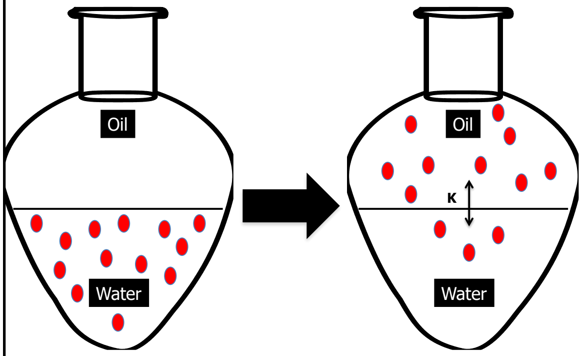
Partitioning &Distribution Phenomena



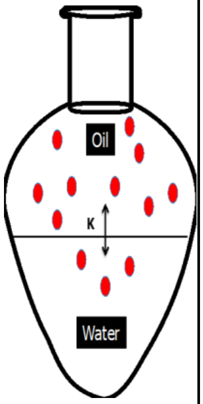
$$K_{o/w} = \frac{C_o}{C_w}$$

Partitioning &Distribution Phenomena

- Solubility is the concentration of solute in saturated solution at a certain temperature.
- A saturated solution is one in which the solute is in equilibrium with the solid phase.
- An unsaturated or subsaturated solution is one containing the dissolved solute in a concentration below that necessary for complete saturation at a definite temperature.

Distribution and Partitioning
Qualitative Description

- When two immiscible liquids are added to each other they form two separate and distinct phases.
- Systems of water and ether or amyl alcohol, octanol or peanut oil are examples of such liquid systems.
- If an excess solid or liquid is added to such a system, it will distribute itself between the two phases so that each become saturated.



Distribution and Partitioning
Qualitative Description

- If the substance is added in an amount insufficient to saturate the solutions, it will still become distributed between the two layers in a definite concentration ratio.
- The movement of a solute from one phase to another is called partitioning.

Distribution and Partitioning
Quantitative Description

- If C_1 and C_2 are the equilibrium concentration of the substance in solvent 1 and solvent 2, the equilibrium expression is:

$$\frac{C_1}{C_2} = K$$

- The above equation is known as the distribution law.
- The equilibrium constant K is known as the distribution or partitioning coefficient.
- When calculating the partitioning coefficient., It should be notified which concentration (oil or aqueous phase) in the numerator.

$K_{o/w}$ or $K_{w/o}$

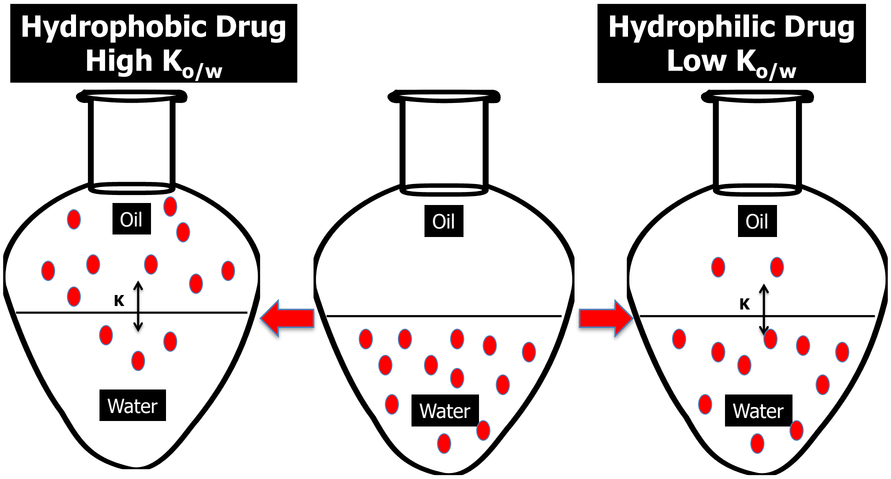
Distribution and Partitioning
Quantitative Description

- The partition or distribution law states that the solute will distribute itself between two immiscible liquids so that the ratio of its concentration in each solvent is equal to the ratio of its solubility in each one.

