Industrial Pharmacy II
5th Stage
College of Pharmacy



Lab 1:
Preformulation

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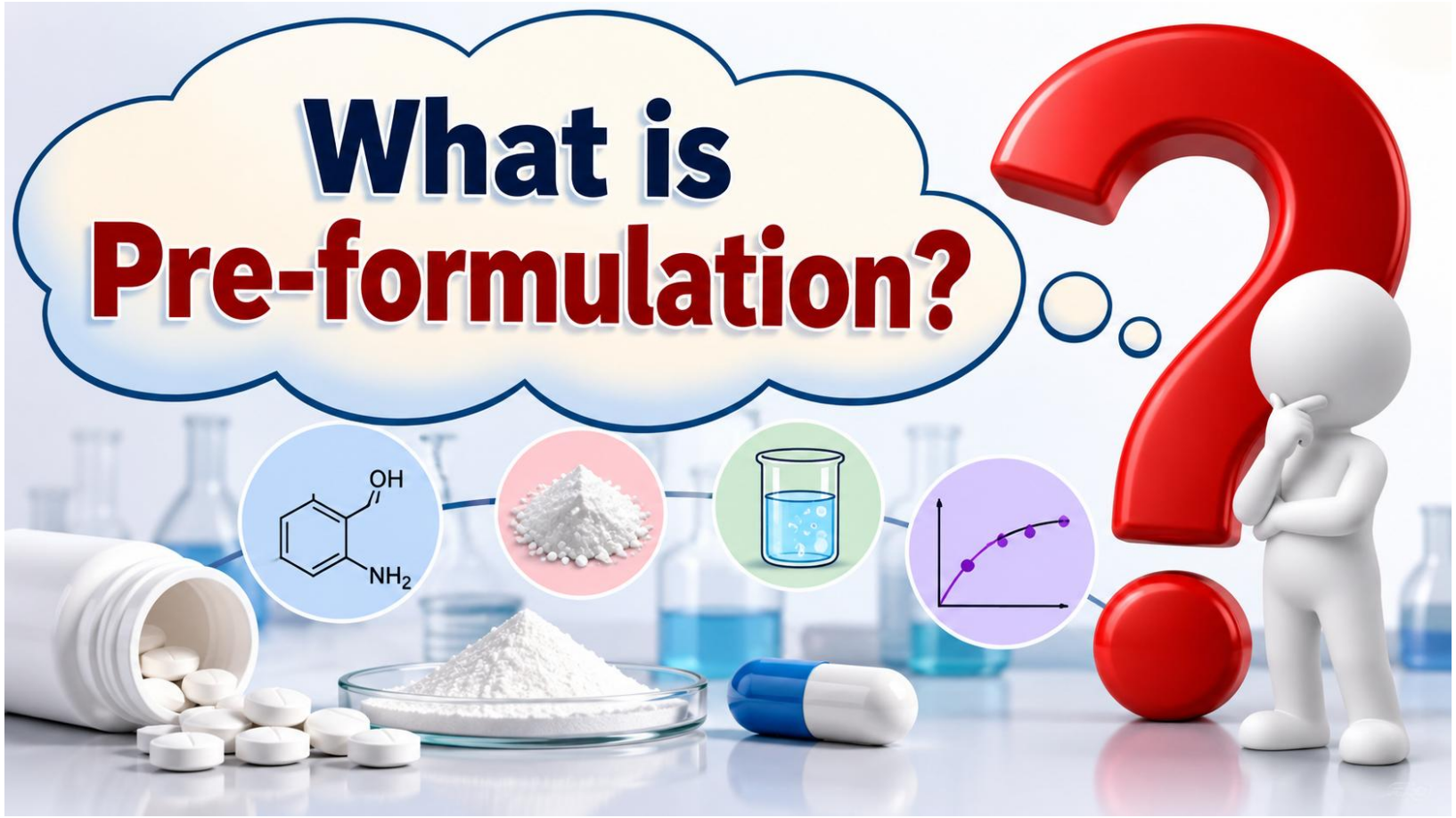
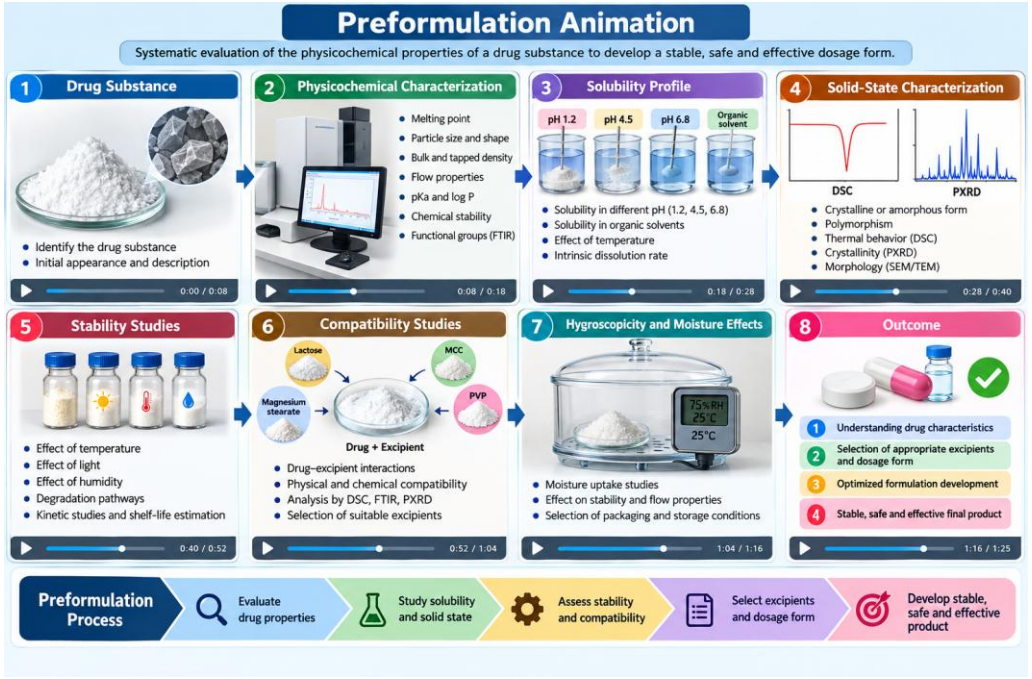
Semester: 1st

