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Research Articles

Dissolution Kinetics of Certain Crystalline Forms of Prednisolone

By DALE E. WURSTER and PALMER W. TAYLOR, JR.

The activity, dissolution rate, and crystal behavior of three crystalline forms of prednisolone, each exhibiting distinctly different properties, have been investigated. By determining the relative dissolution rates of the crystal forms under different agitation conditions, it was found that dissolution could be described by consecutive processes involving a reaction at the interface and transport away from the interface. The data suggested that these processes pose a double barrier to dissolution under the experimental conditions.

RECENTLY, a number of studies (1–3) have investigated the influence of solid phase characteristics on the dissolution rate of pharmaceutical compounds. Studies of such a nature are especially important in the case of steroids since they exhibit a low water solubility and a variety of crystalline states. A knowledge of dissolution rates, solubility, and physical stability of crystalline forms of pharmaceuticals is pertinent to ascertain the limits of their physiological availability.

One of the above studies (1) also pointed out that under certain agitation conditions the relative dissolution rates of different crystalline forms may not reflect their relative rates under *in vivo* conditions. Since under different condi-

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tions of agitation the factors governing the rate of dissolution may vary, a knowledge of the mechanism of dissolution rate control would be helpful in determining the applicability of *in vitro* testing to *in vivo* conditions. Therefore, this study was undertaken to investigate further the processes controlling the dissolution rate of steroid crystal forms.

PLAN OF STUDY

Dissolution and crystallization can be considered as specific types of heterogeneous reactions in which a mass transfer is effected through the net result of escape and condensation of molecules at a solid surface. In most cases dissolution has been treated as being controlled by diffusion from a saturated film existing at the interface. This concept, as first proposed by Nernst and Brunner (4, 5), employs the tacit assumption that the reaction occurring at the interface is infinitely fast. If this film at the interface was saturated, then the dissolution rates of different crystalline forms should be in proportion to their solubility, provided that no variance occurred in their diffusional properties. If under certain conditions the above relationship does not hold, the assumption of a finite intrinsic rate or rate constant for the interfacial reaction may be justified. Thus, a consideration of kinetics of consecutive reactions causing a double barrier to exist may be helpful in describing the dissolution process.

The consecutive reactions involved can be depicted schematically by a concentration profile diagram (Fig. 1). The rate constant for diffusion and the apparent rate constant can be expressed by the respective ratios, D/h and $D/(h + i)$, where D is the diffusivity constant and h is the effective film thickness.[1] The distance, i, if no adsorption layer exists at the interface, can be considered a finite value only in the case of the apparent rate constant.

It must be recognized that this diagram only represents a model for the process. The real concentration gradients might be expected to merge asymptotically with the surrounding field and also possibly at the interface. If isotropic dissolution prevails, C_i can be assumed to have a constant value. In actuality, velocity profiles of a freely moving sphere under convection dictate that the boundary layer will not be concentric with the tablet surface, yet free rotation of the sphere would allow the above condition to hold.

The rate expression for the surface reaction supplying C_i can be represented as

$$\frac{dC_i}{dt} = \frac{S_t}{v} k_r(C_s - C_i) \qquad \text{(Eq. 1)}$$

where S_t is the true surface area at time t, v is the solution volume, and k_r is the rate constant for the reaction at the interface. This relationship is derived from the equilibrium condition where the rates of condensation and liberation at the interface are equal.

[1] The term "effective film thickness" is used in the conventional manner; that is, the calculated film thickness assuming mass transport occurs only by diffusion. It is recognized, however, that convection may aid in this transport process (6).

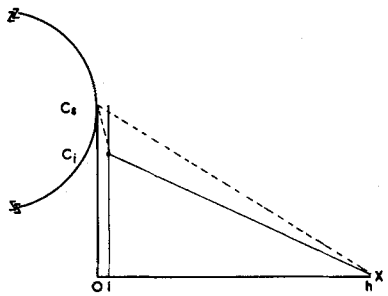

Fig. 1.—Concentration profile existing in the boundary layer during the dissolution of a crystalline form. The saturation concentration activity is C_s, and C_i represents the intermediate concentration at the interface from where the diffusion begins. Thus, $0 < C_i < C_s$. Also, i should be equal to zero, in reality; thus, h is the effective diffusion layer thickness.

