3SHAMBHUNATH INSTITUTE OF PHARMACY

4Ist Sessional Examination 2019-2020

B. Pharm. 2nd Year 3rd sem.

Subject- PHYSICAL PHARMACEUTICS-I

Time: - 1.30 hrs. **Max. Marks: –3 0**

Paper Code: BP302T

Roll No | | | | | | | | | | |

SECTION-A

1. Attempt all the questions: **(5X2=10)**

i. Write the full form of EDTA. Which type of example it is among the following: - a)Tetradentate ligand or b)Hexadentate ligand.
Ans:- Ethylene diaminetetraacetic acid, Hexadentate ligend

ii. What is stagnant layer? What is rate limiting step?
Ans:-Solution of the solid to form a thin layer or film at the solid/liquid interface called as stagnant layer and diffusion of the soluble solute from the stagnant layer to the bulk of the solution is slower. And In chemical kinetics, the overall rate of reaction is often determined by the slowest step known as rate limiting step

iii. What should be the nature of drugs which usually bind to the human serum albumin?
Ans:- Acidic nature

iv. What is BCS? Give classes of BCS with example.
Ans:- Biopharmaceutical Classification System is useful for predicting the intestinal drug adsorption provided by USFDA. Type 1 (Metoprolol), Type 2(Glibenclamide), Type 3(Ranitidine), Type 4(Hydrochlorthiazide)

v. Give the equation of Fick's law. The rate of diffusion of drug across the biological is depending on concentration gradient. True/False
Ans:-
$= \frac{DAKm/w}{h}(C_{GIT} - C)$, True

SECTION-B

2. Attempt any two of the following: **(2X5=10)**

i. What is protein binding? Gives the methods for determining the protein binding.

Ans:-

* Protein Binding

The formation of a drug protein complex is often named as protein binding.

Plasma proteins such as Albumin, Xylobumin and

lipoprotein

α_1 acid glycoprotein are present in our body.

→ Among the plasma protein albumin is the most important one it has ability to bind both acidic & basic drugs.

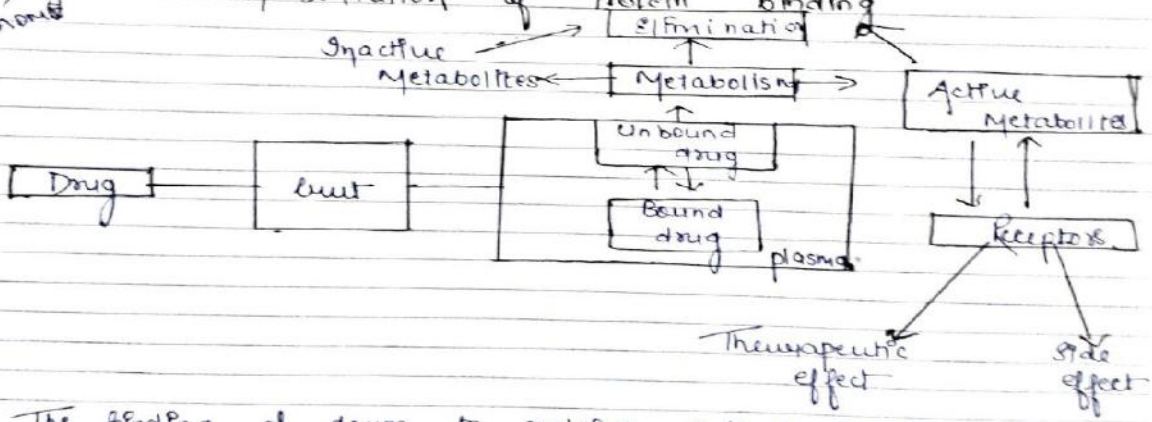
→ Another plasma protein xylotulin has been shown to bind with numerous drugs

→ α_1 acid glycoprotein appear to have greater affinity for basic drug than acidic drugs

→ A protein molecule is a macromolecule which is composed of many hundreds of amino acids linked together

→ The functional groups present in the side-chains of the amino acids provides sites for binding of drug molecule.

* Diagramatic representation of Protein binding



The binding of drugs to proteins content in the body can influence their action in number of ways

① May facilitate the distribution of drug throughout the body.

or tightly

② May inactivate a drug by binding so firmly that sufficient conc^n is not available at the receptor site

③ May alter the duration of action of a drug.

