



Predict Water Solubility of Quinclorac by Henderson-Hasselbalch Equation under Different pH Solutions

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Solubility is one of the most important molecular physico-chemical parameters in herbicide research. However, the reported water solubility values of quinclorac were inconsistent. Since quinclorac is an ionizable pesticide, the water solubility of quinclorac was determined by saturation shake-flask method and the effect of pH on the solubility was observed. The results indicated that equilibrium solubility value of quinclorac in deionized water (20 °C) in the present study was 63.28 ± 1.57 mg/L, the reported solubility 62 to 72 mg/L of quinclorac in deionized water were reliable due to the error from different laboratory system, the solubility 0.065 mg/L might be in error. The equilibrium solubility increased from 3.61 to 10457.65 mg/L when the solution pH increased from 1.0 to 8.95. The Henderson-Hasselbalch equation was used to calculate the solubility in different pH buffer systems and found the Henderson-Hasselbalch equation can predict the pH-dependent solubility of quinclorac.

Keywords: Quinclorac, Solubility, pH, Henderson-Hasselbalch equation.

INTRODUCTION

Solubility is one of the most important molecular physico-chemical parameters that influence the formulation preparation, environmental behaviour, residue extraction and application of pesticide, so the information of pesticide solubility is essential in pesticide research and application. With the increase of synthetic pesticide, a large fraction of the pesticide especially herbicide is ionizable [1]. Since the water solubility are higher and depend on pH, the ionizable pesticides are frequently found in groundwater and surface waters worldwide.

Quinclorac is a substituted quinoline carboxylic acid, a class of highly selective auxin herbicides and have been used to control weed in paddy field. However, the solubility of quinclorac was found different in many papers. The solubility of quinclorac in water was reported as 62 mg/L [2,3], 0.065 mg/L [4,5], 0.065 mg/kg at pH 7 water [4], 64 mg/L [6], Solubility in water 72 mg/L at 20 °C at pH 5.5 (deionized water), 75.9 g/L at 20 °C at pH 10.3 (NaOH, 0.1Mol/L) [7], *etc.*

Why the reported solubility was different? Which one is reliable? The quinclorac is an ionizable herbicide (weak acid), with $pK_a = 4.34$ at 20 °C. The ionizable compound can exist in neutral (uncharged) or ionized (charged) form depending on the pH of the solution. They are more soluble in charged

form and their aqueous solubility is pH-dependent. When the molecule exists only in the monomer state, its pH-dependent equilibrium solubility is described by the Henderson-Hasselbalch equation [8]. For the monocratic acid, the relationship between solubility and pH is the following:

$$\log S = \log S_0 + \log (10^{-pK_a+pH} + 1)$$

where S is the equilibrium (thermodynamic) solubility at a particular pH, S_0 is the intrinsic solubility and pK_a is the negative logarithm of the ionization constant of the molecule [8].

Based on these questions, the object is to determine the water solubility of quinclorac by saturation shake-flask method at deionized water and different pH buffer solution and predict the water solubility by the Henderson-Hasselbalch equation at different pH.

EXPERIMENTAL

Quinclorac (96 % purity) was supplied by BASF Corporation. The Britton-Robinson buffer solution was used between pH 2 and 9, hydrochloric acid solutions were used at pH 1.0 in the shake-flask experiments. Britton-Robinson buffer solution (a mixture of acetic, phosphoric and boric acids, each at 0.04M) was treated with various amounts of 0.2 M NaOH to give the pH required for each shake-flask experiment. Twice-

distilled deionized water was used in the study. All other reagents were of chromatographic grade.

Determination of the equilibrium solubility by saturation shake-flask method: The sample was added to the deionized water or different pH buffer solution until a heterogeneous system (solid sample and liquid) was obtained. The solution containing solid excess of the sample was stirred for a period of 2 h by ultrasonic vibration at 30 °C allowing it to achieve thermodynamic equilibrium. After a further shaking mechanically for 24 h of equilibrium at 20 °C and 150 rpm and the saturated solution was centrifuged at 3,000 g for 10 min. About 3 mL of the supernatant was filtered through a 0.45 mm membrane filter and then injected into a high-performance liquid chromatography system to determine the quinclorac concentration. At least three parallel concentration measurements were carried out. The relative standard deviation varied from 1-6 %.

