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Report

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, soluflazine, 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 μ*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 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 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 μ*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 ± 0.1°C under 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 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 nonlinear least-squares minimization of the added volumes of alkali. All titrations were performed in triplicate.

THEORETICAL

Consider the dissociation of a diacidic salt ($BH_2^{2+} \cdot 2X^-$), such as dilazep · 2HCl, when titrated with a strong base, e.g., KOH.

$$BH_2^{2+} \overset{K_1}{\leftrightarrows} BH^+ + H^+$$

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$$\mathrm{BH^+} \overset{K_2}{\leftrightarrows} \mathrm{B + H^+}$$

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

$$K_1 = [\mathrm{BH^+}] \cdot [\mathrm{H^+}]/[\mathrm{BH_2}^{2+}],$$
$$K_2 = [\mathrm{B}] \cdot [\mathrm{H^+}]/[\mathrm{BH^+}] \qquad (1, 2)$$

Before precipitation occurs (for titration curve of dilazep · 2HCl 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 B in solution remains constant, being the limiting solubility (S_0) of the compound. Electrical neutrality in the saturated solution requires that

$$\mathrm{BH_2}^{2+} + \mathrm{BH^+} + \mathrm{M^+} + \mathrm{H^+} = \mathrm{OH^-} + X^- \qquad (3)$$

where $\mathrm{H^+}$ and $\mathrm{OH^-}$ are the absolute numbers of equivalents of hydrogen and hydroxyl ions, respectively, present in the solution; $\mathrm{M^+}$ 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 $\mathrm{BH_2}^{2+}$ and $\mathrm{BH^+}$ 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

$$[\mathrm{M^+}] = K_w/[\mathrm{H^+}] + [X^-] - [\mathrm{H^+}] - S_0 \cdot [\mathrm{H^+}]/K_2 - S_0 \cdot [\mathrm{H^+}]^2/(K_1 \cdot K_2) \qquad (4)$$

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

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

$$[\mathrm{M^+}] = K_w/[\mathrm{H^+}] + [X^-] - [\mathrm{H^+}] - S_0 \cdot [\mathrm{H^+}]/K_a \qquad (5)$$

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 (± 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.

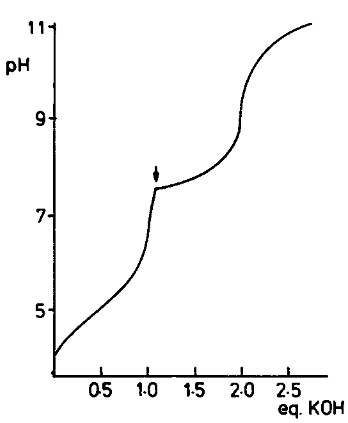


Fig. 1. Titration curve of dilazep · 2HCl in 0.1 *M* KCl (arrow: start precipitation).

MATERIALS

Hexobendine · 2HCl (Chemie Linz Pharma, Linz, Austria), dilazep · 2HCl (Asta/Degussa Pharma, Frankfurt, F.R.G.), soluflazine · 2HCl (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 Nogepha (Alkmaar, The Netherlands) and promethazine HCl was supplied by Brocacef (Maarssen, The Netherlands).

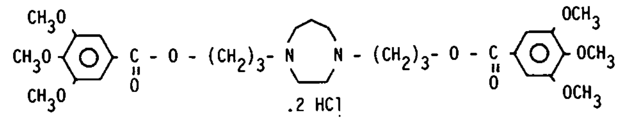
RESULTS AND DISCUSSION

In Fig. 1 a typical titration curve of the nucleoside transport blocking drug dilazep · 2HCl 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).

