

TABLE I.—STREPTOMYCIN ASSAY RESULTS (ZONES OF INHIBITION MEASURED IN mm.)

Plate	Std.		Spray Dried	
	S ₁	S ₂	T ₁	T ₂
1	16.5	19.5	16.5	20
2	17	20	16.5	20.5
3	17.5	19.5	17.5	19.5
4	17	19	17	19
Total	68.0	78.0	67.5	79.0
Av.	17.0	19.5	16.875	19.75

TABLE II.—PENICILLIN ASSAY RESULTS (ZONES OF INHIBITION MEASURED IN mm.)

Plate	Std.		Spray Dried	
	S ₁	S ₂	T ₁	T ₂
1	26.5	28.5	26	29
2	26	28	26	28
3	25.5	28.5	25.5	27
4	26	28.5	26	29
Total	104	113.5	103.5	113
Av.	26	28.375	25.875	28.25

was inoculated with a loopful of a culture of *Micrococcus pyogenes*. Every sample became opalescent within 18 hr., indicating that the broth was capable of supporting growth of microorganisms.

Streptomycin sulfate has been spray dried without loss of activity as shown by the assay laid down in the "British Pharmacopoeia," 1958. Four Petri dishes containing seeded nutrient agar were used for each assay. In each dish 4 × 8 mm. holes were bored and the solutions T₁, T₂, S₁, and S₂ added to each plate. The strengths of the standard and test solutions were 5 and 10 units/ml. (Table I). After spray drying, the potency was 100.3% of the original (limits of results 86.7–115.3%).

A similar assay was carried out on sodium benzyl penicillin. The strengths of the test and standard solutions were 3 and 6 units/ml. (Table II). After spray drying, the potency was 96.6% of the original (limits of results 83.9 to 119.1%).

Seaweed extract, coffee, aluminum hydroxide gel, and an aluminum hydroxide complex have also been dried to produce free-flowing powders, which (except for the alumina) readily redissolved in water. Spores of *Bacillus subtilis* have also been dried with

a 50% mortality. The powders, when viewed under the microscope, all showed the hollow spheres characteristic of spray-dried powders.

SUMMARY

1. The apparatus permits the drying process to be observed continuously; consequently, any obstruction to flow is readily noticed before damage to the product occurs.
2. It can be used to produce sterile powders more rapidly than freeze drying.
3. It is suitable for drying solutions and suspensions of materials which are prone to oxidation in the presence of metals.
4. The dried products are free flowing and lend themselves to aseptic transfer into sterile containers.

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Notes

Dissolution Rate-Solubility Behavior of 3-(1-Methyl-2-pyrrolidinyl)-indole as a Function of Hydrogen-Ion Concentration

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An investigation of the hydrogen-ion dependence of the dissolution rate of 3-(1-methyl-2-pyrrolidinyl)-indole (U-11028) is reported. Theoretical equations are developed which are in good agreement with the experimental data. This agreement shows clearly that it is the much greater diffusion coefficient of hydrochloric acid ($D_H = 3.1 D_B$) that is responsible for the deviation from the Noyes-Whitney theory.

CONSIDERABLE evidence has been presented to show that the initial rate of dissolution of a pellet is directly proportional to the solubility of the compound in a test fluid (1). This relationship, derived from the Noyes-Whitney law (2), states that

$$R = kC_s \quad (\text{Eq. 1})$$

where R is the initial dissolution rate per unit surface area of the pellet (mg./cm.²/hr.), k is a constant (2.24 for the given test conditions), and C_s is the solubility of the compound (mg./ml.). However, some data do not follow Eq. 1. One such compound which shows a significant positive deviation is 3-(1-methyl-2-pyrrolidinyl)-indole (U-11028). Since this deviation is observed in 0.05 *N* HCl but

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TABLE I.—SOLUBILITIES AND DISSOLUTION RATES OF 3-(1-METHYL-2-PYRROLIDINYL)-INDOLE AS A FUNCTION OF pH OF THE DISSOLUTION MEDIUM AT 37°

Dissolution Fluid	Initial pH	Solubility at 37°, mg./ml.	Dissolution Rate ± 95% C.I. of Rate, mg./cm. ² /hr.	Rate-to-Solubility Ratio
0.1 N HCl	1.2	21.0	146 ± 17	6.95
0.05 N HCl	1.3	10.3	89.5 ± 20.5	8.69
0.01 N HCl	2.0	2.35	18.9 ± 1.9	8.04
0.002 N HCl (CO ₂ -free)	2.8	1.02	5.07 ± 0.74	4.97
0.001 N HCl (CO ₂ -free)	3.1	0.837	2.93 ± 0.64	3.50
Distilled H ₂ O (CO ₂ -free)	7.0	0.703	1.89 ± 0.21	2.69
Phosphate buffer	7.2	2.36	6.35 ± 0.38	2.69

not in phosphate buffer (pH 7.2), the reason may be the much greater diffusion coefficient for the HCl. The test of this hypothesis is reported.