④ May alter the therapeutic effect.

* Binding of drugs to Protein

Protein	Drugs that bound
α_1 acid glycoprotein	Basic drugs, Imipramine, Lidocaine
Lipoprotein	Basic, lipophilic drug chloepromazine
α_1 globulin	Steroids
α_2 globulin	Vit. A, D, E & K

* Order of Binding Drugs

Albumin > α_1 acid glycoprotein > Lipoprotein > Globulin.

* Protein [P] and Drug molecule [D]

$$[P] + [D] \rightleftharpoons [PD]$$

The interaction between the protein [P] and drug molecule [D] for a protein drug complex [PD]

can be represented as :—

$$[P] + [D] \rightleftharpoons [PD]$$

Apply K = Equilibrium constant.

$$K = \frac{[PD]}{[P][D]} \quad \text{or}$$

$$[PD] = K[P][D] \quad \text{①}$$

where K — Equilibrium constant or association constant

[P] = Conc. of unbound protein

[D] = Conc. of unbound drugs

[PD] = Conc. of protein - drug complex

Total protein conc. in the body [P_t]

$$[P_t] = [P] + [PD]$$

$$\text{OR} \quad [P] = [P_t] - [PD] \quad \text{②}$$

Substitute eqn ② in ①

$$[PD] = K[D]([P_t] - [PD])$$

$$[PD] = K[D][P_t] - K[D][PD]$$

$$[PD] + K[D][PD] = K[D][P_t]$$

$$[PD](1 + K[D]) = K[D][P_t]$$

$$\frac{[PD]}{[P_t]} = \frac{K[D]}{1 + K[D]}$$

where $\frac{[PD]}{[P_t]}$ represent the average number of drug molecules bound per mole of protein

$$\frac{[PD]}{[P_t]} = r$$

$$r = \frac{K[D]}{1 + K[D]}$$

We have assume that only one bind site exist for 1 molecule of protein suppose there are many no. of binding site (n) then the eqn follows

$$r = \frac{n K[D]}{1 + K[D]}$$

n = Number of binding site

$$r(1 + K[D]) = nK[D]$$

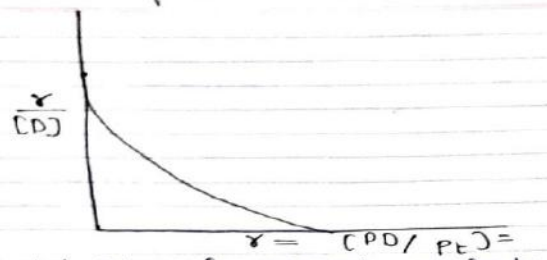
$$r + rK[D] = nK[D]$$

$$r = nK[D] - rK[D]$$

$$r = [D][nk - rk]$$

$$\boxed{\frac{r}{[D]} = nk - rk}$$

Scatchard plot

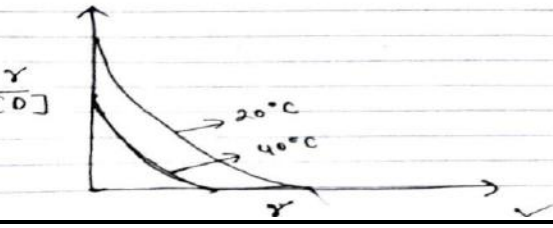


In scatchard plot $\frac{r}{[D]}$ is plotted against r $\left[r = \frac{[PD]}{[P_t]}\right.$ = $\frac{\text{Bound drug}}{\text{Total protein}}$]

