(5) *Ibid.*, **46**, 2519(1968).

(6) A. E. W. Smith, E. Frommel, and S. Radouco-Thomas, *Arzneim.-Forsch.*, **13**, 338(1963).

(7) I. Angelini, L. Angelini, and F. Sparaco, British pat. 1,161,802(1969); through *Chem. Abstr.*, **71**, 112936g(1969).

(8) I. Angelini, L. Angelini, and F. Sparaco, British pat. 1,161,801(1969); through *Chem. Abstr.*, **71**, 112937h(1969).

(9) J. J. Piala and H. L. Tale, U. S. pat. 3,166,566(1965); through *Chem. Abstr.*, **62**, 10444b(1965).

(10) C. Derappe, Fr. M. 5263(1967); through *Chem. Abstr.*, **71**, 81377u(1969).

(11) J. Maillard, M. Vincent, R. Mofrin, and M. Benard, Fr. M. 379(1962); through *Chem. Abstr.*, **57**, 15251g(1962).

(12) E. R. Atkinson and P. B. Milton, *J. Amer. Chem. Soc.*, **69**, 3142(1947).

(13) A. S. Wheeler and W. M. Oats, *ibid.*, **32**, 770(1910).

(14) C. J. Klemme and J. H. Hunter, *J. Org. Chem.*, **5**, 227(1940).

(15) Kuprozewski and T. Sokolowaska, *Acta Biochem. Polon.*, **4**, 85(1957).

(16) A. Silberg and N. Cosma, *Acad. Repub. Pop. Rom. Filiala Cluj, Studii Cercetări Chim.*, **10**, 151(1959); through *Chem. Abstr.*, **54**, 8794(1960).

(17) K. Krajl, *Biochem. Pharmacol.*, **14**, 1684(1965).

(18) D. E. McOskar and L. J. Daniel, *Arch. Biochem.*, **79**, 1(1959).

(19) G. W. Smith, "Progress in Medicinal Chemistry," vol. I, Butterworths, London, England, 1960, p. 1.

(20) C. Bianchi and J. Franceschini, *Brit. J. Pharmacol. Chemother.*, **9**, 280(1954).

Solubility and Dissolution of Triamcinolone Acetonide

L. H. BLOCK▲ and R. N. PATEL

Abstract ☐ Available data on the solubility of triamcinolone acetonide in aqueous media are neither complete nor in agreement. Solubility of the steroid in distilled water and in potassium chloride solutions of varying ionic strength was determined at 28, 37, and 50°. Dissolution rates of the steroid in the aqueous media were determined at 28° *via* a rotating-disk method. Triamcinolone acetonide solubility in distilled water ranged from 21 mcg. ml.$^{-1}$ at 28° to 33.6 mcg. ml.$^{-1}$ at 50°. The differential heat of solution was 4207 cal. mole^{-1}. The intrinsic dissolution rate constant at the maximum agitation intensity employed was 4.51×10^{-3} hr.$^{-1}$ cm.$^{-2}$. Solubilities and dissolution rates were markedly lower in potassium chloride solutions. "Salting-out" coefficients were calculated, for the effect of potassium chloride on triamcinolone acetonide solubility, using the empirical Setschenow equation.

Keyphrases ☐ Triamcinolone acetonide—solubility and dissolution in water and potassium chloride solutions ☐ Solubility, triamcinolone acetonide—water and potassium chloride solutions, Setschenow salting-out coefficients ☐ Dissolution rates, triamcinolone acetonide—water and potassium chloride solutions

Lange and Amudson (1), using a gravimetric procedure, determined the aqueous solubility of triamcinolone acetonide to be 26.4 mg./100 ml. at 25°. Malkinson and Kirschenbaum (2), in their study of the percutaneous absorption of triamcinolone acetonide, noted that the steroid had an aqueous solubility of 1 mg./100 ml., although neither the temperature of the system nor the method used in determining solubility was specified. Florey (3) recently reported solubilities for the compound in water as well as isotonic saline (pH 7) at 23 and 37° as 0.004 ± 0.002% (40 mcg./ml.). The solubility data available thus far are neither adequate nor in agreement. No data have been reported on the

effect of ionic strength on the steroid's solubility, nor are dissolution rate data available. Since the solubility and dissolution of the steroid can ultimately affect its release from matrixes in which it is suspended, these physicochemical properties of triamcinolone acetonide were evaluated.

