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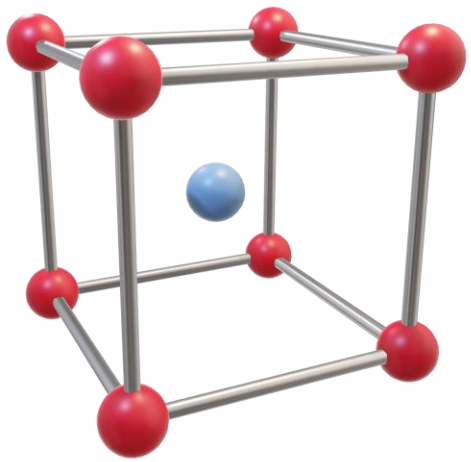
Physical Pharmacy

The Solid State 2



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- Types of Solids
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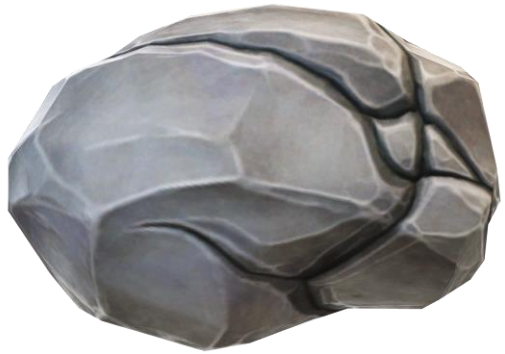
- Crystalline Solids
  A. Structure
  B. Shape
  C. Polymorphism :Definition-Types-Factors affecting polymorphism-Application in Pharmacy
  D. Psueodopolymrophism



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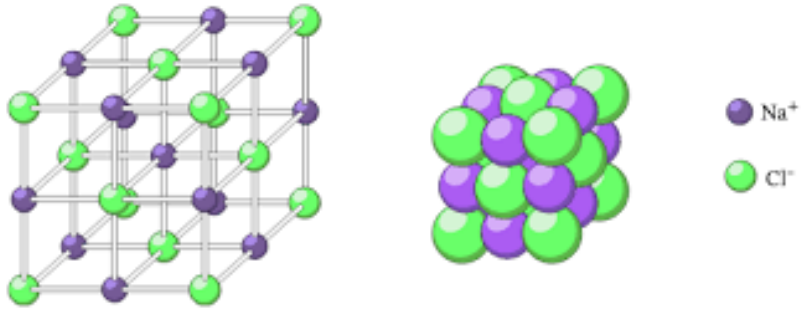
Crystalline solids

Types of Crystalline Solids

- Crystalline solids may be classified based on the nature of constituent particles and the major binding forces operating between them are as follows:

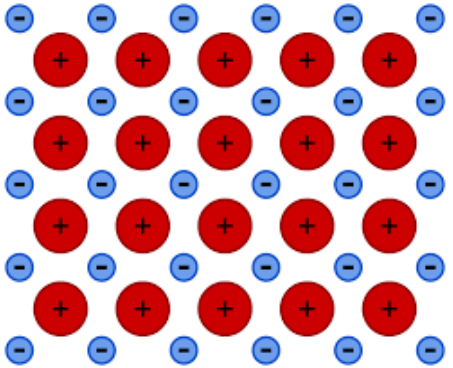
a) Ionic solid (ionic bond) :

Nacl, Caco3 , Mgo



b) Metallic solid (Metallic bond)

Iron Gold Silver



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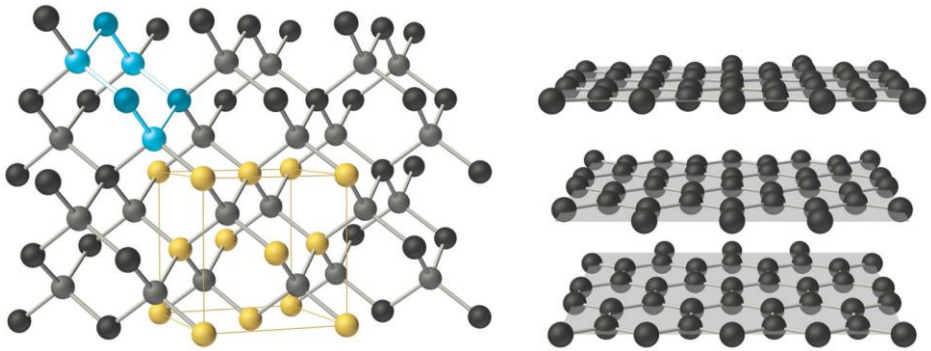
Crystalline solids

