PREFORMULATION STUDY

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PHAR 501 -Industrial Pharmacy-I

Semester-IX

Faculty of Pharmacy

Lecture-I & II

Lecture Content

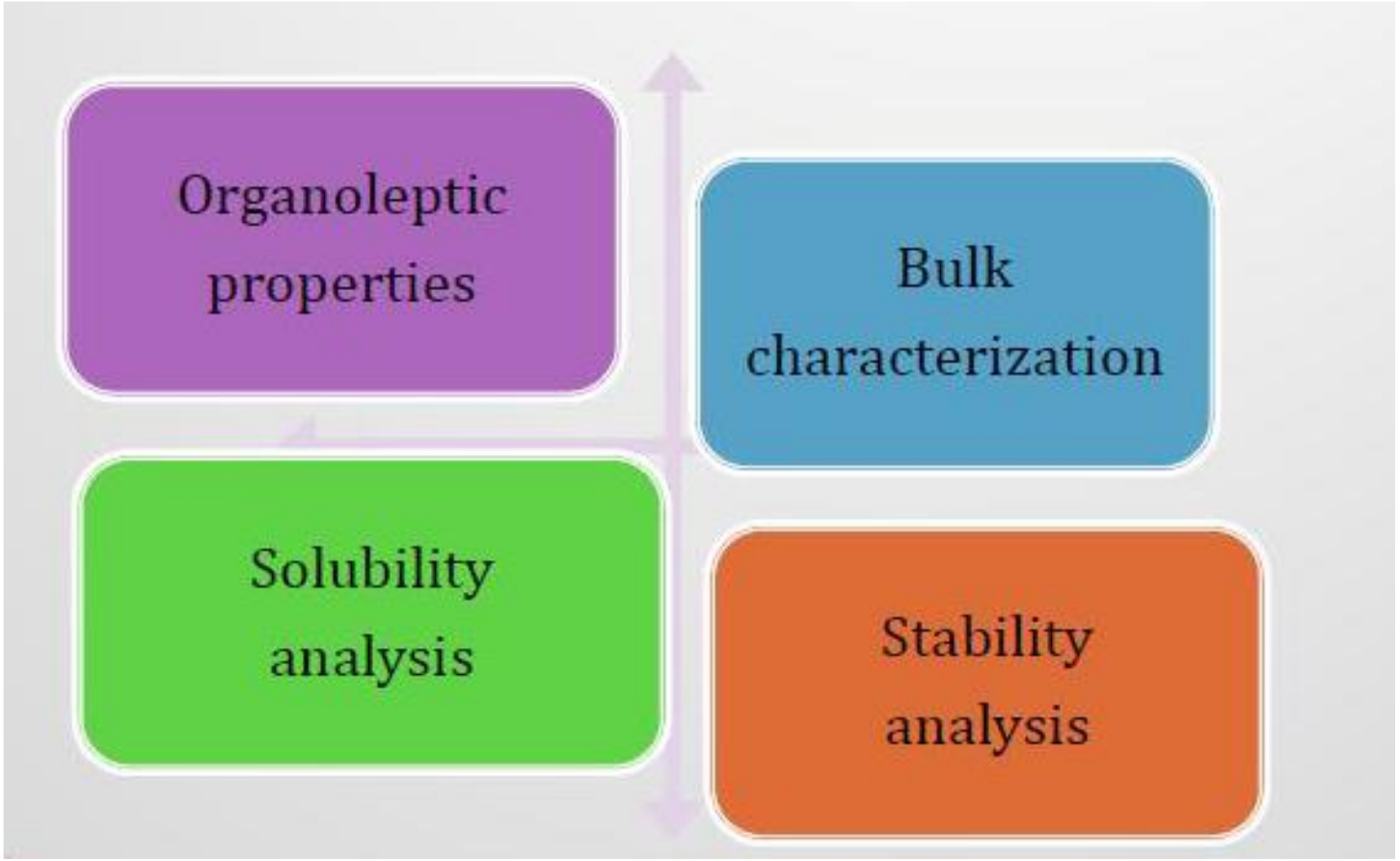
- Preformulation
- Objectives of Preformulation study
- Goals of Preformulation study
- Preformulation study schematic representation
- Principal areas of Preformulation
- Solid state of drug
- Difference between crystalline and amorphous
- Application of crystalline and amorphous forms

Preformulation

- Preformulation studies are known as “Learning before doing”.
- Preformulation is the stage of research and development process where the physical, chemical and mechanical properties of a new drug substance is characterized, in order to develop stable, safe and effective dosage form.

