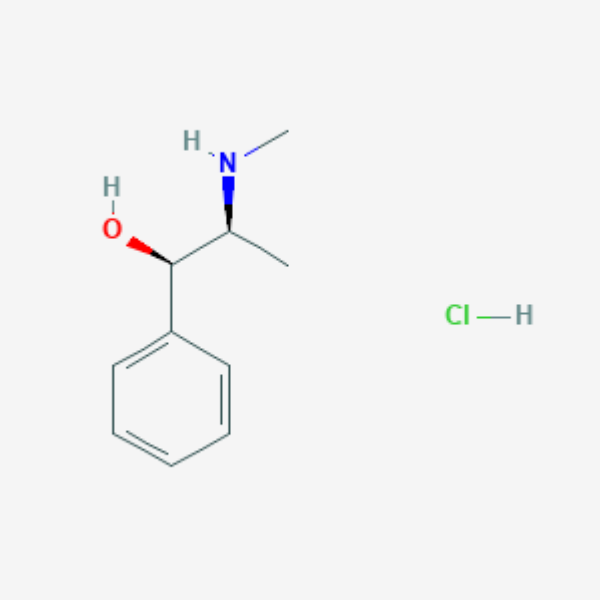
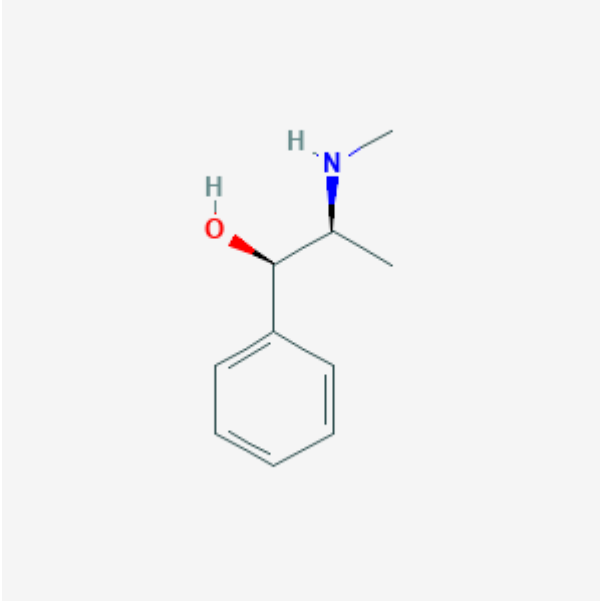
Preformulation

Preliminary Evaluation and Molecular Optimization when the first quality sample of the new drug becomes available, probing experiments should be conducted to determine the magnitude of each suspected problem area. If a deficiency is detected, then the project team should decide on the molecular modification(s) that would most likely improve the drug's properties. Salts, prodrugs, solvat.es, polymorphs, or even new analogues may emerge from this modification effort.

Although each of these modification approaches has proven beneficial, the salt and prodrug approaches are the most common. Most salts of organic compounds are formed by the removal of a proton to form an ionized drug molecule, which is then neutralized with a counter ion. Ephedrine hydrochloride, for example, is prepared by addition of a proton to the basic secondary nitrogen atom on ephedrine, resulting in a protonated drug molecule (ephedrine-HCl), which is neutralized with a chloride anion (ephedrine-HCl). In general, organic salts are more water-soluble than the corresponding un-ionized molecule, and hence, offer a simple means of increasing dissolution rate and improving bioavailability.

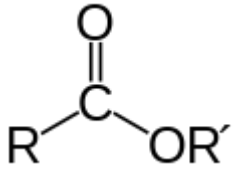


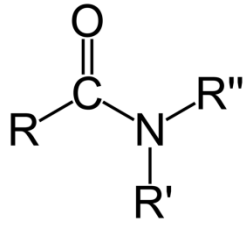


https://pubchem.ncbi.nlm.nih.gov/compound/65326#section=2D-Structure

https://pubchem.ncbi.nlm.nih.gov/compound/Ephedrine#section=2D-Structure

While salt formation is limited to molecules with ionizable groups, prodrugs may be formed With any organic molecule having a chemically reactive functional group.
Prodrugs are synthetic derivatives (e.g., esters and amides) of drug molecules that may have intrinsic pharmacologic activity but usually must undergo some transformation in vivo to liberate the active drug molecule.





Through the formation of a prodrug, a variety of side chains or functional groups may be added to improve the biologic and/or pharmaceutical properties of a compound. Some of the biologic response parameters that may be altered by prodrug formation are absorption due to increased lipophilicity or increased water solubility, duration of action via blockade of a key metabolic site, and distribution to organs due to changes in lipophilicity.

Examples of biologic improvements are abundant in the steriod and prostaglandin prodrug literature. Pharmaceutical improvements resulting from prodrug formation include stabilization, an increase or decrease in solubility, crystallinity, taste, odor, and reduced pain on injection.

