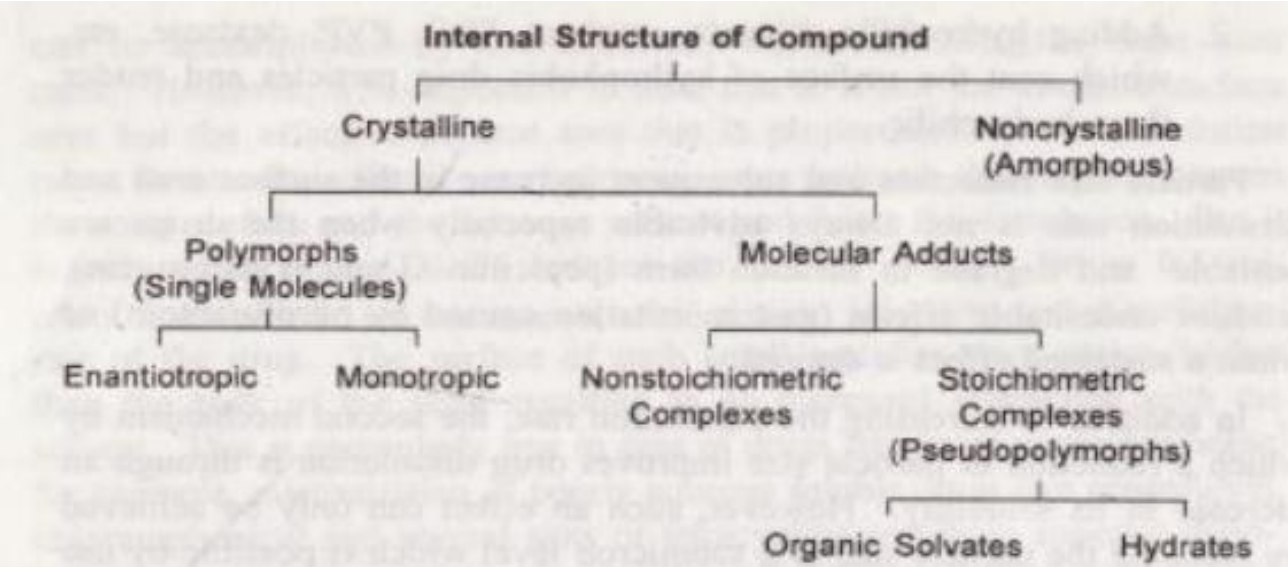
Biopharmaceutical and Pharmacokinetic considerations

Surface area:

- When a drug particle is broken up, **surface area increased**. For drug substances that are poorly or slowly soluble, this generally results in **increase in the rate of dissolution.**

- **To increase surface area**, use **micronized powders** in their solid products. micronized powders consist of drug particles reduced in size to about **5 µm and smaller.**



Crystal or amorphous drug form:

Solid drug materials may occur as crystalline or amorphous.

- **Amorphous** usually **more soluble** than **crystalline form**, different extents of drug absorption;

- Antibiotic chloramphenicol palmitate, are **inactive when administered in crystalline**, but when administered amorphous, absorption from GIT rapidly, with good therapeutic response.

- In other instances: **crystalline forms** of drugs may be used because of **greater stability than amorphous forms**. For example, the **crystalline forms** of penicillin G as potassium salt or sodium salt are more stable than **amorphous forms**. Thus, in formulation work on penicillin G, the crystalline forms are preferred and result in

excellent therapeutic response.

 The **amorphous**, or Prompt Insulin Zinc Suspension, USP, is **rapidly absorbed** upon intramuscular. The larger **crystalline material**, called ultralente insulin or Extended Insulin Zinc Suspension, USP, is more **slowly absorbed** and has a resultant longer duration of action.

 By combining the two types in various proportions, a physician can provide patients with **intermediate-acting insulin of varying degrees of onset and duration of action**. A physical mixture of 70% of the crystalline form and 30% of the amorphous form, called lente insulin or Insulin Zinc Suspension, USP, is intermediate acting and meets the requirements of many diabetics.

Polymorphism:

Only one form of a pure drug is stable, the other is metastable forms, converting in time to the stable crystalline form. It is therefore fairly common for a metastable form of a medicinal agent to change form even in a completed pharmaceutical preparation.

 Time required for a complete change may exceed the normal shelf life of the product.

 Any **change in crystal structure** of agent **affect the stability and therapeutic efficacy of the product**.

Salt form:

The dissolution rate of a salt of a drug is different from that of the parent compound.

 Sodium and potassium salts of weak organic acids and hydrochloride salts of weak organic bases dissolve more than free acids or bases.

 The addition of the **ethylenediamine moiety** to **theophylline** increases the water solubility of theophylline fivefold.

 The use of the ethylenediamine salt of theophylline has allowed the development of oral aqueous solutions of theophylline.

Other factors:

 The state of hydration of a drug molecule **can affect its solubility and pattern of**

absorption.

Usually, the **anhydrous form of an organic molecule is more readily soluble than the hydrated form**. This characteristic was demonstrated with the drug ampicillin, when the **anhydrous form** was found to have a **greater rate of solubility than the trihydrate**. The rate of absorption for the anhydrous form was greater than that for the trihydrate form of the drug.

 A drug's solubility in GIT can be **affected by pH also by food**. A drug may interact with agents present to form **a chemical complex** that result in reduced drug solubility and decreased absorption.

The **classic example** of this complexation: between tetracycline and calcium, magnesium, and aluminum, resulting in **non-absorbable complex** so decreased absorption of the tetracycline.