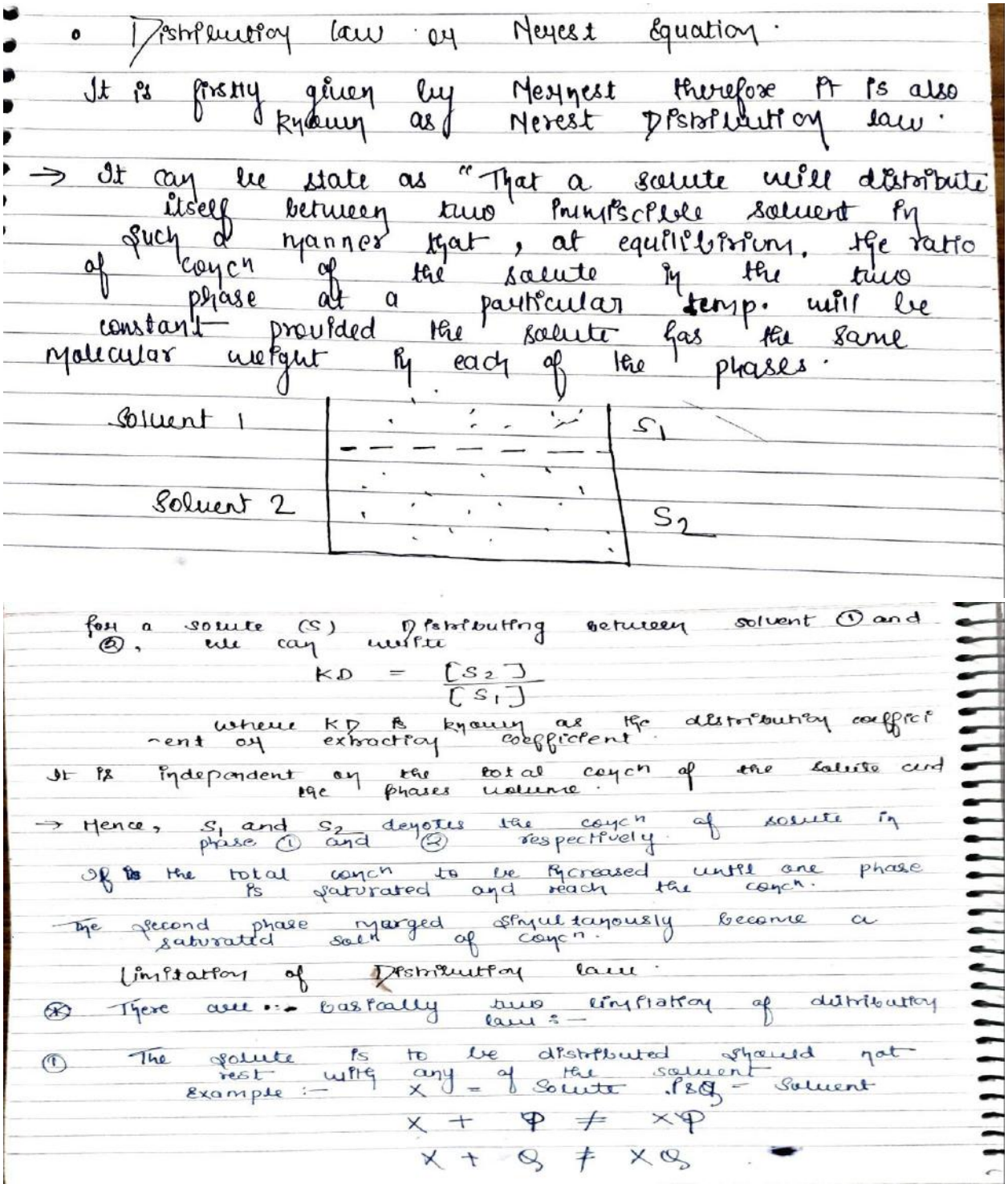
It gives a straight line ~~ost~~ linear relationship, if only one class of binding site is present

If more than one class of binding site exist the graph is not linear but showing a curvature.

Example Binding of Bishydroxy coumarin to Albumin at 20° to 40° C

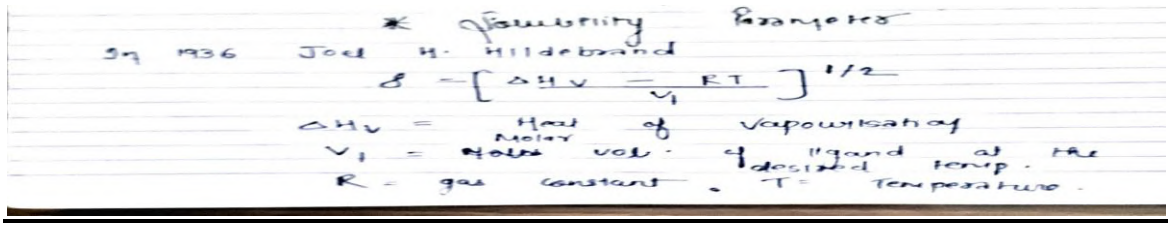


ii. Explain distribution law, its limitations and applications.



OR

What is ideal solubility parameters and give the mechanism of solute solvent interactions.