The rate expression for transport away from the interface is derived from Fick's first law and is given by

$$-\frac{dC_i}{dt} = \frac{S_D}{v} k_D(C_i - C) \qquad \text{(Eq. 2)}$$

where S_D is the surface area of the diffusion layer at time t, and k_D is the rate constant for the diffusion process. If a steady-state concentration for C_i is assumed and the true surface area equals the surface area of diffusion *i.e.*, no leaching of the surface area is apparent, then

$$C_i = \frac{k_r C_s + k_D C}{k_r + k_D} \qquad \text{(Eq. 3)}$$

Substitution into either Eq. 1 or 2 yields

$$-\frac{1}{S}\frac{dw}{dt} = k_{app.}(C_s - C) \qquad \text{(Eq. 4)}$$

where

$$k_{app.} = \frac{k_r k_D}{k_r + k_D} \qquad \text{(Eq. 5)}$$

This formula allows Noyes-Whitney kinetics (7) to be obeyed, yet the boundary layer does not saturate unless $k_r >> k_D$. This treatment of defining an intermediate concentration at the interface was first used by Berthoud (8) to explain varying rates of crystallization of crystal faces. It has been used subsequently in a number of cases to describe heterogeneous reaction kinetics.

The influence of the agitation commonly has been a criteria for determining the process controlling the rate of heterogeneous reactions. The slope of a logarithmic plot of the reaction rate *versus* agitation rate is used often to determine the extent of transport and interfacial control of the rate. A wide variation of resulting slopes has been obtained in similar systems. Other related investigations have led to equations as functions of dimensionless groups (9–11). These relations show a dissolution rate dependence on the degree of laminar and turbulent flow, the heat of reaction, the dissolving substance, its surface characteristics, and the density difference between phases. The dependence on these additional phenomena explains, in part, the variations observed in the above slopes. Since

turbulence in dissolution often is apparent in free convection (12), it would be difficult to assess its influence over a stirring range.

Dissolution–agitation rate data that appear to conform to a logarithmic plot over a restricted stirring range also may fit a Langmuir plot because of their similarity. The implication of this is that a different dissolution rate–agitation rate relationship may be assigned, with one rate parameter independent of the agitation rate and the other an exponential function of the rate of agitation. If k_D in Eq. 5 is equated to the product of the agitation rate to an exponential power and a constant independent of agitation, a Langmuir type relation between the apparent rate constant and the agitation rate results.

A study comparing the relative dissolution rates at different agitation speeds of crystal forms of the same substance possessing different activities could thus prove advantageous over a study of the dissolution rate–agitation rate relation in determining the controlling influence on dissolution. The variable effects of turbulence at varying agitation will be negated in determining the dissolution rate ratios. At a specific stirring speed, each of the crystal forms will experience the same degree and type of agitation.

EXPERIMENTAL

Preparation and Description of Prednisolone Crystal Forms

Form A. Anhydrous.—This crystal form was recrystallized from a 70% (v/v) methanol–water solvent maintained at refrigeration temperatures.

TABLE I.—MEASURED PEAK INTENSITIES OF DIFFRACTION PATTERNS OF PREDNISOLONE SAMPLES

2θ Values, deg.	Form A, Anhydrous	Form B, Anhydrous	Form C, Hydrous
7.8	Medium	Weak	Medium
10.2	...	Medium	...
10.4	Medium	...	...
12.7	...	...	Weak
13.7	Strong	...	...
14.2	...	...	Strong
14.6	...	...	Medium
15.3	Strong	Strong	Medium
15.6	Strong	Strong	...
15.8	...	...	Weak
16.2	Strong	...	...
16.5	...	Medium	...
17.3	...	...	Strong
17.4	...	Medium	...
17.6	Strong	...	Medium
18.7	...	...	Weak
19.2	Weak	...	Weak
20.1	Weak	...	Strong
21.0	Medium	...	Medium
22.3	Bakelite	Bakelite	Bakelite
24.7	Medium	Weak	...
25.5	...	...	Medium
26.1	Medium	...	...
26.3	...	...	Medium
26.5	...	Medium	...
28.6	Weak	...	...
28.9	...	...	Weak
29.6	...	...	Weak
31.8	...	Weak	...
31.9	Medium	...	...
34.6	Weak	...	...
34.7	...	Weak	...