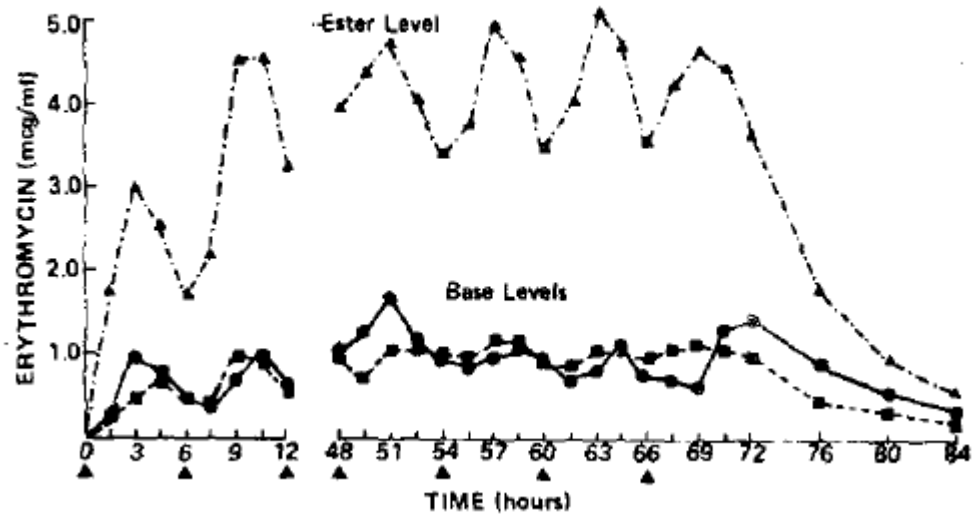
Erythromycin estolate is an example of a prodrug with improved pharmaceutical properties . In aqueous solutions, protonated erythromycin is water-soluble, has a bitter taste, and is rapidly hydrolyzed in gastric acid (t 10% = 9 sec) to yield inactive decay products.

To overcome this problem, the water-insoluble lauryl sulfate salt of the propionate ester prodrug (estolate) was formed for use in both suspension and capsule dosage forms.

Erythromycin propionate is inactive as an antimicrobial and must undergo ester hydrolysis to yield bioactive erythromycin.

In an oral q.i.d. bioavailability comparison between Upjohn's enteric coated tablet formulation of erythromycin base and capsule formulation of erythromycin estolate (Fig. 8-4), the lipophilic ester prodrug was absorbed four times more efficiently than the formulated free base, but hydrolyzed only 24% in serum to produce equivalent plasma levels of bioactive erythromycin base.

Thus, a prodrug was used to overcome a pharmaceutical formulation problem without compromising bioavailability.



To date, most prodrugs have been esters or amides designed to increase lipophilicity. Unfortunately, this type of modification often decrease water solubility and thus decreases the concentration gradient across the cell membrane, which controls the rate of drug absorption.

This trade-off between lipophilicity and concentration gradient is generally assumed to result in a net improvement in absorption. In 1980, Amidon suggested the making of water soluble prodrugs by adding selected amino acids that are substrates for enzymes located in the intestinal brush border.

Assuming that enzyme cleavage was not rate-limiting, and that the liberated drug molecule would remain in the lipophilic membrane, then the resulting membrane transport of the parent compound should be very rapid, owing to the large concentration gradient of liberated drug across the membrane, as illustrated in Figure 8-5.

Using the lysine ester prodrug-of estrone, a potential increase of five orders of magnitude in adsorption rate was found in vivo using perfused rat intestines.

Although any of the modifications discussed may provide an increase in bioavailability, chemical instability or a lack of synthetic feasibility may prohibit the commercial development of a modified drug molecule.

Whatever the case, the molecular form of the drug advancing from this preliminary evaluation should have a substantial chance of successfully progressing through the drug development process.