Another solubility parameter

In 1966 Charles M. Hansen this was developed by Charles M. Hansen in 1966.

This Hansen parameter consist of three parts

⇒A Dispersion component, A Polar component and Hydrogen bonding component. So Hansen parameter is shown as

$\delta t^2 = \delta t^0 + \delta p^2 + \delta h^2$

δt^2 = Total Hildebrand parameter

δt^0 = Dispersion component

δp^2 = polar component

δh^2 = Hydrogen bonding component.

Adhesive - Attraction between unlike molecule

Dielectric - Relation between positive & negative charge or opposite charge

Interaction between polar & non polar

Solute - Solvent Interaction

When the adhesive forces are more than the cohesive forces, the solubility of a solute by a solvent is generally enhanced.

Advantage of

- Polar solvents dissolves polar solutes and non polar solvents dissolves non polar solutes.
- Semi polar solvents such as acetone & alcohol act as intermediate solvent
- Crystalline solids have low solubility. The insoluble nature is due to the crystalline arrangement and low intermolecular forces between solute & solvent
- We can measure the intermolecular forces among solute molecules by melting point.
  Higher the melting point of a solute the less soluble is the solute.
- Electrolyte have good solubility & they solubility is largely governed by electrostatic forces.
  They are easily soluble by solvent with high dielectric constant.
  for ex. water has high dielectric constant & it is a good solvent for polar substances
  (electrolyte).

Mechanism of solute - solvent interaction.

Cleavage of solute - solute intermolecular bonds

↓

Cleavage of solvent - solvent intermolecular bonds

↓

Formation of cavity in solvent phase to accomodate solute molecules

↓

Movement of solute into the cavity of solvent phase.

↓

Formation of solute - solvent bonds

* Solubility Parameter

In 1936 Joel H. Hildebrand

$$\delta = \left[\frac{\Delta H_V - RT}{V_1} \right]^{1/2}$$

ΔH_V = Heat of vapourisation

V_1 = Molar vol. of ligand at the desired temp.

R = gas constant, T = Temperature.

iii. What is Roult's law? Explain the Critical solution temperature and its applications.

Raoult's law

According to Raoult's law at a definite temperature the partial pressure of a component in a liquid mixture is equal to vapour pressure of a pure state multiply by the mole fraction of the component

$$P_A = P_A^\circ x_A$$

where P_A = Partial pressure of a component

P_A° = Vapour pressure in pure state

x_A = mole fraction of the component

Ideal soln obey Raoult's law. when deviation in this law then called real or non ideal soln.

If deviation is negative then solubility increases due to Hydrogen bonding.

If deviation is positive the solubility decrease due to of association of molecules.

→ Two liquid either completely miscible or partially miscible.

Completely miscible liquid mix in all proportion and hence do not create solubility problem.

The mutual solubility of phenol and water / phenol and water, two conjugated liquid phases increases with temp. and at a temp. called critical soln temp. or consolute temp. and at this temp. a homogeneous or a single phase result for any composition.

Phenol and water show a upper critical solution temp. at 66.8°C and are miscible at this temperature.

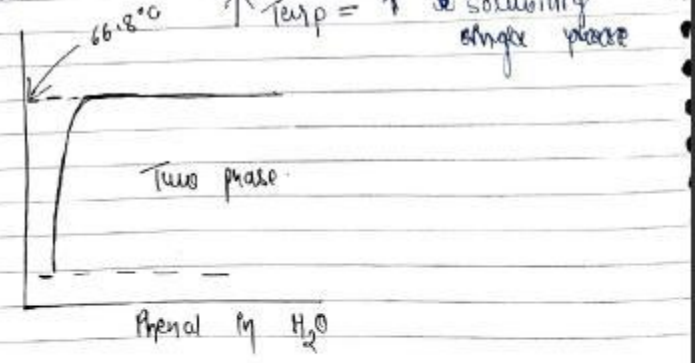
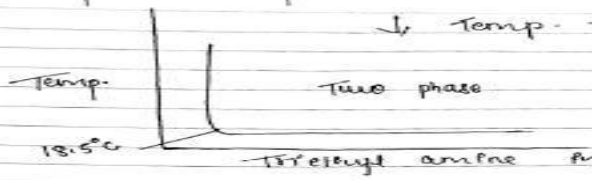


fig. of Consolute temp or Critical soln temp

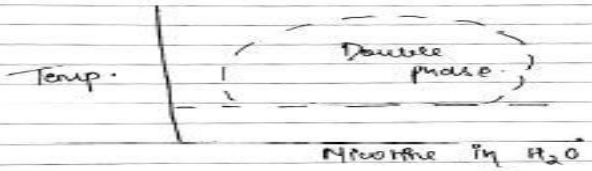
In certain liquid pairs such as triethyl amine & water, solubility increase as the temp. lowers and hence this is known as

Lower consolute temp. or lower critical soln temp.

