Solubility of Strong Electrolytes

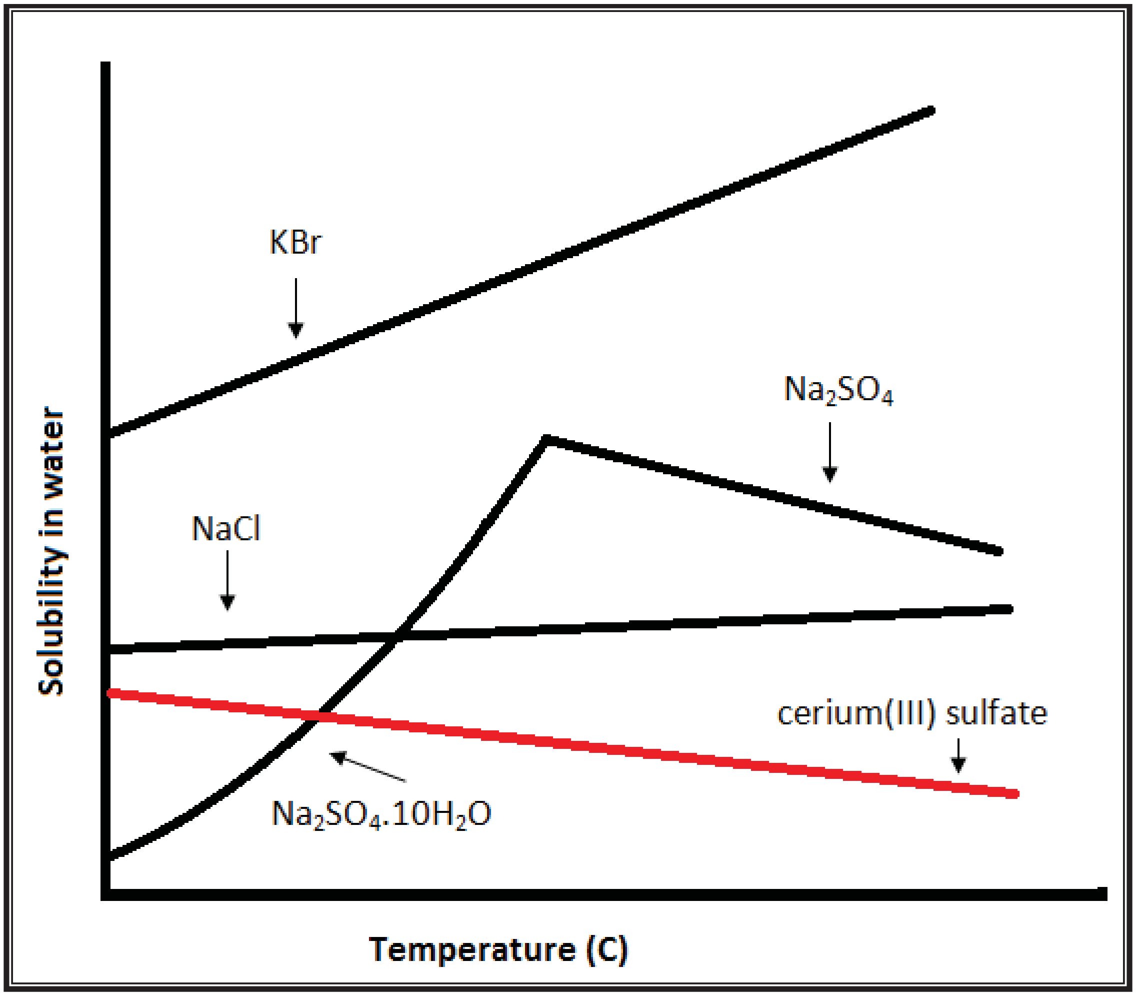
The effect of temperature on the solubility of some salts in water is shown in Figure **10-6.**

A rise in temperature increases the solubility of a solid that absorbs heat *(endothermic* process) when it dissolves. Such as KBr

Conversely, if the solution process *is exothermic*, that is, if heat is evolved, the temperature of the solution rises and the container feels warm to the touch. The solubility in this case decreases with an elevation of the temperature. such as cerium(III) sulfate

Most solids belong to the class of compounds that absorb heat when they dissolve. Sodium sulfate exists in the hydrated form. $Na_2SO_4.10H_2O$, up to a temperature of about 32°C, the solution process (dissolution) is endothermic, and solubility increase with temperature. Above this point, the compound exists as the anhydrous salt, Na_2SO_4, the dissolution is exothermic, and solubility decreases with an increase of temperature.

