Buffered and Isotonic Solutions **Chapter 9**

Buffers: - Are compounds or mixtures of compounds that, by their presence in solution, resist changes in pH upon the addition of small quantities of strong acid or base.
A combination of a weak acid and its conjugate base (i.e., its salt)
like HAC and NaAC
OR a weak base and its conjugate acid (its salt)
like (Ephedrine and ephedrine HCl) OR (NH_3 and NH_4Cl) acts as a buffer

Usually buffer solutions are prepared from combination of a weak acid and its salt

Buffer action : It is the resistance of buffer to a change in pH.
If a small amount of a strong acid or base is added to water or a solution of sodium chloride, the pH is altered considerably; such systems have no buffer action.

Buffer Capacity β: The magnitude of the resistance of a buffer to pH changes

Blood is maintained at pH 7.4 by the presence of buffer (i,e blood has high buffer capacity)

Importance
Buffers are used frequently in pharmaceutical practice when the pH must be held constant as in ophthalmic and I.V injection.

Buffer Action

Why buffer can resist changes in pH?

Example Weak acid and its salt

$CH_3COOH \leftrightarrow CH_3COO^- + H_3O^+$

قليل من الحامض الضعيف

$CH_3COONa \rightarrow CH_3COO^- + Na^+$

كثير من الملح

If strong acid (H_3O^+) is added to a buffer solution:

The solution will be protected by Acetate (CH_3COO^-)

$CH_3COO^- + H_3O^+ \leftrightarrow CH_3COOH + H_2O$

من البفر الحامض القوي

That is mean, the acetate capture the excess protons and uses them to manufacture more weak acid and thus large decrease in pH is prevented

If strong base (OH^-) is added to buffer solution:

The solution will be protected by the acid CH_3COOH

$CH_3COOH + OH^- \leftrightarrow CH_3COO^- + H_2O$

القاعدة القوية

That is mean, acetic acid converts most of excess OH^- to water and thus large increase in pH is prevented.

Buffer Equations (Henderson–Hasselbalch equation)

1- For weak acid and its salt:

$$pH = pKa + \log \frac{[salt]}{[acid]}$$

2- For weak base and its salt

$$pH = pKw - pKb + \log \frac{[base]}{[salt]}$$

Example 9-2

pH and [Salt]/[Acid] Ratio

What is the molar ratio, [Salt]/[Acid], required to prepare an acetate buffer of pH 5.0? Also express the result in mole percent of salt. Knowing that pKa of acetic acid is 4.76

$pH = pKa + \log \frac{[salt]}{[acid]}$ $5 = 4.76 + \log \frac{[salt]}{[acid]}$ $5 - 4.76 = \log \frac{[salt]}{[acid]}$ $0.24 = \log \frac{[salt]}{[acid]}$ $\frac{[salt]}{[acid]} = \frac{1.74}{1}$	Mole % of the salt= $\frac{[salt]}{[salt+acid]}$ x100 $\frac{1.74}{1.74+1}$ x100= 63.5% Mole % of the acid= $\frac{[acid]}{[salt+acid]}$ x100 $\frac{1}{1.74+1}$ x100= 36.4%

Example 9-3

What is the pH of a solution containing 0.10 mole of ephedrine and 0.01 mole of ephedrine hydrochloride per liter of solution? Since the pKb of ephedrine is 4.64

مطلوب

Example 9- 10

The pK_b of pilocarpine is 7.15 at 25°C. Compute the mole percent of free base present at 25°C and at a pH of 7.4. **مطلوب**

Buffer solutions are not ordinarily prepared from weak bases and their salts **because** of the **volatility and instability of the bases** and because of the **dependence of their pH on pKw, which is often affected by temperature changes**.

Note:-

pKw =14 at 24°C

= 13.83 at 30 °C pKw ↓ with ↑ temp.

= 14.53 at 10°C pKw ↑ with ↓ temp.

Some Factors Influencing the pH of Buffer Solutions

1- The addition of **neutral salts** to buffers changes the pH of the solution by altering the ionic strength.

2- The **addition of water** in moderate amounts, although not changing the pH, may cause a small positive or negative deviation because it alters activity coefficients and because water itself can act as a weak acid or base.

3- **Temperature** also influences buffers.

- The pH of acetate buffers was found to increase with temperature,
- whereas the pH of boric acid–sodium borate buffers decreased with temperature
- The pH of most basic buffers was found to change more markedly with temperature, owing to pKw, which appears in the equation of basic buffers and changes significantly with temperature

Buffer Capacity

The magnitude of the resistance of a buffer to pH changes is referred to as the buffer capacity, β. It is also known as buffer efficiency, buffer index, and buffer value.

Buffer capacity can be measured by three ways

1-The approximate buffer capacity

2- Exact Equation for buffer Capacity

3- Maximum buffer capacity

Calculation of Buffer Capacity

1-The approximate formula

Defined it as the ratio of the increment of strong base (or acid) to the small change in pH brought about by this addition.

$$\beta = \frac{\Delta B}{\Delta\, pH}$$

ΔB is the small increment in strong base added to the buffer solution to produce a pH change of Δ pH.

Example

Consider an acetate buffer containing 0.1 mole each of acetic acid and sodium acetate in 1 liter of solution. To this are added 0.01 mole portions of sodium hydroxide.

When the first increment of sodium hydroxide is added, the concentration of sodium acetate, the [Salt] term in the buffer equation, increases by 0.01 mole/liter and the acetic acid concentration, [Acid], decreases proportionately because each increment of base converts 0.01 mole of acetic acid into 0.01 mole of sodium acetate according to the reaction

$$\mathbf{HAC + NaOH \longleftrightarrow NaAC + H_2O}$$

0.1- 0.01 0.01 0.1+ 0.01

The changes in concentration of the salt and the acid by the addition of a base are represented in the buffer equation by using the modified form

$$pH = pKa + \log \frac{[Salt]+[Base]}{[Acid]-[Base]}$$

Table 9-1

Calculate the pH and buffer capacity of a buffer containing equimolar amounts (0.1M) of HAC and NaAC before and after addition of different amount of NaOH. Knowing that the pKa of HAC = 4.76

Moles of NaOH added	pH of the solution	Buffer capacity β
0	4.76	
0.01	4.85	0.11
0.02	4.94	0.11
0.03	5.03	0.11
0.04	5.13	0.1
0.05	5.24	0.09
0.06	5.36	0.08

Solution

Before addition : pH= pKa + log $\frac{[Salt]}{[Acid]}$

After addition : pH= pKa + log $\frac{[Salt]+[Base]}{[Acid]-[Base]}$

$\beta = \frac{\Delta B}{\Delta\, pH}$

Before addition pH = 4.76 +log $\frac{0.1}{0.1}$ pH = 4.76 that is mean pH= pKa	**Addition of 0.05M NaOH** pH = 4.76 + log $\frac{0.1+0.05}{0.1-0.05}$ pH = 4.76 + log $\frac{0.15}{0.05}$ pH = 4.76 +0.477 pH= 5.24 $\beta = \frac{0.05-0.04}{5.24-5.13} = 0.09$
Addition of 0.01M NaOH pH = 4.76 + log $\frac{0.1+0.01}{0.1-0.01}$ pH = 4.76 + log $\frac{0.11}{0.09}$ pH = 4.76 +0.087 pH= 4.85 $\beta = \frac{0.01-zero}{4.85-4.76} = 0.111$	**Addition of 0.06M NaOH** pH = 4.76 + log $\frac{0.1+0.06}{0.1-0.06}$ pH = 4.76 + log $\frac{0.16}{0.04}$ pH = 4.76 +0.6 pH= 5.36 $\beta = \frac{0.06-0.05}{5.36-5.24} = 0.08$

Conclusion

As can be seen from the Table and the example

1- The buffer has its greatest capacity before any base is added.

$\frac{[Salt]}{[Acid]} = 1$ OR pH = pKa OR $H_3O^+ = Ka$

2- The buffer capacity is not a fixed value for a given buffer system but instead depends on the amount of base added.

3- The buffer capacity changes as the ratio log([Salt]/[Acid]) increases with added base.

4- With the addition of more sodium hydroxide, the buffer capacity decreases rapidly .

5- When sufficient base has been added to convert the acid completely into sodium ions and acetate ions, the solution no longer possesses an acid reserve.

The Influence of Concentration on Buffer Capacity

The buffer capacity is affected not only by the [Salt]/[Acid] ratio but also influenced by an increase in the total concentration of the buffer constituents because, obviously, a great concentration of salt and acid provides a greater alkaline and acid reserve.

Example

If the concentration of acetic acid and sodium acetate is raised to **1 M**, what will be the pH of this solution and what will be the approximate β if 0.01M NaOH is added to this buffer? Knowing that the pKa of HAC = 4.76

Solution

Before addition	**After addition**	**Buffer capacity**
pH=pKa + $\log\frac{[salt]}{[Acid]}$ pH= 4.76 + $\log\frac{1}{1}$ pH= 4.76 pH= pKa	pH= pKa + $\log\frac{[Salt]+[Base]}{[Acid]-[Base]}$ pH= 4.76 + $\log\frac{1+0.01}{1-0.01}$ pH= 4.76 + $\log\frac{1.01}{0.99}$ pH= 4.76+ 0.0086 pH= 4.77	$\beta = \frac{\Delta B}{\Delta pH}$ $\beta = \frac{0.01-zero}{4.77-4.76}$ $\beta = \frac{0.01}{0.01}$ β = 1

Therefore, an increase in the concentration of the buffer components results in a greater buffer capacity or efficiency. i.e an increase in the total buffer concentration C = [Salt] + [Acid], obviously results in a greater value of β.

Exact Equation for Buffer Capacity

The buffer capacity calculated from the previous equation is only approximate. It gives the average buffer capacity over the increment of base added.

Koppel and Spiro and Van Slyke developed a more exact equation,

$$\beta = 2.3\ C\ \frac{Ka\ [H3O^+]}{(Ka + [H3O^+])^2}$$

where C is the total buffer concentration, that is, the sum of the molar concentrations of the acid and the salt.

Importance of this Equation :-

Permits one to compute the buffer capacity at any hydrogen ion concentration for example, at the point where no acid or base has been added to the buffer.

Example 9-6

At a hydrogen ion concentration of 1.75×10^{-5} (pH = 4.76), what is the capacity of a buffer containing 0.10 mole each of acetic acid and sodium acetate per liter of solution?

($Ka = 1.75 \times 10^{-5}$)

مطلوب

Maximum Buffer Capacity

An equation expressing the maximum buffer capacity can be derived from the buffer capacity formula of Van Slyke,equation

The maximum buffer capacity occurs where pH = pKa, or, in equivalent terms, where $[H_3O^+] = Ka$.

$$\beta = 2.3\ C\ \frac{Ka\ [H3O^+]}{(Ka + [H3O^+])^2}$$

Substituting Ka by $[H_3O^+]$ gives

$$\beta_{max} = 2.3\ C\ \frac{[H3O^+]\ [H3O^+]}{([H3O^+] + [H3O^+])^2}$$

$$\beta_{max} = 2.3C\ \frac{[H3O^+]^2}{(2\ H3O\ +]^2}$$

$$\beta_{max} = 2.3C\ \frac{[H3O^+]^2}{4[\ H3O\ +]^2}$$

$$\beta_{max} = 2.3C\ \frac{1}{4}$$

$$\boldsymbol{\beta_{max} = 0.576\ C}$$

Example

What is the maximum buffer capacity of an acetate buffer containing 0.013 M acetic acid and 0.026 sodium acetate?

Solution

$C_{Total} = C_{acid} + C_{salt}$

$= 0.013 + 0.026$

$= 0.039$ M

$\beta_{max} = 0.576\ C$

$= 0.576 \times 0.039$

$= 0.022$

Example 9-8

What is the maximum buffer capacity of an acetate buffer with a total concentration of 0.020 mole/liter? مطلوب

General Procedures for Preparing Pharmaceutical Buffer Solutions

The pharmacist may be called upon at times to prepare buffer systems for which the formulas do not appear in the literature. The following steps should be helpful in the development of a new buffer.

1- Select a weak acid having a pKa approximately equal to the pH at which the buffer is to be used. This will ensure maximum buffer capacity.

2- From the buffer equation, calculate the ratio of salt and weak acid required to obtain the desired pH.
The buffer equation is satisfactory for approximate calculations within the pH range of 4 to 10.

3- Consider the individual concentrations of the buffer salt and acid needed to obtain a suitable buffer capacity.
A concentration of 0.05 to 0.5 M is usually sufficient,
and a buffer capacity of 0.01 to 0.1 is generally adequate.

Finally, determine the pH and buffer capacity of the completed buffered solution using a reliable pH meter

Other factors of some importance in the choice of a pharmaceutical buffer include availability of chemicals, sterility of the final solution, stability of the drug and buffer on aging, cost of materials, and freedom from toxicity.

For example, a borate buffer, because of its toxic effects, certainly cannot be used to stabilize a solution to be administered orally or parenterally.

Example 1

You are asked to prepare a buffer solution of pH 4 having a buffer capacity of 0.1 and you have the following materials in your lab.

Materils	Ka of the acid	pKa of the acid
Acetic acid/Sodium acetate	1.75×10^{-5}	4.76
Lactic acid/Sodium lactate	1.39×10^{-4}	3.86
Tartaric acid/Sodium tartarate	9.60×10^{-4}	3.02

A/ Which combination do you prefer and why?

B/ What will be the total buffer concentration?

C/ What will be the concentration of each concentration?

D/ Calculate the maximum buffer capacity

Solution

The steps in the solution of the problem are as follows:

1- Choose a weak acid having a pKa close to the pH desired.

2- Calculate the ratio of salt and acid required to produce a pH of 4.

3- Use the buffer capacity equation to obtain the total buffer concentration,
C = [Salt] + [Acid]:

4- Finally calculate [Salt] & [Acid]

A/ We choose Lactic acid / Sodium lactate because its pKa≈ the required pH to get maximum buffer capacity

B/ $pH = pKa + \log \frac{[salt]}{[acid]}$

$4 = 3.86 + \log \frac{[salt]}{[acid]}$

$4 - 3.86 = \log \frac{[salt]}{[acid]}$

$0.14 = \log \frac{[salt]}{[acid]}$

$\frac{[salt]}{[acid]} = 1.38$

Therefore; [salt] = 1.38 [acid]

$\beta = 2.3\ C\ \frac{Ka\,[H3O^+]}{(Ka + [H3O^+])^2}$

$0.1 = 2.3\ C\ \frac{1.39x\ 10^{-4}\ [1x\ 10^{-4}]}{(1.39x\ 10^{-4} + [1x\ 10^{-4}])^2}$

$0.1 = 2.3\ C\ \frac{1.39\ x\ 10^{-8}}{(2.39x\ 10^{-4})^2}$

$0.1 = 2.3\ C\ \frac{1.39\ x\ 10^{-8}}{5.712\ x\ 10^{-8}}$

0.1 = 2.3 C x 0.243

0.1 = 0.559 C

C= 0.179M

C/ C= [salt] +[acid]

Since, salt = 1.38 [acid]

Therefore; C= 1.38 [acid] +[acid]

0.179 = 2.38 [acid]

[acid]= 0.075 M

So [salt]= 1.38 x 0.075

≈ 0.104M

OR

[salt]= C - [acid]

= 0.179 – 0.075

= 0.104M

D/ β_{max}= 0.576 C

= 0.576 x 0.179

= 0.103

Note

The same above example may be asked as follow

A buffer solution consisting of lactic acid and its salt was prepared with [salt]/[acid] = 1.38 and the total concentration of its constituent is 0.179 M. If you know that the pka of lactic acid is 3.86

Calculate

A/ The pH of this buffer

B/ The concentration of each constituent

C/ Maximum buffer capacity

OR it may be asked as follow

It is required to prepare a buffer solution consisting of 0.075M lactic acid and 0.104M sodium lactate If you know that the pka of lactic acid is 3.86 .Calculate

A/ The pH of this buffer

B/ Maximum buffer capacity

Example 2

It is required to prepare citric acid/sodium citrate buffer with maximum buffer capacity.

If you know that the pKa of citric acid = 3.15 ($Ka=7 \times 10^{-4}$) and the total concentration of the buffer constituents = 0.08. Answer the followings:-

A/What will be the ratio of its salt/ acid? And what will be the concentration of each?

B/ What will be the pH of this buffer?

Solution

(As mentioned in the last lecture)

A/ Since we want to prepare a buffer with maximum buffer capacity,

So the **salt/ acid** should equal to **1** and **[salt] = [acid]**

Since the total concentration is 0.08

Therefore, 0.08/ 2 = 0.04 M is the concentration of each constituent

B/ For buffer with maximum buffer capacity pH= pKa

So the pH of this buffer = 3.15

Example 9-7 (مطلوب)

You are asked to prepare a buffer solution of pH 5.00 having a buffer capacity of 0.02.You have the following materials in your lab.

Materials	Ka of the acid	pKa of the acid
Benzoic acid/Sodium benzoate	6.30×10^{-5}	4.2
Acetic acid/Sodium acetate	1.75×10^{-5}	4.76
Formic acid/Sodium formate	1.77×10^{-4}	3.75

A/ Which combination do you prefer and why?