Introduction



Introduction

- **Preformulation** is branch of Pharmaceutical science that utilizes biopharmaceutical principles in the determination of physicochemical properties of the drug substance. Prior to the development of any dosage form new drug. it is essential that certain fundamental physical & chemical properties of drug powder are determined.



Preformulation

- Before starting a formal program of preformulation pharmacist must consider the following:
- 1- Available physicochemical data (including chemical structure, different salt available).
- 2- Anticipated dose.
- 3- Supply situation and development schedule.
- 4- Availability of stability — indicating assay

Preliminary evaluation

- Compound identity.
- Formula and molecular weight.
- Structure.
- Therapeutic indications:
- Potential hazards
- Initial bulk lots:
- Analytical methods: - HPLC assay - TLC assay - UV/ Visible spectroscopy

Organoleptic properties

- Color is generally a function of a drug's inherent chemical structure relating to a certain level of unsaturation .
- Color intensity relates to the extent of conjugated unsaturation as well as the presence of chromophores .
- Some compound may appear to have color although structurally saturated .



odour

- The substance may exhibit an inherent odor characteristic of major functional groups present
- Odor greatly affects the flavor of a preparation or food stuff

Drug	Consumption period (Day)	Color	Odour	Taste	pH(mean)
Paracetamol syrup	1	Red	Strawberry	Sweet	4.35
	2	Red	Strawberry	Sweet	4.33
	3	Red	Strawberry	Sweet	4.30
	Control	Red	Strawberry	Sweet	4.36
Salbutamol syrup	1	Colorless	Soda smell	Pungent	3.18
	2	Colorless	Soda smell	Pungent	3.18
	3	Colorless	Soda smell	Pungent	3.18
	Control	Colorless	Soda smell	Pungent	3.18
Amoxicillin suspension	1	Yellowish green	Fruity smell	Sweet	4.60
	3	Yellowish green	Fruity smell	Sweet	4.55
	5	Yellowish green	Fruity smell	Sweet	4.49
	Control	Yellowish green	Fruity smell	Sweet	4.62
Cephalexin suspension	1	Orange	Fruity smell	Sweet	5.25
	3	Orange	Fruity smell	Sweet	5.20
	5	Orange	Fruity smell	Sweet	5.17
	Control	Orange	Fruity smell	Sweet	5.27
Lactulose syrup	1	Yellow	No	Sweet	3.68
	2	Yellow	No	Sweet	3.67
	3	Dark yellow	No	Sweet	3.57
	Control	Light yellow	No	Sweet	3.70