It was subsequently dried at temperatures slightly less than 100° for not less than 18 hr.

Form C. Hydrous.—An excess of form *A* was suspended in water with shaking for 72 hr. at 30 ± 0.1°. The crystals were collected then on a filter[2] and the absorbance of the filtrate measured to determine if crystal conversion was complete. Since the crystal hydrate exhibits a lower solubility, a recrystallization, in essence, was performed.

Form B. Anhydrous.—The hydrous prednisolone described above was dried at 104° for 18 hr. The accompanying water loss was measured by weight.

Forms *A* and *B* had the same molar absorptivity, which was 7% higher than that of the hydrate. This checked well with the per cent weight loss on drying of the hydrate (7.1%). Characteristic X-ray powder diffraction patterns and infrared spectra have been obtained for each crystal form. Table I shows the relative peak intensities of reflected radiation at various angles of reflection for the three crystal forms.[3]

Neither of the anhydrous forms were hygroscopic nor exhibited a change in properties under conditions of 93% humidity. Only high-temperature drying of the hydrate appeared to cause a permanent weight loss. Drying in a desiccator over P_2O_5 caused only a transient weight loss as the crystals immediately returned to their original weight in atmospheric humidity.

The above data indicate that anhydrous forms *A* and *B* are polymorphic and that form *C* is a discrete hydrate structure.

Determination of the Activity and Behavior of the Crystal Forms in Water

The pure crystals were added in a fourfold excess of their equilibrium solubility to distilled water at 30 ± 0.1°. Since it was necessary for the solvent medium to be sampled at intermittent time intervals, a magnetic stirrer apparatus similar to that described by Shefter (2) was used. In addition, this study also was performed in individual 15-ml. vials which were assayed after being shaken for specified time intervals.

Separation of the solid phase was accomplished by filters (Millipore), 0.45 M pore size. A syringe equipped with a Swinney adaptor was employed in the first procedure, while a 15-ml. suction apparatus was used in the second. The filtrates were assayed spectrophotometrically on a Cary model 11 spectrophotometer after appropriate dilution.

Dissolution Apparatus and Tablet Production

The dissolution apparatus and the procedure for tablet production were similar to that described in previous investigations (13). Spherical shaped 1/8-in. diameter tablets of the pure material were used. Smooth surface tablets could be prepared only over a limited density range without lubricated punch surfaces. It was necessary not to use a lubricant, since preliminary rate studies showed a lag time when the punch surfaces were lubricated with magnesium stearate. The influence of the lubricant on the lag time and dissolution characteristics appeared to vary with the crystal form. The tablets

[2] Millipore Corp., Bedford, Mass.

[3] The authors thank Dr. G. J. Papariello and the Ciba Pharmaceutical Co. for the X-ray diffraction data on these crystal forms.

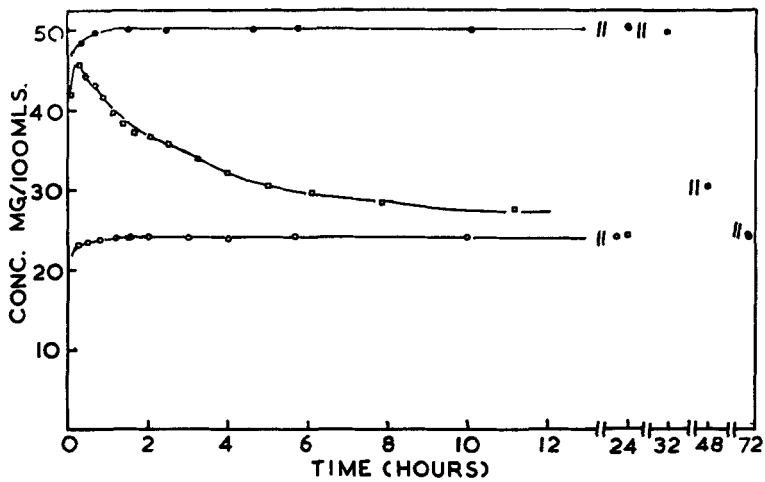

Fig. 2.—A plot of crystal behavior in distilled water determined in the magnetic stirrer apparatus (30°C.). Key: ●, crystal form *B*, anhydrous; □, crystal form *A*, anhydrous; ○, crystal form *C*, hydrous.