B/ What will be the total buffer concentration?

C/ What will be the concentration of each constituent?

D/ Calculate the maximum buffer capacity

E/ What will be the pH and approximate buffer capacity if 0.01 M NaOH is added to the prepared buffer

Measurement of pH of a solution

1- The colorimetric method for the determination of pH is:-

By pH Indicators

Indicators may be considered as weak acids or weak bases that act like buffers and also exhibit color changes as their degree of dissociation varies with pH.

For example,

Methyl red shows its full **alkaline color, yellow, at a pH of about 6**
and its full **acid color**, **red, at about pH 4.**
(pH range 4.2-6.2)

Phenol red shows its full **alkaline color, red, at a pH of about 8.4**
and its full **acid color, yellow , at about pH 6.8**
(pH range 6.8- 8.4)

Phenolphthalein shows its full **alkaline color, red, at a pH of about 10**
and its full **acid color, colorless , at about pH 8.3**
(pH range 8.3-10)

Ex. If an acid - base titration experiments with pH change /range
From
pH 5 - pH 7
Both phenol red and Phenolphthalein will remain in their acidic color
The best is methyl red

pH 9 – pH 11
Both methyl red and phenol red will remain in their basic color
The best is Phenolphthalein

How Indicator work?

The dissociation of an acid indicator is given in simplified form as

$$HIn + H_2O \leftrightarrow H_3O^+ + In^-$$

Acid color Basic color

$$K\,In = \frac{[H3O^+][In^-]}{[HIn]}$$

HIn is the un-ionized form of the indicator, which gives the acid color, and In- is the ionized form, which produces the basic color. KIn is referred to as the indicator constant.

If an acid is added to a solution of the indicator

The hydrogen ion concentration term on the right-hand side of equation is increased. To keep KIn constant, the ionization is decreased due to the common ion effect. Thus the indicator is predominantly in the form of HIn, the acid color.

$$HIn + H_2O \leftrightarrow \mathbf{H_3O^+} + In^-$$

Acid color — Basic color

$\mathbf{H_3O^+}$

Added acid

So the addition of an acid leads to increase in $[H_3O^+]$ that result in increase in Kin (momentary)

To keep KIn constant the reaction should go back to the left, so we get acidic color

If base is added,

$[H_3O+]$ is reduced by reaction of the acid with the base, reaction proceeds to the right, yielding more ionized indicator In-, and the base color predominates

$$HIn + H_2O \leftrightarrow \mathbf{H_3O^+} + In^-$$

Acid color — Basic color

$$OH^- + H_3O^+ \longrightarrow H_2O$$

Added base — From indicator

The added base will react with $H3O^+$ (from indicator) results in decrease $[H3O^+]$and decrease in Kin (momentary)

To keep KIn constant , the reaction should go to the right , so we get the basic color

The advantages of the colorimetric method are:

1- Simple with low coast

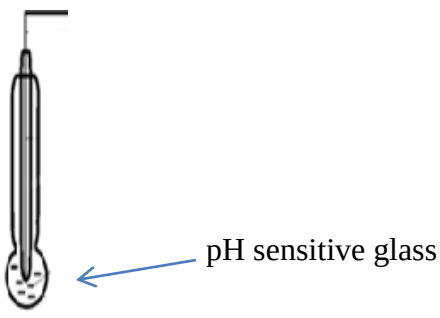
The disadvantages of the colorimetric method are:-

1- Probably less accurate and less convenient than electrometric methods

2- It can be used in the determination of the pH of aqueous solutions that are not colored or turbid.

2/ Electrometric methods

This done by using pH-meter:- which is an instrument that measure the pH of the solution by immersing the pH sensitive electrode in the solution.



Buffers in Biologic Systems

Blood is maintained at a pH of about 7.4 by :-

1- Primary buffers in the plasma

The plasma contains carbonic acid/bicarbonate and acid/alkali sodium salts of phosphoric acid as buffers. Plasma proteins, which behave as acids in blood, can combine with bases and so act as buffers.

2- Secondary buffers in the erythrocytes..

In the erythrocytes, the two buffer systems consist of hemoglobin/oxyhemoglobin and acid/alkali potassium salts of phosphoric acid

It is usually life-threatening for the pH of the blood to go below 6.9 or above 7.8. The pH of the blood in diabetic coma is as low as about 6.8.

Lacrimal fluids, or tears, have been found to have a great degree of buffer capacity, allowing a dilution of 1:15 with neutral distilled water before an alteration of pH

The pH of tears is about 7.4, with a range of 7 to 8 or slightly higher. It is generally thought that eye drops within a pH range of 4 to 10 will not harm the cornea. However, discomfort and a flow of tears will occur below pH 6.6 and above pH 9.0 noticed

Influence of Buffer Capacity and pH on Tissue Irritation

Solutions to be applied to tissues or administered parenterally are liable to cause irritation if their pH is greatly different from the normal pH of the relevant body fluid. Consequently, the pharmacist must consider this point when formulating ophthalmic solutions, parenteral products, and fluids to be applied to abraded surfaces.

The most important points that should be taken in formulation:-

1- Buffer capacity of the solution to be used and the buffer capacity of the body fluid.

2- The volume to be used in relation to the volume of body fluid with which the buffered solution will come in contact

Tissue irritation will be minimal:-

(a) The lower is the buffer capacity of the solution,

(b) The smaller is the volume used for a given concentration, and

(c) The larger are the volume and buffer capacity of the physiologic fluid.

1- For eye solutions

The pH of solutions for introduction into the eye may vary from 4.0 to 10 without marked pain or damage. This statement evidently would be true only if the buffer capacity were kept low.

For example

Sörensen's phosphate buffer produced **irritation** in the eyes of a number of individuals when used outside the narrow **pH range of 6.5 to 8**,

Whereas a **Boric acid solution of pH 5** produced **no discomfort** in the eyes of the same individuals.

This case can be explained to be due to **low buffer capacity of boric acid as compared with that of the phosphate buffer** and partly to the difference of the physiologic response to various ion species

So it is concluded that a pH range of nonirritation cannot be established absolutely but instead depends upon the buffer employed

2- Parenteral solutions for injection into the blood

They are usually not buffered, or they are buffered to a low capacity so that the buffers of the blood may readily bring them within the physiologic pH range.

If the drugs are to be injected only in small quantities and at a slow rate, their solutions can be buffered weakly to maintain approximate neutrality.

Solubility-Chapter 10 Lec.1

Advantages of studying solubility

1-It permits us to choose the best solvent for drug or combination of drugs.

2- Overcome certain difficulties that occur in the preparation of pharmaceutical solutions

3- Test of purity

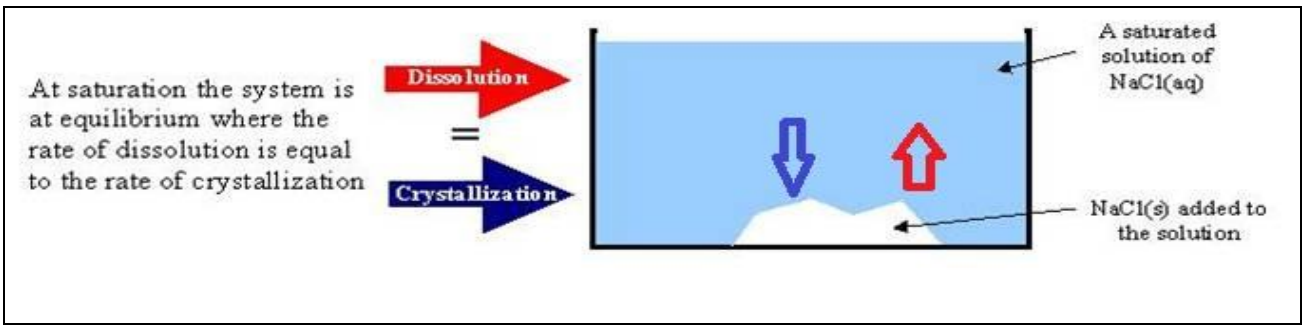
Definitions

Solubility is defined in a **qualitative way**; it can be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion , and in **quantitative terms** as the concentration of solute in a saturated solution at a certain temperature

A saturated solution is one in which the solute in solution is in equilibrium with the solid phase at certain temperature.

OR

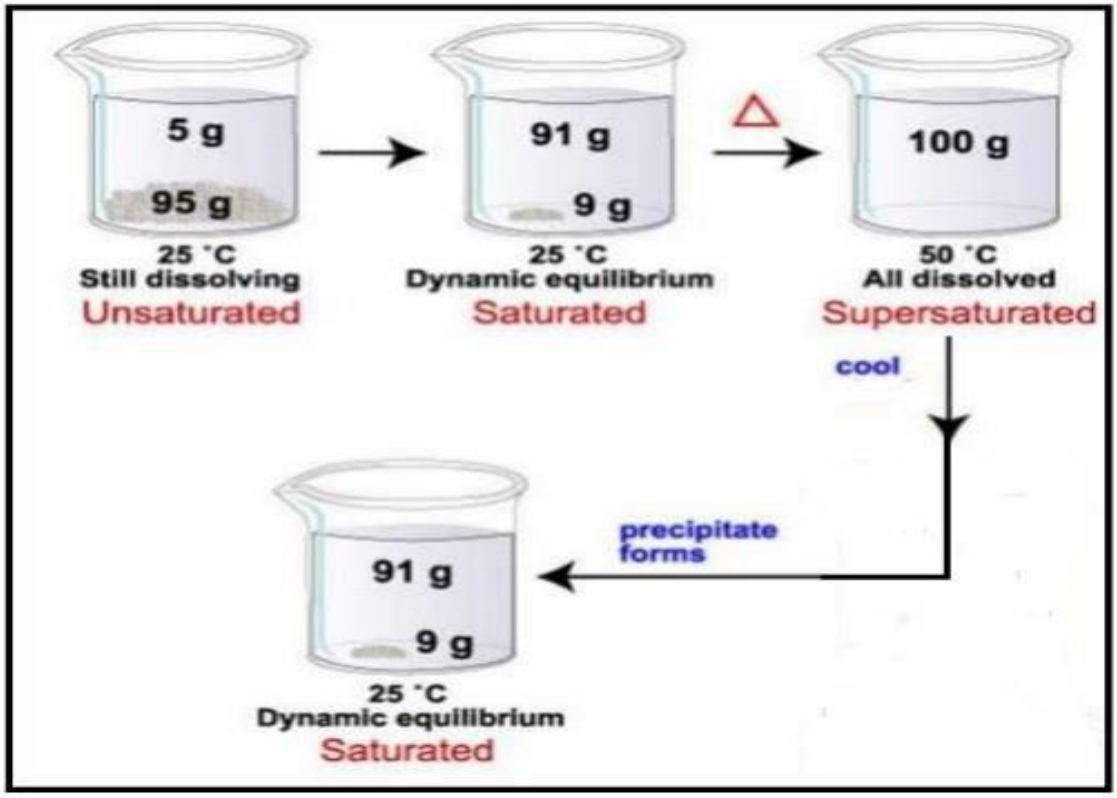
A solution that contains the maximum amount of solute that the solvent can dissolved at the given temprature. Any more solute added will sit as crystals on the bottom of the container.



An unsaturated or subsaturated solution is one containing the dissolved solute in a concentration below that necessary for complete saturation at a definite temperature

A supersaturated solution is one that contains more of the dissolved solute than it would normally contain at a definite temperature,

Supersaturated solutions are made by dissolving a solute in the solution at an elevated temperature. If we slowly cool the mixture back to 25 °C, the solute should precipitate This phenomena can be explained by the following figure:-



But there are some examples out of this rule

Ex. Sodium thiosulfate and sodium acetate can be dissolved in large amounts at an elevated temp. and upon cooling, fail to crystallize from the solution. Nothing will happen until you add a seed crystal. If you drop on some solute into the super saturated solution, it will cause the rest of the salt to come out to

Factors affecting solubility

1- Physical and chemical properties of the solute and the solvent
2- Temperature of the solution
3- Pressure above the solution (For gas in liquid solutions)
4- pH of the solution (For weak electrolytes)
5- State of subdivision of the solute

Solubility Expressions

The solubility of a drug may be expressed in a number of ways.

a) The solubility of a drug can be expressed in terms of:

- Molarity
- Normality
- Molality
- Mole fraction

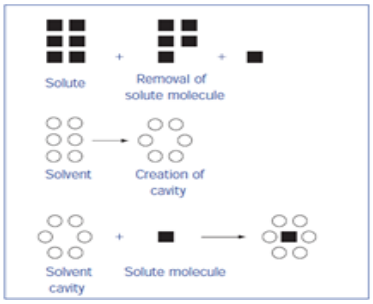
-percentage (% w/w, % w/v, % v/v)

b) The United States Pharmacopeia (USP) describes the solubility of drugs as

- Parts (mls) of solvent required for one part solute.(accurate way) or
- By the use of certain general terms The USP describes solubility using the seven groups listed in Table below.

Description Forms (Solubility Definition)	Parts of Solvent Required for One Part of Solute
Very soluble (VS)	<1
Freely soluble (FS)	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble (SPS)	From 30 to 100
Slightly soluble (SS)	From 100 to 1000
Very slightly soluble (VSS)	From 1000 to 10,000
Practically insoluble (PI)	>10,000

- Solubility is also quantitatively expressed in terms of molality, molarity, and percentage.



The process of solubility can be summerised as follow :-

1- A solute (drug molecule)is removed from its crystal
That is mean the cohesive forces between its molecules must be broken
2- A cavity for the molecule is created in the solvent.
3- The solute molecule is inserted into the cavity.
That is mean adhesive forces between solute and solvent must be formed

Solvent–Solute Interactions

In general the solubility of a solute in a solvent may be predicted by solute- solute, solvent-solvent and solute-solvent interaction

- Adhesive forces > cohesive forces $\rightarrow$ increase solubility
- Crystalline solids have low solubility. The insoluble nature is due to the stable crystalline arrangement and low intermolecular forces between solvent and solute
- $\uparrow$ melting point $\rightarrow$ $\downarrow$solubility (for solid)
- $\uparrow$boiling point $\rightarrow$ $\downarrow$miscibility (for liquid)

Solvents

The pharmacist knows that water is a good solvent for salts, sugars, and similar compounds, whereas mineral oil is often a solvent for substances that are normally only slightly soluble in water. These empirical findings are summarized in the statement, “like dissolves like.” Such a maxim is satisfying to most of us, but the inquisitive student may be troubled by this vague idea of “likeness.”

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Measurement of polarity

Polarity of the solvents can be measured by the use of **Dielectric constant €:-** which indicate the ability of solvent to separate two oppositely charged ions. The higher dielectric constant of a solvent, the easier (higher ability) to separate two oppositely charged ions

	Dielectric constant € Approximate	**Solvent**	**Solute**	
Decreasing Polarity	80	Water	Inorganic salts, organic salts	Decreasing Water Solubility
↓	50	Glycols	Sugars, tannins	↓
	30	Methyl and ethyl alcohols	Caster oil, waxes	
	20	Aldehydes, ketones, and higher alcohols, ethers, esters, and oxides	Resins, volatile oils, weak electrolytes including barbiturates, alkaloids, and phenols	
	5	Hexane, benzene, carbon tetrachloride, ethyl ether, petroleum ether	Fixed oils, fats, petrolatum, paraffin, other hydrocarbons	
	0	Mineral oil and fixed vegetable oils		

Types of solvents

Polar solvents, Semipolar solvents, Nonpolar solvents

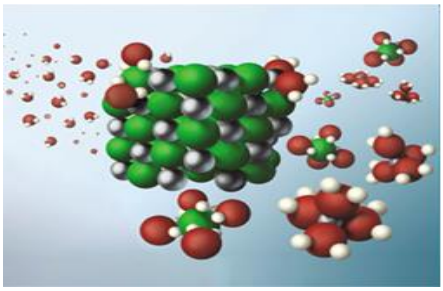
Polar Solvents

The solubility of a drug is due in large measure to the polarity of the solvent, that is, to its dipole moment.

Polar solvents as water act as a solvent for the following compounds by the following mechanisms

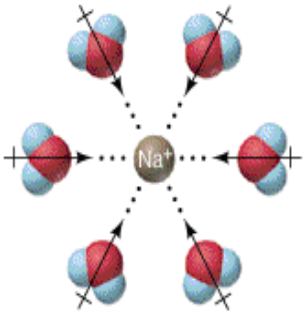
a-They dissolve ionic compounds such as sodium chloride due to their high dielectric constant.