Types of Crystalline Solids

c) **Covalent solid(Covalent bond) :**
Diamond, Graphite


(a) Diamond (b) Graphite

d) **Molecular solid (Covalent bond) :**
Ice, Sugar ,Co2


Carbon dioxide

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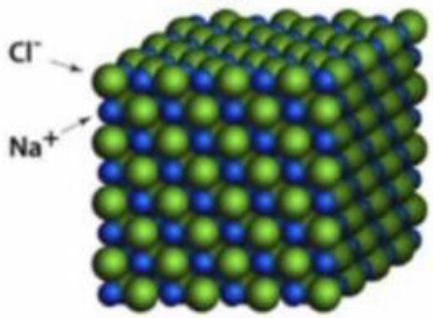
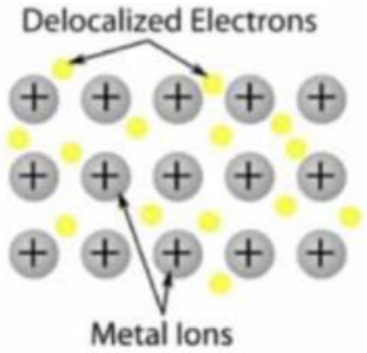
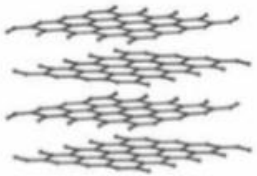
Crystalline solids

Types of Crystalline Solids

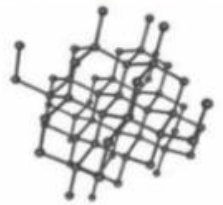


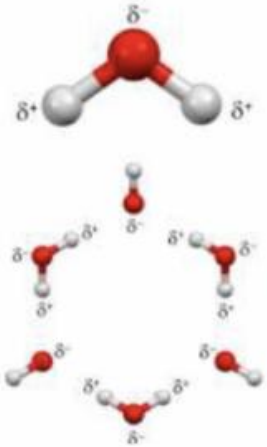


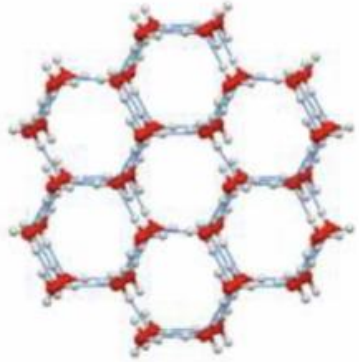
Dull, opaque, soft, common

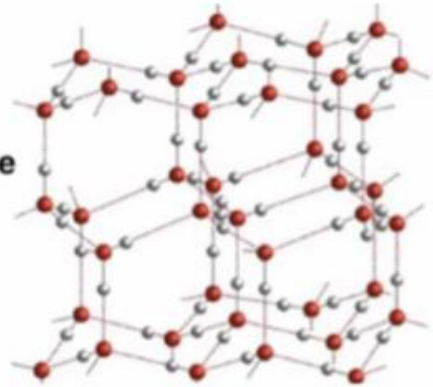


Brilliant, transparent, hard, rare









3-D Structure of Ice

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Crystalline solids

Types of Crystalline Solids (Types of crystals)

Type of Bond	Ionic solids (Ionic bond)	Metallic solids (metallic bond)	Covalent solid (Covalent bond)	Molecular solid (Covalent bond)
Example	NaCl, CacO3, Mgo	Iron ,Gold ,Silver	Diamond , Graphite	Ice ,Sugar Naphthalene
Constituent particle (with example)	Cations & Anions Na^+ , Cl^-	Metal Atoms (Fe atoms) Delocalised electrons	Non Metal Atoms (C atoms)	Molecules (H2o)
Melting point	High Melting Points	High Melting Points	High Melting Points	Low Melting Points
Hardness	Brittle	Malleable & Ductile	Hard	Soft and easy to vaporize
Conductivity	Insulators in Solids (Conductors in Molten state)	Good Conductors (Delocalised electrons)	Poor Conductors (semi conductor)	Insulators