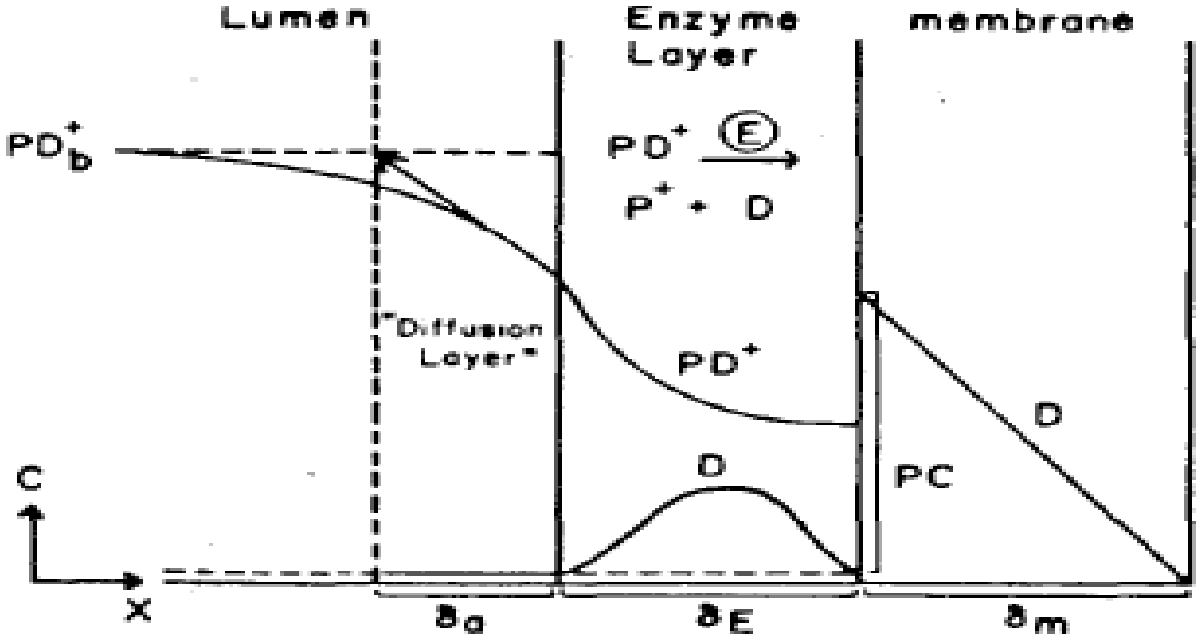


FIG. 8-5. *Concentration (C) versus distance (X) profile for the absorption of water-soluble prodrugs (PD^+), which are enzymatically (E) hydrolyzed in the intestinal brush border to liberate the lipophilic parent compound (D). Key: δ_a, thickness of aqueous diffusion layer; δ_E, enzyme layer thickness; δ_m, membrane thickness; and PC membrane-enzyme layer partition coefficient. (From Amidon, G. L., et al.: J. Pharm. Sci., 69:1363, 1980. Reproduced with permission of the copyright owner.)*

I. Bulk Characterization

Crystallinity and Polymorphism
Hygroscopicity
Fine Particle Characterization
Bulk Density
Powder Flow Properties

II. Solubility Analysis

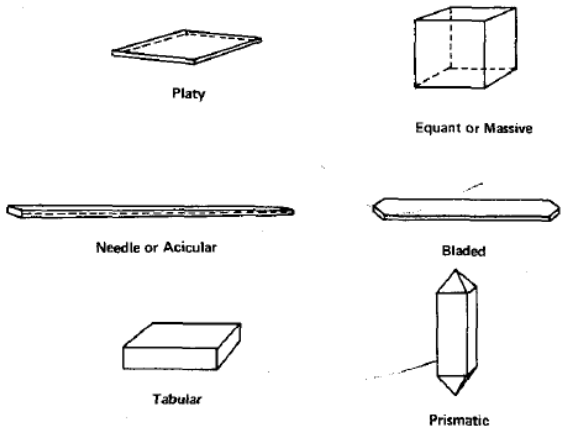
Ionization Constant – pKa
pH Solubility Profile
Common Ion Effect – K_{sp}
Thermal Effects
Solubilization
Partition Coefficient
Dissolution

III. Stability Analysis

Stability in Toxicology Formulations
Solution Stability
    pH Rate Profile
Solid State Stability
    Bulk Stability
    Compatibility

Crystallinity and Polymorphism

Crystal habit and the internal structure of a drug can affect bulk and physicochemical properties, which range from flowability to chemical stability. *Habit* is the description of the outer appearance of a crystal whereas the internal *structure* is the molecular arrangement within the solid. Several examples of different habits of crystals are shown in Figure 8-7.



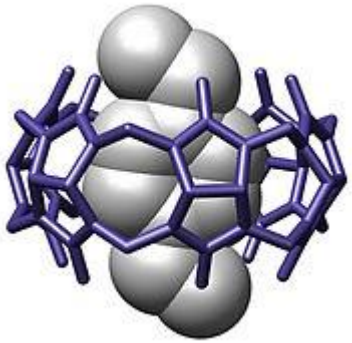
The internal structure of a compound can be classified in a variety of ways, as shown in Figure 8-8. The first major distinction is whether the solid is crystalline or amorphous. Crystals are characterized by repetitious spaces of constituent atoms or molecules in a three-dimensional array, whereas amorphous forms have atoms or molecules randomly placed as in a liquid.

Amorphous forms are typically prepared by rapid precipitation, lyophilisation or rapid cooling of liquid melts. Since amorphous forms are usually of higher thermodynamic energy than corresponding crystalline forms, solubilities as well as dissolution rates are generally greater.

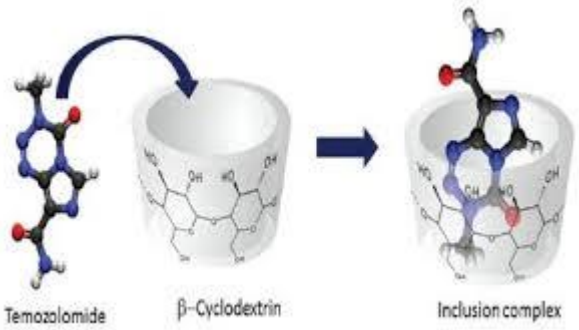
Upon storage, amorphous solids tend to revert to more stable forms. This thermodynamic instability, which can occur during bulk processing.

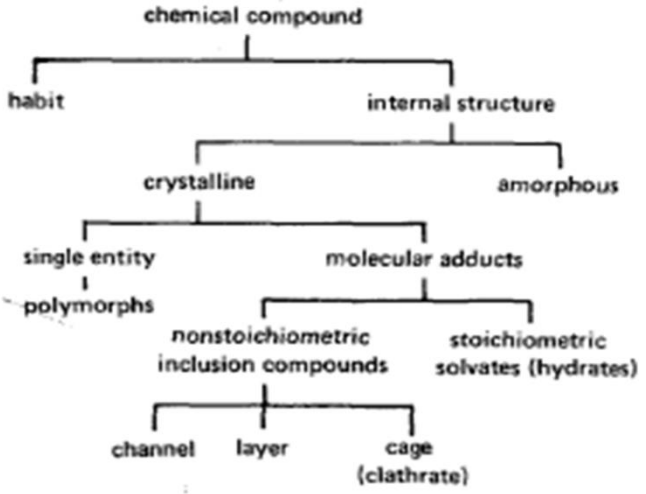
A crystalline compound may contain either a stoichiometric or nonstoichiometric amount of crystallization solvent.

