Dissolution Kinetics of Certain Crystalline Forms of Prednisolone II

Influence of Low Concentrations of Sodium Lauryl Sulfate

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

The crystal behavior, solubilities, and dissolution rates of three crystalline forms of prednisolone were investigated in dilute sodium lauryl sulfate solutions. A solubilization effect was noted at concentrations considerably below the critical micelle concentration. Also, at a concentration of 0.1 per cent sodium lauryl sulfate the release from supersaturation of a metastable anhydrous crystal form was more rapid than in purely aqueous solutions. Substantial dissolution rate increases were observed in the surface-active media. It appeared that these increases could be accounted for by the solubilization effect and an apparent increase in the interfacial reaction rate.

SINCE surface-active agents are commonly a part of both liquid and solid pharmaceutical preparations, their effect on dissolution rates and crystal behavior in solution is of importance in determining the limits of physiological availability of the drug and the physical stability of the preparation. In our previous study with different prednisolone crystal forms (1), complete diffusion or transport control of dissolution did not prevail in water under the employed intensities of agitation. It would be of considerable interest to investigate the influence of a surfactant on dissolution in these systems because here dissolution may be affected in a different manner than expected for diffusion controlled systems.

PLAN OF STUDY

Crystal Behavior Studies.—The three crystalline forms of prednisolone used in this study and their crystal behavior in distilled water have been previously described (1). For comparisons to be made on the crystal behavior, studies using these same methods were carried out in sodium lauryl sulfate solutions with samples taken at specified time intervals. Since the hydrate crystal form was the only stable crystal form in aqueous solution, equilibrium solubilization studies could only be conducted with this crystal form.

Influence of Sodium Lauryl Sulfate on the Dissolution Rate.—Since a surface-active agent affects both the energy relationships at a solid–liquid interface and the solubility of a crystal form through a solubilization effect, an analysis of these phenomena may further aid in predicting the control of the dissolution process. These considerations which would effect an enhanced rate of dissolution preclude the formation of an impeding condensed film of surfactant at the interface. Evidence in the literature suggests that the adsorption of surfactant on a solid–liquid interface is significantly less than monomolecular in the critical micelle concentration (CMC) range (2–4). The relative rates of crystal growth in surface-active media would also indicate whether this factor of film effects would be significant.

EXPERIMENTAL

Determination of the Behavior of the Crystal Forms in Sodium Lauryl Sulfate Solutions.—An identical system and method of assay as that described before (1) was used for the determination of crystal behavior. A better dispersion was noted in the solutions containing the surfactant.

To determine the equilibrium solubilization effect individual vials containing the prednisolone in excess were agitated at constant temperature for 48 hr. The filtrate was then assayed after the appropriate dilution. In all studies a filter[1] (Millipore) pore size of 0.45 μ was used. It was felt that this pore size would allow passage of surfactant aggregates in the concentration range studied (<0.2%), yet would retain the near microcrystalline particles formed in the crystal conversion.

Sodium lauryl sulfate[2] (95%), previously extracted six times with anhydrous ether, analytical reagent, was used in all studies. The pH of the sodium lauryl sulfate solutions was close to that of distilled water (5.7–5.8). In this pH range it can be assumed that degradation in the system by hydrolysis of sodium lauryl sulfate (5) or by oxidative cleavage of the dihydroxyacetone function of prednisolone (6) was negligible.

Dissolution Rate Determinations.—The production of the spherical tablets, their dimensions, the assay of the dissolution medium, and the dissolution apparatus were the same as previously described (1). In all determinations with surfactant, a stirrer speed of 835 r.p.m. was used. As before, at

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* Present address: Laboratory of Chemical Pharmacology, National Heart Institute, U. S. Public Health Service, Bethesda, Md.

[1] Millipore Filter Corp., Bedford, Mass.
[2] Matheson, Coleman & Bell.

