



## Research Article

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Guest Editors: Philip J. Kuehl and Stephen W. Stein

# Effect of pH and Ionic Strength on the Solubility of Quinoline: Back-to-Basics

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**Abstract.** The interest of quinoline as a contaminant agent and as scaffold for the development of new therapeutic agent warrants to revisit the pH-solubility behavior of quinoline (Q) and quinoline derivatives (Q-derivatives) with possible salting-out effect. Q is a weak base with potential hazard upon exposure that may be occupational by inhalation or ingestion of or dermal exposure to particulates in certain industries; or simply by inhalation of cigarette smoke. In contrast, quinoline and its derivatives are useful in diverse therapeutic applications such as anticancer, antiseptic, antipyretic, antiviral, and antimalarial. These claims have raised the possibility of using quinoline motif for the synthesis of new drugs; however, it may act as a pollutant on soil and water as ionizable organic compounds (IOC). The solubility and partitioning behavior of Q may be a critical factor in determining the extent of inhalation and oral absorption or sorption onto soil and water. Studies on the solubility of Q have been reported; however, due to Q-derivatives distinctive usage, it is necessary to revisit and evaluate the solubility profile of Q at different pH levels and ionic strengths. This study reports a simple analytical method for determining the solubility of nitrogen heterocyclic compounds and possible salting-out effect as a function of pH, buffer concentration, and ionic strength. This information can be of value when developing Q-derivatives and to enhance understanding of Q as well as its derivatives behavior in the gastrointestinal tract or when evaluating the presence of Q as an environmental contaminant.

**KEY WORDS:** solubility; salting-out; quinoline; ionic strength; ionizable organic compounds.

## INTRODUCTION

The solubility of compounds starts by understanding the molecular symmetry and thermodynamic properties of crystal compounds (1). The crystallinity of organic compounds is frequently responsible for their poor solubility in aqueous media. Therefore, its control is an important factor in the design of drug formulations for maximum bioavailability and chemical analyses (2) as well as on the detection of organic pollutants in soil and water (3,4).

Several methods are used to determine the physico-chemical properties such as aqueous solubility and octanol-water partition coefficient of a vast number of pollutants hydrophobic compounds (HOC). Correlation of these two properties has been widely studied with different phenomena such as sorption to the

groundwater, transport, fate, and release in the environment (4–8). In the context of in vivo delivery, efforts have been focused on solubilization techniques for poorly water-soluble drugs. Various solubilization approaches including pH adjustment, cosolvency, micellization, and complexation (5) as well as lipid-based formulations (9–11), amorphous and salt forms (12–16), encapsulation (17,18), co-crystals (19–22), and excipients (additives) (23) have been taken to increase dissolution and hence bioavailability in the case of oral administration and avoid precipitation upon dilution in the case of injectables.

However, for ionizable organic compounds (IOC), the information is limited compared to HOC. In addition, these compounds do not fit the same pattern as non-polar compounds. Information on the sorption of IOC is of great value when determining the fate and transport of these substances into the environment. In addition, the extent of drug absorption based on physicochemical properties such as ionization effects of the active pharmaceutical ingredient (API) on formulations may influence drug absorption after oral administration with potential clinical implications (24). Thus, information on solubility and partitioning on the sorption, absorption or adsorption, of IOCs as a function of pH and ionic strength ( $\mu$ ) is important for the development of methodologies and strategies for analysis, formulation, and de-risk the solubility impact on drug candidate success. The environmental

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fate (25–27) or biologic hazard of nitrogen-based heterocyclic compounds (NHC) such as pyridine, acridine, and especially quinolone (Q) and 3-quinoline derivatives (Q-derivatives), continue to be of relevance. More specifically, Q and Q-derivatives for the potential of salting-out effect. It is a versatile heterocyclic weak base with a variety of therapeutic applications (28–30). Over the past decades, the Q scaffold has become an important assembly motif for the development of new drugs with various applications (28–32). A comprehensive review on the advances of quinoline-based anticancer or antimalarial agents has been published recently (31). Quinoline and its functionalized derivatives with biological and pharmacological activity include antimalarials (Quinine and Quinidine) (29), antiviral (Saquinavir) (30), and anticancer (Camptothecin, Irinotecan, and Topotecan) (31); quinoline-5,8-dione moieties are present in antitumor agents such as lavidamycin, streptonigrin, and styrylquinoline (32).