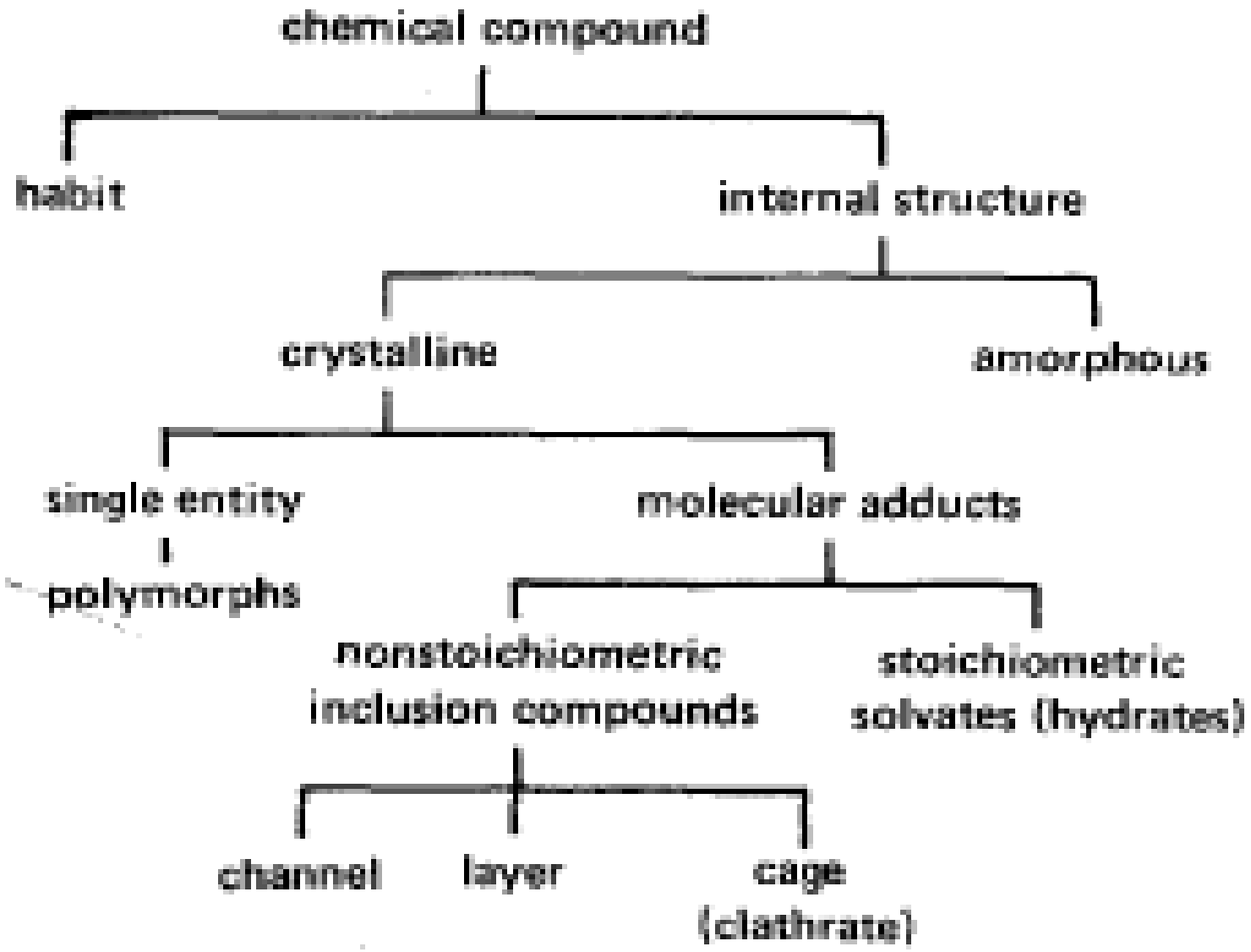
Nonstoichiometric adducts, such as inclusions or clathrates, involve entrapped solvent molecules within the crystal lattice. Usually this adduct is undesirable, owing to its lack of reproducibility, and should be avoided for development. A stoichiometric adduct, commonly referred to as a solvate, is 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, monohydrate, and dihydrate describe hydrated forms with molar equivalents of water corresponding to half, one, and two. A compound not containing any water within its crystal structure is termed anhydrous.