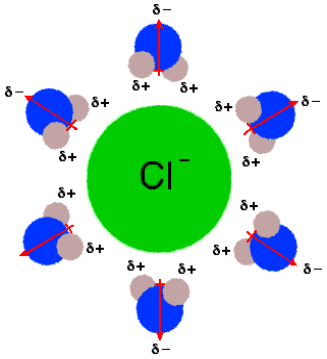
- They reduce the force of attraction between oppositely charged ions (sodium chloride)insoluble in chloroform € = 5, or benzene € = 2



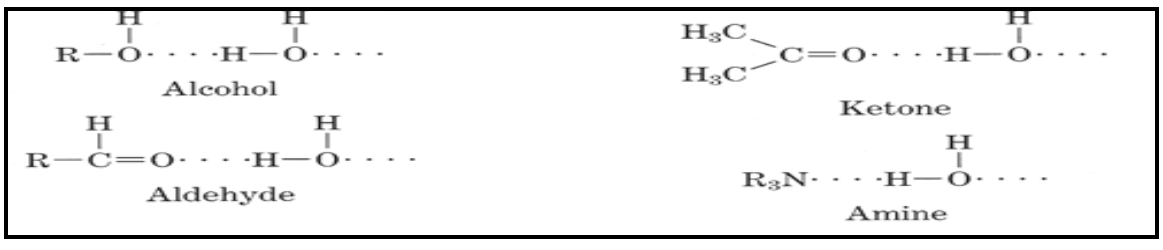
- Polar solvents are capable of solvating molecules and ions through dipole interaction forces (ion dipole)

The solute must be polar in nature since it must compete for the bonds that already associated solvent molecules





b-It dissolves alcohols, aldehydes, ketones, amines, sugars due to formation of hydrogen bonds

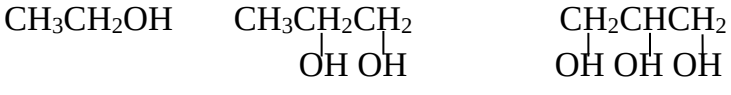


c- Polar solvents break covalent bonds of strong electrolytes by acid-base reaction since these solvents are amphoteric in nature

$HCl + H_2O \longrightarrow H_3O^+ + Cl^-$

The solubility of a substance also depends on **<u>structural features</u>** such as the ratio of the polar to the nonpolar groups of the molecule:-

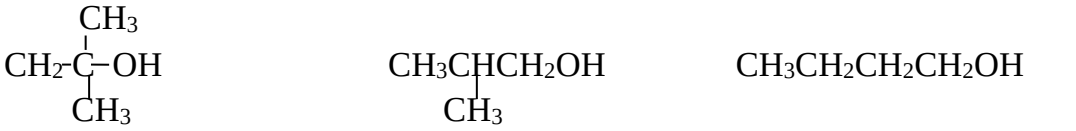
- As the length of a nonpolar chain of an aliphatic alcohol increases, the solubility of the compound in water decreases.
  Straight-chain monohydroxy alcohols, aldehydes, ketones, and acids with more than four or five carbons cannot enter into the hydrogen-bonded structure of water and hence are only slightly soluble.
- When additional polar groups are present in the molecule, as found in propylene glycol, glycerin, and tartaric acid, water solubility increases greatly.



Ethanol Glycol Glycerin

lowest solubility Highest solubility

Branching of the carbon chain reduces the nonpolar effect and leads to increased water solubility. Because branching will decrease the size or volume of the molecule and make it easier to solvate the molecule with the solvent



Highest solubility Lowest solubility

More soluble

- Solubility is affected by molecular size of particle. The solubility of the substance is decreased when molecules have higher molecular weight and high molecular size because larger molecules are more difficult to be surrounded with the solvent molecules in order to solvate substance

More soluble

Semipolar Solvents

Semipolar solvents, such as ketones and alcohols, can induce a certain degree of polarity in nonpolar solvent molecules. In fact, semipolar compounds can act as intermediate solvents to bring about miscibility of polar and nonpolar liquids. Accordingly, acetone increases the solubility of ether in water. Other examples an intermediate solvent action of alcohol on water–castor oil mixtures and the action of propylene glycol on increasing the mutual solubility of water and peppermint oil and of water and benzyl benzoate.

Nonpolar solvents:-

These solvents have the following properties:-

1- They are unable to reduce the attraction between ions of strong and weak electrolytes because of low dielectric constant
2- Cannot break the covalent bonds
3- Cannot form hydrogen bonds

Therefore non polar solvents can dissolve the nonpolar solute by weak vander Waals London forces

Solution of gas in liquid

Pharmaceutical solutions of gases include HCl solution, ammonia water and effervescent preparations containing CO_2 that dissolved and maintained in solution

Aerosol products:- in which the propellant is a gas some of which is dissolved under pressure .

Solubility of gas in a liquid

It is the concentration of the dissolved gas when it is in equilibrium with some of pure gas above the solution

Factors affecting the solubility of gas

The solubility of a gas in a liquid depends on, the partial pressure of the gas over the liquid, temperature, presence of soluble substance and probability of chemical reaction between gas and solvent

1- Pressure (pressure of a gas above the solution)

It is an important factor because the gas solubility is always limited by the equilibrium between the pure gas above the solution and a saturated solution of the gas. The dissolved gas will always follow Henry's law.

Henry's law:- which states that; in **a very dilute solution** at **constant temperature**; the concentration of the dissolved gas is proportional to the **partial pressure** of the gas above the solution at equilibrium (At equilibrium the number of molecules leaving the gas phase to enter the solution equals the number of gas molecules leaving the solution)

Henry's law:-

$C_2 \alpha P$

$C_2 = \Theta P$

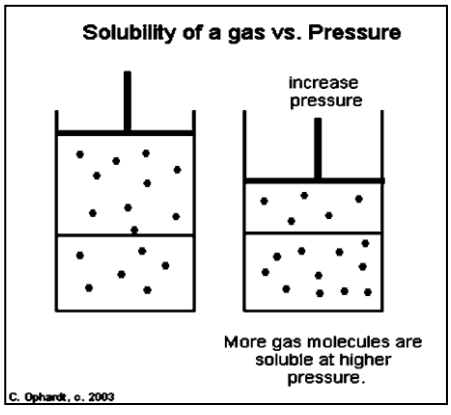
C_2 :- Concentration of the dissolved gas in g/L of solvent

Θ:- Proportionality constant (solubility coefficient)

P:- Partial pressure of gas in mmHg of the undissolved gas above the solution

The partial pressure controls the number of gas molecule collisions with the surface of the solution. If the partial pressure is doubled the number of collisions with the surface will double that is meaning **increasing the pressure will increase the amount of dissolved gas.**

Some gases escape with violence (decrease solubility) when the pressure above the solution is (decreased)



Applications

- All the carbonated beverage are bottled under pressure to increase the solubility of CO_2. When the bottle is opened the pressure above the solution decreases; as a result the solution effervesces and some CO_2 bubbles off.

- The administration of anesthetic gases. If the partial pressure of anesthetic gas is increase; the anesthetic solubility increases in blood.

Example 10-1

If 0.016 g of O_2 dissolved in 1 liter of water at a temp. of 25°C and an O_2 pressure of 300mmHg .Calculate:-

A/ The solubility coefficient (Show by calculation the units of Θ)

$C_2 = \Theta \times P$

$\Theta = C_2 / P$

$= 0.016$ g/L / 300 mmHg

$= 5.33 \times 10^{-5}$ g / L . mmHg

B/ How many grams of O_2 can be dissolved in 250 ml of aqueous solution when the total pressure above the mixture is 760 mmHg ? The partial pressure O_2 is 0.263atm.and the temp. is 25°C

$C_2 = \Theta P$

Since 1 atm = 760 mmHg

The Partial pressure of O_2 = 760 X 0.263

= 199.88 mmHg

$C_2 = 5.33 \times 10^{-5}$ g / L . mmHg X 199.88 mmHg

= 0.0107 g/L

The question ask for 250 ml (0.25L)

ممكن نسوي نسبة وتناسب

0.0107 in 1 Liter

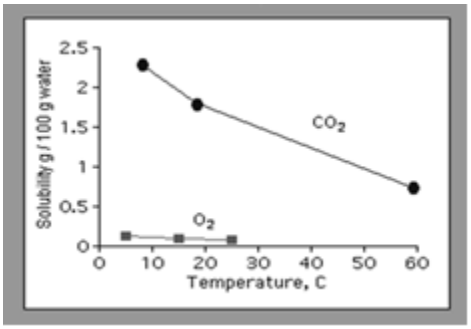
So in 0.25 L will equal to 0.0107 x 0.25 = 0.0027 g / 0.25 L

مطلوب Q3

2- Temperature

As the temperature increase the solubility of gases decrease, owing to the great tendency of the gas to expand (increase the temperature increase the kinetic energy, that causes more motion in the gas molecules which break its intermolecular bonds so it escape from solution)

Therefore, we have to avoid opening the containers of gaseous solution in warm climates and under other condition of elevated temperature and the container should be immersed in ice or cold water some times to reduce the temperature.



Applications

- Pepsi or any opened container of carbonated beverage if it is stands for a while at room temperature ;their taste is very flat since more CO_2 escape

-Boiled water is also taste flat because all of O_2 has been removed by heating.

3- Salting out

Gases liberated from solutions in which they are dissolved by introducing of an electrolyte such as NaCl or nonelectrolyte such as sucrose.

The resultant escape of gas is due to the attraction of the salt ions or the highly polar nonelectrlyte for the water molecules.

"Salting out effect can be demonstrated by adding a small amount of salt or sugar to carbonated solution"

Note:- Salting out can also occur in solution of liquid in liquid and solid in liquid

4- Chemical reaction between gas and solvent

Henry's law applies strictly to a gas that only slightly soluble in a solution and that do not react in any way in the solvent.

HCl, NH_3 and CO_2 show deviation from Henry's law as a result of chemical reaction between the gas and the solvent which results in an increase in the solubility

O_2 with low solubility obey Henry's law.

$HCl + H_2O \rightarrow H_3O^+ + Cl^-$

$NH_3 + H_2O \rightarrow NH_4^+ + OH^-$

$CO_2 + H_2O \rightarrow H_2CO_3$

$O_2 + H_2O \rightarrow$ No reaction , low solubility So it obeys Henry's law

Home work

-What are the best storage conditions for gas solution?

-Some substances are not preferred to be added to the gas solution. T or F? Explain why

- Can you open a container of HCl solution in hot condition?

Solubility of Liquids in Liquids

Frequently two or more liquids are mixed together in the preparation of pharmaceutical solutions. For example

Alcohol is added to water to form hydroalcoholic solutions of various concentrations; volatile oils are mixed with water to form dilute solutions known as aromatic waters; volatile oils are added to alcohol to yield spirits and elixirs.

Real and Ideal solution

Ideal solution

According to Raoult's law: $P=P°X$

The mixture is said to be ideal when both components of binary solution obey Raoult's law

And cohesive forces = adhesive forces (All liquids are miscible with each other)

Real solution

Negative deviation:-

Adhesive forces more than cohesive forces

A-B more than A-A $\longrightarrow$ increase solubility

The interaction of solute with the solvent is known as solvation

So the negative deviations lead to increased solubility

Positive deviation:-

Cohesive forces more than adhesive forces

A- A more than A-B $\longrightarrow$ decrease solubility

Therefore positive deviation leading to decrease solubility, which may result from high cohesive forces of the molecules of one constituent.

The attractive forces which may occur in gases, liquids or solids are called **internal pressures** ;

when the internal pressure or cohesive forces of the constituents of a mixture are quite different they will not be miscible with each other.

Polar solvents have high cohesive forces, that is mean large internal pressure, so they are solvents only for compounds of similar nature.

Non polar solvents (substances) with low internal pressure are not able to overcome the powerful cohesive forces of the polar solvents molecules.

(Like Dissolves Like)

Ex. Water will not readily mix with gasoline or benzene because the polar water molecules are hold together too strong to allow entry of non polar hydrocarbon

According to this; liquid–liquid systems can be divided into two categories according to the solubility of the substances in one another:

(a) Complete miscibility (can be mixed and give one phase system)

That is mean the adhesive forces between different molecules (A-B) >>cohesive forces between like molecules (A-A or B-B). Example Alcohol and water

(b) Partial miscibility (Two liquid layers are formed each containing some of the other liquid in the dissolved state and the miscibility affected by temperature and conc.)

In this system cohesive forces of the constituents of a mixture are quite different).

A-A » B-B Example Phenol and water

The term miscibility refers to the mutual solubility of the components in liquid-liquid systems

Influence of foreign substances on the miscibility of liquids

The addition of substance to a binary liquid system produce a ternary system (Three component system) If the added material is soluble in only one of the two components or if its solubility in the two liquids is markedly different,; the mutual solubility of the liquid pair decreased

Ex. Phenol/water system …..(partially miscible liquids)

Addition of naphthalene $\rightarrow$ decrease miscibility because it dissolves in phenol only

Addition of KCl $\rightarrow$ decrease miscibility because it dissolves in water only

$\therefore$ both naphthalene and KCl cause **salting out**

When third substance is soluble in both liquids to approximately the same extent, the solubility of the liquid pairs will increase.

Ex. Succinic acid is soluble in both phenol and water $\rightarrow$ increase the miscibility between them

Other example :- addition of acetic acid to chloroform / water system.

The increase in mutual solubility of two partially miscible solvents by another agent is ordinarily referred to as **blending.**

Solubility of solid in liquid

Ideal solutions

The solubility of a solid in an ideal solution depends on :-

1- Temperature (↑ temp. → ↑solubility)

2- Melting point (↓m.p. → ↑solubility)

(↑m.p → ↓solubility)

3- Molar heat of fusion ΔHf:- It is the heat absorbed when the solid melts.

In an ideal solution the heat of solution is equal to the heat of fusion, which is assumed to be a constant independent of the temperature.

Heat of solution: - As solid dissolves a change in physical state of the solid analogous to melting take place. As solid dissolves; it takes energy to break a part of the crystal lattice structure and separate it into ions or molecules to get the individual ions or molecules necessary to form a solution

(↑ ΔHf → ↓solubility) since high ΔHf means strong forces

4- Ideal solubility is not affected by the nature of the solvent as shown in the following equation

.

$$- \log X_2^i = \frac{\Delta Hf}{2.303\ R} \left(\frac{T0-T}{T0\ T}\right)$$

X_2^i :- ideal solubility of the solute (mole fraction)

To :- m.p of the solid solute (absolute temp.)

T :- absolute temp. of the solution

R:- gas constant = 1.987 Cal/ mole.deg

ΔHf:- molar heat of fusion

Ex. 10.7 (Relationship between X_2^i and temp.)

What is the ideal solubility of naphthalene at 10°C, 20°C,75°C and 80°Cand 90°C.If you know that its m.p=80°C and the ΔHf=4500 cal/mole?

All the temperatures in °C should be converted to °K

10 +273= 283 °K

20 +273 =293 °K

75 +273 = 348 °K

80 +273= 353°K

90 +273= 363 °K

Then we start the calculation

At 10°C

$$-\log X_2^i = \frac{\Delta Hf}{2.303\,R}\left(\frac{T0-T}{T0\,T}\right)$$

$$-\log X_2^i = \frac{4500}{2.303*1.987}\left(\frac{353-283}{353*283}\right)$$

$$-\log X_2^i = 0.689$$

$$\log X_2^i = -0.689$$

$$X_2^i = 0.2$$

At 20°C: $X_2^i = 0.27$ **At 75°C**: $X_2^i = 0.91$

At 80°C: $X_2^i = 1$ (Complete solubility)

At 90°C: $X_2^i = 1.19$ This is a calculated result , but scientifically the mole fraction should not exceed a value of 1

From the above results it can be concluded that:-

- The ideal solubility ↑with temperature
- At temp. = m.p of the substance :- $X_2^i = 1$ Maximum solubility
- At temp. above m.p, the solute is in liquid state and in an ideal solution, the liquid solute is miscible in all proportion with the solvent. Therefore , there is no need to apply the equation when the temp. of experiment above the m.p of a substance

Q12 (Relationship between m.p and X_2^i)

The m.p and ΔHf of three indomethacin polymorphs I,II and III

Indomethacin polymorh	m.p°C (K)	ΔHf cal/mol	X_2^i
I	158 (431)	9550	
II	153(426)	9700	
VII	95 (368)	2340	

Calculate the ideal mole fraction solubility at 25°C (298K) of the three polymorphs and rank the solubilities in decreasing order . Is the m.p or ΔHf is more useful in ordering the solubilities of the three polymorphs?

Before we do calculation we can suggest the order of solubility

According to the m.p (since ↑ in m.p results in ↓ in solubility) therefore, the solubility of VII > II > I

According to ΔHf (since ↑ in ΔHf results in ↓ in solubility) therefore, the solubility of VII > I > II

Therefore to know which relationship is true . **We have to do calculation** by the same simple direct application of the law

Indomethacin polymorh	m.p°C (K)	ΔHf cal/mol	X_2^i
I	158 (431)	9550	0.0069
II	153(426)	9700	0.0073
VII	95 (368)	2340	0.471

so m.p is more useful in ordering the solubility for this question

Q14. The m.p and heat of fusion for the following three sulfonamides are

Compound	m.p°C (K)	ΔHf cal/mol	X_2^i
Sulfa methoxypyridazine I	180.4 (453.55)	8110	
Sufameter II	211.6(484.75)	9792	
Sulfisomidine III	242.2 (515.35)	10781	

Try to arrange the order of solubility and then calculate the ideal solubilities of these three sulfonamide analogs at 25 °C

Answer

I	X_2^i = 0.0092
II	X_2^i = 0.0017
III	X_2^i = 0.00047

In this question both m.p and ΔHf give us the same suggested results

Non ideal solutions (real solutions)

In non-ideal solution, the electrostatic attraction or intermolecular forces between the solute and solvent should be considered (interaction=solvation)

That is mean solvation and association results in marked deviation from ideal solution

Therefore, the activity of a solute should be considered .The activity of a solute in a solution is expressed as the conc. multiplied by the activity coefficient, when the conc. is given in mole fraction. The activity is expressed as:

$a_2 = X_2 \gamma_2$ $\qquad \gamma_2 = \frac{a2}{X2}$

In which γ_2 on the mole fraction scale is known as the rational activity coefficient.

