2 SOLID DOSAGE FORMS: POWDERS AND GRANULES

To understand the advantages and potentials of controlled release dosage forms, it would be beneficial to learn the conventional dosage forms. Conventional solid dosage forms include powders, granules, capsules, and tablets. Drugs (which are chemicals) are in general more stable in solid state than in liquid state. For this reason, poorly stable drugs are usually prepared in solid dosage forms. In this chapter, we will examine two solid dosage forms, powders and granules.

I. POWDERS

Powder is a mixture of finely divided drugs and/or chemicals in dry form. Powders can be used internally and externally (*e.g.*, external applications to the skin). Dry powders, however, can be taken orally by some patients who are unable to swallow other solid dosage forms such as capsules and tablets. Although powders *per se* are not used extensively in therapeutics, they are widely used in preparation of various dosage forms. Powdered drugs can be blended with other powdered materials prior to fabrication into other solid dosage forms. Powdered drugs are frequently added to other ingredient to make ointments, pastes, suppositories, and others.

Powder properties relevant to pharmaceutical formulations are single-particle properties, bulk properties, particle–particle interactions, powder morphology (particle size, specific surface area, porosity, and particle shape), and mixing and blending properties (mechanisms of mixing, types of mixing equipment, and minimizing segregation tendencies). It is also important for preparing powder formulation to understand hoppers and powder transfer methods, mechanisms of particle-size reduction, and types of mills.

A. PARTICLE SIZES

The particle size of powders is standardized according to the USP descriptive terms, such as, very fine, fine, moderately coarse, coarse, and very coarse. The definition of the terms for powders of vegetable and animal drugs (Table 2.1) is different from that of powders of chemicals (Table 2.2). In some countries, powdered vegetables, plants, and animal drugs are still widely used. Their main application, however, is to extract drug compounds. Leaves or plants which have bioactive compounds can be prepared in powder forms for extraction of the compounds. Animal pancreas may be prepared into powder to extract insulin.

Table 3.2 Definitions of Powders of Vegetable and Animal Drugs

Designation	Maximum Diameter	Requirements
Very Fine	≤ 180 μm (≤ 0.180 mm)	(passes through a No. 80 sieve)
Fine	≤ 250 μm (≤ 0.250 mm)	(passes through a No. 60 sieve)
Moderately Coarse	≤ 425 μm (≤ 0.425 mm)	(passes through a No. 40 sieve)
Coarse	≤ 850 μm (≤ 0.850 mm)	(passes through a No. 20 sieve)
Very coarse	≤ 2360 μm (≤ 2.36 mm)	(passes through a No. 8 sieve)

Table 2.2 Definitions of Powders of Chemicals

Designation	Maximum Diameter	Requirements
Very Fine	≤ 125 μm (≤ 0.125 mm)	(passes through a No. 120 sieve)
Fine	≤ 180 μm (≤ 0.180 mm)	(passes through a No. 80 sieve)
Moderately coarse	≤ 425 μm (≤ 0.425 mm)	(passes through a No. 40 sieve)
Coarse	≤ 850 μm (≤ 0.850 mm)	(passes through a No. 20 sieve)

* There is no “Very Coarse” category.

B. Factors Affected by Particle Size

Particle size can affect a number of factors important to dosage form preparation as well as applications. They are dissolution rate, suspendability, uniform distribution, penetrability, and nongrittiness.

The dissolution rate of particles is dependent on the particle size. The smaller the particle size, the faster is the dissolution. In suspension preparation, it is important to have a good suspendability (*i.e.*, ability to maintain uniform dispersion in liquid vehicle) of particles. In a powder mixture or capsule and tablets preparation, the ability of a drug to have uniform distribution is essential. For intrarespiratory applications, the penetrability of inhaled particles to reach a desired location within the respiratory tract is important for deep deposition in the respiratory tract. The size range of 1–5 μm is widely used. In dermal ointments, creams, and ophthalmic preparations, nongritty fine powders should be used. Fine particles of 50–100 μm in size can be used for this purpose.

C. Particle-Size Analysis

The particle size and the size distribution can be measured by a number of methods.

