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Commentary

Phosphate-buffer induced pH-dependence in solubility of uncharged drugs

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Abstract

Background and purpose: Solubility measurements in phosphate-buffered media are common. At a selected pH, it is generally assumed that for non-ionized drugs, the measured solubility, S_{pH}, is equal to the intrinsic solubility, S_0. However, if the solubility of a non-ionized drug is found to be pH dependent by dint of the medium, then the above equivalence cannot be generally valid. **Computational approach:** Published S_{pH} values of ritonavir, atazanavir, cilnidipine, and felodipine at pH 6.5 to 7.4 in phosphate buffered media were analysed to determine the corresponding S_0 values using the computer program pDISOL-X. 'Constant ionic medium' thermodynamic activity corrections were made based on the Stokes-Robinson hydration theory, as modified recently to include salting-out constants to represent the activity coefficients of uncharged solutes. **Key results:** It was found that the four drugs show a pH dependence in measured solubility in the pH range where none had been expected. This refutes the assumption that in such measurements the two types of solubility are equivalent. The non-equivalence increases as the ionic strength of the buffer exceeds 0.15 M with increasing pH. Salting-out of the uncharged drug appears to explain the effect. **Conclusion:** These findings suggest that critical considerations of the choice of buffers and pH are beneficial and that corrections for activity coefficients can better quantitate the intrinsic solubility.

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Keywords

Solubility at selected pH; intrinsic solubility; constant ionic medium thermodynamic state; Stokes-Robinson hydration theory; drug salting-out constant; buffer capacity; ionic strength

Introduction

This commentary considers whether the solubility of non-ionized drugs could be pH dependent when measurements are performed in phosphate buffered solutions.

Drug solubility in such media at a selected pH, S_{pH}, can be quite useful for ranking research compounds in early discovery projects [1,2]. Total phosphate concentration of 0.05 M is often used. At pH 7.4, the ionic strength, I_{pH}, at this buffer concentration is 0.14 M, a physiologically relevant value. But in specialized applications (*e.g.* to maintain slurry pH during disproportionation), concentrations as high as 0.88 M ('PB 10x') have been reported [3], with I_{pH} = 2.3 M at pH 5. Although these are convenient assays in early drug discovery, nuanced understanding of speciation in drug-saturated solutions may be incomplete from single-point measurements:

- drug self-aggregation reactions can easily be overlooked at the selected pH [4-8];
- formation of drug-phosphate complexes may not be recognized from a single-point measurement [5-8];
- measured ionization constant, pK_a, of the active moiety may not be available [9], which can lead to uncertainties in the *selection* of the buffer pH;
- if the buffer concentration is low and the drug solubility is high, the equilibrium pH of the final drug-saturated solution may not be equal to that expected of the phosphate buffer [10];
- if ionic strength of the solution is high (*e.g.* I > 0.3 M), simple activity corrections may be unreliable.

In contrast, such complications are less likely to be missed in full multi-point solubility-pH profiles (more commonly measured in later stages of drug development), by the analysis of characteristic *curve distortions* when compared to benchmark Henderson-Hasselbalch curves [1,2].

Even in buffer-free drug-saturated solutions, single-point measurements present similar challenges, requiring critical analyses to extract physiologically-appropriate solubility as a function of pH, as has been explored previously [10].

In the cases of weakly-ionizable drugs with known experimental pK_a, in many studies, it continues to be assumed that for pH > pK_a +2 (basic drugs) or pH < pK_a - 2 (acidic drugs), the measured solubility, S_{pH}, defines the intrinsic solubility, S_0 (which is the solubility of the non-ionized form of the drug) [2,11]. Implicit in the above qualified pH range is that if the drug moiety is non-ionized, then solubility will not depend on pH. In such casting, ideal conditions are often implied, and activity corrections are not considered in the interpretation of solubility measurements. Even when simple Debye-Hückel corrections [2] are incorporated, the activity coefficient of the non-ionized form of the drug is generally taken to be unit value. Consequently, the equivalence $S_0 = S_{pH}$ can be problematic, as errors over a log unit can be encountered when high concentrations of phosphate buffers are used.