Converting to **log**

$\log a_2 = \log X_2 + \log \gamma_2$ ……**(non ideal)** …..(1)

In ideal solution:- $a_2 = X_2^{i}$, because $\gamma_2 = 1$

$- \log X_2^{i} = \frac{\Delta Hf}{2.303\ R} \left(\frac{T0-T}{T0\ T}\right)$ (ideal) .... By replacing $\mathbf{a_2}$ instead of X_2^{i} , the ideal solubility equation can be expressed in terms of activity as follow:-

$- \log a_2 = \frac{\Delta Hf}{2.303\ R} \left(\frac{T0-T}{T0\ T}\right)$ ....(2)

By combining 1 and 2 .The resultant equation for calculating the non -ideal mole fraction solubility will be

$$\mathbf{- \log X_2 = \frac{\Delta Hf}{2.303\ R} \left(\frac{T0-T}{T0\ T}\right) + \log \gamma_2}$$

Therefore the mole fraction solubility in various solvents can be expressed as the sum of two terms: The solubility of an ideal solution **and** log activity coefficient of the solute.

The log γ_2 term is obtained by considering the intermolecular forces of attraction or the work that must be done over, in removing a molecule from the solute and depositing it in the solvent.

The log γ_2 depends on the nature of both solute and solvent as well as the temperature of the solution

As real solution becomes more ideal log $\gamma_2 \approx 1$ and the solubility return to the equation of an ideal solution

Q18 The mole fraction solubility X_2 of naphthalene in different solvents at 40 °C is shown in the following table. Calculate γ_2 for naphthalene in each solvent knowing that the m.p of naphthalene is 80 °C and ΔHf=4500cal/mol

Relative to the γ_2 and X_2values. Explain your results

Solvent	**X2 at 40°C**	γ_2
Acetone	0.378	
Hexane	0.222	
Methanol	0.0412	
Acetic acid	0.117	
water	$1.76x10^{-5}$	
chlorobenzene	0.444	

$$-\log X_2 = \frac{\Delta Hf}{2.303\,R}\left(\frac{T0-T}{T0\,T}\right) + \log \gamma_2$$

T0 = 80 +273= 353°K T= 40+273=313°K

Chlorobenzene	**Water**
$-\log 0.444 = \frac{4500}{2.303*1.987}\frac{353-313}{353*313} + \log \gamma 2$	$-\log 1.76x10^{-5} = \frac{4500}{2.303*1.987}\frac{353-313}{353*313} + \log \gamma 2$
0.353 = 0.356 +log γ2 o.353 – 0.356 = log γ2 - 0.003= log γ2 0.99= γ2	4.75= 0.356+ log γ2 4.75 -0.356 = log γ2 4.398= log γ2 $25003 \approx 2.5\ x10^4 = \gamma 2$

Solvent	**X2 at 40°C**	γ_2
Acetone	0.378	1.2
Hexane	0.222	2
Methanol	0.0412	10.8
Acetic acid	0.117	3.8
water	$1.76x10^{-5}$ (lowest solubility)	$2.5x10^4$
chlorobenzene	0.444 (highest solubility)	1

There is an inverse relationship between $\gamma_2$and X_2values since
The log γ_2 term is obtained by considering the work that must be done over, in removing a molecule from the solute and depositing it in the solvent therefore as it increase, the solubility decrease

Home Work

Q13. A/ Calculate the ideal mole fraction solubility X2i of benzoic acid at 25°C. The m.p of benzoic acid is 122°C (395 K) and the ΔHf=4139cal/mol

B/ what about its solubility at 15°C, 122°C and 133°C

Q 16. The mole fraction solubility of an ideal solution of benzoic acid is 0.179 at 25°C And its melting point is 122.4°C. Calculate its heat of fusion at 25 °C

Measurement of solubility:-

The most widely used method for measurement of solubility is known as Shake Flask method.

In this method excess amount of drug is added to certain volume of the required solvent (to ensure saturation)and the mixture is shaken for 24-72 hours (water bath shaker) at the required temperature (25°C, 37°C and sometimes at 4°C)

Then filter through filter paper and the filtrate is assayed for its drug content

Solubility of salts in water (strong electrolyte)

Note:-

- Breaking of bonds require heat
- Formation of bonds release heat

Endothermic reaction:-is the reaction in which heat is absorbed**.**

This reaction occur when heat given off in the dissolving reaction is less than the heat required to break the solid

Reactants (solid solute) + temp. → Product (solution)

Therefore ↑ temp. → ↑ solubility because it provides energy to break the bonds. According to Le Chatelier's principle

KNO_3 dissolve with absorption of heat

Exothermic reaction: - is the reaction in which heat is released, the temperature of the solution rises and the container feels warm to the touch

This reaction occur when heat given off in dissolving process is greater than the heat required to break the solid

Reactants (solid solute) → Product (solution) +temp.

Therefore ↑ temp. → ↓ solubility According to Le Chatelier's princip

Ex. NaOH and cerium(III) sulfate dissolve with liberation of heat.

Isothermic reaction: - This reaction is neither endothermic nor exothermic, so any change in temp. will not affect the solubility and the heat of solution is approximately zero. Ex. Solubility of NaCl in water

Note: Most solids belong to the class of compounds that absorb heat when they dissolve.

Effect of temp. on the solubility of salts can be represented by the use of **solubility curves** which are plots of solubility against temp.

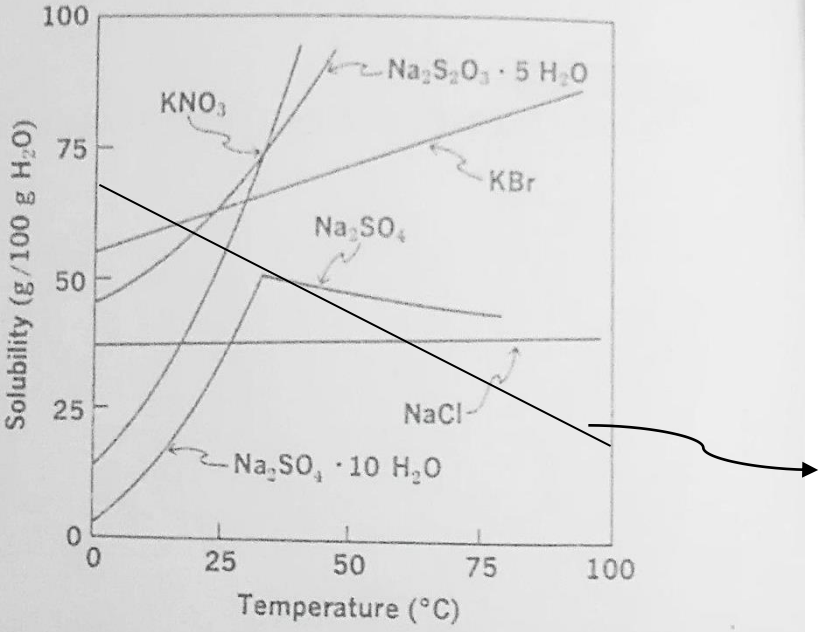


Fig. 10–6. The influence of temperature on the solubility of various salts.

Solubility curves are usually continuous as long as the chemical composition of the solid phase remains unchanged but if there is transition of the solid phase from one form to another, a break will be found in the curve Ex. $Na_2SO_4.10H_2O$ solution process (dissolution) it absorb heat (endothermic) to certain point (32°C), at which there is transition of the solid phase to anhydrous form which dissolve with release of heat (exothermic reaction)

Solubility of weak electrolyte

Factors affecting the solubility of weak acids and weak bases

1/ Effect of pH

(pH adjustment can be used for oral and parenteral administration)

For weak acids:- they are soluble in dilute solution of alkaline solution, due to the reaction which will result in formation of soluble salt, but they may be precipitate as the free acid if strong acid substance is added to the solution.

For example, to prepare 1% solution of phenobarbital sodium (salt of weak acid):-

Phenobarbital is weak acid so it 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

Therefore, if we want to prepare a clear solution of weak acidic drugs, we have to know (calculate) the pH below which the drug starts to precipitate

Examples about weak acidic drugs: phenol, phenobarbital, sulfonamides, non-steroidal anti inflammatory drugs

For weak basic drugs:- they are soluble in diluted acidic solution, due to the reaction which will result in formation of soluble salt, but they may be precipitate as the free base if strong basic substance is added to the solution.

Examples about weak basic drugs: antihistamine, narcotics

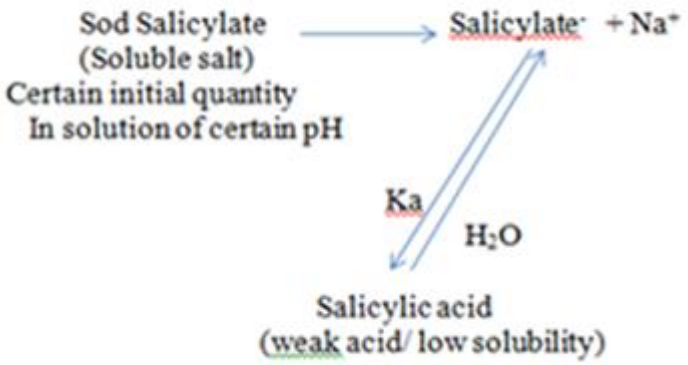
Therefore if we want to prepare a clear solution of weak basic drugs, we have to know (calculate) the pH above which the drug starts to precipitate

Calculating the solubility of weak electrolyte as influenced by pH

1-For weak acidic drugs

In pharmaceutical practice a weak acidic drug of certain pKa is usually added to an aqueous solution in the form of soluble salt. Of the initial quantity of salt that can be added to a solution of certain pH, some of it is converted into the free acid and some remains in the ionized form.

For example: If we want to prepare salicylic acid solution it is preferred to start with its salt Sod.Salicylate



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

pHp= pKa + log $\frac{salt}{acid}$

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

Therefore, changes in solubility brought about by alterations of solvent pH can be predicted by the pHp equation

pHp= pKa +log $\frac{S-S0}{S0}$

pHp : is the pH below which the acidic drug starts to ppt
S: is the molar solubility of drug (amount of drug added initially to the solution)
S0: is the molar solubility of the undissociated part of weak acid

For weak basic drugs

The same principle for weak acidic drugs is to be used to prepare a a clear homogenous solution. Therefore we have to find a relationship between pKb of drug, solubility of free base and solubility of the salt to calculate the optimum pH to get a clear homogenous solution

pHp= pKw- pKb + log$\frac{S0}{S-S0}$

pHp : is the pH above which the basic drug starts to ppt
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Q38 The molar solubility of sulfathiazole (W.A) in water is 0.002M, the pKa= 7.12 and the Mwt of sodium sulfathiazole is 304 . What is the lowest pH allowable for complete solubility in a 5% solution of the salt?

pHp= pKa +log $\frac{S-S0}{S0}$

We have to calculate the solubility of sodium sulfathiazole in molar conc.

S= M= $\frac{wt}{Mwt}\ x\ \frac{1000}{vol\ of\ solution}$

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

= 0.164

pHp= pKa +log $\frac{0.164-0.002}{0.002}$

pHp = 7.12 + log 81

pHp = 7.12+1.908

pHp = 9.03

Therefore below pH 9.03 the free acid start to ppt from the solution

Disadvantages of pH adjustment method

1- Risk of precipitation upon dilution with aqueous media having a pH at which the compound is less soluble

2- This method is useful to enhance the solubility of only weak acids or bases

Therefore pH adjustment is frequently combined with co-solvents to further increase the solubility of poorly soluble drug

Home work

Q40. Calculate pHp for a 0.5% solution of cocaine hydrochloride. The molecular weight of the salt is 339.8and the molar solubility of the base is 5.6 $x10^{-3}$ and the pKb of cocaine is 5.59

Measurement of solubility:-

The most widely used method for measurement of solubility is known as Shake Flask method.

In this method excess amount of drug is added to certain volume of the required solvent (to ensure saturation)and the mixture is shaken for 24-72 hours (water bath shaker) at the required temperature (25°C, 37°C and sometimes at 4°C)

Then filter through filter paper and the filtrate is assayed for its drug content

Solubility of salts in water (strong electrolyte)

Note:-

- Breaking of bonds require heat
- Formation of bonds release heat

Endothermic reaction:-is the reaction in which heat is absorbed**.**

This reaction occur when heat given off in the dissolving reaction is less than the heat required to break the solid

Reactants (solid solute) + temp. → Product (solution)

Therefore ↑ temp. → ↑ solubility because it provides energy to break the bonds. According to Le Chatelier's principle

KNO_3 dissolve with absorption of heat

Exothermic reaction: - is the reaction in which heat is released, the temperature of the solution rises and the container feels warm to the touch

This reaction occur when heat given off in dissolving process is greater than the heat required to break the solid

Reactants (solid solute) → Product (solution) +temp.

Therefore ↑ temp. → ↓ solubility According to Le Chatelier's princip

Ex. NaOH and cerium(III) sulfate dissolve with liberation of heat.

Isothermic reaction: - This reaction is neither endothermic nor exothermic, so any change in temp. will not affect the solubility and the heat of solution is approximately zero. Ex. Solubility of NaCl in water

Note: Most solids belong to the class of compounds that absorb heat when they dissolve.

Effect of temp. on the solubility of salts can be represented by the use of **solubility curves** which are plots of solubility against temp.

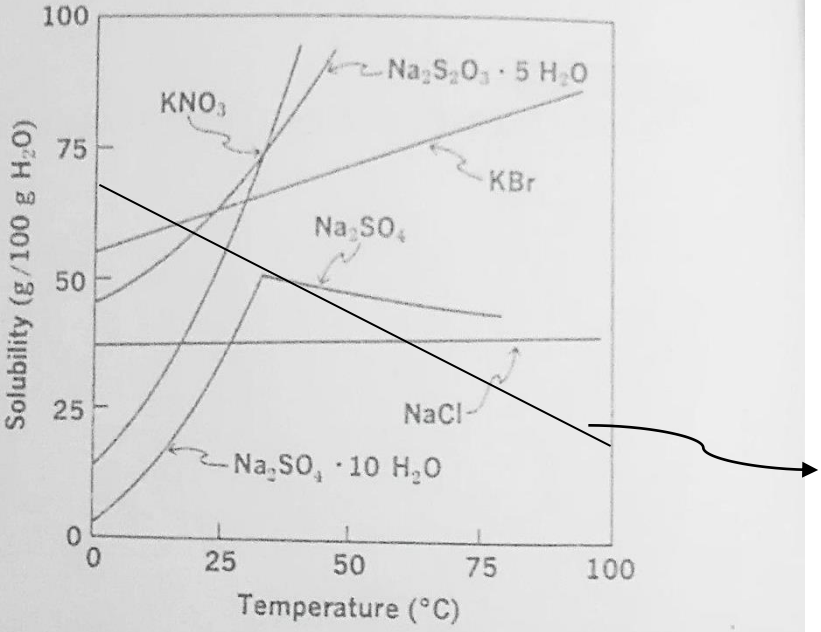

Fig. 10–6. The influence of temperature on the solubility of various salts.

Solubility curves are usually continuous as long as the chemical composition of the solid phase remains unchanged but if there is transition of the solid phase from one form to another, a break will be found in the curve Ex. $Na_2SO_4.10H_2O$ solution process (dissolution) it absorb heat (endothermic) to certain point (32°C), at which there is transition of the solid phase to anhydrous form which dissolve with release of heat (exothermic reaction)

Solubility of weak electrolyte

Factors affecting the solubility of weak acids and weak bases

1/ Effect of pH

(pH adjustment can be used for oral and parenteral administration)

For weak acids:- they are soluble in dilute solution of alkaline solution, due to the reaction which will result in formation of soluble salt, but they may be precipitate as the free acid if strong acid substance is added to the solution.

For example, to prepare 1% solution of phenobarbital sodium (salt of weak acid):-

Phenobarbital is weak acid so it 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

Therefore, if we want to prepare a clear solution of weak acidic drugs, we have to know (calculate) the pH below which the drug starts to precipitate

Examples about weak acidic drugs: phenol, phenobarbital, sulfonamides, non-steroidal anti inflammatory drugs

For weak basic drugs:- they are soluble in diluted acidic solution, due to the reaction which will result in formation of soluble salt, but they may be precipitate as the free base if strong basic substance is added to the solution.