Overall, physicochemical properties of Q-derivatives for pharmaceutical use are diverse, for instance, compounds with anti-microbial activity may show low melting point  $\sim 135^\circ\text{C}$  and a molar mass of  $340 \text{ g}\cdot\text{mol}^{-1}$ . However, low melting and low molecular weight (MW) do not translate to a desired aqueous solubility, for example, quinoline-based anticancer drugs or antimalarial are practically insoluble in water ( $\sim 0.05 \text{ mg/mL}$ ) (31). Owing significance of the quinoline motif, in many chemical processes and the synthesis of functional compounds in various areas of chemistry, food, and pharmaceutical, the goal of this study was to evaluate the salting-out effect assessing the solubility of Q at different pH values, buffer concentrations, and ionic strengths. The procedures chosen to assess this are simple and robust. The hypothesis to be tested is that the protonated (ionized) drug  $\text{QH}^+$  and neutral Q species will be influenced by the concentration and presence of other ions or excipients in the formulation. The solubility issue is particularly complex in the case of ionizable drugs such as poorly water-soluble weak bases. The systems were chosen because of their potential dissociation and hence competing dissolution. Thus, depending on the situation, inhibition or improvement of the release characteristics occurs. Consequently, the bioavailability of specie-rich phase  $\text{QH}^+$  or Q when a certain concentration is exceeded. Hence, these findings are of high practical importance for pharmaceutical development and *in vitro* assessment of solubilization approaches like lipid-based formulation (LBF) (33) dispersion and digestion and precipitation behavior using weakly basic drugs derived from quinoline.

## THEORY

The ionization of acids and bases was proposed by Brønsted-Lowry (1923). A base is defined as species which accept a hydrogen ion (proton acceptor). The ionization process for a base such as Q is:



and the ionization constant,  $K_a$ , is given by:

$$K_a^T = \frac{\{H^+\}\{Q\}}{\{\text{QH}^+\}} \quad (2)$$

Where  $K_a$  is the thermodynamic ionization constant at a given temperature,  $T$ . The  $\{ \}$  represents the activity of the ionic species

The equation for  $K_a$  can be written as follows:

$$pK_a = \text{pH} + \log \frac{[\text{QH}^+]}{[\text{Q}]} \quad (3)$$

where  $[\ ]$  denotes concentration and  $pK_a = -\log K_a$  and  $\text{pH} = -\log H^+$ .  $pK_a$  is a measure of the strength of acids and bases; the stronger the base, the higher the  $pK_a$ .

The ionic strength  $\mu$  is the contribution of the total number of ions present in solution to the activity coefficient. The ionic strength ( $\mu$ ) is dependent on the concentration of an ion and its valency and it is given by:

$$I = \frac{1}{2} \sum C_i Z_i^2 \quad (4)$$

where  $C_i$  is the molar concentration of the ion and  $Z_i$  is its valency.

It is important to consider the concentrations of the protonated and non-protonated species as well as Q and  $\text{QH}^+$  at equilibrium. Likewise, the concentration of the ionized species into its effective concentration activity coefficient ( $\gamma$ ). After a combination of equations involving  $[\text{Q}]/[\text{QH}^+]$  (not shown) and activity coefficient for ionized species  $\gamma_{\text{QH}^+}$ , the following equation is derived:

$$pK_a^T = \text{pH} + \log \frac{[\text{QH}^+]\gamma_{\text{QH}^+} + -[\text{H}^+]}{[\text{Q}] + [\text{H}^+]^+} \quad (5)$$

The thermodynamic  $pK_a$  values from the titrations performed in this study were calculated using Eq. 5.

