# ÷ Industrial Pharmacy ÷ 5th Semester

## ← Unit - 1st →

**Preformulation Study ÷** It is an investigation of the physical chemical properties of a drug substance to develope a safe effective and stable dosage form.

**Objectives of Preformulation ÷**

→ To establish the physio chemical parameter of a new drug.

→ To determine the kinetics and stability.

→ To establish the compatibility with common excipient.

→ It provides direction into how drug product should be processed and stored to ensure their quality.

### Major area of preformulation research

(1) Organoleptic Character.

(2) Bulk Character.
- → Crystallinity and polymorphism.
- → Hygroscopicity.
- → Fine Particle charecterization.
- → Powder flow Properties.

3) Solubility Analysis ÷
- → Ionization Constant Pka.
- → PH Solubility profile.

→ Common ion effect.
→ Thermal effect.
→ Solubilization.
→ Partition coefficient.
→ Dissolution

(4) Stability Analysis :-

→ Stability in toxicology formulation.
→ Solution stability.
→ pH rate profile.
→ Solid state stability
→ Bulk stability.
→ Compatibility.

## Parameter of Study of preformulation

1. Organoleptic Character →

Organoleptic
↓ ↓
Sensary organ  Lower.

organoleptic properties is those properties of any compound which can be identified by the odour, smell, taste etc.

(a) Color :- Color is a generally a function of a drugs enhence chemical structure relating to a certain level of unsaturation.
→ If the color is undesirable or variable in corporation of a dye in the final product is recommended.

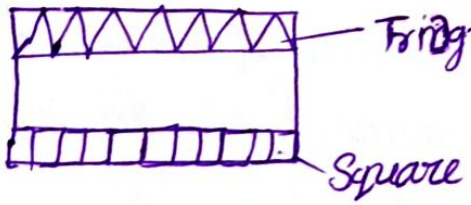
b) Taste :- If the taste unpalatable it is recommended to use the less soluble or ester form of the drug.

⇒ The odour and taste may be supressed by using suitable flavour and exipients or by coating the final product.

2) Bulk character :-

a) Crystallanity :- In the bulk of any material that is solid the atom or molecule are arranged in a regular manner The molecule of solid has same structure in crystallinity form.

Crystal < Crystal Habit
Crystal Internal Structure.



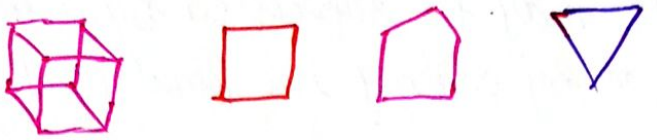

The crystallanity of any molecule can be characterised into two classes.

a) Crystal Habit :- Crystal Habit source the outer Appearance of any molecule.

b) Crystal Internal Structure :- The crystal habit are outer appearance of particle is depend upon the crystal Internal Structure.

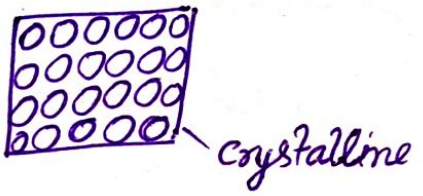
⇒ Changing in internal structure crystals habit also will be change.

## Different shape of crystal:-

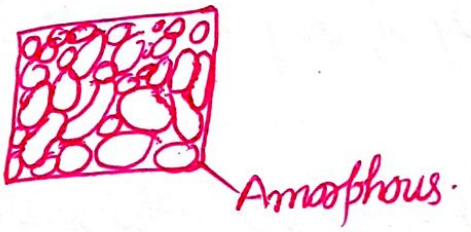


## Depending on Internal structure compound are classified as-

→ **Crystalline**:- Crystalline solid are those solid in which the particle have the same shape and they have a fixed arrangement they are called crystalline solid.




→ **Amorphous Solid**:- The molecule of the amorphous solid has different shape and arrangement in an irregular manner.




**Note**:- The solubility rate of amorphous solid is higher than the crystal solid due to the voids the voids is greater in crystal than Amorphous.

### (B) Polymorphism:-

Those solid particle which do not have a fix geometry and the fix structure.

→ The shape of the particle change one form to another form in continuity. are called polymorphism. and the phenomenon is known as polymorphism.

⇒ polymorphism are devided into two types.

i) Enantiotropic :- Those polymorphism compound which continuously change their structure form. one to two and another form at any temp or pressure. is called enantiotropic.

