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General Treatment of pH–Solubility Profiles of Weak Acids and Bases and the Effects of Different Acids on the Solubility of a Weak Base

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Abstract □ The pH–solubility profile of a weak acid or base is shown to be a function of its pK_{sp}, pK_a, and uncharged species solubility. Equations are presented that can be used to calculate the solubility as a function of pH. These equations can also be used when there is added salt present. Experimental data was obtained in three cosolvent systems consisting of methanol–water and ethanol–water. Also, the effect of different acids on the solubility of a weak base is reported. A pronounced effect on the solubility by the addition of salt is explained in terms of the K_{sp}.

Keyphrases □ pH—profiles *versus* solubility, weak acids, weak bases □ Solubility—profiles *versus* pH, weak acids, weak bases

It is well known that the solubility of an acid or base is dependent on its ionization constants and the maximum solubility of the various species of the compound (1–12). In these reports, equations were presented that can be used to calculate the solubility profile as a function of pH. The pH range over which these equations are applicable are, however, limited as some only consider the pH region where the uncharged species is saturated and none consider the effects of additional salt added to the system. Introduction of salts to a saturated solution will frequently alter the solubility of the compound. This change in solubility is related to solubility product (K_{sp}) effects as well as changes in the activity coefficients. It will be shown that by combining the known expressions for solubility as a function of pH with the appropriate solubility product expression, equations can be obtained which, over a wide pH range, correlate the measured solubility data with calculated values. To perform the calculations, the ionization constant(s), uncharged species solubility, and solubility product(s) for the compound need to be known. Although these expressions are typically used for pure aqueous solvent systems, some of the experimental data reported utilized methanol–water and ethanol–water cosolvent systems and show the applicability of these equations to cosolvent systems. The effect of different pH-adjusting acids on the solubility of a weak base in water is also reported.

THEORETICAL SECTION

Expressions have been reported for the solubility of weak acids and bases as a function of pH (1–12). The number of equations required to describe the solubility over the entire pH range is dependent on the number of equilibrium constants that the compound has. Each equation, representing a different region in the solubility profile, contains a different species saturating the region[1]. For monoprotic compounds these equations are:

$$S_{1,0} = \left(\frac{1}{Y_0} + \frac{K}{Y_1\{H\}}\right)\{HD\} \qquad \text{(Eq. 1)}$$

$$S_{1,1} = \left(\frac{1}{Y_1} + \frac{\{H\}}{KY_0}\right)\{D\} \qquad \text{(Eq. 2)}$$

where $S_{m,j}$ is the total concentration of all species of compound D in solution, *i.e.*:

$$S_{m,j} = \sum_{p=0}^{m} [H_{m-p}D] \qquad \text{(Eq. 3)}$$

where m is the number of equilibrium constants, j is the region, $[H_{m-p}D]$ is the concentration of species $H_{m-p}D$, $\{H_{m-j}D\}$ is the activity (maximum solubility) of species $H_{m-j}D$, K is the equilibrium constant, $\{H\}$ is the hydrogen ion activity, and Y_i is the activity coefficient for species i (Y_0 is that of the most protonated species).

When the species which is saturated in a region is charged, the species activity in Eqs. 1 and 2 can be replaced by the corresponding solubility product which for monoprotic compounds in the presence of 1:1 electrolytes are:

$$K_{sp} = \{M\}\{D\} \quad \text{weak acid} \qquad \text{(Eq. 4)}$$

$$K_{sp} = \{HD\}\{X\} \quad \text{weak base} \qquad \text{(Eq. 5)}$$

If the compound is a weak acid, the quantity $K_{sp}/\{M\}$ would be substituted

[1] See Appendix I.

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for {D} in Eq. 2, while $K_{sp}/\{X\}$ would be substituted for {HD} in Eq. 1 for a weak base. The terms {M} and {X} are the corresponding cation and anion activities for the salt MX.

Since the solubility is dependent on species other than those of the weak acid or weak base, the addition of salts to the solution will alter the solubility. If the salt concentration is sufficiently large that the solubility product in Eqs. 4 or 5 is exceeded, there will be a decrease in the solubility. There will also be an effect on the activity coefficients since the total ionic strength will increase with the addition of a salt. This change in the activity coefficients can result in either an increase or decrease in the solubility depending on the salt concentration. When the salt concentration is not sufficiently large that the solubility product is exceeded, only the effect on the activity coefficients will be present.

An equation can be derived which can be used to determine the pH at which the solubility expression changes from one region to a second region. The derivation takes into consideration the fact that at the pH where the saturated species changes, the solution will be saturated in two species, and the resulting equation is obtained by combining the equilibrium expressions for K_a and K_{sp} with the charge balance equation[2].