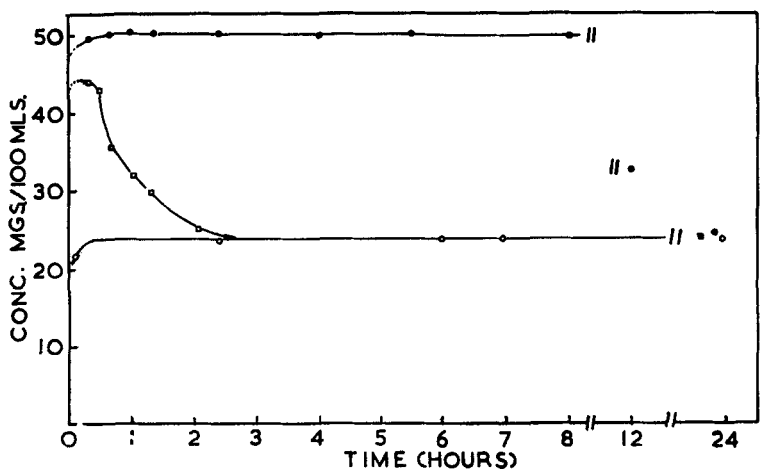

Fig. 3.—A plot of crystal behavior in distilled water determined by assaying individual vials (30°C.). Key: ●, crystal form *B*, anhydrous; □, crystal form *A*, anhydrous; ○, crystal form *C*, hydrous.

were weighed on a microbalance[4] to 1 × 10^{-6} Gm. and their dimensions measured with an optic micrometer.[5] The average tablet weight was about 22 mg.

Dissolution Rate Determinations

All dissolution studies were conducted at 30 ± 0.1°. Thirty-five-milliliter samples of the dissolution medium were removed at 0.5-hr. intervals and immediately replaced with an equal volume of distilled water at the same temperature. The samples were assayed on the same day, as described previously. In this case, however, a 10-cm. cell was used with no dilution.

A cumulative correction was made for the previously removed samples in determining the total amount dissolved by the formula

$$C_n = C_{n\,\text{meas.}} + \frac{35}{2000} \cdot \sum_{s=1}^{n-1} (C_{s\,\text{meas.}})$$

$C_{n\,\text{meas.}}$ denotes the spectrophotometrically measured concentration, while C_n is the concentration of nth sampling expected in the medium if previous samples had not been removed. The dissolution rate was calculated from slopes of the $W_0^{1/3} - W^{1/3}$ *versus* time plots, as reported previously (13). W_0 is the initial weight of the tablet, while W is the weight at time t. The data were processed by the use of an IBM model 1410 computer with a Fortran program. By designing the system and sampling methods as described above, dissolution could be carried out for a 6-hr. interval without the concentration in the medium exceeding 1% of saturation. Dissolution runs were made over a 5–7-hr. interval allowing 40–60% of the tablet to be dissolved. Upon termination of dissolution, the tablets were weighed again to see if a mass balance was achieved. At least three rate determinations were made for each case mentioned.

So that dissolution rates could be quantitated to the thermodynamic activity of the crystal form, the hydrous prednisolone data were treated in terms of transport of anhydrous prednisolone between phases. This treatment is consistent with diffusion control or partial diffusion control of the rate if the density of the tablet is considered as the weight of anhydrous prednisolone per unit volume.

[4] Mettler Instrument Corp., Hightstown, N. J.
[5] Gaertner Scientific Corp., Chicago, Ill.

TABLE II.—SOLUBILITIES OF THE CRYSTAL FORMS

Crystal Form	Solubility, mg./100 ml.
Form *A*, anhydrous	45.7[a]
Form *B*, anhydrous	50.4
Form *C*, hydrous	24.0

[a] Denotes an unstable crystal form, so it is likely that the above values represent a steady-state solubility.