1. Sieving

Sieving is the simplest and probably the most commonly used method for determining the particle-size distribution. A powder mass is placed on top of a sifter (mechanical shaker) that is made of a series of screens with sequentially smaller apertures. The horizontal sieve motion loosens the packing of particles allowing subsieve particles to pass through.

Most widely used screens are woven-wire screens ranging in size starting from 400 openings per inch. In the United States, Tyler standard and

Table 2.3 Mesh Conversion Table

ASTM Sieve No. (mesh/inch)	Sieve opening (mm)
400	38
325	45
270	53
230	63
200	75
170	90
140	106
120	125
100	150
80	180
70	212
60	250
50	300
45	355
40	425
35	500
30	600
25	710
20	850
8	2,360

US standard (ASTM E11-70) are commonly used. The two standards are different slightly, but can be used interchangeably.

2. Microscopy

Particle size is measured using a calibrated grid background. The microscopic images of particles can be forwarded to a computer and the size and size distribution can be analyzed by an image analyzer. The resolution limit by light microscopy is 0.2 μm. Electron microscopy can be highly useful for the particles smaller than 0.2 μm.

3. Sedimentation Rate

The terminal settling velocity of particles through a liquid medium in a gravitational and centrifugal environment can be used to calculate the particle size based on Stokes' law, which is:

$$\frac{dx}{dt} = \frac{d^2(\rho_s - \rho_0)g}{18\eta_0}$$

where dx/dt is the rate of settling in cm/s, d is the diameter of the particle in cm, ρ_s is the density of the particles (g/cm^3), ρ_0 is the density of the medium (g/cm^3), g is the acceleration due to gravity (981 cm/s^2), and η_0 is the viscosity of the medium in poise (g/(cm·s)). (This was covered in IPPH 362: Suspension.)

4. Coulter Counter

Coulter counter determines the volume distribution of particles suspended in an electrolyte-containing solution. When a particle passes through a small orifice, it blocks the electric current. The information on particle volume is used for calculating particle size assuming a spherical shape.

5. Light Scattering

Other automatic particle-size measuring instrument employs the light scattering principle. This can be performed either in solution or in the dry powder state.

6. Gas Adsorption

The surface area of powdered materials can be measured by adsorption of solute from solution or of a gas. This method results in the specific surface area (area/unit mass). Usually, an inert gas, such as nitrogen, is adsorbed as a monolayer and the total volume of gas adsorbed is used to calculate the specific surface area, which in turn provides information on the particle size.

D. Disadvantages of the Powder Dosage Form

Powders have several disadvantages as a dosage form as described below:

1. Patient may misunderstand the correct method of use. Without clear instruction, patients may inhale through the nose a drug intended for oral administration. In oral administration, it may have to be clear whether the drug has to be dissolved first in water or taken as is.
2. It is undesirable to take bitter or unpleasant tasting drugs by oral administration. Many herbal drugs (mainly infusions in boiling water) have very bitter tastes. To overcome the unpleasant taste of the extracts, it was often told that "bitter medicine is better medicine." This may not necessarily be true.
3. It is difficult to protect powders containing hygroscopic, deliquescent (tending to melt or dissolve in humid environment), or aromatic materials from decomposition.
4. Uniform, individually wrapped doses of powders (sachets) are required and this may increase the manufacturing expense. (It is possible to include a spoon in a packet of powder drug. This may result in inaccurate amount of drug delivered).
5. Powder must be a homogeneous blend of all of the components and must be of the most advantageous particle size. The particle size of a drug influences the rate of solubility in water. It may also influence the biological activity of a drug.

II. GRANULES

Granules are agglomerates of powdered materials prepared into larger, free flowing particles. They typically fall within the range of 850 μm (No.

20 sieve) to 4.75 mm (No. 4 sieve) size. The shape of granules is generally irregular.