The equation obtained will depend on whether the compound is a weak acid or a weak base. For a weak acid, the hydrogen ion concentration is given by:

$$\{H\} = \frac{[X] + \left[[X]^2 + 4\left(\frac{K_{sp}}{K\{HD\}Y_M} + \frac{1}{Y_H}\right)\left(\frac{K\{HD\}}{Y_D} + \frac{K_w}{Y_{OH}}\right)\right]^{1/2}}{2\left(\frac{K_{sp}}{K\{HD\}Y_M} + \frac{1}{Y_H}\right)} \quad \text{(Eq. 6)}$$

For a weak base it is:

$$\{H\} = \frac{-[M] + \left[[M]^2 + 4\left(\frac{\{D\}}{KY_{HD}} + \frac{1}{Y_H}\right)\left(\frac{KK_{sp}}{\{D\}Y_X} + \frac{K_w}{Y_{OH}}\right)\right]^{1/2}}{2\left(\frac{\{D\}}{KY_{HD}} + \frac{1}{Y_H}\right)} \quad \text{(Eq. 7)}$$

For monoprotic compounds, the total solubility given by Eqs. 1 and 2 can be rewritten to include the K_{sp} and addition of salt[3]. For a weak acid, Eq. 1 will remain the same, but Eq. 2 will become:

$$S_{1,1} = \frac{-\left([X] - \frac{\{H\}}{Y_H} + \frac{K_w}{\{H\}Y_{OH}}\right) + \left[\left([X] - \frac{\{H\}}{Y_H} + \frac{K_w}{\{H\}Y_{OH}}\right)^2 + 4\frac{K_{sp}}{Y_M Y_D}\right]^{1/2}}{2\left(\frac{KY_{HD}}{\{H\}Y_D + KY_{HD}}\right)} \quad \text{(Eq. 8)}$$

In the case of a weak base Eq. 2 remains the same while Eq. 1 becomes:

$$S_{1,0} = \frac{-\left([M] + \frac{\{H\}}{Y_H} - \frac{K_w}{\{H\}Y_{OH}}\right) + \left[\left([M] + \frac{\{H\}}{Y_H} - \frac{K_w}{\{H\}Y_{OH}}\right)^2 + 4\frac{K_{sp}}{Y_{HD}Y_X}\right]^{1/2}}{2\left(\frac{\{H\}Y_D}{KY_{HD} + \{H\}Y_D}\right)} \quad \text{(Eq. 9)}$$

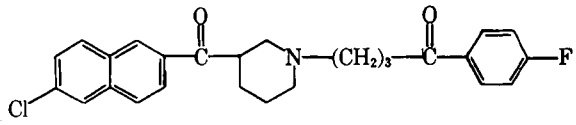
A number of methods have been reported (1, 2, 4, 13–15) for determining the pK_a, pK_{sp}, and uncharged species maximum concentration. Any of these could be applied to Eqs. 1 and 8 or 2 and 9 with slight modification. It was found that when the uncharged species solubility is established, values for pK_a and pK_{sp} can be obtained by fitting calculated solubility curves to the experimental data. The calculated curves were sensitive to the values of pK_a and pK_{sp} used and could be estimated to within ± 0.01 units by this approach. In performing these calculations, it is important to realize that, whenever possible, estimations of the activity coefficients should be made. This is because typical values for the activity coefficient of a singly charged species in a solution having a total ionic strength of 0.05 M is ~0.75. Factors this large entering into the above equations will have significant effects.

[2] See Appendix II.

[3] See Appendix III.

EXPERIMENTAL SECTION

Solubility In Cosolvent Systems—The solubility of 4-[4-[(6-chloro-2-naphthalenyl)carbonyl]-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone (I)[4] was determined in several solvent systems as a function of pH. Additional sodium chloride was added into several of the systems to see the effect of an added salt and determine how accurately the computer program used to calculate the solubility profiles could match the experimental data.



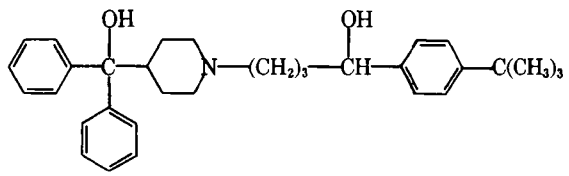
I

Solution Preparation—*85% Methanol*—Ampules were prepared containing 8.5 mL of methanol, 1.5 mL of water with 0–1.2 equivalents of HCl per equivalent of I, and 100 mg of I. In selected ampules, sodium chloride was present at concentrations of 0.01, 0.025, and 0.05 M. The ampules were sealed and placed into a 25.0°C constant-temperature bath, attached to a vibrating device, and allowed to equilibrate for 4 d. Following equilibration, the ampules were removed, and the contents were assayed.

50% Ethanol—Ampules were prepared containing 5 mL of ethanol, 5 mL of water with 0–1.2 equivalents of HCl per equivalent of I, and 100 mg of I. In selected ampules, sodium chloride was present at 0.01 and 0.05 M. The ampules were treated in the same manner as the methanol samples except they were allowed to equilibrate for 3 d.

25% Ethanol—Ampules were prepared containing 2.5 mL of ethanol, 7.5 mL of water with 0–1.2 equivalents of HCl per equivalent of I, and 100 mg of I. In selected ampules, sodium chloride was present at 0.01 and 0.05 M. The ampules were sealed and treated in the same manner as the methanol samples.