It is well reported that the solubility of a compound in water can be influenced by the presence of other electrolytes by changing the activity coefficients of the ions of the salt that in turn causes changes in the ionic strength (34). The solubility of weak electrolytes is strongly influenced by the pH of the solution. If the unionized form Q represents the free base and the soluble ionized form is represented by  $\text{QH}^+$ , then the concentration of Q in solution is the intrinsic solubility constant, such that,  $S_o = Q$ , and Eq. (3) can be arranged to:

$$[\text{QH}^+] = \frac{[\text{H}^+][\text{Q}]}{K_a} \quad (6)$$

and the total solubility,  $S$ , of the compound at a given pH is the sum of the solubility of the unionized form Q and the ionized form  $\text{QH}^+$ , such that:

$$S = [\text{QH}^+] + [\text{Q}] \quad (7)$$

The total solubility can be expressed as a function of the hydrogen ion,  $H^+$ , concentration, intrinsic solubility,  $S_o$ , and the ionization constant  $K_a$ , obtaining:

$$S = S_o + \frac{[\text{H}^+]^+ S_o}{K_a} \quad (8)$$

or

$$S = S_o \left[ \frac{[\text{H}^+]}{K_a} \right] + 1 \quad (9)$$

and the logarithm form:

$$\log (S/S_o - 1) = pK_a - \text{pH} \quad (10)$$

The  $pK_a$  values at the equilibrium solubilities of quinoline at different pH levels and ionic strengths can be calculated by using Eq. (10).

## MATERIALS AND METHODS

### Materials

Quinoline was purchased from Sigma Chemical Company (St. Louis, MO) then it was distilled under reduced pressure of 20 mmHg at 118°C. The purified quinoline was used to perform all solubility studies. A summary of the physico-chemical properties of quinoline is summarized in Table I.

The solubility of quinoline was measured using McIlvaine's buffer, which is a mixture of one part of citric acid ( $H_3C$ , Fisher Scientific, Fair Lawn, NJ) and two parts of disodium phosphate ( $Na_2HPO_4$ , Fisher Scientific, Fair Lawn, NJ). This buffer system was chosen because of the versatility of the pH range (2–8) without changing the acidic-basic species. Distilled, deionized, and filtered water (Milli-Q Water System, Millipore) was used to prepare the various buffer solutions at different concentrations, pH values, and ionic strength as well as for dilutions of saturated samples. The pH of all the buffer solutions was measured prior to the addition of quinoline.

### Methods

#### Determination of pH-Solubility Profile

The buffer systems were equilibrated at 20°C with an excess of quinoline. The solutions were placed in Teflon-lined screw-capped glass test tubes. The test tubes were covered with aluminum foil to prevent photodecomposition. Replicates of the quinoline buffer systems were rotated on a test tube rotator (Berkley, CA) for 24 h. The equilibrated samples were centrifuged at 500 rpm for 15 min in a Beckman centrifuge (Fullerton, CA). The supernatant was removed

with a Pasteur pipette and placed in a clean test tube. The pH of the supernatant was measured (Table II) and analyzed by both a UV spectrophotometer (Beckman DU-8, Fullerton, CA) at a wavelength of 225 nm and by high performance liquid chromatography (HPLC). In the event of high concentrations, samples were diluted with water prior to analysis.

The solubility of quinoline was also determined in water, hydrochloric acid (HCl), and sodium hydroxide (NaOH) at different pH values. The samples were equilibrated and pH was adjusted to the desired value with HCl or NaOH as necessary.

#### Chromatographic Procedure

Quinoline was assayed by HPLC. The HPLC system (Hewlett Packard) consisted of a fully end-capped RSIL  $C_{18}$  HL column, mobile phase of acetonitrile/water (85:15) at a flow rate of 1.0 mL/min at a wavelength of 225 nm using a Kratos Analytical Spectroflow with variable wavelength absorbance detector. The retention time ( $t_R$ ) of quinoline was 4.30 min. Several replicates of the solutions at different pH, buffer concentrations, and ionic strengths were analyzed.