Tast

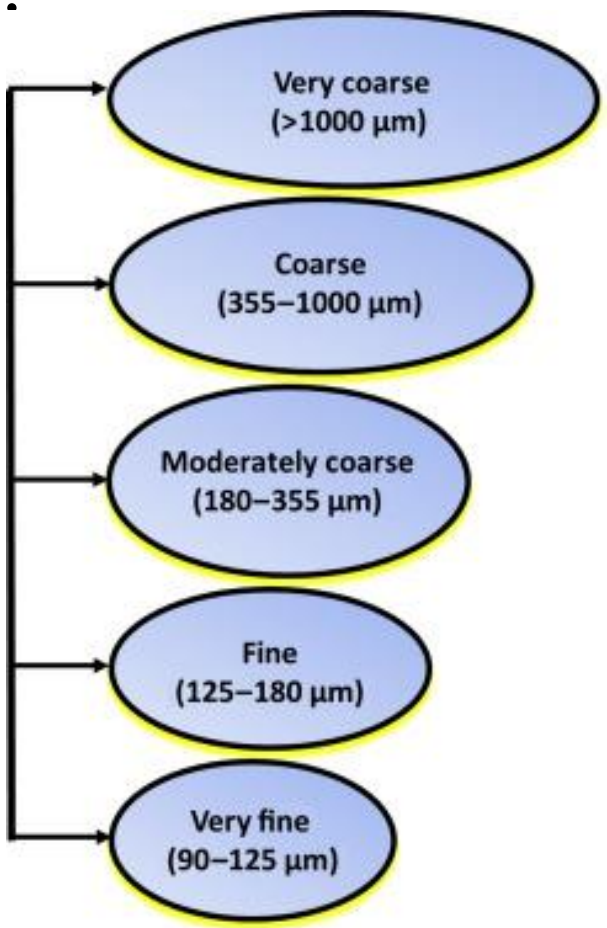
- If taste is considered as unpalatable, consideration is to be given to the use of a less soluble chemical form of the drug
- The odor and taste may be suppressed by using appropriate flavors and excipients or by coating the final product

Purity

- Designed to estimate the levels of all known and significant impurities and contaminates in the drug substance under evaluation
- It is another parameter which allows for comparison with subsequent batches
- Occasionally, an impurity can affect stability
- e.g. metal contamination
- Appearance Thin layer chromatography is a wide ranging applicability and is an excellent tool for characterizing the purity. HPLC, paper chromatography and gas chromatography are also useful.

Particle size

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

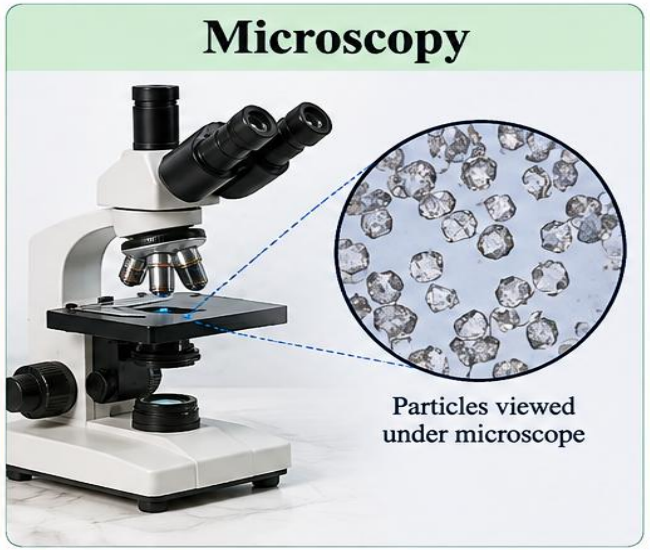


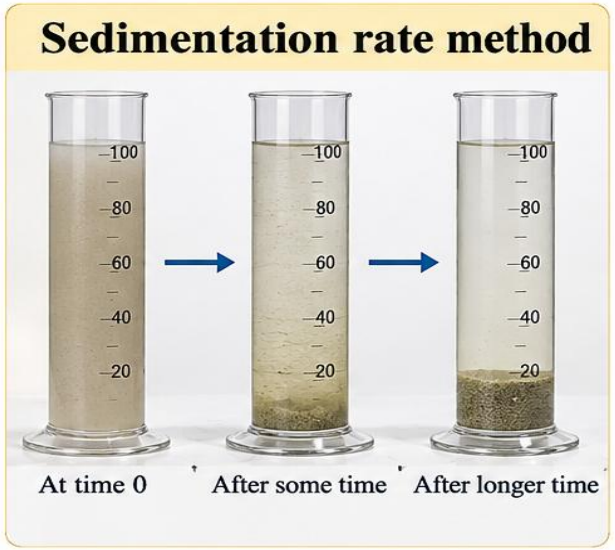
Particle size can influence on variety of important factors

