Polymorphism

Polymorphs can be classified as one of two types: *enatiotropic* (one polymorph can be reversibly changed into another by varying temperature or pressure, e.g., sulfur or *monotropic* (one polymorphic form is unstable at all temperatures and pressures, e.g., glyceryl stearates).

There is no general way of relating enatiotrophy and monotrophy to the properties of the polymorphs, except by locating the transition temperature or the lack of one. At a specified pressure, usually 1 atmosphere, the temperature at which two polymorphs have identical free energjes is the transition temperature, and at that temperature, both forms can coexist and have identical solubilities in any solvent as well as identical vapor pressures.

Below the solid melting temperatures, the polymorph with the lower free energy, corresponding to the lower solubility or vapor pressure, is the thermodynamically stable form.

During prefomulation, it is important identify the polymomph that is stable at room temperature and to determine whether polymerphic transitions are possible within the temperature range used for stability studies and during processing (drying, milling, etc.).

A free energy-temperature curve at 1 atmosphere should be constructed since temperature is usually a more critical variable than pressure in pharmaceutics. As previously discussed, chloramphenicol palmitate has three known polymorphic forms, which are thermodynamically described by a van't Hoff plot of free energy (as determined from solubility measurements) versus temperature (Fig. 8-14). Transition temperatures are shown by intersection of the extrapolated lines; 50°C for forms A and C, and 88°C for forms A and B. Form A is the stable form at temperatures less than 50°C. Transition temperatures obtained by extrapolation of van't Hoff plots are susceptible to large errors.

Direct measurements of transitions are preferred to support the extrapolated intersection points in the solubility-temperature diagrams. The most direct means for determining transition temperatures is microscopic observation of samples held at constant temperatures. Unfortunately, these solid-solid or solid-vapor solid transitions usually occur slowly, owing to large activation energies and slow nucleation. To facilitate the conversion rate, a single polymorph or a mixture of forms can be granulated in a "bridging" solvent at various temperatures. The drug should be only sparingly soluble in the bridging solvent, and solvate formation should not occur. These experiments can be conducted quickly with a polarizing microscope, or samples can be stored in sealed containers at controlled temperatures and periodically examined by other suitable analytic methods.

