TABLE I.—EFFECT OF DIVERSE AMINE COMPOUNDS
ON ABSORBANCE

| 40 mcg.<br>Chlorpheni-<br>ramine Maleate<br>+ | Compd. Added, mcg. | Absorbance |
|---|---|---|
| | ... | 0.461, 0.460 |
| + 800 | Methapyrilene HCl | 0.460, 0.462 |
| + 800 | Pyrilamine maleate | 0.461, 0.459 |
| +2000 | Phenylpropanolamine HCl | 0.463, 0.459 |
| +2000 | Phenylephrine HCl | 0.464, 0.460 |
| +2000 | Racephedrine HCl | 0.458, 0.461 |
| +2000 | Dextromethorphan HBr | 0.460, 0.459 |

sodium acetate into 40 ml. water and dilute to 175 ml. with 95% ethanol.

**Aqueous Hydrochloric Acid 0.25 *N*.**—The normality was adjusted to ±2.0%.

**Cyanogen Bromide Solution.**—Dissolve 2.0 Gm. cyanogen bromide into 50 ml. water and keep under refrigeration.

**Stock Standard Solution.**—This is a solution of chlorpheniramine maleate in 0.25 *N* HCl, concentration = 1.00 mg./ml. Prepare solutions containing 0.01, 0.02, 0.04, and 0.08 mg./ml. chlorpheniramine maleate in 0.25 *N* HCl from this solution.

Pipet 7.0 ml. of buffered sulfanilic acid solution into each of five 50-ml. glass-stoppered Erlenmeyer flasks. Pipet 1.0 ml. of the serial dilutions into the flasks; pipet 1 ml. of 0.25 *N* HCl for a reagent blank into one flask. Add 3.0 ml. cold cyanogen bromide solution to each with swirling. Determine the absorbance of the solutions relative to the reagent blank at 1-minute intervals at 480 mμ on a Beckman DU spectrophotometer. A plot of absorbance *versus* time is shown in Fig. 1; a plot of maximum absorbance *versus* concentration is shown in Fig. 2. The maximum absorbance is linear with respect to concentration.

**Interference from Other Amines**

To determine the interference from certain other amines, solutions of chlorpheniramine maleate (concentration = 0.040 mg./ml. in 0.25 *N* HCl) were prepared containing added amounts of the various

compounds. As previously described 1 ml. of each solution was used for the color reaction and the maximum absorbance recorded. The results of duplicate runs are shown in Table I. No significant interference was observed at the stated concentrations. Normal tablet excipients and compounds such as aspirin, phenacetin, caffeine, and ascorbic acid do not cause interference.

**Chromatographic Identification**

A paper chromatographic separation is used to ascertain which of the three similarly reacting antihistamines (pheniramine, brompheniramine, or chlorpheniramine maleate) is present in a sample. The sample and control spots (pipeted as ether extracts from aqueous alkaline solutions) are chromatographed using an ascending technique on Whatman No. 1 paper which has been pretreated by soaking in 2.0% aqueous ammonium sulfate and thoroughly air drying. The developing solvent is made by shaking 100 ml. of *n*-butanol with 100 ml. aqueous 6.0% citric acid. After separation of the phases, the butanol layer is used as the mobile solvent and the aqueous layer as the immobile solvent. After chromatographing for 15 hours, the paper is air dried and dipped into Dragendorff's reagent (2) to locate the spots. The $R_f$ values for pheniramine, brompheniramine, and chlorpheniramine are 0.25, 0.58, and 0.53, respectively.

**SUMMARY**

A colorimetric method based upon the Koenig reaction has been described for determining chlorpheniramine maleate in certain pharmaceutical preparations. The method requires very little time to perform and has very good precision. (Standard deviation is 0.4%.)

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# Solubility and Dissolution Rates in Reactive Media

By W. I. HIGUCHI, EINO NELSON†, and J. G. WAGNER‡

The relationship between the diffusion-controlled dissolution rate of a substance in a reactive medium and the solubility of the substance in the medium has been analyzed. The results reconcile the total solubility method and the simultaneous diffusion and chemical reaction method of interpreting data on dissolution rates.