$$\frac{C_1}{C_2} = K \cong \frac{C_{s1}}{C_{s2}}$$

$$K_{o/w} = \frac{C_o}{C_w} \approx \frac{Solubility_o}{Solubility_w}$$

The partition coefficient is measures of how hydrophilic ("water-loving") or hydrophobic ("water-fearing") a chemical substance is



Hydrophobic Drug
High $K_{o/w}$

Hydrophilic Drug
Low $K_{o/w}$

Distribution and Partitioning

Quantitative Description

- The most commonly used method for the determination of the partitioning coefficient of a drug is the Shake-Flask method.
- A drug whose Ko/w is to be determined is traditionally added initially to the water (or sometime to the oil) phase in a to a separating funnel followed by addition of the oil phase (n-octanol) and vigorous shaking (usually 30 minutes).
- the concentration of drug in each phase is determined and Ko/w is calculated.

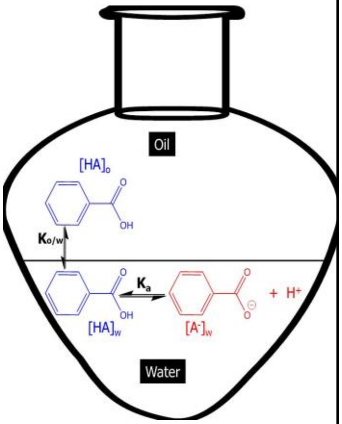
Distribution and Partitioning: Methods of determination

For Weak-electrolyte Drug

- **Shake-Flask method is used**. However, ionization may occur in the aqueous phase. Remember that partition is limited to the unionized form and that the analysis of the aqueous layer will count both ionized and un-nionized forms. For this reason, we need to suppress (prevent) the ionization in the aqueous layer by selecting a proper pH. To ensure complete **UNIONIZATION:**

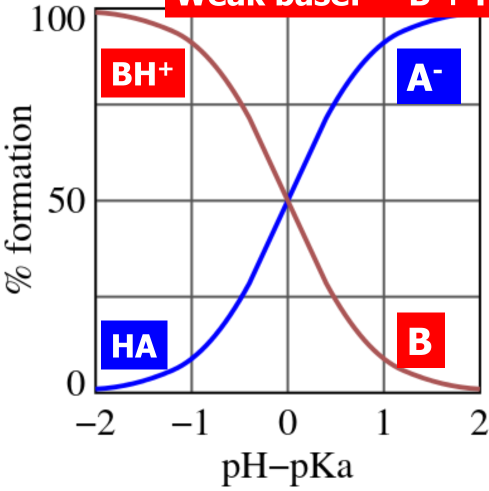
  we use pH=pKa-2 for weak acid

  and pH=pKa+2 for weak base



Weak acid: **HA ………………>A^- + H^+**

Weak base: **B + H^+………………> BH^+**



Henderson-Hasselbalch Equation

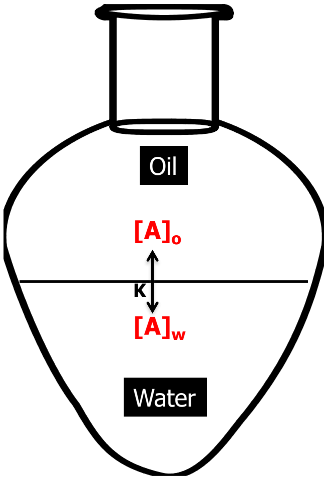
$$Generally: pK_a - pH = \log\frac{C_{unionized}}{C_{ionized}}$$

$$acids: pK_a - pH = \log\frac{[HA]_w}{[A^-]_w}$$

$$beases: pK_a - pH = \log\frac{[B]_w}{[BH^+]_w}$$

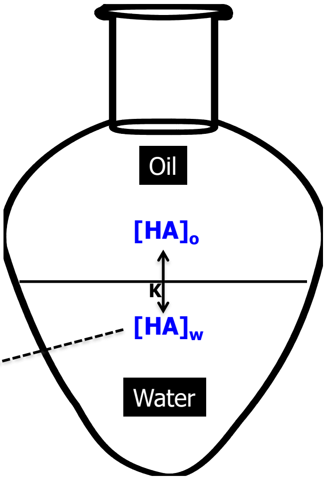
For Non-electrolyte solute

$$K_{o/w} = \frac{C_o}{C_w} = \frac{[A]_o}{[A]_w}$$



For weak electrolyte with adjusted pH to suppress the ionization (pH=pKa-2) for weak acids and (pH=pKa+2) for weak bases

