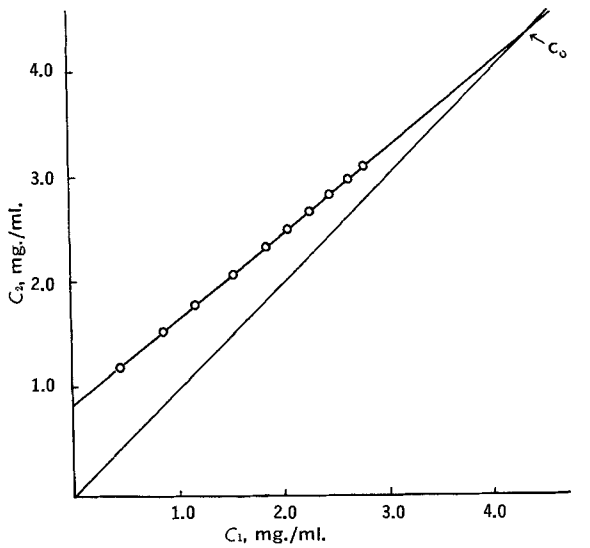


**Figure 3**—*Finite differences diagram for the dissolution of aspirin in 0.1* N *HCl at 30° and 430 r.p.m. Key:* $C_1$, *concentration at time* $t_1$; $C_2$, *concentration at time* $t_2 = t_1 + 10$ *min.*; -O-, $C_2$ versus $C_1$; *and* ——, $C_1 = C_2$.

and the initial slope is related to the solubility of the more soluble form (*B*) by

$$\left(\frac{dc}{dt}\right)_{t=0} = k_t C_{sB} \qquad \text{(Eq. 2)}$$

where $k_t$ is the rate constant of the transport process, and $C_{sA}$ and $C_{sB}$ are the respective solubilities. $C_{sA}$ is known from the bulk-dissolution experiments and the finite differences method; hence, $k_t$ can be calculated from Eq. 1. Using the initial slope and substituting $k_t$ into Eq. 2 give $C_{sB}$.

From the values of $k_t$, obtained at different temperatures and rotation rates, the overall dissolution-rate constant, $K_T$, can be calculated from the Noyes–Nernst equation:

$$\frac{dc}{dt} = k_t(C_{sA} - C_t) = \frac{S}{V} K_T(C_{sA} - C_t) = \frac{S}{V}\frac{D}{h}(C_{sA} - C_t) \qquad \text{(Eq. 3)}$$

where $S$ is the surface area of the disk, $V$ is the volume of the solution, $D$ is the diffusion coefficient, and $h$ the diffusion layer thickness; $C_t$, the concentration at time $t$, can be neglected over the short time interval of the experiment.

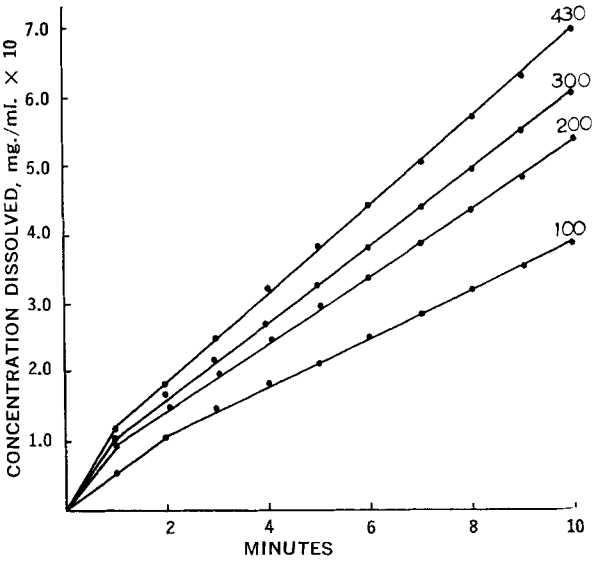


**Figure 4**—*Initial dissolution curves of aspirin at 30° using rotating disk method at various rotation rates.*

**Table III**—Diffusion Coefficient, $D$, and Diffusion Layer Thickness, $h$, for Aspirin in 0.1 $N$ HCl at Different Temperatures and Rotation Rates