Ex - Sulpher.

ii) Monotropic :- The polymorphism which do not change continously and unstable at all temp and pressure is called monotropic.

Ex:- Glyceryl Stearate

## (c) Hygroscopicity :-

. Those compound which absard moisture and become wet by the called as hygroscopic compound and the process is known as Hygroscopicity.

→ Absorption and moisture depends upon the Atmospheric. humidity, temperature, surface Area, Exposure. and the mechanism of moisture uptake

→ The degree of hygroscopicity is classified into four classes-

1) Slightly hygroscopic:- Increase in weight is $\geq 0.2\%$ w/w and $< 2\%$ w/w

2) Hygroscopic:- Increase $\geq 0.2\%$ w/w $< 15\%$

3) Very hygroscopic:- Increase weight is $\geq 15\%$ w/w

4) Deliquesent:- Suffecient water is absorb to form a solution.

## Analytical Method to determine the hygroscapicity:-

1) Gravimetry.
2) Karl fisher Titration.
3) Gas Chromatography.

## D) Fine Particle Charecterization:-

**Particle Size, Shape & Surface Area:-** The study of particle size particle shape & Particle surface area is very important for the determination of the Physical as well as chemical property of the drug.

⇒ The physical and chemical properties like -

- Dissolution Rate
- Solubility.
- Bioavailibility.
- Density
- Bulk density.
- Angle of repose.
- Cars Index.

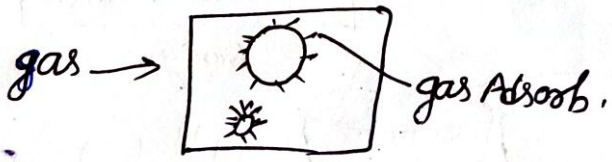
→ Everything is depends upon the particle size and shape parameter.

## : Particle Size determination :

Particle size can be determine by the microscopy method by the sieving method etc.

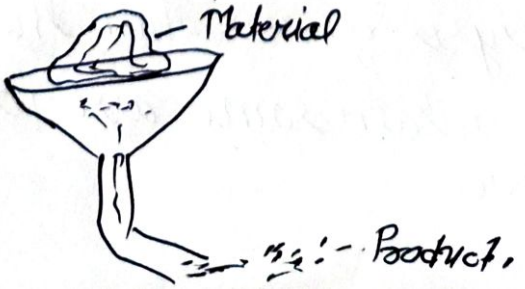
## Particle Surface area determination (BET)

→ Surface area of any particle is determined by the BET Theory of absorption. (Brunauer Emette Teller) (BET)
→ In this method the gas is Adsorb on the surface of particle and by the conc. of gas surface area of partice is determine.




## (E) Powder flow Properties :

→ The flow property of powder depends upon the partice size and shape
→ And the physical, chemical properties of powder like Angle of repose, Cars Index, is depends of flow property.



## (F) Density of Powder :-

→ It is the ratio of the mass and volume of the powder.

$$d = \frac{M}{V}$$

It is of two types –

(i) Bulk density.

