Industrial Pharmacy I

Main references:

- **LACHMAN (Textbook)**
- **Aulton**

Industrial pharmacy:

Is a discipline which includes **manufacturing, development, marketing and distribution of drug products** including quality assurance of these activities.

Or it is an area of the pharmaceutical field that is specialized in creating drugs and medications.

Important terms:

Pharmaceutical Company

Production line

cGMP, Iso

The course, will include:

- Pre-formulation
- Mixing
- Milling
- Drying
- Filtration
- Sterilization
- Sterile products

Pharmaceutical Pre-formulation

Topics:

- Introduction
- Preliminary evaluation and molecular optimization
- Bulk characterization
- Solubility analysis
- Stability analysis

Introduction:

Pre-formulation includes studies of the physicochemical properties of the new compound that could affect drug performance and development of an efficacious dosage form.

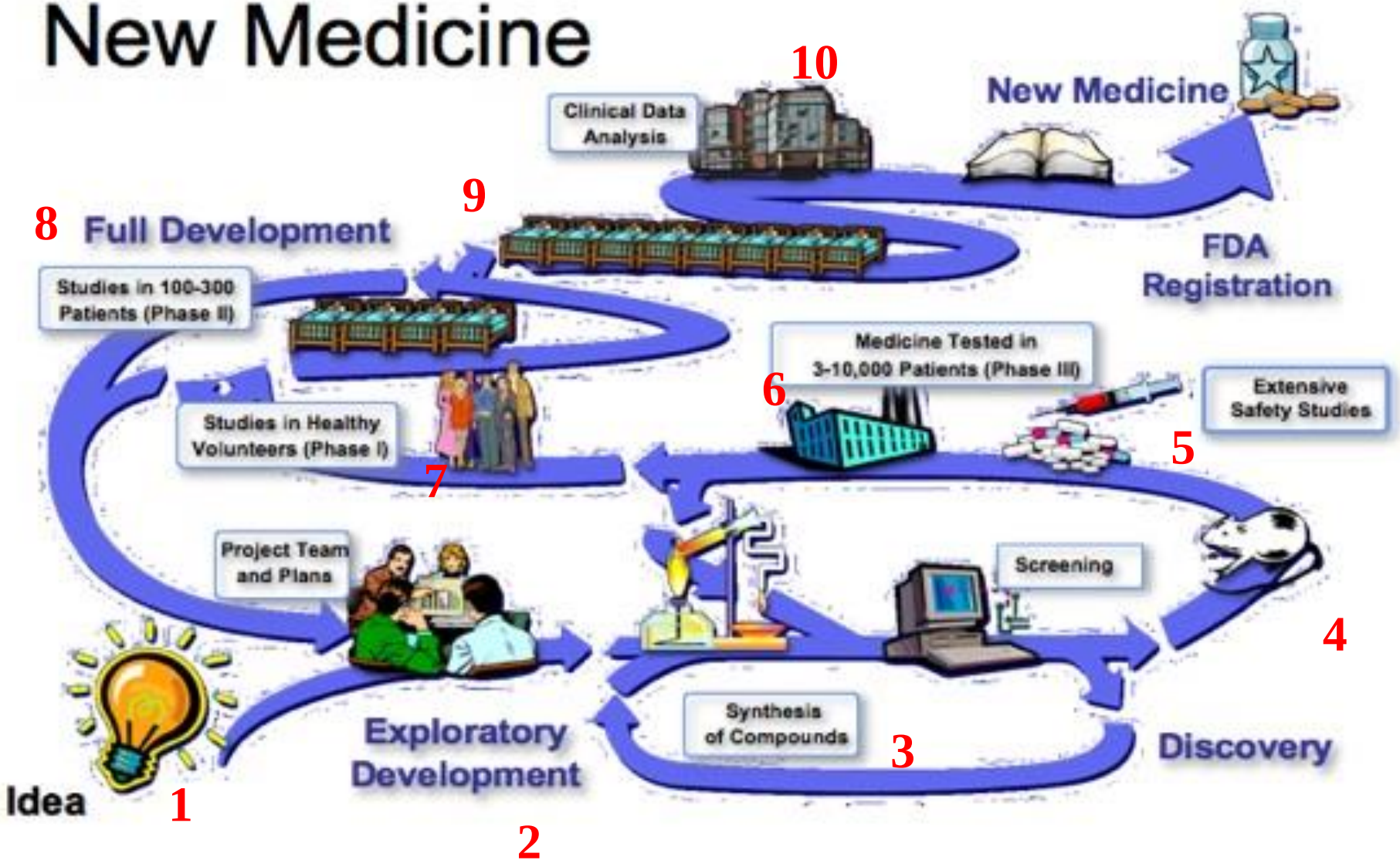
This new compound was showed sufficient pharmacologic effects in animal models.

These properties may be provided by physical pharmacist and medicinal chemist.

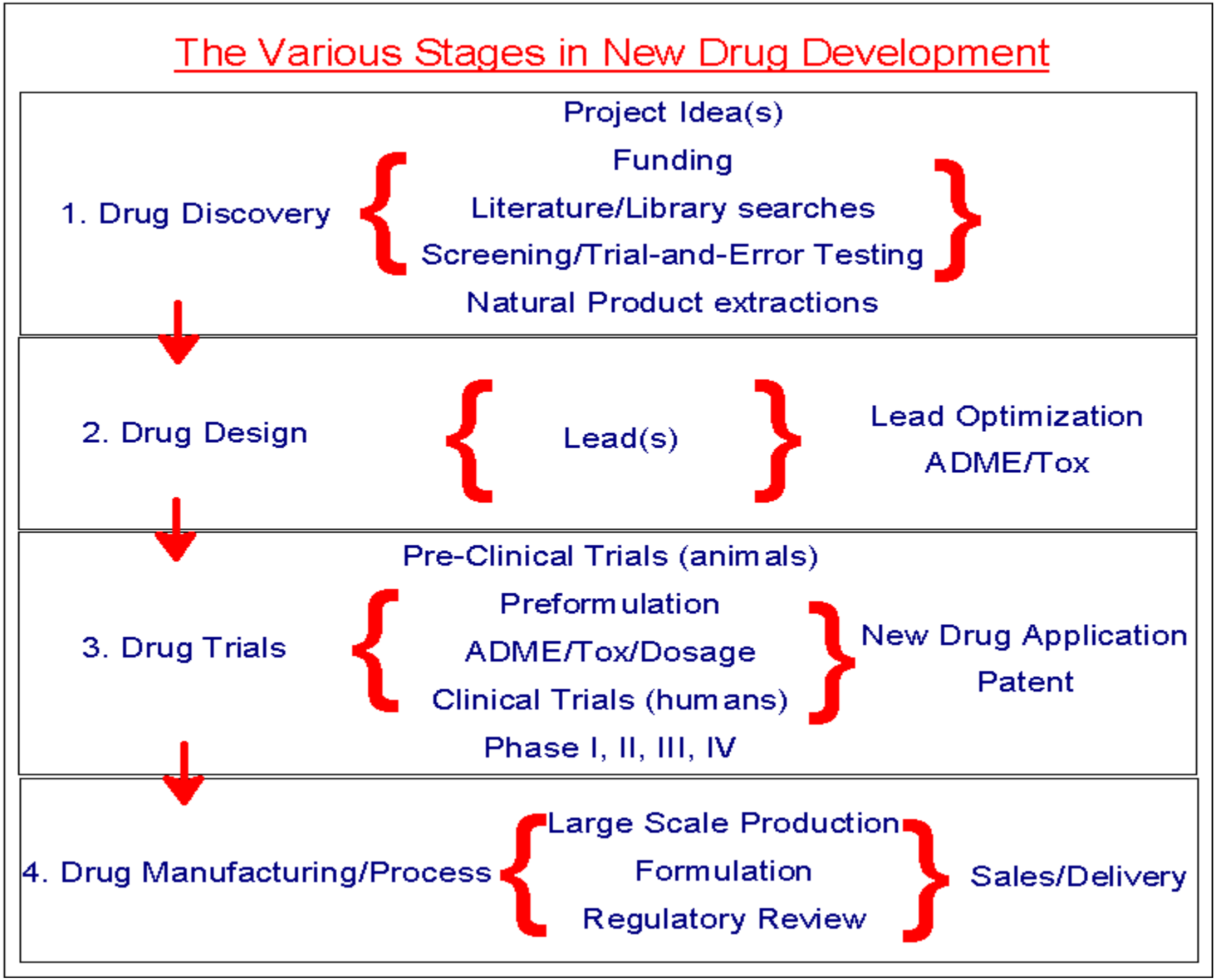
Then, it is the stage in drug and dosage form development before formulation proper.