To address some of the above possible uncertainties, specifically in the case of the phosphate buffer, the present commentary critically re-examines the speciation characteristics of saturated solutions of four sparingly-soluble drugs (ritonavir, atazanavir, cilnidipine, felodipine - Figure 1) measured in pH 6.5, 6.8 and 7.4 buffered solutions (total phosphate concentrations of 0.0, 0.05, 0.1 and 0.2 M), drawing on previously published data [12-21].

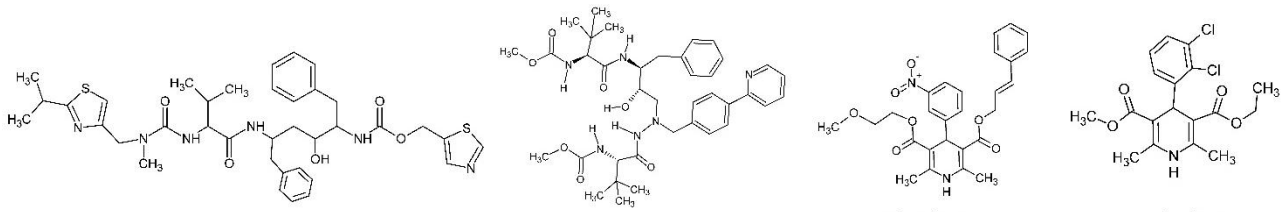


Figure 1. Structures of drugs considered

Consequently, this commentary focuses on the use of phosphate as buffer in solutions where the drug is assumed to be un-charged. Equilibrium solubility values are generally reported in concentration units (molarity, mg mL^{-1}, *etc.).* If such concentrations are determined under conditions (*e.g.* temperature, ionic strength) that deviate from an accepted thermodynamic reference framework, activity corrections need to be applied to align measurements to the reference state. Therefore, a reliable means to convert activity to concentration is required. Our study is part of an ongoing interest in enhancing the quality of solubility measurements and interpretations of weakly ionizable sparingly-soluble druglike molecules [22]. The present study may provide new perspectives to aid in the analysis, interpretation, and assay design of solubility measurements of such molecules, particularly when the buffer concentration is relatively high.

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Computational approach

Determination of equilibrium constants

The *p*DISOL-X™ computer program (*in-ADME* Research) was used to perform the equilibrium solubility analysis, comprising refinement of equilibrium constants and applying them in analytic continuation [10] across a broad range of pH. The mechanistic dual-phase mass action algorithm in the program continues to evolve. It has been applied in studies involving multifactorial equilibria, often addressing drug self-aggregation reactions [1,2,4-9,23-28], and rigorously factoring in activity corrections, most recently including salting-out of non-ionized species [10,29]. In several cases considered, the drug moiety appeared to form water-soluble complexes with counterions and components in buffers [6-8,25].

The equilibrium data analysis method takes pH, log *S* (molarity based), and corresponding estimated standard deviations as measured input data at a specified temperature. The analytical concentrations of all added reagents (*e.g*. acid and base titrants, inert salt, buffer, excipients, cosolvents, *etc*.) need to be specified.

The methods of electrode standardization (described below) are needed but are seldom reported in publications. The mass action approach considers the possible contribution of all species proposed to be present in the solution. The constant ionic medium (CIM) thermodynamic state was selected at the physiologically-appropriate reference ionic strength, I_{ref} = 0.15 M [2]. (In legacy literature, extrapolation to zero ionic strength was the common alternative reference state.) The mass action algorithm internally sets up its implicit multiple polynomial equations, for a set of equilibrium reactions and the corresponding roughly-estimated 'seed' constants that the user provides, as detailed elsewhere [2]. The initial constants are iteratively refined in a weighted nonlinear regression procedure, in which the concentrations of all the assumed reactants and product species are calculated, along with the acid-base titrant volumes, the ionic strength, *I*, and the buffer capacity at each pH. Underpinning this procedure, operational values of all equilibrium constants are adjusted at each point for activity deviations from the CIM I_{ref} benchmark level. Therefore, final values of equilibrium constants are reported in molarity units, harmonized to I_{ref}.