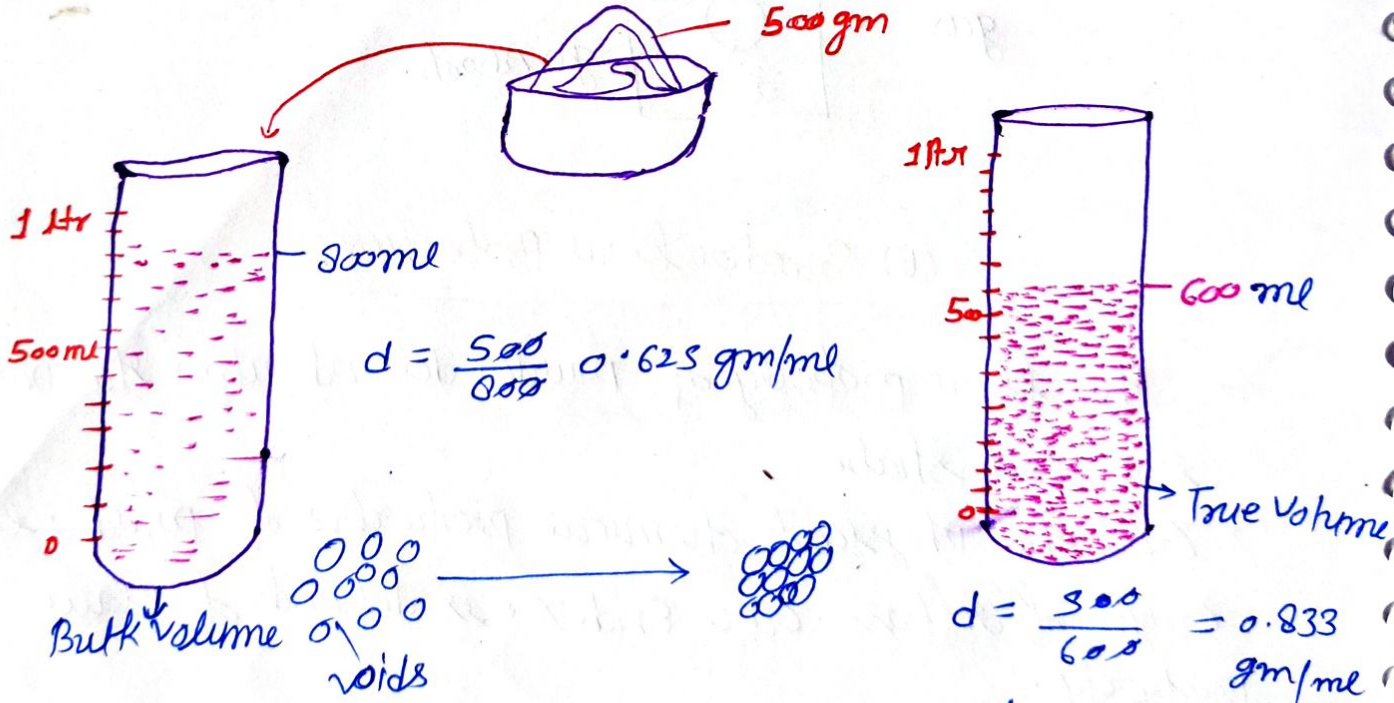
(ii) Tapped density (Absolute density)

(i) **Bulk density :-** It is the ratio of the mass of the powder to bulk volume.

$$d = \frac{\text{Mass}}{\text{Bulk volume}}$$

(ii) **Tapped density :-** It is the ratio of the mass of the powder to true volume.

$$d = \frac{\text{Mass}}{\text{True Volume}}$$




→ Always tapped density is greater than the bulk density because bulk density contain some air particle or some intermolecular space.

(G) Carrs Index :- Carrs Index is a mathmetical expression. Which is defind as it is the ratio of difference of Tapped density to Poured density upon tapped density.

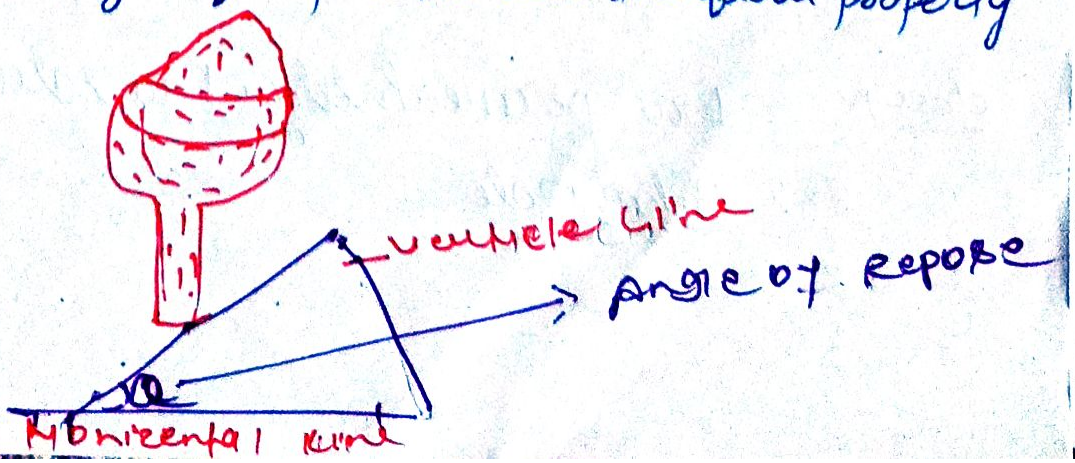
$$\text{Carrs Index \%} = \frac{\text{Tapped density} - \text{Poured density}}{\text{Tapped density}} \times 100$$

