PREFORMULATION STUDIES: PHYSICOCHEMICAL CHARACTERIZATION OF NEW DRUG MOLECULES

Ms. Pratiksha Jayaswal

Assistant Professor

Faculty of Pharmaceutical Scienves

Rama University, KANPUR (U.P.)

CONTENTS

PREFORMULATION

- It is defined as the phase of research and development in which preformulation studies characterize physical and chemical properties of a drug molecule in order to develop safe, effective and stable dosage form.

OBJECTIVES

- To establish the physico-chemical parameters of a new drug entity
- To determine its kinetics and stability
- To establish its compatibility with common excipients
- It provides insights into how drug products should be processed and stored to ensure their quality

Major Area of Preformulation Research

- **ORGANOLEPTIC CHARACTERS**
- **BULK CHARACTERS**
  - Crystallinty and polymorphism
  - Hygroscopicity
  - Fine particle characterization
  - Powder flow properties
- **SOLUBILITY ANALYSIS**
  - ionization constant-PKa
  - pH solubility profile
  - Common ion effect-Ksp
  - Thermal effects

- Solubilization
- Partition co-efficient
- Dissolution
- **STABILITY ANALYSIS**
- Stability in toxicology formulations
- Solution stability
- pH rate profile
- Solid state stability
- Bulk stability
- Compatibility

ORGANOLEPTIC CHARACTERS

- Colour,odour, taste of the new drug must be recorded

COLOUR	ODOUR	TASTE
❑Off-white	❑pungent	❑Acidic
❑Cream yellow	❑sulphurous	❑Bitter
❑tan	❑Fruity	❑Bland
❑shiny	❑Aromatic	❑Intense
	❑Odourless	❑Sweet
		❑Tasteless

BULK CHARACTERIZATION

Crystallinity

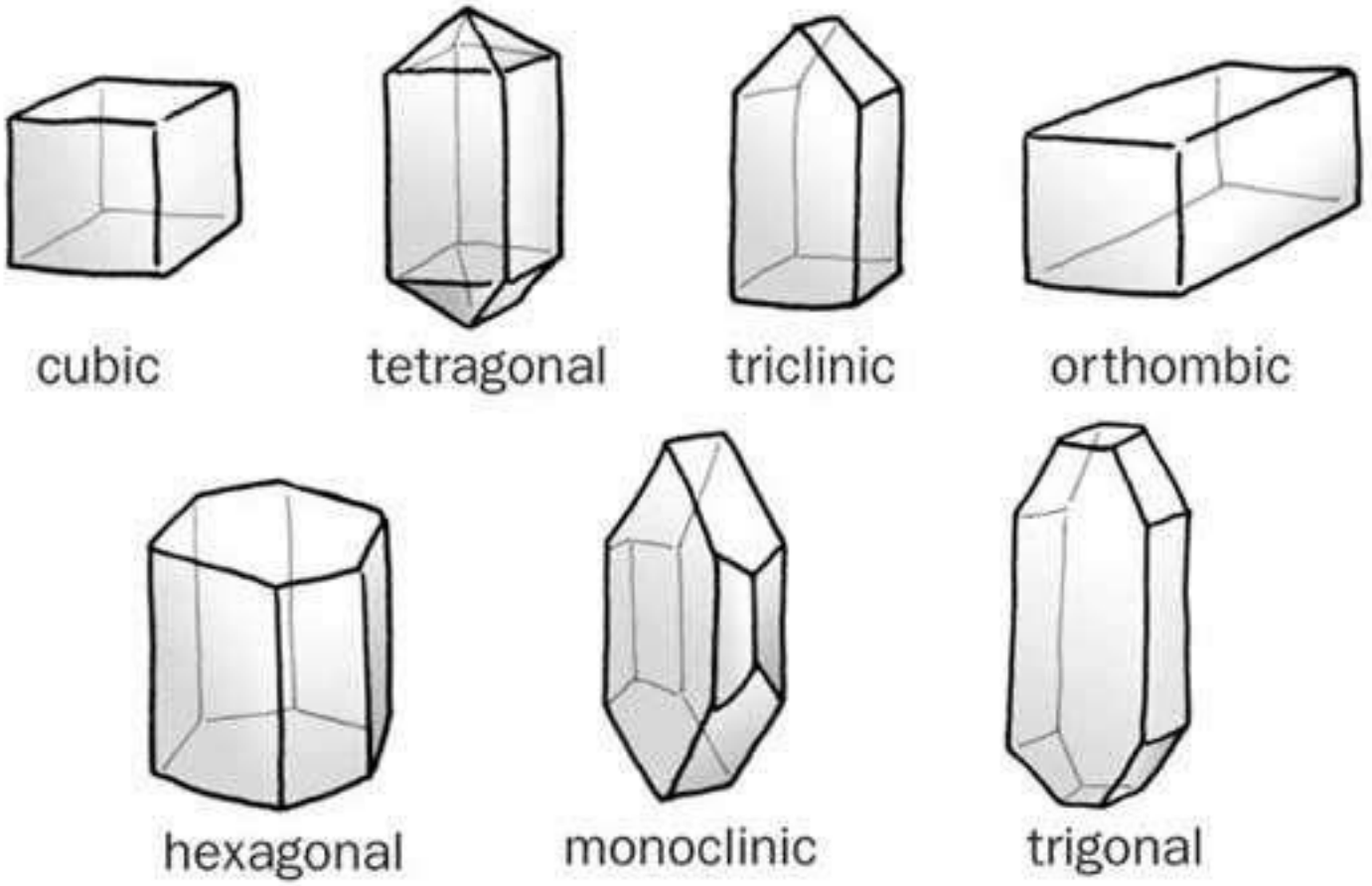
- Crystal habit & internal structure of drug can affect bulk & physicochemical property of molecule.