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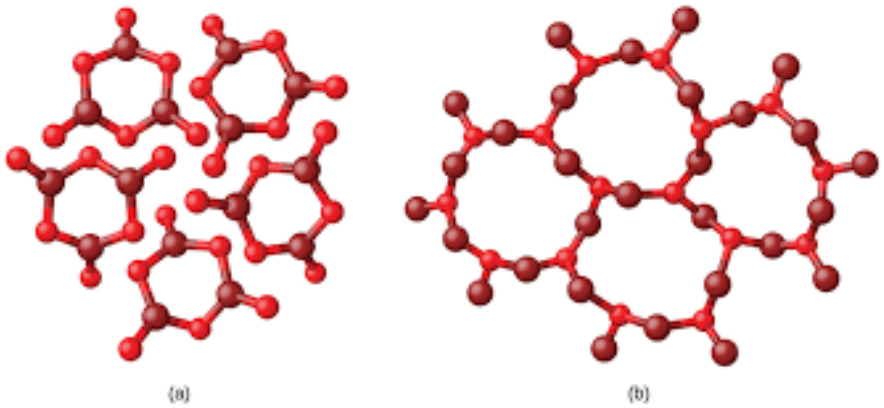
Crystalline solids

Types of Crystalline Solids (Types of crystals)

Note:

- There are certain solid substances which exhibit properties and characteristics of more than one of these types.

- This may be due either to the presence of two different types of bonds and the presence of bonds which are intermediate in character



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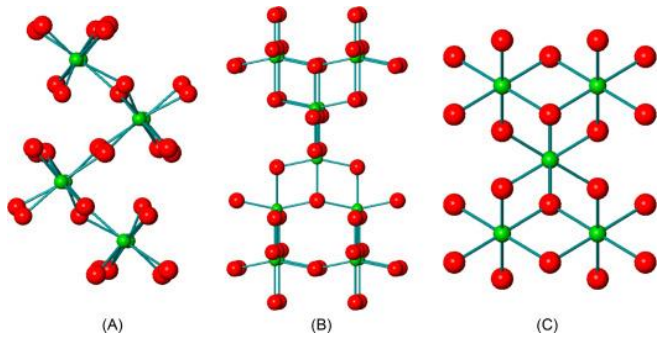
Crystalline solids

Polymorphism

- Polymorphism is defined as “**the ability of a solid crystalline material to exist in more than one form or crystal structure**” (i.e., one molecule can exist in two or more different unit cell types).

- Polymorphism occurs since during drug production, there are changes in the conditions used during crystallization process.

- Any materials with two polymorphs are dimorphic, with **three polymorphs are trimorphic,** and so on.



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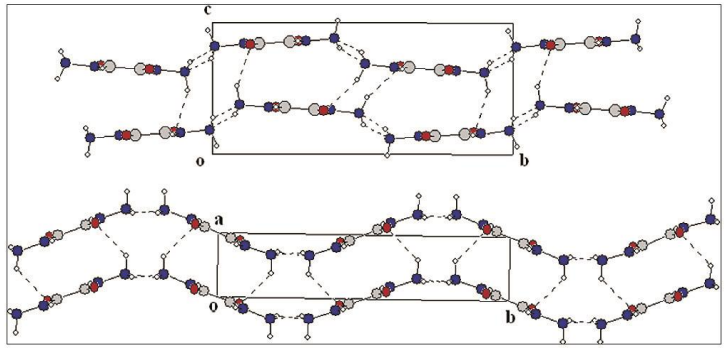
Crystalline solids

Polymorphism

- Various polymorphs of a substance exhibit difference in physical properties such as **melting point, color, hardness, density electrical conductivity, hygroscopicity, latent heat of fusion, solubility,** and dissolution rate, as well as variance in chemical reactivity.

- Under a given set of conditions, polymorphs have different stabilities:

a. Polymorphic form with the lowest free energy will be the most stable, and other polymorphs will **spontaneously transform from** the metastable to the stable form.