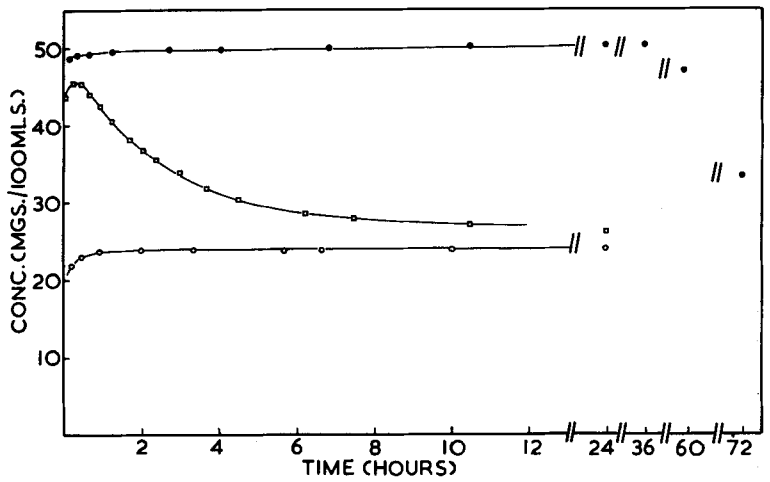

Fig. 1.—A plot of crystal behavior in 0.01% sodium lauryl sulfate solutions determined in the magnetic stirrer apparatus (30°C.). Key: ●, crystal form *B*, anhydrous; □, crystal form *A*, anhydrous; O, crystal form *C*, hydrous.

each concentration of surfactant, dissolution runs were made in triplicate with the determined rates falling within a 2% range. The sodium lauryl sulfate solutions were prepared on the same day as the dissolution experiment.

Blank determinations were run with sodium lauryl sulfate solutions, and it was found that the lack of optical clarity that influences ultraviolet absorption amounted to less than 1% of the slope of absorption values with respect to time. This was also confirmed by mass balance calculations upon completion of dissolution. In the employed concentration range of sodium lauryl sulfate the ultraviolet absorption spectrum of prednisolone was not altered.

RESULTS AND DISCUSSION

Behavior of the Crystal Forms in Sodium Lauryl Sulfate Solutions.—The behavior of each crystal form in 0.01% sodium lauryl sulfate is quite similar to that observed in water (1) (Fig. 1). No increase in solubility nor any marked change in the stability of the anhydrous crystal forms occurs. Sodium lauryl sulfate at a concentration of 0.1%, however, causes changes in the maximum solubility exhibited as well as alterations in the tendency for crystal conversion (Fig. 2).

Anhydrous form *B*, which was metastable when dissolved in water, is rapidly released from supersaturation at this concentration of surfactant. The apparent rate of hydrate crystallization also is significantly enhanced in these solubilized systems. This could also be a result of the increase in the tendency for spontaneous nucleation to occur.

This decrease in the induction period of nucleation, that is, the more rapid release from supersaturation conceivably could be the result of a greater degree of supersaturation or the ability of a surface-active agent to decrease the free energy of formation of an effective critical nucleus. By considerations similiar to those of Volmer and Weber (7), the free energy of activation necessary