#### Determination of $pK_a$

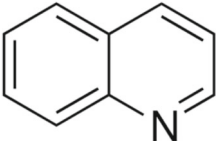
The ionization constant of quinoline was determined by titration at 20°C. Titrations were conducted in a 100-mL beaker. The pH values were measured with a pH meter. Solutions of quinoline at a concentration of 0.01 M in water and saline solutions at constant ionic strengths of 0.16 and 1.1 were prepared. The titrant used was HCl at 0.1 M and ionic strengths of 0.16 and 1.1 and added with a syringe.

## RESULTS AND DISCUSSION

### Intrinsic, Equilibrium, and pH Solubility of Quinoline

The total solubility ( $S$ ) of the ionizable compound  $QH^+$  can be expressed as a function of the ion concentration, the

**Table I.** Summary of the Physical-Chemical Properties of Quinoline (35)

Name & Formula	Mol. Wt.	Log PC	B.P. (°C)	Density (g mL <sup>-1</sup> )	$\lambda_{max}$	log $\epsilon$
Quinoline C <sub>9</sub> H <sub>7</sub> N	129.5	2.05	237.7	1.09	225	4.49
					275	3.51
					299	3.46
					312	3.52

**Table II.** Intrinsic and Equilibrium Solubility of Quinoline in Citric-Phosphate Buffer at Different Ionic Strengths ( $n = 4$ )

Ionic strength ( $\mu$ )	0.010	0.05	0.16	0.55	1.10
Buffer [H3C], M	0.001	0.01	0.01	0.10	0.20
Equilibrium pH	8.05	8.18	8.03	8.01	8.22
Intr. solub.	5.790	5.83	5.26	4.47	3.20
$S_o$ (mg/mL)					
Equilibrium pH	5.93	5.57	5.48	4.84	4.62
Equil. solubility	8.19	10.97	9.12	32.05	74.44
$S$ (mg/mL)					
$pK_a$ from solubility data	6.07	5.65	5.42	5.54	5.80
$r^2 \approx$	0.87	0.92	0.95	0.99	0.99

solubility of the unionized form (Q) is the intrinsic solubility ( $S_o$ ) and the ionization constant  $K_a$ . Then, in terms of pH and  $pK_a$ , the solubility equation is:

$$S = S_o \left( 1 + 10^{(pK_a - \text{pH})} \right) \quad (11)$$

The data suggest that quinoline is ionized in acid solutions suggesting higher solubility at lower pH values. It was found that the solubility of Q decreases with increasing ionic strength ( $\mu$ ); this also affects the ionization constant.

Using Eq. (9), a plot of pH versus the logarithm term has a slope of  $\approx -1$ , the intercept on the pH axis is the  $pK_a$  of the quinoline. The value of the  $pK_a$  determined by this method corresponds to the apparent ionization constant. The  $pK_a$  value was obtained at each ionic strength ( $\mu$ ). Table II provides the total and intrinsic solubility data and equilibrium pH and  $pK_a$  values obtained from Eq. (10).

The solubility of a compound can be influenced by the presence of other electrolytes (ions of the buffer and ions of the salt used to change the ionic strength of the solution). The solubility of quinoline in citrate-phosphate buffer was determined to be  $> 70$  mg/mL at an ionic strength ( $\mu$ ) of 1.1 and pH 4.6 (Table II). Quinoline solubility was increased by the presence of citrate-phosphate buffer compared to the solubility in water, HCl, and NaOH. The solubility data for quinoline in water, NaOH, and HCl are given in Table III.

It was noticed that there was a somewhat linear relationship between the citric acid molar concentration and quinoline solubility at pH value  $\sim 5$ . The data from Table II

may suggest the formation of a soluble quinolone-citrate-phosphate complex. The increased solubility in acidic solutions may be due to two factors: the compound is ionized, and a considerable amount is in the form of complex quinoline. On the other hand, the presence of citrate-phosphate had an impact on the quinoline's intrinsic solubility at higher pH value ( $\sim 8$ ) and ionic strengths. The intrinsic solubility decreased likely due to the suppression of ionization. At the pH around 8 or  $\geq 8$ , the  $pK_a$  for the phosphate-citrate buffer is 7.20/6.40, the efficiency decreases.