Examples about weak basic drugs: antihistamine, narcotics

Therefore if we want to prepare a clear solution of weak basic drugs, we have to know (calculate) the pH above which the drug starts to precipitate

Calculating the solubility of weak electrolyte as influenced by pH

1-For weak acidic drugs

In pharmaceutical practice a weak acidic drug of certain pKa is usually added to an aqueous solution in the form of soluble salt. Of the initial quantity of salt that can be added to a solution of certain pH, some of it is converted into the free acid and some remains in the ionized form.

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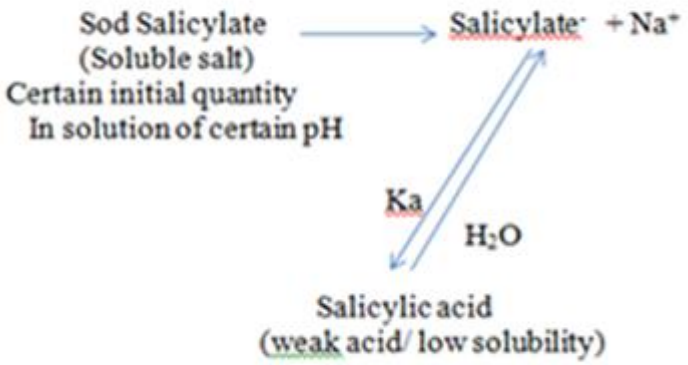

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Solubility of weak electrolyte

The Influence of solvents on the solubility of weak electrolyte

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 the 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.

Co- solvents are mixtures of water and one or more water miscible solvents. It is the most widely used technique because it is simple procedure and can be applied to many types of drug categories. Co-solvency method can enhance the solubility of the poorly soluble drugs by adjusting the polarity of the solution

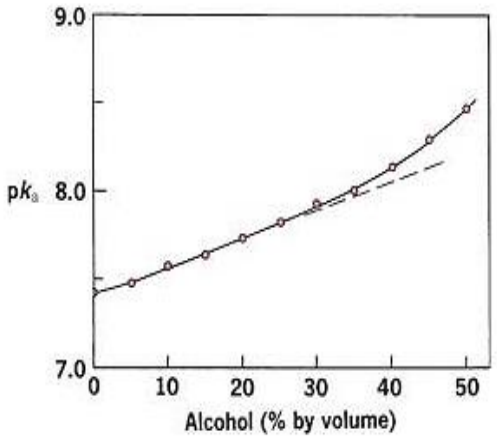
Examples of the most widely used co- solvents are alcohol, propylene glycol and glycerin

Combined effect of pH and solvent

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. (increase S0)

(b) Because it is less polar than water, alcohol decreases the dissociation of a weak electrolyte (decrease Ka and, pKa is increased).



(For weak basic drug , the co- solvent increase S0, decrease Kb And increae pKb)
For the same reasons as that of weak acidic drug

Example (16 and 17)

What is the minimum pH required for the complete solubility of the drug in a stock solution containing 6 g. sodium phenobarbital in 100ml. of 30% alcohol solution? if you know that pka=7.92, S0=0.082. Compare your result with minimum pH required for complete solubility of phenobarbital in aqueous solution (without alcohol)

S0= 0.005, pKa=7.41 , Mwt=254

$$S = M = \frac{wt}{Mwt} \; x \; \frac{1000}{vol\ of\ solution}$$

$$= \frac{6}{254} \; x \; \frac{1000}{100}$$

$$= 0.236$$

Water	Alcohol
$pHp = pKa + \log \frac{S-S0}{S0}$ $= 7.41 + \log \frac{0.236-0.005}{0.005}$ $= 9.07$	$pHp = pKa + \log \frac{S-S0}{S0}$ $= 7.92 + \log \frac{0.236-0,028}{0.028}$ $= 8.79$

Therefore the suitable pH for preparation will be changed by changing the vehicle

Q39. Home work

What is the pHp of a 2% w/v solution of Sod. Phenobarbital in a hydroalcoholic solution containing 15% by volume alcohol ? The solubility of phenobarbital in 15% alcohol is 0.22% w/v. The of pKa of phenobarbital in this solution is 7.6.The Mwt of Sod.phenobarbitalis 254.22 g/mole and that of phenobarbital is 232. 23g/mole (Answer pHp=8.5)

Disadvantages

1- Furthermore, formulations rarely use pure non-aqueous solvent, particularly injections. For example, ethanol should only be used up to 10% in an injection to prevent haemolysis and pain at the injection site.

* In oral the allowed % of ethanol depends on the age
Children under 6 years … 0.5%
Children 6-12 years …5%
Children 12 years and adult … 10%

2- Uncontrolled precipitation occurs upon dilution with aqueous media

3- The mixture of water and co-solvent decrease the solubility of strong electrolyte (highly polar) , since this mixture is of lower dielectric constant (lower polarity)

Solubility of slightly soluble electrolyte

When slightly soluble electrolytes are dissolved in water to form saturated solutions, the solubility is described by a special constant known as **solubility product constant.**

Examples about such compounds are:-

$AgCl$, $Al(OH)_3$, $Fe(OH)_3$, Ag_2CrO_4, PbI_2, $PbCl_2$, $CaSO_4$,

For AgCl

The excess solid is in equilibrium with ions in saturated solution at specific temp. is represented by the equation

$$AgCl \leftrightarrow Ag^+ + Cl^-$$

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:

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

Since the conc. of the solid phase is constant and we deal with soluble product so:-

$Ksp = [Ag^+]\,[Cl^-]$

The equation is only approximate for slightly soluble salts. It does not applied for salts that are freely soluble in water such as NaCl

Ex 13 Calculate the Ksp of silver chloride if you know that its water solubility is $1.12x10^{-5}$

$$AgCl \leftrightarrow Ag^+ + Cl^-$$

$1.12x10^{-5}$ $1.12x10^{-5}$

$Ksp = [Ag^+]\,[Cl^-]$

$= [1.12x10^{-5}]\,[1.12x10^{-5}]$

$= 1.25x\,10^{-10}$

In case of $Mg(OH)_2$ to calculate Ksp; the conc. of each ion should be raised to a power equal to the number of ions appearing in the formula

Example- Calculate the Ksp of $Mg(OH)_2$ if you know that its solubility is 1.5×10^{-4}

$$Mg(OH)_2 \leftrightarrow Mg^{+2} + 2OH^-$$

$1.5x\,10^{-4}$ $2x1.5\,x10^{-4}$

$Ksp = [Mg]\,[OH]^2$

$Ksp = [1.5x\,10^{-4}]\,[2x1.5\,x10^{-4}]^2$

$= 1.4 \times 10^{-11}$

Home work : Calculate the Ksp of $Al(OH)_3$, if you know that its solubility =4.1x 10^{-4}
(Answer: Ksp=7.7x10^{-13})

Ex. What is the solubility of $Mg(OH)_2$ if you know that its Ksp= = 1.4 x 10^{-11} and what will be the concentration of each ion

$Mg(OH)_2 \leftrightarrow Mg^{+2} + 2OH^-$

X 2X

$Ksp = [X][2X]^2$

$1.4 \times 10^{-11} = X.\ 4X^2$

$1.4 \times 10^{-11} = 4\ X^3$

$X^3 = 3.5 \times 10^{-12}$

$X = 1.5 \times 10^{-4}$ (conc. of Mg^{+2})

$2X = 2x\ 1.5 \times 10^{-4} = 3 \times 10^{-4}$ (conc. of OH^{-1})

Factors affecting the solubility of slightly soluble electrolyte and the Ksp

1- Temperature

↑ Temp.→ ↑solubility →↑ conc. of each ion →↑Ksp

2- Common ion

Ex. AgCl

If an ion in common with AgCl that is Ag or Cl is added to a solution of AgCl the equilibrium is altered:-

The addition of $AgNO_3$ will increase the conc. Ag in solution

$ACl \leftrightarrow \mathbf{Ag^+} + Cl^-$ ……. (1)

$AgNO_3 \rightarrow \mathbf{Ag^+} + NO_3^-$ ……. (2)

Common ion

$Ksp = [Ag^+][Cl^-]$ Before addition

$Ksp = [Ag^+_{(AgCl + AgNO3)}][Cl^-]$ After addition

So $[Ag^+_{(AgCl + AgNO3)}][Cl^-]$ will be higher than the normal Ksp (momentarily)

So to keep Ksp constant, the first reaction will go back to the left to ↓ Ag+ which will decrease the solubility of AgCl and keep the Ksp constant.

Ex. Calculate the solubility of AgCl in water and in presence of 0.1M $AgNO_3$ if you know that its Ksp = 1.25 x10 $^{-10}$

$AgCl \leftrightarrow Ag^+ + Cl^-$

In water	In presence of 0.1M $AgNO_3$
Ksp= $[Ag^+][Cl^-]$ 1.25 x10 $^{-10}$ = [X][X] = X^2 X= 1.12 x10^{-5}	Ksp= $[Ag^{+}_{(AgCl + AgNO3)}][Cl -]$ 1.25 x10 $^{-10}$ = [X + 0.1][X] $Ag^{+}_{(AgCl)}$ is very small so it is neglected 1.25 x10 $^{-10}$ = 0.1 X X =1.25x10^{-9}

(The same thing if we add NaCl)

(So, the common ion will decrease the solubility of the slightly soluble salt but not affect Ksp)

Ex 14.

What is the solubility of silver chromate (Ag_2CrO_4)in mole/ liter in aqueous solution containing 0.04 M silver nitrate ($AgNO_3$). The solubility of Ag_2CrO_4 in **water is 8 x 10 $^{-5}$** and its Ksp is 2 x 10 $^{-12}$. Compare the solubility of Ag_2CrO_4 with and without the presence of $AgNO_3$

$Ag_2CrO_4 \leftrightarrow 2\mathbf{Ag}^{+1} + CrO4^{-2}$

2X X

$AgNO_3 \rightarrow \mathbf{Ag}^{+1} + NO_3^{-1}$

0.04 0.04 0.04

Ksp = $[Ag^{+1}_{(Ag2CrO4 + AgNO3)}]^2 [CrO_4^{-2}]$

Since the Ag from Ag_2CrO_4 is very small so it is neglected

2 x 10^{-12} = [0.04]^2 [X]

2 x 10 $^{-12}$ = 0.0016 X

X = 1.29 x 10 $^{-9}$

That is mean the solubility decreases from 8 x 10 $^{-5}$ to 1.29 x 10 $^{-9}$ due to the presence of common ion, while the Ksp remains constant

3- Effect of other electrolytes

The solubility of a slightly soluble electrolytes (salt) **may be** increased by the addition of a second electrolyte that **does not possess common ions** due to ionic interactions.

That is mean, the oppositely charged ions produced by dissociation of both electrolytes are strongly associated with each other, so the reaction of slightly soluble salt will go to the right which will lead to increase the solubility

In other words "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".

Application of Ksp:

How can you increase the solubility of the slightly salt?

OR How can you prevent its precipitation in water?

This is done by adding compound which tie up and reduce the conc. of one of the ions, so more salt will pass from the undissolved to the dissolved state until the Ksp is reached and the equilibrium is re-established (keep Ksp constant)

Ex. To increase the solubility of **$Fe(OH)_3$** or decrease its precipitation

$$Fe(OH)_3 \longleftrightarrow Fe^{+3} + 3OH^-$$

$$Ksp = [Fe^{+3}]\,[OH^-]^3$$

If we add substance that for complex Fe^{+3} such as sodium citrate more Fe^{+3} will pass into solution

That is mean $[Fe^{+3}]\,[OH^-]^3$ will be less than Ksp (momentarily)

So the reaction should be go to the right to increase the conc. of Fe^{+3} to keep the Ksp constant and that will lead to increase the solubility of $Fe(OH)_3$

Other factors affecting the solubility of solid in liquid

1- Influence of size and shape of the particles

- Particle size

Decrease of particle size → ↑ surface area → ↑ the rate of solubility (faster) but not the amount of the dissolved solute

However, micronizing (very small particle size)of drugs often leads to aggregation and agglomeration of particles, which results in poor wettability

- Arrangement of molecules within the crystal

Symmetric → compact crystal → low solubility (crystalline substance)

Unsymmetric → packed less efficiency → high solubility (amorphous)

2- Influence of surfactant

Slightly soluble substances may be brought in to solution by the solubilizing action of surface active agents

3- Influence of complexation

Complexation either increase solubility (if the complexing agent is soluble)

Ex . complexation of aspirin with trisodium citrate

OR complexation decrease the solubility (if the complexing agent is insoluble)

Ex. Tetracycline with calcium containing compounds such as milk

4- Influence of hydration

The hydrous compound such as **$X.H_2O$** is less soluble than the anhydrous form **X**

Distribution of Solutes between Immiscible Solvents

If an excess of liquid or solid 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 distribution law

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

Therefore, 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 10-21

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?

$$K = \frac{C\ H2O}{C\ alc.} = \frac{0.051}{0.0155} = 3.29 \text{ aq/ org at } 25°C$$

$$\text{OR } K = \frac{C\ alc.}{C\ H2O} = \frac{0.0155}{0.051} = 0.304 \text{ org / aq. at } 25°C$$

In both cases the partition coefficient gives us idea about the solubility of the compound

Importance of Partition knowledge

1- Give us idea about solubility
2- Solvent extraction
3- Preservation of oil-water systems
4- Drugs partition between aqueous phases and lipid biophases
   Ex. Antibiotics partition into microorganisms
5- Absorption and distribution of drugs throughout the body
6- Chromatography

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 original liquid and extracting liquid should be immiscible)

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

For example :Extraction of sugar from vegetable oil is done by addition of water , since sugar is more soluble in water than in vegetable oil, in addition, **water is immiscible with the oil.**

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

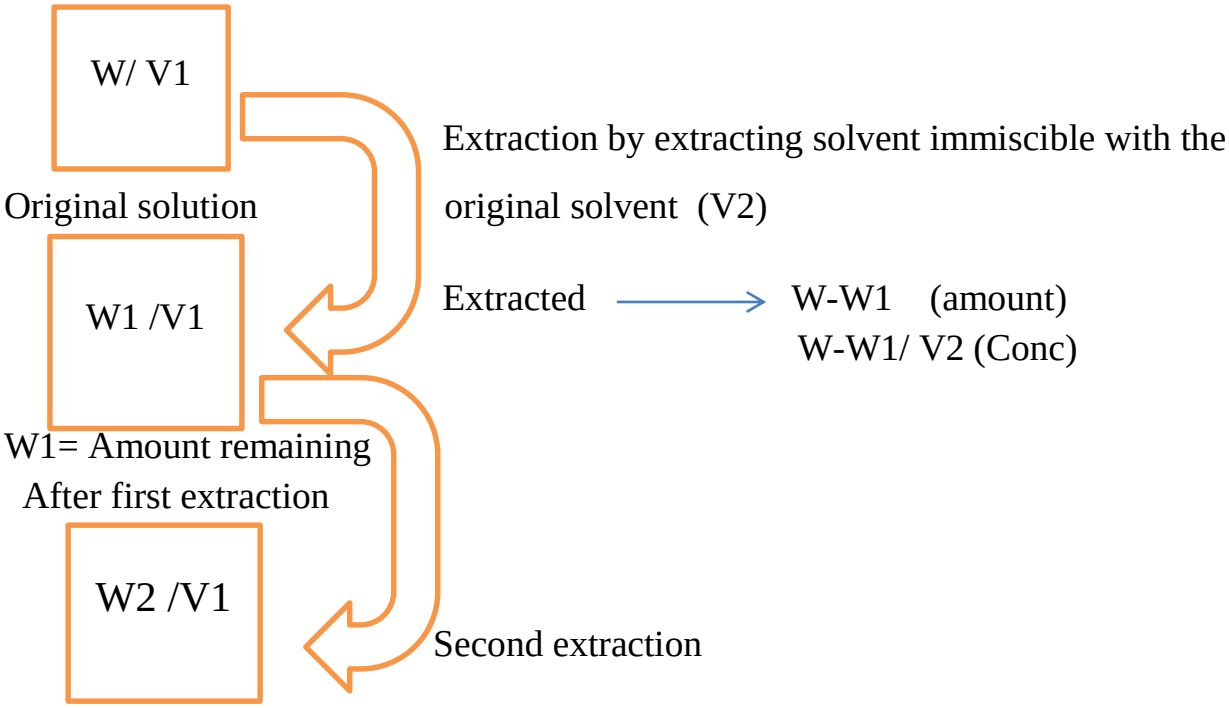
At the end, the water phase tastes sweet, because the sugar is moved to the water phase upon shaking. ****You extracted sugar from the oil with water. ****

The extraction process may be done as follow:-

Suppose that **W** grams of a solute is extracted repeatedly from **V1** ml of **one solvent (Original solvent)** with successive portions of **V2** ml of a **second solvent (Extracting solvent)**, which is immiscible with the first.

Let **w1** be the **weight of the solute remaining in the original solvent after extracting with the first portion of the other solvent**.