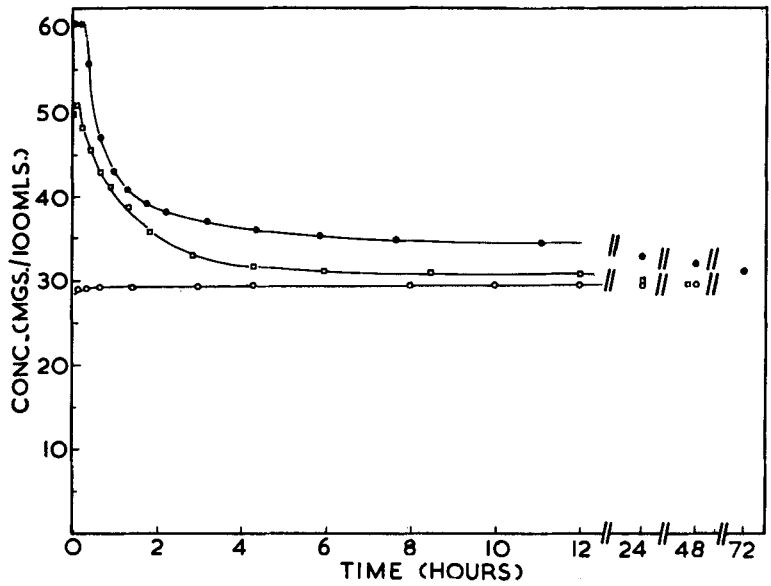

Fig. 2.—A plot of crystal behavior in 0.1% sodium lauryl sulfate solutions determined in the magnetic stirrer apparatus (30°C.). Key: ●, crystal form, *B*, anhydrous; □ crystal form *A*, anhydrous; O, crystal form *C* hydrous.

for the formation of an effective critical nucleus, $\Delta G\ddagger$, can be represented by

$$\Delta G\ddagger = \frac{16\pi\,\sigma^3 V_B^2}{3\left(kT \ln \frac{C}{C_\infty}\right)^2}$$

where σ is the interfacial tension, V_B the volume per molecule in the newly formed phase, C the supersaturation concentration in solution, C_∞ the solubility of the stable crystal form, k Boltzmanns constant, and T the absolute temperature. The use of $\Delta G\ddagger$ in a rate expression or its consideration in density or energy fluctuations within volume elements shows that the degree of supersaturation, C/C_∞, as an exponential will greatly affect the nucleation rate or probability. For this factor to be significant, however, the solubilized or associated prednisolone must be free to participate in nucleation, which is uncertain. The role of the solubilized steroid existing as a foreign surface or the solubilizing agent imparting impurities into the system is also obscure.

From the above equation, it is also evident that a reduction in interfacial tension will increase the nucleation probability or rate. The interfacial tension at a solid–liquid interface is not directly measurable, but its change should be in the same direction as the tension at the liquid–air interface or the surface tension. The above interfacial tension term must, though, be considered as an instantaneous value rather than an equilibrium one. Consequently, it becomes difficult to predict the exact influence of a surfactant on this term since at the time of formation of a new phase a concomitant migration of surfactant to the interface must also be effected.

The solubility values shown in Fig. 3, which plots the equilibrium solubility in mg./100 ml. of the stable crystal hydrate as a function of sodium lauryl sulfate concentration, are in agreement with those of the crystal behavior study in 0.01 and 0.1% sodium lauryl sulfate solutions. From Fig. 3, it is apparent that at higher sodium lauryl sulfate concentrations the concentration of solubilizate rendered soluble is a linear function of the surfactant concentration. No solubilization is evident at low sodium lauryl sulfate concentrations; however, a marked solubilization effect results at fractional concentrations of the listed CMC of 0.23% (8, 9).

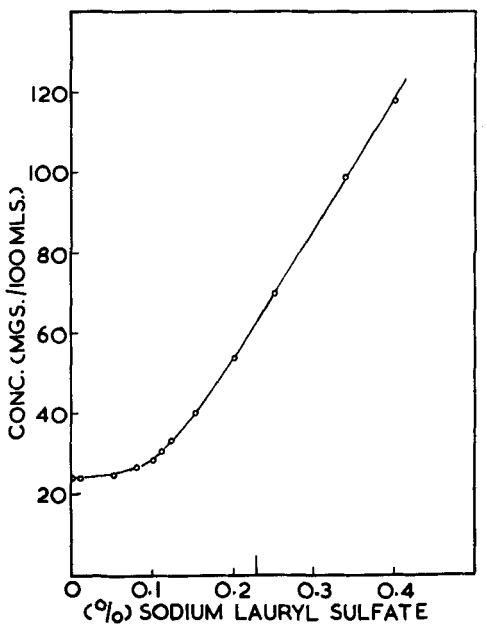

Fig. 3.—Solubilization of hydrous prednisolone by sodium lauryl sulfate at 30°C. The mark at 0.23% denotes the CMC of sodium lauryl sulfate in water (30°C.).

