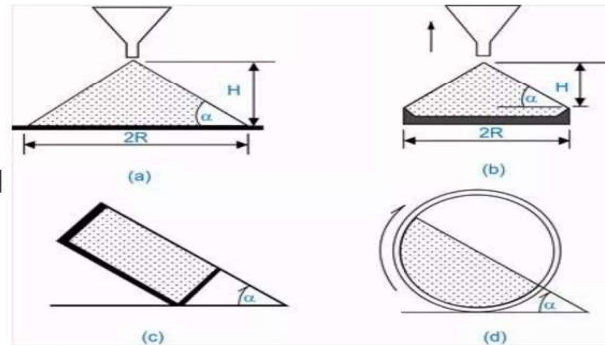


## Methods to determine angle of repose

- Static angle of repose
  - Fixed-funnel method
  - Fixed-cone method
- Kinetic or dynamic method
  - Rotating cylinder method
  - Tilting box method



## Determination of Powder Flow Properties

- Measurement of free flowing powder by *compressibility*.
- Also known as *Carr's index*.

$$CARR'S\ INDEX(\%) = \frac{(TAPPED\ DENSITY - POURED\ DENSITY)}{TAPPED\ DENSITY} \times 100$$

- It is simple, fast & popular method of predicting powder flow characteristics.

### Determination of Powder Flow Properties

Carr's Index	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair To Passable
23-35	Poor
33-38	Very Poor
>40	Extremely Poor

### SOLUBILITY STUDIES

1. Solution phase equilibrium with solid phase at a stated temperature and pressure .
2. Determines amount of drug dissolved , amount of drug available for absorption.
3. **Solubility reduction** is carried out in certain conditions:
  - ❖ Enhancement of chemical stability.
  - ❖ taste masking products.
  - ❖ Production of sustained release products.

Descriptive term	Parts of solvent required for 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

- The equilibrium solubility is based on the phase-solubility technique proposed by **Higuchi-Connors**.

#### Method

Drug dispersed in solvent in a closed container



agitated at a constant temperature using **shakers**



samples of the slurry are withdrawn as a function of time



clarified by centrifugation and assayed by HPLC, UV, GC etc

## pKa determination

- pKa is the dissociation constant of a drug
- The un-ionized drug is lipid soluble thus permeates through lipid membrane.
- The ionized substance is lipid insoluble therefore permeation is slow
- Degree of ionization depends on pH

#### Henderson-Hasselbalch equation

- For basic compounds:**  $pH = pKa + \frac{[ionized]}{[un-ionized]}$

- For acidic compounds:**  $pH = pKa + \frac{[un-ionized]}{[ionized]}$

$$\%ionized = \frac{10^{(pH-pKa)}}{1 + 10^{(pH-pKa)}}$$

- Determined by uv **spectroscopy, potentiometric titration, titrimetric method**

## SOLUBILIZATION

“Solubilization is defined as the spontaneous passage of poorly water soluble solute molecules into an aqueous solution of a soap or detergent in which a thermodynamically stable solution is formed”.

### SOLUBILIZATION...

➤ It is the process by which apparent solubility of an otherwise sparingly soluble substance is increased by the presence of surfactant micelles .

□ *MICELLES:* -

➤ The mechanism involves the property of surface active agents to form colloidal aggregates known as micelles .

## SOLUBILIZATION.....

- When surfactants are added to the liquid at low concentration they tend to orient at the air-liquid interface .
- On further addition of surfactant the interface becomes completely occupied and excess molecules are forced into the bulk of liquid.
- At very high concentration surfactant molecules in the bulk of liquid begin to form micelles and this concentration is known as *CRITICAL MICELLE CONCENTRATION (CMC)*

## General Method of Increasing the Solubility

- Addition of co-solvent
- pH change method
- Reduction of particle size
- Temperature change method
- Hydrotrophy
- Addition of Surfactant
- Dielectrical Constant
- Complexation