	Characterization	Physical form	Formulation	Stability
Small molecules	Crystallinity Hygroscopicity Particle size, shape, surface area Moisture / solvent content	Polymorph screening Salt / cocrystal screening Amorphous dispersion screening Stable form determination	pH-solubility profile, pKa and logP Permeability (Caco-2) BCS classification Solubility in pharmaceutical solvents & bio-relevant buffers formufast™ screening	Development of stability indicating LC-MS method Solid state stability (heat, humidity, light)
Peptides	LC-MS Absorption and fluorescence spectroscopy Circular dichroism NMR	Enabling salt screen	Solubility in pharmaceutical solvents & bio-relevant buffers Precipitation assessment	Solution stability (pH, oxidation, heat, light)

Major Areas of Preformulation



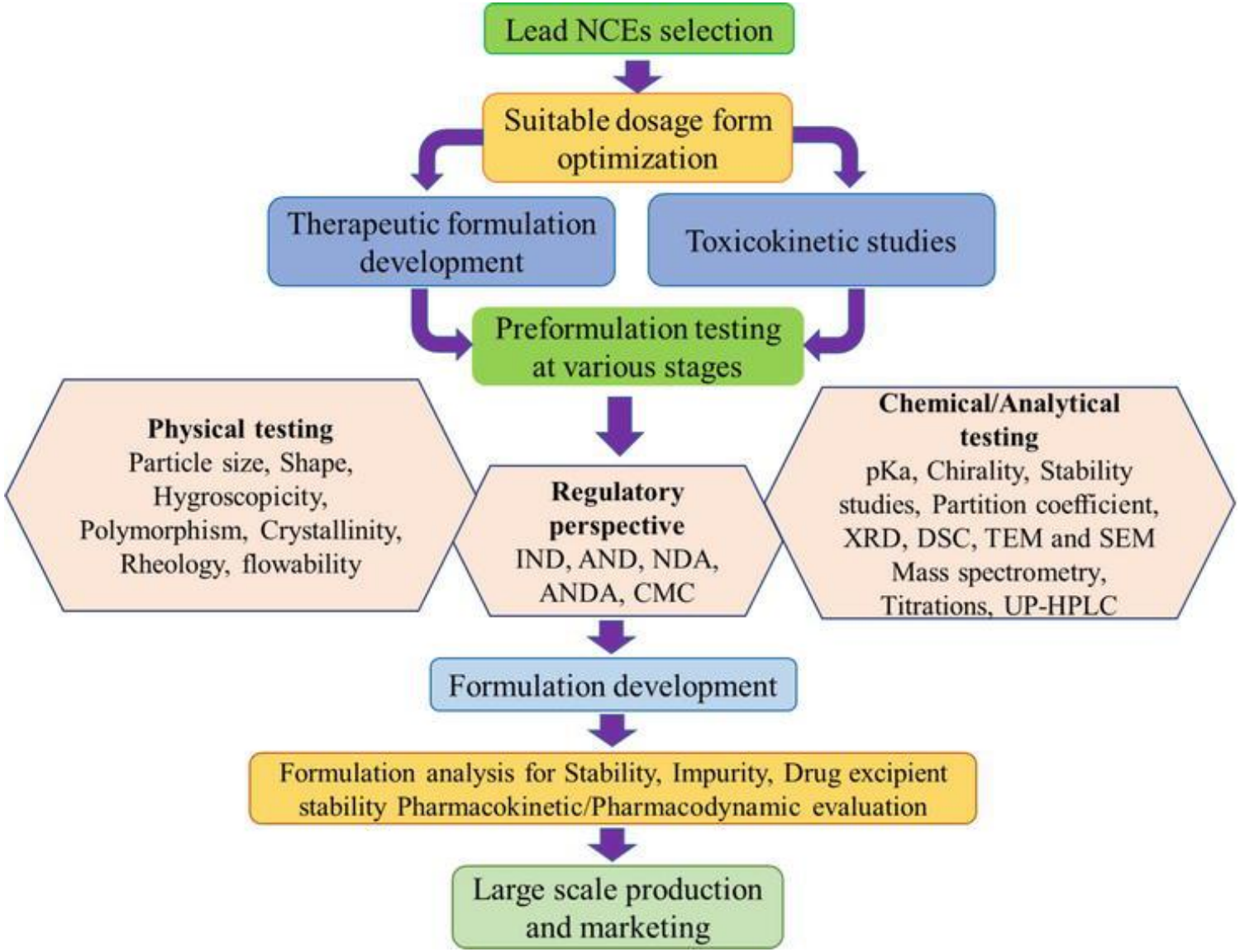
Objectives of Preformulation study

- ✓ Tool for making decisions:
- ✓To determine the appropriate dosage form.
- ✓To determine the best drug administration route.
- ✓Understanding of a drug molecule's physical characteristics and how these affect its biological activity.
- ✓Development of desired, practical, reliable, efficient, and inexpensive products.
- ✓Choosing appropriate excipients and additives that work effectively with pharmaceutical components.
- ✓To develop acceptable dose forms or create the best possible drug delivery system.

Goals of Preformulation study

- Finding the physicochemical characteristics results in the development of a drug candidate.
- Determine the medication molecule's pharmacokinetics and biodistribution profile.
- Determination of the compatibility of common excipients with drug molecules.
- Significant obstacles in the way of the production of viable pharmaceuticals

Preformulation study schematic representation



Principal areas of Preformulation

Physical State

- Crystalline
- Amorphous
- Polymorph
  - Enantiotropic
  - Monotropic
- Pseudo-polymorph
- Hydrates
- Solvates

Bulk characterization

- Bulk volume
- True volume
- Bulk density
- True density
- Void volume
- Porosity
- Angle of repose
- Carr's index
- Hausners index
- Fine particle characterization

Solubility analysis

- Solute
- Melting point
- Hygroscopicity
- Deliquescent materials
- Moisture content
- Solvent
- Absolute solubility
- Intrinsic solubility
- Ionization constant (pK_a and pK_b)
- Solubility profile at various pH
- Solubility profile in solvents of different polarity
- Solubility at body temperature
- Solubility at storage temperature

- Common ion effect – K_{SP}.
- Dielectric constant
- Thermal effects
  - Exothermic reaction
  - Endohermic reaction
- Solubilization
- Cosolvency
- Hydrotrophy
- Salt forms
- Type of counter ion
- Size of counter ion
- Ionic strength of counter ion
- Complexation
- Partition coefficient
- Dissolution

- Stability Analysis
- Stability of formulation
- Solution stability
  -pH stability profile
  -Temperature stability profile
- Bulk stability
- Compatibility

Solid State of Drug

- **Crystal habit:** The external shape is called the crystal habit and this is aconsequence of the rate at which different faces grow.
- A single internal-structure (arrangement of atoms in a crystal lattice) for a compound can have several different habits, depending on the environment for growing crystals.
- Habit is the description of the outer appearance of a crystal. Habit affects the dissolution of drug, bulk properties (Bulk volume, flow properties, compression characteristics) etc.