It aims to optimize the process of turning a drug candidate into a drug product (safe, effective and stable)

The Long Road to a New Medicine



The Various Stages in New Drug Development



Preliminary Evaluation and Molecular Optimization

- **Preliminary evaluation include drug discovery as pharmacologically active compound under supervision of team consisting of medicinal chemist, pharmacologist, toxicologist, physical pharmacist ….etc. within research and development department (R & D), to be ready for development process in its optimum molecular form.**

- **If the first quality sample of the new drug becomes available, analyses are preformed to detect any defect (in the physicochemical properties), so can be solved by molecular modification(s) if possible or not.**

Examples:

Ephedrine HCl (salt) = increase solubility

Erythromycin estolate (pro-drug*)= increase stability in acidic media and masking the bitter taste.

Then, whatever the modification, the molecular form of the drug advancing from the preliminary evaluation should have a substantial chance of successfully progressing through development process.

***What means? Its benefits?**

Bulk characterization

It is important to be studied because if there is any change in bulk properties, it can affect other properties of drugs like solubility and stability.

Include:

- Crystallinity and polymorphism
- Hygroscopicity
- Fine particle characterization
- Bulk density
- Powder flow properties

Crystallinity and polymorphism

Crystallinity:

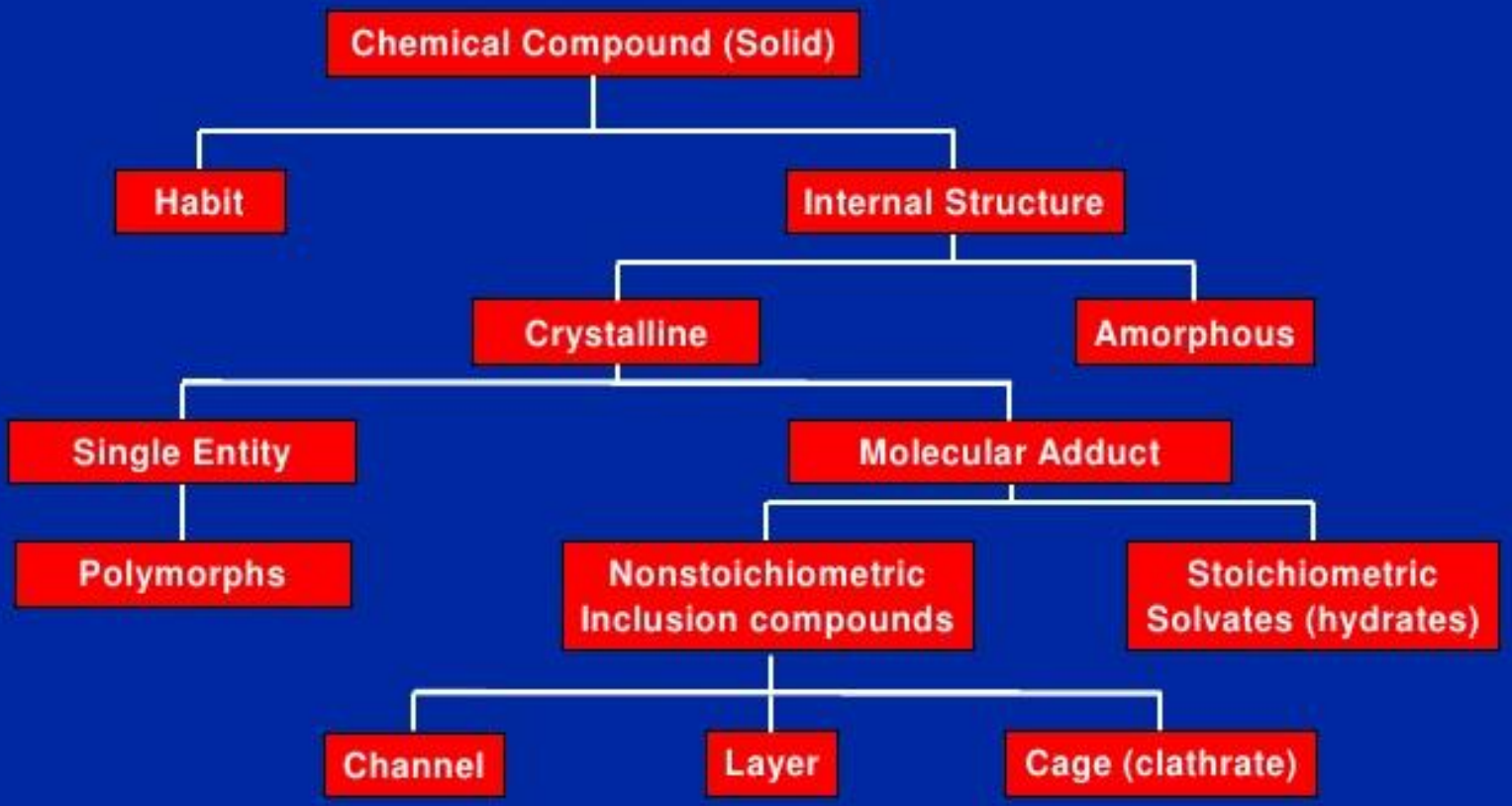
- Crystal habit and the internal structure of a drug can affect bulk and physicochemical properties, which range from flow-ability to chemical stability.
- **Habit** is the description of the outer appearance of a crystal.