$$K_{o/w} = \frac{C_o}{C_w} = \frac{[HA]_o}{[HA]_w}$$



Ionization is suppressed by low pH in the case of weak acid here

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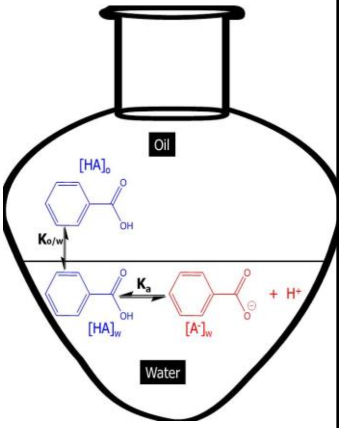
If we can not stop dissociation: We need to learn more on the effect of ionic dissociation on partitioning

- Many pharmaceutical preparations and biological compartments are buffered at physiological pH values (typically=7.4) so for weak acids or bases, ionization is expected. e.g.: 50% of phenobarbital (pK_a=7.4) will be ionized in blood!!
- Benzoic acid (pK_a=4.2) exist in two forms: an ionized (dissociated) form and an associated (unionized) form in water (upon addition of benzoic acid, pH will be slightly acidic around 5)
- In the flask to the right, only the unionized form of the benzoic acid (called the “common” specie) will partition to the oil phase in a water/peanut oil system



Partitioning of benzoic acid between water and oil

No dissociation!!

$$K_{o/w} = \frac{C_o}{C_w} = \frac{[HA]_o}{[HA]_w}$$

$K_{o/w}$ is the true distribution coefficient

Benzoic acid concentration obtained by the analysis of the aqueous phase is **total** benzoic acid concentration of **both ionized and unionized forms**

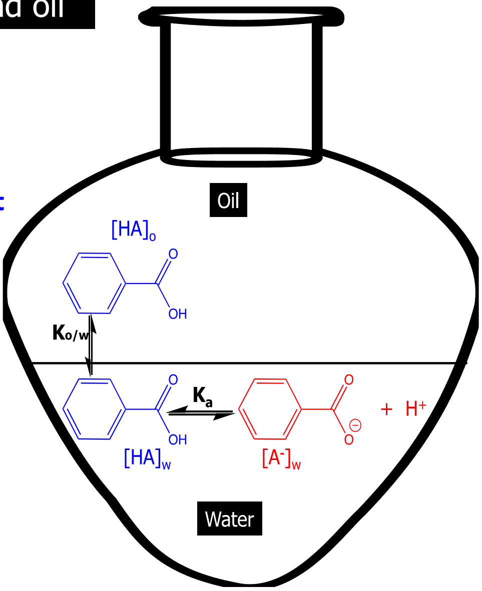
Dissociation!!

$$K'_{o/w} = \frac{C_o}{C_w} = \frac{[HA]_o}{[HA]_w + [A^-]_w}$$

$$K'_{o/w} = \frac{[HA]_o}{[HA]_w} , \frac{[HA]_w}{[HA]_w + [A^-]_w}$$

$$K'_{o/w} = K_{(true)} * F_{(unionized)}$$

$K'_{o/w}$ is the apparent or observed distribution coefficient



Experimental Aspect: Partitioning of benzoic acid between water and oil

The **true** distribution coefficient, **$K_{o/w}$**, can be obtained:

1. at a low pH (i.e. 2) at which the acid would exist completely in the un-ionized form.