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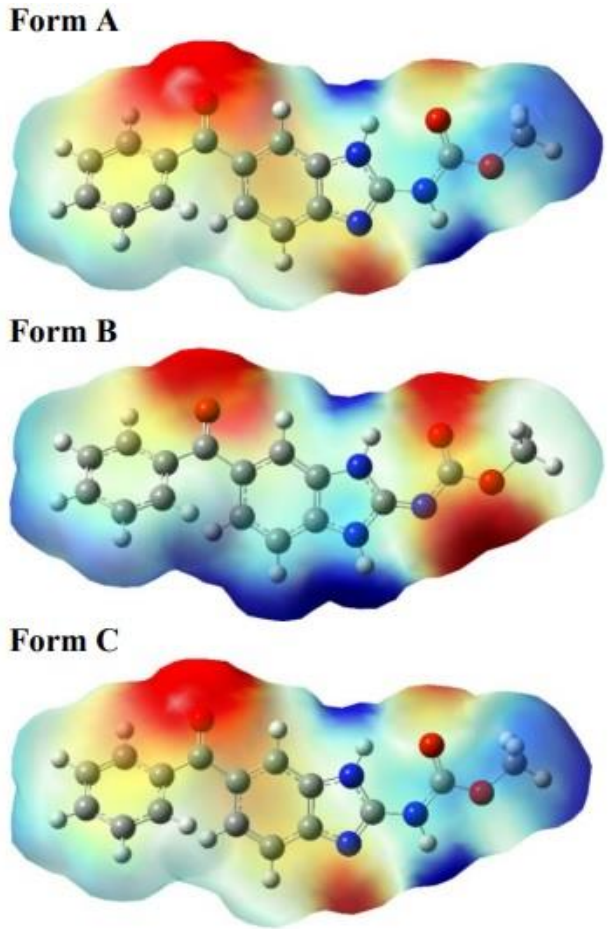
Crystalline solids

Polymorphism (Cont.) :Application of Polymorphism in Pharmacy

- Different polymorphs have different compressibility: e.g., **paracetamol powder**

- Owing to the variations in the solubility of polymorphs, there will be a difference in bioavailability of drugs: this will have one of the following consequences:

a. The difference in the bioavailability of different polymorphic forms of a drug is usually insignificant



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Polymorphism (Cont.) :Application of Polymorphism in Pharmacy

b. One polymorph can be more therapeutically successful than another polymorph of the same product and use.

c. One polymorph may be poorly absorbed and is problematic, e.g., in the case of the chloramphenicol palmitate, (form A) of the three polymorphic forms of which is **poorly absorbed.**

Crystalline solids

Polymorphism (Cont.) :Factors Affecting Polymorphism

- **The following factors are known to cause polymorphic changes during crystallization**:

a. Solvent types (the packing of crystal may be different in polar and non polar solvents)
b. Some impurities that inhibit the growth of certain polymorphic forms, which can favor the growth of a metastable polymorph
c. The rate of crystallization, which can be affected by the degree of supersaturation from which a material is crystallized (generally, the higher a concentration is above the solubility, the more likely it is to create a metastable polymorph)
d. Temperature at which crystallization is carried out
e. Change in stirring hydrodynamics

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Crystalline solids

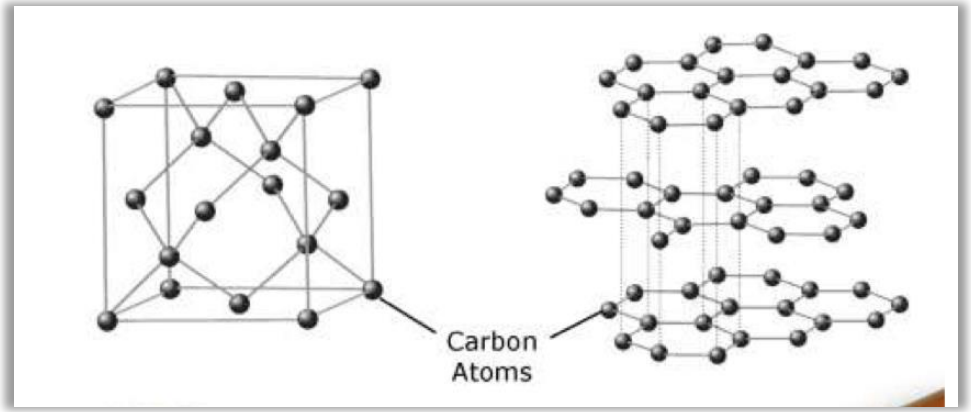
Polymorphism (Cont.) :Examples

- Certain classes of drug are particularly susceptible to polymorphism; for example, the following drugs exist in several polymorphic forms:

a. **Nearly all long-chain organic compounds exhibit polymorphism**

b. **About 65% of the commercial sulfonamides**

c. **About 70% of the barbiturates used medicinally**



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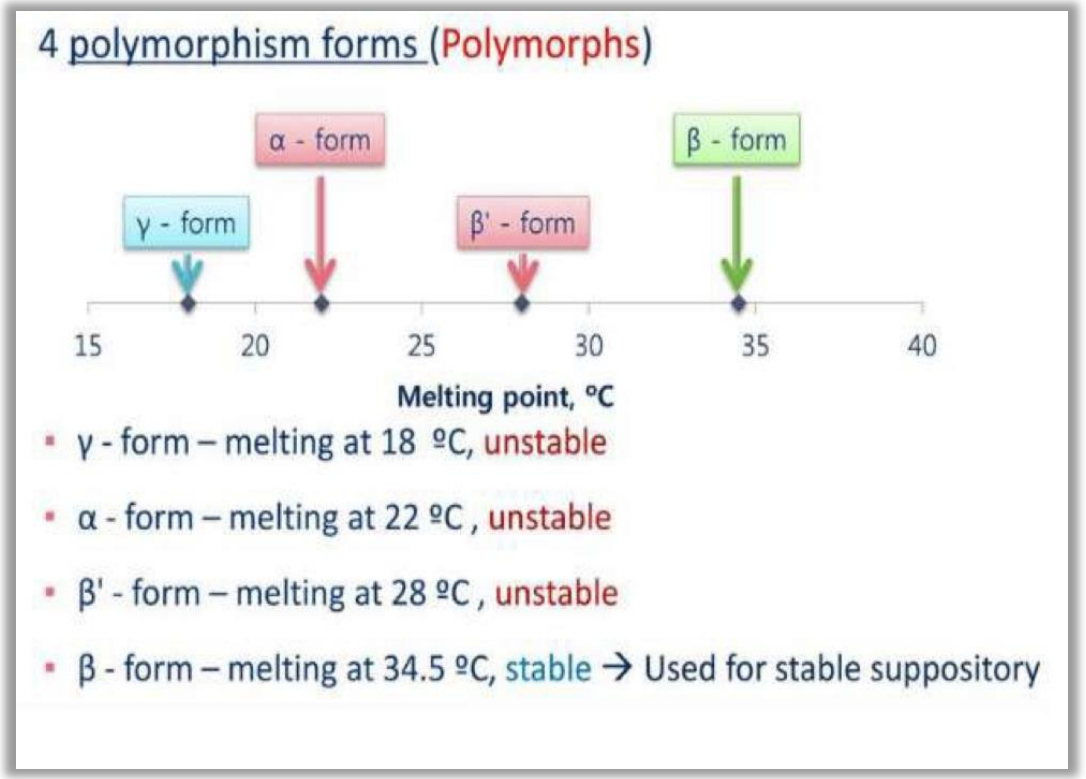
Crystalline solids

Polymorphism (Cont.) :Examples

d. **Cortisone acetate** exists in at least five different forms, four of which are unstable in the presence of water and change to a stable form.

e. **Theobroma oil**, or cacao butter, is a polymorphous natural fat capable of existing in four polymorphic forms, only the **β-form is stable.**