- **The internal structure** is the molecular arrangement within the solid, a single internal structure for a compound can have several different habits depending on the environment for growing crystals.
- Changes with internal structure usually alter the crystal habit while such chemical changes as conversion of a sodium salt to its free acid form produce both a change in internal structure and crystal habit.
- **Then characterization of a solid form involves:**

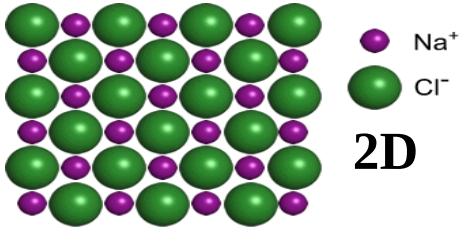
1) **Verifying that the solid is the expected chemical cpd.**
2) **Characterizing the internal structure.**
3) **Describing the habit of the crystal.**

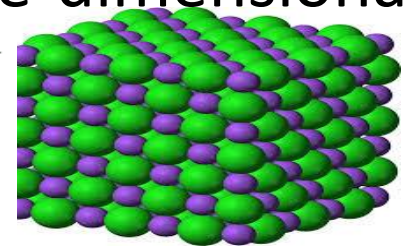
Differentiating Habit and Crystal Chemistry of a Compound

J. K. Haleblian, "Characterization of habits and crystalline modification of solids and their pharmaceutical applications," J. Pharm. Sci., 64(8), 1270 (1975).

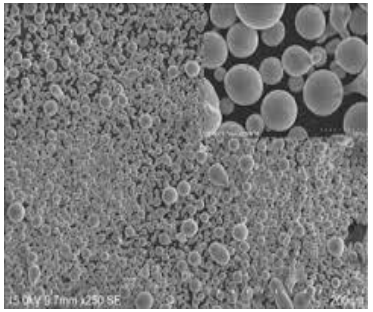


- **Crystals** are characterized by repetitious spacing of constituent atoms or molecules in a three-dimensional array.