EXPERIMENTAL

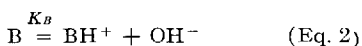
The procedures for determining the initial rate of dissolution and solubility of U-11028 in the test fluids of varying hydrogen-ion concentration were reported previously (1). All tests were run at 37°. The test fluids listed in Table I all have the same ionic strength ($\mu = 0.1$) by adjustment with sodium chloride. Assays were made by ultraviolet spectrophotometry using a Cary model 11 recording spectrophotometer.

The rate of dissolution and solubility data are recorded in Table I as a function of the pH of the test fluid. The rate-to-solubility ratio, equivalent to k in Eq. 1, for each set of data serves as a measure of the deviation from the reference value of 2.69.

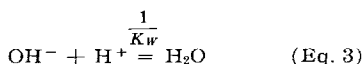
An apparent pK_a value of 8.9 for this compound was determined by potentiometric titration of a dilute solution in CO₂-free deionized water at room temperature.

RESULTS AND DISCUSSION

Solubility of U-11028 as a Function of Initial H⁺.—The important reactions are:



and



Let (B)₀ be the unionized base concentration in equilibrium with the solid, and let (H)₀ be the initial hydrogen-ion concentration, *i.e.*, the H⁺ concentration before addition of any solid base. Let x = moles/L. of BH⁺ formed by the reaction given in Eq. 2, and let y = the moles/L. of the reaction in accordance with Eq. 3. Therefore, $x - y$ would be equal to the moles/L. of remaining OH⁻ at equilibrium and (H)₀ - y the concentration of the remaining H⁺.

Therefore,

$$K_B = \frac{x(x - y)}{(B)_0} \quad (\text{Eq. 4})$$

and

$$K_W = [(H)_0 - y](x - y) \quad (\text{Eq. 5})$$

Neglecting K_W/K_B (B)₀ as compared to unity, one obtains from Eqs. 4 and 5

$$x = \frac{(H)_0 + [(H)_0^2 + 4K_B(B)_0]^{1/2}}{2} \quad (\text{Eq. 6})$$

Therefore, the total solubility is

$$C_s = (B)_0 + x$$

or

$$C_s = (B)_0 + \frac{(H)_0 + [(H)_0^2 + 4K_B(B)_0]^{1/2}}{2} \quad (\text{Eq. 7})$$

Since K_A for U-11028 is about 6×10^{-10} , and since K_W for water is around 2×10^{-14} , $K_B \approx 3 \times 10^{-6}$. (B)₀ may be calculated by taking this value for K_B and the solubility, $C_s = 3.5 \times 10^{-3} M$, for U-11028 in pure water. Noting that (H)₀ $\approx 1 \times 10^{-7} M$ is negligible compared to $K_B(B)_0$, one obtains from Eq. 7

$$(B)_0 \approx 3.2 \times 10^{-3} M$$

Therefore, Eq. 7 becomes

$$C_s = 3.2 \times 10^{-3} + \frac{(H)_0 + [(H)_0^2 + 3.8 \times 10^{-7}]^{1/2}}{2} \quad (\text{Eq. 8})$$

In Fig. 1, Eq. 8 is plotted (smooth curve) and compared with the experimental data. The agreement of the data with theory is very satisfactory.

Dissolution Rate of U-11028 as a Function of Initial H⁺.—Consideration of simultaneous diffusion and chemical reaction leads to the following equation for the initial dissolution rate of a base, B, in HCl solutions (see *Appendix* for derivation). The initial rate, G , is

$$G = \frac{1}{h} \left\{ D_B(B)_0 + \frac{D_H(H)_0 + D_H(H)_0 \left[1 + \frac{4D_{OH}K_B D_{BH}(B)_0}{D_H^2(H)_0^2} \right]^{1/2}}{2} \right\} \quad (\text{Eq. 9})$$

Here h is the diffusion layer thickness, (B)₀ is the free base concentration in equilibrium with the solid, (H)₀ is the initial hydrogen-ion concentration in the dissolution medium, and the D 's are the respective diffusion coefficients of the species (indicated by subscripts).

Equation 9 may be written

$$\frac{Gh}{D_B} = (B)_0 + \frac{1}{2} \left(\frac{D_H}{D_B} \right) (H)_0 + \frac{1}{2} \left(\frac{D_H}{D_B} \right) (H)_0 \left(1 + \frac{4D_{OH}D_{BH}K_B(B)_0}{D_H^2(H)_0^2} \right)^{1/2} \quad (\text{Eq. 10})$$

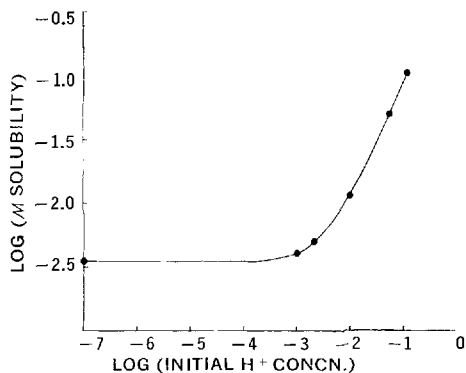


Fig. 1.—Solubility of 3-(1-methyl-2-pyrrolidiny)l-indole as function of initial H^+ concentration. Key: ●, experimental data; —, theory, Eq. 8.