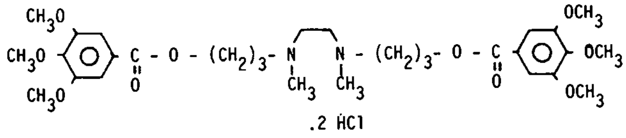
In Fig. 2 the chemical structures, pK_a values, and solubilities of dilazep and the other two nucleoside transport blockers, hexobendine and soluflazine, are shown. In order to assess the reliability of the described method we also determined the pK_a value and limiting solubility of a well-known antidepressant, *viz.*, imipramine HCl. The respective values, 9.40 ± 0.02 and 65 ± 1 μ*M*, closely agree with data from the literature, 9.5 and 65 μ*M* (1) and 66 μ*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-



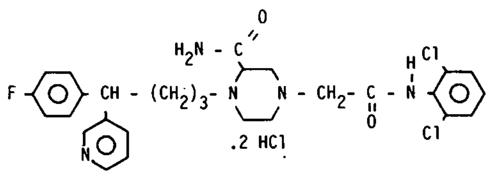
dilazep.2HCl

pK_1 = 5.14 ± 0.11 pK_2 = 8.25 ± 0.08 S_0 = 320 ± 3 μM



hexobendine.2HCl

pK_1 = 4.52 ± 0.01 pK_2 = 8.47 ± 0.01 S_0 = 567 ± 8 μM



soluflazine.2HCl

pK_1 = 5.09 ± 0.09 pK_2 = 5.74 ± 0.08 S_0 = 343 ± 7 μM

Fig. 2. Macroscopic ionization constants (pK_1 and pK_2) and limiting solubilities (S_0) of nucleoside transport inhibitors.

cedures for the determination of pK_a values and limiting solubilities? First, the conventional determination of the limiting solubility from the variation of solubility with pH, is a very tedious procedure, prone to errors which are discussed in the literature (2). Thus, any procedure that circumvents the actual measurement of solubilities is a welcome addition. Second, the low solubility of a compound is frequently thought to preclude the determination of its pK_a value in aqueous, and hence, biologically relevant, media. Indeed as early as 1925, Mizutani (12) introduced the use of mixed solvents (e.g., water/ethanol). "Aqueous" pK_a values could be obtained by extrapolation, but several authors have questioned this also time-consuming procedure (13,14).

Table I. Macroscopic Ionization Constants and Limiting Solubilities of Some Antipsychotic Drugs

	pK_a	pK_a mean	S_0 (μM) Calculated	S_0 (μM) Literature
Chlorpromazine HCl	9.26[a] 9.40[b]	9.33	7.2 ± 0.1	8[c]
Promethazine HCl	9.09[a] 8.99[b]	9.04	53.5 ± 0.8	55[c]
Thioridazine HCl	9.16[a] 9.62[b]	9.39	4.9 ± 0.3	1.5[c]
Triflupromazine HCl	9.41[a] 9.29[b]	9.35	3.7 ± 0.1	—

[a] See Ref. 10.
[b] See Ref. 11.
[c] See Ref. 1.

In contrast, the method described in this paper takes advantage of precipitation during an aqueous potentiometric titration, since it allows the concomitant determination of ionization constants as well as solubilities of mono- and bifunctional acidic salts. Immediate precipitation on titration with alkali (as was the case for the phenothiazines in the design of our experiments) renders a direct determination of pK_a values impossible (without precluding the calculation of solubilities). Often, however, precipitation can be "delayed" by lowering both the concentration of the compound to be titrated and the normality of the titrant. From the titration data of imipramine it is probable that accurate determinations for all physicochemical parameters can be obtained for bases with solubilities not lower than 30 μM.

Ionization constants are preferably determined in 0.1 M KCl (to prevent changes in ionic strength during titration), and, thus, values for solubilities are obtained in the presence of the same ionic concentration. Of course, variations in the latter may affect solubility due to "salting out." As the very low concentrations of drugs used in this study do not markedly influence the ionic strength, one can freely choose other aqueous media of lesser ionic strength, and even water, to obtain meaningful pK_a values and solubilities.

Finally, for only marginally soluble bases ($S_0 < 30\ \mu M$), reliable estimates (including standard error) for the limiting solubility can be obtained (as shown in Table I), once the pK_a value of the compound is known. On the assumption that in a series of congeneric substances (e.g., imipramine derivatives with identical aliphatic side chains) ionization constants are virtually identical, solubilities of all congeners are easily determined from their aqueous potentiometric titration curves after precipitation, provided that one pK_a value is known.

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