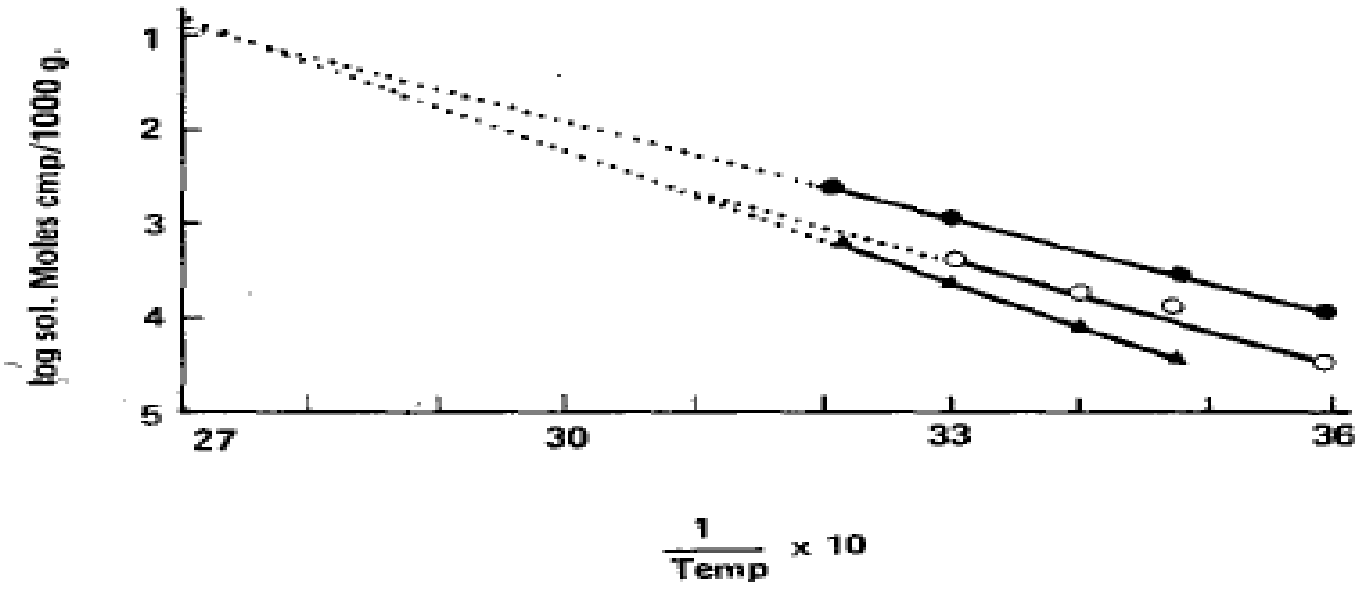


FIG. 8-14. *The van't Hoff plot of solubility vs. reciprocal absolute temperature for polymorphs A, B, and C of chloramphenicol palmitate. Key: Polymorphs A (▶—▶); B (●—●); and C (○—○). (From Aguiar, A. J., et al.: J. Pharm. Sci., 58:983, 1969. Reproduced with permission of the copyright owner.)*

Hygroscopicity

Many drug substances, particularly water-soluble salt forms, have a tendency to adsorb atmospheric moisture. Adsorption and equilibrium moisture content can depend upon the atmospheric humidity, temperature surface area, exposure, and the mechanism for moisture uptake, as described by Van Campen and coworkers. Deliquescent materials adsorb sufficient water to dissolve completely, as is observed with sodium chloride on a humid day. Other hygroscopic substances adsorb water because of hydrate formation or specific site adsorption. With most hygroscopic materials, changes in moisture level can greatly influence many important parameters, such as chemical stability, flowability, and compactibility.

To test for hygroscopicity, samples of bulk drug are placed in open containers with a thin powder bed to assure maximum atmospheric exposure. These samples are then exposed to a range of controlled relative humidity environments prepared with saturated aqueous salt soluitions.

Moisture uptake should be monitored at time points representative of handling (0 to 24 hours) and storage (0 to 12 weeks). Analytic methods for monitoring the moisture level (i.e., gravimetry, TGA, or gas chromatography) depend upon the desired precision and the amount of moisture adsorbed onto the drug sample.

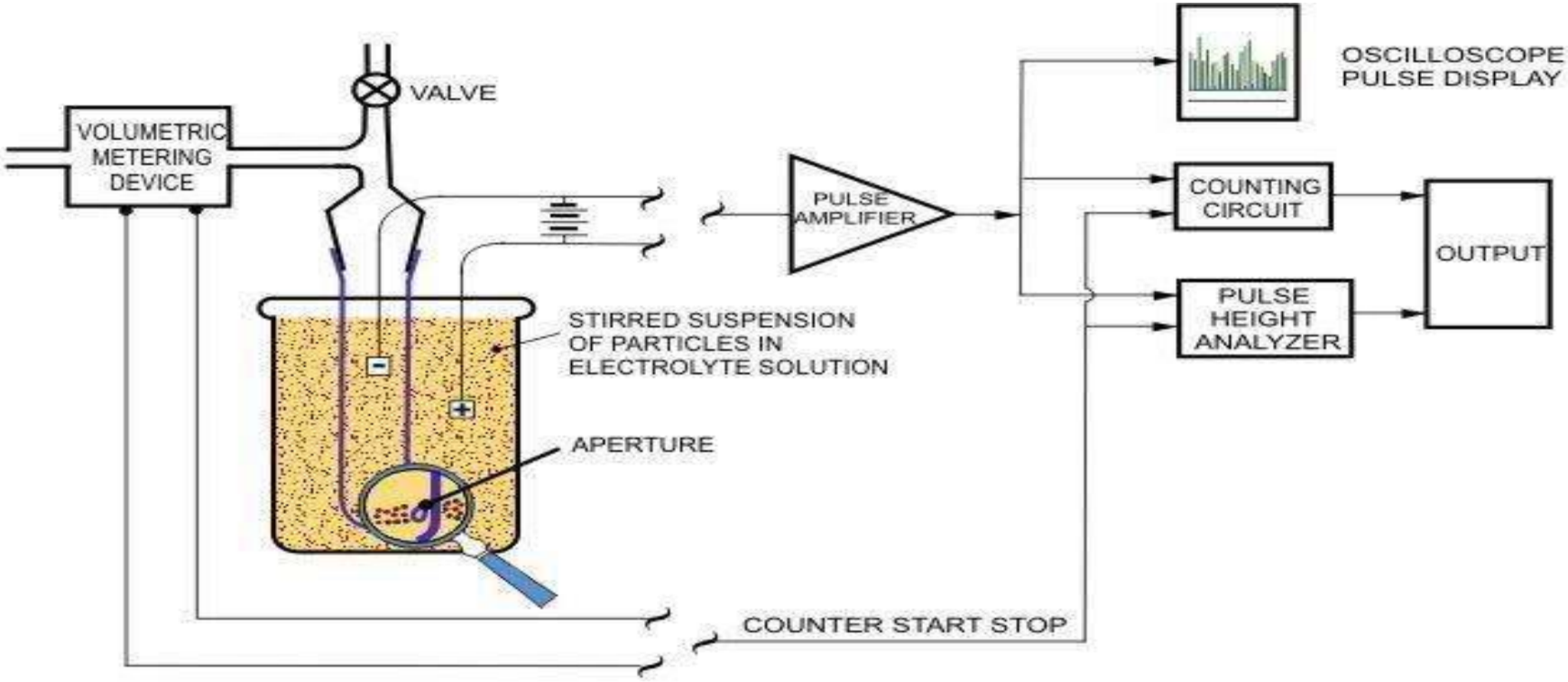
Normalized (mg H20/g sample) or percentage- of-weight-gain data from these hygroscopic studies are plotted against time to justify special handling procedures kinetically. A plot of normalized equilibrium versus relative humidity data may support the need for storage in a low humidity environment or for special packaging with a desiccant. As these studies proceed, additional testing of powder flow, dissolution, or stability of "wet" bulk may be warranted to lend further support to the need for humidity controls.