A. Advantages of Granules

Granules are usually made as a step to prepare tablets. Granules flow into the dies more evenly and more freely than particles from the hopper (the funnel-like container holding the drug to guide its flow into the tableting press). A few advantages of granules over powders are listed below:

1. Granules flow better than powders. The easy flow characteristics are important in supplying drug materials from the hopper or feeding container into the tableting presses. For this reason powder mixtures are usually granulated if they are intended to be compressed into tablets. Granules also eliminate or control dust.
2. Granules increase compressibility.
3. Granules have smaller surface area than a comparable volume of powders. This makes granules more stable physically and chemically than the corresponding powders. Granules are less likely to cake or harden upon standing than are powders.
4. Granules are more easily wetted by a solvent than are certain powders, so that granules are also preferred in making solutions. Example: Principen® (ampicillin) for Oral Suspension (Squibb). Ampicillin is unstable in aqueous solution, so it is usually prepared as granules and reconstituted by a pharmacist with purified water just prior to dispensing. The granules also contain colorants, flavorants, and other pharmaceutical ingredients, so the resulting solution or suspension has all the desired medicinal and pharmaceutical features of a liquid pharmaceutical.
5. Granules produce particle-size uniformity, thus content uniformity.

B. Granulation Methods

1. Wet Granulation

In wet granulation, a liquid binder or an adhesive is first added to the powder mixture. The wetted mass is then passed through a screen of the desired mesh size, and resulting granules are dried. The dried granules can be passed through a second screen of a smaller mesh to reduce the size of the granules even further. Overwetting usually results in granules that are too hard for proper tableting, while underwetting usually results in the preparation of tablets that are too soft and tend to crumble.

Binding agents commonly used in wet granulation are a 10–20% aqueous solution of corn starch, a 25–50% of glucose solution, molasses, various polysaccharides (*e.g.*, acacia gum), cellulose derivatives (such as methylcellulose, carboxymethylcellulose, and microcrystalline cellulose), gelatins, and povidone (polyvinylpyrrolidone, PVP).

2. Dry Granulation

In dry granulation, granules are formed by compacting large masses of the powder mixture and subsequently crushing into pieces. These pieces are then sized into smaller granules. The dry-granulation method requires the drug or the diluent to have cohesive properties for the large masses to be formed.

The powder is "slugged" or compressed into large flat tablets or pellets of about 1 inch (3/4 inch or larger) in diameter. In slugging, lubricants are required for release tablets from die. The slugs are then broken up and pass through a desired mesh for sizing.

In roller compaction, the powder is fed between two rollers (both are either flat or complementarily patterned) to form a ribbon of compacted powder. The ribbon is subsequently milled and sieved to produce a powder with better flow properties.

These methods are chosen when a drug and other materials cannot be processed by wet granulation method owing to their degradation by moisture or by elevated temperature for drying. Thus, it is ideal for processing moisture- and heat-sensitive materials. Aspirin is commonly prepared into tablets after slugging, since it is hydrolyzed on exposure to moisture.

3. Fluid Bed Granulation

Since microparticles are considered as granules, approaches of making microparticles, such as fluid-bed drying technology (described in Chapter 7. IV: Microencapsulation), can be used for granulation. A granulating solution is sprayed onto the suspended particles that are then dried rapidly in the suspending air.

C. Drying Process

1. Methods of Drying

Dryers used in the pharmaceutical industry can be divided into four classes:

1. static-bed dryers
2. moving-bed dryers
3. fluidized-bed dryers
4. pneumatic dryers

Static-bed dryers involve no relative movement of the material being dried, although the material may be conveyed in moving containers. Only a portion of the material is directly exposed to the heat source. The amount of exposed surface of the material can be increased by decreasing the thickness of the bed. The most common type of static-bed dryer is a tray or truck dryer, although the use of tray dryers has declined in recent years. A tray dryer consists of perforated trays in which the moist material is placed and the trays slid onto slotted shelves in a forced-air oven. A truck dryer is simply a tray dryer in which the perforated trays are placed on racks equipped with wheels that are then rolled into the forced-air ov-

en. Truck dryers are more amenable to drying large batches of material while simple tray dryers are used to dry laboratory-scale batches.