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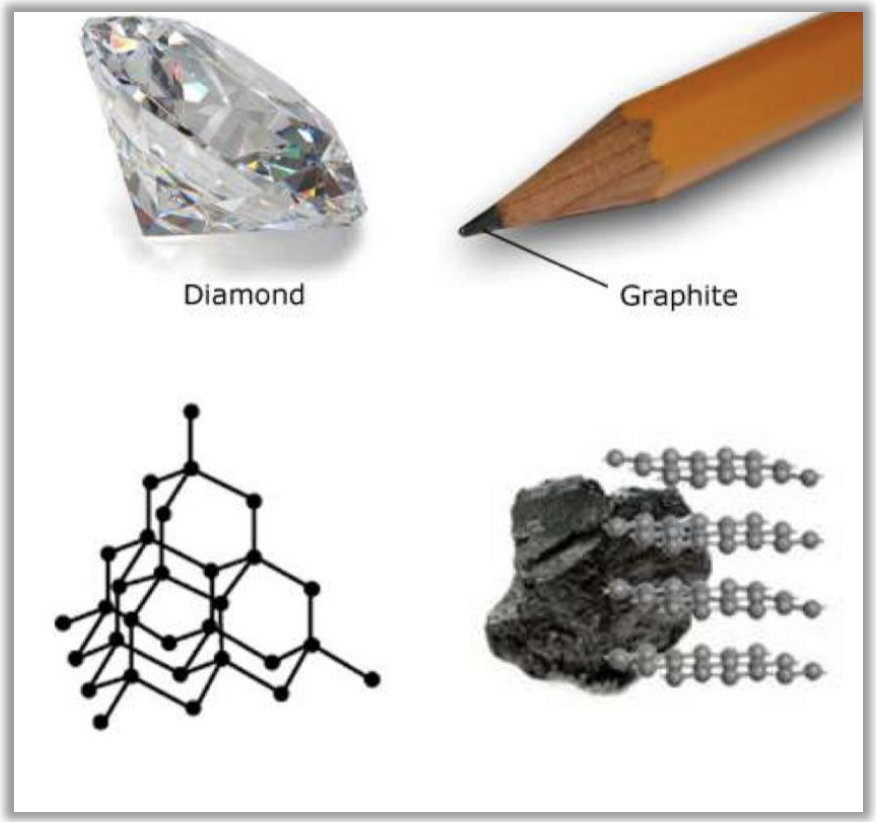
Crystalline solids

Polymorphism (Cont.) :Examples

f. Diamond and graphite: what are the difference? Find it out !!



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Polymorphism (Cont.) :Types of Polymorphism

- Considering the stability of the solid crystals with respect to pressure and temperature below the melting point, we can classify polymorphism into two broad categories:

a. Enantiotropic polymorphism

1. The change from one form to another is reversible.
2. Only one polymorph is stable for all acceptable temperatures
3. **Example:** metolazone

Polymorphism (Cont.) :Types of Polymorphism

b. Monotropic polymorphism

1. The transition takes place in one direction only.

2. There are different polymorphs, and each polymorph is stable under a specific range of temperature.

3. Thus, one polymorph can be stable at a low-temperature while the other is stable at a high-temperature range.

4. **Example**: acetazolamide, carbamazepine

Crystalline solids

Polymorphism (Cont.) :How do you determine polymorphism?

- Polymorphs are chemical compounds that although have the same chemical formula, exhibit different lattice structure.

- Polymorphic purity of drug samples can be checked using techniques such as:

a) Polarizing optical microscopy and thermomicroscopy.

b) Thermal analysis procedures, such as differential scanning calorimetry (**DSC**) and thermogravimetric analysis (**TGA**), can be used to obtain additional information.

c) Powder X-ray diffraction

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Crystalline solids

Polymorphism (Cont.) :How do you determine polymorphism?

d. IR/Raman spectroscopy

e. Gel Electrophoresis:

1. is most widely adapted technique for detecting polymorphism.
2. Samples are loaded into a gel and allowed to migrate in an electric field.

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Crystalline solids

Pseudopolymorphism : crystal solvates and hydrates

- During the production of pharmaceutical ingredients, they are often crystallized out of different types of solvents.
- When crystals obtained contain a solvent other than water, the crystals are called “**solvates**”
- When crystals obtained contain water, the crystals are called “**hydrates**”
- When the crystals obtained contain no water of crystallization they are termed “**anhydrates**” or**“anhydrous form”**