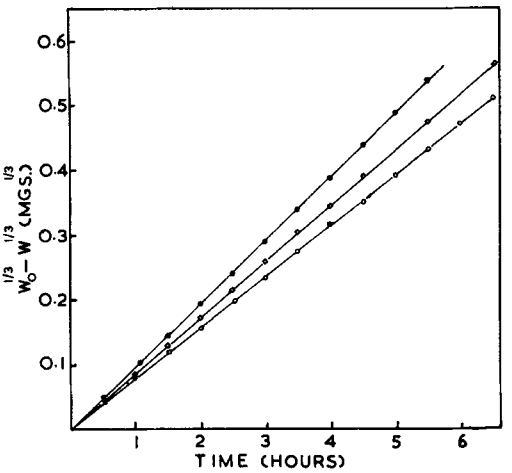

Fig. 4.—$W_0^{1/3} - W^{1/3}$ as a function of time plots for crystal form *A* at varying stirring speeds (30°C.). Key: ●, 1775 r.p.m.; □, 835 r.p.m.; ○, 417 r.p.m

Dissolution Studies at Varying Agitation Rates

A change in the revolutions per minute of the paddle stirrer supplying agitation to the free rotational system of the tablet was the method used for varying agitation. By using an electronic stroboscope,[6] it was possible to determine the true stirrer revolutions per minute with dissolution in process. The path of the tablet appeared to be similar over the stirring range employed.

RESULTS AND DISCUSSION

Crystal Activity and Behavior Determinations in Distilled Water.—Figures 2 and 3 illustrate the crystal behavior of each of the crystal forms for the two methods of agitation. The data appear to vary only with respect to the rate and onset of conversion to the stable crystal form. The conversion is more rapid with the study in separate vials, as would be expected with the more intense agitation conditions. Table II gives the maximum solubilities (mg./100 ml.) of the crystal forms shown in Figs. 2 and 3.

The activity of the hydrous crystal form represents the stable equilibrium state. Dissolution of crystals possessing higher activities[7] forms solutions initially supersaturated to the stable hydrous form.

[6] General Radio Co., Concord, Mass.

[7] The standard state convention of the supercooled liquid at the specified temperature provides a convenient reference for activity relations with solids existing in more than one crystalline form. Since the same reference state is referred to in the cases of the solid and solute in solution, the equilibrium condition determines the activity of the solid phase (14).

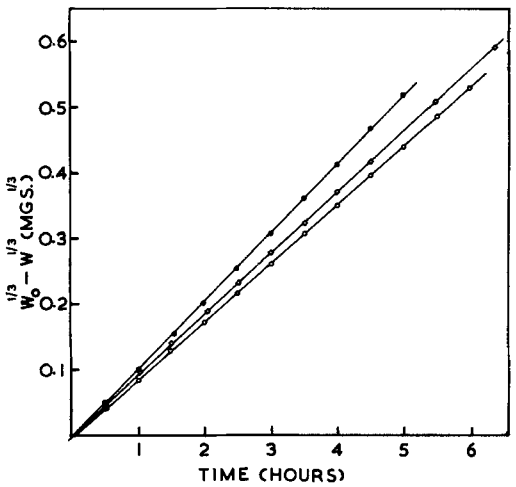

Fig. 5.—$W_0^{1/3} - W^{1/3}$ as a function of time plots for crystal form *B* at varying stirring speeds (30°C.). Key: ●, 1775 r.p.m.; □, 835 r.p.m.; ○, 417 r.p.m.

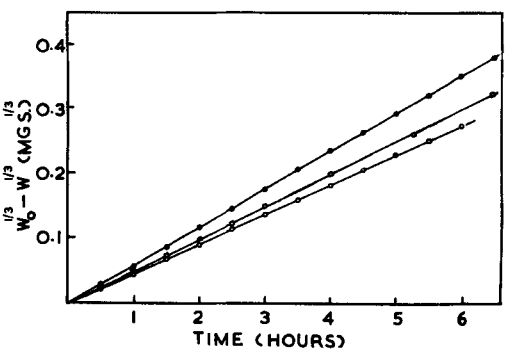

Fig. 6.—$W_0^{1/3} - W^{1/3}$ as a function of time plots for crystal form *C* at various stirring speeds (30°C.). Key: ●, 1775 r.p.m.; □, 835 r.p.m.; ○, 417 r.p.m.

TABLE III.—DISSOLUTION RATES (mg./cm.²/hr.) OF THE CRYSTAL FORMS AT VARYING STIRRING SPEEDS

Crystal Form	Stirring Speeds, r.p.m. 417	835	1775
Form *A*, anhydrous	5.10–5.18	5.66–5.67	6.31–6.32
Form *B*, anhydrous	5.61–5.75	5.97–6.07	6.78–6.81
Form *C*, hydrous	2.81–2.86	3.09–3.14	3.59–3.62

The activity of the solute eventually decreases due to nucleation and subsequent growth of the hydrous crystal form.