- Crystal habit is description of outer appearance of crystal.

- Internal structure is molecular arrangement within the solid.
- Change with internal structure usually alters crystal habit.

Eg. Conversion of sodium salt to its free acid form produce both change in internal structure & crystal habit.

Different shapes of crystals



Different shapes of crystals

- Depending on internal structure compounds is classified as

  1. Crystalline
  2. Amorphous

- Crystalline compounds are characterized by repetitious spacing of constituent atom or molecule in three dimensional array.
- In amorphous form atom or molecule are randomly placed.
- Solubility & dissolution rate are greater for amorphous form than crystalline, as amorphous form has higher thermodynamic energy.

Eg. Amorphous form of Novobiocin is well absorbed whereas crystalline form results in poor absorption.

Polymorphism

- It is the ability of the compound to crystallize as more than one distinct crystalline species with different internal lattice.
- Different crystalline forms are called polymorphs.
- Polymorphs are of 2 types
  1. Enatiotropic
  2. Monotropic
- The polymorph which can be changed from one form into another by varying temp or pressure is called as Enantiotropic polymorph.

  Eg. Sulphur.
- One polymorph which is unstable at all temp. & pressure is called as Monotropic polymorph.

  Eg. Glyceryl stearate.

Polymorphism

- Polymorphs differ from each other with respect to their physical property such as
- Solubility
- Melting point
- Density
- Hardness
- Compression characteristic

Eg. 1)Chloromphenicol exist in A,B & C forms, of these B form is more stable & most preferable.

ANALYTICAL METHODS FOR THE CHARACTERIZATION OF SOLID FORMS

- Microscopy
- Hot stage microscopy
- Thermal analysis
- X-ray diffraction
- Infrared (IR) spectroscopy
- Proton magnetic resonance (PMR)
- Nuclear magnetic resonance (NMR)
- Scanning electron microscopy (SEM)

Microscopy

- Material with more than one refractive index are anisotropic & appear bright with brilliant colors against black polarized background.
- The color intensity depends upon crystal thickness.
- Isotropic material have single refractive index and this substance do not transmit light with crossed polarizing filter and appears black.
- Advantage :

  By this method, we can study crystal morphology & difference between polymorphic form.

- Disadvantage :