Fine Particle Characterization

Bulk flow, formulation homogeneity, and surface area controlled processes such as dissolution, chemical reactivity are directly affected by size, shape, and surface morphology of the drug particles.

In general, each new drug candidate should be tested during preformulation with the smallest particle size as is practical to facilitate preparation of homogeneous samples and maximize the drug's surface area for interactions.

In conjunction with light microscopy, stream counting devices, such as the Coulter counter & and HIAC counter often provide a convenient method for characterizing the size distribution of a compound. Samples are prepared for analysis by the Coulter counter by dispersing the material in a conducting medium such as isotonic saline with the aid of ultrasound and a few drops of surfactant. A known volume (0.5 to 2 ml) of this suspension is then drawn into a tube through a small aperture (0.4 to 800 microns in diameter), across which a voltage is applied. As each particle passes through the hole, it is counted and sized according to the resistance generated by displacing that particle's volume of conducting medium. Given that the instrument has been calibrated with standard spheres, the counter provides a histogram output (frequency versus size) within the limits of that particular aperture tube. Several different sizes of aperture tubes should be used to assure accurate counting of single particles. Other stream counters are based on the principles of light blockage or laser light scattering for sizing each particle.



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Although the Coulter method is quick and statistically meaningful, it assumes that each resistance arises from a spherical particle; thus, nonspheres are sized inaccurately. Other limitations with the Coulter counter are the tendency of needle-shaped crystals to block the aperture hole, the dissolution of compound in the aqueous conducting medium, and stratification of particles within the suspension.

Additional methods of particle size analysis are image analysis and sieve analysis. Sieve methods are used primarily for large samples of relatively large particles(-100 microns). Computer interfacing of image analysis techniques offers the greatest promise for particle size analysis in the '80s. Kinetic processes involving drug in the solid state, such as dissolution and degradation, may be more directly related to available surface area than to particle size. If drug particles have a shape that can be defined mathematically, then light microscopy size analysis or Coulter counter analysis with appropriate geometric equations may provide a reasonable estimation of surface area.