Then, the **concentration of solute remaining in the first solvent is (w1/V1) g/ml** and the concentration of the **solute in the extracting solvent is (w - w1)/V2 g/ml**.



W2 = Amount remaining / After second extraction

To determine the efficiency with which one solvent can extract a compound from a second solvent we can use the distribution coefficient principle as follow

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

$$K= \frac{Conc.of\ solute\ remaining\ in\ the\ original\ solvent}{Conc.of\ solute\ in\ the\ extracting\ fluid}$$

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

Re arrangement of the above equation

$$W1= W\frac{KV1}{KV1+V2}$$

The process can be repeated, and after n extraction:-

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

By use of this equation, it can be shown that most efficient extraction results when n is large and V2 is small, in other words, when a large number of extractions are carried out with small portions of extracting liquid

Example 10-23

The distribution coefficient for iodine between water and carbon tetrachloride at 25°C is $K=H_2O/CCl_4 = 0.012$. 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?

$$W1 = W \frac{KV1}{KV1+V2}$$

$$= 0.1 \frac{0.012*50}{0.012*50+10}$$

= 0.0057g remaining

Therefore the amount extracted = W- W1

= 0.1 – 0.0057 = 0.0943g

$$W2 = W \left(\frac{KV1}{KV1+V2} \right)^n$$

$$= 0.1 \left(\frac{0.012*50}{0.012*50+5} \right)^2$$

= 0.0011 g of iodine remaining

Therefore the amount extracted = W- W2

= 0.1- 0.0011= 0.0989 g extracted (Higher amount)

So most efficient extraction result is obtained when a large number of extractions are carried out with small portions of extracting liquid

Home work: can you use ethanol instead of CCl_4 to extract iodine from water?

Q48- If 0.15 g succinic acid in 100 ml of ether is shaken with 10 ml portion of water

K = 0.125 ether/water

A/ How many grams of succinic acid are left in the ether layer? And how many grams are extracted?

B/ How many grams of succinic acid are left in the ether layer when the phase is extracted with additional 10 ml water? And how many grams are extracted?

C/ How many grams of succinic acid are left in the ether layer when the phase is extracted two times with 5 ml of water?

A/ $W1 = W \frac{KV1}{KV1+V2}$

$= 0.15 \frac{0.125*100}{0.125*100+10}$

= 0.083g remaining

Amount extracted = 0.15 – 0.083= 0.069g

B/ $W2 = W \left(\frac{KV1}{KV1+V2}\right)^n$

$W2 = 0.15 \left(\frac{0.125*100}{0.125*100+10}\right)^2$

= 0.046 g remaining

Amount extracted = 0.15 – 0.046 = 0.104 g extracted (Higher than the first one)

C/ $W2 = W \left(\frac{KV1}{KV1+V2}\right)^n$

$W2 = 0.15 \left(\frac{0.125*100}{0.125*100+5}\right)^2$

= 0.076 g remaining

Amount extracted = 0.15 – 0.076 = 0.074 g extracted (Higher than the first one)

So most efficient extraction results are obtained with large number of extractions and also when a large number of extractions are carried out with small portions of extracting liquid

Preservation action of weak acids in oil- water systems

Solutions of food, drugs, and cosmetics are subjected to deterioration by microorganisms. Sterilization and 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 as preservative.

The preservative action of benzoic acid and similar acids is due almost entirely to the **un-ionized** acid and **not to the ionic form** and this **is due to** the relative ease with which the un-ionized molecule penetrates living membranes, since it consists of a large nonpolar portion, that is soluble in the lipid membrane of the microorganism so it can penetrate rapidly.

Bacteria in oil- water systems are generally located in the aqueous phase and at the oil- water interphase. 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 un-ionized acid in the aqueous phase.

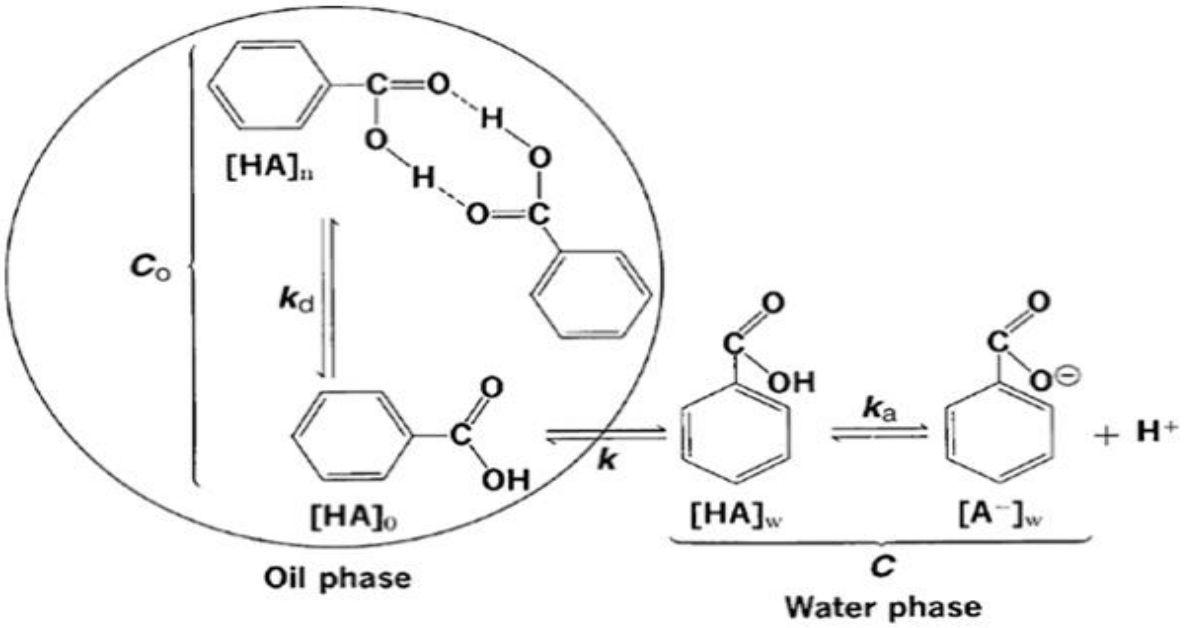
As shown in the figure below, the distribution of total benzoic acid between the oil and water phases depends upon

1- The distribution coefficient, K,

2- The dissociation constant, Ka, of the acid,

3- The phase volume ratio and

4- The hydrogen ion concentration of the aqueous phase.



Schematic representation of the distribution of benzoic acid between water and an oil phase. The oil phase is depicted as a magnified oil droplet in an oil-in-water emulsion.

Calculation of the total conc. of benzoic acid that must be added to preserve an oil-water system

When benzoic acid is distributed between the two phases, Two cases will be treated:-
1- Monomer as in peanut oil and water.
2- Dimer (association to form two molecules) in many nonpolar solvents

1- As Monomer

$C = q\,C_o + C_w$

$C = q\,[HA]_o + [HA]_w + [A^-]_w$

C:- Total conc. of acid that must be added to the two phase system
q :- Vo/ Vw the volume ratio of the two phases when the volumes are not equal
Co :- is the molar conc. of the acid in the oil phase ≈ [HA]o
Cw:- is the molar conc. of the acid in the water phase

Since the preservative action is related to **[HA]w**, Therefore we re- write the above equation by the use of **[HA]w** instead of **[HA]o** and **[A-]w**

Since $K = \frac{[HA]o}{[HA]w} \longrightarrow \longrightarrow [HA]o = K \,.\, [HA]w$

$$Ka = \frac{[A-][H3O+]}{[HA]w} \rightarrow \rightarrow [A^-] = \frac{Ka\,[HA]w}{[H3O+]}$$

$$C = q\,K.\,[HA]w + [HA]w + \frac{Ka\,[HA]w}{[H3O+]}$$

$$\mathbf{C = [HA]w\ \left(qK+1+\frac{Ka}{[H3O+]}\right)}$$ …. For calculation of the total conc. of acid that should be added to the system

OR

$$\mathbf{[HA]w = \frac{C}{qK+1+\frac{Ka}{[H3O+]}}}$$ …. For calculation of the conc. of the unionized acid in the water phase

2- As Dimer

C=q Co + Cw

Co = $[HA]_O^2$

C= q $[HA]o^2$ + [HA]w+[A-]w

ولتحويل المعادلة بدلالة [HA]w نستعمل العلاقات السابقة

Therefore $C = q[K . [HA]w]^2 + [HA]w + \frac{Ka\ [HA]w}{[H3O+]}$

$$C = q\ K^2 . [HA]w^2 + [HA]w + \frac{Ka\ [HA]w}{[H3O+]}$$

$\mathbf{C= [HA]\ w\ (\ qK^2\ .[HA]w\ +1+\ \frac{Ka}{[H3O+]})}$ … For calculation of the total conc. of acid that should be added to the system

OR

$\mathbf{[HA]\ w = \frac{C}{qK^2\ .\ [HA]W+1+\frac{Ka}{[H3O+]}}}$ …. For calculation of the conc. of the unionized acid in the water phase

Q49 How much benzoic acid Ka= 6.3x 10^{-5} will remain undissociated in the aqueous phase of 50% oil- water emulsion if the initial conc. of benzoic acid in aqueous phase is o.5%. The aqueous phase is bufferd at pH 5 and the oil/ water partition coefficient = 5.33 " assume that benzoic acid remains as monomer"

Compare the results at pH3 and pH8

50% oil- water emulsion:- means equal volumes so q =1

$$\textbf{[HA]w} = \frac{\boldsymbol{C}}{\mathbf{qK+1+}\frac{\boldsymbol{Ka}}{[\boldsymbol{H3O}+]}}$$

At pH5

$$[HA]w = \frac{0.5\%}{1*5.33+1+\frac{6.3x\ 10-5}{1x10-5}}$$

[HA]w = 0.0396%

At pH3

$$[HA]w = \frac{0.5\%}{1*5.33+1+\frac{6.3x\ 10-5}{1x10-3}}$$

[HA]w = 0.078%

At pH8

$$[HA]w = \frac{0.5\%}{1*5.33+1+\frac{6.3x\ 10-5}{1x10-8}}$$

[HA]w = 0.000079%

Conclusion:-

pH 3 is the best pH because of high conc. of the undissociated acid remains in the aqueous phase

because low pH $\longrightarrow$ $\downarrow$ dissociation of the weak acid $\longrightarrow$ $\uparrow$ [HA]w

while high pH (pH8) $\longrightarrow$ $\uparrow$ dissociation of the weak acid $\longrightarrow$ $\downarrow$ [HA]w

Example 25

If benzoic acid is distributed between equal volumes of peanut oil and water, **what must be the original conc**. in the water phase in order that 0.25 mg/ml of undissociated acid remains in the aqueous phase buffered at pH = 4 .Knowing that The oil/ water partition coefficient benzoic acid = 5.33, Ka= 6.3×10^{-5}

Compare your results with those at pH3 and pH7

Equal volumes of peanut oil and water means q=1

$$\mathbf{C = [HA]w\ (qK+1+} \frac{\boldsymbol{Ka}}{[\boldsymbol{H3O+}]}\mathbf{)}$$

تطبيق مباشر للقانون (مطلوب الحل بالتفصيل)

At pH 4

C= 1.74 mg/ml

At pH3

C= 1.6mg/ml

At pH7

C= 159.08mg/ml

Therefore the best preservative action is obtained at pH3 since lowest amount of the preservative is required

CHEMICAL KINETICS AND STABILITY

The stability of drug product with time is important in determination of shelf life and expired date.

The stability affected by factors, such as temperature, humidity, and light.

This chapter studies the rates and mechanisms of reactions specially the decomposition and stabilization of drug products.

For example, thiamine hydrochloride is most stable at a pH of 2 to 3 and is unstable above pH 6, so in preparation, the pharmacist should select the buffered vehicle that prevents the degradation.

Applications of chemical kinetics in pharmacy result in the production of more-stable drug preparations.

FUNDAMENTALS AND CONCENTRATION EFFECTS

Rates, Order, and Molecularity of Reactions

Molecularity

molecularity is the number of molecules, atoms, or ions reacting in an elementary process. molecularity classify the reaction into unimolecular, bimolecular, and Termolecular. molecularity cannot gives complete detail about order of reaction specially those of several steps while kinetic study gives details.

Example:

$Br_2 \longrightarrow 2Br$

Unimolecular: because the single molecule, Br2, decomposes to form two bromine atoms

$H_2 + I_2 \longrightarrow 2HI$

Bimolecular: because two molecules, one of H2 and one of I2, must come together to form the product HI, in single-step reaction

$2NO + O_2 \longrightarrow 2NO_2$

Termolecular : three molecules interact with each other

But the real detail mechanism revealed by kinetic study as follows:

$2NO \rightleftharpoons N_2O_2$ (fast)

$N_2O_2 + O_2 \longrightarrow 2NO_2$ (slow)

Rate

The rate, velocity, or speed of a reaction is given by the expression dc/dt, where dc is the increase or decrease of concentration over an infinitesimal time interval dt.

In the reaction

$$\text{Reactant} \longrightarrow \text{Products}$$

$$\text{Rate} = -\frac{d[Reactant]}{dt} = K[\text{Reactant}]^{a}$$

where k is the rate constant and exponent a represent the order of reaction.

Specific Rate Constant

The constant, k, appearing in the rate law associated with a single-step (elementary) reaction is called the specific rate constant for that reaction.

Any change in the conditions of the reaction, for example, in temperature or solvent, or a slight change in one of the reacting species, will lead to a rate law having a different value for the specific rate constant

The half-life is the time required for one-half of the material to disappear; the time at which C has decreased to 1/2 C.

The shelf-life is the time required for 10% of the material to disappear; it is the time at which C has decreased to 90% of its original concentration (i.e., 0.9C).

Kinetic study

Zero-Order Reactions

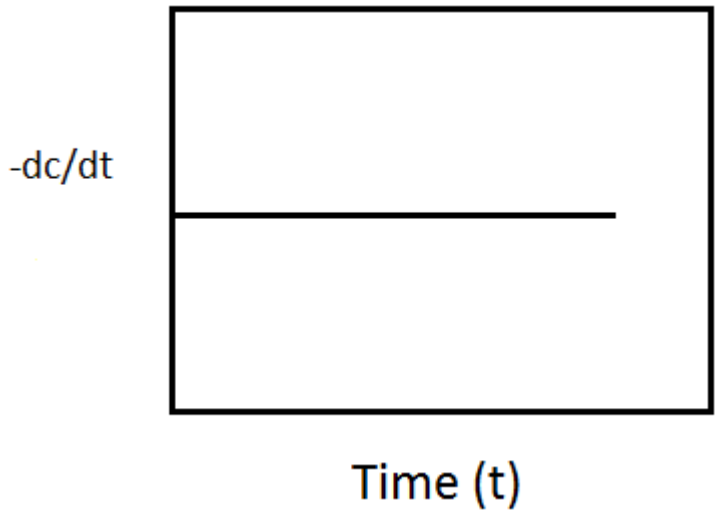
Ex. Garrett found that the loss in color of a multisulfa product followed a zero-order rate, it means that the velocity of fading is seen to be constant and independent of the concentration of the colorant used

The rate expression for the change of concentration, C, with time is therefore

$$-\frac{dC}{dt} = k_0$$

It means that the rate of reaction not depend on concentration of reactant, it is constant with time and the velocity of the reaction is constant.

where the minus sign signifies that the concentration (decrease in fading) of a substance is decreasing

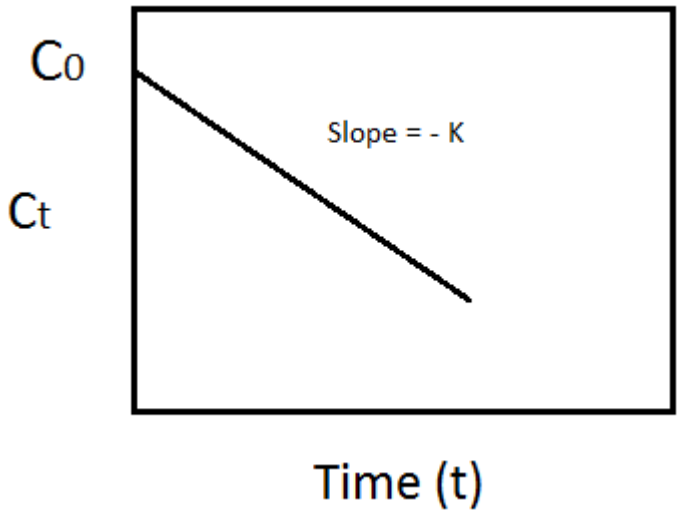


The rate equation can be integrated between the initial concentration, C_0, at t = 0, and C_t, the absorbance after time (t):

$$C_t = C_o - k_o t$$

$$t = \frac{Co - Ct}{ko}$$

$$ko = \frac{C0 - Ct}{t}$$



Because the half-life is the time required for one-half of the material to disappear, in the present case, after one half, the concentration becomes $1/2C_o$.

$$t_{1/2} = \frac{½Co}{ko}$$

For shelf life $t_{90\%} = \frac{Co-0.9Co}{ko} = \frac{0.1C0}{K0}$

- The unit of zero order rate constant is:

$k_0 = -\frac{dC}{dt} = \frac{mole/liter}{second} = \frac{mole}{liter\ second}$ = mole liter^{-1}second^{-1}

First-Order Reactions

A first-order reaction is one where the rate of reaction is directly proportional to the concentration of one of the reactants

Harried showed that the decomposition rate of hydrogen peroxide catalyzed by 0.02 M KI was proportional to the concentration of hydrogen peroxide remaining in the reaction mixture at any time. The data for the reaction

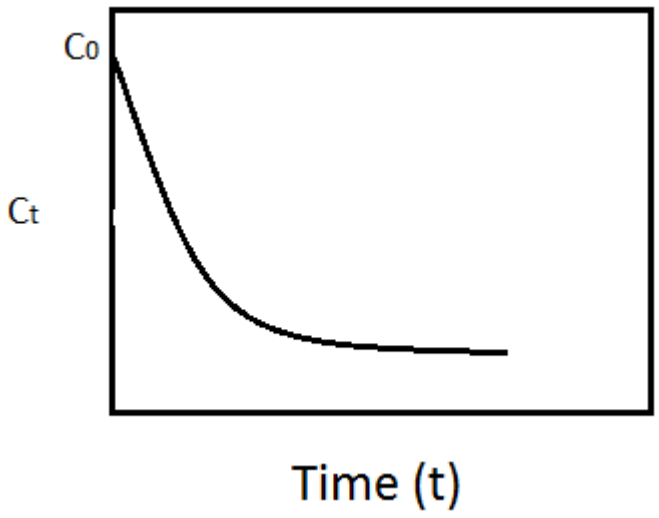
$$2H_2O_2 = 2H_2O + O_2$$

Although two molecules of hydrogen peroxide appear in the equation, the reaction was found to be first order.