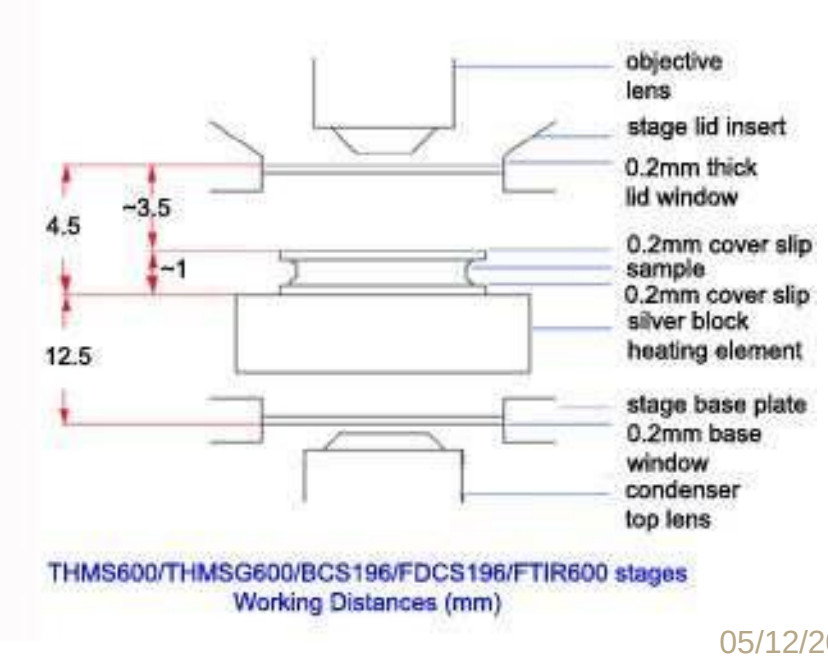
  This require a well trained optical crystallographer, as there are many possible crystal habit & their appearance at different orientation.

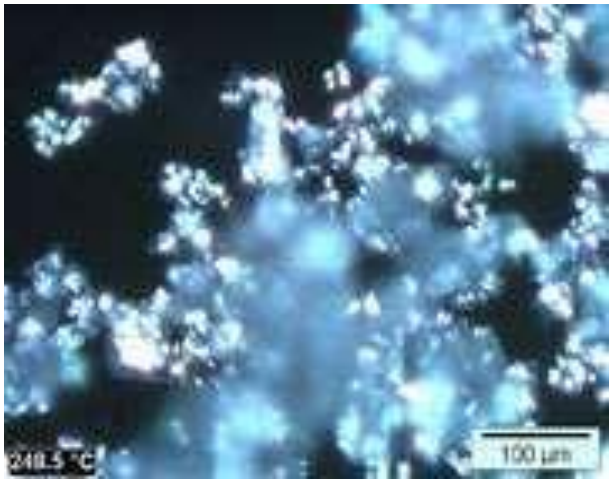
Hot stage microscopy

- The polarizing microscope fitted with hot stage is useful for investigating polymorphism, melting point & transition temp.

- <u>Disadvantage</u> :

  In this technique, the molecules can degrade during the melting process.





Thermal analysis

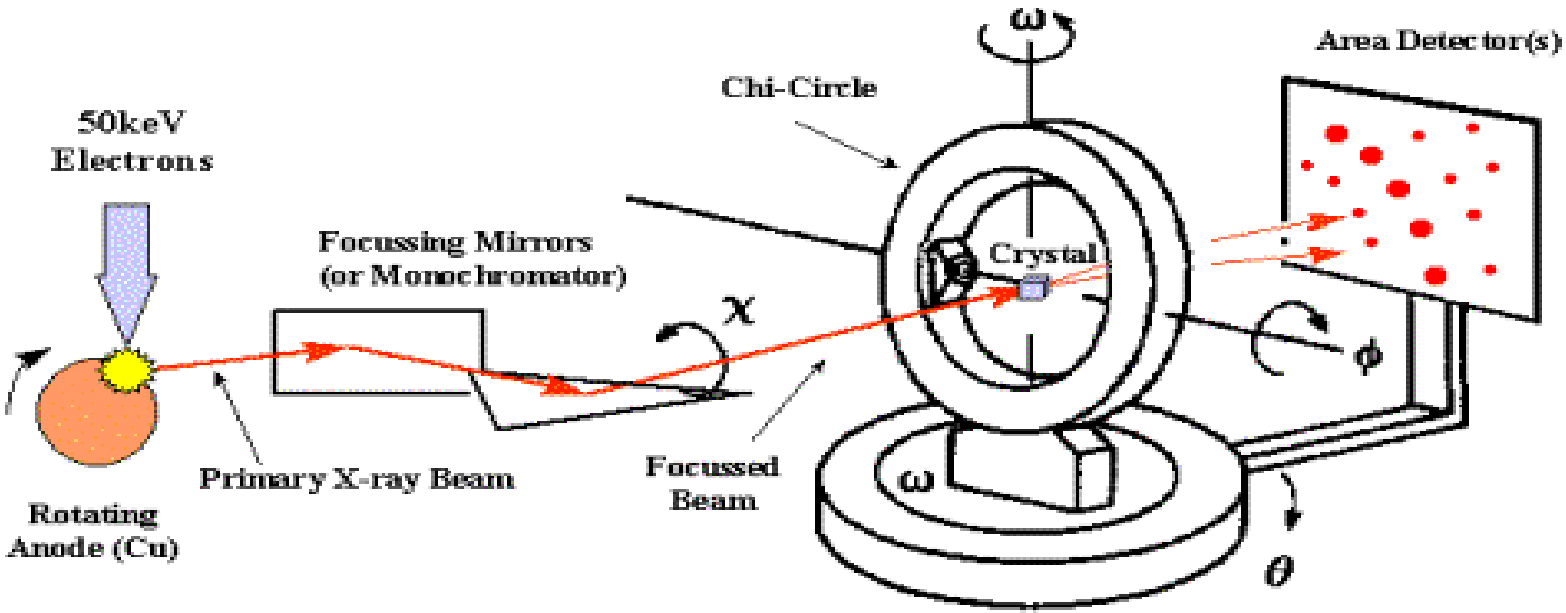
- Differential scanning calorimetry (DSC) & Differential thermal analysis are (DTA) are particularly useful in the investigation of polymorphism.
- It measures the heat loss or gain resulting from physical or chemical changes within a sample as a function of temp.
- For characterizing crystal forms , the heat of fusion can be obtained from the area under DSC- curve for melting endotherms.
- Similarly, heat of transition from one polymorph to another may be calculated.
- A sharp symmetric melting endotherm can indicate relative purity of molecule.
- A broad asymmetric curve indicates presence of impurities.