THE PROBLEM OF dissolution rates of solids in reactive solutions has been recently examined

by the total solubility method (1–3) and by the simultaneous chemical reaction and diffusion (SCRD) method (4). Because of the differences between the two concepts and because the problem is important, it appears that a clarification of the data is necessary.

Both theories are based on the diffusion layer (or film) model; therefore, they both assume that the dissolution rate is controlled by diffusion rates of the important species through this layer. The model assumed in the SCRD method takes into account simultaneous rapid reversible chemical reaction and diffusion of all the important species. The resulting equations for dissolution rate, *G*, in this case are relatively complicated. On the other

hand, the total solubility method assumes that $G$, the rate of dissolution per unit area of solid may be expressed by the conventional Noyes-Whitney law (5)

$$G = k (C_s - C) \qquad \text{(Eq. 1)}$$

Here $C_s$ is the total solubility of the solid in the medium, $C$ is the solute concentration in solution, $k$ is a function including the diffusion coefficients, and $h$, the thickness of the diffusion layer. For a single component solid dissolving in a nonreactive medium

$$k = \frac{D}{h} \qquad \text{(Eq. 2)}$$

where $D$ is the diffusion coefficient of the solute in the solvent.

The problem in this communication is the meaning of $k$ and $C_s$ in Eq. 1 in terms of the SCRD model and the ramifications thereof. To accomplish this best, let us take two specific cases: (*a*) a weak acid dissolving in a basic medium and (*b*) a salt of a weak acid and a strong base dissolving in an acidic medium. For sake of simplicity we shall examine only the initial dissolution rates.

**Weak Acid Dissolving in Basic Medium.**—Consider the situation in which a solid weak acid, $HA$, is dissolving in a buffer solution of a base, $B^-$, and its conjugate acid, $HB$. Equation 10 in *Reference 4* gives[1] the following initial dissolution rate expression based on the SCRD method for this case

$$G = \frac{D_{HA}(HA)_o}{h} - \frac{D_{HB}(HB)_h}{2h} - \frac{D_{HB}D_A K(HA)_o}{2D_B h} + \frac{1}{2D_B h} [D_{HB}{}^2 D_A{}^2 K^2 (HA)_o{}^2 + 4D_B{}^2 D_{HB}D_A K(HA)_o (B^-)_h + D_B{}^2 D_{HB}{}^2 (HB)_h{}^2 + 2D_A D_B D_{HB}{}^2 K(HB)_h (HA)_o]^{1/2} \quad \text{(Eq. 3)}$$

Here the $D$'s are the diffusion coefficients of the species indicated by the subscripts, $(HA)_o$ is the unionized acid concentration in equilibrium with the solid, and $(B^-)_h$ and $(HB)_h$ are, respectively, the base concentration and the conjugate acid concentration in solution. The concentration equilibrium constant $K$ is defined

$$K = \frac{K_{HA}}{K_{HB}} = \frac{(HB)(A^-)}{(HA)(B^-)} \qquad \text{(Eq. 4)}$$

Now let us compare this equation with Eq. 1. The total solubility, $C_s$, of the weak acid in a buffer solution of initial concentrations $(B^-)_h$ and $(HB)_h$ may be calculated from Eq. 4

$$K = \frac{[(HB)_h + x][x]}{(HA)_o[(B)_h - x]} \qquad \text{(Eq. 5)}$$

where $x$ is the concentration of $A^-$ at equilibrium. Solving Eq. 5 we obtain

[1] There were two minor typographical errors in the original equation. The corrected equation is

$$C_1 = \frac{D_B(B)h - D_{HA}(HA)h + D_{HA}(HA)_o}{h} - \frac{D_B(L_1 + L_2) + D_{HB}D_A K(HA)_o \pm \{[D_B(L_1 + L_2) + D_{HB}D_A K(HA)_o]^2 - 4L_1 L_2 D_B{}^2\}^{1/2}}{2D_B h}$$

where $C_1$ is the same as the present $G$. Note that this is a general expression; Eq. 3 applies to initial rates only, *i.e.*, $(A)_h = (HA)_h = 0$.