Table III shows the solubility of quinoline in acidic, basic, and water (pH of distilled water slightly acidic,  $\sim 5.81$  not 7, due to absorption of carbon dioxide from the environment). There was no buffer or ionic strength control. It is observed that on the various acidic solution concentrations, the initial pH changed substantially upon the addition of quinoline, having as a result a decrease in the solubility. On the other hand, on the basic solutions, the pH had a slight change after the addition of quinoline; this led to a slight change on the solubility of quinoline. It was noticed that at higher pH and a strong basic solution concentration the solubility of the solute is lower than that of the low buffer concentrations with similar pH; this can be due to as salting-out phenomenon.

The solubility-pH curves for quinolone are depicted in Figs. 1, 2, 3, 4, 5 using Eq. (11) after determining the  $pK_a$  and free base solubility and in acidic-basic solutions as well as in water. The overall experimental and calculated values were very similar for the various ranges of pH and  $\mu$  except for pH = 5.5 in Fig. 1. This discrepancy is attributed to the low regression coefficient at the  $\mu = 0.01$  and the very dilute buffer concentration [0.001 M] making it inefficient.

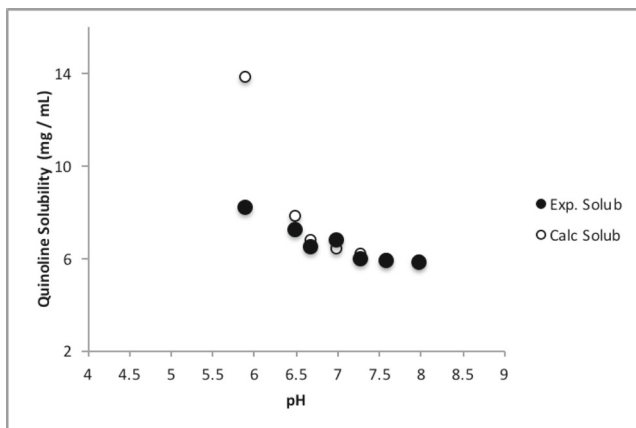
In Figs. 3, 4, and 5, the buffer concentration and high ionic strength result in reduction of the solubilization of the unionized pH ( $> 8$ ); this is attributed to salting-out effect.

### $pK_a$ and Ionic Strength

The influence of ionic strength on the observed ionization constant was noticeable in that the  $pK_a$  calculated from the solubility data was not constant as it changed with ionic strength. Thus, the  $pK_a^C$  and  $pK_a^T$  were measured by titrimetry as a function of ionic strength to confirm if the above observation was real. The  $pK_a^C$  measured was found also to be a function of ionic strength. Hence, it was confirmed that the  $pK_a$  changes with ionic strength ( $\mu$ ) as indicated by the solubility data.

**Table III.** Quinoline Solubility in Water, Hydrochloric Acid (HCl), and Sodium Hydroxide (NaOH)

Quinoline in solutions	Soln. concentration [M]	Initial pH	pH <sub>equil</sub>	Quinoline solubility (mg/mL)	Quinoline solubility [M]
HCl	1.0	0.55	4.50	61.31	0.47
	0.1	1.47	5.13	16.62	0.13
	0.01	2.28	5.70	8.42	0.07
	0.001	3.07	6.82	6.46	0.05
NaOH	1.0	13.21	12.71	4.62	0.05
	0.1	12.56	12.20	6.08	0.05
	0.01	10.65	10.32	6.28	0.05
	0.001	10.08	9.63	6.70	0.05
Water	5.81	8.32	6.31	0.05	