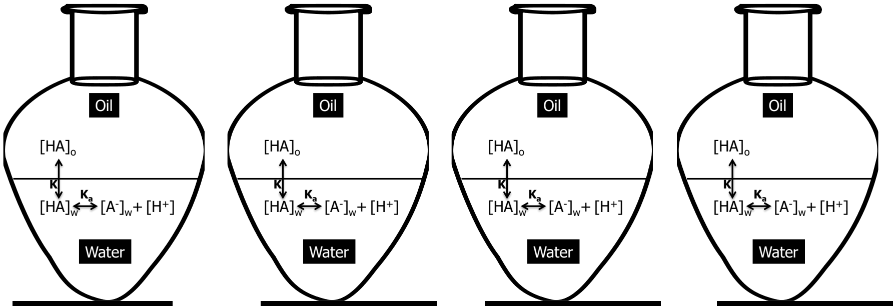
$$K_{o/w} = \frac{C_o}{C_w} = \frac{[HA]_o}{[HA]_w}$$

2. Or, alternatively, **$K_{o/w}$** can be obtained from the following equation:

$$\frac{ka + [H_3O^+]}{Cw} = \frac{ka}{C} + \frac{K_{o/w} + 1}{C}[H_3O^+]$$

$$Y = a + b X$$

- **Assumption: equal volumes of oil and water**
- C_w: Drug concentration In aqueous phase at equilibrium ($[AH]_w + [A^-]_w$)
- C: initial concentration of drug in water phase (or oil phase) before distribution.
- In this case, the oil phase need not to be analyzed: only the hydrogen ion concentration (pH) and C_w in the aqueous phase.



pH=1.2
C_w=5mg/mL

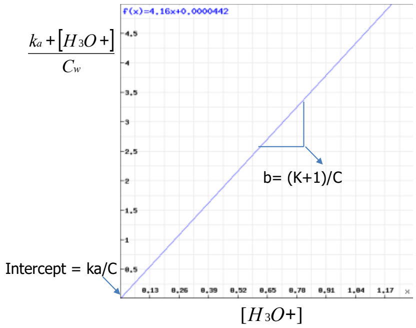
pH=4.5
C_w=6.3mg/mL

pH=5.5
C_w=7.1mg/mL

pH=7.5
C_w=8.2mg/mL

$$\boxed{\frac{k_a+[H_3O+]}{C_w}=\frac{k_a}{C}+\frac{K_{o/w}+1}{C}[H_3O+]}$$

⍰ **C_w⍰**	⍰ **pH⍰** ⍰	$[H_3O+]$	$\frac{k_a+[H_3O+]}{C_w}$



b= (K+1)/C

Intercept = ka/C

Effect of Ionic Dissociation Partitioning

Example 9-6 page 194 (Martin's Physical Pharmacy 6th ed.):

$[H_3O^+]$ *vs.* $(ka+[H_3O^+])/Cw$: linear relationship with :

Intercept (a)= 4.22 x 10^{-5}

Slope (b)= 4.16

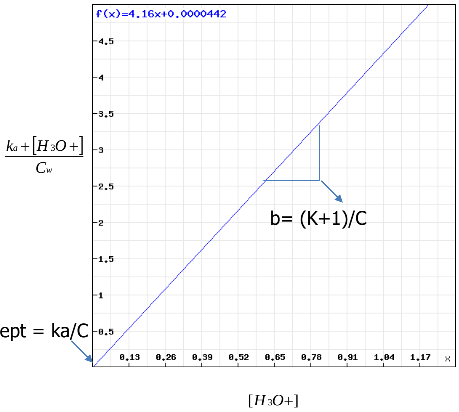
Ka= 6.4 x 10^{-5}

Find K.

$$\frac{k_a+[H_3O+]}{C_w}=\frac{k_a}{C}+\frac{K+1}{C}[H_3O+]$$

a= ka/C ………… C= 1.52

b= (K+1)/C …… **K= 5.31**



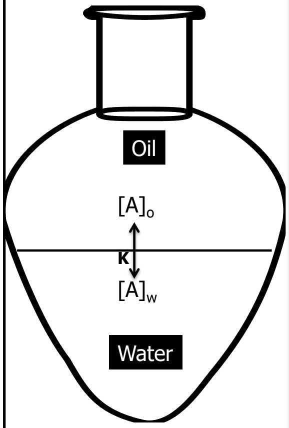
b= (K+1)/C

Intercept = ka/C

Summary

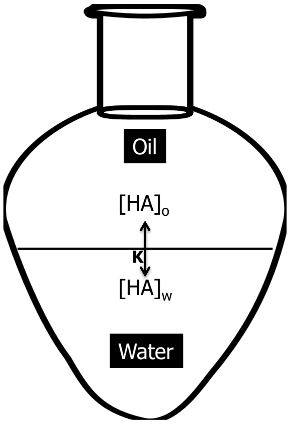
For Non-electrolyte solute

$$K_{o/w}=\frac{C_o}{C_w}=\frac{[A]_o}{[A]_w}$$



For weak electrolyte with adjusted pH to suppress the ionization (pH=pKa-2) for weak acids and (pH=pKa+2) for weak bases

