# *MODULE 1: Preformulation Studies*

## *Lecture 2*

DISCLAIMER

All the content material provided here is only for teaching purpose

# Polymorphism

- Ability of a compound or element to crystallize as more than one distinct crystalline species with different internal lattices.
- Chemical stability and solubility – Drug's bioavailability
- Physicochemical parameter that alter
  - Melting point
  - Density
  - Hardness, crystal shape, optical properties

- Eg.: Chloramphenicol Palmitate
  - 3 crystalline polymorphic forms, A,B,C and amorphous form
  - Physicochemical properties vary : MP, Density, hardness, optical properties etc

# Polymorphism

Classification-

1. Monotropic polymorphs - one stable crystal form and one meta stable regardless of temperature change/

   Only one polymorph is stable at all reasonable Temp.

Eg. Glyceryl stearates, metalazone

2. Enantiotropic polymorphs - One polymorph is stable over one temperature range, another polymorph is stable over a different temperature range

E.g. carbamazepine and acetazolamine,Sulfur

# Polymorphism

- Preformulation study-
- Identifies polymorph stable at room temp
- stability of polymorph in dosage form

# Analytical Techniques for characterization of solid forms

- Microscopy
- Hot Stage Microscopy
- Thermal Analysis
- X-ray diffraction
- Infrared
- NMR
- SEM

# Objective

- To develop portfolio of information about drug substances
- Helps in development formulation
- Design to identify physicochemical properties and excipients that influences formulation design
- Method to Manufacture

# Important table for preformulation

| S.No | Parameters | Evaluation parameters |
|---|---|---|
| 1. | Stability | Temperature, Light, humidity |
| | Solid State | Solvent, Ph |
| 2. | Solid State Compatibility | TLC and DRS Analysis |
| 3. | Physico-chemical Properties Color, odor, particle size, shape crystallinity | Molecular Structure and Weight, melting point |
| | Thermal Analysis Profile Solubility | DTA, DSC,TGA |
| 4. | Water and other solvent, pH | Salt forms, co-solvent, Complexation, pro-drug |
| 5. | Absorbance Spectra | UV, IR |
| 6. | Other properties Hygroscopicity | Potential Bulk characterization Volatility, optical activity, solvate formation Crystalli polymorphism |

| | | |
|---|---|---|
| 7. | Physico-mechanical Properties Bulk and | Tapped density, compressibility Photomicrograph |
| 8. | In Vitro Availability Properties Rat Everted Gut Technique | Dissolution and analysis of Drug Crystal, pallets |
| 9. | Other Studies Plasma Protein-Binding, Ionization Constant | Effect of Compatible Excipients on dissolution, Kinetic Studies of Solution Degradation, Use of Radio-labeled Drug |

# Analytical method for characterization of polymorph

Microscopy-

# Microscopy

- With more than one refractive index anisotropic and appear bright and brilliant colors against black polarized background.
- Colour intensity depends upon crystalline thickness

- Isotropic material-Single refractive index and does not transmits light and appears black

- HOT STAGE MICROSCOPY
- Polarizing microscope fitted with hot stage is useful for investigating polymorphism, melting point and transition temperature.

- Disadvantages: Molecules can dregarde during melting process

# Thermal Analysis

1. DSC- measures Heat Loss/ Gain resulting from chemical or physical changes.

1. TGA- measures changes in sample weight as a function of time/ temp

Eg. Endothermic and Exothermic reactions

Eg. Anhydrous, Dihydrate form

# Hygroscopicity

**Factors**

- Adsorption & equilibrium moisture content depends upon
  - Atmospheric humidity
  - Temperature
  - Surface Area
  - Exposure & mechanism for moisture uptake

**Types**

**Deliquescent:** adsorbs sufficiently water to dissolves completely

**Hygroscopic**: adsorb water and forms hydrate

**Changes in moisture level are affects**

- Chemical stability
- Flow ability
- Compactibility

# Hygroscopicity

Karl Fischer titration, gas chromatography, TGA

Based on data, Specific handling during manufacturing (Humidity control) / special storage (Dessicant)can be recommended

# Fine Particle Characterization

Microscopy

Anderson Pippete

Coulter counter

Sieve method

BET method (Surface area)

SEM method

Powder Flow Properties

Different densities

# Principal areas of Pre-formulations-

## Solubility Analysis

- Ionization constant –pKa
- pH solubility profile
- Common ion effect – Ksp
- Thermal effects
- Solubilization
- Partition co-efficient
- Dissolution

# Solubility Analysis

- Solubility study done in various solvents

  -Aqueous solvent

  - water, buffers

  -Nonaqueous solvents

  - Organic solvents

  - Glycerol, PEG

# Solubility Analysis

- Focus on drug-solvent system that could occur during the delivery of the drug candidate
- Provides basis for formulation work.
- Determination of
  - pKa
  - Temperature dependence
  - pH solubility profile
  - Solubility products
  - Solubilization mechanisms
  - Rate of dissolution

# Solubility Analysis

- Factors to be defined for solubility and Dissolution study -
  - pH
  - Temperature
  - Buffer concentrations

# Solubility Analysis

| | |
|---|---|
| Very soluble | less than 1 part |
| Freely soluble | from 1 to 10 parts |
| Soluble | from 10 to 30 parts |
| Sparingly soluble | from 30 to 100 parts |
| Slightly soluble | from 100 to 1000 parts |
| Very slightly soluble | from 1000 to 10,000 parts |
| Practically insoluble | more than 10,000 parts |

# REFERENCES


- The Theory and Practice of Industrial Pharmacy By Leon Lachman, H.A Lieberman, Joseph Kanig, 3rd edition ,page: 171-176