Limiting Solubilities and Ionization Constants of Sparingly Soluble Compounds: Determination from Aqueous Potentiometric Titration Data Only

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A new method is described for the concomitant determination of limiting solubilities and ionization constants of sparingly soluble compounds, i.e., drugs. Aqueous potentiometric titration data were recorded both before and after precipitation of the compound and subjected to computer-assisted analysis. Limiting solubilities and ionization constants were obtained for nucleoside transport inhibitors, viz., dilazep, sulfoxazine, and hexobendine. The method was validated by comparison of titration results for known antidepressants with data from the literature. The procedure was found to be rapid and reliable for compounds with limiting solubilities as low as 30 \( \mu M \), and it circumvents problems of direct methods for measuring limiting solubilities.

KEY WORDS: ionization constant; solubility, limiting; nucleoside transport inhibitors; potentiometric titration; antidepressant.

INTRODUCTION

The solubility of a sparingly soluble drug is an important parameter in formulation studies, since dissolved drugs will be absorbed only from the gastrointestinal tract. Determination, however, of the limiting solubility (the solubility of the neutral molecular species of the drug) is a tedious and time-consuming procedure and is subject to many practical problems (1,2). It usually consists of the shaking of a solid in a medium in which the solubility is thought to be minimal (e.g., an amine salt or a free base in 0.01 \( M \) sodium hydroxide). Upon equilibrium (which has to be verified experimentally) the undissolved material is removed by centrifugation, which offers considerable difficulties, among them inadequate clarification and temperature changes of the solution and, hence, solubility. The concentration of the dissolved drug is then assayed in the remaining solution.

Bearing these difficulties in mind, several authors have looked for other procedures. Based on the ideas of Krebs and Speakman (3), a method was developed by Zimmermann (4,5), and refined with respect to data analysis by Lewis (6). It was demonstrated that at constant ionic strength, both the \( pK_a \) value and the limiting solubility of a substance can be calculated from its solubility as a function of the \( \text{pH} \) of the medium. Although direct determination of the limiting solubility is avoided, this method still requires a lot of experimentation, since now solubilities have to be measured at several \( \text{pH} \) values.

In a recent paper we described the assessment of the macroscopic ionization constants (as \( pK_a \) values) of the acidic salts of sparingly soluble drugs from aqueous potentiometric titration curves (7).

Here we report on the evaluation of both \( pK_a \) values and limiting solubility, again from potentiometric titration curves in aqueous media with computer-aided data analysis. It appears to be a simple, reliable, and rapid procedure for drugs with a limiting solubility of not less than ca. 30 \( \mu M \).

EXPERIMENTAL

The compounds (ca 0.05 mEq in 0.1 \( M \) KCl) were potentiometrically titrated with 0.1 \( M \) KOH (0.005 mEq with 0.01 \( M \) KOH for imipramine HCl) from a calibrated Radiometer ABU 11 micropipettor at 25.0 \( \pm 0.1^\circ C \) under \( \text{N}_2 \). The pH was measured with a Radiometer PHM 62 standard pH meter. The volume of the solution was 10–15 ml. The ionic strength was assumed to be 0.1 \( M \) KCl (activity coefficient, 0.775). The titration was stopped below \( \text{pH} \) 11, in order to avoid any anomaly of the glass electrode.

Data analysis was performed with two computer programs (for fundamentals see Theoretical), following a non-linear least-squares minimization of the added volumes of alkali. All titrations were performed in triplicate.

THEORETICAL

Consider the dissociation of a diacidic salt (\( \text{BH}_2^{2+} \cdot 2X^- \)), such as dilazep \( \cdot 2\text{HCl} \), when titrated with a strong base, e.g., KOH.

\[
K_1 \quad \text{BH}_2^{2+} \Leftrightarrow \text{BH}^+ + \text{H}^+ 
\]
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\[ K_2 \]
\[ \text{BH}^+ \rightleftharpoons \text{B} + \text{H}^+ \]

The (macroscopic) ionization constants \( K_1 \) and \( K_2 \) are defined as follows:

\[ K_1 = \frac{[\text{BH}^+][\text{H}^+]}{[\text{BH}_2^{2+}]}, \]
\[ K_2 = \frac{[\text{B}][\text{H}^+]}{[\text{BH}^+]}. \]

Before precipitation occurs (for titration curve of dilazep \( \cdot 2\text{HCl} \) see Fig. 1), titration data are analyzed with a modified SCOGS computer program (8), according to a recently described procedure (7), yielding both \( K_1 \) and \( K_2 \).