| Temperature | $D \times 10^6$, cm.$^2$ sec.$^{-1}$ | $h \times 10^3$, cm. 100 r.p.m. | 200 r.p.m. | 300 r.p.m. | 430 r.p.m. |
|---|---|---|---|---|---|
| 30° | 8.8 | 4.60 | 3.28 | 2.71 | 2.37 |
| 37° | 12.9 | 4.90 | 3.51 | 2.80 | 2.28 |
| 45° | 16.4 | 5.26 | 3.77 | 3.24 | 2.24 |
| 50° | 21.0 | 5.51 | 3.93 | 3.29 | 2.41 |

**Table IV**—Crystallization Rate Constant, $k_r$, for Aspirin in 0.1 $N$ HCl at Different Temperatures and Rotation Rates

| Temperature | $k_r \times 10^2$, min.$^{-1}$ 100 r.p.m. | 200 r.p.m. | 300 r.p.m. | 430 r.p.m. |
|---|---|---|---|---|
| 30° | 57.2 | 57.5 | 61.1 | 59.6 |
| 37° | 85.5 | 85.2 | 85.1 | 88.2 |
| 45° | 122.0 | 124.1 | 123.3 | 130.5 |
| 50° | 144.0 | 153.0 | 164.1 | 153.1 |

The diffusion coefficient is calculated by substituting $K_T$ into the Levich equation (18):

$$K_T = 0.620 \times D^{2/3} \times v^{-1/6} \times w^{1/2} \qquad \text{(Eq. 4)}$$

where $v$ is the kinematic viscosity of the solvent, and $w$ is the angular velocity of the rotating disk. By knowing $K_T$ and $D$, the diffusion layer thickness is calculated from Eq. 3. The values of $K_T$, $D$, and $h$ are shown in Tables II and III.

The rate constant for the recrystallization of the less soluble phase, $k_r$, is calculated from Eq. 5 (10):

$$b = \frac{k_t(C_{sB} - C_{sA})}{k_r} \qquad \text{(Eq. 5)}$$

where $b$ is the intercept on the ordinate obtained by extrapolation of the linear portion of the dissolution curve (Fig. 4). The values of $k_r$ (Table IV), are independent of the rotation rate, as expected for a surface-controlled reaction.

The activation energy of the transport process obtained from an Arrhenius plot (Fig. 5) was 5.6 kcal. mole$^{-1}$. This is within the range 2.8–6.5 kcal. mole$^{-1}$ accepted for transport-controlled processes and agrees with the value of about 5 kcal. mole$^{-1}$ reported by

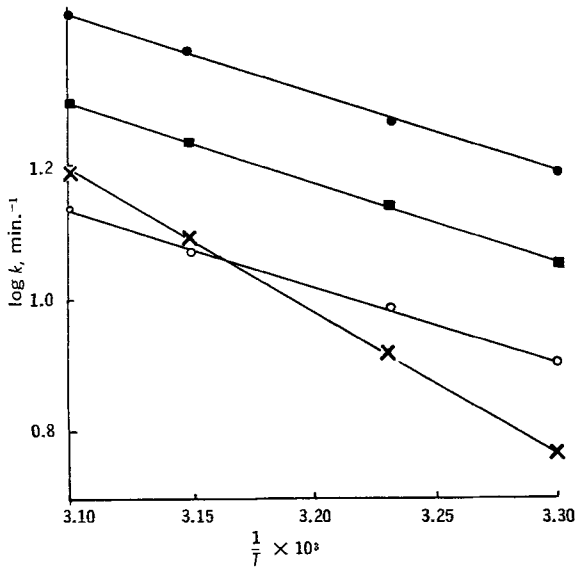


**Figure 5**—*Arrhenius plot for the effect of temperature on the transport and crystallization rate constants. Key:* ●, ($k_t \times 10^3$) *at 300 r.p.m.;* ■, ($k_t \times 10^3$) *at 200 r.p.m.;* ○, ($k_t \times 10^3$) *at 100 r.p.m.; and* ×, (*mean* $k_r \times 10$).