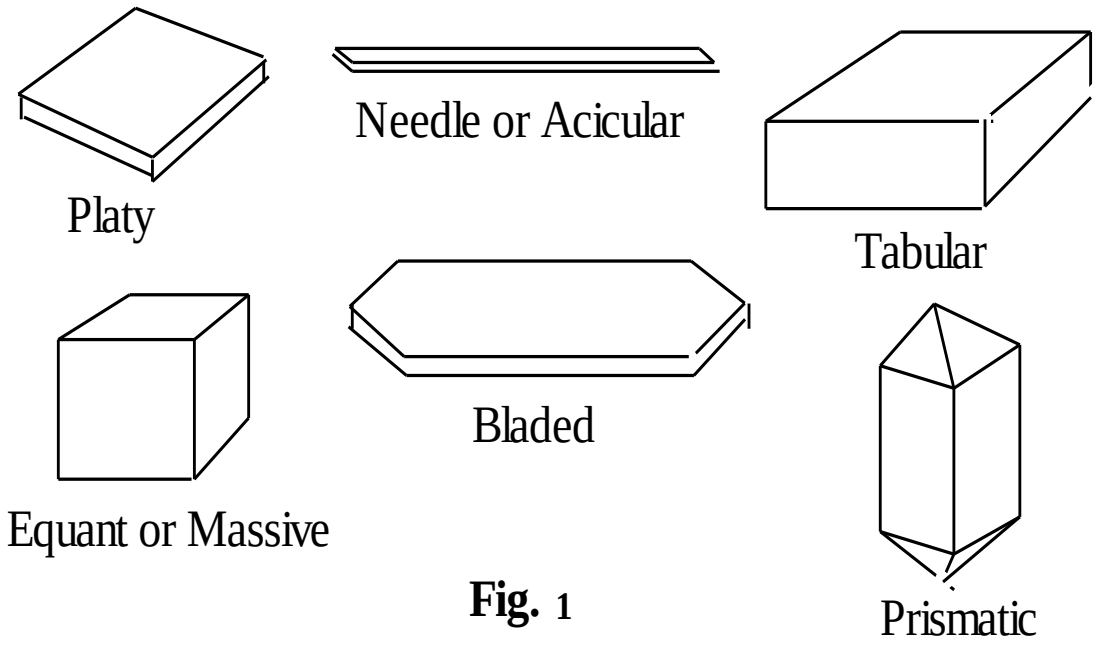
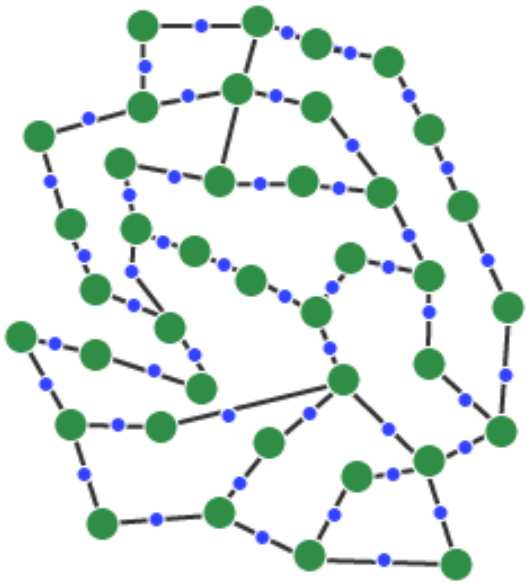
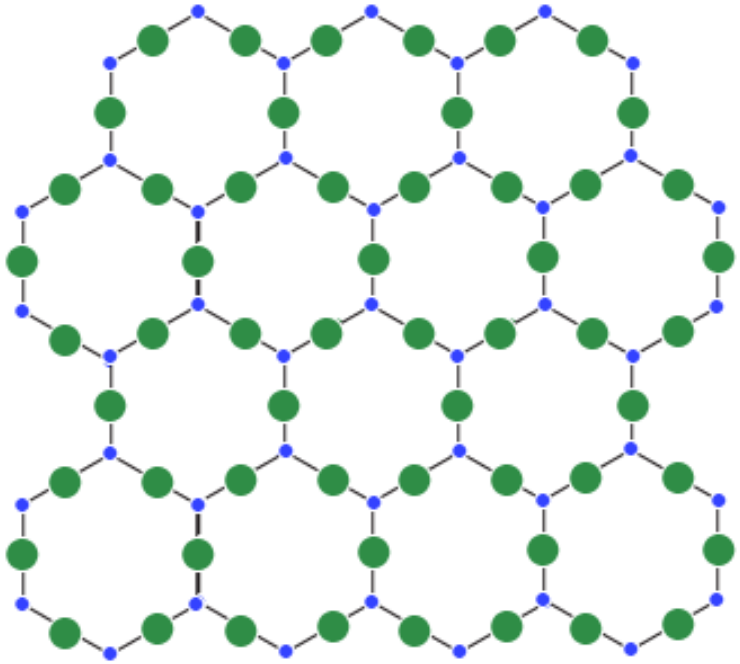


Fig. 1

Crystalline forms	Amorphous forms
(i) Crystalline forms have fixed internal structure	(i) Amorphous forms do not have any fixed internal structure
(ii) Crystalline form has lesser thermodynamic energy as compared to its amorphous form.	(ii) Amorphous form has higher thermodynamic energy than its crystalline form.
(iii) Crystalline forms are more stable than its amorphous forms.	(iii) Amorphous forms are less stable than its crystalline forms.
(iv) Crystalline form has less solubility than its amorphous form.	(iv) Amorphous forms have greater solubility than its crystalline forms.
(v) Crystalline form has less tendency to change its form during storage.	(v) Amorphous tend to revert to more stable forms during storage.
Example: NaCl, KCl.	**Example:** Amorphous Novobiocin



Amorphous Solids



Crystalline Solids

Application of crystalline and amorphous forms

- Novobiocin is an antibiotic, is used to prepare the suspension using amorphous form. It tends to convert into crystalline form on storage resulting in precipitation and over/low dosing.

