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Size reduction is not required in following cases:

1.
2.
3.
4.

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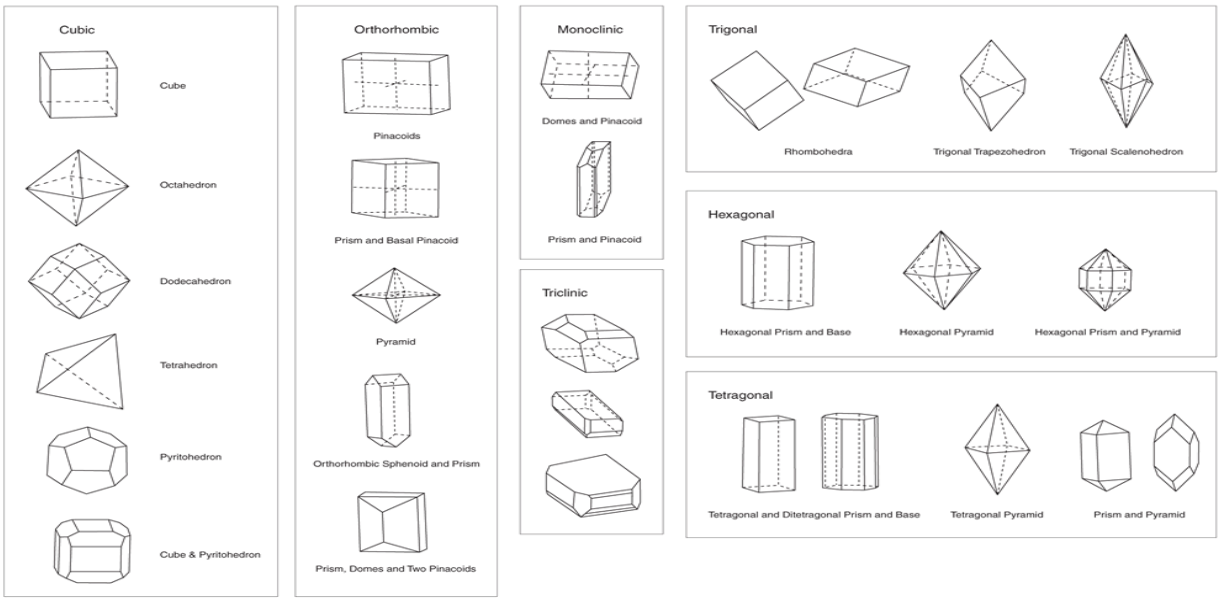
Crystallinity

- Crystal habit & internal structure of drug can affect bulk & physicochemical property of molecule.
- Crystal habit is description of outer appearance of crystal.
- Internal structure is molecular arrangement within the solid.
- Change with internal structure usually alters crystal habit.

  Eg. Conversion of sodium salt to its free acid form produce both change in internal structure & crystal habit.



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Different shapes of crystals

- Depending on internal structure compounds is classified as
  1. Crystalline
  2. Amorphous
- Crystalline compounds are characterized by repetitious spacing of constituent atom or molecule in three dimensional array.
- In amorphous form atom or molecule are randomly placed.
- Solubility & dissolution rate are greater for amorphous form than crystalline, as amorphous form has higher thermodynamic energy.

Eg. Amorphous form of **Novobiocin** is well absorbed whereas crystalline form results in poor absorption.

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Polymorphism

- Polymorphism: the ability of solids to exist in multiple physical forms or crystal structures.
- It has been estimated that at least one third of all organic compounds exhibit polymorphism.
- Polymorphic forms usually exhibit different physicochemical properties, including melting point and solubility and stability.

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Polymorphism

- The changes in crystal characteristics can influence bioavailability and chemical and physical stability.
- Can have important implications in dosage form process functions.
  - For example, it can be a significant factor relating to tablet formation because of flow and compaction behaviors.

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Polymorphism

- Solid-state hydrolysis of carbamazepine from needle-shaped crystals is faster than that of beam-shaped and prismatic forms.
- Reactivity of carbamazepine to light also depends on the crystalline form of the drug.

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Polymorphism

- 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 of 2 types
  1. Enatiotropic
  2. Monotropic

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Polymorphism

- The polymorph which can be changed from one form into another by varying temp. or pressure is called as Enantiotropic polymorph.

  Eg. Sulfur.

- One polymorph which is unstable at all temp. & pressure is called as Monotropic polymorph.

  Eg. Glyceryl stearate.

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Polymorphism

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

  Solubility, Stability

  Melting point

  Density

  Hardness

  Compression characteristic

  Optical properties and vapor pressure

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Polymorphism

- During preformulation it is important to identify the polymorph that is stable at room temp.
- Usually the highest melting point polymorph is the stable one.

Eg. 1) **Chloromphenicol** exist in A,B & C forms, of these B form is more stable & most preferable.

2) **Riboflavin** has I,II & III forms, the III form shows 20 times more water solubility than form I.

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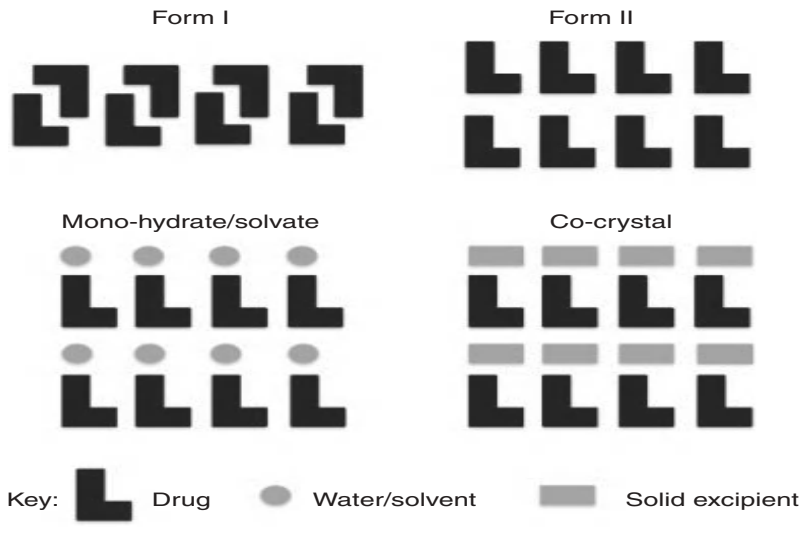

Figure 7.7 Schematic representation of polymorphic forms of a drug (top left and right) as well as a monohydrate or solvate (bottom left) and a co-crystal (bottom right).