MATERIALS AND METHODS

Materials—Hydrochloric acid[1], potassium chloride[1], recrystallized blue tetrazolium[1], tetramethylammonium hydroxide (10% in water)[2], and triamcinolone acetonide[3] were used as received.

One potential source of error—the polymorphic form of the steroid—was eliminated following differential thermal analyses of the three lots of steroid received. No marked differences in the thermograms obtained[4] were noted. It could thus be concluded that the steroid employed was of a single polymorphic form.

Reagents—Blue tetrazolium solution (0.2% w/v) was prepared by accurately weighing 100 mg. of blue tetrazolium, suspending the material in 35 ml. of alcohol, and agitating the suspension at 45° until dissolution was complete. Following the attainment of ambient thermal equilibrium, the solution volume was adjusted to 50 ml. with alcohol. The solution was freshly prepared before use. Tetramethylammonium hydroxide solution (1% v/v) was prepared from the commercial 10% solution by accurately transferring 10 ml. of the concentrate to a volumetric flask and adjusting the volume to 100 ml. with alcohol. Hydrochloric acid (1 *N*) was prepared by diluting 12.5 ml. of concentrated acid to 100 ml. with distilled water.
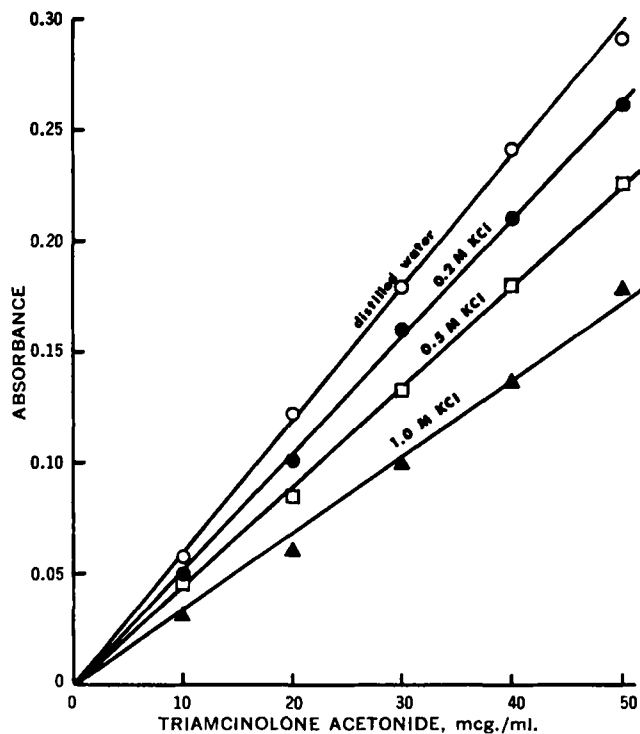
Figure 1—*Beer's plots for triamcinolone acetonide–blue tetrazolium reaction in distilled water and potassium chloride solutions.*

Assay of Aqueous Solutions of Triamcinolone Acetonide—*Standard Solution*—A standard solution of triamcinolone acetonide (1000 mcg./ml.) was prepared by dissolving 100 mg. of steroid, accurately weighed, in enough alcohol to yield a final solution volume of 100 ml.

