PREFORMULATION STUDIES

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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

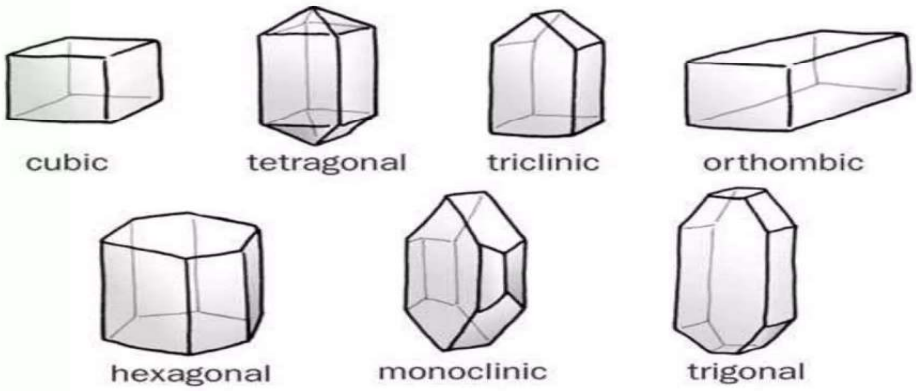
BULK CHARACTERIZATION

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 :

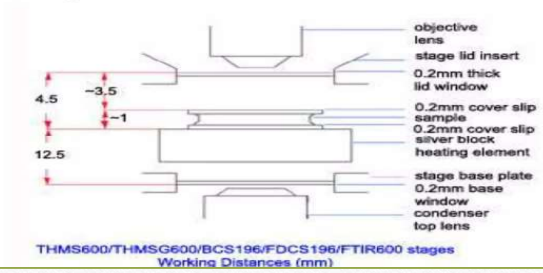
  By this method, we can study crystal morphology & difference between polymorphic form.
- Disadvantage :

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

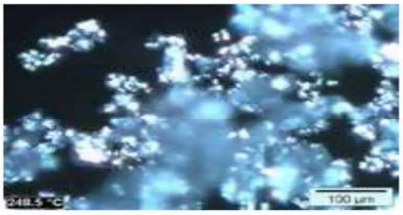
Hot stage microscopy

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

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



THMS600/THMSG600/BCS196/FDCS196/FTIR600 stages
Working Distances (mm)



Thermal analysis

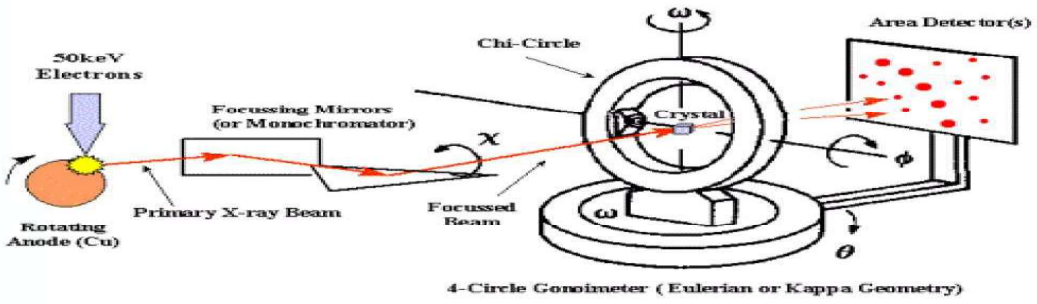
- Differential scanning calorimetry (DSC) & Differential thermal analysis are (DTA) are particularly useful in the investigation of polymorphism.
- It measures the heat loss or gain resulting from physical or chemical changes within a sample as a function of temp.
- For characterizing crystal forms , 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 duc to crystal which acts as 3 dimcnsional 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