Determining quinclorac using HPLC: The chromatographic separation was performed at 30 °C using an Agilent 1260 series liquid chromatography (Palo Alto, CA, USA), with a quaternary pump, a vacuum degasser and a thermostated column compartment. For detection, HPLC was equipped with in series diode array (DAD). Separations were carried out using a ZORBAX SB-C18, 5 µm particle size column (150 mm × 4.6 mm i.d.) (Agilent Technologies, USA) preceded by an analytical guard column ZORBAX SB-C18, 5 µm (12.5 × 4.6 mm i.d.), (Agilent Technologies, USA) a mobile phase of methanol and 0.2 % acetic acid (60:40, v/v) at a flow rate of 1.0 mL/min. The quinclorac sample (10 µL) was injected into the HPLC system and recorded at 240 nm with a retention time of approximately 3.12 min.

RESULTS AND DISCUSSION

The equilibrium solubility value of quinclorac in deionized water in the present study was 63.28 ± 1.57 mg/L, which was consistent with the solubility 64 mg/L measured by EPA [6]. According to the Henderson-Hasselbalch equation [9], the ratio of anionic form/neutral form = $10^{\text{pH}-\text{pK}_a}$, the approximately calculated proportions of the neutral form of quinclorac at the pH 1 is 99.95 %. The intrinsic solubility at pH 1 was 3.61 mg/L. In the present study, the intrinsic solubility was determined only by the saturation shake-flask method, previous study indicate the intrinsic solubility determined by the saturation shake-flask method is in excellent agreement with the chasing equilibrium solubility method [10]. Due to the error from different laboratory system, the solubility of quinclorac in deionized water ranged from 62 to 72 mg/L was reasonable. However, the solubility of quinclorac in deionized water 0.065 mg/L maybe wrong because the intrinsic solubility is just 3.64 mg/L.

The effect of pH on the water equilibrium solubility was observed in the pH ranged from 1.0-8.95. The equilibrium solubility increased from 3.61 to 10457.65 mg/L when the solution pH increases from 1.0 to 8.95 (Fig. 1). Similarly, 75.9 g/L at 20 °C at pH 10.3 (NaOH, 0.1 Mol/L) was observed [7].

In order to study the validity of the Henderson-Hasselbalch equation in the case of weak acid quinclorac, the equation $\log S = \log S_0 + \log (10^{-\text{pK}_a+\text{pH}} + 1)$ was used to calculate the log S and the calculated log S and the determined log S were shown in the Fig. 2A. Both the calculated log S and the measured log S

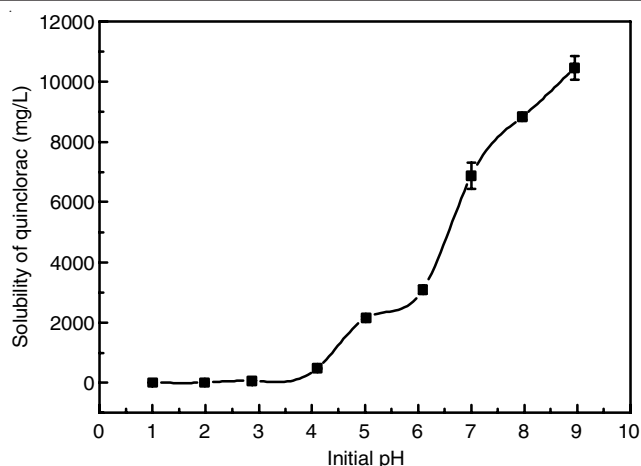


Fig. 1 Equilibrium solubility of quinclorac in different pH solution measured by the saturation shake-flask