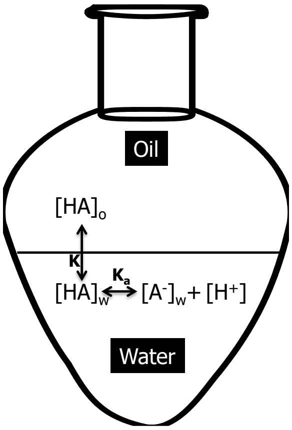
$$K_{o/w}=\frac{C_o}{C_w}=\frac{[HA]_o}{[HA]_w}$$



Weak-electrolyte solute

$$K_{o/w}=\frac{C_o}{C_w}=\frac{[HA]_o}{[HA]_w}$$

$$K'_{o/w}=\frac{C_o}{C_w}=\frac{[HA]_o}{[HA]_w+[A^-]_w}$$



Distribution and Partitioning

Pharmaceutical Relevance

- Partitioning and distribution phenomena are involved in several areas of pharmaceutical interest including preservation of oil-water systems, drug action and the absorption and distribution of drugs throughout the body.

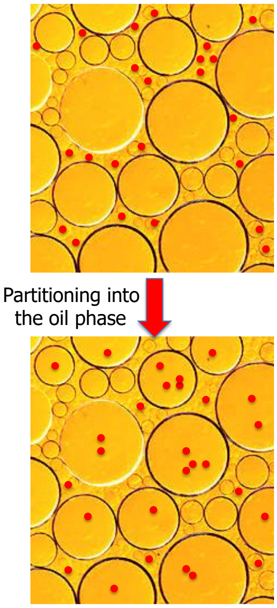
Preservative Action in Oil-Water Systems

- The addition of chemical preservatives is a common approach to preserve drug solutions, suspensions or emulsions against attack by various microorganisms.

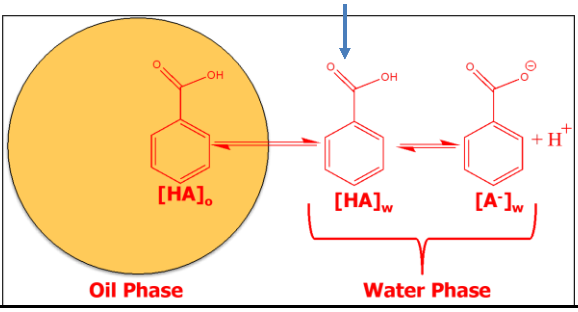
- Benzoic acid in the form of its soluble salt, sodium benzoate, is often used for this purpose.

- It was found that the preservative or bacteriostatic action of benzoic acid is due almost entirely to the undissociated acid and not to the ionic form

Pharmaceutical Relevance of Partitioning: preservation of oil-water systems (emulsions, creams,..etc)



The active form as preservative



Preservative Action in Oil-Water Systems

•The preservative action of the undissociated benzoic acid as compared with the ineffectiveness of sodium benzoate is presumably due to the relative ease with which the un-ionized molecule penetrates living membranes.

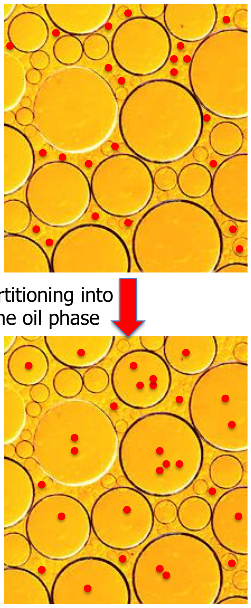
•Bacterial growth in an oil/water emulsion may be present in the aqueous phase or the oil-water interface. Therefore, the efficacy of a preservative depends on the concentration of the undissociated acid in the aqueous phase (i.e. $[HA]_W$).