Sodium chloride does not absorb or evolve an appreciable amount of heat when it dissolves in water; thus, its solubility is not altered much by a change of temperature (isothermic reaction), and the heat of solution is approximately zero.


KBr
Na_2SO_4
NaCl
cerium(III) sulfate
$Na_2SO_4.10H_2O$
Solubility in water
Temperature (C)

Solubility of Weak Electrolytes

Many important drugs belong to the class of weak acids and bases.

Weak acids react with dilute alkalis to form water-soluble salts, but they can be precipitated as the free acids if stronger acidic substances are added to the solution.

For example, a 1% solution of phenobarbital sodium is soluble at pH values high in the alkaline range. The soluble ionic form is converted into molecular phenobarbital as the pH is lowered, and below 9.3, the drug begins to precipitate from solution.

Weak bases react with dilute acids (decrease the pH) to form water-soluble salts, but they can be precipitated as the free bases if stronger basic substances (increase the pH) are added to the solution.

For example, alkaloid salts such as atropine sulfate begin to precipitate as the pH is elevated.

To ensure a clear homogeneous solution and maximum therapeutic effectiveness, the preparations should be adjusted to an optimum pH.

Calculating the Solubility of Weak Electrolytes as Influenced by pH

According to the Henderson-Hasselbach equation, the relationship between pH, pKa, and relative concentrations of an acid and its salt is as follows:

$$\mathrm{pH} = \mathrm{pKa} + \log \frac{[A-]}{[HA]}$$

where $[A^-]$ is the molar concentration of the salt (dissociated species) and [HA] is the concentration of the undissociated acid. When the concentrations of salt and acid are equal, the pH of the system equals the pKa of the acid.

As the pH decreases, the concentration of the molecular acid increases and that of the salt decreases.

Changes in solubility brought about by alterations of solvent pH can be predicted by the pHp equation. The pHp is the pH below which an acid or above which a base will begin to precipitate.

$$\mathrm{pH} = \mathrm{pKa} + \log \frac{S-S0}{S0} \quad \text{(For weak acid)}$$

$$\mathrm{pH} = \mathrm{pKw} - \mathrm{pKb} + \log \frac{S0}{S-S0} \quad \text{(For weak base)}$$

where,

- S_o = the molar solubility of the undissociated acid or base
- S = the molar concentration of the salt form of the drug initially added

Example 10.16

Below what pH will free phenobarbital begin to separate from a solution having an initial concentration of 1 g of sodium phenobarbital per 100 mL at 25°C? The molar solubility, S_o, of phenobarbital is 0.0050 and the pK_a is 7.41 at 25°C. The molecular weight of sodium phenobarbital is 254.

The molar concentration of salt initially added is

(g/liter)/m.wt= 10/254= 0.039mole/liter

$\mathrm{pHp} = 7.41 + \log\frac{(0.039-0.005)}{0.005} = 8.24$

Q38. The molar solubility of sulfathiazole (weak acid) in water is 0.002, the pka=7.12, m.wt of sodium sulfathiazole = 304, what is the lowest pH allowable for complete solubility in a 5% solution of salt?

pka =7.12 S_o=0.002

M salt = $\frac{wt}{m.wt} x \frac{1000}{vol}$

= $\frac{5}{304} x \frac{1000}{100}$ = 0.164

pHp= 7.12+log$\frac{(0.164-0.002)}{0.002}$ =9.03

The Influence of Solvents on the Solubility of Drugs

Weak electrolytes can behave like strong electrolytes or like nonelectrolytes in solution.

When the solution is of such a pH that the drug is entirely in the ionic form, it behaves as a solution of a strong electrolyte--------> no problem.

However, when the pH is adjusted to a value at which un-ionized molecules are produced in sufficient concentration to exceed the solubility of this form, precipitation occurs. --------> (Problem)

To solve this problem, a solute is more soluble in a mixture of solvents than in one solvent alone. This phenomenon is known as cosolvency, and the solvents that, in combination, increase the solubility of the solute are called cosolvents.

For example phenobarbital solubility is increased when add alcohol or glycerin to water.