## Partition Coefficient

- A measurement of drug lipophilicity i,e the ability to cross the cell membrane

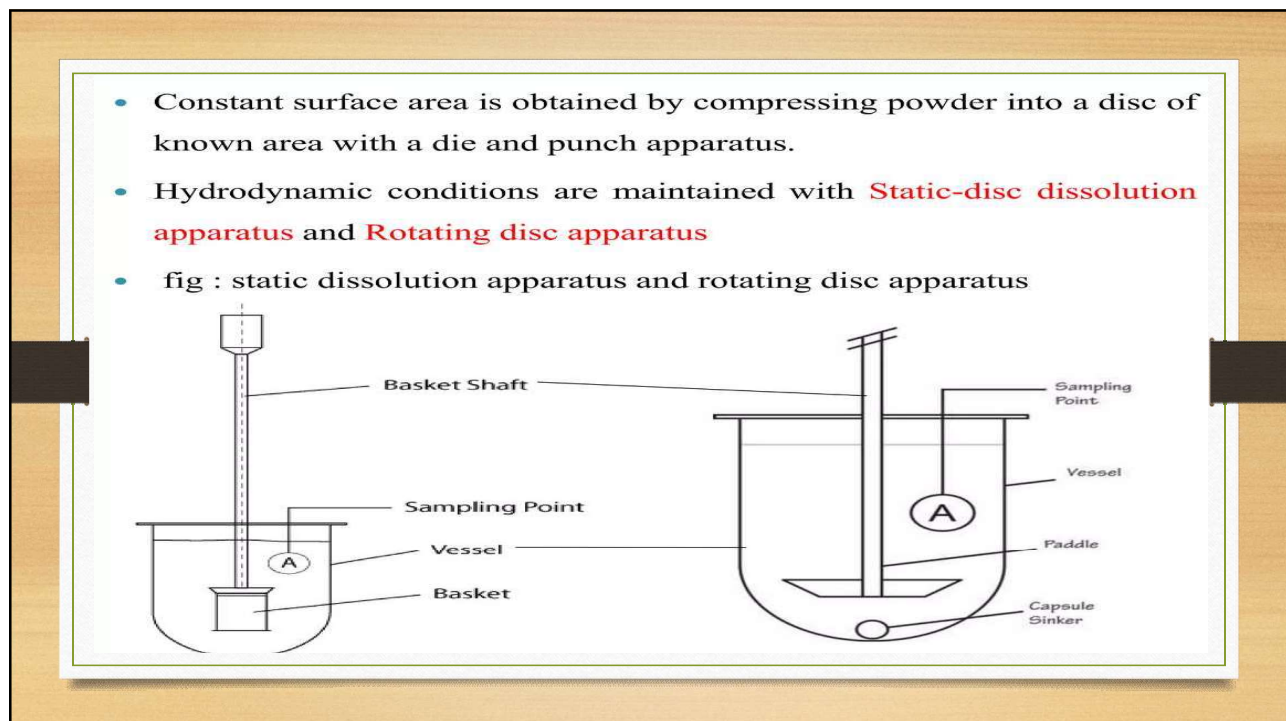
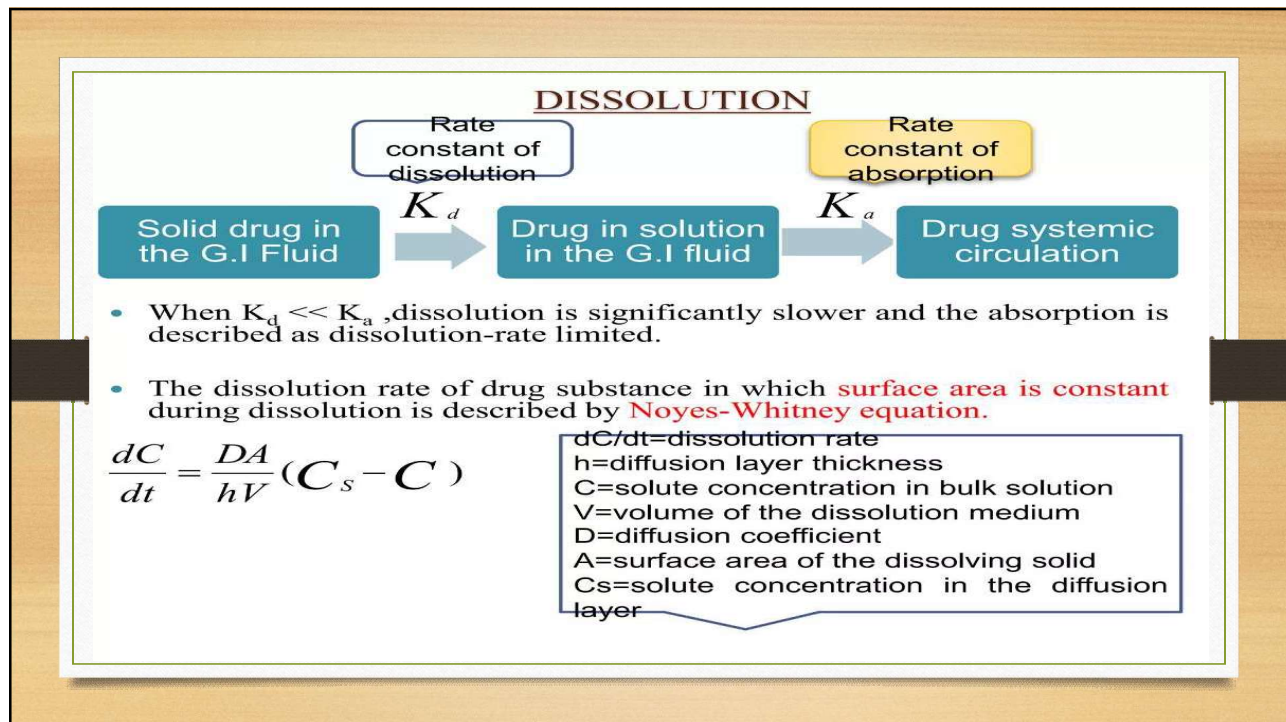
$$P_{o/a} = \frac{C_{organic}}{C_{aqueous}}$$