Assay Procedure—The analytical method employed was that of Umeda *et al.* (4); 1.0 ml. of the steroid-containing solution, 1.0 ml. of alcohol, 2.0 ml. of blue tetrazolium solution, and 1.0 ml. of tetramethylammonium hydroxide solution were transferred to a screw-capped test tube. The mixture was kept at 30–35° in a water bath for 25–30 min., and 1.0 ml. of 1 N hydrochloric acid was then added. A blank solution was prepared using 1.0 ml. of the dissolution medium instead of the steroid-containing solution. The absorbance of the steroid-containing solution, relative to the blank, was measured at the λ_{max}, 525 nm., for each dissolution medium employed (distilled water and 0.2, 0.5, and 1.0 M potassium
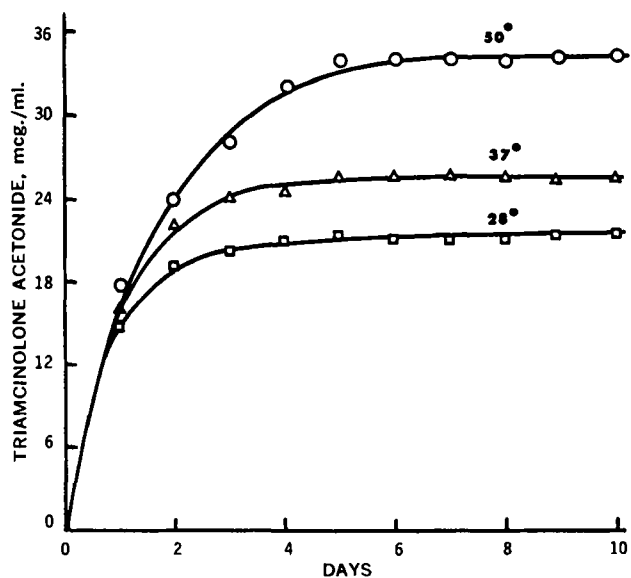

Figure 2—*Solubility of triamcinolone acetonide in distilled water as a function of time.*
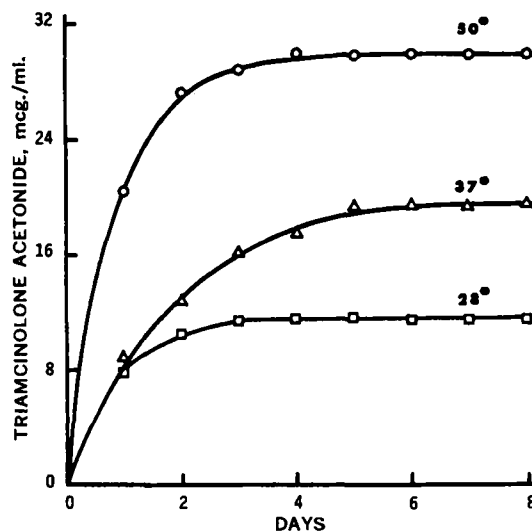
Figure 3—*Solubility of triamcinolone acetonide in 0.2 M potassium chloride solution as a function of time.*

chloride)⁵. Beer's plots are shown in Fig. 1. The slopes of the curves were calculated by the method of least squares with the aid of a programmable calculator⁶. The reciprocals of the absorptivities thus calculated were used in the calculation of solution steroid concentrations.

Solubility Determinations—Triamcinolone acetonide solubility in distilled water and in 0.2, 0.5, and 1.0 M potassium chloride solutions was determined as a function of temperature in the following manner. An excess of steroid (50 mg.) was added to amber, screw-capped, 180-ml. (6-oz.) bottles containing 100 ml. of the appropriate dissolution medium. A Saran⁷ liner was inserted and the bottle cap was tightened in place. The bottles were manually shaken and then suspended in constant-temperature baths⁸ maintained⁹ at 28 ± 0.5, 37 ± 0.5, and 50 ± 0.5°, respectively. The bottles were shaken periodically. Samples were withdrawn from the con-
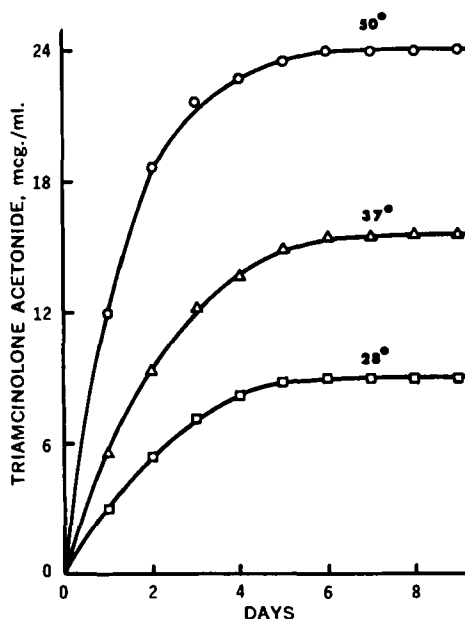