Combined Effect of pH and Solvents

The solvent affects the solubility of a weak electrolyte in a buffered solution in two ways:

(a) The addition of alcohol to a buffered aqueous solution of a weak electrolyte increases the solubility of the un-ionized species by adjusting the polarity of the solvent to a more favorable value.

(b) Because it is less polar than water, alcohol decreases the dissociation of a weak electrolyte, and the solubility of the drug goes down as the dissociation constant is decreased (pKa is increased).

Influence of Surfactants

Weakly acidic and basic drugs can he brought into solution by the solubilizing action of surface-active agents such as detergent.

Influence of complexation

complexation may be used to increase the solubility such as addition of potassium iodide to iodine.

Sometimes complexation cause decrease in solubility such complex between tetracycline and calcium produce insoluble complex

Influence of size and shape of particles

The size particles affect solubility. Solubility increases with decreasing particle size as consequence of increase in surface area.

The configuration of a molecule and the type of arrangement in the crystal also has some influence on solubility, and a symmetric particle can be less soluble than an unsymmetrical one.

Solubility of Slightly Soluble Electrolytes

When slightly soluble electrolytes are dissolved to form saturated solutions, the solubility is described by a special constant, known as the solubility product, Ksp , of the compound.

Silver chloride is an example of such a slightly soluble salt. The excess solid in equilibrium with the ions in saturated solution at a specific temperature is represented by the equation

$$\mathrm{AgCl}_{\text{solid}} \rightleftharpoons \mathrm{Ag}^{+} + \mathrm{Cl}^{-}$$

and because the salt dissolves only with difficulty and the ionic strength is low, the equilibrium expression can be written in terms of concentrations instead of activities:

$$\frac{[Ag+][Cl-]}{[AgCl\ solid]} = \mathrm{K}$$

Moreover, because the concentration of the solid phase is essentially constant,

$$[\mathrm{Ag}^{+}][\mathrm{Cl}^{-}] = \mathrm{Ksp}$$

As in the case of other equilibrium expressions, the concentration of each ion is raised to a power equal to the number of ions appearing in the formula. Thus, for aluminum hydroxide, $\mathrm{Al(OH)_3}$.

$$\boxed{\mathrm{Al(OH)}_{3\ \text{solid}} \rightleftharpoons \mathrm{Al}^{3+} + 3\mathrm{OH}^{-}}$$

$$[A1^{3+}][OH^{-}]^{3} = Ksp$$

EXAMPLE 10-13: The measured solubility of silver chloride in water at 20°C is 1.12×10^{-5} mole/liter. This is also the concentration of the silver ion and the chloride ion because silver chloride is nearly completely dissociated. Calculate the solubility product of this salt. We have

$$Ksp = (1.12 \times 10^{-5}) \times (1.12 \times 10^{-5}) = 1.25 \times 10^{-10}$$

If an ion in common with AgCI, that is, Ag^{+} or Cl^{-}, is added to a solution of silver chloride, the equilibrium is altered.

The addition of sodium chloride, for example, increases the concentration of chloride ions so that momentarily $[Ag^{+}][Cl^{-}] > Ksp$
and some of the AgCl precipitates from the solution (the reaction shift to left) until the equilibrium $[Ag^{+}][Cl^{-}] = Ksp$ is reestablished. Hence, the result of adding a common ion is to reduce the solubility of a slightly soluble electrolyte

Salts having no ion in common with the slightly soluble electrolyte produce an effect opposite to that of a common ion: At moderate concentration, they increase rather than decrease the solubility because they lower the activity coefficient.

Distribution of Solutes between Immiscible Solvents

If an excess of substance is added to a mixture of two immiscible liquids, it will distribute itself between the two phases so that each becomes saturated.

If the substance is added to the immiscible solvents in an amount insufficient to saturate the solutions, it will still become distributed between the two layers in a definite concentration ratio.

If C1 and C2 are the equilibrium concentrations of the substance in Solvent1 and Solvent2, respectively, the equilibrium expression becomes

$$K = \frac{C1}{C2}$$

The above equation is known as the **distribution law**

The equilibrium constant, K, is known as the distribution ratio, distribution coefficient, or partition coefficient.