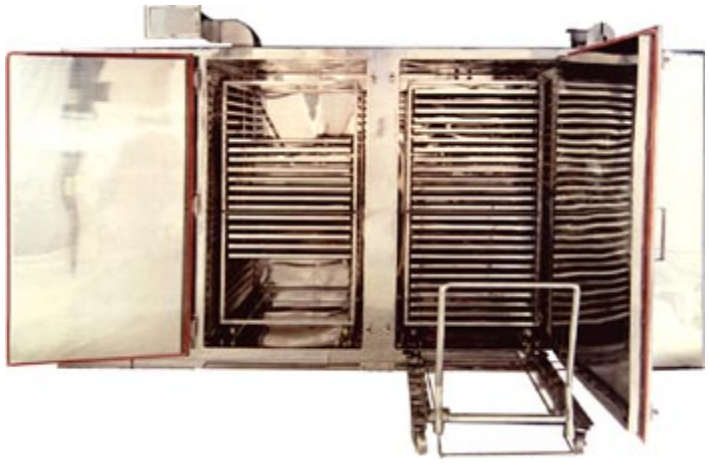

Figure 2.1 Atmospheric tray dryer (Grovers International: Mumbai, India).

Moving-bed dryers and pan dryers are extensions of tray dryers. In turbo-tray dryers, a series of circular trays arranged in a vertical stack slowly rotate while heated air from turbo fans mounted in the center of the stack is circulated over the trays. Wet mass is added through a port in the top of the dryer and stationary wipers level the material on each tray as it rotates. After about seven-eights of a revolution, the material is pushed through slots in the tray to the stage below where it is spread and leveled on the tray. It requires only one revolution for the complete transfer of material from one level to the next. Throughout the process, drier material is transferred to successively lower trays and the material is dry by the time it exits the bottom of the dryer. Pan dryers consist of a shallow, flat-bottomed circular pan with vertical sides. The bed of material is heated from below while sets of rotating plows continually scrape the bottom of the pan and churn the moist mass to expose new surfaces to make contact with the heated pan until the desired moisture content is obtained.

Fluid-bed dryers employ a heated stream of gas, usually air, at a velocity such that the material is partially suspended in the gas flow. The resulting mixture of solid and gas has liquid-like behavior and is said to be fluidized. The solid particles in the fluidized bed are continually entrained in eddies and fall back to the bed in a motion reminiscent of boiling. There are two types of fluid-bed dryers: vertical and horizontal. Vertical fluid-bed dryers are common in pharmaceutical process and are well suited for the batch processes employed in the industry. In vertical fluid-bed dryers, a cylindrical bowl (sometimes with sloping sides) and a fine-meshed screen for the bottom is placed on a perforated plate through which the entrainment gas is passed. An expansion chamber sitting on top of the bowl allows the fluidized bed to expand during the drying process. Attached to the top of the expansion chamber is a filter assembly that traps

the fine particle entrained by the inlet gas. The filters are periodically shaken or purged to rid them of the entrapped particles and return them to the bed of material. Horizontal fluid-bed dryers are amenable for continuous process. The wet material is loaded onto a vibrating, perforated conveyor belt through which the heated air is passed. As the material travels through the dryer, it becomes progressively drier. The dried material is discharged into a hopper at the end of the dryer. The air flow and the rate of travel through the dryer is adjusted to obtain the desired moisture content in the product.

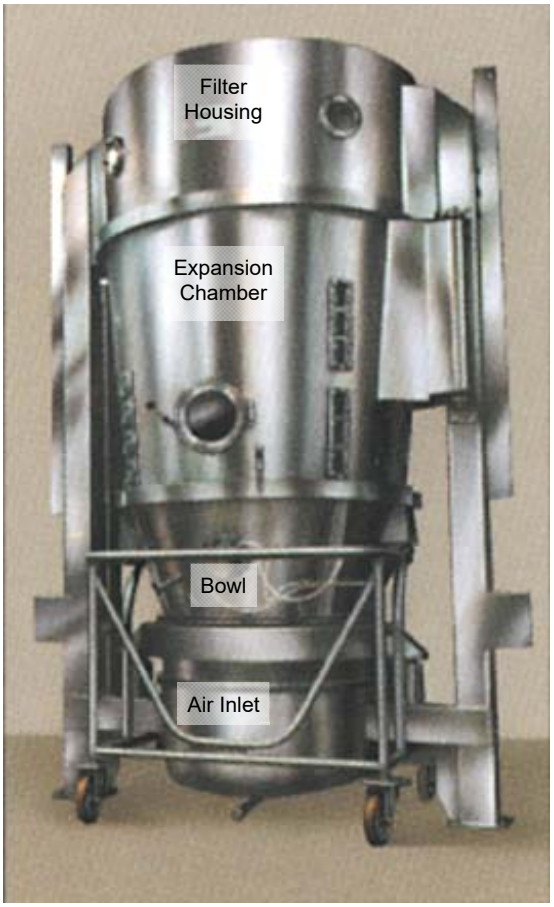

Figure 2.2 Vertical fluid-bed dryer (Glatt Air Techiniques Inc.: Ramsey, NJ).