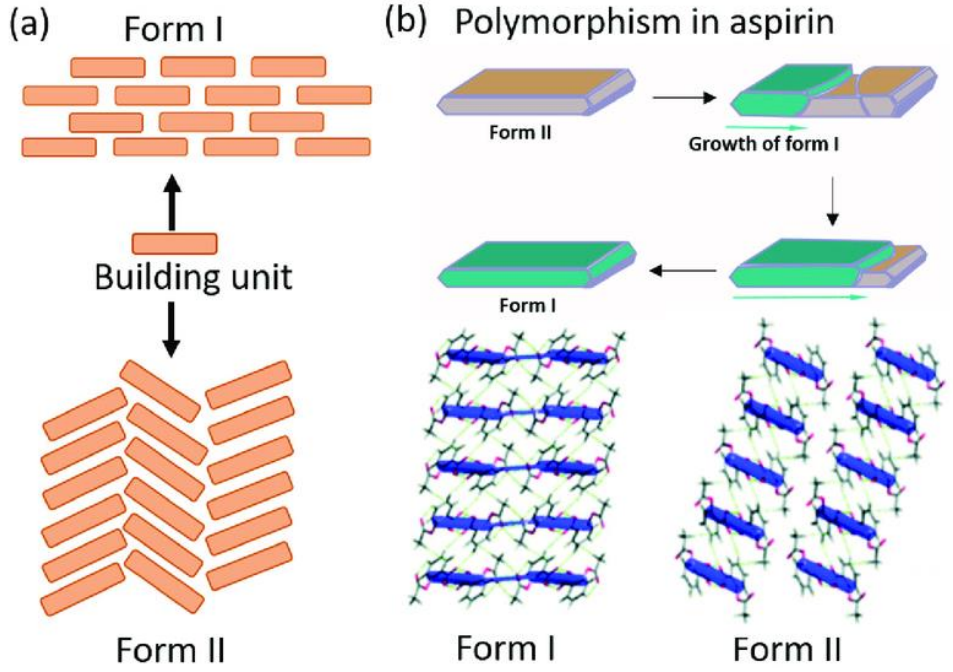
- Lente insulin is the combination of Semi lente insulin (70% crystalline form) and Ultra lente insulin (30% amorphous form) gives an intermediate type of drug release.

- Semi lente insulin is a crystalline form of insulin (Low aqueous solubility than amorphous form, slow absorption, long duration of action).

- Ultra lente insulin is an amorphous form of insulin (High aqueous solubility than crystalline form, fast absorption, short duration of action).