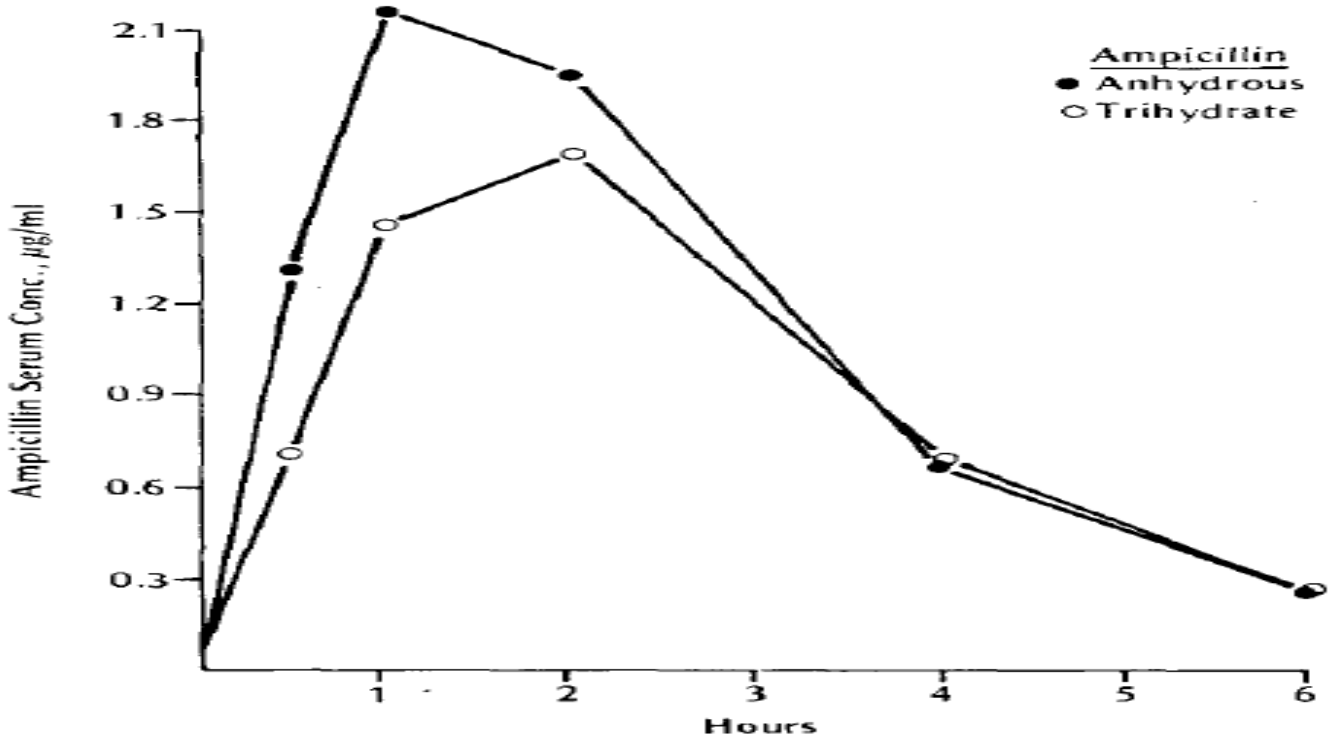
Inclusion compound host-gust






chemical compound
habit
internal structure
crystalline
amorphous
single entity
polymorphs
molecular adducts
nonstoichiometric
inclusion compounds
stoichiometric
solvates (hydrates)
channel
layer
cage
(clathrate)

Identification of possible hydrate compounds is important since their aqueous solubilities can be significantly less than their anhydrous forms . Conversion of an anhydrous compound to a hydrate within the dosage form may reduce the dissolution rate and extent of drug absorption. An example of the in vivo importance of solvate forms is shown in Figure 8-9, where the anhydrous and trihydrate forms of ampicillin were administered orally as a suspension to human subjects. The more soluble anhydrous form (10 mg/ml) produced higher and earlier peaks in the blood serum levels than the less soluble trihydrate form.



Polymorphism is the ability of a compound (or element o crystalize as more than one distinct crystalline species with different internal lattices.

Chemical stability and solubility changes due to polymorphism can have an impact on a drug's bioavailability and its development program.

Chloramphenicol palmitate exists in three crystalline polymorphic forms (A, B, and C) and an amorphous form. Aguiar and co-workers investigated the relative absorption of polymorphic forms A and B from oral suspensions administered to human subjects. As summarized in Figure 8-10, "peak" serum levels increased substantially as a function of the percentage of form B polymorph, the more soluble polymorph the internal structure of the solid. Many physicochemical properties vary with the internal structure, melting point, density, hardness, crystal shape. optical properties. and vapor pressure.

Characterization of polymorphic and solvated forms involves quantitative analysis of these differing physicochemical properties.