Table I.—Solubilities (mg./100 ml.) of the Crystal Forms at Varying Sodium Lauryl Sulfate Concentrations

Crystal Form	H_2O	0.01% Sodium Lauryl Sulfate	0.1% Sodium Lauryl Sulfate
Form *A*, anhydrous	45.7[a]	45.6[a]	51.0[a]
Form *B*, anhydrous	50.4	50.5	60.5[a]
Form *C*, hydrous	24.0	24.1	29.5

[a] Represent a maximum (steady-state) solubility only due to the rapid conversion to a stable crystal form.

Table II.—Dissolution Rates (mg./cm.²/hr.) of the Crystal Forms at Varying Sodium Lauryl Sulfate Concentrations

Crystal Form	H_2O	0.01% Sodium Lauryl Sulfate	0.1% Sodium Lauryl Sulfate
Form *A*, anhydrous	5.66–5.67	6.01–6.14	5.58–5.62
Form *B*, anhydrous	5.97–6.07	6.89–6.91	8.91–9.13
Form *C*, hydrous	3.09–3.14	3.37–3.83	4.30–4.38

This effect has been observed previously and explained by separate concepts. Some workers maintain that a penetration or incorporation of the solubilizate into the micelle induces a lowering of the CMC (10, 11). The solubilizate is believed to be oriented between aligned surfactant molecules, thus reducing the repulsive forces between them and facilitating micelle formation at lower concentrations. Others feel that limited association or aggregation between the solubilizate and surfactant at concentrations considerably below the CMC is responsible for the increase in solubility (12, 13). With both of these concepts it was recognized that this effect was quite selective with respect to the nature of the solubilizate. An examination of the maximum solubility exhibited in 0.1% sodium lauryl sulfate solutions by the metastable and stable crystal forms (*B* and *C*) indicate that the extent of solubilization may be related to the activity of the crystal form (Table I).

If these results were borne out over a concentration range, the data could be represented by the following equation:

$$\text{apparent solubility} = S + K_s(S)$$

S is the equilibrium solubility (activity) of the crystal form in water, and K_s represents a dimensionless quantity dependent on the surface-active agent, its concentration, and temperature. With the data shown here, K_s is in the range of 0.20–0.22

for forms *B* and *C*. The slight spread in values could well be due to the inability of the anhydrous form to reach an equilibrium solubility before crystallization occurs and the slight decrease in free sodium lauryl sulfate due to the additional solubilization of the anhydrous form.

A further study of this would aid in determining to what degree solubilization at low concentrations of surfactants is a cooperative phenomenon as opposed to adsorption on fixed sites.

Influence of Sodium Lauryl Sulfate on the Dissolution Rate.—The plots of $W_0^{1/3} - W^{1/3}$ as a function of time show a linear relationship in sodium lauryl sulfate solutions as shown before (1). Measurement of the tablet dimensions and inspection of its surface indicate that the shape-volume factor remains constant through dissolution.

Dissolution in 0.01% Sodium Lauryl Sulfate Solutions.—A 9% increase in rate is noticed with the hydrous form while a 15% increase is exhibited by the metastable anhydrous form *B* (Table II). The previously discussed equations, describing dissolution in terms of consecutive reactions in which a double barrier existed in the dissolution process (1), will be considered here from the standpoint of the influence of a surface-active agent. In the above kinetics, the apparent rate constant $k_{app.}$, was equal to $k_r k_D/(k_r + k_D)$, where k_r and k_D are the rate parameters for the interfacial reaction and diffusion, respectively. The apparent rate constant was identical to that described by the Noyes-Whitney equation (14) or

$$dw/dt = k_{app.} S(C_s - C)$$

Since no solubilization is apparent in the neighborhood of 0.01% sodium lauryl sulfate concentration, the saturation concentration value, C_s, should not be affected. Consequently, the observed rate increase must be ascribed to a change in $k_{app.}$. An increase in k_r, assuming a similar effect with both crystal forms, would reflect a greater percentage increase in $k_{app.}$ for the anhydrous form since the calculated k_r for this form in water is approximately one-half that of the hydrous form (1). The data for dissolution in 0.01% solutions show the greater percentage increase in $k_{app.}$ for the anhydrous form as well as a fractional increase in $k_{app.}$ for both forms (Table III).