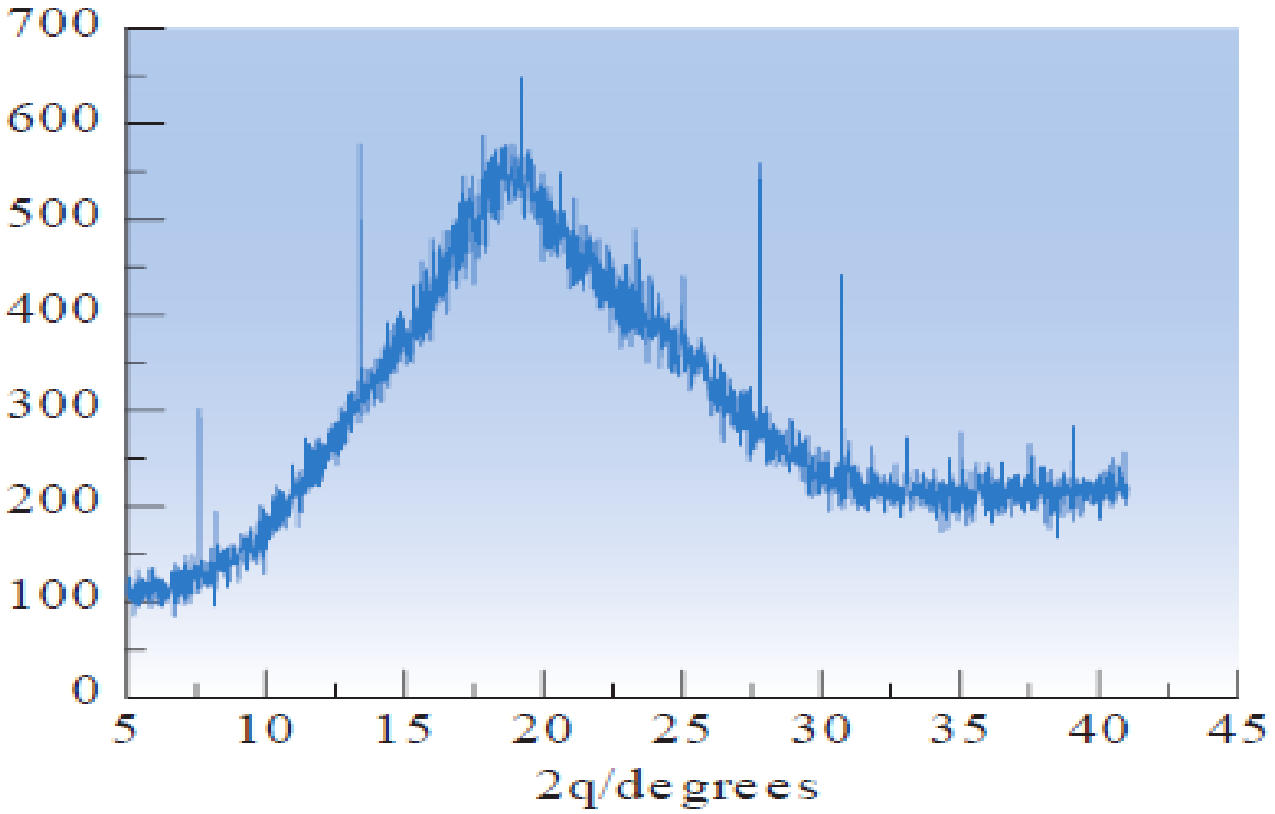




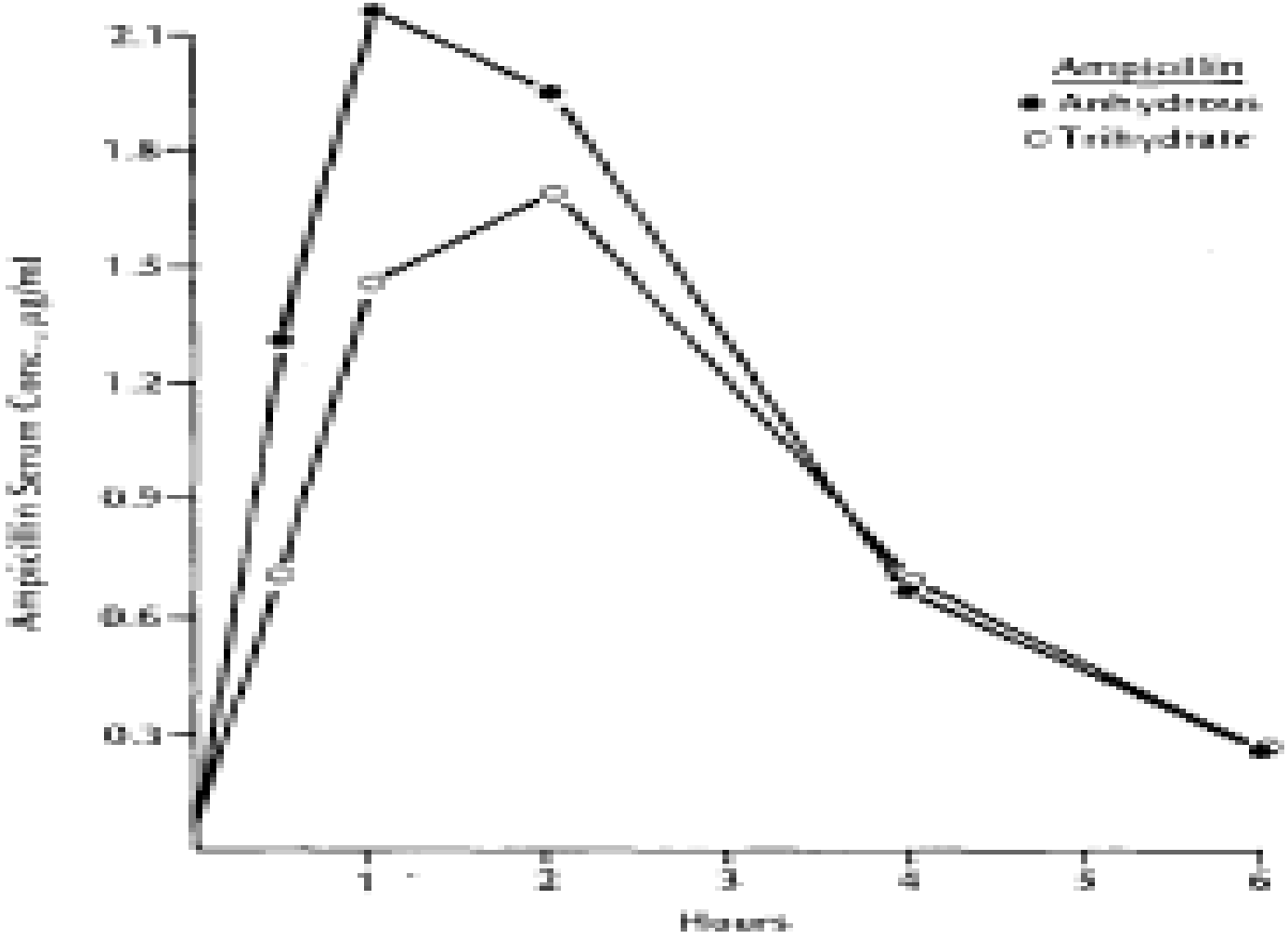
- **Amorphous forms** have atoms or molecules randomly placed as in a liquid, typically prepared by rapid precipitation, milling, lyophilization, or rapid cooling of liquid melts. They have a higher thermodynamic energy than corresponding crystalline forms (with greater solubility and dissolution rates).
- Upon storage, amorphous solids tend to convert to more stable forms **(thermodynamic instability)**.



- Conformation that a material is amorphous can be achieved with **XRPD** (X-ray powder diffraction). In this case, no specific peaks as a function of diffraction angle should be seen, rather, a broad diffraction pattern, known as a (halo) is the defining characteristic.



- **Non-stoichiometric adducts** involve entrapped solvent molecules within the crystal lattice. Usually they are undesirable owing to its lack of reproducibility, and should avoided for development.
- **A stoichiometric adduct (solvate)** is a molecular complex that has incorporated **the crystallizing solvent molecules** into specific sites within the crystal lattice. When the incorporated solvent is water, the complex is called a **hydrate**, and the terms **hemihydrate, mono-hydrate and di-hydrate** describe hydrated forms with molar equivalent of water corresponding to half, one and two. A compound not containing any water within its crystal structure is termed **anhydrous**. **(this can affect processing steps, solubility and dissolution rate)**


Ampicillin
Anhydrous
Trihydrate
2.1
1.8
1.5
1.2
0.9
0.6
0.3
1
2
3
4
5
6
Hours

P 177

Polymorphism:

- Is the ability of a compound (or element) to crystallize as more than one distinct crystalline species with different internal lattices.
- It has effects on chemical stability, solubility and bioavailability.
- Polymorphs can be classified as one of two types: **enatiotropic** (one polymorph can be reversibly changed into another by varying temperature or pressure, e.g. sulfur) or **monotropic** (one polymorphic form is unstable at all temperatures and pressures, e.g. glyceryl stearates).

- The form with the highest melting temperature, is called the stable polymorphic form and all other forms are metastable.
- the stable form might, however, have the worst processability **(ex. The stable form I of paracetamol has poor compressibility, while the metastable form II has good compressibility)**, or **different bioavailability (ex. chloramphenicol palmitate) exists in three crystalline polymorphic forms A (stable), B (metastable, the most effective one), C (instable) and an amorphous form**.
- Then many physicochemical properties vary with the internal structure of the solid drug, including M.P., density, hardness, crystal shape, optical properties and vapor pressure.

Therefore, characterization of polymorphic and solvated forms involves quantitative analysis of these differing physicochemical properties, by:

1) Microscopy
2) Thermal analysis
3) X-ray powder diffraction

1) Microscopy:

- ✓ All substances that are transparent when examined under a microscope that has crossed polarizing filters are either isotropic or anisotropic.
- ✓ Amorphous substances, such as super-cooled glasses and non-crystalline solid organic compounds, or substances with cubic crystal lattices, such as NaCl, are isotropic materials, which have a single refractive index. With crossed polarizing filters, these substances do not transmit light and they appear black.