Polymorph

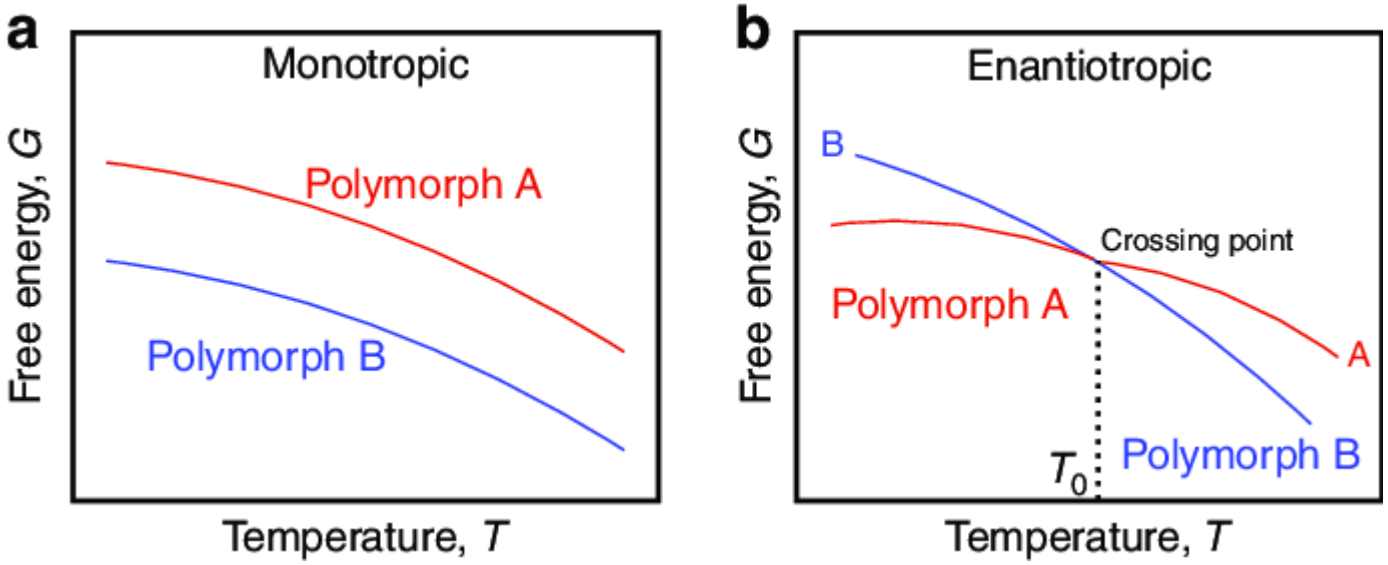
- A substance exists in more than one crystalline form, the various forms are called Polymorphs and the phenomenon as polymorphism.
- e.g . Aspirin has two polymorphs A,and B .
- Polymorphs can be prepared by crystallizing the drug from different drugs under diverse conditions.
- Depending on their relative stability, one of the several polymorphic forms will be physically more stable than the others. Such a stable polymorph represents the lowest energy state, has highest melting point and least solubility.
- The representing polymorphs are called metastable forms which represents higher energy state, the metastable forms have a thermodynamic tendency to convert to the stable form .
- A metastable form cannot be called unstable because if it is kept dry, it will remain stable for years.



Types of Polymorph

- **Enantiotropic:** Can be converted from one polymorphic form to other polymorphic form by change in temperature and pressure. E.g. Sulfur
- **Monotropic:** Unstable at all temperature and pressure. E.g.Glyceryl monosterate.