pH measurement and conversion to the pcH^+ scale

In the CIM thermodynamic reference state, hydrogen ion activities, a_H, are converted to concentrations using Equation (1) [30]:

$$p_aH = \alpha + k_S\, p_cH + j_H\, c_{H^+} + j_{OH}\, K_w / c_{H^+} \quad (1)$$

where the concentration $p_cH = -\log c_{H^+}$ and the operational $p_aH = -\log a_H$. The latter is what the pH electrode normally indicates. The hydrogen ion activity coefficient, $f_H = a_H / c_{H^+}$. The α term corresponds to the negative logarithm of the activity coefficient of H^+ ($-\log f_H$) at the working temperature and ionic strength; the k_s term denotes the ratio between the actual slope and the temperature-dependent Nernst slope; K_w is the ionization constant of water, taken as a function of temperature and ionic strength [2]. The j_H term corrects pH readings for any nonlinearity due to liquid junction and glass asymmetry potentials in highly acidic solutions (pH <2), whereas the j_{OH} term corrects for high pH (pH > 11) nonideal behaviour.

Manufacturers of instruments for measuring pK_a constants (*e.g.* https://www.pion-inc.com/) normally include an automated procedure based on a 'blank titration' (at 25 °C and I_{ref} = 0.15 M) to determine the parameters in Equation (1). The procedure is also practiced at several universities and pharmaceutical companies.

In the present study, the four empirical parameters at 25 °C and I_{ref} = 0.15 M were taken to be: α = 0.09, k_S = 1.0019, j_H = 0.5 and j_{OH} = -0.5, based on legacy average values associated with research-grade pH electrodes [2]. Since the parameters depend on ionic strength, which in the present study extends from 0.05 to

0.5 M (pH 3 to 10 interval), the four parameters are further adjusted automatically in the program as a function of ionic strength and temperature deviations from the reference level at each solubility-pH point (detailed in [2], pp. 64-65).

Automatic ionic strength compensation for changes in activities of species

The ionic strength, I, generally changes with pH during an acid-base solubility-pH titration. This change affects equilibrium constants. Since the local I_{pH} at any given pH point in such a titration is likely to be different from I_{ref}, all equilibrium constants at base level I_{ref} are automatically transformed to I_{pH}, the local ionic strength at each point in the calculation of local concentrations. The procedure uses activity corrections based on the hydration theory originally proposed by Stokes and Robinson in 1948 [31], slightly modified recently by us to include explicit salting-out constants to represent the activity coefficients of uncharged solutes [10,29]. The new procedure is well-suited to correct for activity effects at high ionic strength, as fully detailed elsewhere [29].

In the modified procedure, the activity coefficient of the *uncharged* species, $f_{neutral,}$ is defined by the Setschenow *salting-out factor*, K_{Setsch}, according to Equation (2):

$$\log f_{neutral} = \log (S_0 / S_{pH}) = K_{Setsch} (I_{pH} - I_{ref}) \quad (2)$$

Estimated values of K_{Setsch} were calculated, as described elsewhere [29]. The drug H-bonding potential decreases K_{Setsch}, whereas molecular volume increases the constant. Table 1 summarizes the various equilibrium constants applied to the four drug molecules studied here.