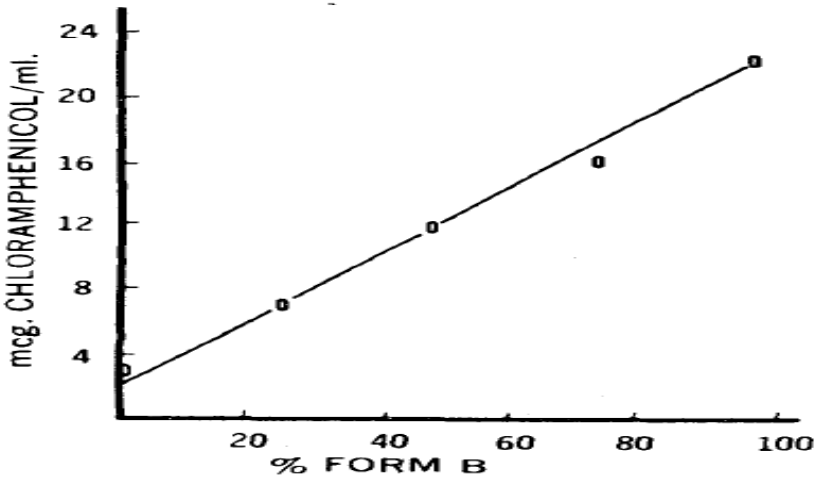


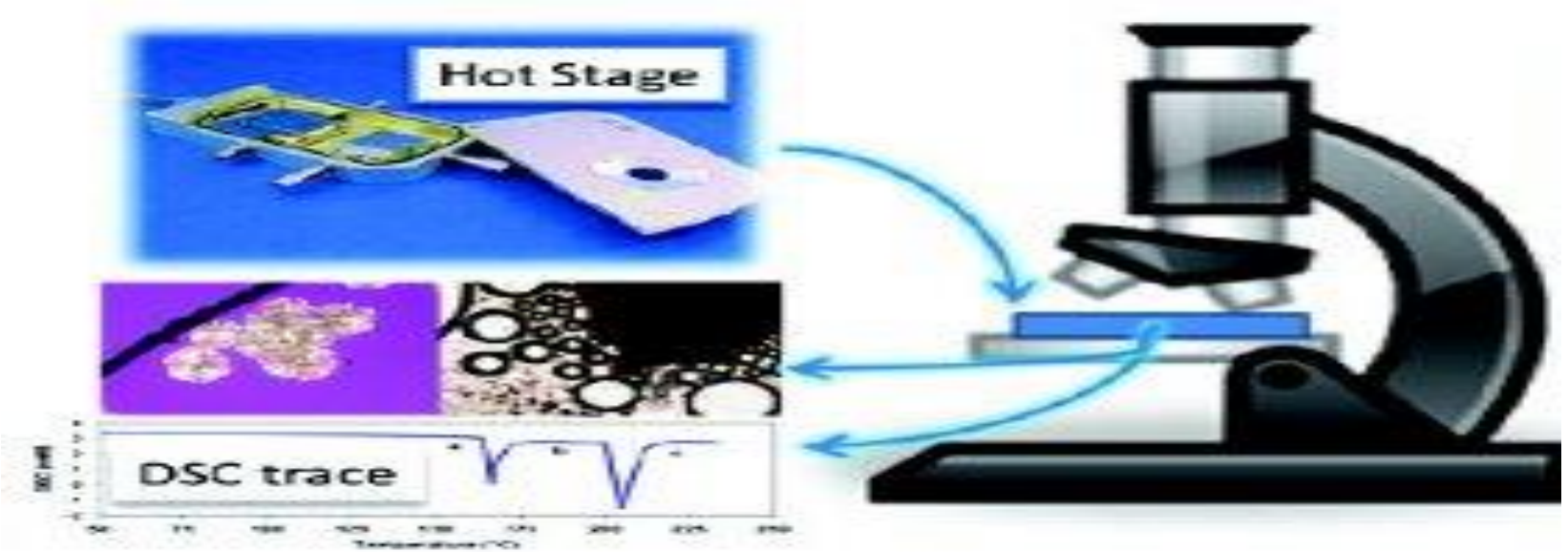
FIG. 8-10. *Correlation of "peak" blood serum levels (2 hr) of chloramphenicol vs. percentage of concentration of polymorph B. (From Aguiar, A. J., et al.: J. Pharm. Sci., 56:847, 1967. Reproduced with permission of the copyright owner.)*

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 supercooled glasses and noncrystalline solid organic compounds, or substances with cubic crystal lattices, such as sodium chloride, are isotropic materials, which have a single refractive index. With crossed polarizing filters, these isotropic substances do not transmit light, and they appear black materials with more than one refractive index are anisotropic and appear bright with brilliant colors (birefringence) 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.

The polarizing microscope fitted with a hot stage is a useful instrument for investigating polymorphism, melting points, transition temperatures, and rates of transition at controlled heating rates. In addition, the hot-stage microscope facilitates differentiation of DSC endotherms for polymorphic transitions from desolvation processes A problem often encountered during thermal microscopy is that organic molecules can degrade during the melting process, and recrystallization of the melt may not occur, because of the presence of contaminant degradation products.



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Thermal Analysis.

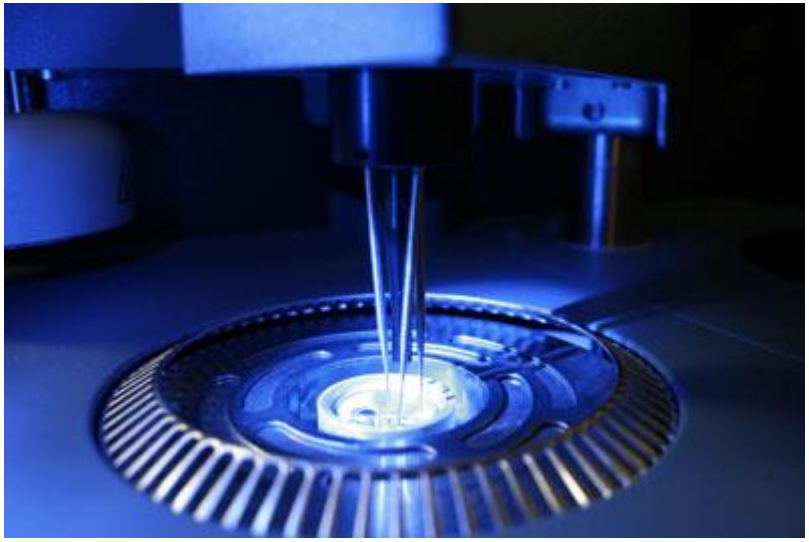
Differential scanning calorimetry (DSC) and differential thermal analysis (DTA) measure the heat loss or gain resulting from physical or chemical changes within *a* sample as a function of temperature. Examples of endothermic (heat-absorbing) processes are fusion, boiling, sublimation, vaporization. Desolvation, solid-solid transitions and chemical degradation. crystallization and degradation are usually exothermic processes.