↓ Temp. = ↑ Solubility



A few mixture such as Nicotine & water exhibit an upper critical solution temp. as well as lower critical soln. temperature



→ Between this temp. they are partially miscible. A final type of mixture such as ethyl — ether & water has neither an upper or lower critical temp. and this mixture remain partially miscible over the entire temp. range.

OR

What is the difference between ideal solution and real solution? Explain the factors influencing solubility of drugs.

Non Ideal Solution.

When heat of soln is positive then it is non ideal soln. It is due to various attractive forces between solute, solvent and solute-solvent molecules.

Application.

→ Help in practical demonstration

→ It enhance the solubility.

→ It decrease the partial miscibility

factor affecting solubility of drug.

- Effect of pressure
When pressure increases then solubility also increases According to Henry's law
$C = kP$
where
C = Conc^n of dissolve in gas per litre (solvent)
P = partial pressure in mm Hg
k = solubility constant or proportionality constant

- Effect of Temperature
In gaseous form temp. increases then solubility decrease and in liquid form temp. increases the solubility increase
In gaseous form solubility decreases because of greater tendency of the gases to expand in comparison of solvent.

- Effect of electrolyte and Non-electrolyte
Solubility of electrolyte also increases
Ex- NaCl and non electrolyte such as sugar is also known as salting out

- Effect of Chemical reaction.
When the chemical reaction increase then solubility also increases. Chemical reactions of any between a gas or a solvent greatly increases the solubility of gases in the solvent.

Ex- HCl reaction with H_2O by H-bonding when dissolve in water

- Particle size effect
When particle size is small then solubility is increases and vice-versa.

- Effect of pH
Most of the drugs are weak acid and weak bases, it is partially soluble in water.
for weak acidic drug in it unionise form, generally less soluble than ionise form., when the solubility of decreases with decrease in pH, for weak basic drug solubility decrease with decrease in pH.

- Effect of complex formation.
It may be increase or decrease in complex formation -
→ Soluble complexation like Iodine with povidone to form water soluble povidone iodine complex.
I_2 + Povidone → Iodine complex formation
→ Insoluble complexation, it decreases the solubility
Ex - Tetra cycline with Calcium ions
Present in milk or any other preparation is less soluble.

* Solubility of gas in liquid, solubility of liquid in liquid.