Table 1. Literature equilibrium constants of drugs at 37 °C, I_{ref} = 0.15 M [a]

Drug	MW	pK_a	log (S_0 / μg mL^{-1}) [b]	S_0 / μg mL^{-1}	K_{Setsch} / M^{-1} [c]	Ref. (pK_a)
Ritonavir	720.94	2.28 (base)	-5.47	2.4	0.663	[32]
Atazanavir	704.86	4.52 (base)	-5.73	1.3	0.602	[33]
Cilnidipine	492.52	11.4 (acid)	-7.11	0.04	0.529	[34]
Felodipine	384.25	un-ionized[d]	-5.63	0.90	0.423	[35]

[a]Equilibrium constants are at the CIM thermodynamic reference state; [b]Molarity-based average value from Wiki-pS_0 database [11]. Standard deviations and number of independent reports: ritonavir (±0.30, n = 9), atazanavir (±0.33, n = 7), cilnidipine (±0.32, n = 2), felodipine (±0.16, n = 8); [c]Estimated salting-out constants [29]. [d]No ionization constants were detected in the pH 1.3 to 12.9 interval [35].

Values of pK_a

Reliable pK_a values, including those of the buffer, are needed for the analysis and interpretation of the solubility-pH data. We could not find convincing experimental pK_a values of felodipine published in the open literature. According to the AstraZeneca felodipine Product Information [35], there was no finding of ionization in the range of pH 1.3 – 12.9. ADMET Predictor® (Simulation Plus, Inc.; www.simulations-plus.com) predicts an acid pK_a of 11.15, which is in close agreement with that of cilnidipine. These citations strongly suggest that felodipine is un-ionized at pH 6.5 and 6.8.

The three pK_a values of phosphoric acid used here were derived from the empirical fitting (weighted multiple linear regression) of published data from 102 sources (0 to 60 °C, I = 0 to 2 M), Equations (3) to (5):

$$pK_{a1} = 136.2/T + 0.0057T - 0.779I^{½} / (1 + I^{½}) - 0.00025IT \quad (3)$$

$$pK_{a2} = 1179.1/T + 0.011T - 1.766I^{½} / (1 + I^{½}) - 0.00006IT \quad (4)$$

$$pK_{a3} = 2432.0/T + 0.014T - 2.212I^{½} / (1 + I^{½}) - 0.0006IT \quad (5)$$

At 37 °C with I_{ref} = 0.15 M, pK_{a1} = 1.98 ± 0.09, pK_{a2} = 6.69 ± 0.04, pK_{a3} = 11.56 ± 0.21, with standard deviations estimated from the propagation-of-errors in the four fitted parameters. At the highest ionic strength considered in this study, I_{pH} = 0.40 M, the pK_a values are empirically estimated to be 1.87, 6.50, and 11.28. But at I_{pH} = 2.13 M ('PB 10x' at pH 6.3) [3], the estimated pK_a values are 1.58, 6.10, and 10.50.

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Results and discussion

Solubility analysis

From the published S_{pH} 37 °C data for the four drugs considered, it was possible to determine the corresponding thermodynamic S_0 intrinsic constants (harmonized to 0.15 M ionic strength). The results are summarized in Table 2. At the reported buffer pH, the ionic strength affects the relationship between S_{pH} and S_0, even though the drug is effectively non-ionized. In the case of ritonavir at pH 6.8, as the total phosphate concentration changes from 0.1 to 0.2 M, S_{pH} systematically decreases from 1.3 to 0.9 μg mL^{-1}, as anticipated by activity corrections. Yet, both 0.1 and 0.2 M cases indicate the *same* CIM-harmonized S_0 of 1.4 μg mL^{-1}. The ratio S_0/S_{pH} increases by about 50 % as the $c_{phosphate\text{-}total}$ increases to 0.2 M.

Table. 2. Solubility of drugs at 37 °C in phosphate buffered solutions at pH where drugs are not ionised [a]