Assay Procedure—The contents of the ampules were filtered through a 0.2-μm membrane filter[5]. An appropriate aliquot was removed, and the pH of the remaining sample was measured[6]. The aliquot removed was placed in a volumetric flask and diluted with the mobile phase used in the HPLC assay. The following conditions were used in the HPLC assay: column, Partisil 10 ODS-3 (25 cm × 4.6 mm)[7]; mobile phase, acetonitrile–water (50:50) containing 0.005 M octanesulfonic acid and 0.2% acetic acid; flow rate, 120 mL/h; sample size, 10 μL (0.3–1.4 μg of I); wavelength, 246 nm[8]. The saturated concentrations were determined from the areas under the peaks, calculated with a centralized computer system[9].



II

Effect of Different Acids on the Solubility of a Weak Base—The solubility of terfenadine, α-[4-(1,1-dimethylethyl)phenyl]-4-(hydroxydiphenylmethyl)-1-piperidinebutanol (II), was determined in water as a function of pH using lactic acid, methanesulfonic acid, hydrochloric acid, and phosphoric acid. Samples were prepared by placing 200 mg of terfenadine into washed 30-mL vials and adding 25 mL of aqueous solution containing various amounts of the selected acids. The vials were capped with a polytef-laminated rubber stopper (previously autoclaved in water to remove any extractable materials) and sealed with aluminum ferrules. The samples were placed in a sonic water bath maintained at 25°C and allowed to equilibrate for 4 d.

[4] MDL 17,214; Merrell Dow Pharmaceutical.

[5] Fluoropore filter; Millipore Corp.

[6] Model 4500 with a Radiometer GK 2321C combination electrode; Beckman Instruments.

[7] Whatman Chemical Separation, Inc.

[8] SpectroMonitor III; Laboratory Data Control.

[9] Computer Automated Laboratory System run on a Hewlett-Packard Computer/Disc system; Computer Inquiry Systems, Inc.

After equilibration, the lactic acid and phosphoric acid samples were prefiltered through filter paper[10], followed by filtration through a disposable 0.45-μm membrane filter[11]. This was necessary due to a gel formation with these acids at high concentrations. The hydrochloric acid and methanesulfonic acid solutions were filtered through disposable 0.45-μm membrane filters[11].

After filtering, the pH of the solutions was measured[12], and the solutions were assayed. To obtain peaks of reasonable area, some samples were injected directly and others were diluted with 1% aqueous acetic acid solution. The conditions were: column, μ-Bondapak C-18[13]; mobile phase, acetonitrile–water containing 20% 1 M phosphate buffer (pH 7) and 1.2% diethylamine (50:50, v/v); flow rate, 2 mL/min[14]; injection volume, 50 μL[15]; wavelength, 235 nm[8]. The saturated concentrations were determined from areas under the peaks using a centralized computer system[9].

RESULTS AND DISCUSSION

The results of the cosolvent solubilities are shown in Figs. 1–3. Adjustments to the measured pH were needed due to changes in the standard state with the cosolvent systems used (16). These corrections were 0.13 in 85% methanol, −0.17 in 50% ethanol, and −0.02 in 25% ethanol.

Using Eqs. 2 and 9, the pH–solubility profiles were calculated (lines in Figs. 1–3). The calculations were made using the Davies equation (17) for the activity coefficients:

$$-\log Y_i = AZ_i^2\left(\frac{\sqrt{I}}{1+\sqrt{I}} - 0.2I\right) \qquad \text{(Eq. 10)}$$

where A is a constant for a given temperature and solvent system, Z_i is the charge on the ion, and I is the total ionic strength. Since the calculations are complex and would require a significant amount of time to hand calculate, a computer program was written to solve the equations[16].

In Table I, the values for pK_a, pK_{sp}, and the uncharged species solubility for each solvent system are given. There is good correlation between the calculated curves (Figs. 1–3) and the observed solubility. Also shown in these figures is the dependence of the solubility of I on chloride ion. In 85% methanol at pH 5, the solubility decreases by 26, 46, and 61% in the presence of 0.01, 0.025, and 0.05 M chloride ion, respectively. A 0.05 M sodium chloride solution is about one-third the concentration of an isotonic saline solution (0.154 M). Calculations at pH 5 indicate a solubility of ~1.2 mg/mL in a 0.15 M sodium chloride solution, which would be a decrease of 80% in the solubility compared with no added sodium chloride. Similar decreases in solubility were calculated for the 50 and 25% ethanol solutions at pH 5; however, the percentage decrease is greater in these solutions, ~90 and 98% in 50 and 25% ethanol, respectively (Table II).

Inspection of the curves in Figs. 1–3 reveals the following about the solubility profile of a weak base. As the solution pH increases there is initially an increase in the solubility followed by a region in which there is little change. With a further increase in pH, there is again an increase in the solubility until a maximum is obtained. Finally, after reaching the maximum, there is a rapid decrease in the solubility.