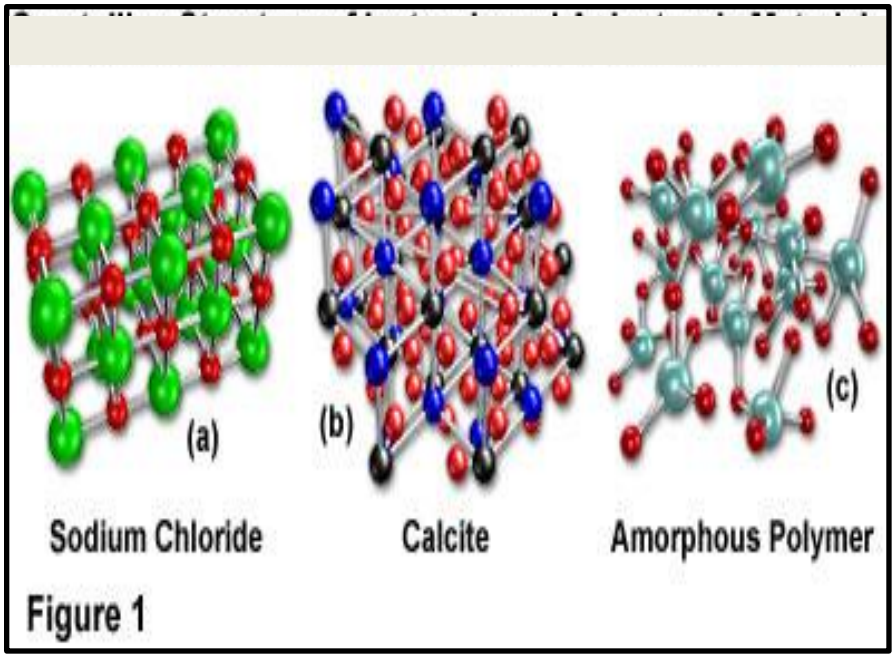
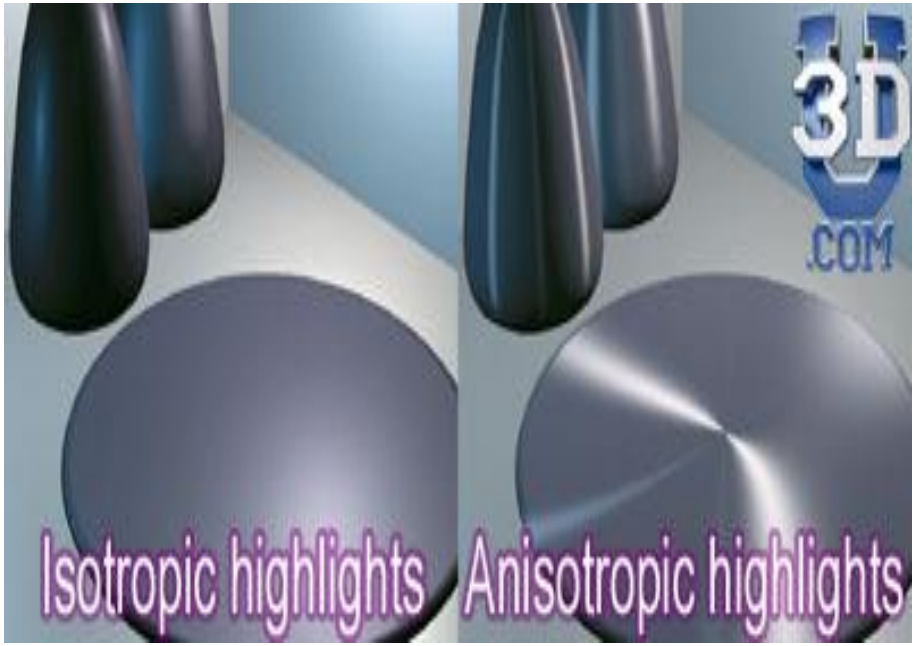


Figure 1



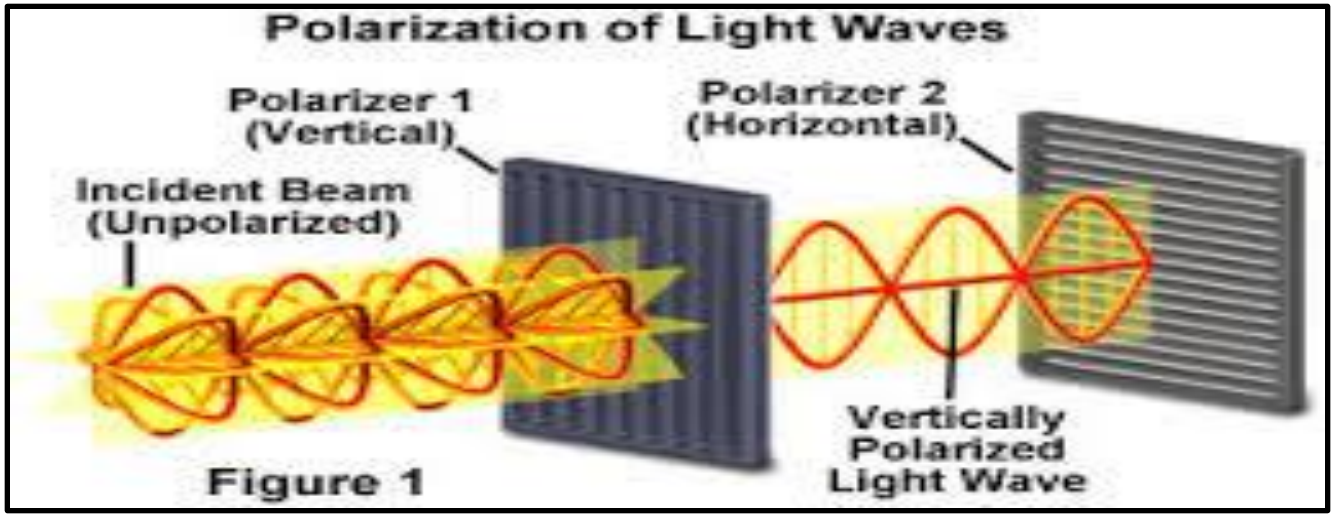
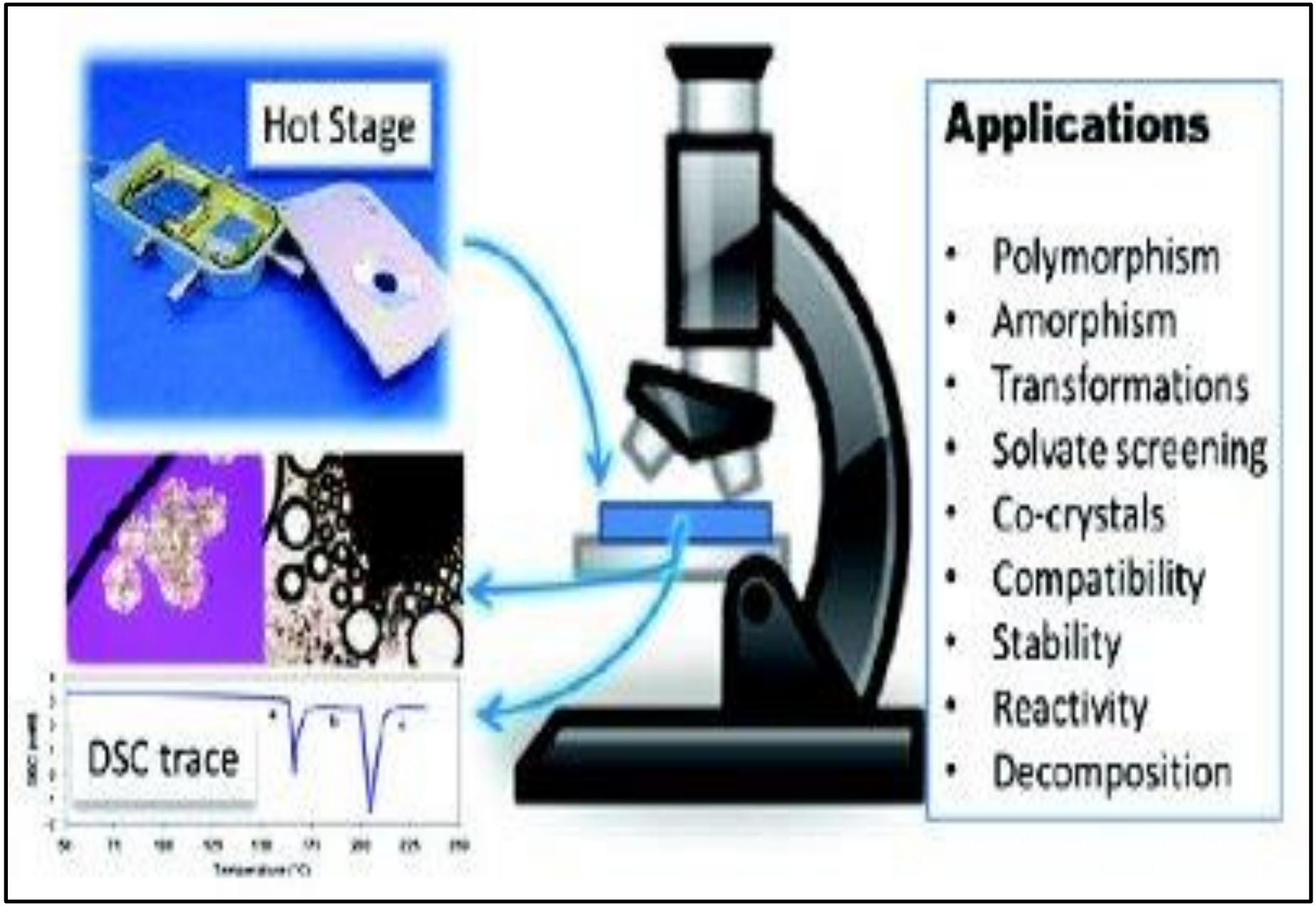