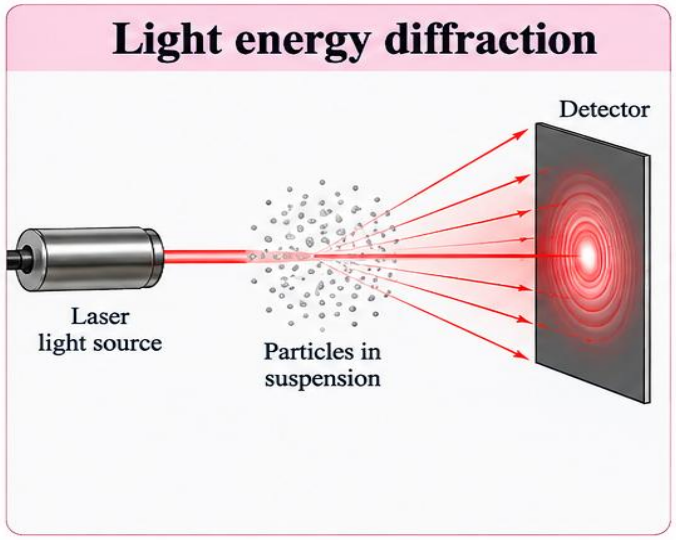
- Dissolution rate
- suspendability
- Uniform distribution
- Penetrability
- Lack of grittiness