This behavior in the profile can be explained by considering the various equilibria and species which are present in solution. Initially, the increase in solubility is due to a decrease in the anion concentration (Cl^-). This effect is subject to the solubility product (Eq. 5), where the solubility is given by Eq. 9. The total anion concentration is approximately equal to the sum of the concentrations of the weak-base protonated species and the hydrogen ion. As the pH increases, the hydrogen-ion concentration becomes very small compared with the weak-base protonated species. When this occurs, there will be little change in the solubility with pH. The maximum shown in these curves is due to the presence of both the charged and uncharged species of the weak base. The increase in solubility up to the maximum is due to an increase in the weak base uncharged species concentration up to its maximum. The rapid decrease in solubility after the maximum is due to a decrease in the weak base charged species concentration. These concentrations are controlled by the equilibrium constant. The total solubility at pH values greater than the maximum is given by Eq. 2. As the maximum solubility of the weak base uncharged species decreases, the height of the maximum will decrease (see Figs. 1 and 3). This is because at the maximum, the solution is saturated in both the weak base charged and uncharged species. Finally, the differences shown between the curves for a specific solvent system at pH values greater than the maxima are due to activity coefficient effects. If all activity coefficients were equal to one, the curves after the maxima would be superimposable.

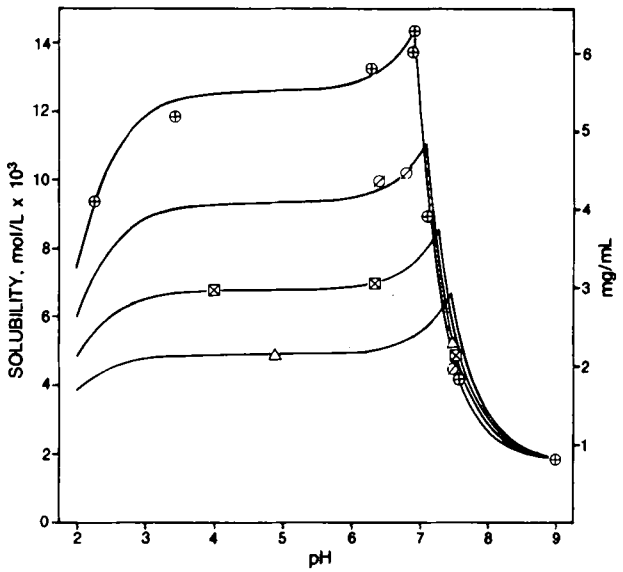


Figure 1—*pH–solubility profile of I with hydrochloric acid (solvent system, 85% methanol–water). Effect of salt on the solubility of I. Key: (⊕) no NaCl added; (Ø) 0.01 M NaCl; (□) 0.025 M NaCl; (△) 0.05 M NaCl.*

It is not possible to make direct comparisons of the pK_a value with those reported in the literature for similar compounds because of the solvent systems used. Decreases of >1 in the pK_a values compared with pure water for weak bases have been reported with 80% ethanol (18). Literature pK_a values for *N*-substituted piperidine compounds are typically 9–10 in pure water (19). This indicates that the values reported here are not unreasonable.

The pK_{sp} values used for the solubility of terfenadine with phosphoric, hydrochloric, methanesulfonic, and lactic acids are 5.6, 4.8, 4.6, and 4.05, respectively. The pK_{sp} value is largest for phosphoric acid and smallest for lactic acid. The higher the value of pK_{sp}, the lower the solubility of that salt; therefore, the solubility of terfenadine will be lowest in solutions pH-adjusted with phosphoric acid and will be highest in those solutions adjusted with lactic acid. The solubility profiles of terfenadine using these four acids are shown in Fig. 4. There is a maximum solubility between pH 4.5 and pH 5.5. The

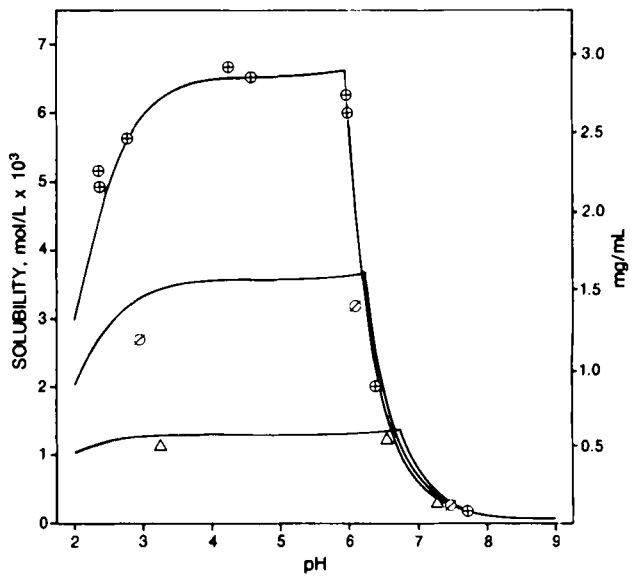


Figure 2—*pH–solubility profile of I with hydrochloric acid (solvent system, 50% ethanol–water). Effect of salt on the solubility of I. Key: (⊕) no NaCl added; (Ø) 0.01 M NaCl; (△) 0.05 M NaCl.*

[10] No. 2; Whatman.
[11] Gelman Aerodisc.
[12] Century SS-1 pH meter with an Orion combination single glass electrode; Beckman Instruments.
[13] Waters Associates.
[14] 6000A pump; Waters Associate.
[15] WISP auto injector; Waters Associates.
[16] A copy of the program can be obtained by writing the authors. It is written in Extended BASIC and was run on a PDP 11-70 computer.