The partition law states that:

- At a given temperature, the ratio of the concentrations of a solute in two immiscible solvents (solvent 1 and solvent 2) is constant when equilibrium has been reached
- This constant is known as the partition coefficient (or distribution coefficient)

Example 9-5

When boric acid is distributed between water and amyl alcohol at 25°C, the concentration in water is found to be 0.0510 mole/liter and in amyl alcohol it is found to be 0.0155 mole/liter. What is the distribution coefficient? We have

$$K=\frac{\mathbf{C}\quad \grave{}\ 6}{\text{æ}}=\frac{\qquad\qquad}{}\quad=3.29$$

No convention has been established with regard to whether the concentration in the water phase or that in the organic phase should be placed in the numerator. Therefore, the result can also be expressed as

$$K=\frac{\text{æ}}{\text{æ}\ \grave{}\ 6}=\frac{\qquad\qquad}{}\quad=0.304$$

One should always specify, which of these two ways the distribution constant is being expressed.

Importance of partition Knowledge

The principle is involved in several areas:

1- Drugs partitioning between aqueous phases and lipid biophases

2-Preservation of oil–water systems

3- Absorption and distribution of drugs throughout the body

4- Antibiotics partitioning into microorganisms

5-Solvent extraction

6-Chromatography

Partition law holds true

1-at constant temperature

2-when the solute exists in the same form in both solvents (the species are common to both phases)

Effect of Ionic Dissociation and Molecular Association on Partition

Some compounds have more than one species in oil phase and in aqueous phase which produce complicated case in calculation of partition coefficient.

Example, benzoic acid that is used as preservative present in oil phase as monomer and as dimer in equilibrium.

$$[HA]_O \overset{K_d}{\rightleftharpoons} [HA]_d$$

Benzoic acid present in aqueous phase as unionized (HA) and as ionized (A^-) in equilibrium.

$$[HA]_w \overset{K_a}{\rightleftharpoons} [A^-]_w$$

The true distribution coefficient, K is the ratio of molar concentration of the species common to both the oil and water phases

$$K = \frac{[HA]_O}{[HA]_w}$$

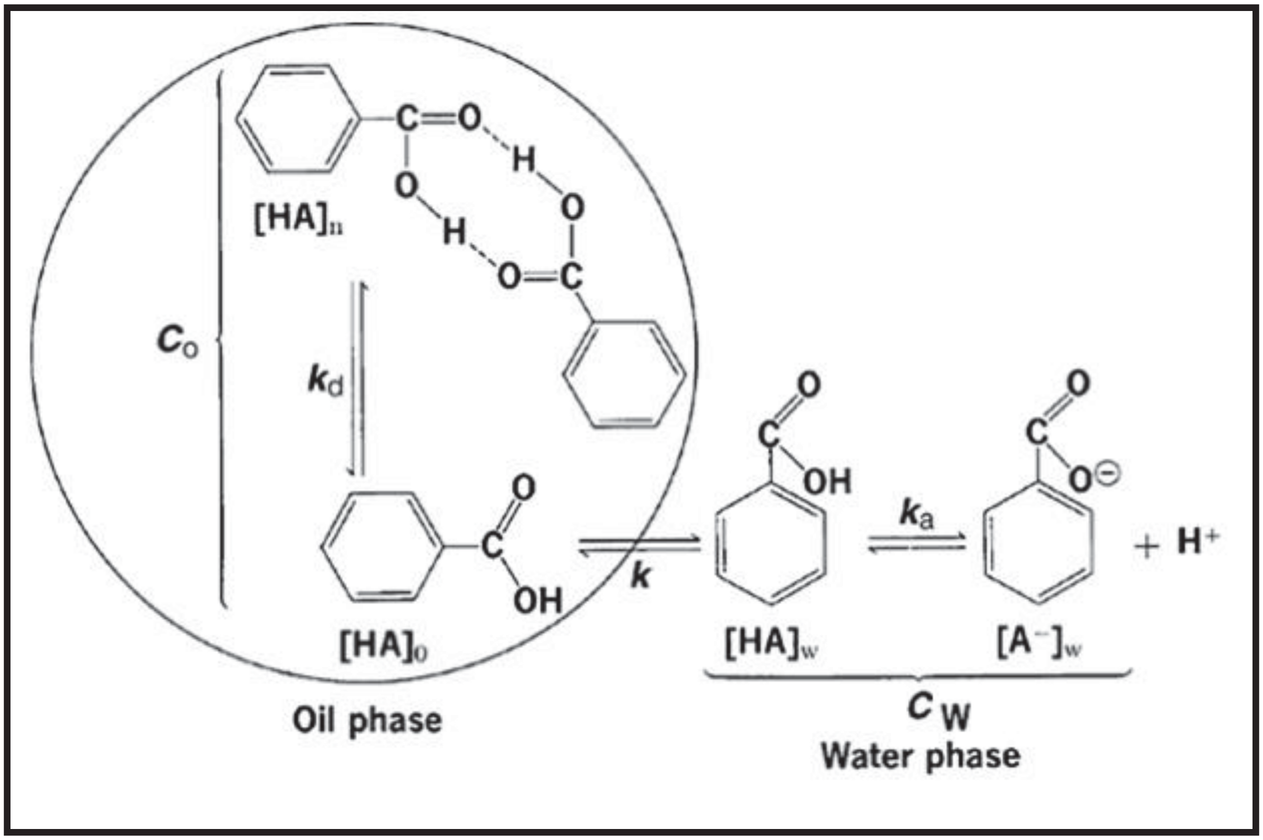
The experimentally observed or apparent distribution coefficient determined by using the total acid concentration (all species) obtained by analysis is