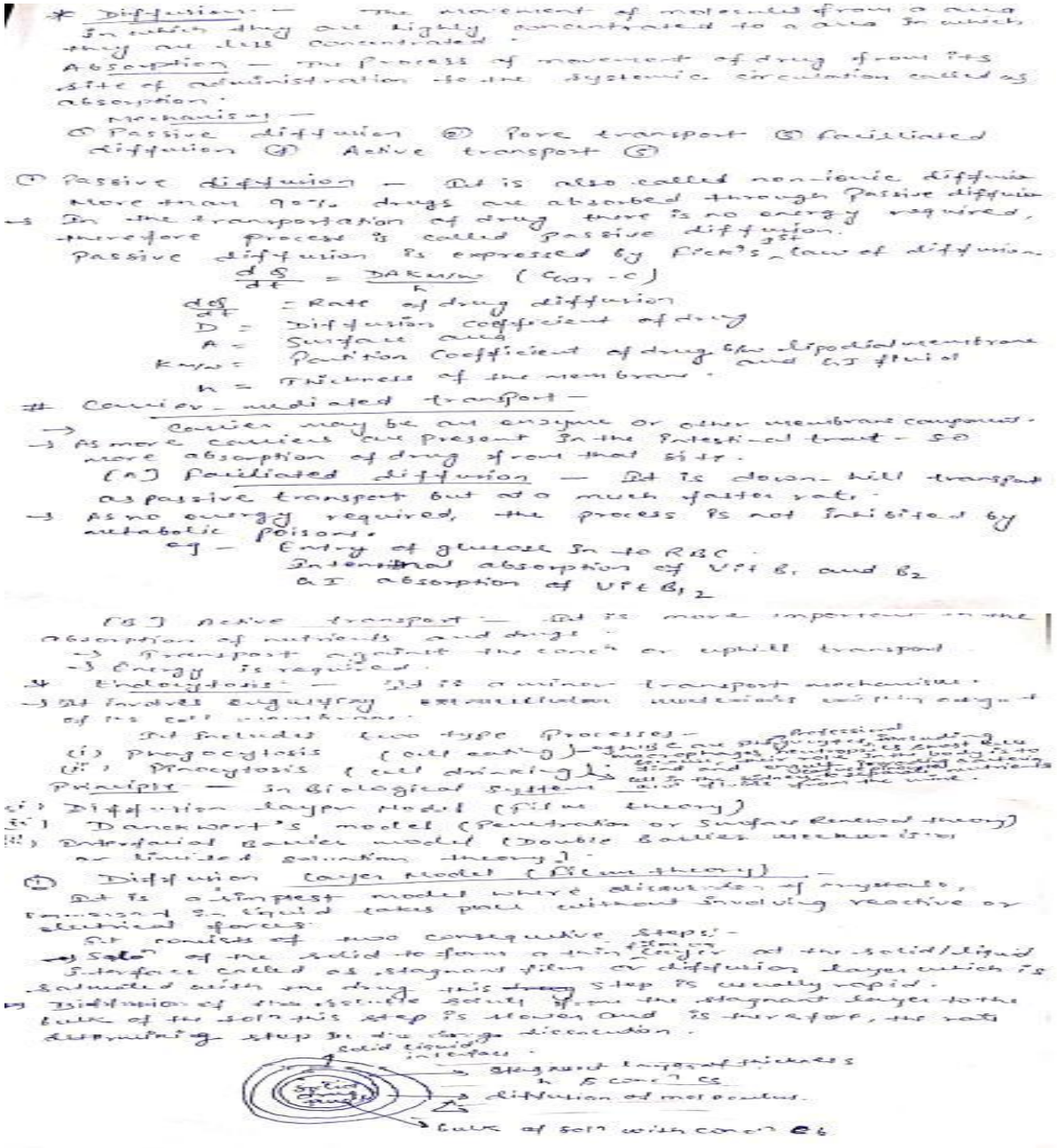
Ex Solubility of gas in liquid like O_2 and Nitrogen used as propellant in pharmaceutical aerosal formulation.

Solubility of gas in liquid represent the conc^n of dissolve gas in the liquid when it is in equilibrium with some of the pure gases above the solution.
→ Liquid in liquid like aromatic waters such as chloroform water and peppermint water, spirit and elixir.
- Lotion, spray - also consider as solution of one liquid to another

SECTION-C

3. Attempt any one of the following: (1x10=10)

i. Define the term Diffusion and explain its mechanism. Describe the diffusion principles in biological system.



Nernst Noyes only diffusion under steady state conditions. Modified by Noyes & Whitney established another eqn -

$$\frac{dC}{dt} = k(C_s - C_b)$$

$\frac{dC}{dt}$ = dissolution rate of the drug
k = dissolution rate constant (first order)
C_s = Conc of drug in stagnant layer
C_b = Conc of the drug in bulk of the soln time t.

(2) Danckwert's Model (Penetration or surface Renewal theory) -

Acc to this model, the agitated fluid consist of mass of eddies or packets of fresh solvent are continually being exposed to new surface of solid, and then are due to which the drug conc at the solid/liquid interface never reaches C_s and has a lower limiting value of C_i since, the solvent packets are exposed to new solid surface each time, the theory is called as surface renewal theory.

The Danckwert's model is expressed by eqn —

$$V\frac{dC}{dt} = \frac{dm}{dt} = A(C_s - C_b)\sqrt{sD}$$

where m = mass of solid dissolved
and s = rate of surface renewal

(3) Interfacial Barrier Model (Double Barrier or Limited Solvation theory)

The diffusion layer Model and the Danckwert's model were based on two assumptions:

(a) the rate determining step that controls dissolution is the mass transport.
(b) Solid - Soln equilibrium is achieved at the solid/liquid interface.

→ A/C to interfacial barrier model, an intermediate conc C_i can exists at the interface as a result of solvation mechanism and is a function of solubility rather than diffusion.