Quantitative measurements of these processes have many applications in preformulation studies including purity, polymorphism, solvation, degradation, and excipient compatibility.

For characterizing crystal forms, the heat *of* fusion, ΔHf, can be obtained from the area-under- the DSC-curve for the 'melting endotherm. Similarly, the heat of transition from one polymorph to another may be calculated as shown by Guillory for several sulfonamides.

A sharp symmetric melting endotherm can indicate relative purity, whereas broad, asymmetric curves suggest impurities or more than one thermal process. Heating rate affects the kinetics and hence the apparent temperature of solid solid transitions.

A variable with DSC experiments is the atmosphere in contact with the sample. Usually, a continual nitrogen purge is maintained within the heating chamber; however, the loss of a volatile counter ion such as ethanolamine or acetic acid during a polymorphic transition may produce misleading data unless the transition occurs within a closed system. In contrast, desolvation of a dihydrate-species, as shown in Figure 8-11; releases water vapor, which if unvented can generate degradation prior to the melting point of the anhydrous form. During initial testing, a variety of atmospheres should be tried until the observed thermal process becomes fully understood.



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Thermogravimetric analysis (TGA) measures changes in sample weight as a function of time (isothermal) or temperature. Desolvation and decomposition processes are frequently monitored by TGA. Comparing TGA and DSC data recorded under identical conditions can greatly aid in the interpretation of thermal processes.

In Figure 8-11, the dihydrate form of an acetate salt loses two moles of water via an endothermic transition between 70° and 90°C. The second endotherm at 155°C corresponds to the melting process, with the accompanying weight loss due to vaporization of acetic acid as well as to decomposition.

TGA and DSC analysis can also be used to quantitate the presence of a solvated species within a bulk drug sample. For the above example, 10% of the dihydrate form was easily detected by both methods.

Degradation during thermal analysis may provide misleading results, but may be detected by high-performance liquid chromatography (HPLC) analysis of samples heated under representative conditions for retention of drug or appearance of decay products