Figure 4—*Solubility of triamcinolone acetonide in 0.5 M potassium chloride solution as a function of time.*

⁵ Hitachi Perkin-Elmer spectrophotometer, model 139 UV-VIS, Perkin-Elmer Corp., Norwalk, Conn.
⁶ Wang 700B/701, Wang Laboratories, Tewksbury, Mass.
⁷ Dow Chemical Co., Midland, Mich.
⁸ Unitized constant-temperature water baths, Fisher Scientific Co., Chicago, Ill.
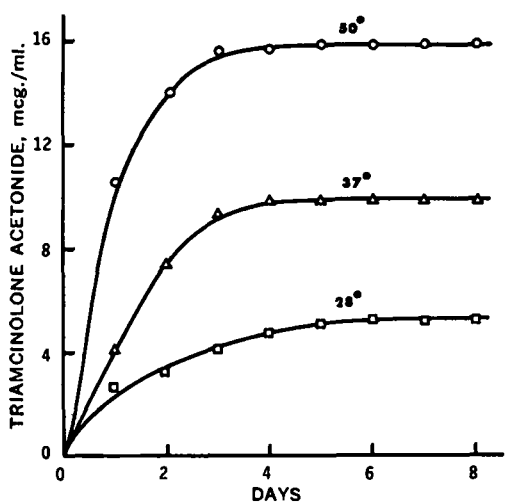⁹ Porta-Temp, Precision Scientific Co., Chicago, Ill.

Figure 5—*Solubility of triamcinolone acetonide in 1.0 M potassium chloride solution as a function of time.*

tainers every 24 hr. using 2-ml. tuberculin syringes[10] fitted with Whitacre spinal needles[11]. The samples were filtered through 0.22-μ filters[12] and assayed for triamcinolone acetonide.

Dissolution Rate Studies—The dissolution apparatus employed consisted of a 2000-ml., three-necked, round-bottom flask immersed in a constant-temperature bath and an acrylic turbine-bladed stirrer/pellet holder attached to an electronically controlled precision stirring motor[13].

Flat-faced, 1.3-cm. (0.5-in.) diameter pellets of pure triamcinolone acetonide were prepared by suitable compression with a pellet press[14]. The pellets were then mounted in the acrylic pellet holder, with the aid of beeswax, in such a way that only one flat face of a pellet was exposed. The pellet holder, with the pellet in place, was attached to a metal shaft connected to an electronically controlled precision stirring motor.

After adding 1500 ml. of the dissolution medium to the three-necked flask immersed in the constant-temperature bath, the temperature of the dissolution medium was allowed to equilibrate with
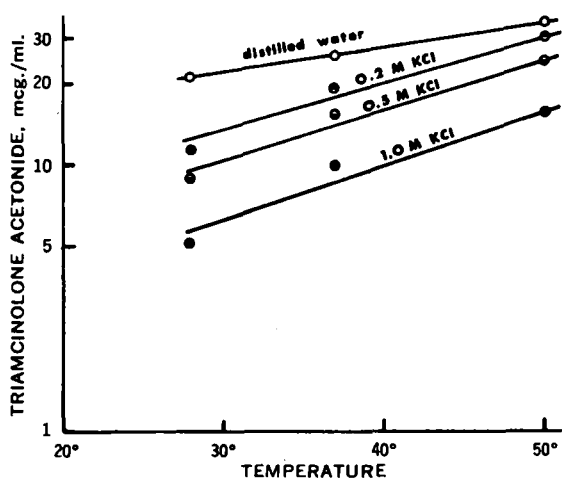

Figure 6—*Solubility of triamcinolone acetonide in dissolution media as a function of temperature.*

[10] B-D Yale 2019, 2yyP, Becton, Dickinson and Co., Rutherford, N. J.
[11] B-D 1331, W46Z, LNR, Becton, Dickinson and Co., Rutherford, N. J.
[12] MF-Millipore filters, GSWP 0 25 00, Millipore Corp., Bedford, Mass.
[13] Laboratory stirrer and motor controller, model GT-21, G. K. Heller Corp., Floral Park, N. Y.
[14] Research and Industrial Instruments Co., London, England.