$k = C_i = k_i(C_s - C_b)$

where, C_i = dissolution rate per unit area
and k_i = effective interfacial transport constant.

→ In this theory, diffusivity D may not be independent of saturation conc C_s. The interfacial barrier model can be extended to both diffusion layer model and the Danckwert's model.

ii. Define complexation. Give the classification. Explain the crystalline structures of complexes and thermodynamic treatment of stability constant.

Complexation :- It is defined as an association of two or more chemical constituent - complexes generally result form a donor acceptor mechanism which by two or more chemical constituent forming it coordinate compounds.

→ The donor should be a ion metallic ion or an atom to donate a pair of e⁻ to the acceptor, the acceptor should be a metallic ion or an atom.

→ During the formation of complexes various intermolecular forces like coordinate and involve of these are Vanderwaal's force electrostatic force, Dipolar & sometime hydrogen bonding is also involve.

• Classification of Complexes :-
According to the type of complex which from there are classified into the following type.

① Metal ion compound
— Inorganic type
— Chelates
— Olefin type
— Antipatric type
— π bond] → Sandwich
— σ - bond
—

2. Organic Molecular
— Ejuishome Complexes
— Biare acid
— Caffine
— Pigment type

3. No bond Compound
- Cathrate
- Channel lattice type
- Layer type
- Manomolecular
- Macromolecular

① Metal ion [Inorganic type] :-
In this an inorganic metal complex is formed which ligand is co-ordinated with co-valent bond.
During this process the intermolecular forces involved are electrostatic forces.

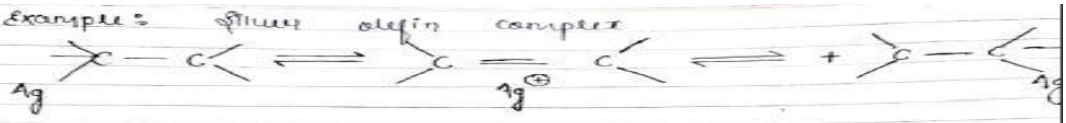
② Co-ordinate Number
It is defined as maximum number of group that can combined to coordinate with central atom.
Example :- Here ammonia is co-ordinating with the central atom
i.e Cobalt chloride forming a inorganic metal complex of hexamine cobalt III chloride $[Co(NH_3)_6]^{3+}Cl^-$

In this co-ordinate number is 6.

Chelate
A substance containing two or more donor group combined with a metal ion to forming complex known as chelate.
Example : EDTA - It is a popular chelating agent is a hexadentate

Olefin type :- Aqueous solution of certain metal ion such as Pt, Pd, Hg, Ag can absorbs olefin such as ethelene to yield water soluble ~~organometallic~~ complexes.

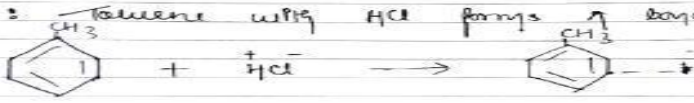
Example: Silver olefin complex



① Aromatic Complexes

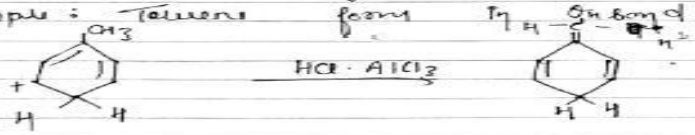
① π bond complexes:
Aromatic bases such as benzene, toluene & xylene form π bond complexes

Example: Toluene with HCl forms π bond complex



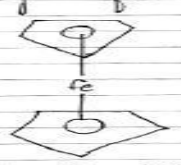
② σ- bond
It involves the formation of σ bond with the aromatic ring.

Example: Toluene form π-σ bond with HCl – AlCl3



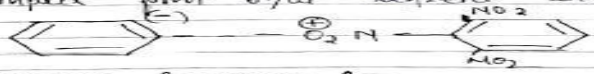
③ Sandwich:- In this one e⁻ of each ring is used in binding the metal atom and it exhibit an aromatic character. Such compounds are known as sandwich compound

e.g Ferrocene



2. Organic Molecular compleration
These are also known as addition complexes which are formed by the union of two organic molecules held together by electrostatic forces or hydrogen bond.