X-ray diffraction

- Working :

  When beam of nonhomogenous X-ray is allow to pass through the crystal, X-ray beam is diffracted & it is recorded by means of photographic plate.

- Diffraction is due to crystal which acts as 3 dimensional diffraction grating toward X-ray.



4-Circle Goniometer (Eulerian or Kappa Geometry)

- Random orientation of crystal lattice in the powder causes the X-ray to scatter in a reproducible pattern of peak intensities.
- The diffraction pattern is characteristic of a specific crystalline lattice for a given compound.
- An amorphous form does not produce a pattern mixture of different crystalline forms.
- Single – Crystal x-ray provide the most complete information about the solid state.

HYGROSCOPICITY

- Many drug substances, particularly water –soluble salt forms, have a tendency to adsorb atmospheric moisture.
- Adsorption and moisture content depend upon the atmospheric humidity, temperature, surface area, exposure and the mechanism of moisture uptake.
- The degree of Hygroscopicity is classified into four classes:

✓ **Slightly hygroscopic**: increase in weight is ≥ 0.2% w/w and < 2% w/w

✓ **Hygroscopic** : increase in weight is ≥ 0.2 % w/w and < 15 % w/w

✓ **Very hygroscopic** : increase in weight is ≥ 15% w/w

✓ **Deliquescent** : sufficient water is adsorbed to form a solution

Hygroscopicity is tested by:

Samples are exposed to the moisture

exposed to controlled relative humidity environments

moisture uptake is monitored at different time points

Analytical methods which is used are :

- ✓ Gravimetry
- ✓ Karl Fischer Titration
- ✓ Gas chromatography

PARTICLE SIZE

- Particle size is characterized using these terms :
- Very coarse, Coarse, Moderately coarse, Fine ,Very fine .

- Particle size can influence variety of important factors :

  - Dissolution rate

  - Suspendability

  - Uniform distribution

  - Penetrability

  - Lack of grittiness

Methods to Determine Particle Size

- Sieving (5µ-150µ)
- Microscopy(0.2µ-100µ)
- Sedimentation rate method(1µ-200µ)
- Light energy diffraction(0.5µ-500µ)
- Laser holography(1.4µ-100µ)

POWDER FLOW PROPERTIES

- Powder flow properties can be affected by change in particle size, shape & density.

- The flow properties depends upon following-

1. Force of friction.
2. Cohesion between one particle to another.

- Fine particle posses poor flow by filling void spaces between larger particles causing packing & densification of particles.