Drug	pH	S_{pH} /mg ml^{-1} [b]	$c_{phosphate\text{-}total}$ / M	c_{NaCl} / M	I / M [c]	S_0 / μg mL^{-1} [d]	S_0 / S_{pH}	Ref.
Ritonavir	7.4	2.4	0.00	0.0	0.000	1.9	0.80	[13]
Ritonavir	6.5	2.2	0.05	0.0	0.076	2.0	0.89	[19]
Ritonavir	6.8	1.3	0.10	0.0	0.198	1.4	1.08	[13]
Ritonavir	6.8	0.9	0.20	0.0	0.408	1.4	1.48	[13]
Atazanavir	6.5	1.1	0.05	0.0	0.076	1.0	0.89	[19]
Atazanavir	6.8	1.0	0.05	0.0	0.120	0.9	0.95	[21]
Atazanavir	6.8	1.1	0.05	0.0	0.122	1.0	0.96	[14]
Atazanavir	6.5	0.4	0.025	0.106	0.146	0.4	0.98	[18]
Atazanavir	7.4	1.7	0.10	0.0	0.282	2.0	1.20	[15]
Cilnidipine	6.5	0.023	0.029	0.106	0.153	0.023	1.00	[20]
Cilnidipine	6.8	0.50	0.10	0.0	0.233	0.055	1.11	[16]
Felodipine	6.5	0.60	0.05	0.0	0.076	0.56	0.93	[17]
Felodipine	6.8	0..94	0.10	0.0	0.201	0.99	1.05	[12]

[a]Analysis harmonized to the constant ionic medium thermodynamic reference state (I_{ref} = 0.15 M); [b]Published value of drug solubility at the specific buffer pH; [c]Calculated ionic strength at the specific pH; [d]Intrisic solubility calculated by mass-action analysis using the pDISOL-X program. The average calculated value od S0 for ritonavir, atazanavir, cilnidipine and felodipine are 1.7±0.3, 1.1±0.6, 0.039±0.023 and 0.77±0.30 mg mL^{-1}, respectively.

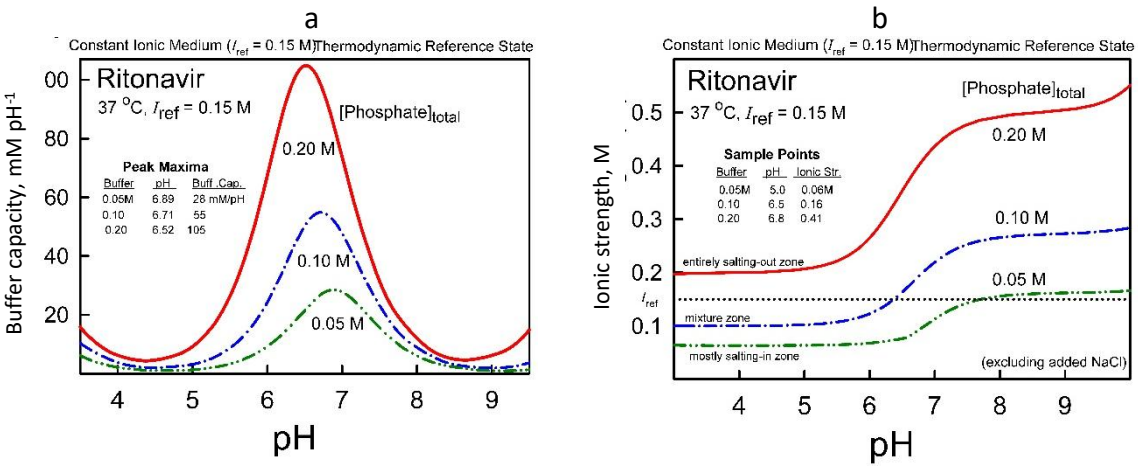


Figure 2. Phosphate buffer properties as a function of pH at total concentrations 0.05, 0.1 and 0.2 M, based on the ritonavir examples in Table 2. (a) Buffer capacity - pH curves, with nil contribution from the sparingly-soluble drug; (b) Ionic strength - pH curves, with nil contribution from the drugs considered

Although systematic and predictable, the buffer-induced shifts from S_{pH} to S_0 are small in the selected examples. In some cases, they are smaller than the standard deviations in the measurements (*cf.*, last footnote in Table 2). On the other hand, if solubility assay designs were better standardized across laboratories, one might expect lower interlaboratory standard deviations in solubility measurements [22]. However, it is reasonable to anticipate much larger shifts were the ionic strength as high as 2.13 M as in the case of the PB 10x buffer. In complicated media buffered by phosphate ions, mechanistic interpretations of solubility-pH profiles that may be systematically distorted from the benchmark Henderson-Hasselbalch curves can be challenging. Appropriate activity corrections could mitigate some of the uncertainties.