$$C_s = (HA)_o + x = (HA)_o - \frac{(HB)_h}{2} - \frac{K(HA)_o}{2} + 1/2 [K^2(HA)_o{}^2 + 4K(HA)_o(B^-)_h + 2K(HA)_o(HB)_h + (HB)_h{}^2]^{1/2} \quad \text{(Eq. 6)}$$

Now if Eq. 6 is substituted into Eq. 1 with $C = 0$ and $k = D/h$, it is clear that Eqs. 1 and 3 become identical when all diffusion coefficients are equal to $D$.

If the base happens to be the hydroxide ion, Eq. 12 in *Reference 4* may be used[2] for the initial dissolution rate of a weak acid solid. We have in this case then the SCRD method giving

$$G = \frac{D_{HA}(HA)_o}{h} + \frac{D_B{}^2(OH^-)_h}{h} \times \left( \frac{D_A \frac{K_a}{K_w}(HA)_o}{D_B{}^2 + D_A D_B \frac{K_a}{K_w}(HA)_o} \right) \quad \text{(Eq. 7)}$$

where $K_w$ is the ion product for water, $K_w = (H^+)(OH^-)$. In this instance the total solubility, $C_s$, is

$$C_s = (HA)_o + x$$

where $x$ again is the concentration of $A^-$ at equilibrium and is given by

$$\frac{K_a}{K_w} = \frac{x}{(HA)_o[(OH^-)_h - x]}$$

therefore

$$C_s = (HA)_o + \frac{\frac{K_a}{K_w}(HA)_o(OH^-)_h}{1 + \frac{K_a}{K_w}(HA)_o} \quad \text{(Eq. 8)}$$

It is again clear that substitution of Eq. 8 into Eq. 1 with $k = D/h$ and $C = 0$ will give the same expression as Eq. 7 when all the diffusion coefficients are set equal to $D$.

**Sodium Salt of a Weak Acid Dissolving in Acid.**—Consider the dissolution of a salt, $NaA$, in a solution containing hydrogen ions at a concentration, $(H^+)_h$. The SCRD method gives (6) the following implicit expression for the initial dissolution rate, $G$, in this case[3]

$$\frac{D_A D_{HA}}{D_H K_A} \left( \frac{D_{Na} K_{sp}}{Gh} \right)^2 + \left( \frac{D_{Na} K_{sp}}{Gh} \right) \left( D_A + D_{HA} \frac{(H^+)_h}{K_A} \right) - \frac{D_{HA} D_{Na} K_{sp}}{D_H K_A} - Gh = 0 \quad \text{(Eq. 9)}$$

The expression for the total solubility, $C_s$, for this case may be set up according to

$$K_{sp} = C_s(C_s - x) \qquad \text{(Eq. 10)}$$

and

$$K_a = \frac{(C_s - x)[(H^+)_h - x]}{x} \qquad \text{(Eq. 11)}$$

where $K_{sp}$ is the solubility product for the salt, $K_a$ is

[2] While Eq. 12 of *Reference 4* involved uncharged species, the same equation may be used here. It is only important that the form of the equilibrium constant expression is the same.

[3] Assumes that solubility of weak acid itself is not exceeded anywhere in the system under the conditions of the dissolution experiment. If such is not the case or if another solid phase is formed during dissolution, the present equation may not apply. (See *References 7–9* for examples of the precipitation of a weak acid onto the surface of the salt during dissolution.)

as before the dissociation constant for the weak acid, $HA$, and $X$ is the amount of $HA$ formed per unit volume at equilibrium. Solving Eqs. 11 and 12 we get

$$\frac{K_{sp}^2}{C_s^2} - K_{sp} + \frac{K_{sp}(H^+)_h}{C_s} + \frac{K_a K_{sp}}{C_s} - K_A C_S = 0$$

(Eq. 12)

Now substitution of Eqs. 1 and 2 with $C = 0$ into Eq. 12 will show that Eqs. 12 and 9 are again identical when all the diffusion coefficients are set equal to $D$.

