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pH-metric solubility.☆: 3. Dissolution titration template method for solubility determination

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Abstract

The main objective of this study was to develop an effective potentiometric saturation titration protocol for determining the aqueous intrinsic solubility and the solubility–pH profile of ionizable molecules, with the specific aim of overcoming incomplete dissolution conditions, while attempting to shorten the data collection time. A modern theory of dissolution kinetics (an extension of the Noyes–Whitney approach) was applied to acid–base titration experiments. A thermodynamic method was developed, based on a three-component model, to calculate interfacial, diffusion-layer, and bulk-water reactant concentrations in saturated solutions of ionizable compounds perturbed by additions of acid/base titrant, leading to partial dissolution of the solid material. Ten commercial drugs (cimetidine, diltiazem hydrochloride, enalapril maleate, metoprolol tartrate, nadolol, propoxyphene hydrochloride, quinine hydrochloride, terfenadine, trovafloxacin mesylate, and benzoic acid) were chosen to illustrate the new titration methodology. It was shown that the new method is about 10 times faster in determining equilibrium solubility constants, compared to the traditional saturation shake-flask methods.

Keywords: Solubility; Dissolution; Solubility-ph profile; Potentiometric; Titration; Oral absorption

Article Outline

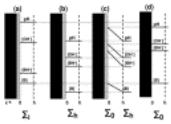

Fig. 1.

Schematic representing the three-state model (see text). Depicted is the case of a weak base, B, titrated with HCl in an alkaline solution at a pH near the pK_a. The vertical direction represents concentration of reactants; the horizontal direction represents distance from the surface of the solid. The solid is represented by rectangles. The lighter shaded rectangle represents the amount of solid which dissolves as a result of HCl titrant addition. Block (a) represents the initial state, Σ_i, before titrant addition. Block (b) represents the situation right after titrant addition, where the bulk solution is equilibrated by convective mixing, but none of the solid has dissolved (t=0). Block (c) represents the equilibration of the solution adjacent to the surface of the solid and the establishment of the initial steady state (t≤2 s). Block (d) represents the equilibrium state (t=∞), where a portion of the solid has been dissolved, and a lower-pH solution has been formed. The transition from states (a) to (b) is nearly instantaneous; from (b) to (c) takes less than 2 s; from (c) to (d) takes minutes or hours. The vertical dashed lines represent the boundary between the diffusion layer and bulk solution. The horizontal dashed lines assist in visualizing that pH has decreased in block (d) compared to block (a), but that the concentration of the uncharged (free) base has remained the same in (d) as in (a), as is characteristic of a saturated solution.

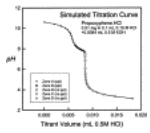

Fig. 2.

Template simulation for 0.51 mg propoxyphene hydrochloride in 5.1 ml 0.15 M KCl, using the pK_a 9.06 and log P_{ow} 4.37.

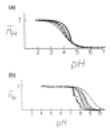

Fig. 3.

Bjerrum plots: (a) benzoic acid, indicating ideal behaviour (squares, 96 mM; triangles, 130 mM; hexagons, 500 mM), and (b) propoxyphene hydrochloride, showing some incomplete dissolution (squares, 0.11 mM; triangles, 0.25 mM; hexagons, 0.73 mM).

Table 1. Diffusion layer and bulk solution concentrations[a]

Table 2. Simulated dissolution rates during titration of propoxyphene

Table 3. Potentiometric titrations

Table 4. Intrinsic solubilities and solubilities at selected pH values[a]

☆Avdeef et al. (2000) is Part 2 of the series.

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