Table I—Solubility of Triamcinolone Acetonide in Dissolution Media (mcg. ml.$^{-1}$)[a]

| Temperature | Distilled Water | Potassium Chloride Solution | | |
		0.2 M	0.5 M	1.0 M
28°	21.0	11.4	8.9	5.1
37°	25.5	19.0	15.4	9.9
50°	33.6	29.5	24.1	15.8

[a] Results represent the averages of two determinations.

Table II—Differential Heats of Solution of Triamcinolone Acetonide in Dissolution Media, Calculated from Arrhenius Plots of the Solubility Data

Dissolution Medium	ΔH_{soln}, cal. mole^{-1}
Distilled water	4207
Potassium chloride solution:	
0.2 M	8340
0.5 M	8722
1.0 M	9855

that of the bath (28 ± 0.5°). The pellet holder, with pellet in place, was then immersed in the dissolution medium to a depth of 5 cm. The stirrer was switched on and maintained at constant speed. Aliquots of 2.0 ml. were removed from the flask at appropriate time intervals, using tuberculin syringes fitted with Whitacre spinal needles, and then filtered through 0.22-μ Millipore filters.

RESULTS AND DISCUSSION

Solubility—The approach to equilibrium, as a function of time, is shown in Figs. 2–5. Concentration plateaus were reached within 4–5 days. The solubility of triamcinolone acetonide as a function of temperature in distilled water and in potassium chloride solutions is shown in Fig. 6. The saturation equilibria are summarized in Table I. The differential heats of solution, ΔH_{soln}, of the steroid in the dissolution media were calculated by the method of least squares in accordance with the Arrhenius relationship:

$$\log X = -\frac{\Delta H_{soln}}{2.303R} \cdot \frac{1}{T} + b \qquad \text{(Eq. 1)}$$

where X is the mole fraction of steroid in solution, R is the molar gas constant, T is the absolute temperature, and b is a constant. The values are tabulated in Table II.

The effect of electrolyte on the solubility of the steroid is particularly evident (Fig. 7); it is apparent that a "salting-out" phenomenon
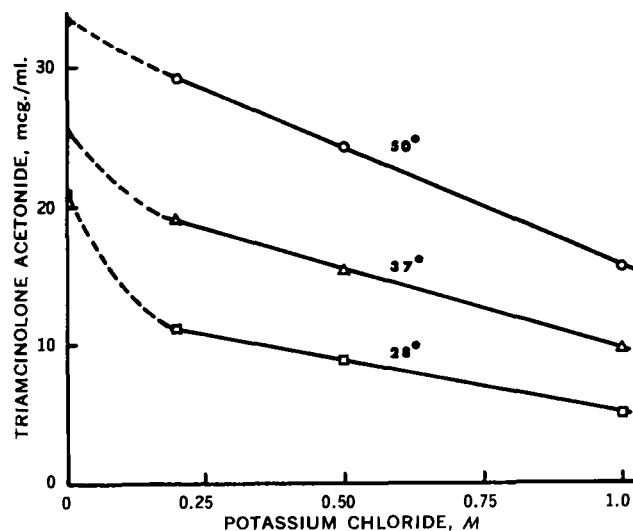