- **Pseudo-polymorph:**
- One component exist in different crystalline structure due to entrapment of solvent between crystal lattice.



Hydrates

- When the incorporated solvent is water, the complex is called hydrates Depending on the ratio of water molecules within a complex the following nomenclature is followed.
- *Anhydrous* : 1 mole compound + 0 mole water
- *Hemihydrate*: 1 mole compound + ½ mole water
- *Monohydrate*:1 mole compound + 1 mole water
- *Dihydrate*: 1 mole compound + 2 moles water
- Generally, the anhydrous form of a drug has greater aqueous solubility than its hydrates. This is because the hydrates are already in equilibrium with water and therefore have less demand for water.
- e.g. anhydrous forms of theophyline and ampicillin have higher aqueous solubility than the hydrates.

Solvates

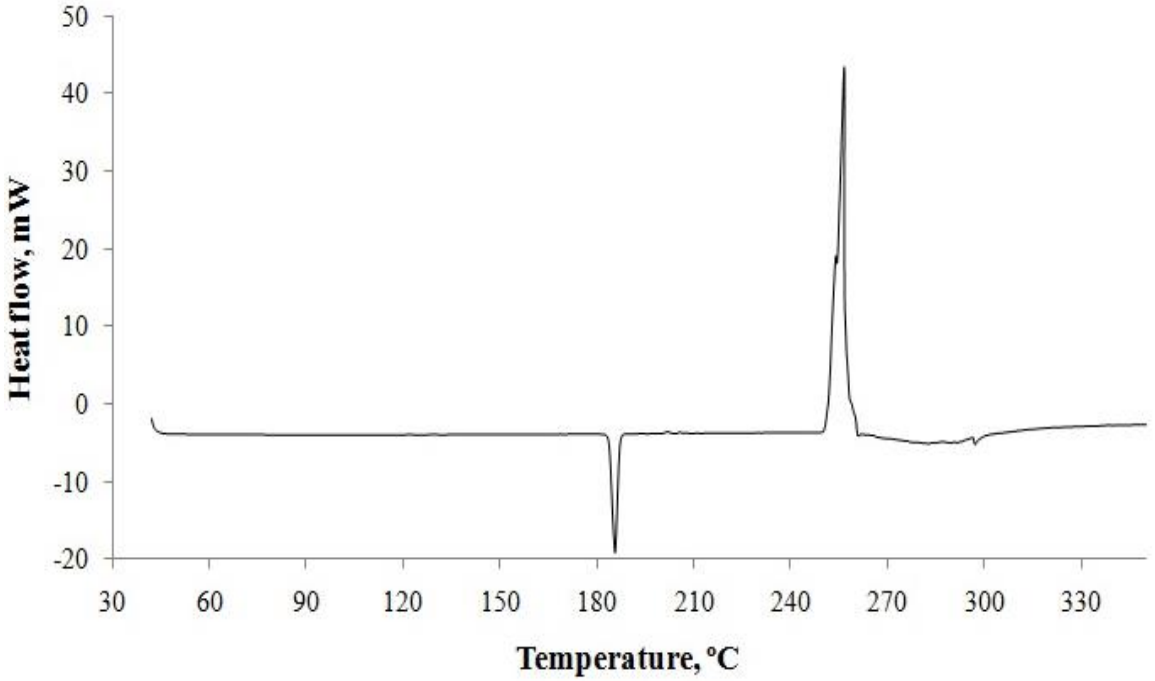
- When the incorporated solvent is any solvent except water, the complex is called solvate.
- Non aqueous solvates have greater aqueous solubility than the non-solvates.