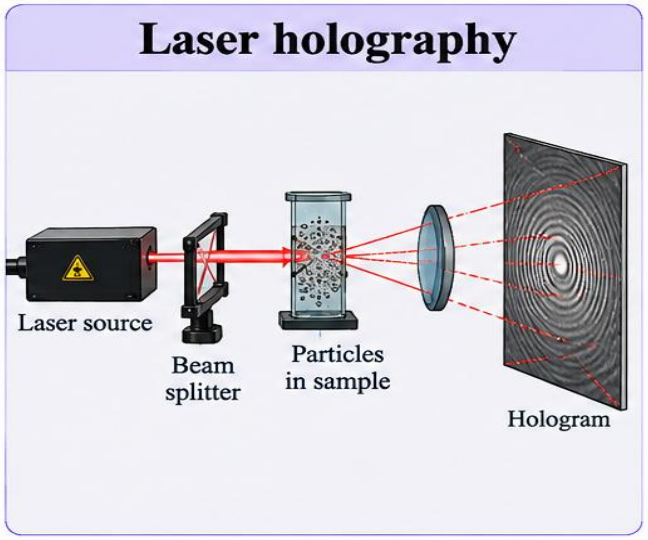
Method of determine particle size

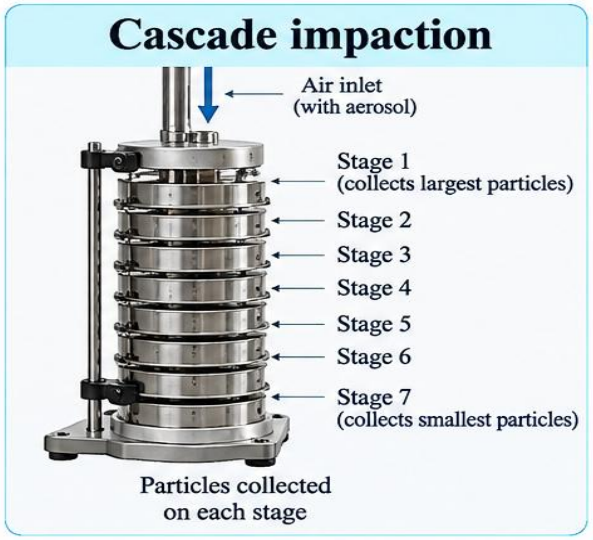










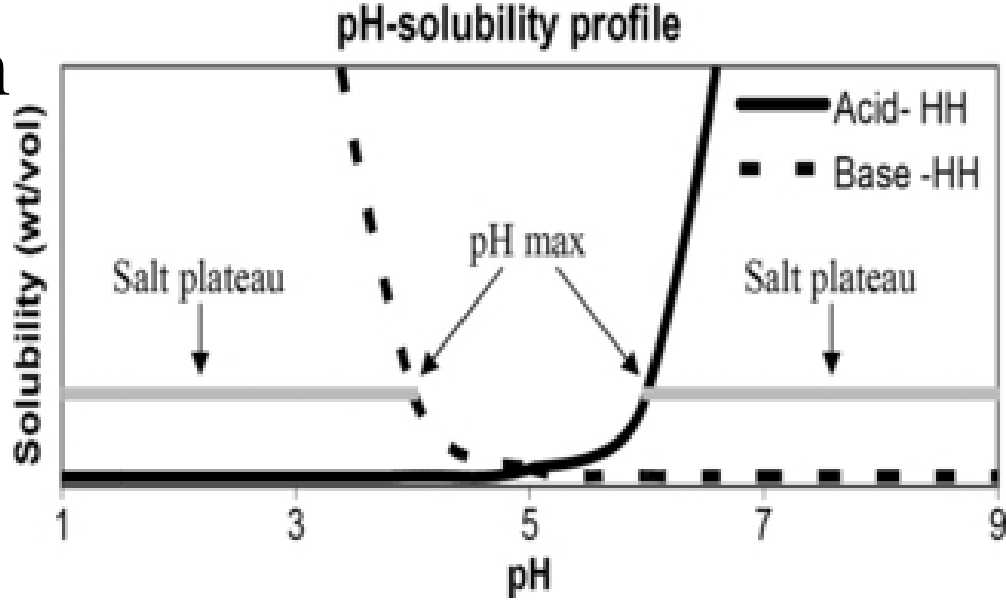


Solubility

- If the solubility is< 1 mg/ml indicates need for salt formation to improve solubility
- If the solubility is< 1 mg/ml in pH=1 to 7, preformulation study should be initiated
- Solubility should ideally be measured at two temperature 4°C and 37°C
- 4°C to ensure physical stability and 37°C to support biopharmaceutical evaluation

Ph solubility profile

- The solubility of acidic or basic drug will show difference in solubility with changes in pH
- pH solubility profile of drug can be established by running the equilibrium solubility experiment within pH range 3-4 .

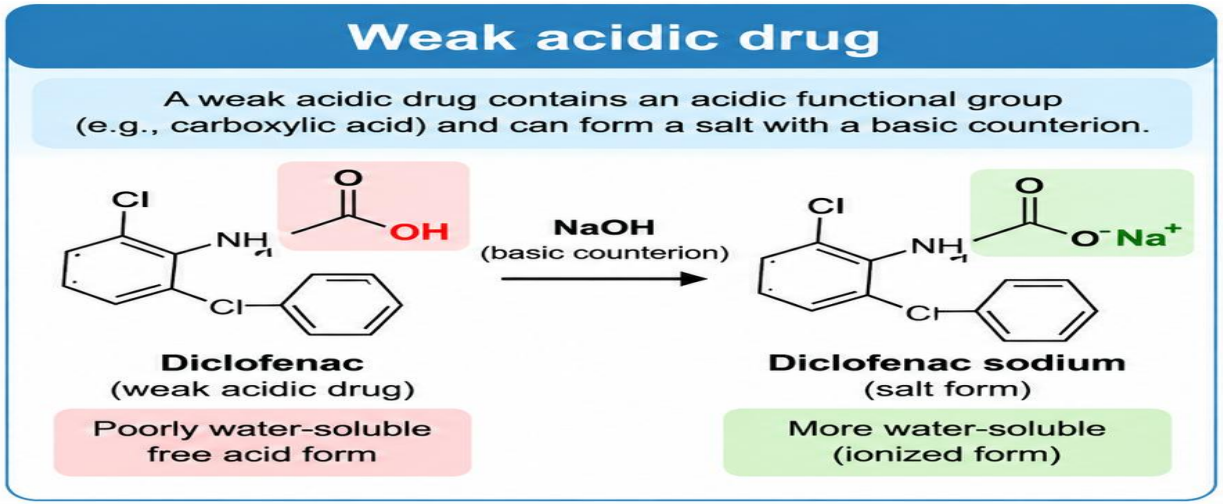


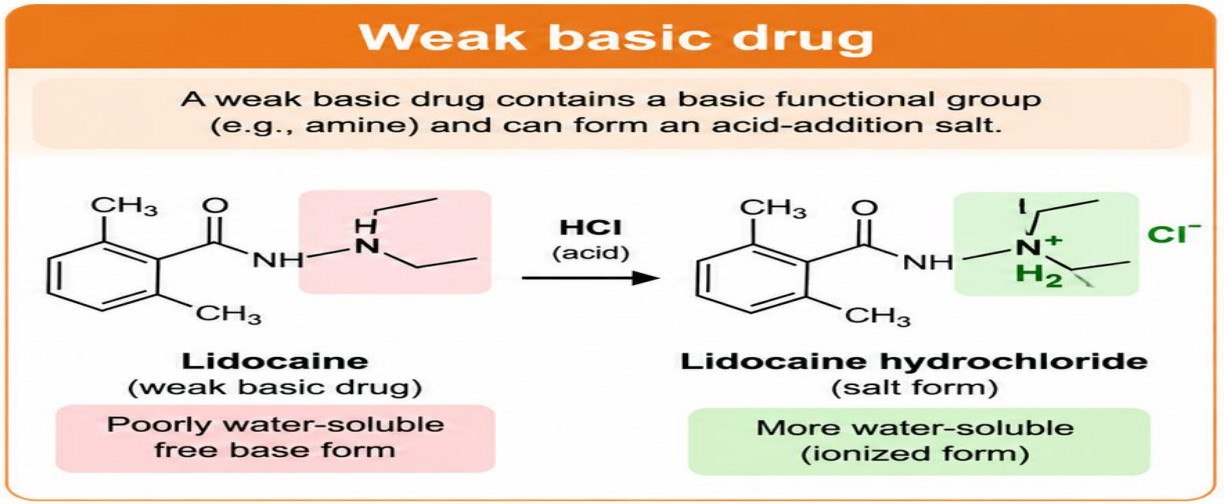
General method for increasing solubility