The rate equation is written

$$-\frac{dC}{dt} = k\,C$$

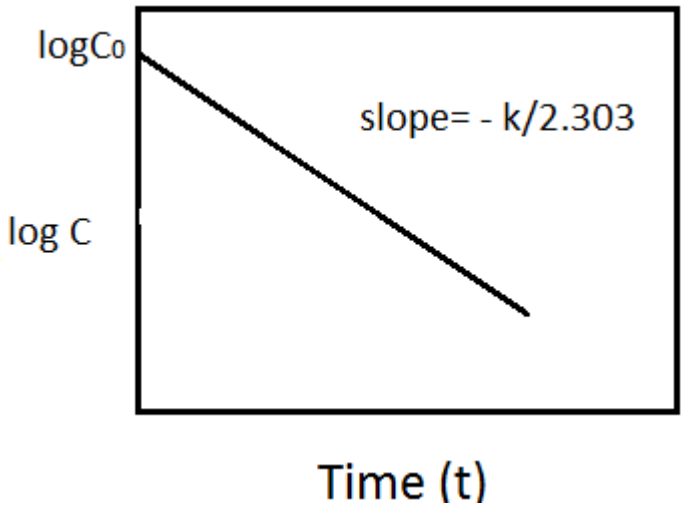
where c is the concentration of hydrogen peroxide(reactant) remaining undecomposed at time t and k is the first-order rate constant.



Integrating above equation, we have

$$\ln C = \ln C_0 - Kt$$

(Common logarithm) $\log C = \log C_0 - \frac{k}{2.303}\ t$



For calculation of half life of reaction follows first order;

$\log Ct = \log Co - \frac{Kt}{2.303}$ …… Re - Arrangement

$\log Co - \log Ct = \frac{Kt}{2.303}$

$\log \frac{C0}{Ct} = \frac{K\ t}{2.303}$

At half life; t= t1/2, Ct= ½ C_0

$\log \frac{C0}{½\ C0} = \frac{K\ t1/2}{2.303}$

$\log 2 = \frac{K\ t\ 1/2}{2.303}$

$0.3 = \frac{K\ t\ 1/2}{2.303}$

$t_{1/2} = \frac{0.3\ x\ 2.303}{K}$

$t\ ½ = \frac{0.693}{K}$

For shelf life $t_{90;}$

$$\log \frac{C0}{0.9\,C0} = \frac{K\,t90\%}{2.303} \quad ,$$

$$\log 1.11 = \frac{K\ t\ 90\%}{2.303}$$

$$0.045 = \frac{K\ t\ 90\%}{2.303}$$

$$t_{90\%} = \frac{0.045\ x\ 2.303}{K}$$

$$t_{90\%} = \frac{0.105}{K}$$

- The unit of first order rate constant is:

$$-\frac{dC}{dt} = K\,C$$ ….RE- Arrangement

$$k = -\frac{dC}{dt}\frac{1}{C} = \frac{mole/liter}{second.mole/liter} = \frac{1}{second} = \text{second}^{-1}$$

EXAMPLE .

Decomposition of Hydrogen Peroxide

The catalytic decomposition of hydrogen peroxide can be followed by measuring the volume of oxygen liberated in a gas burette. From such an experiment, it was found that the concentration of hydrogen peroxide remaining after 65 min, expressed as the volume in milliliters of gas evolved, was 9.60 from an initial concentration of 57.90.

(a) Calculate k using equation ($k=\frac{2.303}{t}\log\frac{C0}{C}$).

(b) How much hydrogen peroxide remained undecomposed after 25 min?

(a)

$k=\frac{2.303}{t}\log\frac{C0}{C}$ $k=\frac{2.303}{t}\log\frac{57.90}{9.60}$ = 0.0277 min^{-1}	**OR** $\log Ct = \log C0 - \frac{K\,t}{2.303}$ $\log 9.6 = \log 57.9 - \frac{K\ 65}{2.303}$ $0.982 = 1.763 - \frac{K\ 65}{2.303}$ K = 0.0277 min^{-1}

b

$0.0277 = \frac{2.303}{25} \log \frac{57.90}{C}$ c = 29.01	OR $\log Ct = \log C0 - \frac{Kt}{2.303}$ $\log Ct = \log 57.9 - \frac{0.0277\ x\ 25}{2.303}$ $= 1.462$ Ct = 28.97

EXAMPLE

First-Order Half-Life

A solution of a drug contained 500 units/mL when prepared. It was analyzed after 40 days and was found to contain 300 units/mL. Assuming the decomposition is first order, at what time will the drug have decomposed to one-half of its original concentration?

$k=\frac{2.303}{40} \log \frac{500}{300}$ $= 0.0128\ day^{-1}$ $t=\frac{2.303}{0.0128} \log \frac{500}{250}$ $= 54.3$ days	**OR** $\log Ct = \log Co - \frac{K\ t}{2.303}$ $\log 300 = \log 500 - \frac{K\ x\ 40}{2.303}$ $2.477 = 2.699 - \frac{K\ 40}{2.303}$ $K = 0.01278\ day^{-1}$ $t_{1/2} = \frac{0.693}{K}$ $= \frac{0.693}{0.0128} = 54.22$ day

Determination of Order

The order of a reaction can be determined by several methods.

1. **Substitution Method**. The data from kinetic study can be substituted in the equations for each order. When the calculated k values remain constant for different Ct, the reaction is considered to be of that order.

2. **Graphic Method**. A plot of the data in the form of a graph can also be used to ascertain the order.
If a straight line results when concentration is plotted against t, the reaction is zero order.
The reaction is first order if log (concentration) versus t yields a straight line, and **it is second-order if 1/(concentration) versus t gives a straight line**.

3. **Half-Life Method**. In a zero-order reaction, the half-life is proportional to the initial concentration, **a**, as observed in Table 15-2. **(Later next lectures)**
The half-life of a first-order reaction is independent of initial concentration **a;**
t1/2 for a second-order reaction, in which a = b, is proportional to 1 /a.

Suspensions, Apparent Zero-Order Kinetics

Suspensions are another case of zero-order kinetics, in which the concentration in solution depends on the drug's solubility. As the drug decomposes in solution, more drug is released from the suspended particles, so that the concentration remains constant. The equation for an ordinary solution, with no reservoir of drug to replace that depleted, is the first-order expression, equation

$-\frac{dC}{dt} = k_f[C]$ where c= concentration of drug in solution

= solubility

K_f= first order rate constant of solution

When the concentration [C] is rendered constant, as in the case of a suspension, we can write

$K_f [C] = K_0$ where K_0= zero order rate constant of suspension

Thus, **$K_0 = K_f$ x Solubility**

$-\frac{dC}{dt} = K_0$ (Apparent zero – order equation)

Ex. Shelf Life of an Aspirin Suspension-

A prescription for a liquid aspirin preparation is called for. It is to contain 325 mg/5 mL or 6.5 g/100 mL. The solubility of aspirin at 25°C is 0.33 g/100 mL; therefore, the preparation will definitely be a suspension. The other ingredients in the prescription cause the product to have a pH of 6.0. The first-order rate constant for aspirin degradation in this solution is 4.5×10^{-6} sec^{-1}. Calculate the zero-order rate constant. Determine the shelf life, t_{90}, for the liquid prescription, assuming that the product is satisfactory until the time at which it has decomposed to 90% of its original concentration (i.e., 10% decomposition) at 25°C.

Answer: $k_o = k \times$ [Aspirin in solution], from equation ($k [A] = k_0$). Thus,

$k_o = (4.5 \times 10^{-6}\ sec^{-1}) \times (0.33\ g/100\ mL)$

$k_o = 1.5 \times 10^{-6}$ g/100 mL sec^{-1}

$t_{90} = \frac{0.1\ A0}{K0} = \frac{0.10X6.5\ g/100\ mL}{1.5 \times 10-6\ g/100\ mL sec-1}$

$= 4.3 \times 10^5$ sec = 5.0 day

Increased Shelf Life of Aspirin

Aspirin is most stable at pH 2.5. At this pH the apparent fist-order rate constant is 5×10^{-7} sec^{-1} at 25°C. The shelf life of aspirin in solution under these conditions can be calculated as follows:

$t_{90} = \frac{0.105}{K}$

$t_{90} = \frac{0.105}{5x10^{-7}} = 2.1 \times 10^5$ sec

= 2 days

As one can see, aspirin is very unstable in aqueous solution.

Would making a suspension increase the shelf life of aspirin?

The solubility of aspirin is 0.33g/100mL. At pH 2.5, the apparent zero- order rate constant for an aspirin suspension is

ko = 5×10^{-7} sec^{-1} x 0.33 g/100 mL = 1.65×10^{-7} **g/mL • sec**

If one dose of aspirin at 650 mg per teaspoonful is administered, then

650 mg/5 mL = 13 g/100 mL. For this aspirin suspension,

$t_{90} = \frac{0.1\ A0}{K0}$

$t_{90} = \frac{0.1x\ 13}{1.65\ x\ 10^{-7}} = 7.9 \times 10^6$ sec = 91 days

The increase in the shelf-life of suspensions as compared to solutions is a result of the interplay between the solubility and the stability of the drug. In the case of aspirin, the solid form of the drug is stable, whereas when aspirin is in solution it is unstable. As aspirin in solution decomposes, the solution concentration is maintained as additional aspirin dissolves up to the limit of its aqueous solubility.

Second-Order Reactions

The rates of bimolecular reactions, which occur when two molecules come together, are frequently described by the second-order equation.

$$A + B \longrightarrow \text{Products}$$

When the speed of the reaction depends on the concentrations of A and B with each term raised to the first power, the rate of decomposition of A is equal to the rate of decomposition of B, and both are proportional to the product of the concentrations of the reactants:

$$-\frac{d[A]}{dt} = -\frac{d[B]}{dt} = K\,[A][B]$$

If **a** and **b** are the initial concentrations of A and B respectively, and **x** is the concentration of each species reacting in time t, the rate law can be written as

$$\frac{dx}{dt} = K(a-x)(b-x)$$

where dx/dt is the rate of reaction and **a - x** and **b - x** are the **concentrations of A and B, respectively, remaining at time t**

Integrating and write the second order equation according to 3 possibilities:

1. When, in the simplest case, both A and B are present in the same concentration so that a = b,

$$\frac{dx}{dt} = (a-x)^2 \quad \ldots\text{Integration}$$

$\frac{1}{a-x} = \frac{1}{a} + Kt$ لاثبات الرسم It may also written as $\frac{1}{At} = \frac{1}{Ao} + Kt$

By several steps

$\frac{x}{a(a-x)}$ = Kt لسهولة التطبيق

The rate constant, k, in a second-order reaction therefore has the dimensions liter/(mole sec) or liter $mole^{-1}$ sec^{-1}.

The half-life of a second-order reaction is

$$t1/2 = \frac{1}{ak}$$

2. When, in the general case, A and B are not present in equal concentrations but the difference in concentration is not big, integration of equation yields:

$$\frac{2.303}{a-b} \log \frac{b(a-x)}{a(b-x)} = Kt$$

3. When A and B are not present in equal concentrations and the difference in concentration is very big

(*Pseudo-first-order reaction):*

Suppose that in this reaction, A was in great excess and B was in a relatively low concentration.

As the reaction proceeded, **B** would change appreciably from its original concentration, whereas the concentrations of **A** would remain essentially unchanged because they are present in great excess. In this case the contribution of **A** to the rate expression is considered constant and the reaction rate can be written as

$$A + B \longrightarrow \text{Products}$$

$$-\frac{d[B]}{dt} = K\,[A][B]$$

K is constant and [A] is constant

$$-\frac{d[B]}{dt} = K'\,[B]$$

where K'= K [A], K'= Pseudo-first-order constant

Example: Saponification of Ethyl Acetate

Walker investigated the saponification of ethyl acetate at 25°C:

$$CH_3COOC_2H_5 + NaOH \longrightarrow CH_3COONa + C_2H_5OH$$

The initial concentrations of both ethyl acetate and sodium hydroxide in the mixture were 0.01000 *M*. The change in concentration, *x*, of alkali during 20 min was 0.000566 mole/liter, therefore, (a - x) = 0.01000 - 0.000566 = 0.009434. Compute (a) the rate constant and (b) the half-life of the reaction.

(a) Using equation

$$\frac{x}{a(a-x)} = Kt$$

or

$$k = \frac{1}{at}\left(\frac{x}{a-x}\right)$$

, we obtain

a=0.01

x=0.000566

a-x=0.009434

$$K = \frac{1}{0.01\times 20}\frac{0.000566}{0.009434} = 0.299 \text{ liter mole}^{-1}\text{min}^{-1}$$

(b) The half-life of a second-order reaction is

$$t1/2 = \frac{1}{aK}$$

It can be computed for the reaction only when the initial concentrations of the reactants are identical. In the present example,

$$t_{1/2} = \frac{1}{0.01\times 0.299} = 334.44\text{min}$$

Example

In the reaction of acetic anhydride with ethyl alcohol to form ethyl acetate and water,

$(CH_3CO)_2O + 2C_2H_5OH = 2CH_3CO_2C_2H_5 + H_2O$

The rate of reaction is

Rate = $-\frac{d[(CH3CO)2O]}{dt}$

$= k\,[(CH_3CO)_2O]\,[C_2H_5OH]^2$

What is the order of the reaction with respect to acetic anhydride? With respect to ethyl alcohol? What is the overall order of the reaction?

If the alcohol, which serves here as the solvent for acetic anhydride, is in large excess such that a small amount of ethyl alcohol is used up in the reaction, write the rate equation for the process and state the order.

Answer: The reaction appears to be first order with respect to acetic anhydride, second order with respect to ethyl alcohol, and overall third order. However, because alcohol is the solvent, its concentration remains essentially constant, and the rate expression can be written

$-\frac{d[(CH3CO)2O]}{dt} = k'[(CH_3CO)_2O]$

Kinetically the reaction is therefore a pseudo-first-order reaction.

Order	**Integrated equation**	**Units of K**	**Half- life**	**Shelf -life**	**Straight line obtained by drawing**
Zero	Ct= Co-kt	mole liter $^{-1}$ sec^{-1}	$t_{1/2}=\frac{\frac{1}{2}Co}{K}$	$t_{90\%}=\frac{0.1Co}{K}$	Ct Vs time
First	log Ct=log Co- $\frac{Kt}{2.303}$	time $^{-1}$	t ½= $\frac{0.693}{K}$	$t_{90\%}=\frac{0.105}{K}$	log Ct vs. time
Second	$\frac{1}{a-x}=\frac{1}{a}+Kt$	liter mole^{-1} sec^{-1}	$t_{1/2}=\frac{1}{aK}$		$\frac{1}{Conc.}$.vs time

Factors effects on stability

A number of factors other than concentration may affect the reaction velocity. Among these are temperature, solvents, catalysts, and light.