(H) Hausner Ratio :- Hausner ratio is a mathmetical expression for the density it is defind as the Tapped density to its Poured density.

$$\text{Hausner Ratio} = \frac{\text{Tapped density}}{\text{Poured density}}$$

(I) Angle of Ripose :-

- Angle of Ripose decide the flow property of any powder
- $\theta$ is the angle b/w Horizental line and Verticle line any Hip of the powder.
- As well as the angle of ripose is less the flow property is less.



| Flow | Angle of Repose | Carr's Index |
|---|---|---|
| (i) Excellent | < 25° | 5 – 15 |
| (ii) Good | 25° – 30° | 12 – 16 |
| (iii) Fare to Possible | 30° – 40° | 18 – 21 |
| (iv) Poor | 40° – 50° | 23 – 35 |
| (v) Very poor | 50 – 60° | 33 – 38 |
| (vi) Extremely Poor | > 60 | > 40 |

## (J) Biological classification System (BCS)

Class-I → High permeability, High solubility.

Ex- Metoprolol, Paracetamol.

class-II → High permeability, low solubility.

Ex. Glibenclamide, Bicalutamide, Ezetimibe, Aceclofenac,

→ The bioavailability of these products is limited.

class-III → Low permeability, High solubility.

Ex- Cimetidine.

Class IV → Low permeability, Low solubility.

Ex: Bifonazole

| | Solubility | Permeability |
|---|---|---|
| Class - I | High ↑ | High ↑ |
| Class - II | High ↑ | Low ↓ |
| Class - III | Low ↓ | High ↑ |
| Class - IV | Low ↓ | Low ↓ |

L - 5

## ÷ Solubility characterization ÷

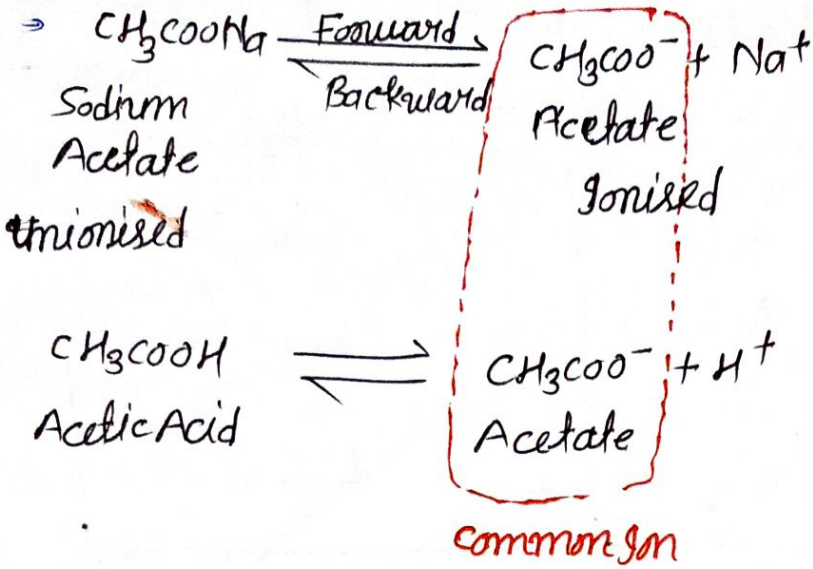
(A) **Ionization Constant (PKa):** The degree of Ionization of any week electrolyte drug is very imp. for the study of their solubility and dissolution rate.

→ With the help of Henderson-Hasseslebach equation. we can calculate the fraction of ionization of any drug molecule at particular pH.

For Acidic Compounds ÷ $pH = pKa + \log \frac{(Unionized\ drug)}{(Ionized\ drug)}$

For Basic compound - $pH = pKa + \log \frac{(Ionized\ drug)}{(Unionized\ drug)}$

(B) **Common Ion Effect ÷** When any common ion is present in the solution then the solubility of any drug is decrease. this is called common ion effect.




⇒ Suppose we dissolve (any solution) drug Sodium Acetate in a acetic Acid solution.

- Because we know that in acetic Acid solution Acetate ion is allready present and now when sodium Acetate is dissolve. it breaks into the Acetate ion and sodium ion.