- Addition of co-solvent
- pH change method
- Reduction of particle size
- Temperature change method
- Addition of surfactant
- Dielectrical constant
- Complexation HgI2(mercuric iodide) is sparingly soluble in water. Its solubility in water is increased by forming complex with KI

Effect of Ph

- Weak electrolytes undergo ionization and are more soluble when in ionized form (salt formation).
- The degree of ionization depends on dissociation constant (pKa) and the pH of the medium.
- Solubility is a function of pH, that is related to its pKa which gives ratio of ionized and unionized forms of the substance.



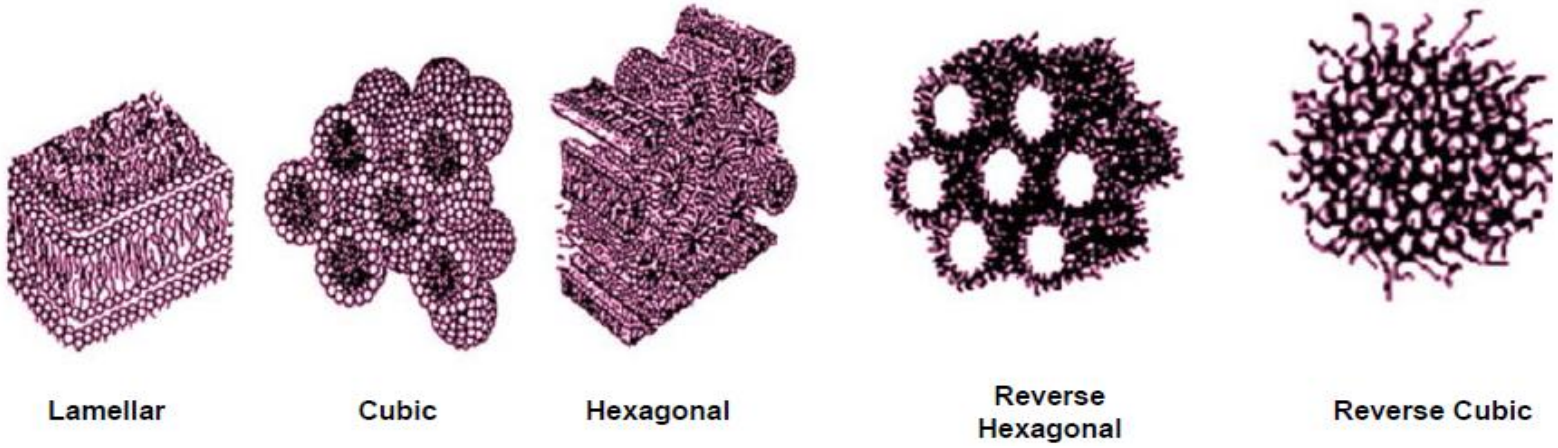


Crystallinity

- **Crystal Habit and Internal Structure**
- The **crystal habit** and **internal structure** of a drug can affect its bulk and physicochemical properties.
- **Crystal habit** means the **external shape** and **appearance** of a crystal.
- **Internal structure** means how the **drug molecules** are arranged **inside the crystal.**
- A change in the internal molecular arrangement can also cause a change in the crystal shape (habit).
- Example: Changing a drug from its sodium salt form to its free acid form may change both its internal crystal structure and external crystal shape.
- Internal molecular arrangement → Crystal shape → Drug properties