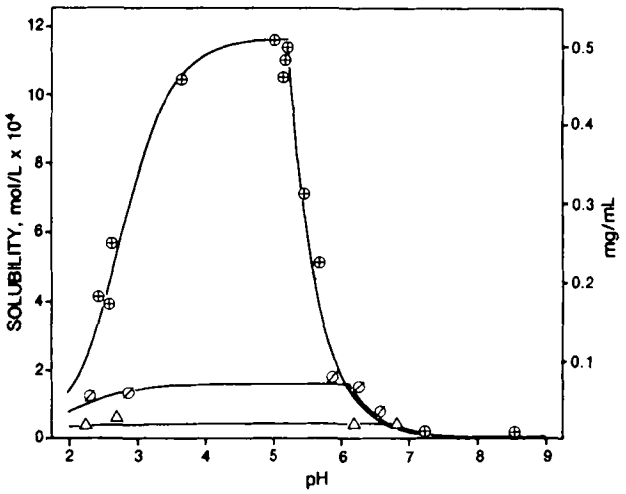


Figure 3—*pH-solubility profile of I with hydrochloric acid (solvent system, 25% ethanol-water). Effect of salt on the solubility of I. Key: (⊕) no NaCl added; (Φ) 0.01 M NaCl; (△) 0.05 M NaCl.*

decrease in solubility at higher pH is due to the solutions being saturated with respect to the uncharged form of terfenadine. At low pH, the terfenadine is forced out of solution due to the presence of additional anion from the pH adjustment.

Utilizing these pK_{sp} values, calculations were made to show the effects of the addition of sodium chloride to hydrochloric acid–terfenadine solutions and monobasic sodium phosphate to phosphoric acid–terfenadine solutions (Figs. 5 and 6). There is a pronounced effect on the solubility with the addition of even low concentrations of salts to these solutions.

These studies show the dependence of the solubility of a weak base on the pK_{sp}, pK_a, and maximum solubility of the uncharged species. Equations were presented which permit the calculation of pH-solubility profiles knowing the above constants. The effect of added salt is also shown where the solubility was significantly reduced on the addition of sodium chloride.

APPENDIX I

The derivation of Eqs. 1 and 2 and those for polyprotic compounds have been reported in detail elsewhere (1-12). They can be obtained by considering Eq. 3, the standard proton dissociation expressions, and individual species. For a monoprotic compound, Eq. 3 becomes:

$$S_{1,j} = [HD] + [D] \qquad \text{(Eq. 3a)}$$

In region $j = 0$ the HD species is saturated and, therefore, substitution of the equilibrium expression Eq. 3b into Eq. 3a for [D] will result in Eq. 3c:

$$K = \frac{\{H\}[D]}{\{HD\}} = \frac{\{H\}[D]Y_1}{\{HD\}} \qquad \text{(Eq. 3b)}$$

$$S_{1,0} = [HD] + \frac{K\{HD\}}{Y_1\{H\}} \qquad \text{(Eq. 3c)}$$

It is actually the activity of the species which is constant and not the concentration. Therefore, Eq. 3c should be expressed as Eq. 1:

Table I—Equilibrium and Solubility Constants of I

Solvent	pK_{sp}	pK_a	[A], mol/L	[A], μg/mL
85% Methanol	4.08	7.65	1.76×10^{-3}	771
50% Ethanol	4.51	7.81	7.5×10^{-5}	32.8
25% Ethanol	5.91	8.27	1×10^{-6}	0.44

Table II—Effect of Sodium Chloride On the Solubility of I at pH 5

Solvent	Solubility Without NaCl, μg/mL[a]	Solubility With NaCl, μg/mL[a]
85% Methanol	5520	1200
50% Ethanol	2870	272
25% Ethanol	509	7.8

[a] Concentration of NaCl is 0.15 M, approximately isotonic saline.