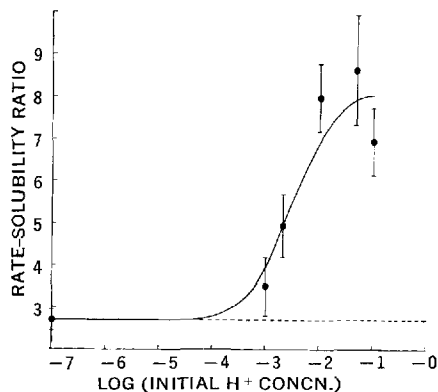


Fig. 2.—The rate-to-solubility ratio for 3-(1-methyl-2-pyrrolidiny)l-indole as a function of initial H^+ concentration in dissolution medium. Key: ●, experimental data; —, theory (Eq. 10 with $D_H/D_B = 3.1$); ----, Noyes-Whitney prediction.

It is apparent by comparing Eq. 10 with Eq. 7 that if all of the diffusion coefficients were equal, the dissolution rate would always be directly proportional to the solubility. However, the rate-to-solubility ratio for U-11028 is not constant (Table I) over the range of HCl concentrations. Therefore, consider the possibility that D_H is much greater than D_B .

In Fig. 2, the results of the rate-to-solubility ratios calculated employing Eq. 10 with $D_H = 3.1 D_B$ are plotted as the smooth curve. In these theoretical calculations, the rate-to-solubility ratio value of 2.69 in distilled water was used to fit the theory to data at this one point.

It is worthwhile to point out that the term involving D_{OH} and D_{BH} in Eq. 10 is small compared to unity, except for the case involving distilled water. Therefore, the choice of values for D_{OH} and D_{BH} is not critical. In the distilled water case, the square root term contributes less than 10% to the rate. So again, the choice of values for D_{OH} and D_{BH} is not critical. Therefore, in these calculations, D_{OH} and D_{BH} were taken to be equal to D_B , the diffusion coefficient for the unprotonated base.

The good agreement of theory with data taken

from Table I clearly shows that it is the much greater diffusion coefficient of HCl that is responsible for the deviation from the Noyes-Whitney law. The value of $D_H = 3.1 D_B$ is reasonable. The diffusion coefficient for HCl in water is about $3.0 \times 10^{-5} \text{ cm.}^2 \text{ sec.}^{-1}$ at room temperature (3), while that for U-11028 is expected to be as much as 5 times smaller according to Stokes' law. Therefore, although the 3.1 factor appears to be a little low, it is of the right order of magnitude.

As discussed previously (4) where electrolytes are involved, the effective diffusion coefficient of an ion is appreciably influenced by the nature and the concentrations of other ions in the solution. In this regard the primary effect is often the diffusion potential effect which is caused by the greater inherent mobility of 1 ion in the presence of more slowly moving ions of the opposite charge. Thus, the effective diffusion coefficient of the hydrogen ion in an HCl solution is not determined entirely by the inherent mobility of the hydrogen ion, but is influenced greatly by the restraining effect of the chloride ion. Despite the retarding effect of the chloride ion, the diffusion coefficient of HCl is still relatively large. The effective diffusion coefficient of the protonated U-11028 also is influenced by the chloride ion, but, in this instance, the relatively large size of the U-11028 molecule should be the main factor.

It is reasonable then to expect D_H to be relatively large compared to D_B and D_{BH} , with the latter 2 being about the same order of magnitude. While D_{OH} would be expected to be also significantly greater than D_B or D_{BH} , it can be seen from concentration considerations that the OH^- does not play an important role.

APPENDIX

Derivation of Eq. 9.—Consideration of the physical situation allows one to write 2 independent equations for G , the dissolution rate,

$$G = -D_B \frac{d(B)}{dX} - D_{BH} \frac{d(BH)}{dX} \quad (\text{Eq. 1a})$$

and

$$G = D_H \frac{d(H)}{dX} - D_B \frac{d(B)}{dX} - D_{OH} \frac{d(OH)}{dX} \quad (\text{Eq. 2a})$$

As boundary conditions, at $X = 0$: $(B) = (B)_0$, $(BH) = (BH)_0'$, $(H) = (H)_0'$ and $(OH) = (OH)_0'$, and at $X = h$: $(H) = (H)_0$ and all other species are at 0 concentration. With these boundary conditions and with the approximation that $K_w \ll K_B (B)_0$, Eqs. 1a and 2a may be solved by eliminating $(H)_0'$, $(BH)_0'$, and $(OH)_0'$ to give Eq. 9 in the same manner as was done previously for similar problems (4, 5).

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