After precipitation (of, most likely, the neutral molecule) the concentration of \( \text{B} \) in solution remains constant, being the limiting solubility (\( S_0 \)) of the compound. Electrical neutrality in the saturated solution requires that

\[ \text{BH}_2^{2+} + \text{BH}^+ + \text{M}^+ + \text{H}^+ = \text{OH}^- + \text{X}^- \]

where \( \text{H}^+ \) and \( \text{OH}^- \) are the absolute numbers of equivalents of hydrogen and hydroxyl ions, respectively, present in the solution; \( M^+ \) is the absolute number of equivalents of alkali added to the solution; \( X^- \) is the absolute number of equivalents of acidic salt originally added to the solution; and \( \text{BH}_2^{2+} \) and \( \text{BH}^+ \) are the absolute numbers of equivalents of bi- and monovalent cation, present in the saturated solution.

Combining Eqs. (1) and (2) with Eq. (3), we get

\[ [\text{M}^+] = K_w/[\text{H}^+] + [\text{X}^-] - [\text{H}^+] - S_0 \cdot [\text{H}^+]/K_2 \]
\[ - S_0 \cdot [\text{H}^+]^2/(K_1 \cdot K_2) \]

where \( K_w/[\text{H}^+] = [\text{OH}^-] \) (\( K_w \) is the ionic product of water).

For a monoacidic salt Eq. (4) is shortened to

\[ [\text{M}^+] = K_w/[\text{H}^+] + [\text{X}^-] - [\text{H}^+] - S_0 \cdot [\text{H}^+] / K_a \]

where \( K_a \) is the ionization constant.

Based on Eqs. (4) and (5) a computer program was written for the analysis of titration data after precipitation to yield the limiting solubility (\( \pm \) SE) of a mono- or bifunctional compound, once its \( pK_a \) value(s) is(are) known. In this computer-assisted curve-fitting procedure allowance is made for the temperature, activity coefficients, (changing) volume of the solution, and normality of the titrant.

Fig. 1. Titration curve of dilazep \( \cdot 2\text{HCl} \) in 0.1 \( M \) KCl (arrow: start precipitation).

MATERIALS

Hexobendine \( \cdot 2\text{HCl} \) (Chemie Linz Pharma, Linz, Austria), dilazep \( \cdot 2\text{HCl} \) (Asta/Degussa Pharma, Frankfurt, F.R.G.), solufrazine \( \cdot 2\text{HCl} \) (Janssen Pharmaceutica, Beerse, Belgium), chlorpromazine HCl (Rhone Poulenc Specia, Amstelveen, The Netherlands), thioridazine HCl (Sandoz, Uden, The Netherlands), and triflupromazine HCl (Squibb, Rijswijk, The Netherlands) were all gifts, which are gratefully acknowledged. Imipramine HCl was obtained from Nogeap (Alkmaar, The Netherlands) and promethazine HCl was supplied by Brocacef (Maarsen, The Netherlands).

RESULTS AND DISCUSSION

In Fig. 1 a typical titration curve of the nucleoside transport blocking drug dilazep \( \cdot 2\text{HCl} \) is shown. Just after the first equivalence point the compound starts to precipitate (indicated by the arrow), giving rise to a deviation from "normal," smooth titration curves of materials that remain soluble during titration.

The ionization constants (\( pK_1 \) and \( pK_2 \) values) for dilazep are derived from the part of the titration curve before precipitation occurs, as mentioned under Theoretical, whereas the (limiting) solubility of this compound is determined from data after precipitation, now with the values of \( K_1 \) and \( K_2 \) fixed. The value of the limiting solubility remains identical regardless of whether all data or only the data between the first and the second equivalence point are used. However, the standard error increases with data after the second equivalence point are also considered. Therefore, the calculation was based on the approximately 15 data points between the first and the second equivalence point. Because of the full correlation between ionization and solubility parameters, appearing in quotients, it is impossible to approximate all parameters from Eq. (4) or (5) simultaneously (see Theoretical).

In Fig. 2 the chemical structures, \( pK_a \) values, and solubilities of dilazep and the other two nucleoside transport blockers, hexobendine and solufrazine, are shown. In order to assess the reliability of the described method we also determined the \( pK_a \) value and limiting solubility of a well-known antidepressant, viz., imipramine HCl. The respective values, 9.40 \( \pm \) 0.02 and 65 \( \pm \) 1 \( \mu M \), closely agree with data from the literature, 9.5 and 65 \( \mu M \) (1) and 66 \( \mu M \) (9), and thus validate our method. Furthermore, we determined the solubilities of four antipsychotics with known physicochemical properties already determined by other methods. Table I summarizes the \( pK_a \) values, available from the literature (not determined from solubility data). The arithmetic means were used to calculate the limiting solubilities from the respective titration curves by the curve-fitting procedure. The calculated solubilities are also tabulated in Table I, together with solubility data from the literature. \( pK_a \) values could not be determined for these compounds from aqueous potentiometric titrations, since they precipitated immediately after the first addition of alkali (at least at the concentrations used). Nevertheless, our calculated solubilities agree rather well with the data of Green (1), as can be seen in Table I as well.

How does the described method compare to other pro-