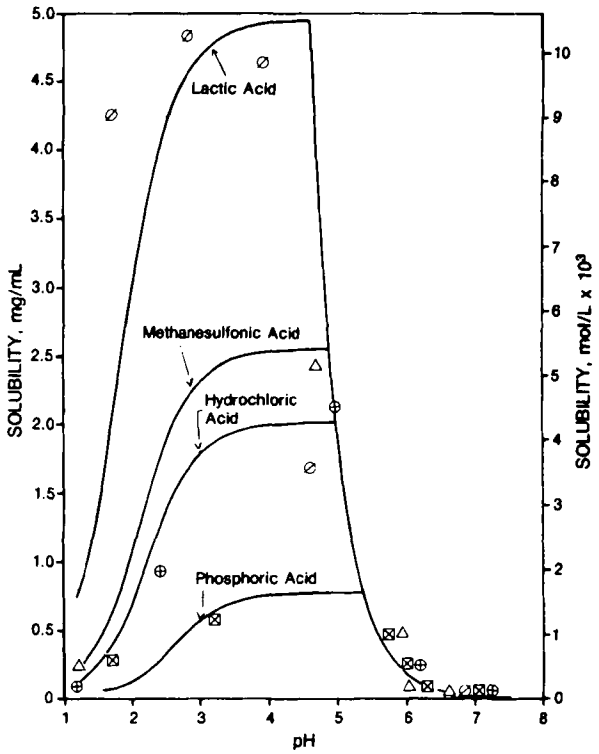


Figure 4—*pH-solubility profile of terfenadine with different acids. Effect of different acids on the solubility of terfenadine. Key: (Φ) lactic acid; (△) methanesulfonic acid; (⊕) hydrochloric acid; (□) phosphoric acid.*

$$S_{1,0} = \left(\frac{1}{Y_0} + \frac{K}{Y_1\{H\}}\right)\{HD\} \qquad \text{(Eq. 1)}$$

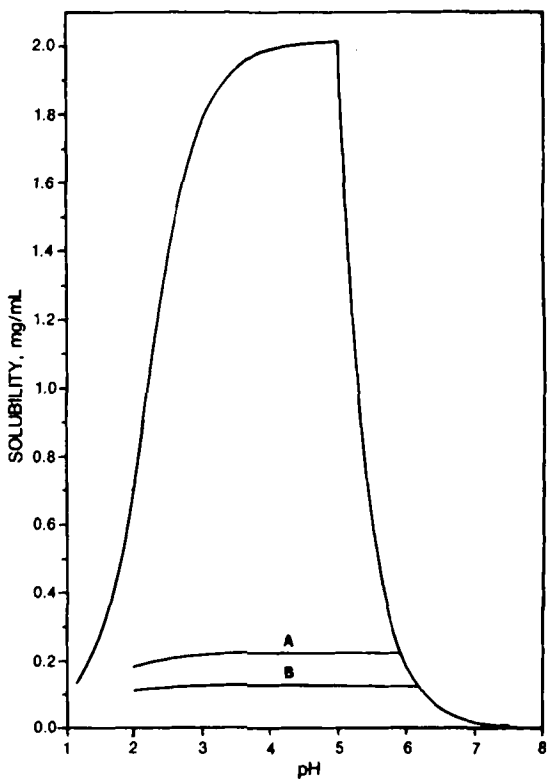


Figure 5—*pH-solubility profile of terfenadine with hydrochloric acid and salt. Calculated solubility profiles of terfenadine in solution with 0.05 M NaCl (A) and 0.1 M NaCl (B).*

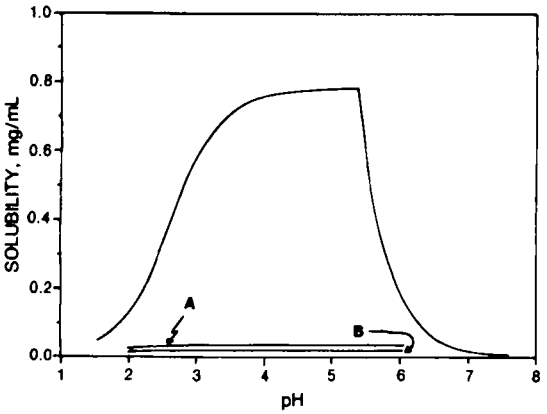


Figure 6—*pH-solubility profile of terfenadine with phosphoric acid and salt. Calculated solubility profiles of terfenadine in solution with 0.05 M NaH_2PO_4 (A) and 0.1 M NaH_2PO_4 (B).*

Similarly, Eq. 2 can be obtained by substituting the equilibrium expression into Eq. 3a for [HD], where in this case the region corresponds to $j = 1$.

Equations 1 and 2 can be generalized into the equation:

$$S_{m,j} = \sum_{j=0}^{m} \frac{\{H\}^j}{Y_0}\left[\left(\prod_{\alpha=0}^{j}\frac{1}{K_\alpha}\right)\left(1 + Y_0\sum_{i=1}^{m}\frac{1}{\{H\}^i Y_i}\prod_{t=1}^{i}K_t\right)\right]\{H_{m-j}D\} \quad \text{(Eq. 11)}$$

where $K_0 = 1$, and the other symbols are defined as above. This expression allows the determination of all equations necessary to describe the pH-solubility profile of any compound with protons that dissociate. For example, with a diacidic compound in which $m = 2$, the following equations are obtained:

$$S_{2,0} = \left(\frac{1}{Y_0} + \frac{K_1}{\{H\}Y_1} + \frac{K_1K_2}{\{H\}^2Y_2}\right)\{H_2D\} \quad \text{(Eq. 12)}$$

$$S_{2,1} = \left(\frac{1}{Y_1} + \frac{\{H\}}{K_1Y_0} + \frac{K_2}{\{H\}Y_2}\right)\{HD\} \quad \text{(Eq. 13)}$$

$$S_{2,2} = \left(\frac{1}{Y_2} + \frac{\{H\}^2}{K_1K_2Y_0} + \frac{\{H\}}{K_2Y_1}\right)\{D\} \quad \text{(Eq. 14)}$$

These equations are applicable to both weak acids and weak bases with appropriate charge assignments made to the activity coefficients and species.