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Crystalline solids

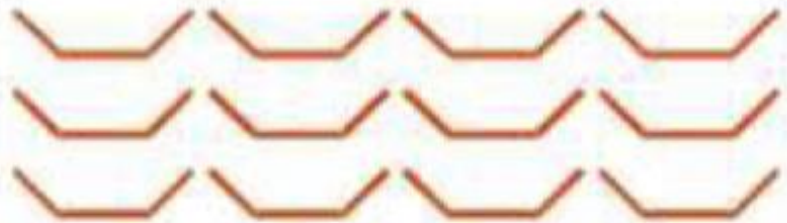
Pseudopolymorphism

Solvates / Hydrates

Molecular adducts that incorporate solvent molecules in their crystal lattices;

Solvent is water ⟶ Hydrates

Solvent is other solvents ⟶ Solvates



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Crystalline solids

Pseudopolymorphism

- The phenomenon wherein a compound is obtained in crystalline forms that differ in the nature or stoichiometry of included solvent molecules is known as "**Pseudopolymorphism**"

- Note: All the previous discussion about polymorphs, such as different physicochemical properties (**e.g., melting points, solubilities, and hygroscopicities**, etc.) directly applies to solvates and hydrates, thus the term "**pseudopolymorph**".

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Crystalline solids

Pseudopolymorphism : hydrates

- **Melting point:** melting point of the anhydrous crystal is usually > of the hydrate
- **Solubility in water**: aqueous solubilities of anhydrous crystals is usually > of the hydrate
- Anhydrous form is usually favored over **hydrate**.
- However,stable hydrates with acceptable bioavailability can be developed:

  a. may have better physicochemical properties;
  b. may be the only crystalline form of drug.

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Crystalline solids

Pseudopolymorphism : hydrates

Note:

- When you are working with a drug, it is very important to know if it will form a hydrate.
- **For example,** during the process of granulation used to make granules that can be compressed into tablets, you have to add water and then remove the water.
- If the drug forms a hydrate during granulation or loses a hydrate during drying, the properties of the drug can completely change, and this could affect drug release rate via changes in solubility and stability.
- Plus, many other important properties of the drug could change, which could lead to product to failure.

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Crystalline solids

Pseudopolymorphism : Solvates

- The particular solvate formed by a drug depends on the conditions of crystallization, particularly the solvent used.

- The solvated forms of a drug have different physicochemical properties from the non-solvated form:

a. **Solubility in water:** aqueous solubilities of solvate crystals is usually > of the non solvate crystals

b. **Rate of dissolution:** rate of dissolution of solvate crystals is usually > of the anhydrous crystals

- Differences in solubility and dissolution rate between solvates can lead to measurable differences in their **bio-availabilities**

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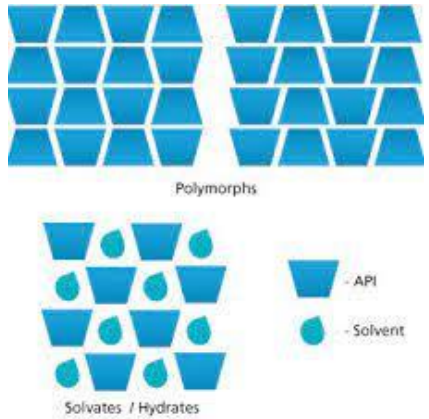
Crystalline solids

Pseudopolymorphism : Solvates

- There may be measurable differences in **bioavailabilities** of the solvates of a particular drug; **for example**

a. **the monoethanol solvate** of prednisolone tertiary butyl acetate has an absorption rate in vivo nearly five times greater than that of the anhydrous form of this drug.

- **Crystal solvates exhibit** a wide range of behaviour depending on the interaction between the solvent and the crystal structure.



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Crystalline solids

Pseudopolymorphism : Solvates

- There are **two main** types of crystal solvate:

- **Polymorphic solvates:**

a. solvent plays a key role in holding the crystal together; for example, it may be part of a hydrogen-bonded network within the crystal structure.

b. The polymorphic solvates are very stable and are difficult to desolvate.

c. When these crystals lose their solvent they collapse and recrystallize in a new crystal form.

Crystalline solids

Pseudopolymorphism : Solvates

- There are **two main** types of crystal solvate:

- **Pseudopolymorphic solvates:**

a. solvent is not part of the crystal bonding and merely occupies voids in the crystal.

b. These solvates lose their solvent more readily and desolvation does not destroy the crystal lattice.

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Thank You !

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