Figure 7—*Solubility of triamcinolone acetonide in potassium chloride solutions.*
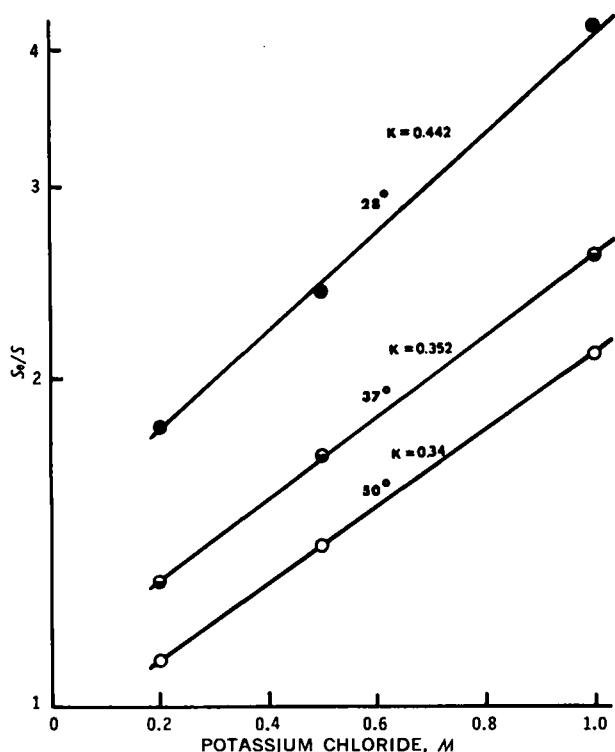
Figure 8—*Setschenow plots for triamcinolone acetonide in potassium chloride solutions.*

is encountered. Setschenow (5, 6) proposed an empirical relationship for the effect of an electrolyte on the solubility of a nonelectrolyte:

$$\log (S_0/S) = kC \qquad \text{(Eq. 2)}$$

where S_0 is the solubility of the nonelectrolyte in pure solvent, S is the solubility of the nonelectrolyte in an electrolyte solution of a given molar concentration C, and k is the salting-out coefficient and is a function of the composition of the system and the temperature. The ratio S_0/S is equal to f, the activity coefficient of the nonelectrolyte in the electrolyte solution. Setschenow plots of the solubility data are shown in Fig. 8 along with the respective slopes or k values for each system. The k values range from about 0.3–0.4 and are higher than those reported for other types of nonelectrolytes such as diacetone alcohol (0.03–0.14) (7), mesityl oxide (0.02–0.18)
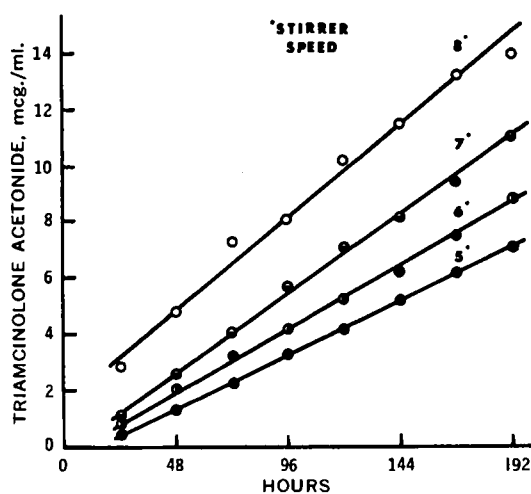

Figure 9—*Triamcinolone acetonide dissolution in distilled water as a function of agitation intensity (stirrer speed 5 = 147 r.p.m., 6 = 248 r.p.m., 7 = 308 r.p.m., and 8 = 398 r.p.m.).*
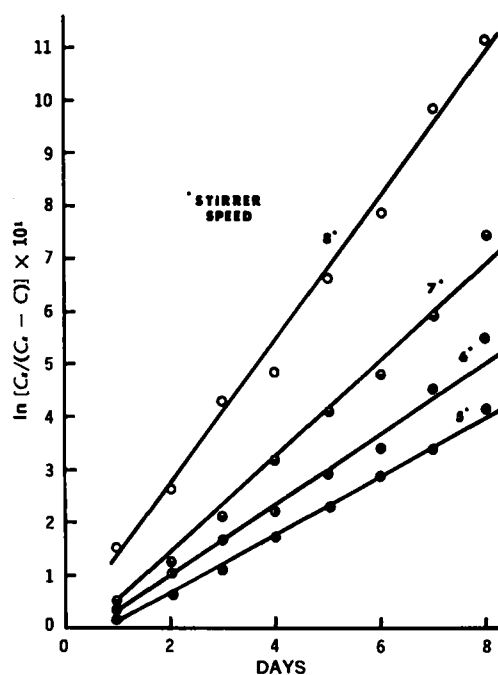

Figure 10—*Triamcinolone acetonide dissolution in distilled water, plotted in accordance with the integrated form of the modified Noyes–Whitney equation.*

(7), ethyl acetate (0.02–0.17) (7), and certain barbiturates (0.04–0.21) (8).