⇒ And due to the presence of common acetate ion concentration of ionised form is more. so reaction moves backward direction. and the solubility of sodium acetate is decrease it is called common ion effect.

(C) Theromal effect :- When any solute is dissolve into the solvent then they form the solution during the formation of solution they release some energy or absorb some energy this is called heat of Solution.

⇒ The solubility is a thermodynamic process when the solute is dissolve in to solvent and after making solution. they involve some amount of heat this is called heat of solution.

→ According to heat of solution it is of two type of process

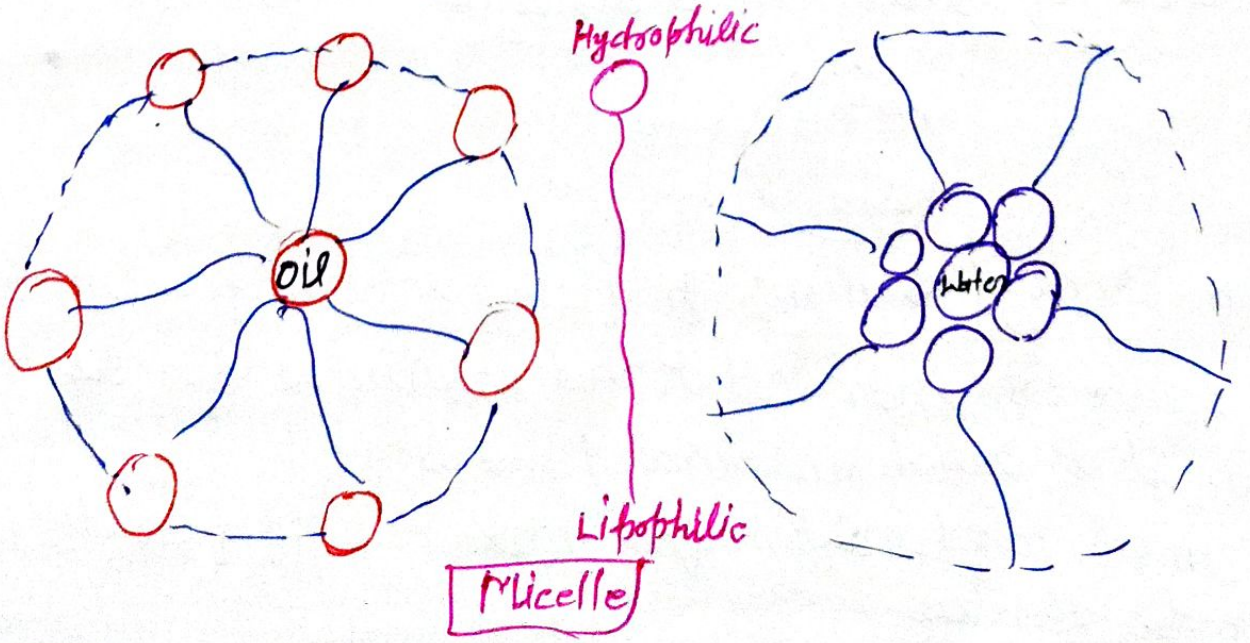
(i) Endothermic Process.
(ii) Exothermic Process.

→ When the process is Endothermic then after increasing the heat solubility is increase.

→ When the process is Exothermic then after increasing the temperature solubility is decrease.

## (P) Solubilization

- When two immiscible liquid are mixed then they are not solubelize in one another.
- But after the use of surfectant they are solubelize in one another and this is called solubelization.
- The mechanism of solubelization is based on micelle formation.
- The hydrophilic head of surfectant bind with water and the lipophilic tail is bind with the oil so they comes closer and their Interfacial tension is reduce and they solubelize easy



**Solubility :-** The mixture of solute and solvent is called solution.

→ Solute are those component of solution which are present in less amount and solvent which are present in large amount. And when solute particle completly dissolve in solvent then it is called solution.

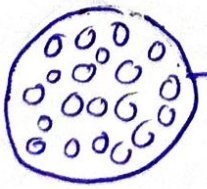
⇒ The maximum amount of solute which can be dissolve in 100g of solvent is called solubility of the drug.

⇒ The solubility of drug is depends upon the nature of solute and solvent, particle size, surface area and Temprature etc.