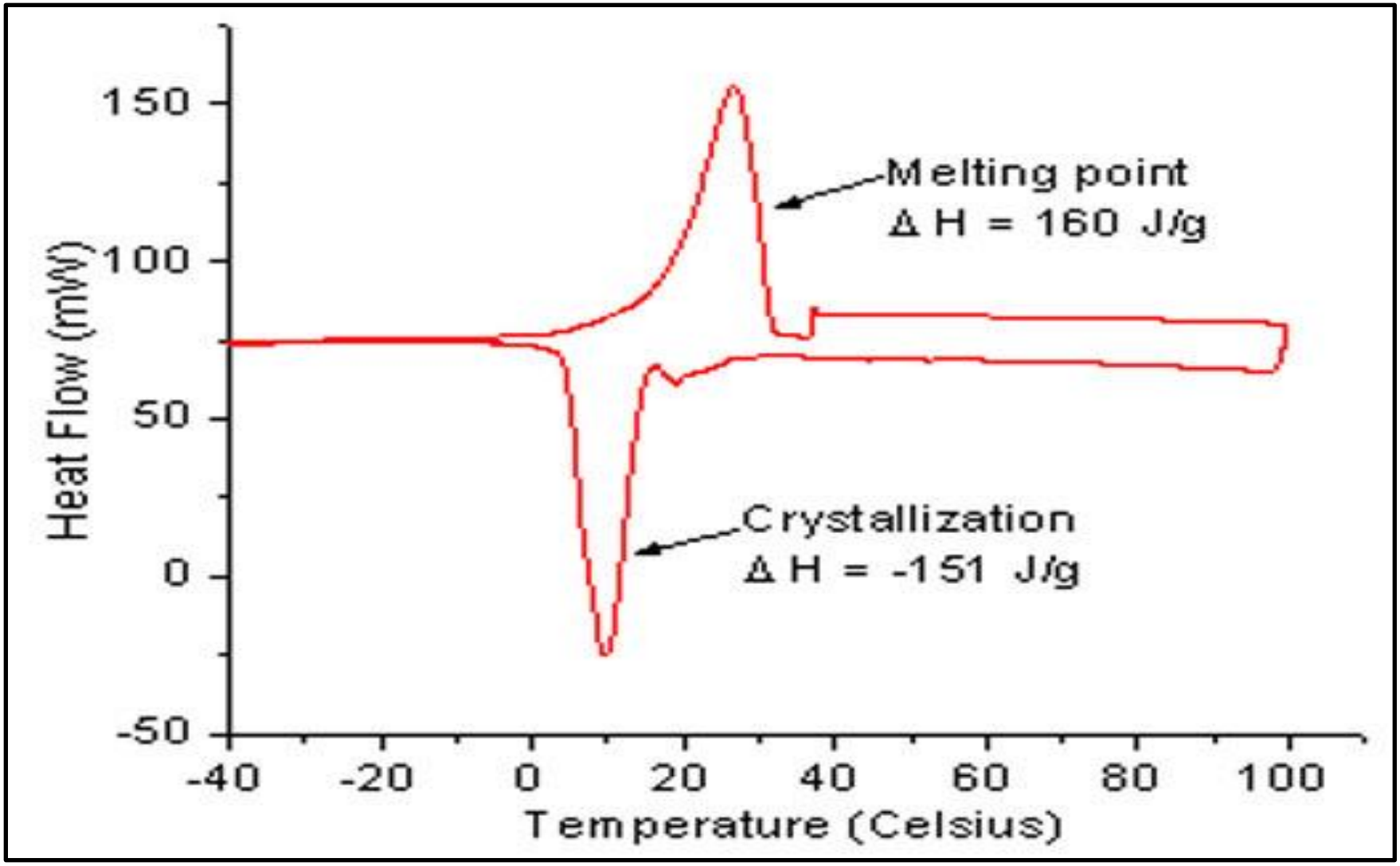
Figure 1

- ✓ Materials with more than one refractive index are anisotropic and appear bright with brilliant colors against the black polarized background.
- ✓ The interference colors depend upon the crystal thickness and the differences in refractive indices.
- ✓ Anisotropic substances are either uniaxial, having two refractive indices, or biaxial, having three principal refractive indices.
- ✓ Most crystalline drugs are biaxial.
- ✓ The polarizing microscope fitted with a hot stage is a useful instrument for investigating polymorphism, melting points and transition temperatures.