Buffers are generally selected for their tendency to minimize pH shits that may be introduced by added ionizable solutes. Buffer capacity is a measure of such a tendency. Figure 2a shows a plot of buffer capacity in the ritonavir example as a function of pH for three typical values of total phosphate concentrations listed in Table 2. In the table, the selected pH values, 6.5-7.4, align with the region of maximum buffer capacity. The peak maxima in the curves shift slightly to lower pH values with increasing phosphate concentration, due to slight differences in ionic strengths which affect the phosphoric acid pK_a values (Equations (3) to (5). Figure 2b illustrates how ionic strength changes with pH for the three levels of total phosphate concentrations. Ritonavir, being low-soluble and non-ionized in the pH range, does not contribute to the value of the ionic strength.

Figure 3 shows two curves (solid and dash-dot) of solubility as a function of pH for the ritonavir system at total phosphate concentrations of 0.1 and 0.2 M [13], over a pH range where the drug is expected to be uncharged (weak base pK_a = 2.28 [32]). These curves are analytic continuations [10] of the reported values of S_{pH} at pH 6.8 (filled circle and square symbols). Different values of the S_{pH} align with the equilibrium constant, S_0 (filled diamond) when the 'salting-out' contribution in activity corrections is applied [10,29]. The three unfilled symbols at pH 5 are hypothetical positions on the curves. The S_{pH} values taken from the curves at pH 5 harmonize to the same S_0 as with the measured pH 6.8 data. The salting-out effect at pH 5 is evident for the 0.2 M case (I_{pH} > 0.15 M), but at 0.1 M phosphate concentration, the effect is of the 'salting-in' type (I_{pH} < 0.15 M), as indicated in Figure 2b.

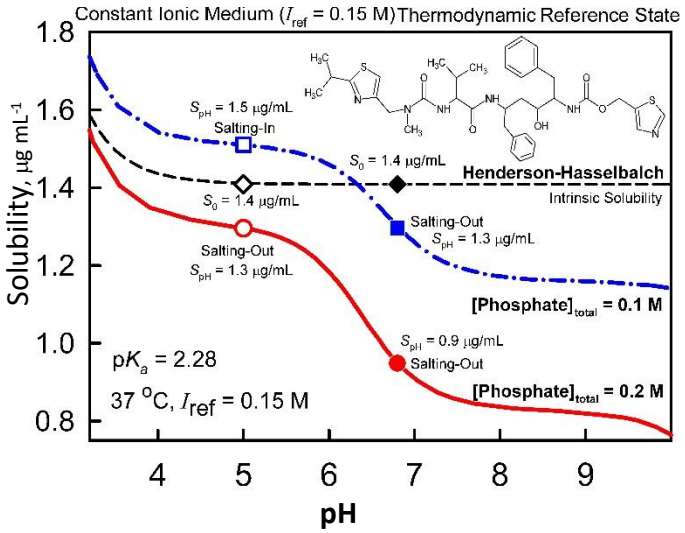


Figure 3. Ritonavir solubility-pH curves at 0.1 and 0.2 M total phosphate concentrations generated by analytic continuation [10] based on analysis of the reported S_{pH} measurements [13] (filled circle and square symbols). The dashed curve is calculated by the Henderson-Hasselbalch (HH) equation using refined equilibrium constants harmonized to the '*constant ionic medium*' thermodynamic state at I_{ref} = 0.15 M. Two hypothetical points were selected at pH 5 (open circle and square symbols) to illustrate examples of both salting-out and salting-in at the same selected pH

Experimental evidence of salting-out constants

The Setschenow equation [31] in the CIM reference state (*cf.* Equation (2)) may be used to confirm the predicted K_{Setsch} constants listed in Table 1 from the slopes in the plot of log (S_0/S_{pH}) *vs.* (I_{pH} - I_{ref}). Figure 4 illustrates such a plot for each of the four compounds. All four drugs in the figure show linear plots that intersect at the reference frame (0, 0) origin.