APPENDIX II

The pH of maximum solubility for a monoprotic weak acid in the presence of added salt can be determined as follows[17]. For the equilibria:

$$HD \rightleftharpoons H + D \quad \text{(Eq. 6a)}$$

the equilibrium expression is given by Eq. 3b, and the solubility product is given by:

$$K_{sp} = \{M\}\{D\} \quad \text{(Eq. 4)}$$

where the added salt is MX. The charge balance equation is:

$$[M] + [H] = [OH] + [D] + [X] \quad \text{(Eq. 6b)}$$

Rearranging Eq. 3b yields:

$$\{H\} = \frac{K\{HD\}}{\{D\}} \quad \text{(Eq. 6c)}$$

Substituting for {D} from Eq. 4 into Eq. 6c gives:

$$\{H\} = \frac{K\{HD\}\{M\}}{K_{sp}} \quad \text{(Eq. 6d)}$$

Substituting for {M} from the charge balance equation (Eq. 6b) into Eq. 6d:

$$\{H\} = \frac{K\{HD\}}{K_{sp}}([D] + [X] + [OH] - [H])\,Y_M \quad \text{(Eq. 6e)}$$

Further substitution into Eq. 6e for [D] (from the equilibrium expression) and for [OH] from:

$$K_w = \{H\}\{OH\} \quad \text{(Eq. 6f)}$$

(the ionization constant product of water) results in:

$$\{H\} = \frac{K\{HD\}}{K_{sp}}\left(\frac{K\{HD\}}{HY_1} + [X] + \frac{K_w}{\{H\}Y_{OH}} - \frac{\{H\}}{Y_H}\right)Y_M \quad \text{(Eq. 6g)}$$

Rearranging Eq. 6g results in the quadratic equation:

$$\{H\}^2\left(\frac{K_{sp}}{K\{HD\}Y_m} + \frac{1}{Y_H}\right) - \{H\}[X] - \left(\frac{K\{HD\}}{Y_D} + \frac{K_w}{Y_{OH}}\right) = 0 \quad \text{(Eq. 6h)}$$

Solving Eq. 6h for {H} results in the desired equation for a monoprotic weak acid:

$$\{H\} = \frac{[X] + \left[[X]^2 + 4\left(\frac{K_{sp}}{K\{HD\}Y_M} + \frac{1}{Y_H}\right)\left(\frac{K\{HD\}}{Y_D} + \frac{K_w}{Y_{OH}}\right)\right]^{1/2}}{2\left(\frac{K_{sp}}{K\{HD\}Y_M} + \frac{1}{Y_H}\right)} \quad \text{(Eq. 6)}$$

A similar procedure is followed for a monoprotic weak base, but the solubility product is given by Eq. 5 and the charge balance is given by:

$$[M] + [H] + [HD] = [OH] + [X] \quad \text{(Eq. 7a)}$$

Substitution for {HD} from Eq. 5 is made into Eq. 6c and into the resulting equation for {X}. On rearranging and solving the resulting quadratic expression, Eq. 7 is obtained.

APPENDIX III

The equation for the total solubility of a monoprotic weak acid (Eq. 8) in the region saturated by the charged species D can be derived as follows[17]. Starting with Eq. 2 and substituting for {D} from Eq. 4 gives:

$$S_{1,1} = \left(\frac{1}{Y_D} + \frac{\{H\}}{KY_{HD}}\right)\frac{K_{sp}}{\{M\}} \quad \text{(Eq. 8a)}$$

Substituting into Eq. 8a for {M} from the charge balance equation 6b) results in:

$$S_{1,1} = \left(\frac{1}{Y_D} + \frac{\{H\}}{KY_{HD}}\right)K_{sp}/([D] + [X] + [OH] - [H])Y_M \quad \text{(Eq. 8b)}$$

Substituting Eq. 2 into Eq. 8b for [D], the ionization product constant of water (Eq. 6f) for [OH], and the hydrogen ion activity for [H] gives:

$$S_{1,1} = \left(\frac{1}{Y_D} + \frac{\{H\}}{KY_{HD}}\right)K_{sp}\Bigg/\Bigg(\frac{S_{1,1}}{\left(\frac{1}{Y_D} + \frac{\{H\}}{KY_{HD}}\right)Y_{HD}} + [X] + \frac{K_w}{\{H\}Y_{OH}} - \frac{\{H\}}{Y_H}\Bigg)Y_M \quad \text{(Eq. 8c)}$$

Equation 8c can be rearranged to the quadratic equation:

$$S_{1,1}^2\left[\frac{1}{\left(\frac{1}{Y_D} + \frac{\{H\}}{KY_{HD}}\right)Y_{HD}}\right] + S_{1,1}\left([X] + \frac{K_w}{\{H\}Y_{OH}} - \frac{\{H\}}{Y_H}\right) - \frac{K_{sp}}{Y_M}\left(\frac{1}{Y_D} + \frac{\{H\}}{KY_{HD}}\right) = 0 \quad \text{(Eq. 8d)}$$