$$K' = \frac{[HA]_O + [HA]_d}{[HA]_w + [A^-]_w}$$

Thus the observed distribution coefficient depends on two equilibria.

In the oil phase, the concentration of monomer or dimer depends on the type of oil, for example benzoic only present as monomer in peanut oil.

In the aqueous phase, the concentration of unionized or ionized depends on the pKa of compound and pH of solvent.


$[HA]_n$
C_o
k_d
$[HA]_o$
k
k_a
$+ H^+$
$[HA]_w$
$[A^-]_w$
C_W
Oil phase
Water phase

Extraction

Liquid-liquid extraction is a useful method to separate components of a mixture.

Liquid-liquid extraction is based on the transfer of a solute substance from one liquid phase into another liquid phase according to the solubility.

The success of this method depends upon the difference in solubility of a compound in various solvents. For a given compound, solubility differences between solvents is quantified as the "distribution coefficient"

Example, suppose that you have a mixture of sugar in vegetable oil (it tastes sweet!) and you want to separate the sugar from the oil. You suspect that the sugar is partially dissolved in the vegetable oil.

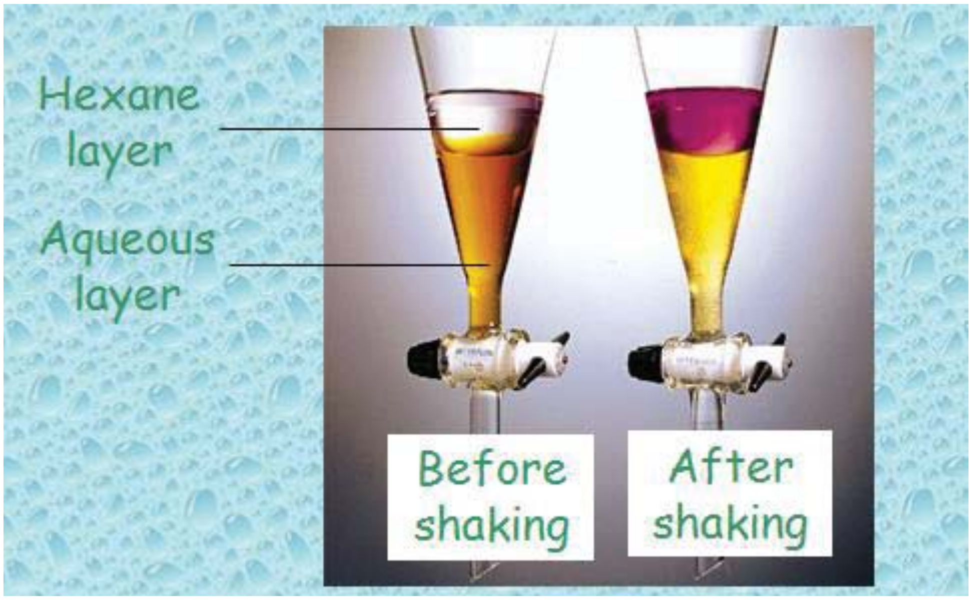
To separate the sugar from the oil we add water to the mixture with shaking.

Sugar is much more soluble in water than in vegetable oil, and water is ***immiscible*** (=not soluble) with oil.