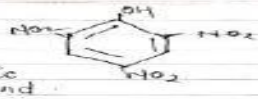
④ Charge transfer complexes:
These complexes are formed by sharing of π-e⁻
e.g- Complex form b/w benzene and m-nitro benzene



(A) Quinhydrone Complexes:-
Mixing of alcoholic sol^n of equally molar quantities of hydroquinone and benzoquinone, green crystal of quinhydrone complex settle down

Hydroquinone + Benzoquinone → Quinhydrone (green crystals complex)

(B) Picric acid

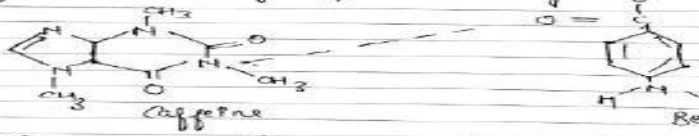


Polynuclear aromatic compound

e.g - Bupivacaine picrate - local anaesthetic

Picric acid complexes with many polynuclear aromatic compound

(C) Caffeine:- (Hydrogen bonding)



Caffeine

Benzocaine

A large number of compound containing -OH, -NH linkage exhibit hydrogen bonding.

By this the five hydrogen atom of one molecule are attracted to the negative oxygen atom of other molecule

Hydrogen bonds are relatively weak bonds with 10% of the energy

(B.) No Bond complexes

→ These complexes are formed due to the ability one of the constituents of the complex to get entrapped in the cage like crystal structure of the other

→ These complexes generally do not form any attractive forces b/w constituents and therefore there are also known as no Bond complex

> Co-grate
Ex: Warfarin - sodium - (anti coagulant) - water - propyl alcohol

2) Channel lattice complex

Vitamin A palmitate
↓
Urea

Vitamin A palmitate can be easily complex with urea

Layer type

Bentonite → Mono molecular
↓
No. of H2O, Alcohols glycols

Monomolecular: the principle constituents of bentonite are almost a no. of H2O, alcohol and glycol b/w the layers of lattice

IV. Monomolecular type
(B) Cyclodextrin → Mono molecular
molecular

(A) Not dependent on the guest
the size of the guest no. of guest molecules

Cyclodextrin molecular structure represent A monomolecular glass molecular which can get entrapped a no. of guest

V. Macromolecular type:
Synthetic Zeolite
Dextrins
Silica gel
→ MWS
No. of GM

Macromolecular: Inclusion compound includes synthetic zeolite dextrin and silica gel.

Thermodynamic treatment of stability constant for binding constant and equilibrium constant:

* Stability constant is a binding constant, equilibrium constant for the formation of a complex in soln.
→ It is a measure of the strength of the interaction between the reagents that come together to form the complex.

The stability constant of the metal complexes are related to thermodynamic property such as
① free energy change (ΔG)
② Enthalpy change (ΔH) Internal energy along with Temp. Pressure & Volume
③ Entropy (ΔS) Energy which is unable to do work.

The relationship between standard free energy change ΔG of complexation and the overall stability constant K can be given by the eqn

$$\Delta G = -2.303 RT \log K$$

Standard enthalpy change ΔH may be obtained from the slope of a plot of log K versus 1/T

$$\log K = \frac{\Delta H}{2.303 R} \frac{1}{T} + \text{Constant}$$

When the values of K at two temp. are known then the following eqn may be used.

$$\log \frac{K_2}{K_1} = \frac{\Delta H}{2.303 R} \cdot \frac{T_2 - T_1}{T_1 T_2}$$

The standard entropy change ΔS may be obtained by the following eqn.

$$\Delta G_1 = \Delta H - T\Delta S$$

As the stability constant for complexation increases, ΔH and ΔS become more negative.

As the binding between the donor and the acceptor becomes stronger the ΔH becomes more negative.

Inorganic molecules type - Polymeric Complexes.

— Polymeric materials such as polyethylene glycols, polysorbate, polyvinyl pyrrolidone, sodium carboxy methyl cellulose ($C_6H_{12}O_6$) forms complexes with a large number of drugs.

Such interactions can result in precipitation, flocculation, solubilization and alteration in pharmacological effects.

PVP has been shown to form molecular complexes with many substances.

PVP + Tannic acid or polyacrylic acid → Water insoluble complex

Crystalline structure of Complexes

face centred cubic

simple cubic

simple cubic

body centered cubic

Crystal line structure is a description of the ordered arrangement of atoms, ions, or molecules in a crystalline material.

The smallest group of particles or atoms in the material that constitutes the repeating pattern in the unit cell of the structure.