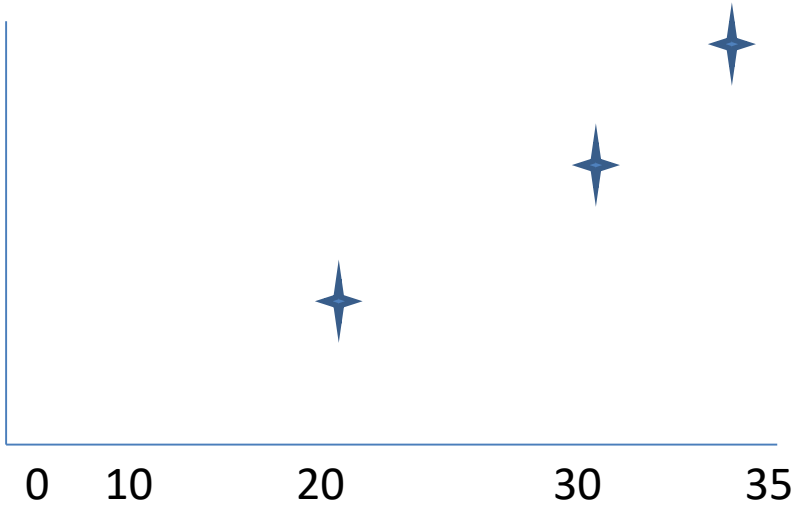
A more precise measurement of surface area is made by Brunauer, Emmett, and Teller (BET) nitrogen adsorption in which a layer of nitrogen molecules 'is adsorbed to the sample surface at -196°C.· Once surface adsorption has reached equilibrium, the sample is heated to room temperature, the nitrogen gas is desorbed, and its volume is measured and converted to the number of adsorbed molecules via the ideal gas law.

Since each nitrogen molecule (N2) occupies an area of 16 A2 , one may readily compute the surface area per gram for each pre weighed sample.

By determining the surface area at several partial pressures of nitrogen (5% to 35% N2 in He), extrapolation to zero nitrogen partial pressure yields the true monolayer surface area. While BET measurements are usually precise and quickly obtained with current commercial equipment, errors may arise from the use of impure gases and volatile surface impurities (e.g., hydrates).

Surface morphology may be observed by scanning electron microscopy (SEM), which serves to confirm qualitatively a physical observation. During preparation for SEM analysis, the sample is exposed to high vacuum during the gold coating process, which is needed to make the samples conductive, and concomitant removal of water or other solvents may result in a false picture of the surface morphology. Variable vacuum treatment of an identical sample prior to the gold coating step may confirm the effects of sample preparation on surface morphology.

Most modern SEM instruments also provide energy dispersive x-ray spectroscopy analysis of surface metal ions, which may prove beneficial in deciphering an instability or incompatibility problem.



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Bulk Density

Bulk density of a compound varies substantially with the method of crystallization, milling, or formulation. Once a density problem is identified, it is often easily corrected by milling, slugging, or formulation. Usually, bulk density is of great importance when one considers the size of a high-dose capsule product or the homogeneity of a low-dose formulation in which there are large differences in drug and excipient densities.

Apparent bulk density (g/ml) is determined by pouring presieved (40-mesh) bulk drug into a graduated cylinder via a large funnel and measuring the volume and weight "as is." Tapped density is determined by placing a graduated cylinder containing a known mass of drug or formulation on a mechanical tapper apparatus, which is operated for a fixed number of taps (~ 1000) until the powder bed volume has reached a minimum.

Using the weight of drug in the cylinder and this minimum volume, the tapped density may be computed. Knowing the anticipated dose and tapped formulation density, one may use Figure 8-15 to determine the appropriate size for a capsule formulation.