Hot Stage
DSC trace
Applications
• Polymorphism
• Amorphism
• Transformations
• Solvate screening
• Co-crystals
• Compatibility
• Stability
• Reactivity
• Decomposition

2) Thermal analysis:

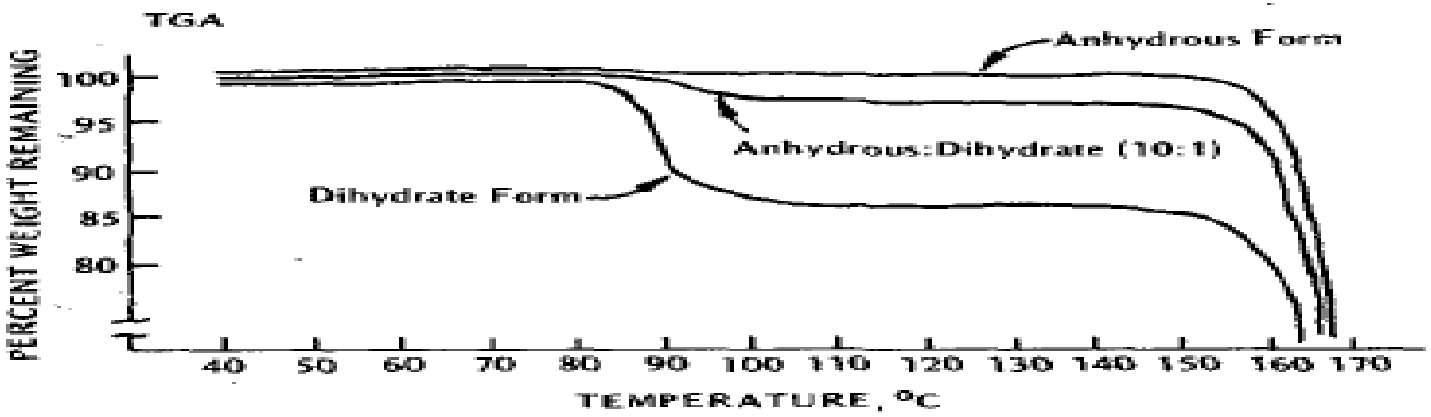
- ✓ DSC and DTA measure the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature.
- ✓ Examples of endothermic processes are fusion, boiling, sublimation and vaporization. While crystallization and degradation are usually exothermic processes.
- ✓ In DSC, a sharp symmetric melting endotherm can indicate relative purity, whereas broad, asymmetric curves suggest impurities or more than one thermal process.



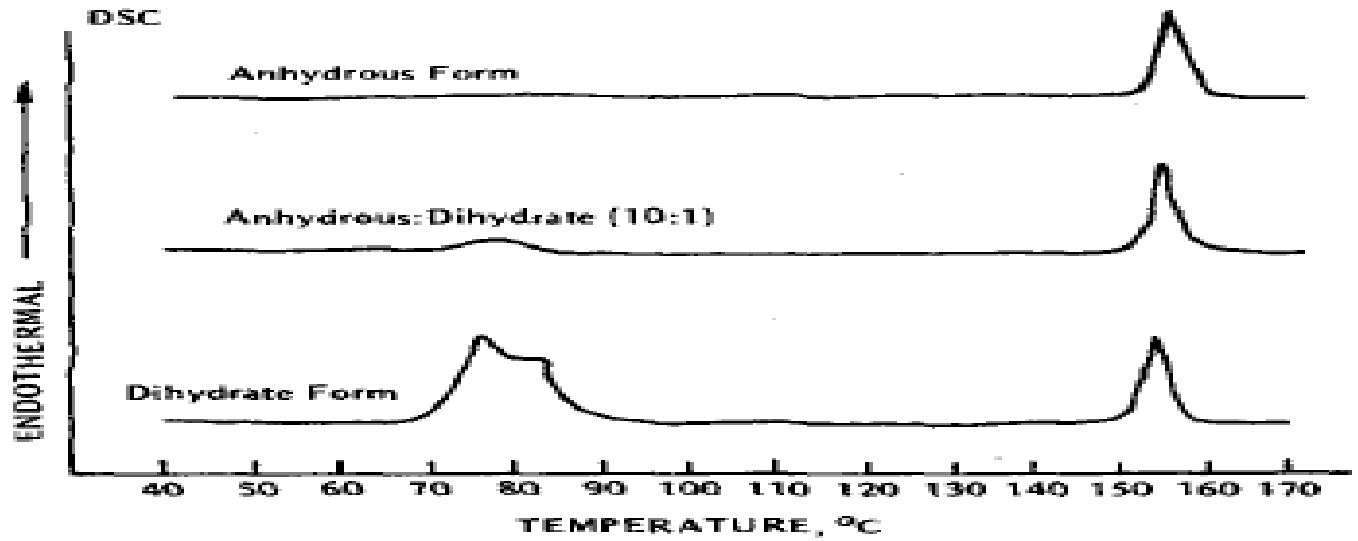
DSC Thermogram

- ✓ **DTA measures changes in sample weight as a function of temperature.**
- ✓ **Desolvation and decomposition processes are frequently monitored by TGA.**

TGA



DSC



As factors affecting these methods are:

1) **Sample homogeneity, size, atmosphere and preparation.**
2) **Particle size.**
3) **Heating rate**

3) X-ray powder diffraction:

- ✓ An important technique for establishing the batch-to-batch reproducibility of a crystalline form.
- ✓ Random orientation of a crystal lattice in a powder sample causes the X-rays to scatter in a reproducible pattern of peak intensities at distinct angles (Θ) relative to the incident beam.
- ✓ Each diffraction pattern is characteristic of a specific crystalline pattern for a given compound.

- ✓ It can provides structural data to identify and differentiate polymorphs, qualitatively and quantitatively (different peak intensities).