E.g. chloroform solvates of griseofulvin are more water soluble than their nonsolvate forms.

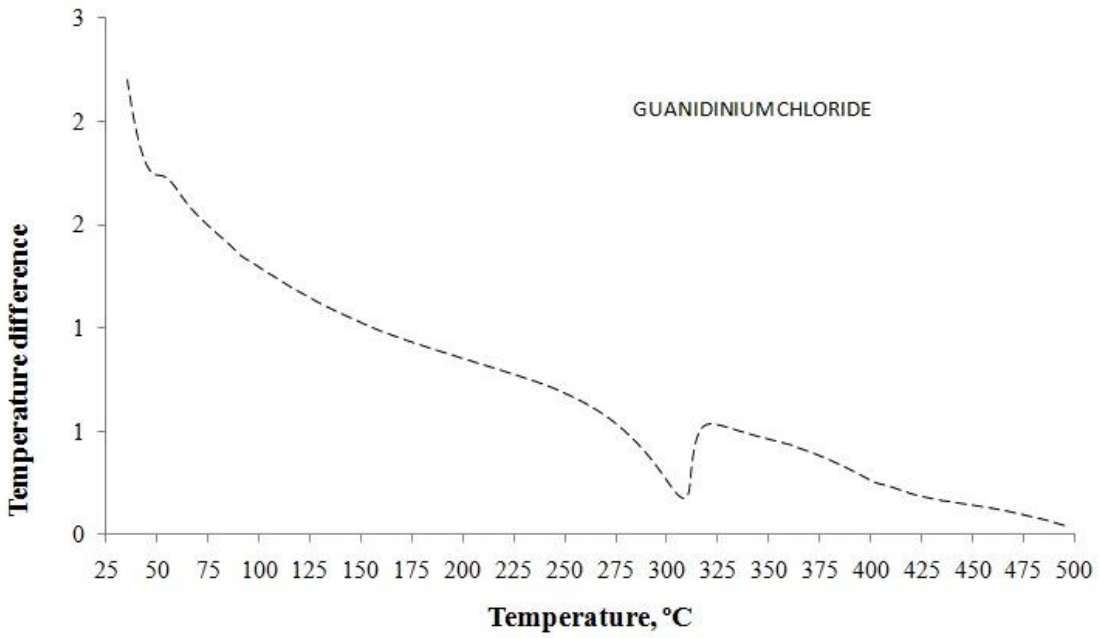
Techniques used to determine various physical states of drugs:

- **1. Melting point**
- **2.Hot-stage microscopy: T**he polarizing microscope is fitted with a hot stage to investigate polymorphism, melting points, transition temperatures and rates of transition at controlled rates.
- **3.Differential Scanning Calorimetry (DSC):** In DSC method the difference in energy inputs (ΔH) into a sample and reference material is measured as a function of temperature as the specimens are subjected to a identically controlled temperature program.
- **4.Differential Thermal Analysis (DTA):** DTA instrument a record is produced where temperature difference (ΔT) (between the sample and reference material) is plotted against temperature (T) when two specimens are subjected to an identically controlled temperature regime.
- **5.X-ray diffraction** (**XRD):** When a X-ray beam falls on a powder the beam is diffracted. This diffraction in found only in case of crystalline powder. Amorphous forms do not show X-ray diffraction. Sharp peaks indicate the crystalline structure of solid while blunt peaks indicates the amorphous form of drug.