Different shapes of crystals

I. cubic or isometric
II. Tetragonal
III. Orthorhombic
IV. Hexagonal
V. Trigonal
VI. Triclinic
VII. Monoclinic



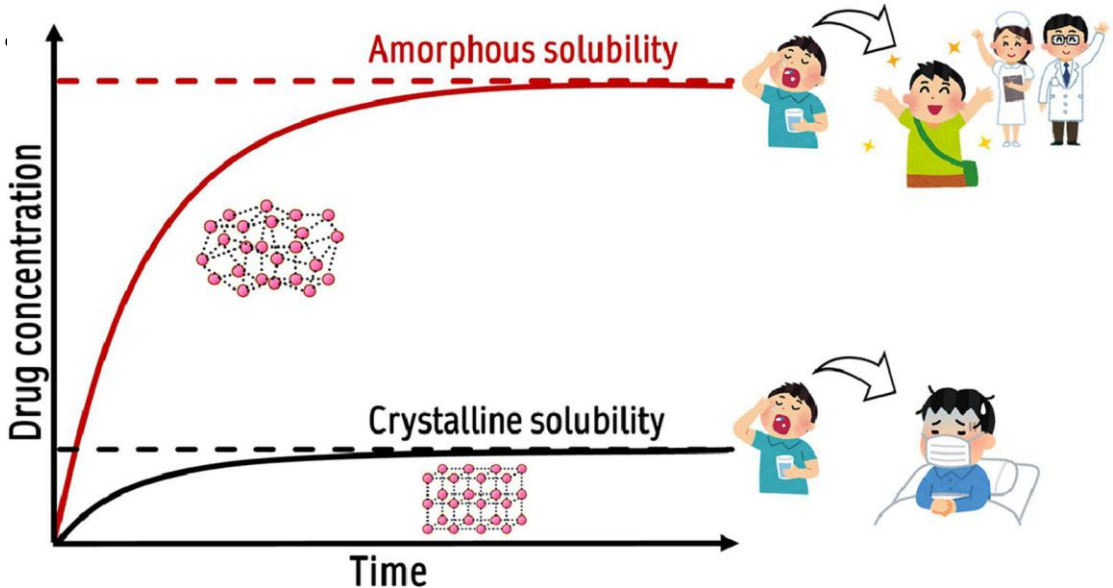
- **Depending on internal structure compounds is classified as: Crystalline or Amorphous**

crystalline :compound are characterized by **repetitious spacing** of constituent atom or molecule in three dimensional arrays

amorphous form : atom or molecule are randomly placed

- Solubility and dissolution rate are great for **amorphous form** than **crystalline**, as **amorphous form** has **higher thermodynamic energy**
  E.g. amorphous form of Novobiocin is well absorbed whereas crystalline form results in poor absorption.

Which prefer amorphous or crystalline ?



Polymorphisim

- 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 2 type
- Enatiotropic
- Monotropic
- The polymorph which can be changed from one form into another by varying temp. or pressure is called as Enantiotropic polymorph e.g. Sulfur
- One polymorph which is unstable at all temp. and pressure is called as monotropic polymprph e.g. Glyceryl stearate

Polymorphisim

- Polymorph differ from each other with respect to their physical property such as