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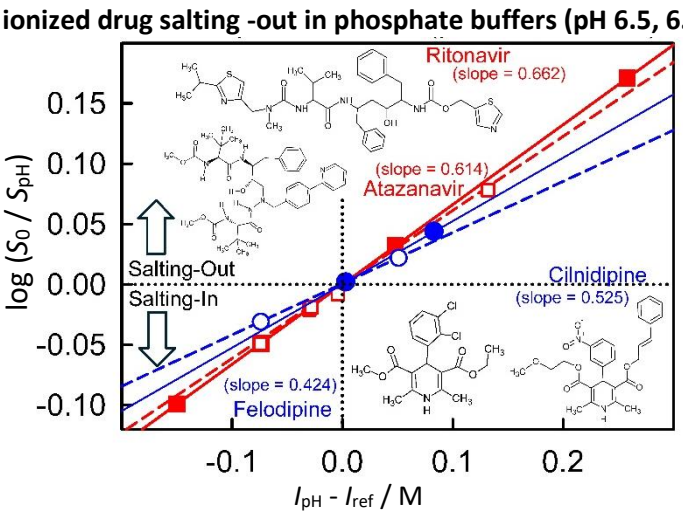


Figure 4. The logarithm of the activity coefficient of the uncharged drug, which is equal to the log of the ratio of the *p*DISOL-X calculated S_0 and the literature S_{pH}, when plotted against (I_{pH} - I_{ref}), is expected to be linear with a slope equal to K_{Setsch}. For the drugs studied, linearity is suggested and the slope values in the plot are very close to the predicted values in Table 1. The vertical dotted line denotes where the experimental ionic strength is at the reference value; the horizontal dotted line is at the point where the intrinsic solubility is equal to the solubility measured at the selected pH (unit activity coefficient for the un-ionized drug)

Conclusion

This commentary investigated the inherent subtlety in the widely-held assumption that if the selected pH for solubility measurement of an ionizable drug is more than 2 log units away from its pK_a, then the compound would be sufficiently un-ionized and that the intrinsic solubility would be defined by the solubility measured at the selected pH, namely, $S_0 = S_{pH}$. It was shown that in phosphate-buffered media with buffer total concentrations ≤0.2 M, small but systematic differences between the measured solubility and the intrinsic solubility do occur. This is primarily because the buffer contributes ions to the medium. These ions can increase the ionic strength well above the reference value of 0.15 M of the '*constant ionic medium*' thermodynamic state. The effects may be small in the studied systems, especially in 0.05 M buffer concentrations, however, there have been reported specialty cases where total buffer concentrations are as high as 0.88 M, where ionic strength varies from 1.4 to 4.1 M in the pH 2-10 interval. In buffer-free suspensions, salting-in effects can also require consideration. In such instances with (or without) buffer, unless activity corrections are considered, the interpretations of solubility-pH profiles can be challenging. In our previous work and in the present study, we have developed new computational methods to mitigate such uncertainties, so that mechanistic equilibrium models would be internally coherent. The focus in the present study was on phosphate buffers, but the principles apply to any other buffers or excipients that can alter the ionic strength in predictable amounts.

Dedication: *This study is dedicated to the memory of Jerome J. Bucher who died in February 2026. Equation (1) was developed in collaboration with Jerome at the Lawrence Berkeley Laboratory in the late 1970s and continues to be used to date [30].*

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Conflict of interest*: The author declares no conflicts of interest.*

Author Contributions: *Material preparation, data gathering and analysis were performed by the author.*

Data availability*: pDISOL-X computational summaries will be made available on request.*

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