Preservative Action in Oil-Water Systems

- Emulsion are usually produced by dissolving the water soluble components including preservatives in the aqueous phase and the oil soluble components in the oil phase then the two phases are mixed and dispersed.

- The preservative then distributes to the oil phase after the emulsion is formed.

Preservative Action in Oil-Water Systems



- If C is the concentration of the preservative originally in the water phase before the emulsion formation then:

$$C = (V_o/V_w)\,C_o + C_w$$

$$C = q_{o/w}\,C_o + C_w$$

- Where q is the volume ratio of the two phases and C_o and C_w are the concentrations of benzoic acid in the oil and water phase respectively.

Preservative Action in Oil-Water Systems

- Since C_o and C_w are related through the distribution coefficient as:

$$K_{o/w} = [HA]_o/[HA]_w$$

- Then

$$[HA]_o = K_{o/w}\,[HA]_w$$

Preservative Action in Oil-Water Systems

- In the water phase, the concentration of benzoic acid measured is the summation of the concentrations of the ionized and unionized species.
- So:

$$C_w = [HA]_w + [A\text{-}]_w$$

- Since $[HA]_w$ and $[A\text{-}]_w$ are related through the dissociation constant K_a as:

$$K_a = [A\text{-}]_w[H_3O^+]/ [HA]_w$$

By rearrangement

$$[A\text{-}]_w \quad = K_a\ [HA]_w/[H_3O^+]$$

Preservative Action in Oil-Water Systems

- By substituting the equation describing C as a function of C_w and C_o we get:

$$C = K_{o/w}\ q_{o/w}\ [HA]_w + [HA]_w + K_a[HA]_w/[H_3O^+]$$

- Factoring $[HA]_w$ out gives:

$$C = [HA]_w\ (K_{o/w}\ q_{o/w} + 1 + K_a/[H_3O^+])$$

- And

$$[HA]_w = C\ /\ (K_{o/w}\ q_{o/w} + 1 + K_a/[H_3O^+])$$

Preservative Action in Oil-Water Systems

Example:

- How much benzoic acid, Ka = 6.4 X10^{-5}, will remain undissociated in the aqueous phase of a 50% oil-water emulsion if the initial concentration of benzoic acid in the aqueous phase is 0.5% w/v? The aqueous phase is buffered at pH 5 and the o/w partition coefficient = 5.33. Assume that benzoic acid remains as a monomer in the oil phase.

$$[HA]_w = C / (K_{o/w}q_{o/w} + 1 + K_a/[H_3O^+])$$

Answer: 0.393 mg/ml

Calculating final concentration of preservatives $[HA]_w$ stay in water phase after partitioning as function of ($K_{0/w}$; $[H_3O^+]$; $K_{a;}$ q)

Example:

•How much benzoic acid, K_a = 6.4 X10^{-5}, will remain undissociated in the aqueous phase of a 50% oil-water emulsion if the initial concentration of benzoic acid in the aqueous phase is 0.5%? The aqueous phase is buffered at pH 5 and the o/w partition coefficient = 5.33. Assume that benzoic acid remains as a monomer in the oil phase.

Given

C= 0.5% (0.5g/100mL)

$K_{0/w}$= 5.33

$[H_3O^+]$= 10^{-5}

K_a=6.4X10^{-5}

$$[HA]_w = \frac{C}{K_{o/w}q + 1 + \frac{ka}{\left[H_3O^+\right]}}$$

$$[HA]_w = \frac{0.5}{5.33 + 1 + \frac{6.4X10^{-5}}{10^{-5}}}$$

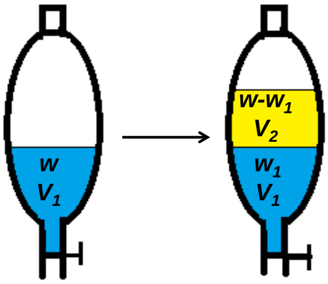
$[HA]_w$ = 0.039%= 0.039 g/100 mL

Extraction

- Extraction of a compound from a solvent is an operation commonly employed in analytical chemistry, organic chemistry and phytochemistry.
- Extraction depends on the partition and distribution properties of the extracted solute.
- K = solubility in organic solvent/solubility in water, solubility is usually in g/ml.
- K (original solvent/extracting solvent) should be <<<<1 for efficient extraction. If K = 1, we don't get a good separation.