## DISCUSSION

The present analysis demonstrates that within the framework of the diffusion layer model the total solubility method and the SCRD method give the same results when all of the diffusion coefficients may be set equal to the same value. Because diffusion coefficients of solute molecules do not differ[4] much in general and other uncertainties—such as variation of dissociation constants and solubilities with ionic strength and other solute interaction

effects—are frequently the overriding factors, it would be expected that the total solubility method should explain experimental results as well as the SCRD method. Nelson found this to be the case in many instances (1–3).

Where the two methods will significantly differ would be primarily those situations in which the reacting agent is a colloid, e.g., micellar surfactants which solubilize the solute and nonionic polymers and polyelectrolytes which react with and bind the solute. In these instances, the relatively small diffusion coefficients of colloids will lead to much smaller dissolution rates for the SCRD theory under certain conditions.

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[4] Neglecting effects of solvation, Stokes-Einstein law predicts the diffusion coefficients vary approximately as the cube root of the molecular weight for materials of the same density.

# Use of Solubility Analysis in Pharmaceutical Stability Studies

By J. P. COMER and L. D. HOWELL

Purity determined by solubility analysis was used to evaluate the efficacy of other analytical methods for measuring thermal degradation. Techniques for filtration and a method for calculation of confidence interval for solubility analysis are described.

THE VALIDITY of a stability assay procedure may be confirmed in different ways. If the assays on samples stored at elevated temperatures decrease with time, the method is confirmed. The method of analysis may also be checked by a comparison with a method which is known to measure stability. Several tests of purity are available to the analysts in such cases. Those commonly used include vapor phase, thin layer, and paper chromatography. Garrett (1) reviewed other tests for solvolytic stability of drugs. The purpose of this study was to investigate the possibility of using solubility analysis as a reference assay to evaluate a proposed assay procedure on thermally degraded drug substances. It is not practical to use solubility analysis as the stability assay because of cost, time, and the fact that solubility analysis is only applicable to the drug substance free of excipients. If the proposed or conventional assay procedure is confirmed by the purity test, the procedure may then be used with a fair degree of certainty on the finished pharmaceutical if thermal instability is the main consideration.

## EXPERIMENTAL

Three newly developed and two older drug substances were stored at varying temperatures and

were periodically withdrawn and assayed by solubility analysis and by an alternate procedure.

### Solubility Analysis Procedure (2)

Varied amounts of the material being tested were allowed to equilibrate at 25° with 2 ml. of an appropriate solvent. After equilibrium was reached, the solution was filtered with a Swinny filter, using S and S No. 740 E filter pads. The filtrate was transferred to a previously tared drying flask and weighed. (The drying flasks were prepared by Ace Glass Co. with an average weight of 6.0 Gm.) The solvent was removed under vacuum at 40°. All weights were recorded to the nearest 0.02 mg. Ratios of mg. solute per Gm. solvent and mg. residue per Gm. solution were calculated for each amount of solute. The data were plotted as mg. residue per Gm. solution (ordinate) versus mg. solute per Gm. solvent (Fig. 1). The per cent purity and 95% confidence interval about this purity were calculated by a variation of the method of least squares (3).

Calculations for per cent purity measured by solubility analysis and the 95% confidence limits about this purity are % purity = $100 - 100\,\theta$

$$\theta = \frac{[n\Sigma x^2 - (\Sigma x)^2] - [n\Sigma y^2 - (\Sigma y)^2]}{2\,[n\Sigma xy - \Sigma x\Sigma y]} \pm$$

$$\sqrt{\left[\frac{[n\Sigma x^2 - (\Sigma x)^2] - [n\Sigma y^2 - (\Sigma y)^2]}{2\,[n\Sigma xy - \Sigma x\Sigma y]}\right]^2 + \lambda}$$