**Types of Solution :-** On the basis of solubility solution can be expressed as following three types :-

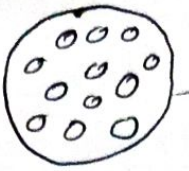
(i) **Saturated Solution :-** In a 100g solvent at room temp the maximum amount of solute which can be dissolve is called saturated solution.

⇒ In a saturated solution at same temp no any extra particle of solute can be dissolve.




(ii) **Unsaturated Solution :-** In a 100g solvent few amount of solute less than saturated solution is dissolve then it is called unsaturated solution.

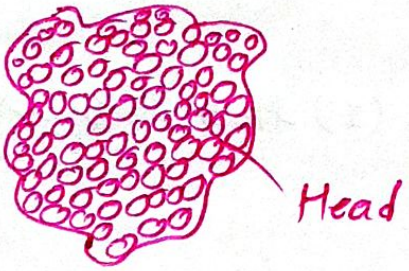
⇒ In unsaturated solution few more amount of solute can be dissolve




(iii) Super Saturated Salution:- In a 100g solvent in maximum amount of solute can dissolve after heating is called super saturated solution.

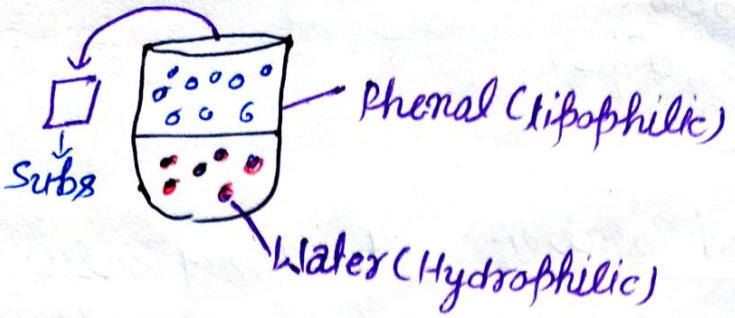
→ When temp is increase then the surface area of solvent is increase. so some more amount of solute can be dissolve in saturated solution

→ After reaching supersaturated condition no any solute particle can be dissolve.




Partition Cafficent (Distribution law) - In a binary solution of two immiscible liquid when any drug is mixed then some fraction of drug is dissolve in oil phase and some fraction of drug is dissolve in water phase this is called Distribution law.

→ The ratio of drug is dissolve in lipophilic medium to the drug dissolve in hydrophilic medium is called distribution coefficient or partition coefficient.




$$\text{Partition Cofficent} = \frac{\text{Drug dissolve in oil Phase}}{\text{Drug dissolve in water phase}}$$

$$P = \frac{X_o}{X_w}$$

→ if (P) is more than one (1) then subs is lipophilic in nature

→ (P) is less than one (1) then subs is hydrophilic in nature.

→ P = Partition Cofficent.

$X_o$ = Friction of drug dissolve in oil.

$X_w$ = Friction of drug dissolve in water

→ If the value of partition cofficent is greater than one it means the value of $X_o$ is more so the nature of drug is licophilic.

→ If the value of partition cofficent is less than one then the value of $X_w$ is more and the nature of drug will be hydrophilic. main application of partition cofficent is determine the nature of unknown drug sample.

→ After determination of nature we can choose the suitable solvent.

## Method of determination of partition Cofficent :-

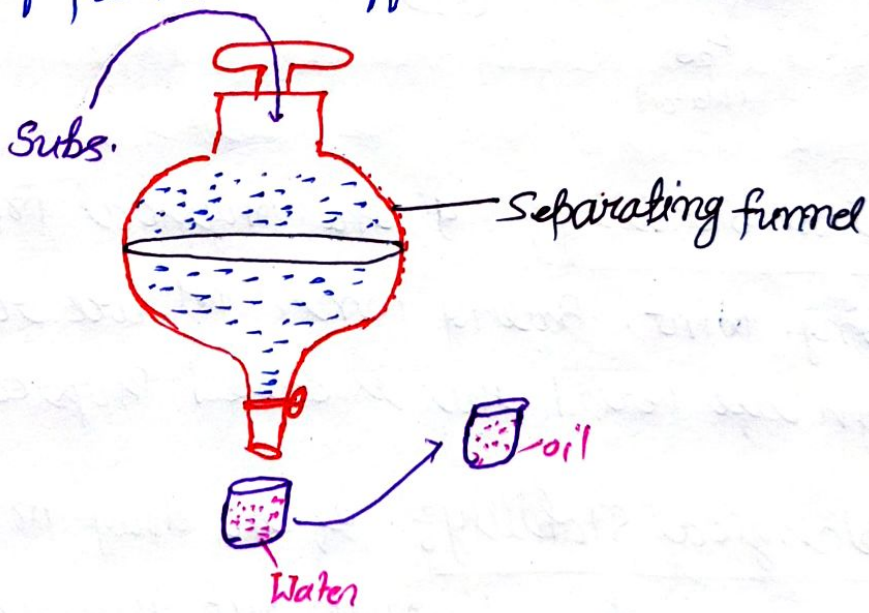
It is determine by using separating funnel apparatus Add 50 ml water and 50 ml octanal (oil) in separating funnel.