- By using glident we can alter the flow properties.

  e.g. Talc

Determination of Powder Flow Properties

- By determining **Angle of Repose.**
- A greater angle of repose indicate poor flow.
- It should be less than 30°. & can be determined by following equation.

$$\tan \theta = h/r.$$

where, θ = angle of repose.

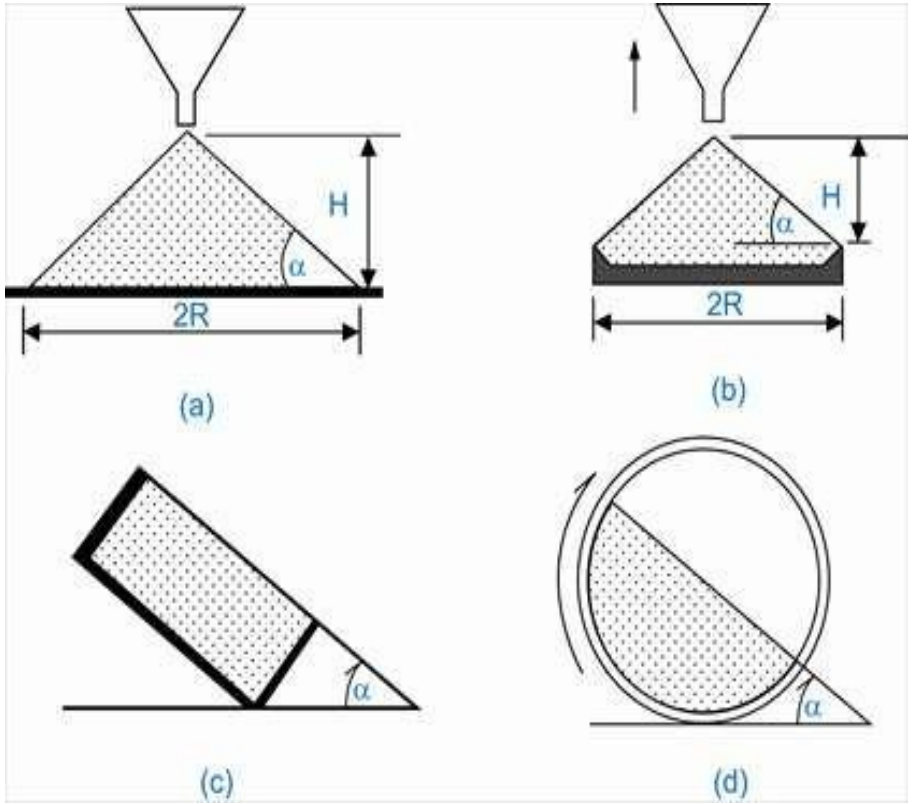
h=height of pile.

r= radius.

Angle of Repose (In degree)	Type of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

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.*

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

- 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 know 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
- Hydotrophy
- 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

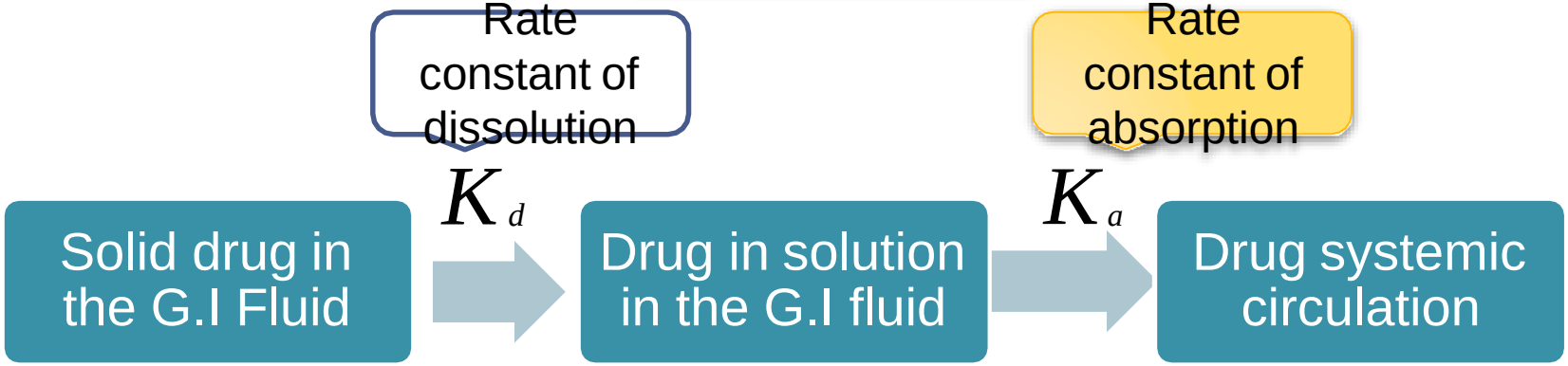
- For acids: $\log_{10} D = \log_{10} P - \log_{10}(1 + 10^{(pH - pKa)})$
- For bases : $\log_{10} D = \log_{10} P - \log_{10}(1 + 10^{pKa - pH})$
- The octanol-water system is widely accepted to explain these phenomenon.
- Buccal membrane : butanol-pentanol system
- Blood-Brain barrier: chloroform-cyclohexane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