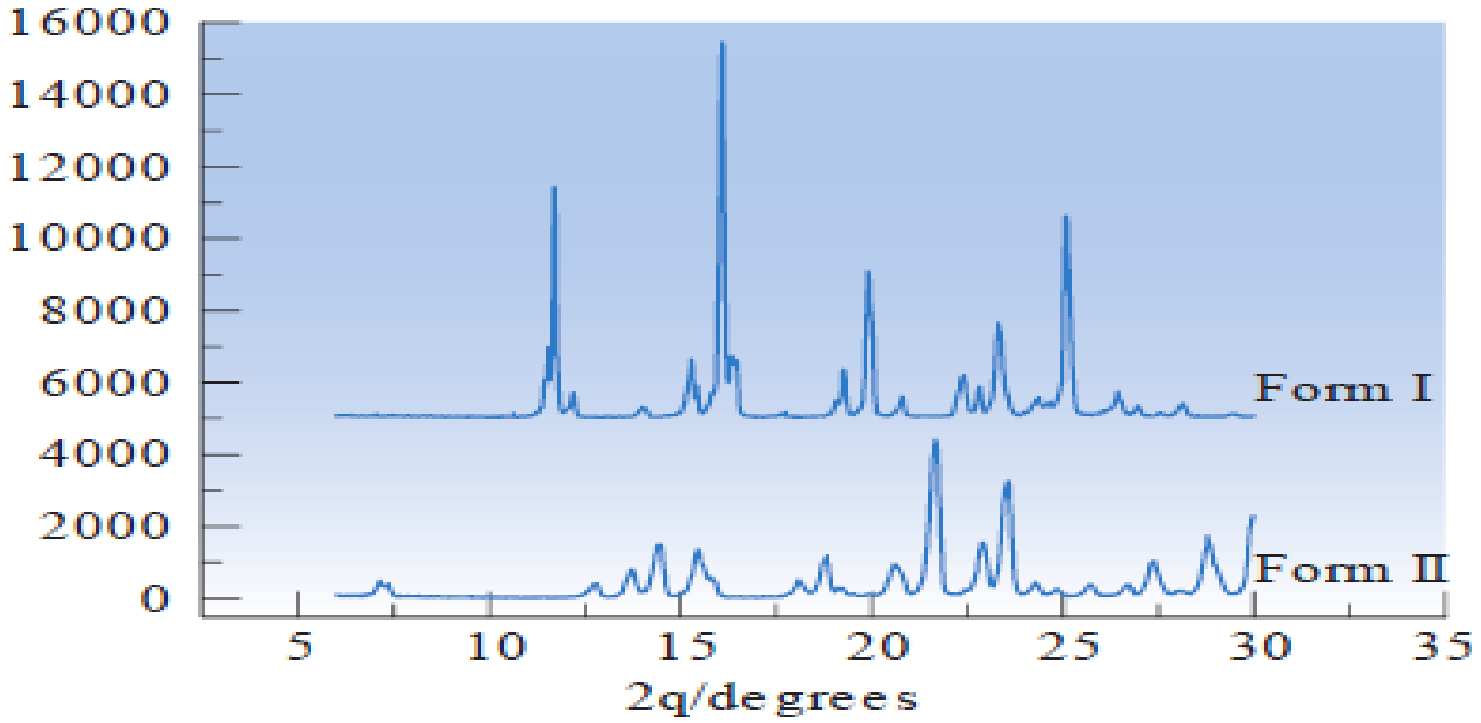


Fig. 23.13 • XRPD diffractograms for two polymorphs of sulfapyridine.

Hygroscopicity

- ✓ Many drug substances, particularly water soluble salt form, have a tendency to adsorb atmospheric moisture.
- ✓ Adsorption and equilibrium MC can depend upon:

1) The atmospheric humidity 2) Temperature 3) Surface area 4) Exposure 5)The mechanism for moisture uptake 6) Compound type (salt or not)

- ✓ Deliquescent materials adsorb sufficient water to dissolve completely, as it observed with NaCl (on a humid day), KOH and $MgCl_2$. Then, as results many important parameters are affected like chemical stability, flowability and compatibility.
- ✓ As analytic methods for monitoring the moisture level like gravimetry, TGA, DVS (Dynamic vapor sorption) ….are used.

Fine particle characterization

- ✓ Include characterization of particle size, shape and surface morphology.
- ✓ They are important for flow, mixing, milling, compression and dissolution.
- ✓ They are generally characterized by microscopy methods, Coulter counter, sieving, BET adsorption method and light/laser scattering methods.
- ✓ SEM can be used for observation of surface morphology in which the sample is gold-coated for more conduction and then more resolution.
- ✓ BET method is used for measurement of surface area depending on adsorption of nitrogen molecules on the surface of sample.

Bulk density

- ✓ it varies substantially with the method of crystallization, milling or formulation.
- ✓ How assayed? Why assayed?

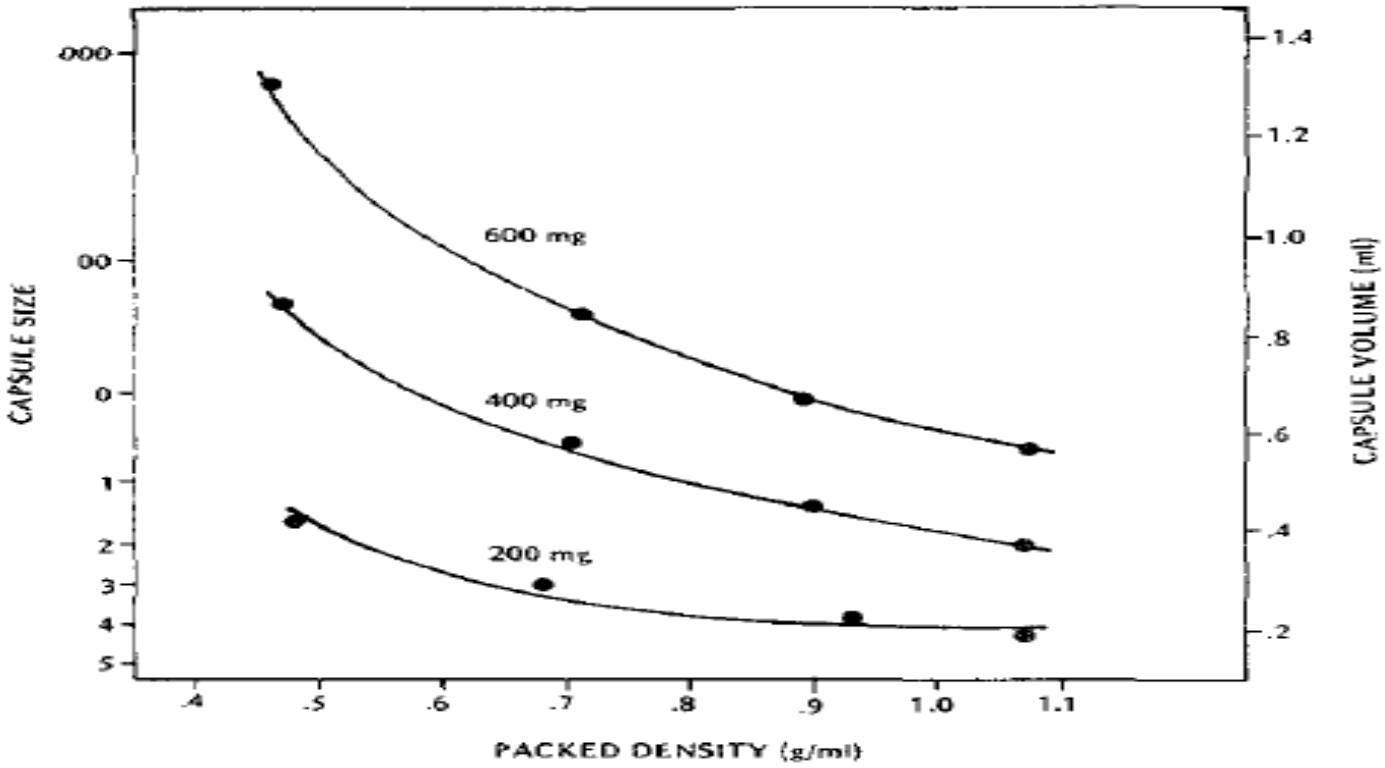


FIG. 8-15. *Correlation between capsule size and packed density for different fill weights (200–600 mg).*

Powder flow properties

- ✓ They are significantly affected by particle size, density, shape, electrostatic charge and adsorbed moisture which may arise from processing or formulation.
- ✓ They can affect mixing, filling (for tablets and capsules) and content uniformity.
- ✓ Assayed by???
- ✓ Compressibility can be used for evaluation of flow properties and to give idea about the plastic properties of powder (deformation) during tabletting methods