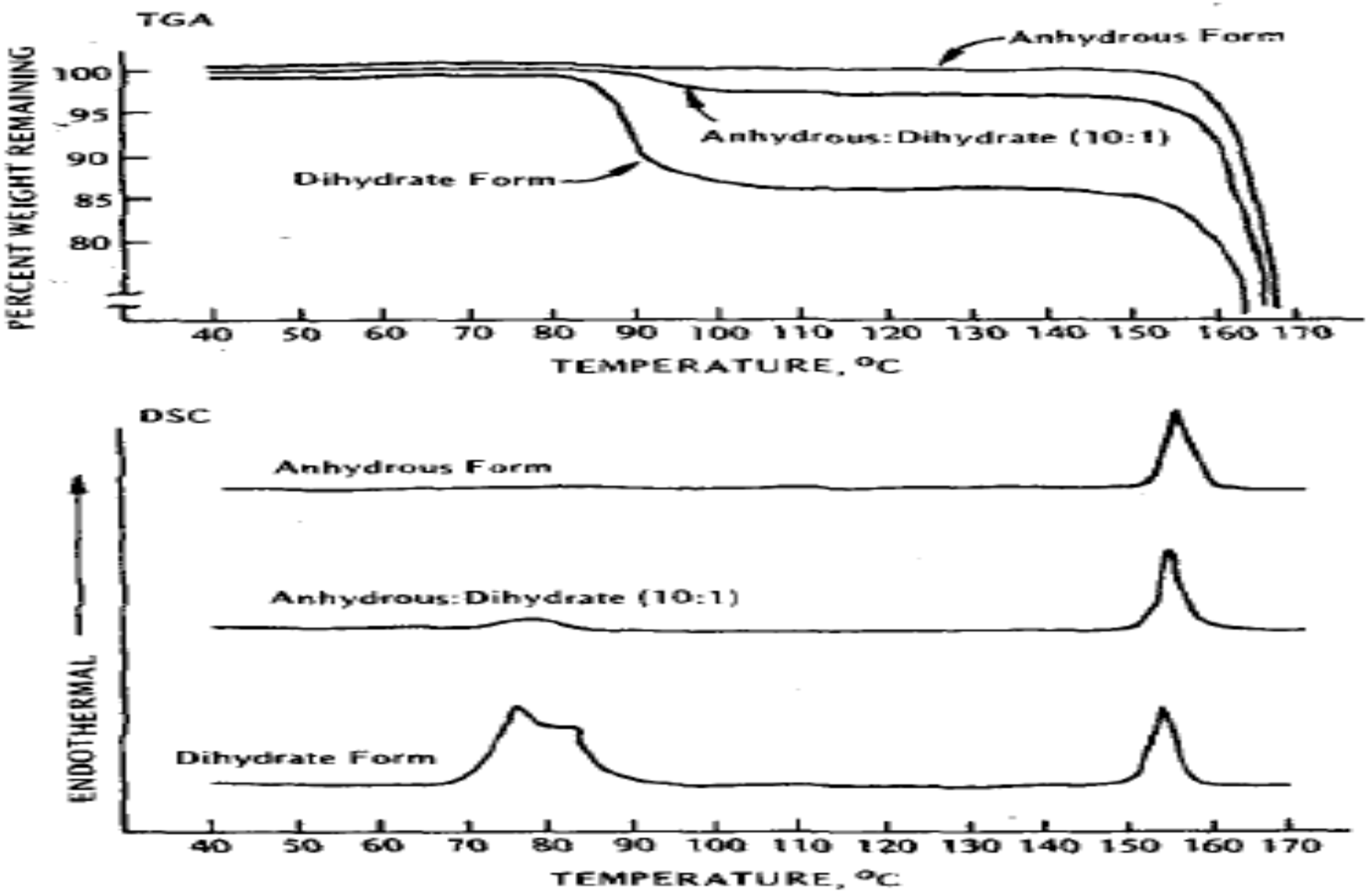

FIG. 8-11. *Thermogravimetric (TGA) and differential scanning calorimetric (DSC) analysis for an acetate salt of an organic amine that has two crystalline forms, anhydrous and dihydrate. Anhydrous/dihydrate mixture was prepared by dry blending. Heating rate was 5°/min.*

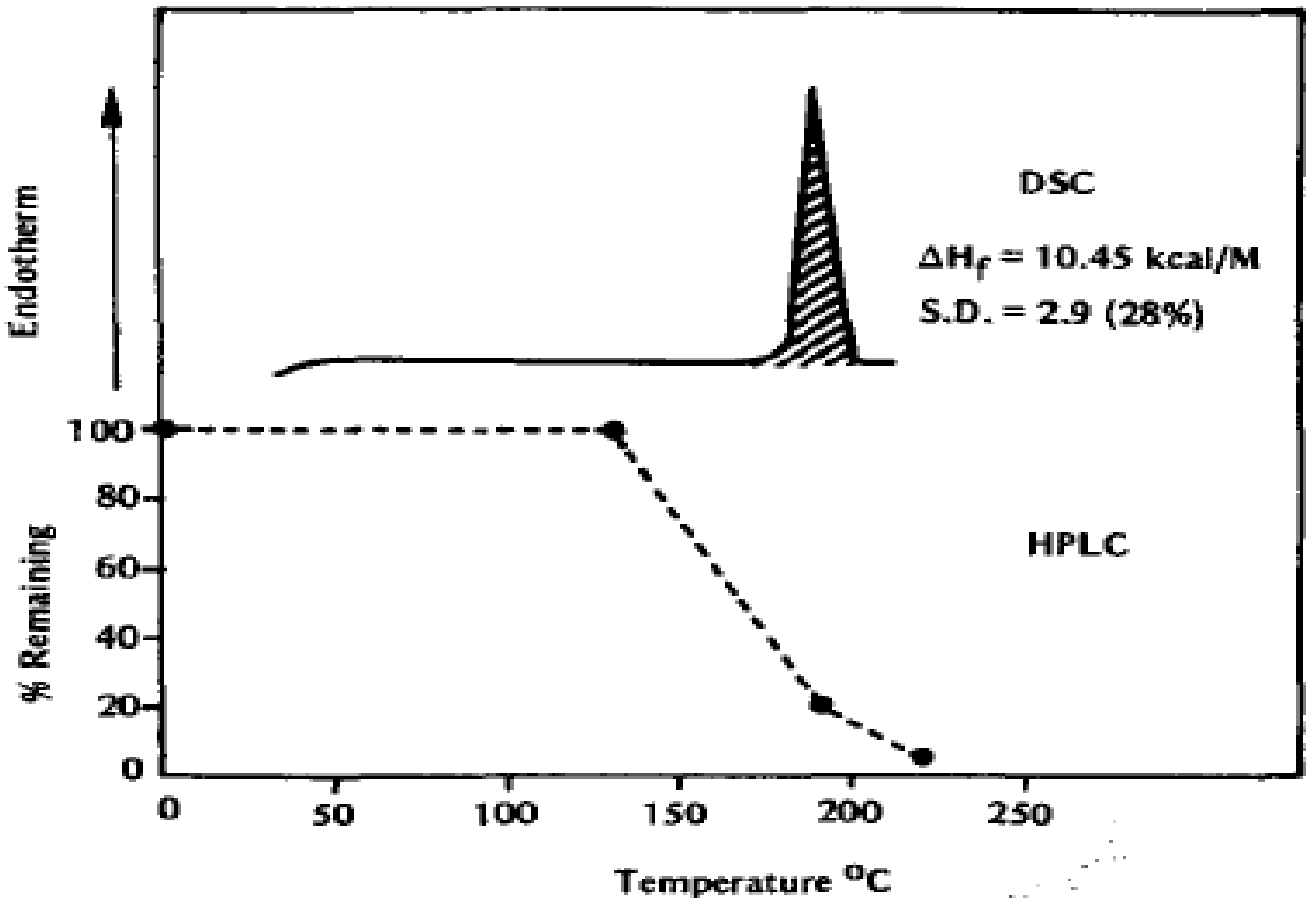

FIG. 8-12. *Differential scanning calorimetric (DSC) analysis and HPLC stability analysis of an organic amine hydrochloride salt that undergoes decomposition upon melting.*

X-Ray

An important technique for establishing the batch-to-batch reproducibility of a crystalline form is x-ray powder diffraction. 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 (Ɵ) relative to the incident beam