DISSOLUTION



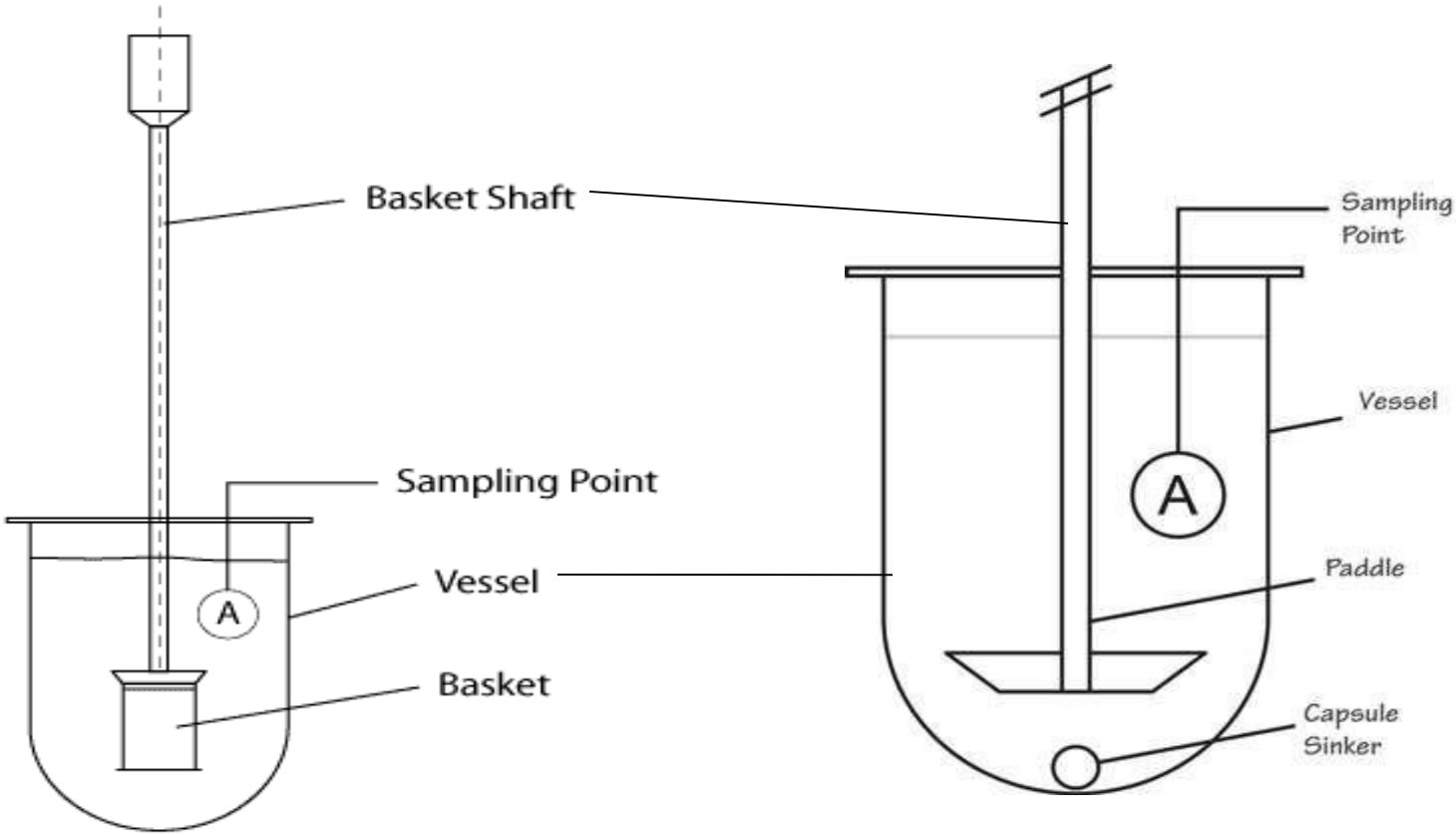
- When $K_d << K_a$,dissolution is significantly slower and the absorption is described as dissolution-rate limited.