[H<sub>3</sub>CP] = 0.001 μ = 0.01

**Fig. 1.** pH-solubility profile of quinoline in citrate-phosphate buffer at ionic strength  $\mu = 0.01$

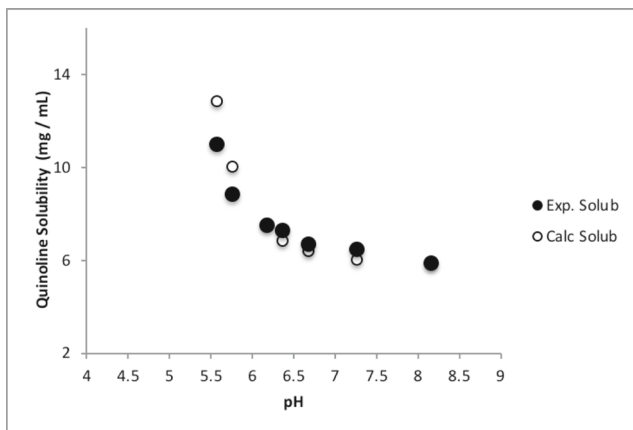
Figure 6 shows the solubility of quinoline in water and in acid and base solutions from the data in Table III. Clearly, the solubility is high (~60 mg/mL) for the strongest 1.0 M acid solution indicating a potential creation of a soluble complex, whereas with a very strong base (1.0 M), the solubility seems to be the lowest. The nitrogen in quinoline has a lone pair of electrons reacting as a Brønsted-Lowry acid (35). When those electrons of nitrogen react with a hydrogen in water, they form a hydrogen bond between the nitrogen and H leaving a hydroxide anion in the solution, producing a charged R-(NH<sup>+</sup>)-R group. This is essentially the same reaction as for the base, NH<sub>3</sub>, reacts with water to form HN<sub>4</sub><sup>+</sup> and OH<sup>-</sup> (22).

The  $pK_a$  of quinoline was determined by titration according to the method described by Albert and Serjeant (36). Three different ionic strengths were tested.

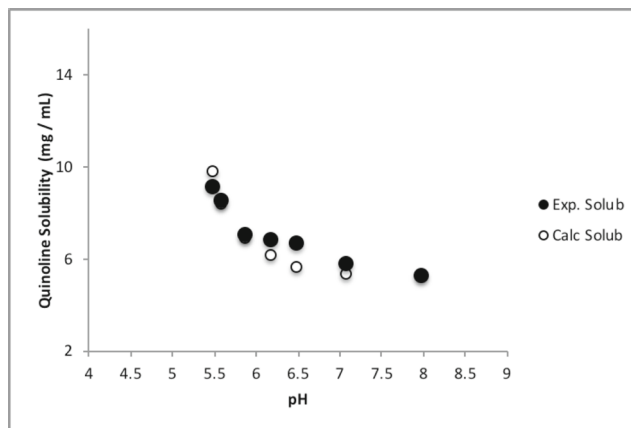
The ionization process for a base such as quinoline is:



The ionization constant,  $K_a$ , is given by the activity of ionic species {H<sup>+</sup>}, {Q}, and {QH<sup>+</sup>} in mole/liter.  $K_{aT}$  is the

[H<sub>3</sub>CP] = 0.01 μ = 0.05

**Fig. 2.** pH-solubility profile of quinoline in citrate-phosphate buffer at ionic strength  $\mu = 0.05$

[H<sub>3</sub>C] = 0.01 μ = 0.16

**Fig. 3.** pH-solubility profile of quinoline in citrate-phosphate buffer at ionic strength  $\mu = 0.16$

thermodynamic ionization constant at a given temperature. In addition, the ionization constant,  $K_{aC}$ , is defined by the concentration of each ionic species [H<sup>+</sup>], [Q], and [QH<sup>+</sup>].  $K_{aT}$  and  $K_{aC}$  are identical in an ideal system or as the solution becomes more dilute near to infinite dilution, i.e., activity coefficient,  $\gamma = 1$ .