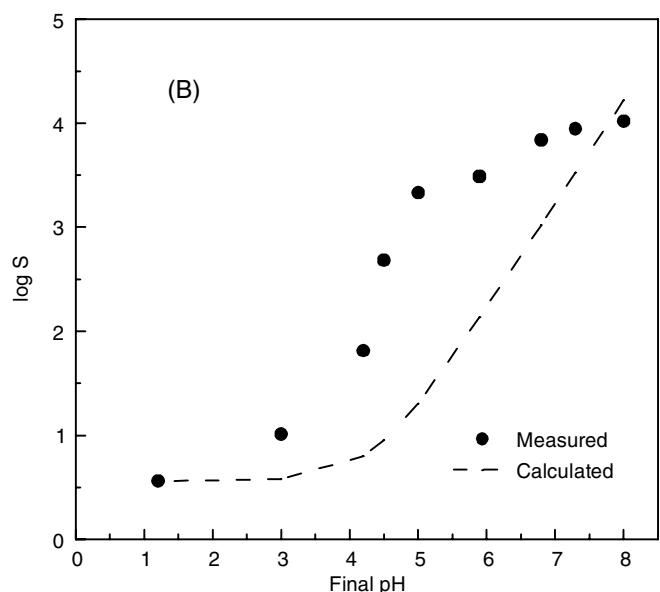
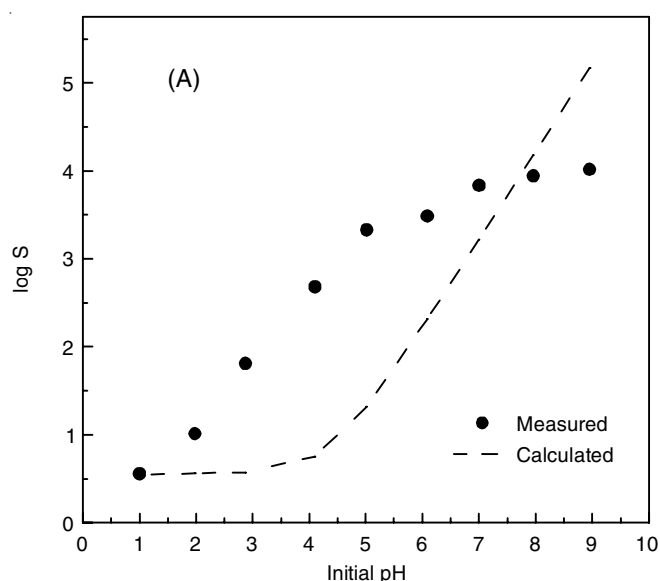


Fig. 2. pH-dependent equilibrium solubility profiles of the quinclorac investigated. The dashed line shows the theoretical estimation of the pH-dependent solubility given by the Henderson-Hasselbalch equation and points are log S values measured by shake-flask method

increased with the increased pH, but the measured log S increased quickly at the low pH and increased slowly at the high pH than the calculated log S. Bergstrom *et al.* [5] found the Henderson-Hasselbalch equation in many cases give rough estimations of the pH-dependent solubility of ionizable drugs in divalent buffer systems. That might because the solution real pH tends to the pKa of quinclorac 4.34. When pH lower than 4.34, the amended quinclorac increased buffer solution pH, when pH higher than 4.34, the amended quinclorac decreased buffer solution pH. According to the guidelines for industry the solution pH should be verified after addition of the drug substance to a buffer [11]. In the present study, the addition of quinclorac make the pH tends to pKa, when the final pH was used to calculate the log S, the Henderson-Hasselbalch equation can improve the prediction of the water solubility (Fig. 2B).

Ionizable pesticides comprise a significant and increasing proportion of the pesticide [12]. The pesticides most frequently determined in surface fresh waters and groundwater, half of which is ionizable pesticides [1]. The solubility might be predict according to the environmental pH by Henderson-Hasselbalch equation and the risk of polluting to the fresh waters or groundwater can be estimated to make sure pesticide safety to human health.

Conclusion

The reported solubility of quinclorac in deionized water is the solubility of quinclorac in deionized water ranged from 62 to 72 mg/L were reliable, the solubility 0.065 mg/L might be in error. The solubility of quinclorac sharp increases with

the increased pH, Henderson-Hasselbalch equation can give rough estimations of the pH-dependent solubility of quinclorac in buffer systems.

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