The reference material is alumina, keiselguhr.

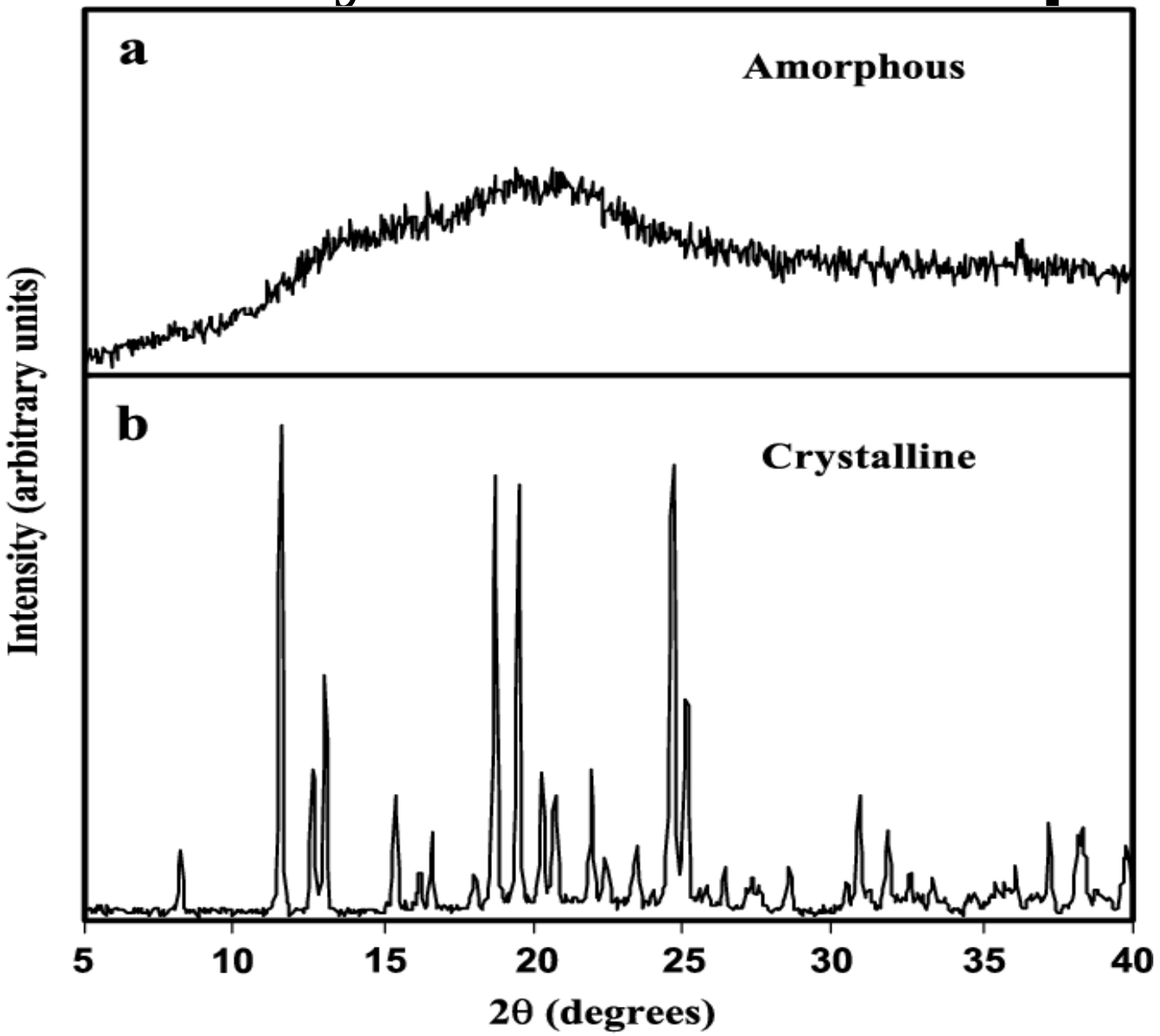


DSC



DTA

XRD of Crystalline and amorphous



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2. Kevin M.G. Taylor and Michael E. Aulton (2021). Aulton's Pharmaceutics. Elsevier Publication.