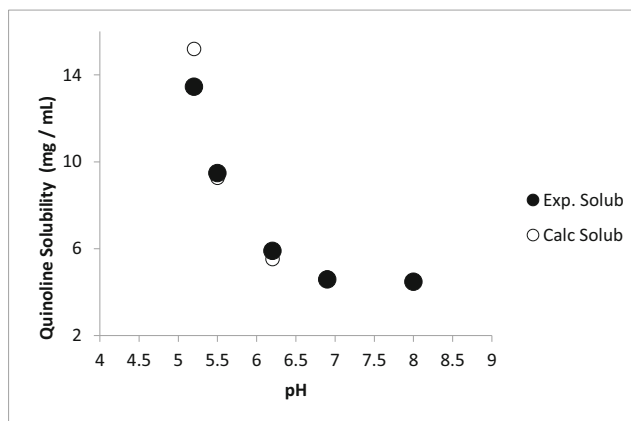
$$pK_a^C = pH + \log[QH^+]/[Q] \quad (13)$$

The ionization constant can be converted to the thermodynamic ionization constant by the equation:

$$pK_a^T = pK_a^C - \frac{0.507I^{1/2}}{1 + 1.5I^{1/2}} \quad (14)$$

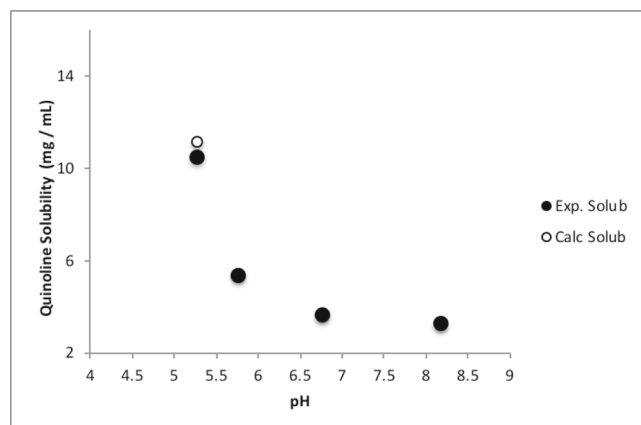
Table IV shows the  $pK_a$  values obtained by using Eqs. 13 and 14. The  $pK_a$  value of 4.90 for quinoline in water obtained by this method was in agreement with the measured via absorption spectra 4.92 by El-Ezaby *et al.* (37).

The  $pK_a$  in Table II do not agree very well with the ones determined by potentiometry as shown in Table IV, especially

[H<sub>3</sub>C] = 0.1 μ = 0.55

**Fig. 4.** pH-solubility profile of quinoline in citrate-phosphate buffer at ionic strength  $\mu = 0.55$

$[H_3C] = 0.2 \mu = 1.1$

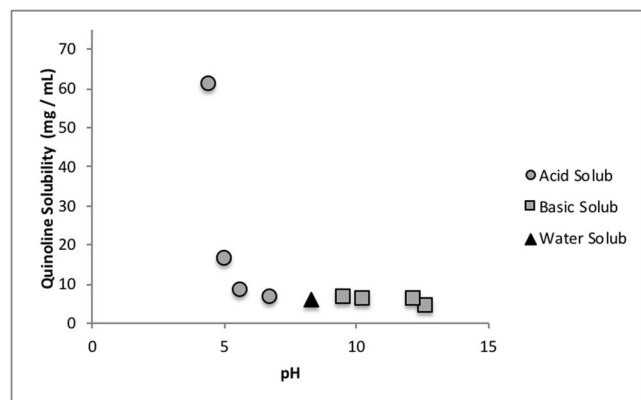


**Fig. 5.** pH-solubility profile of quinoline in citrate-phosphate buffer at ionic strength  $\mu = 1.1$

at the low ionic strength ( $\mu$ ) region. This may suggest the formation of aggregates of uncharged quinoline at low ionic strength (38) or another possibility is the salting-out effect.

The effect of pH on UV absorption has shown that the protonation of N-heterocyclic six-membered ring bases of free base species to form the conjugate acid results in a shift of the long wavelength absorption and fluorescence spectra to longer wavelengths (39). Thus, quinolines in acidic solutions have large red shifts in the absorption spectra. This may be the result of a shift in the ground state energy level due to protonation.