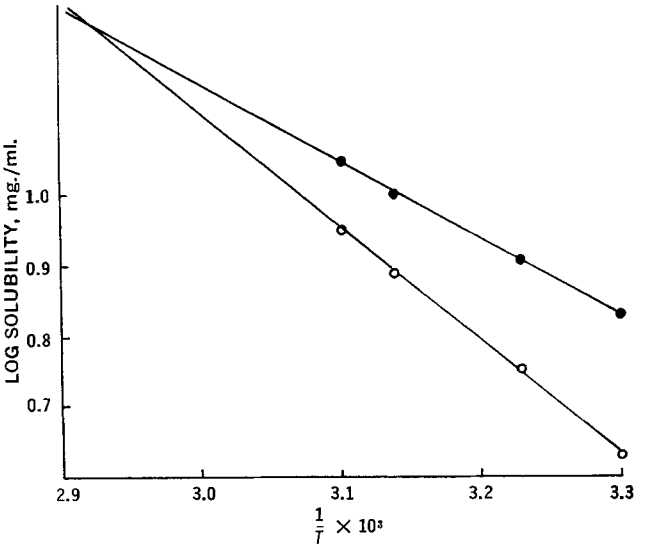


**Figure 6**—*Effect of temperature on the solubility of aspirin. Key:* ○, *Form* A; *and* ●, *Form* B.

Edwards (19) for the dissolution of aspirin in 0.1 $N$ sulfuric acid. From Fig. 5, the activation energy of the crystallization process was found to be 9.5 kcal. mole$^{-1}$.

The transition temperature of the two forms of aspirin, obtained from a Van't Hoff-type plot (Fig. 6) was 343°K. The enthalpy change from Form $B$ to Form $A$, $\Delta H_{B\to A}$, calculated from the difference in slopes was −2.4 kcal. mole$^{-1}$. The free energy change, $\Delta G$, at any temperature, $T$, can be calculated from Eq. 6:

$$\Delta G_T = -RT \ln \frac{C_{sB}}{C_{sA}} \qquad \text{(Eq. 6)}$$

Similarly, the entropy change, $\Delta S_T$, at any temperature, $T$, is given by Eq. 7:

$$\Delta S_T = \frac{\Delta H_{B\to A} - \Delta G_T}{T} \qquad \text{(Eq. 7)}$$

At the transition temperature, $\Delta G_T$ is zero and $\Delta S$ is −7.0 e.u.

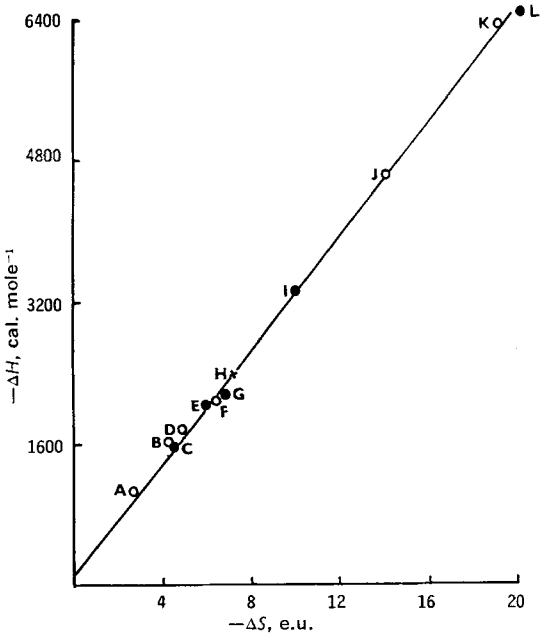


**Figure 7**—*Isergonic plot of the relation between enthalpy and entropy changes in polymorphic and hydration phase transformations. Key:* ○, *polymorphic changes;* ●, *hydration changes; and* ×, *this work. See Table V for explanation of A–L.*