Solving Eq. 8d for $S_{1,1}$ results in:

$$S_{1,1} = \frac{-\left([X] - \frac{\{H\}}{Y_H} + \frac{K_w}{\{H\}Y_{OH}}\right) + \left[\left([X] - \frac{\{H\}}{Y_H} + \frac{K_w}{\{H\}Y_{OH}}\right)^2 + 4\frac{K_{sp}}{Y_MY_D}\right]^{1/2}}{2\left(\frac{KY_{HD}}{\{H\}Y_D + KY_{HD}}\right)} \quad \text{(Eq. 8)}$$

A similar procedure is followed for a monoprotic weak base to arrive at Eq. 9. Substitutions are made in Eq. 1 for {HD} (from Eq. 5) and for [X] (from

[17] The charges on the ions have not been included in these equations: H and M are +1; OH, D, and X are −1.

the charge balance equation, Eq. 7a). On solving the quadratic equation, Eq. 9 is obtained.

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Pharmacokinetics of Gliclazide in Healthy and Diabetic Subjects

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Abstract □ The pharmacokinetics of total and free gliclazide, 1-(3-azabicyclo[3,3,0]oct-3-yl)-3-(*p*-tolylsulfonyl)urea, a potential hypoglycemic drug, was studied in healthy (n = 12) and diabetic (n = 12) subjects. The serum level of gliclazide was determined by a high-performance liquid chromatographic method (HPLC). The free fraction of gliclazide was obtained from serum by an ultrafiltration technique using a collodion membrane. The mean adsorption of gliclazide to the membrane was ~50% when the membrane was used more than twice. Therefore, the gliclazide level in the filtrate was corrected by doubling the apparent value. The ratio of gliclazide-protein binding remained constant at ~92% in serum after administration to healthy and diabetic subjects. The mean pharmacokinetic parameters of elimination rate (k_e), time to reach the peak level (t_{max}), elimination half-life ($t_{1/2}$), and volume of distribution (Vd) were 0.07 h^{-1}, 2.8 h, 12.3 h, and 17.4 L, respectively. The parameters did not differ significantly between healthy and diabetic subjects or between single and successive administrations; moreover, they did not differ between the free and total drug level. Although there were intersubject variations, the therapeutic effects of oral administration of gliclazide on serum glucose and insulin levels were found in four diabetic patients. The results of this study show that the pharmacokinetics of the total gliclazide level reflect those of the free gliclazide in serum.

Keyphrases □ Gliclazide—protein binding in healthy and diabetic human serum □ Pharmacokinetics—serum gliclazide level after administration in healthy and diabetic subjects □ Ultrafiltration—protein binding of gliclazide in healthy and diabetic human serum

The pharmacokinetic study of serum drug levels is important in the assessment of intrinsic properties of a drug (*e.g.*, absorption, distribution, metabolism, and excretion) to plan effective drug administration. Sulfonylureas, such as tolbutamide and chlorpropamide, bind to several circulating serum proteins (1). In particular, serum albumin strongly interacts with many sulfonylureas (2–4) and other drugs (5). Moreover, free sulfonylureas are the forms that exert the pharmacological effect of hypoglycemic activity (6–8). Therefore, the pharmacokinetics of the free sulfonylurea level in blood may be useful in programming drug administration.

The drug level in a protein-free solution must be measured to determine the free drug level in blood. Ultrafiltration (9), equilibrium dialysis (2, 3, 10), and gel filtration (11) techniques have been used to measure free drug level. Equilibrium dialysis has been commonly used to study the binding of drugs and proteins, but the time required to reach equilibration (8–24 h) is a major disadvantage. Due to simplicity, convenience, and speed, an ultrafiltration technique was used to separate the protein-free phase from serum in the present study.

In this study, a sensitive high-performance liquid chromatographic (HPLC) method (12) was used to determine the total and free levels of gliclazide (13), during a pharmacokinetic study.

EXPERIMENTAL SECTION

Subjects—Twelve male volunteers (age, 32–42 years; weight, 54–72 kg) served as test subjects. All were healthy according to clinical examinations and routine tests. Twelve patients (seven males, five females; age, 35–76 years; weight, 45–80 kg) were patients with maturity-onset diabetes mellitus (FBS: 121–302 mg/100 mL). They did not have impaired renal function, nor hepatic or endocrine disease.

Methods of Drug Administration—One tablet containing 40 mg of gliclazide[1] was administered orally before breakfast to the healthy subjects who had fasted overnight. Blood samples were obtained without an anticoagulant before and at 1, 2, 3, 4, 6, 10, and 24 h after drug administration. After the blood had clotted, the tube was centrifuged at 2500 rpm for 10 min and the supernatant serum was separated. All serum samples were stored at −20°C until use. The volunteers had regular mealtimes throughout the experiment. Twelve diabetic patients were orally administered two tablets containing 40 mg of gliclazide (therapeutic dose) in the morning; eight of them continued to take the drug (40 mg × 2) daily for 7 d. Blood samples were obtained as

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