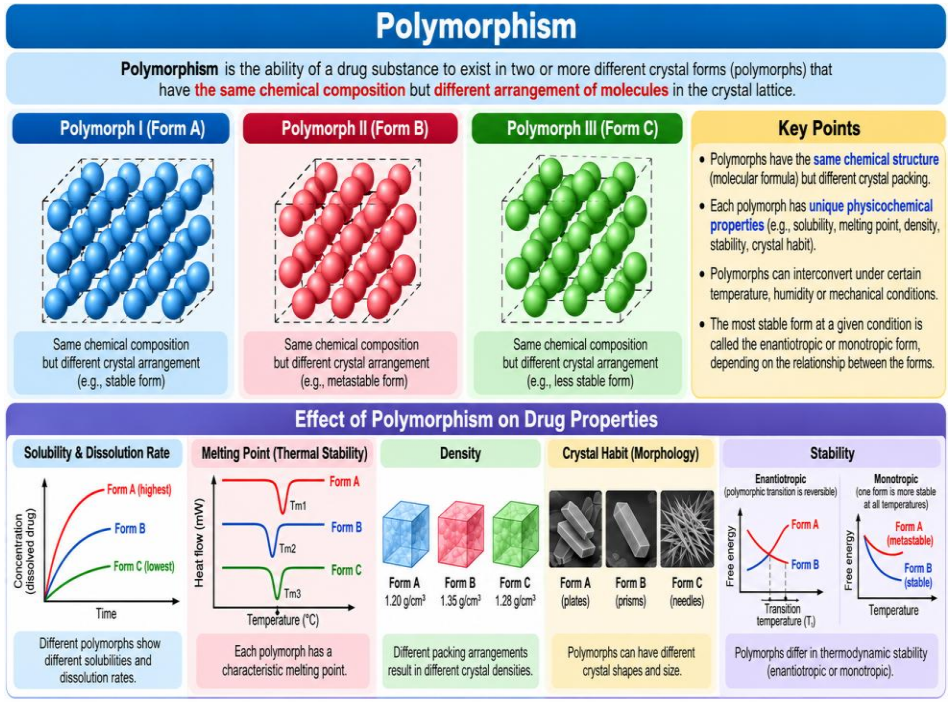
I. Solubility Melting point

II. Density

III. Hardness

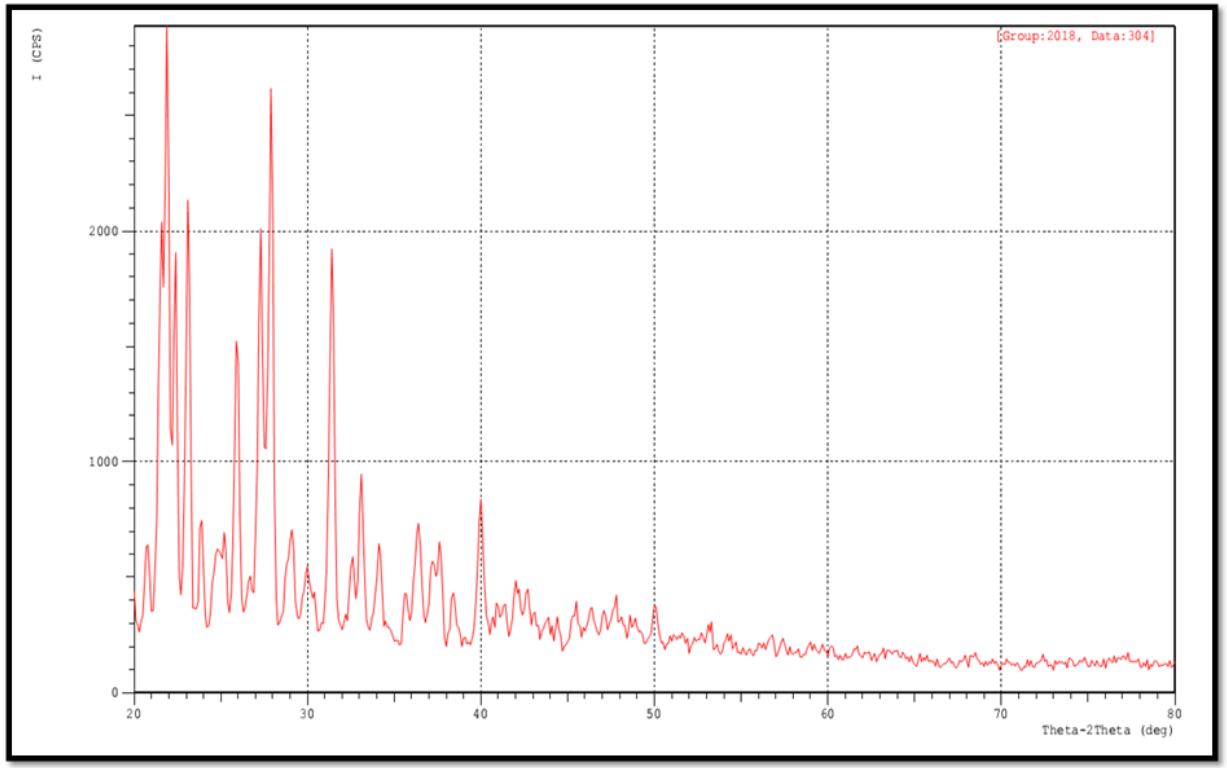
IV. Compression characteristic

- During preformulation it is important to identify the polymorph that is stable at room temp.
- E.g. 1) Chloromphenicol exist in A,B and C forms of these B form is more stable and most preferable
- E.g.2) Riboflavin has I,II,III forms, the III form shows 20 times more water solubility than form I



Technique for crystalline study

I. Microscopy
II. Hot stage microscopy
III. Thermal analysis
IV. X- ray diffraction



X-ray curve

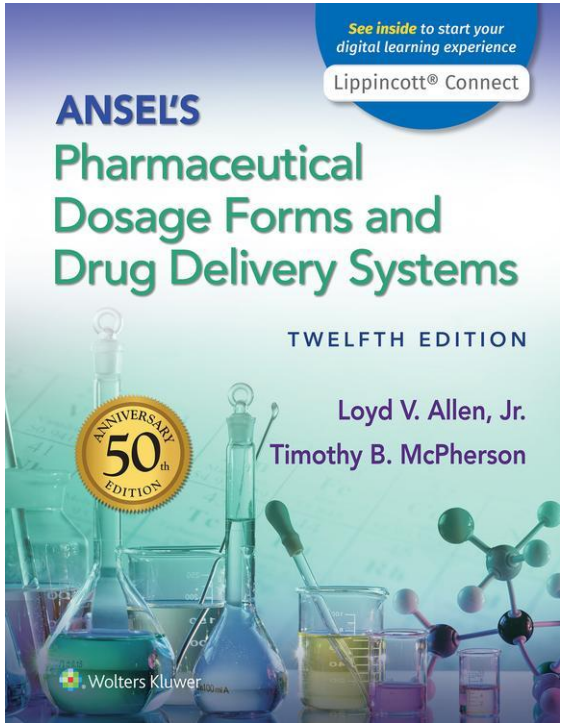
Stability

- Provide a evidence on how the quality of a drug substance or drug product varies with time under the influence of variety of environmental factors such as .. Temperature, humidity, and light .
- Establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions
- Because physical, chemical or microbiological changes might impact the efficiency and security of the final product



Reference:

- Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 12th ed., Wolters Kluwer.




Thank You