The salting-out effect is most apparent in the transition from distilled water to 0.2 M potassium chloride solution. At higher temperatures, however, the effect of added electrolyte is less marked.

Dissolution Rate—Dissolution of triamcinolone acetonide in distilled water at 28° under sink conditions is shown in Fig. 9 as a function of time for various agitation intensities. The data are in accordance with the integrated form of the modified Noyes–Whitney equation (9):

$$\ln \frac{C_s}{C_s - C} = k'At = \frac{DA}{Vh} \cdot t \qquad \text{(Eq. 3)}$$

Table III—Dissolution Rates and Dissolution Rate Constants for Triamcinolone Acetonide in Distilled Water at 28°

Stirrer Speed, r.p.m.	dC/dt, (mcg. ml.$^{-1}$ hr.$^{-1}$) $\times$ 10^2	k'^a, (hr.$^{-1}$ cm.$^{-2}$) $\times$ 10^3
147	4.01	1.86
248	4.70	2.33
308	5.82	3.15
398	6.63	4.51

^{a} Surface area of pellet exposed to dissolution medium was ~1.271 cm.^{3}.

Table IV—Dissolution Rates and Dissolution Rate Constants for Triamcinolone Acetonide in Potassium Chloride Solutions at 28°^{a}

Potassium Chloride Solution	dC/dt, (mcg. ml.$^{-1}$ hr.$^{-1}$) $\times$ 10^2	k'^b, (hr.$^{-1}$ cm.$^{-2}$) $\times$ 10^3
0.2 M	3.61	3.91
0.5 M	1.98	2.37
1.0 M	1.85^c	3.60^c

^{a} Stirrer speed = 308 r.p.m. ^{b} Surface area of pellet exposed to dissolution medium was ~1.271 cm.^{3}. ^{c} For data within the period of 96–192 hr. only.
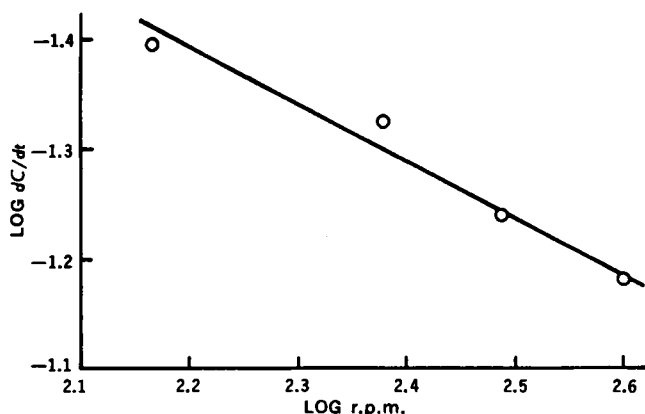
Figure 11—*Log-log plot of triamcinolone acetonide dissolution rate in distilled water versus stirrer speed (r.p.m.).*
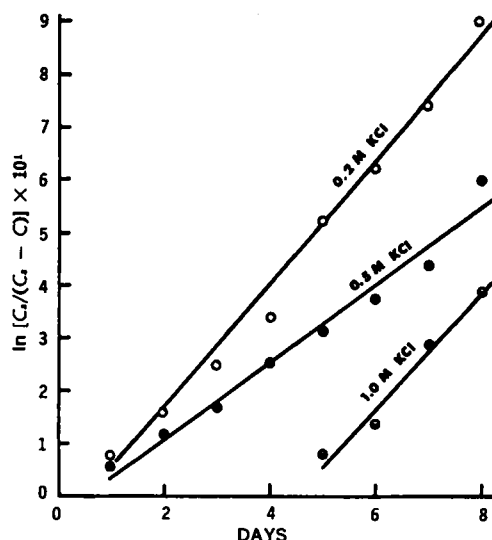