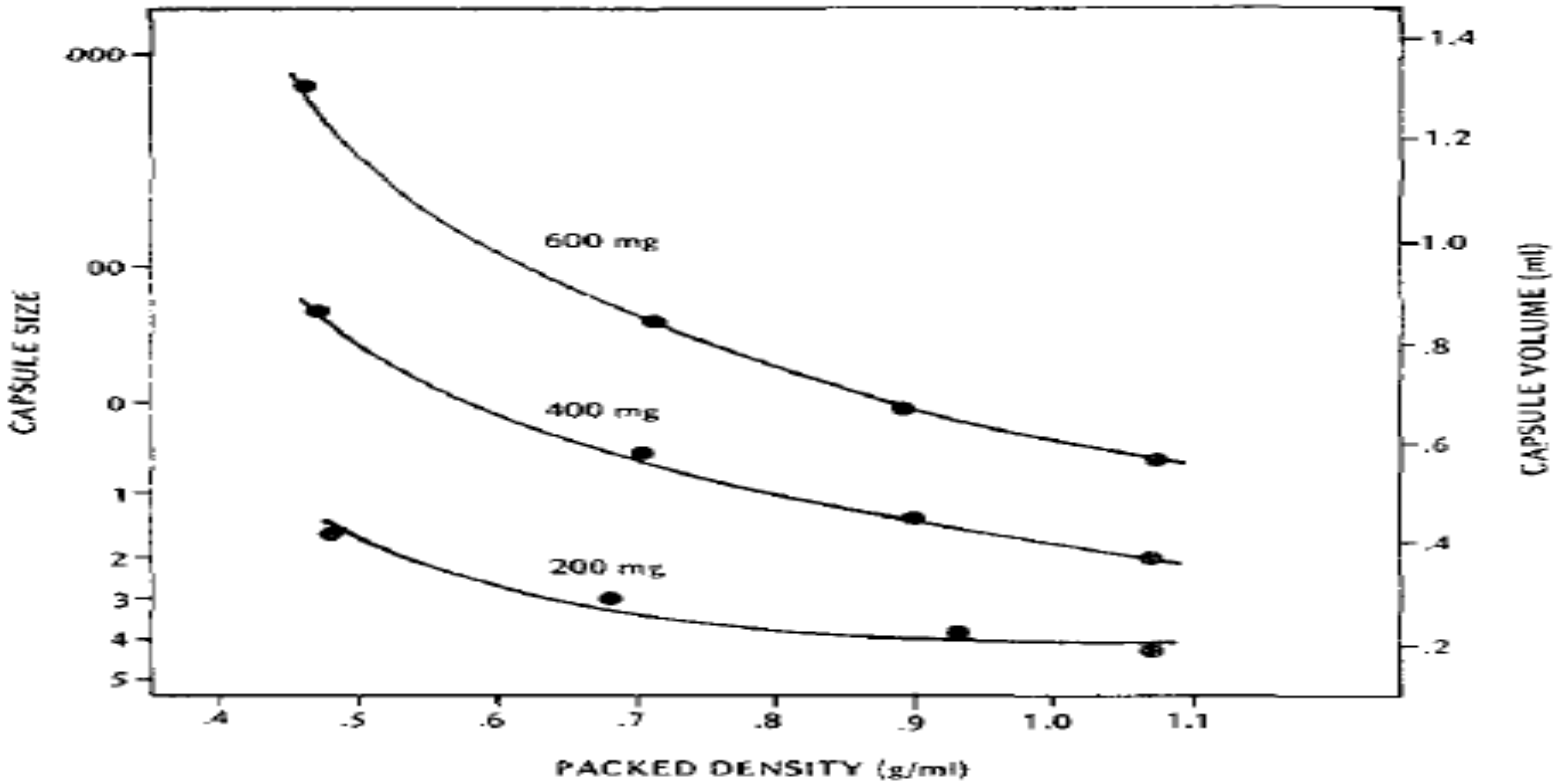

FIG. 8-15. *Correlation between capsule size and packed density for different fill weights (200—600 mg).*

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Powder Flow Properties

Pharmaceutical powders may be broadly classified as free- flowing or cohesive non-free-flowing.

Most flow properties are significantly affected by changes in particle size, density, shape, electrostatic charge, an adsorb moisture, which may arise from processing or formulation.

As a result, a free-flowing drug candidate may become cohesive during development, thus necessitating an entirely new formulation strategy.

Preformulation powder flow investigations should quantitatively assess the pharmaceutical consequences of each process improvement and provide direction for the formulation development project team.

This direction may consist of a formulation recommendation such as granulation or densification via slugging, the need for special auger feed equipment, or a test system for evaluating the improvements in flow brought about by formulation. This subject becomes paramount when attempting to develop a commercial solid dosage form containing a large percentage of cohesive material.

While angle of repose determinations are usually useless because of their lack of precision, observation of powder flow from a glass funnel and then a grounded metal funnel provides insight into the drug's flow properties, electrostatic properties, and tendency to brige in a cone shaped hopper.