With crystal forms *B* and *C*, the ratio of their activities only varied from the ratio of the dissolution rates by approximately 2%. By the formula

$$\frac{1}{k_{app.}} = \frac{1}{k_r} + \frac{1}{k_D}$$

If $k_r \gg k_D$, then $k_{app.} \cong k_D$. At this concentration of sodium lauryl sulfate, association or viscosity changes should not alter the diffusional properties; hence k_D will remain unaffected by the addition of surfactant. On this basis then it would appear that $k_{app.}$ in 0.01% sodium lauryl sulfate solution could be considered as an approximation for k_D. (Table IV.)

This proposed increase in k_r with sodium lauryl sulfate could be attributed to a lowered interfacial tension causing better wetting and penetration properties of the solvent. Since the tablet is composed of compressed crystals, the surface would be expected to possess slight irregularities. A surface-active agent, as demonstrated by Wurster and Seitz (15), will cause a more complete penetration into existing fissures by the solvent, thus increasing the available surface for dissolution. In the case of a poor solvent such as water with prednisolone this effect may be more predominant owing to the higher contact angle.

A surface-active agent may also cause a real increase in k_r by changing the wetting properties and contact angle on the crystal face *per se*. Surface-active environments have been shown to influence the extent of etching (16), and investigators in this area contend that dissolution is effected from points of crystal defect or imperfections (16–18). The availability of solvent at these microscopic points on the crystal face will be critical to the dissolution process. Since a lack of continuity exists at these points, the contact angle of solvent will again be of importance.

Dissolution in 0.1% Sodium Lauryl Sulfate Solutions.—This concentration of surfactant produces a 39% increase in the dissolution rate of the hydrate and a 50% rate increase for anhydrous form *B* (Table II). A comparison of the $k_{app.}$ values illustrates that the solubilization effect causing an increase in C_s is the major reason for the increase over that observed in 0.01% solutions (Table III). The $k_{app.}$ values for dissolution in 0.1% sodium lauryl sulfate are only 4–5% greater than those in 0.01% solutions.

TABLE III.—CALCULATED APPARENT RATE CONSTANTS, $k_{app.}$, IN CM./HR., OF THE CRYSTAL FORMS AT VARYING SODIUM LAURYL SULFATE CONCENTRATIONS

Crystal Form	H_2O	0.01% Sodium Lauryl Sulfate	0.1% Sodium Lauryl Sulfate
Form *A*, anhydrous	12.4[a]	13.2–13.5[a]	10.9–11.0[a]
Form *B*, anhydrous	11.8–12.0	13.7	14.7–15.0[a]
Form *C*, hydrous	12.8–13.1	14.0	14.6–14.8

[a] Unstable crystal form in the respective solution; therefore, the above value only represents an approximation.

TABLE IV.—RATIOS OF THE DISSOLUTION RATES OF THE CRYSTAL FORMS AT VARYING SODIUM LAURYL SULFATE CONCENTRATIONS (835 r.p.m.)

Crystal Form Ratio	H_2O	0.01% Sodium Lauryl Sulfate	0.1% Sodium Lauryl Sulfate
$\frac{\text{Form } B}{\text{Form } C}$	1.93	2.05	2.07–2.08
$\frac{\text{Form } A}{\text{Form } C}$	1.81–1.83	1.78–1.82	1.28–1.30
$\frac{\text{Form } B}{\text{Form } A}$	1.06–1.07	1.13–1.15	1.60–1.62
Solubility Ratio			
$\frac{\text{Form } B}{\text{Form } C}$	2.10	2.10	2.05[a]

[a] Solubility ratio containing a steady-state solubility; therefore, this ratio may not express the activity ratio of the crystal forms.