Anhydrous form *B*, in solution, exists in a metastable equilibrium state, evidenced by the distinct plateaus observed in Figs. 2 and 3. This solubility safely could be considered to represent the activity of the respective crystal form. Since prednisolone exhibits a low water solubility,[8] a free energy of

[8] Under these conditions the activity coefficient approaches unity, and the mole fraction is approximately proportional to the weight/volume composition.

TABLE IV.—DISSOLUTION RATE RATIOS AT VARYING STIRRING SPEEDS

Ratio of Crystal Forms	Stirring Speeds, r.p.m. 417	835	1775	Solubility Ratio
Form *B* / Form *C*	2.00–2.01	1.93–1.94	1.88–1.89	2.10
Form *A* / Form *C*	1.81–1.82	1.80–1.83	1.75–1.76	1.90[a]
Form *B* / Form *A*	1.10–1.11	1.06–1.07	1.07–1.08	1.10[a]

[a] Represents a solubility ratio containing a steady-state solubility; therefore, the ratios do not express the activity ratio of the crystal form.

TABLE V.—CALCULATED APPARENT RATE CONSTANTS (cm./hr.), $k_{app.}$, OF THE CRYSTAL FORMS AT VARYING STIRRING SPEEDS

Crystal Form	Stirring Speeds, r.p.m. 417	835	1775
Form *A*, anhydrous[a]	11.2–11.3	12.4–	13.8
Form *B*, anhydrous	11.1–11.4	11.8–12.0	13.4–13.5
Form *C*, hydrous	11.7–11.9	12.8–13.1	15.0–15.1

[a] Represents an unstable crystal form; therefore, the listed value will only be an approximation.

hydration between forms *B* and *C* ($\Delta F_{hyd.}$ 303°) of −445 cal./mole can be calculated from their solubilities (2).

Since anhydrous form *A* upon dissolution rapidly converts to the hydrate form, the solubility maximum exhibited is not necessarily the true solubility but only reflects a steady state between dissolution of the anhydrous form and subsequent crystallization of the hydrate. No definite statement can, therefore, be made concerning the activity of this crystal form. A steady-state condition could result easily since both dissolution and crystallization should be concentration gradient controlled. Since as many as three phases are present within the system, causing variable conditions and surface areas for dissolution, nucleation, and crystal growth, the shape of the curves (Figs. 2 and 3) varies, as expected, with the excess of anhydrous form *A* initially added.

Dissolution Rate Studies Under Varied Agitation Conditions.—Figures 4–6 show that plots of ($W_0^{1/3} - W^{1/3}$) *versus* time are linear for each crystal form under all agitation conditions. This indicated that the shape–volume relationship is maintained throughout dissolution. Measurements of the tablet dimensions upon completion of dissolution confirm this. Reproducibility of dissolution rates were obtained within 2% (Table III).

A comparison of the ratios of the dissolution rates of the crystal forms to the ratios of their solubilities shows a tendency for them to approach each other at low stirring rates (Table IV). This trend is not quite so apparent with anhydrous form *A*. With this unstable crystal form, it is possible that some recrystallization may occur at the interface. The extent of this occurrence will be dependent on the agitation rate. In a subsequent paper it will be shown that this significantly influences the dissolution rate in a system more prone to nucleation.

Since $C_s - C$ does not vary by more than 1%, an apparent rate constant, $k_{app.}$, can be calculated from the ratio of the dissolution rate and solubility (Table V). In crystal form *A*, the values only represent an approximation since the maximum solubility observed will, at best, only be close to the activity of this form.

The expression for $k_{app.}$ can be rearranged to the form

$$1/k_{app.} = 1/k_D + 1/k_r$$

The diffusion rate constant, k_D, is equal to the ratio of the diffusivity constant, D, and the effective diffusion layer thickness, h. k_D can be assumed to be invariant at the same stirring speed for the different crystal forms of prednisolone because of their low solubility. D and h have been shown to be independent of the concentration gradient, provided viscosity changes do not become significant (9, 11, 15, 16). k_r, the rate constant for the reaction at the interface, should not vary with agitation conditions. With the above restrictions, the following equations may be set up using average values for the determined apparent rate constants.