→ Now add the powder drug mixture in separating funnel and shake vigorously.

→ Left the separating funnel for thirty minute and takes out the oil and water in separate beaker.

→ By using UV spectroscopy or HPLC we can determine the concentration in water and oil.

→ The value of partition cofficent is determine by using formula.

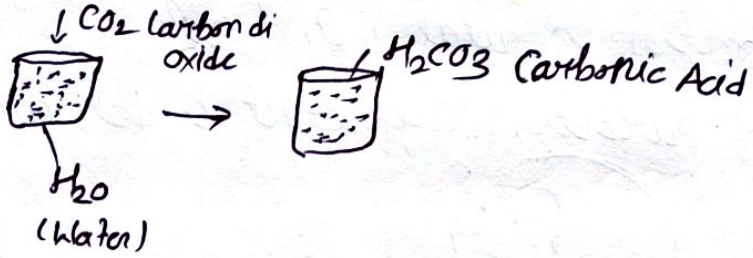


# ÷ Stability Characterization ÷

**Stability ÷** The physical, chemical, Microbiological Therapeutical and Toxicological properties of any drug or material is remains constent as per the beginning.

It is of following type -

(i) **Chemical Stability ÷** The chemical nature of drug remain constent through out the light or Period This is called chemical stability.




(ii) **Physical Stability ÷** If the physical properties like Melting point, Boiling point, pH are remain constent through life period this is called Physical stability.

(iii) **Microbiological Stability ÷** If the drug product is remain free from microbes through out the life period is called Microbiological Stability.

(iv) **Therapeutical Stability ÷** Any drug molecule which have same therapeutic responce through out there time period this is called Therapeutical stability.

**Toxicalogical Stability:** If the drug product free from toxic substance through the life period this is called toxicalogical Stability.

→ Solubility can be determine by two method -

(i) **Solution Stability method :**

(ii) **Solid State Stability method :-**

## (i) Solution Stability Method:

**Hydrolysis:** When the any drug is dissolue in to the water then it may gives the hydrolysis reaction.

→ And after Hydrolysis reaction it breaks into two parts.

→ If dissociate into two parts then it is hydrolysis.

⇒ Then it is unstable and it is remain same in the the water this is called Hydrolysis.

KCl Potassium Chloride

$H_2O$ ↓

KOH + HCl

**Oxydation:** → $R-OH \xrightarrow{O_2} R-COOH$ (Acid)

**Photolysis:** Some drugs are Photolised in the presence of sunlight

$CHCl_3 \xrightarrow[\text{Sunlight}]{h} CCl_3$

(2) Solid Stability Study :-

(i) Compatibility :- Compatibility is a term (it means) when the drug API Molecule is mixed with the excipient molecule at high temperature then it do not show any kind of reaction and the nature of API is not change

How to Perform Compatibility Stability :- Take one gram of the API dissolve in 50 ml of water and mixed with one gram of excipient.

→ Hold this solution for 50°C temp. for 24 hr. and after 24 hr when there is any change in chemical Properties of API it means API is reacts with the excipients.

→ And if the chemical nature of API is not change it means it is compatible with the excipient.

API + Excipient

1 gm + some water

+ 1 gm Excipient

→ 50°C Heat.

(iii) Stability Storage condition :- For Study the drug sample during the expiry period is called control sample

Mfg - Aug-20
Exp. - July-22

Feb-21

Aug-21

Feb-22

**Accelerated Stability Study:** When the drug stability is determined in diff-2 temp., Pressure and Humidity condition this is called Accelerated Stability Study.