By shaking the **sugar will move to the phase in which it is most soluble: the water layer**

At the end, the water phase tastes sweet, because the sugar is moved to the water phase upon shaking. ****You extracted sugar from the oil with water**. **

Example, Iodine can be extracted from water by adding hexane, shaking and separating the two layers in a separating funnel.



To determine the efficiency with which one solvent can extract a compound from a second solvent we use the following equations:

The distribution coefficient is

$$K=\frac{W1/V1}{(W-W1)V2}$$

By rearrangement, weight of solute extracted can be calculated using this equation:

$$\boxed{W_n = W\left(\frac{KV1}{KV1+V2}\right)^n}$$

w = weight in grams of a solute is extracted repeatedly

V_1 = volume in mL of original solvent

V_2 = volume in mL of a second solvent (extraction solvent)

w_1 = weight of the solute remaining in the original solvent after extraction

n= number of extraction repeating

Note: It can be shown from the equation that a most efficient extraction result when n is large and V_2 is small.

Example 9-7

The distribution coefficient for iodine between water and carbon tetrachloride at 25°C is $K = C_{H2O}/C_{CCl4} = 0.012$. How many grams of iodine are extracted from a solution in water containing 0.1 g in 50 mL by one extraction with 10 mL of CCl_4? How many grams are extracted by two 5-mL portions of CCl_4? We have

$$W_1 = 0.10 \text{ X } \frac{0.012 \, X \, 50}{(0.012 \, X \, 50)+10}$$

= 0.0057 g remains or 0.0943 g is extracted

$$W_2 = 0.10 \text{ X } \left(\frac{0.012 \, X \, 50}{(0.012 \, X \, 50)+5}\right)^2$$

= 0.0011 g of iodine

Thus, 0.0011 g of iodine remains in the water phase, and the two portions of CCl_4 have extracted 0.0989 g.

Preservative Action of Weak Acids in Oil-Water Systems

Solutions of foods, drugs, and cosmetics are subject to deterioration by microorganisms. Sterilization and the addition of chemical preservatives are common methods used in pharmacy to preserve drug solutions.

Benzoic acid in the form of its soluble salt, sodium benzoate, is often used for this purpose.

The preservative action of benzoic acid and similar acids is due almost entirely to the undissociated acid and not to the ionic form and this due to the relative ease with which the un-ionized molecule penetrates living membranes, and, conversely, the difficulty with which the ion does so.

The undissociated molecule, consisting of a large nonpolar portion, is soluble in the lipoidal membrane of the microorganism and penetrates rapidly.

Bacteria in oil-water systems are generally located in the aqueous phase and at the oil-water interface. Therefore, the efficacy of a weak acid, such as benzoic acid, as a preservative for these systems is largely a result of the concentration of the undissociated acid in the aqueous phase.

The distribution of total benzoic acid among the various species in this system depends upon the distribution coefficient, K, the dissociation constant, Ka, of the acid in the aqueous phase, the phase volume ratio, and the hydrogen ion concentration of the aqueous phase.

To calculate the total concentration of benzoic acid that must be added to preserve an oil-water mixture, we can use the following equations:

$$C = (Kq + 1 + Ka/[H_3O^+])[HA]_w$$

where,

C= total concentration of acid that must be added to the two-phase system to obtain a final specified concentration $[HA]_w$ of undissociated acid in the aqueous phase buffered at a definite pH or hydrogen ion concentration

K= the distribution coefficient= $[HA]_o / [HA]_w$

q = the volume ratio of the two phases, is needed when the volumes are not equal = V_o/V_w

Ka= the dissociation constant of the acid in the aqueous phase

By rearrangement the equation we can calculate the $[HA]_w$

$$[HA]_w = \frac{C}{Kq + 1 + Ka/[H3O+]}$$

EXAMPLE 10-25

If benzoic acid is distributed between equal volumes of peanut oil and water, what must be the original concentration in the water phase in order that 0.25 mg/mL of undissociated acid remains in the aqueous phase buffered at a pH of 4.0? The partition coefficient,

$K = [HA]_o/[HA]_W$, is 5.33 and the dissociation constant of the acid in water is 6.4×10^{-5}. Because the two phases are present in equal amounts, $q = V_o/V_w = 1$.

$$C = (Kq + 1 + Ka/[H_3O^+])[HA]_w$$

$C = (5.33+1+(6.4 \times 10^{-5}/10^{-4}))0.25$

= 1.74 mg/ml