There are a number of important implications that result from our experimental observations and subsequent solubility analysis. Clearly, the effect of buffer concentration and ionic strength resulted in influencing quinoline's solubility compared to that of single pH acidic or basic solutions. Given the increasing trend to use quinoline scaffold as an important construction motif for the development of new drugs (28–32), more attention needs to be paid to the phenomenon of protonation (ionized) drug  $QH^+$  and neutral Q species that can be influenced by the concentration and presence of other ions or excipients in the formulation. The presence of ionized species, but non-ionized, makes possible the formation of complexes or salts which can have an impact on solubility measurements. This will probably cause false positives when



**Fig. 6.** Solubility of quinoline in acid and base aqueous solutions as well as in water

**Table IV.** Comparison of the Experimentally Determined Ionization Constant,  $pK_{aC}$ , and the Thermodynamic Ionization Constant,  $pK_{aT}$ , of 0.01 M Quinoline at 20°C

Ionic strength	$pK_{aC}$	$pK_{aT}$	Difference
Water	4.90	4.89	0.01
0.16	5.29	5.16	0.13
1.10	5.52	5.23	0.29

dissolution is being evaluated. This active migration of species and subsequent transformations to unionized and ionized species are sensitive or due to environmental conditions such as pH, buffer concentration, ionic strength, or other ions and anions present in the system. It has been well-established that there is an extent of solubility of water in non-polar solvents (5–8,40) (hydrocarbons) studying HOC partitioning in soil and water (3,4). The solubility of water in hexane is 90 ppm, whereas hexane in water is 12.4 ppm (40), indicating that the intermolecular attractions occur by London dispersion forces; this attraction releases energy resulting in poor solubility (41), and the dissolved water follows Henry's law (42). Likewise considering similar behavior of the HOCs in the environment, it is reasonable to believe that water can migrate to the lipophilic or hydrophobic phase of the emulsion (43) or LBF systems. In addition, it is well-established that the unionized small molecules interact with these systems. However, the phenomenon of water migration into the "fat or oily" phase seems possible that the ionized molecules as well such as in the quinoline-based drugs are present in the hydrophobic phase. Thus, where water is present, knowing the same facts as HOC in the environment, it is reasonable to suggest the same scenario, i.e., the ionized and unionized small molecules will be present in the lipid phase and solubilized to a certain extent. For formulation development of emulsions (43, 44) and LBF, changes on solubility in water and "fat or oily" phase should be considered, both are of particular relevance with potential implications for bioavailability and precipitation behavior of quinoline functionalized derivatives with biological and pharmacological activity such as antimalarials (Quinine and Quinidine), antiviral (Saquinavir), and anticancer (Camptothecin, Irinotecan and Topotecan) where the therapeutic agents have achieved maximum solubility and are frequently formulated or dosed with other compounds in LBFs or emulsions.

## CONCLUSIONS

Fundamental insights on the solution behavior of solids like quinoline in aqueous systems at various ranges of pH, buffer concentration, and ionic strength can help in the control, manipulation, and stabilization of this type of species whether is one or more than one solute. With the increasing trend toward the use of fixed dose combination products for cancer or other diseases where therapeutic agents are administered simultaneously not necessary co-formulated with quinoline based analogs, it is necessary to understand potential physicochemical interactions or ionizable/non-ionizable species that may influence solubility and therefore bioavailability. This is equally important to determine the

mechanisms of which the precipitation or salting-out of the species in vivo occur. These results suggested that the environmental conditions can influence the pharmaceutical development of weakly basic drugs derived from quinoline. The pH-solubility profiles under different experimental conditions should be routinely performed in formulation screening to better understand the biopharmaceutical behavior of emulsions or LBFs. The in vitro assessment of solubilization approaches of LBFs such as dispersion and digestion as well as the precipitation behavior will offer a level of certainty and control on the type of species involved in the formulation. The current study is relevant to drugs that undergo ionization in the gastrointestinal tract or in the soil-water systems. The latter remediation approaches should be necessary to avoid contamination.

## ACKNOWLEDGMENTS

The worked presented herein is the result of a M.S. thesis in the Pharmaceutical Sciences at the College of Pharmacy, University of Arizona. It has never been published but the entire thesis is available on the online repository of the university.

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