For hydrous prednisolone

$$1/11.8 = 1/k_{D,1} + 1/k_{r,H}$$
$$1/12.9 = 1/k_{D,m} + 1/k_{r,H}$$
$$1/15.1 = 1/k_{D,h} + 1/k_{r,H}$$

For anhydrous prednisolone (form *B*)

$$1/11.2 = 1/k_{D,1} + 1/k_{r,A}$$
$$1/11.9 = 1/k_{D,m} + 1/k_{r,A}$$
$$1/13.5 = 1/k_{D,h} + 1/k_{r,A}$$

The subscripts, 1, *m*, *h*, denote the stirring ratio, while *A* and *H* denote crystal form. These equations as such show differences between the rate constants for the interfacial relation; however, without evaluating an additional parameter, an estimation of the k's cannot be made.

Additional work to be reported in a subsequent paper indicates that dissolution in a dilute sodium lauryl sulfate solution (<CMC) may approach closely a completely diffusion-controlled process. In this solvent medium, under the same agitation conditions, even though there was no increase in the equilibrium solubility, a significant increase in the dissolution rate was observed for both crystal forms. Also the dissolution rate ratio of the crystal forms approached their solubility ratio within 2%. Both of these observed phenomena are in agreement with the formula for the apparent rate constant if the surface-active agent was to influence the interfacial reaction rate constant. This can be seen best if the parameters composing the apparent rate constant are viewed as characteristic additive resistances.

TABLE VI.—CALCULATED RATE CONSTANTS (cm./hr.) FOR DIFFUSION DETERMINED FROM THE PROPOSED MODEL

Crystal Form	Diffusion Rate Constants, k_D at Stirring Speeds, r.p.m. 417	835	1775	k_R
Form *C*, hydrous	12.7	14.0[a]	16.5	170
Form *A*, anhydrous	13.0	14.0[a]	16.3	79

[a] The value 14.0 is an approximation for k_D taken from additional work with surface-active agents.

TABLE VII.—CALCULATED CONCENTRATION (mg./100 ml.) AT THE INTERFACE OF THE BOUNDARY LAYER, C_i, FROM THE PROPOSED MODEL

Crystal Form	Stirring Speeds, r.p.m. 417	835	1775
Form *B*, anhydrous	43.3	42.8	41.7
Form *C*, hydrous	22.3	22.2	21.9

If complete diffusion control nearly prevails, then the apparent rate constant will be a good estimation of the rate constant for diffusion control, k_D. Since the above studies were carried out at 835 r.p.m., $k_{app.}$ for dissolution in sodium lauryl sulfate $\cong k_{D,m}$. Further study in sodium lauryl sulfate solutions at other stirring rates may provide a better estimate of the diffusion control constants.

Since the apparent rate constants for the two crystal forms involve independent sets of data, a comparison of $k_{D,h}$ and $k_{D,l}$ for the two crystal forms will test the fit of the model. Table VI shows that they are in agreement, considering that the determinations of the rate constants do vary almost 2%.

This proposed model of consecutive reactions posing a double barrier to dissolution seems to afford a suitable explanation for the divergence of the dissolution rate ratios from the solubility ratios at higher agitation as shown here and previously (1). The calculated concentration at the interface of the boundary layer, C_i, is given in Table VII. The boundary layer is by no means saturated; yet, because of the relatively high concentration existing here, transport from the interface is still the important factor controlling dissolution under these conditions.

The calculated width of the effective diffusion layer, h, using the Stokes-Einstein equation as a measure of D, varies from 1.3–1.6 $\times$ 10^{-3} cm., depending on the stirring speed. These values are in accord with those calculated in this laboratory under similar conditions (17).

SUMMARY

The activity, dissolution, and crystal behavior of three crystalline forms of prednisolone, each exhibiting distinctly different solubility and physical stability properties, were investigated. The dissolution rates of each of the crystalline forms were studied using an essentially isotropic crystalline solid in a free rotational agitation system. By determining the relative dissolution rates of the crystal forms under different agitation conditions, factors influencing the control of dissolution could be described. The data suggested that consecutive processes involving a reaction at the interface and transport away from the interface pose a double barrier for dissolution. A related study for the same solid systems in surface-active dissolution media tended to confirm this. The details of these findings will be reported in a subsequent paper.

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