Table V—Isergonic Relationship between Change of Enthalpy ($\Delta H$) and Change of Entropy ($\Delta S$) for the Phase Transformation of a Number of Pharmaceutical Compounds

| Key Fig. 7 | Compound | Type of Phase Change | Transition Temperature | $\Delta H$ (cal. mole$^{-1}$) | $\Delta S_{298}$ (e.u.) | Reference |
|---|---|---|---|---|---|---|
| A | Mefenamic acid | Polymorphic | 89° | −1031 | −2.6 | 14 |
| B | Methylprednisolone | Polymorphic | 118° | −1600 | −4.2[a] | 21 |
| C | *p*-Hydroxybenzoic acid | Hydration | 84° | −1550 | −4.4[a] | 10 |
| D | Sulfathiazole | Polymorphic | 95° | −1744 | −4.7[a] | 22 |
| E | Glutethimide | Hydration | 52° | −2000 | −5.8 | 15 |
| F | Phenobarbital | Polymorphic | 34° | −2300 | −6.4[a] | 9 |
| G | Phenobarbital | Hydration | 37° | −2140 | −6.9[a] | 10 |
| H | Aspirin | — | 70° | −2420 | −7.1 | This work |
| I | Theophylline | Hydration | 73° | −3300 | −10.0 | 15 |
| J } | Chloramphenicol | Polymorphic $C \rightarrow A$ | 50° | −4600 | −13.8[a] | 14 |
| K } | Palmitate | Polymorphic $B \rightarrow A$ | 88° | −6350 | −18.7[a] | 14 |
| L | Ampicillin | Hydration | 42° | −6400 | −20.0 | 23 |

[a] Values for $\Delta S_{298}$ calculated from data given in the reference.

**X-Ray Studies and ATR**—X-ray powder patterns on samples of aspirin before and after bulk-dissolution experiments were identical. However, since the crystals were powdered before the X-ray determination, any changes occurring in the surface layer only would not be detected. Samples of powder scraped from the surface of the disk after exposure to the dissolution medium also failed to show any change in the X-ray powder pattern.

ATR is particularly suited to a study of surface layers, since IR energy penetrates to a depth of about 5–10 $\mu$. It was hoped that the method described by Higuchi *et al.* (12) would provide direct evidence of a surface transformation during dissolution. Unfortunately, spectra obtained after exposure of a disk to the solvent were very poor compared with the original spectrum.

**Isergonic Relationship in Polymorphic and Hydrate Transformations**—A linear relationship between enthalpy and entropy changes of chemical reactions is well known. Such a plot is referred to as an isokinetic or isergonic plot (20). The relationship is normally applied to a series of closely related compounds undergoing an identical reaction. Literature values of enthalpy and entropy changes for polymorphic phase reversions and anhydrate to hydrate changes are shown in Table V. These values and those for aspirin determined in this work can be fitted on a straight-line relationship (Fig. 7):

$$-\Delta H = -0.117 - 0.322\Delta S \qquad \text{(Eq. 8)}$$

with a correlation coefficient of 0.992 compared with a theoretical correlation coefficient ($P' = 0.05$) of 0.58. Although the significance of isergonic plots is not fully understood (20), the relation between $\Delta H$ and $\Delta S$ for phase transformations in compounds as diverse as aspirin, methylprednisolone, and chloramphenicol palmitate is intriguing.

## SUMMARY

A solvent-mediated change to a less soluble form occurs when aspirin is dissolved in 0.1 *N* hydrochloric acid. The "repeatability" of the bulk dissolution experiments suggests that the phase change occurs in the surface layer of the aspirin crystals. This suggestion is supported by the kinetic analysis of the rotating disk dissolution results and the X-ray, ATR, and other physical measurements which show that the bulk of the crystalline material is unchanged.

The nature of the surface phase transformation cannot be established from the kinetic and thermodynamic data. Crystallizations of an hydrate or a more stable polymorph are both possible, and work is being continued on this problem.

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