This difference may partially be accounted for by a consideration of two possible factors. (*a*) The possibility of migration of excess surface-active agent to the interface resulting in additional solubilization in the boundary layer. On the basis of the solubilization curve (Fig. 3), there would be an enhanced likelihood for this to occur here because of the positive slope in this concentration range. However, it does not appear too energetically feasible for the excess concentration at the interface, which is believed to be less than monomolecular, to participate in solubilization to a significant extent in the boundary layer. (*b*) A further increase in k_r due to increased interfacial tension reduction. If this were the case without complicating influences being apparent, then the $k_{app.}$ values in 0.1% sodium lauryl sulfate may be a better estimate of the diffusion control constants.

The exact role played by these respective factors is somewhat indeterminant since solubilized prednisolone will exhibit a slightly different diffusion coefficient. The influence of this is, in turn, dependent on the width of the effective diffusion layer which can vary with the diffusion coefficient.

An examination of the dissolution rate and solubility of form *A* shows that this form exhibits disparate dissolution behavior in 0.1% sodium lauryl sulfate solutions. Its dissolution rate decreases, yet an increase in its maximum solubility is observed. This observation can probably be best explained by postulating that a less soluble layer composed of crystal hydrate is formed and adsorbed at the interface. This layer is most likely not continuous since it will tend to dissolve, and the nucleation tendency at localized areas on the surface will vary. The frequency of nucleation at the interface should be dependent on the excess of supersaturation in the immediate area and hence the surface coverage of the hydrate form. Thus, an apparent steady-state condition could easily be maintained with the observed dissolution rate being the resultant of dissolution of the hydrous and anhydrous forms. The influence of each will be dependent on the respective areas they occupy on the surface.

Data on the maximum solubilities of the crystal forms and the crystal hydrate growth rates (treated in terms of first-order control by the concentration gradient) further support this postulate. With crystal forms *B* and *C* being the more stable crystal forms, the same ratio of solubilities prevails throughout the solvent systems (Table I). For form *A*, though, the ratio is about 10% lower in 0.1% sodium lauryl sulfate solutions. This observed difference is probably due to the more rapid nucleation of the stable crystal form. Its apparent crystal growth rate under these conditions also appears to be the most rapid. These studies demonstrate that the greatest susceptibility toward nucleation and crystal conversion is exhibited by form *A* in 0.1% sodium lauryl sulfate.

SUMMARY

The crystal behavior, solubilities, and dissolution rates of three crystalline forms of prednisolone were investigated in dilute sodium lauryl sulfate solutions. The crystal behavior, upon dissolution, was essentially the same in 0.01% sodium lauryl sulfate solutions as that noted in water. However, in 0.1% solutions, an increase in the maximum solubilities as well as a more rapid release from supersaturation of the anhydrous crystal forms were exhibited. The solubilization effect occurred at surfactant concentrations considerably below the CMC, and the extent of solubilization appeared to be related to the activity of the crystal form, suggesting that a cooperative phenomenon was responsible for the increased apparent solubility.

The results obtained for dissolution in surface-active media are consonant with the double barrier dissolution kinetics previously described (1). In 0.01% solutions, a concentration where no solubilization effect was observed, there was a significant increase in the dissolution rate. This was believed to be due to an apparent increase in the intrinsic rate of the interfacial reaction. The close approach of the ratio of the dissolution rates to the solubility ratio of the two stable crystal forms suggest that the transport process essentially completely controls the dissolution rate in these solutions.

In 0.1% solutions marked increases in the rate of dissolution of the metastable and stable crystal forms are noted. The solubilization effect seems to be responsible for nearly all of this additional increase. The rapidly converting anhydrous form, however, exhibits a decreased dissolution rate in 0.1% solutions. It appears that this can be ascribed to crystallization of the hydrate on the dissolving tablet surface.

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