Figure 12—*Triamcinolone acetonide dissolution in potassium chloride solutions at speed 7 (308 r.p.m.) and 28°, plotted in accordance with the integrated form of the modified Noyes-Whitney equation.*

where C_s and C are the concentrations of a saturated solution of the solute and of a solution of the solute at time t, respectively; k' is the intrinsic dissolution rate constant; A is the surface area of the solid exposed to the dissolution medium; D is the diffusion coefficient of the solute in the dissolution medium; V is the volume of the solution; and h is the diffusion layer thickness. The integrated Noyes-Whitney plot of the dissolution data is shown in Fig. 10. The dissolution rates and dissolution rate constants for triamcinolone acetonide in distilled water at 28° are given in Table III.

The influence of agitation intensity in the unbaffled system employed in this study is quite evident. Cooper and Kingery (10) showed that dissolution from a rotating-disk face is proportional to the square root of angular velocity, ω, i.e.:

$$dC/dt = K\omega^{1/2} \qquad \text{(Eq. 4)}$$

where K is a proportionality constant. If the angular velocity is given in revolutions per minute and if Eq. 4 is transformed logarithmically, then:

$$\log (dC/dt) = \log K + \frac{1}{2} \log \text{r.p.m.} \qquad \text{(Eq. 5)}$$

A double logarithmic plot of dC/dt as a function of stirrer speed should yield a straight line with a slope of 0.5. Linear regression analysis of the data depicted in Fig. 11 indicates a slope of 0.515, with a correlation coefficient of 0.981.

The evaluation of steroid solubility in potassium chloride solutions as a function of time under sink conditions was only determined at speed 7 (~308 r.p.m.), since vortex formation tended to occur in this system at higher speeds. A plot of the data in accordance with the integrated Noyes-Whitney equation is shown in Fig. 12. The data, however, are not at all indicative of adherence to Eq. 3, since a zero ln $[C_s/(C_s - C)]$ intercept at $t = 0$ is not obtained. Rather, a lag in dissolution is apparent, particularly for dissolution in 1.0 M potassium chloride solution. Dissolution rates and dissolution rate constants for the steroid at speed 7, as a function of potassium chloride concentration, are given in Table IV.

The data for solubility and dissolution appear to be reasonable in view of the most reliable data available to date (3) and in view of the results of linear regression analysis of Beer's plots which yielded correlation coefficients of 0.9985 to 0.9998 for the systems employed. Additional work is underway involving the synthesis of ^{14}C-labeled triamcinolone acetonide. Isotopic methods will be employed to measure its solubility in comparison with the data reported here.

REFERENCES

(1) W. E. Lange and M. E. Amudson, *J. Pharm. Sci.*, **51**, 1102(1962).
(2) F. D. Malkinson and M. B. Kirschenbaum, *Arch. Dermatol.*, **88**, 427(1963).
(3) K. Florey, "Analytical Profiles of Drug Substances," vol. 1, Academic, New York, N. Y., 1972, p. 408.
(4) M. Umeda, S. Toubota, and A. Kajita, *Takamine Kenkyusho Nempo*, **14**, 87(1962); through *Chem. Abstr.*, **58**, 4779f(1963).
(5) M. Setschenow, *Ann. Chim. Phys.*, **25**, 226(1892); through K. S. Pitzer and L. Brewer, "Thermodynamics," 2nd ed., McGraw-Hill, New York, N. Y., 1961, p. 584.
(6) M. Randall and C. Failey, *Chem. Rev.*, **4**, 285(1927).
(7) K. S. Pitzer and L. Brewer, "Thermodynamics," 2nd ed., McGraw-Hill, New York, N. Y., 1961, p. 586.
(8) R. L. Sedam, A. R. Gennaro, and A. Osol, *J. Pharm. Sci.*, **54**, 215(1965).
(9) L. Brunner and S. Tolloczko, *Z. Phys. Chem.*, **35**, 283(1900).
(10) A. R. Cooper, Jr., and W. D. Kingery, *J. Phys. Chem.*, **66**, 665(1962).