1. Temperature effect

Collision Theory

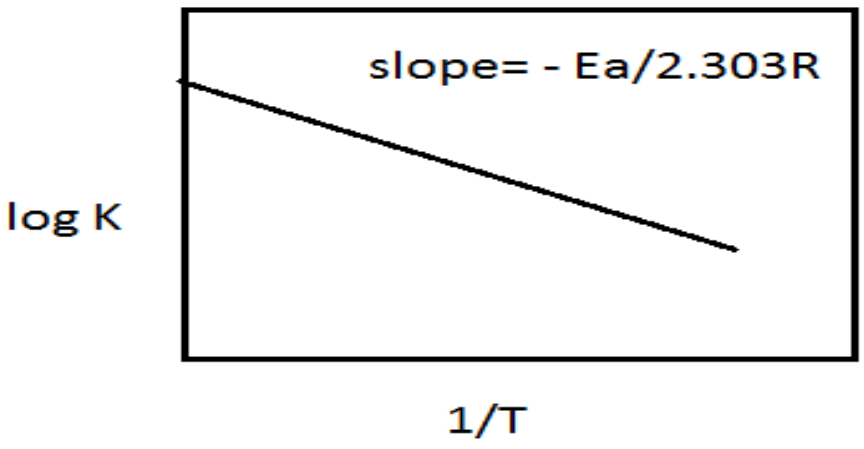
Reaction rates are expected to be proportional to the number of collisions per unit time. Because the number of collisions increases as the temperature increases, the reaction rate is expected to increase with increasing temperature.

The effect of temperature on reaction rate is given by the equation, first suggested by Arrhenius,

$k = Ae^{-Ea/RT}$

or $\log K = \log A - \frac{Ea}{2.303R}\frac{1}{T}$

where k is the specific reaction rate, A is a constant known as the Arrhenius factor or the frequency factor, *Ea* is the energy of activation. R is the gas constant, 1.987 calories/deg mole, and T is the absolute temperature.

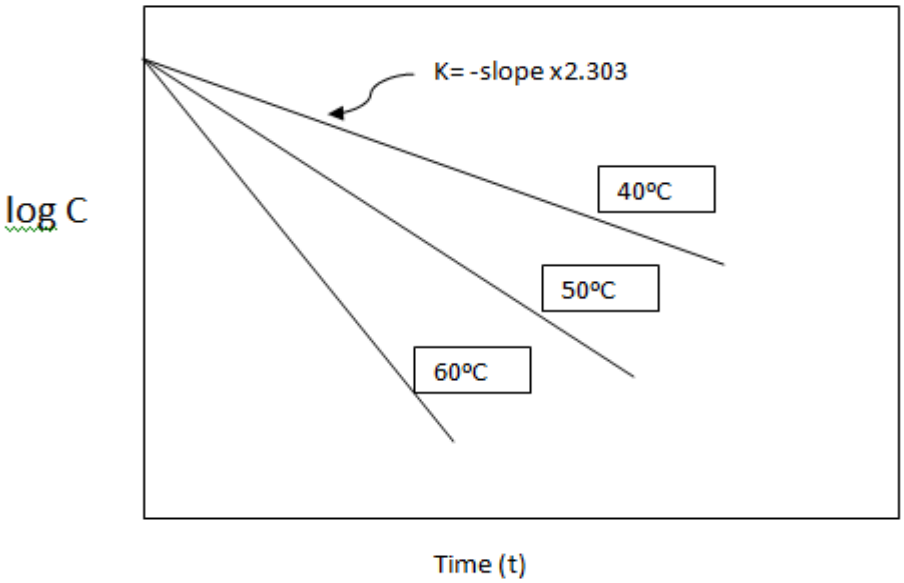


In case at 2 temperatures t1 and t2, the equation becomes:

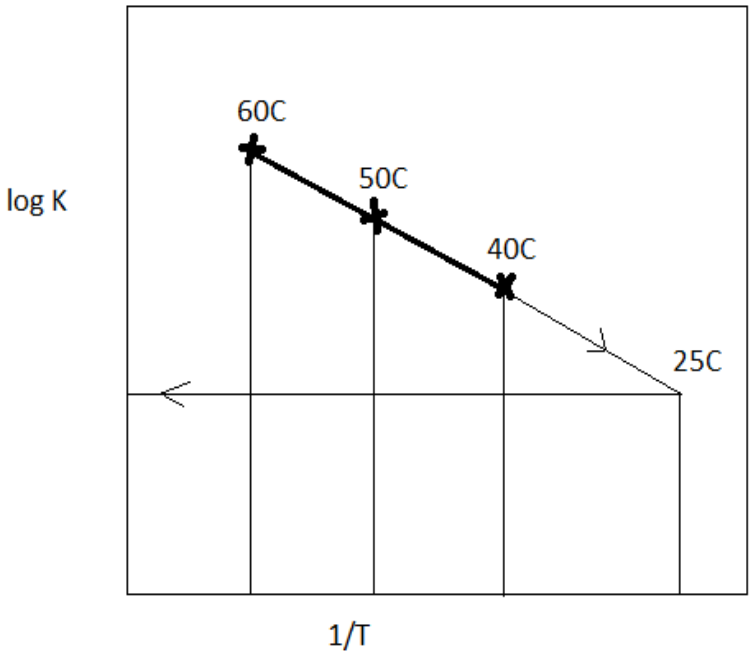
$$\log \frac{K2}{K1} = \frac{Ea}{2.303R}\left(\frac{T2-T1}{T2T1}\right)$$

Accelerated stability testing

The k values for the decomposition of drug at various elevated temperatures are obtained by plotting log of concentration against time as shown in this figure:



Then the logarithm of rate constants (k) at various temperatures are plotted against reciprocal of absolute temperature and the resulting line extrapolated to the room temperature to get K_{25}°C as shown in this figure:



The shelf life $t_{90\%}$ can be calculated from equation

$t_{90\%} = 0.105/ K_{25}°C$

2. **Medium Effects: Solvent, Ionic Strength, Dielectric Constant**

a. Effect of the Solvent

In summary, it can be said that the polarity of solvents affects the rate of reactions depending on the polarity of reactant.

“ Depending on the specific reaction and the polarity of the reactants, the choice of solvent can either accelerate or decelerate the reaction rate. Selecting a solvent with an appropriate polarity that complements the polarity of the reactants can optimize reaction conditions and improve reaction efficiency”

b. Effect of the ionic strength

For ionic compound, the ionic strength affects the rate of reaction while for neutral molecule, the rate of reaction independent on ionic strength.

c. Effect of the Dielectric Constant

The dielectric constant affects the rate constant of an ionic reaction. For a reaction between ions of opposite sign, an increase in dielectric constant of the solvent results in a decrease in the rate constant.

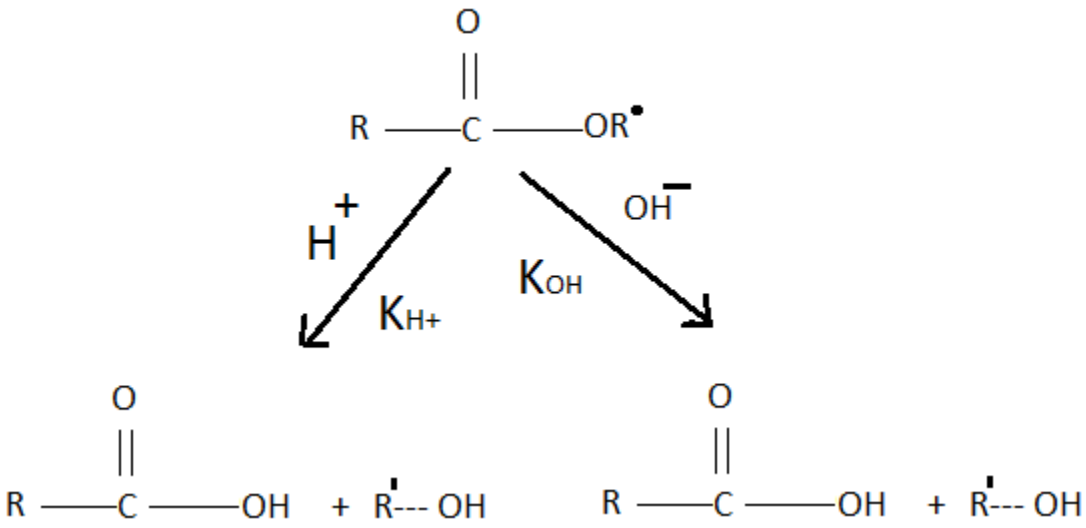
For ions of like charge, on the other hand, an increase in dielectric constant results in an increase in the rate of the reaction.

“For reactions between ions of opposite sign, increasing the dielectric constant decreases the rate constant by reducing the electrostatic attraction between the ions. Conversely, for reactions between ions of like charge, increasing the dielectric constant increases the rate constant by improving the solvation of the ions and reducing their mutual repulsion’

3. **Catalysis effect: Specific Acid-Base Catalysis Effects**

The rate of a reaction is frequently influenced by the presence of a catalyst. Solutions of a number of drugs undergo accelerated decomposition on the addition of acids or bases.

If the drug solution is buffered, the decomposition may not be accompanied by an appreciable change in the concentration of acid or base, so that the reaction can be considered to be catalyzed by hydrogen or hydroxyl ions. Best example of specific acid-base catalysis, is the hydrolysis of esters.



The general formula for hydrolysis of ester which affected by both H^+ and OH^- is

$$-\frac{dc}{dt} = K_{observed}[ester]$$

$$K_{observed} = K_{H^+}[H^+] + K_{OH^-}[OH^-]$$

$K_{observed}$ = total rate constant of the system

K_{H^+} = rate constant for acid catalysis reaction

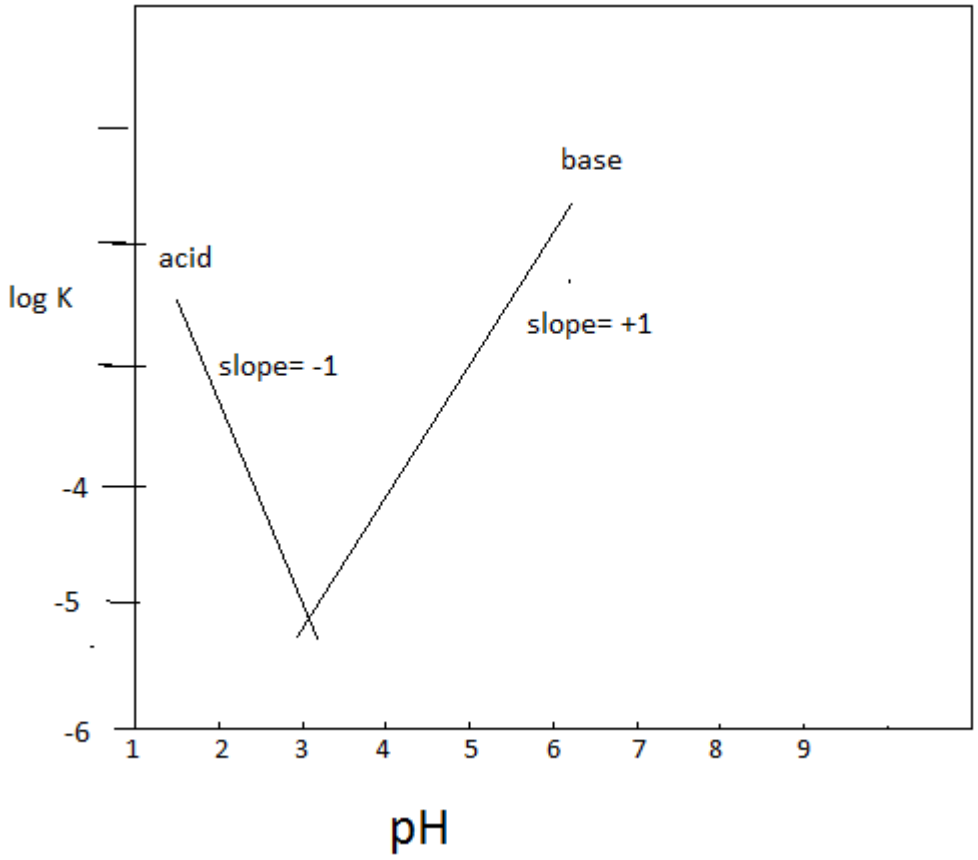
K_{OH^-} = rate constant for base catalysis reaction

$[H^+]$ = hydrogen ion concentration

$[OH^-]$ = hydroxide ion concentration

Note: K_{H^+} and K_{OH^-} are second order rate constants.

The pH- Rate profile for the specific acid-base-catalyzed hydrolysis of ester as shown in this figure:



Explanation of pH- Rate profile

1. at low pH

$$K_{observed} = K_{H^+}[H^+] + K_{OH^-}[OH^-]$$

Since $[OH^-]$ concentration value is very low, thus the part $(K_{OH^-}[OH^-])$ is neglected from equation at low pH.

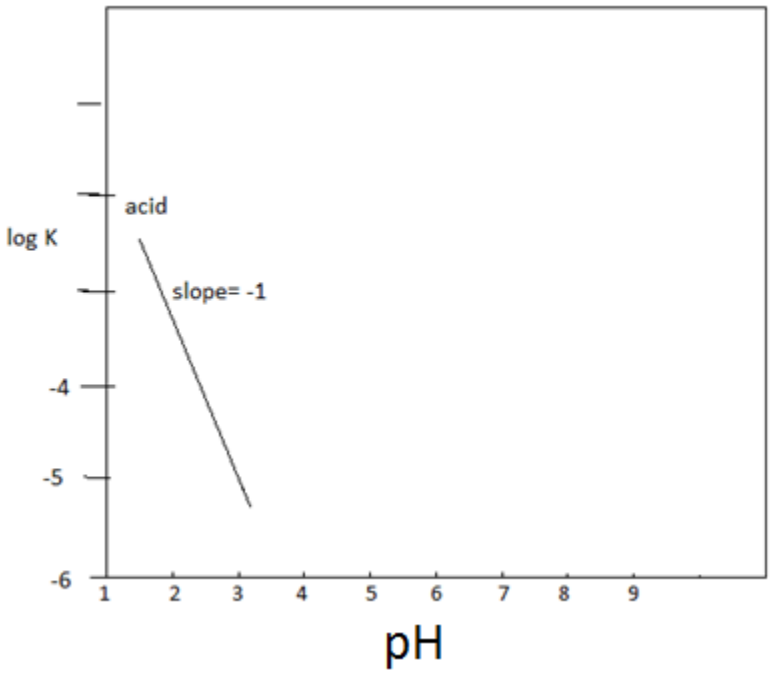
So, $K_{observed} = K_{H^+}[H^+]$

$\log K_{observed} = \log K_{H^+} + \log [H^+]$

$\log K_{observed} = \log K_{H^+} - (- \log [H^+])$

$\log K_{observed} = \log K_{H^+} - pH$

$\log K_{observed} = \log K_{H^+} \mathbf{-1} x\ pH$



2. At high pH

$$K_{observed} = K_{H^+}[H^+] + K_{OH^-}[OH^-]$$

Since $[H^+]$ concentration value is very low, thus the part $(K_{H^+}[H^+])$ is neglected from equation at high pH.

So, $K_{observed} = K_{OH^-}[OH^-]$

$Kw = [H^+][OH^-] \longrightarrow [OH^-] = Kw/[H^+]$

$K_{observed} = K_{OH^-}[OH^-]$

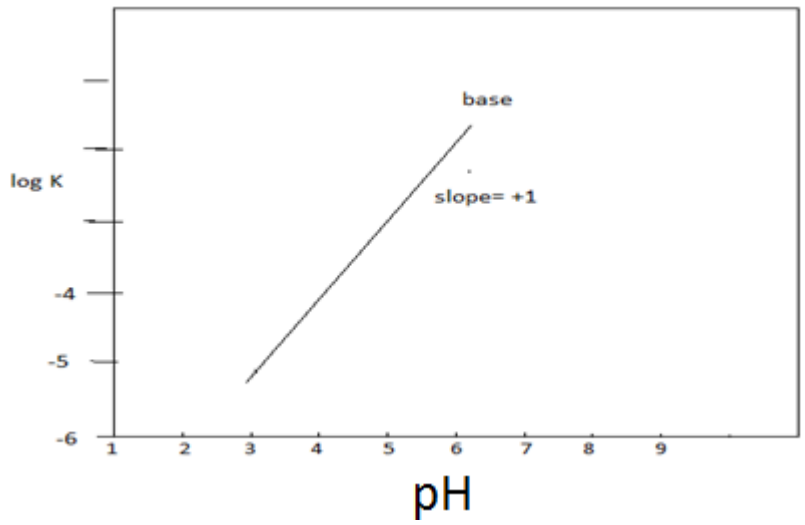
$K_{observed} = K_{OH^-} \frac{kw}{[H+]}$

$\log K_{observed} = \log K_{OH^-} + \log kw - \log [H^+]$

$\log K_{observed} = \log K_{OH^-} + \log kw + (-\log [H^+])$

$\log K_{observed} = \log K_{OH^-} + \log kw + pH$

$\log K_{observed} = (\log K_{OH^-} + \log kw) + \mathbf{1} \times pH$



STABILITY OF PHARMACEUTICALS

Decomposition and Stabilization of Medicinal Agents

Pharmaceutical decomposition can be classified as hydrolysis, oxidation, isomerization, epimerization, and photolysis, and these processes may affect the stability of drugs in liquid, solid, and semisolid products.