Extraction

- Suppose that w grams of a solute are extracted repeatedly from V_1 mL of one solvent with successive portions of V_2 mL of a second solvent which is immiscible with the first solvent.



- Assume that w_1 is the weight remaining in the original solvent after extracting with the first portion of the second solvent.
- ∴ the concentration of the solute remaining in the first solvent is w_1/V_1 g/mL and the concentration of the solute in the extracting solvent is $(w - w_1)/V_2$ g/mL.

Extraction

- Thus the distribution coefficient ($K_{\text{original solvent/extracting solvent}}$) is:

$$K = \frac{w_1 / V_1}{(w - w_1)/V_2}$$

So…….

$$w_1 = w \frac{KV_1}{KV_1 + V_2}$$

- The process can be repeated for *n* times and the weight remaining after *n* repetitions is w_n:

$$w_n = w \left(\frac{KV_1}{KV_1 + V_2} \right)^n$$

Extraction

Example:

The distribution coefficient for iodine between water and CCl_4 at 25°C is $K = C_{H_2O}/C_{CCl_4} = 0.012$

- How many grams of iodine are extracted from a solution in water containing 0.1 gm in 50 ml by one extraction with 10 ml of CCl_4?
- How many grams of iodine are extracted from a solution in water containing 0.1 gm in 50 ml by one extraction with 5ml of CCl_4?
- How many grams of iodine are extracted from a solution in water containing 0.1 gm in 50 ml by two 5 ml portions of CCl_4?

Extraction

Answer:

- For a single extraction with 10 ml of CCl_4, the amount remaining in water is:

$$w_n = w\left(\frac{KV_1}{KV_1 + V_2}\right)^n$$

$$w_1 = 0.10\left(\frac{0.012 \times 50}{(0.012 \times 50) + 10}\right) = 0.0057gm$$

- And the amount extracted is 0.1-0.0057= 0.0943 gm

Extraction

Answer (cont.):

- For a single extraction with 5 ml of CCl_4, the amount remaining in water is:

$$w_n = w\left(\frac{KV_1}{KV_1 + V_2}\right)^n$$

$$w_1 = 0.10\left(\frac{0.012 \times 50}{(0.012 \times 50) + 5}\right) = 0.0107gm$$

- And the amount extracted is 0.1-0.0057= 0.0892 gm

Extraction

Answer (cont.):

- For extraction with two 5 ml portions of CCl_4, the amount remaining in water is:

$$w_n = w\left(\frac{KV_1}{KV_1 + V_2}\right)^n$$

$$w_2 = 0.10\left(\frac{0.012\times 50}{(0.012\times 50)+5}\right)^2 = 0.0011 gm$$

- And the amount extracted is 0.1- 0.0011= 0.0989 gm

Extraction

- The most efficient extraction results when *n* is large and V_2 is small (i.e. large number of extractions using small volumes of extracting solvent)

V_2(mL)	**n**	**W_1**	**Amount Extracted**
10	1	0.00566	0.094339623
5	2	0.001148	0.098852041
2	5	6.54E-05	0.099934553
1	10	5.5E-06	0.099994501
0.5	20	5.43E-07	0.099999457

Extraction

Example:

If 0.15 g of succinic acid in 100 mL ether is shaken with:

a) One (100) mL lot of water.

b) 10 successive (10) mL portions of water.

Calculate the percentage recovery in each case. $K_{o/w}$ = 0.125 at 25°C.

Answer:

a) 89%

b) 99.7%

$$w_n = w\left(\frac{KV_1}{KV_1 + V_2}\right)^n$$

Extraction

Example:

- If 0.15g of succinic acid in 100ml of ether is shaken with a 10-ml portion of water, how much succinic acid is left in the ether layer? The distribution coefficient K= (concentration in ether)/(concentration in water) = 0.125 at 25°C. How much succinic acid is left in ether when the phase is extracted with an additional 10ml of water?

Answer: 0.083g after the first extraction; 0.046g after the second extraction