- The dissolution rate of drug substance in which surface area is constant during dissolution is described by Noyes-Whitney equation.

$$\frac{dC}{dt} = \frac{DA}{hV}(C_s - C)$$

dC/dt=dissolution rate
h=diffusion layer thickness
C=solute concentration in bulk solution
V=volume of the dissolution medium
D=diffusion coefficient
A=surface area of the dissolving solid
Cs=solute concentration in the diffusion layer

- Constant surface area is obtained by compressing powder into a disc of known area with a die and punch apparatus.
- Hydrodynamic conditions are maintained with Static-disc dissolution apparatus and Rotating disc apparatus
- fig : static dissolution apparatus and rotating disc apparatus



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

$$R'\text{-}COOR + H^+ + OH^- \longrightarrow RCOOH + ROH$$

ester — acid — alcohol

b) Amide hydrolysis

$$RCONHR' + H^+ + OH^- \longrightarrow RCOOH + H_2N\text{-}R'$$

amide — acid — amine

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^{o} 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)

$$k_H = [gpl].k_0$$

gpl= concentration of water in atmosphere in units of grams of water per liter of dry air .

k_o = decay rate constant at zero relative humidity

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

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

ΔH_{fus} -molar heat of fusion

T_m - absolute melting point

T - absolute temperature

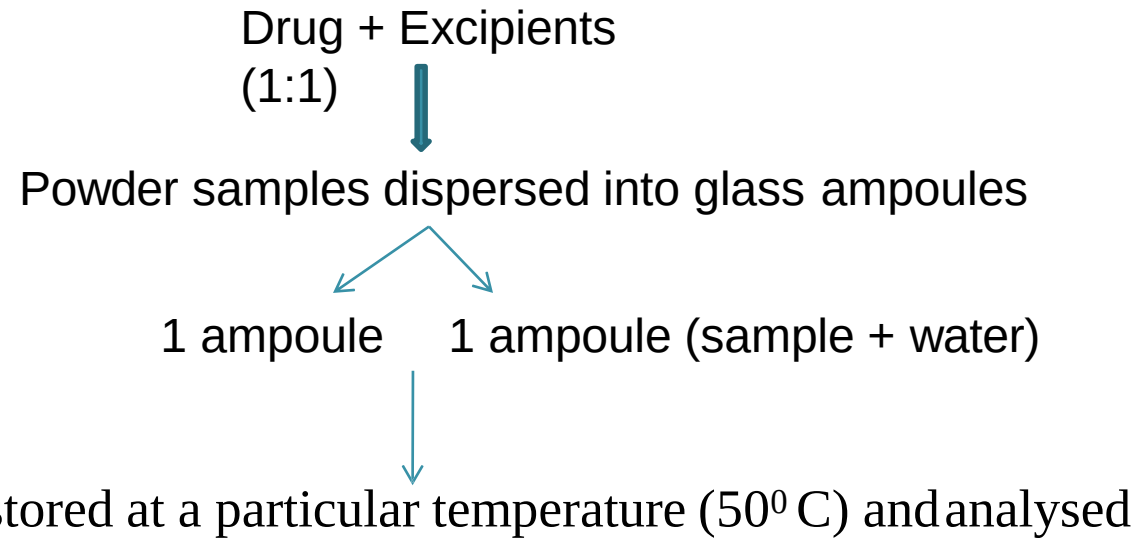
R - gas constant

Drug- excipient compatibility

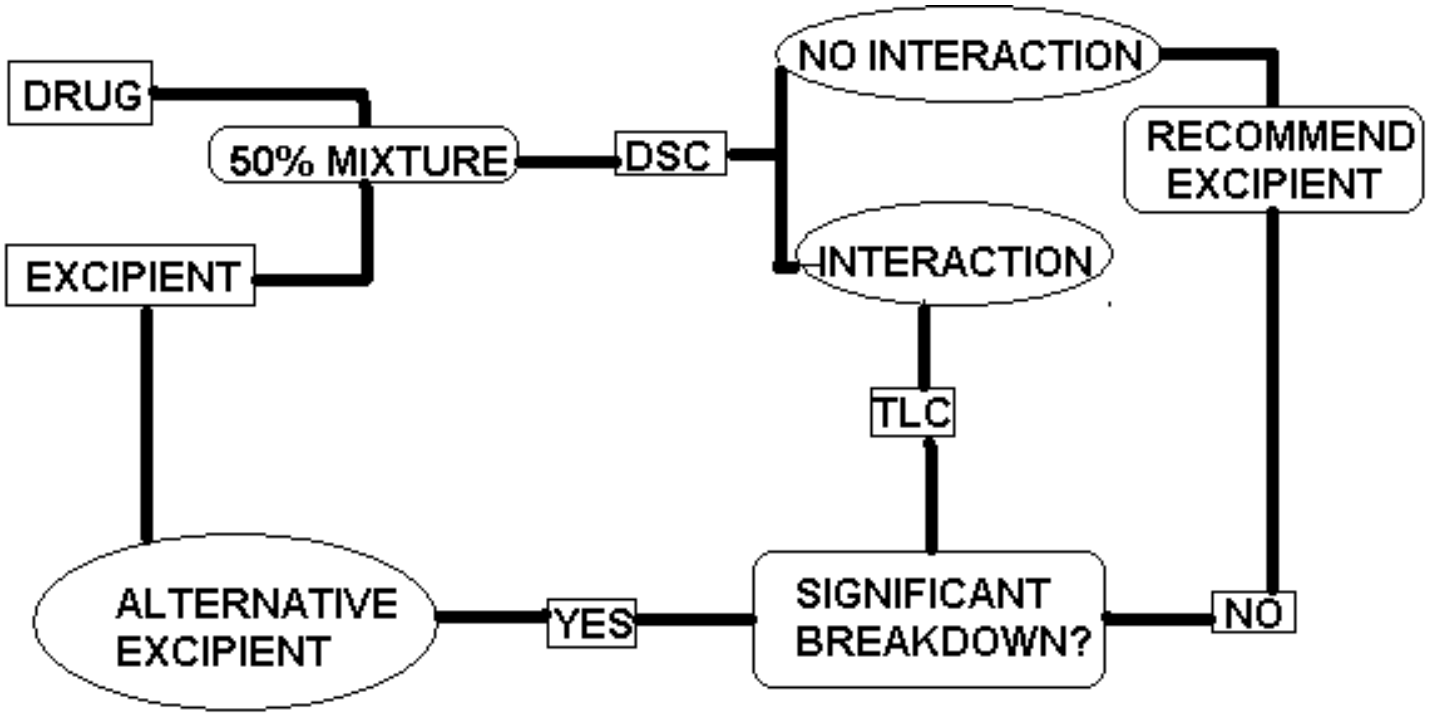
- Compatibility test play a very important role in the preformulation studies of oral dosage forms
- An incompatibility in the dosage form can result in any of the following changes:

- Changes in organoleptic properties
- Changes in dissolution performance
- Physical form conversion
- An decrease in potency

METHOD



- 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)


DRUG
50% MIXTURE
DSC
NO INTERACTION
RECOMMEND EXCIPIENT
EXCIPIENT
INTERACTION
TLC
ALTERNATIVE EXCIPIENT
YES
SIGNIFICANT BREAKDOWN?
NO

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.

REFERENCE

- Leon Lachman, Liberman. The theory and practice of Industrial pharmacy, Edn 4. CBS publishing house, New Delhi.2013 p:217-307.
- Banker GS, Rhodes CT. Modern pharmaceutics, Edn 4. Marcel Dekker, New York. 2002 p:167-184.
- Loyd V. Allen, Nicholas G.popovich, Howard C. Ansel. Ansel's pharmaceutical Dosage forms & Drug delivery systems, Edn 8. B.I.Publication pvt. Ltd, p:187-193,42 & 43,126-133.
- Brahmankar D.M, Jaiswal BS. Biopharmaceutics and pharmacokinetics a Treatise, Edn 2. Vallabh Prakashan, Nagpur. 2009; p: 37-45.

Thank You