## Distribution coefficient

- For acids:  $\log_{10} D = \log_{10} P - \log_{10} (1 + 10^{(pH - pKa)})$
- For bases :  $\log_{10} D = \log_{10} P - \log_{10} (1 + 10^{(pKa - pH)})$
- The **octanol-water** system is widely accepted to explain these phenomenon.
- Buccal membrane : butanol-pentanol system
- Blood-Brain barrier: chloroform-cyclohexane
- Determined by SHAKE FLASK METHOD

## SHAKE FLASK METHOD

- Drug is shaken between octanol and water.
- Aliquot is taken and analyzed for drug content
- **RULE OF FIVE** : for drug permeates through passive diffusion
  1. Log P is greater than 5
  2. Molecular weight >500
  3. There are more than 5 hydrogen bond donors (number of NH + OH)
  4. There are more than 10 hydrogen bond acceptors (number of hydrogen + oxygen )
  5. Molar refractivity should be between 40-130



## STABILITY ANALYSIS

1. Solution stability
2. Solid state stability

### SOLUTION STABILITY

- The decomposition of drug occurs through **hydrolysis, oxidation, photolysis.**

#### ➤ Hydrolysis (anaesthetics, vitamins etc )

##### a) Ester hydrolysis



##### b) Amide hydrolysis



#### ➤ Oxidation

- used to evaluate the stability of pharmaceutical preparations
- Eg : steroids, vitamins, antibiotics, epinephrine

#### • Autoxidation

Materials + molecular oxygen

↓  
homolytic fission

Free radicals are produced.

- Oxygen sensitivity is measured by **bubbling air through the compound** or adding **hydrogen peroxide**.

➤ Photolysis

pharmaceutical compounds



exposure to uv light



absorbs the radiant energy

undergoes degradative reactions

SOLID-STATE STABILITY

- 1° objective: identification of stable storage conditions.  
identification of compatible excipients.
- Solid-state stability depends on the temperature , light, humidity, polymorphic changes, oxidation.

Solid-State Stability profile of a new compound

- Samples are placed in open vials and are exposed directly to a variety of temperatures, humidities, and light intensities for up to 12 weeks.
- Vials exposed to oxygen and nitrogen to study the surface oxidation and chemical stability , polymorphic changes and discolouration.
- Stability data obtained at various humidities may be linearized with respect to moisture using the following **apparent decay rate constant ( $K_H$ )**

$$k_H = [gp^l] \cdot k_0$$

gp<sup>l</sup>= concentration of water in atmosphere in units of grams of water per liter of dry air .

k<sub>0</sub> = decay rate constant at zero relative humidity

- Mole fraction of the solid that has liquefied ( $F_m$ ) is directly proportional to its decay rate.

$$\ln k_{app} \propto \ln F_m = \frac{-\Delta H_{fus}}{R} \left[ \frac{1}{T} - \frac{1}{T_m} \right]$$

- $\Delta H_{fus}$  - molar heat of fusion  
 $T_m$  - absolute melting point  
 $T$  - absolute temperature  
 $R$  - gas constant

### Drug- excipient compatibility

- Compatibility test play a very important role in the preformulation studies of oral dosage forms
- An incompatibility in the dosage form can result in any of the following changes:
  - Changes in organoleptic properties
  - Changes in dissolution performance
  - Physical form conversion
  - An decrease in potency

### METHOD

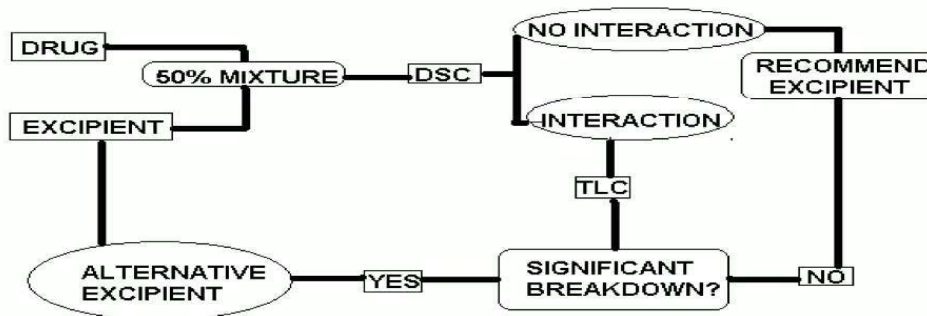
Drug + Excipients  
(1:1)

Powder samples dispersed into glass ampoules

1 ampoule      1 ampoule (sample + water)

stored at a particular temperature (50<sup>0</sup> C) and analysed

- In emulsions the studies include measuring the critical micelle concentration of the formulations
- For oral use preparations compatibility of the ingredients (ethanol, glycerine, syrup, sucrose, buffers and preservatives)



## **CONCLUSION**

- Preformulation studies on a new drug molecule provide useful information for subsequent formulation of a physicochemically stable and biopharmaceutically suitable dosage form.
- Preformulation work is the foundation of developing efficacious and economical formulations.