Pneumatic dryers are divided into three types: spray dryers, flash dryers, and freeze dryers. Spray dryers are common in the pharmaceutical industry to produce product that is amorphous (non-crystalline) and differ from the other dryers mentioned above in that they dry fluids: solutions, slurries, or thin pastes. A stream of fluid is dispersed as fine droplets into a flow of hot air where the solvent quickly evaporates before the particles reach the cylindrical wall of the drying chamber (see Figure). The resulting dry powder is carried to the collection chamber by both gravity and air flow. In flash dryers, a finely-divided moist solid is suspended in a high-

velocity stream of super-heated air. The flash-dried particles may be carried to an impact mill or, because of the high velocity of the air, the dried particles may undergo attrition if they are friable. Freeze dryers (lyopholizers) are commonly used for aseptic products and biopharmaceuticals where the products are generally heat sensitive or react with oxygen. An aqueous solution is first frozen, usually rapidly, and then a high vacuum is applied to remove the frozen water by sublimation below 0 °C. The resulting product is called a cake and usually consists of amorphous material that is readily reconstituted by the addition of sterile water.

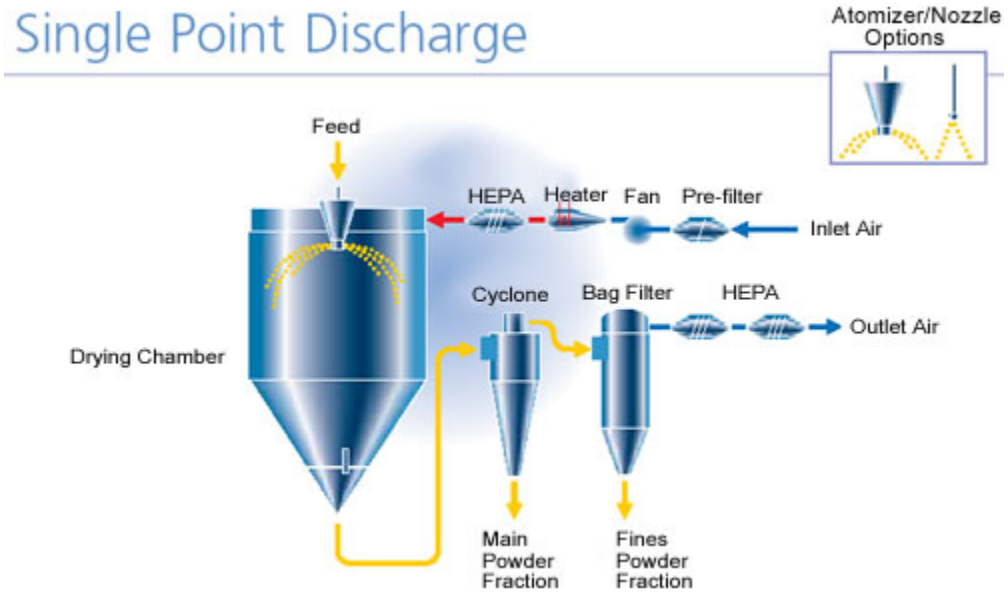

Figure 2.3 Single-point discharge spray drying equipment (Niro Inc.: Columbia, MD).

2. Endpoint Detection

For fluid-bed dryers, the most widely used technique to estimate the drying endpoint is the exit temperature from the dryer. The drying process can be split into two theoretical stages. In the first stage, the loosely-bound water evaporates from the surface of the wet material. In so doing, the temperature drops because of evaporative cooling. In this region, the exit temperature remains fairly constant and is less than the temperature of the inlet air (see Figure). After a critical fraction of moisture has been removed, the moisture in the powder bed must diffuse through the particles before it can be removed. In this diffusive stage, the temperature of the exit gas slowly rises because evaporative cooling in insufficient to efficiently cool the air stream. Eventually, the exit gas temperature is equal to the inlet gas temperature.

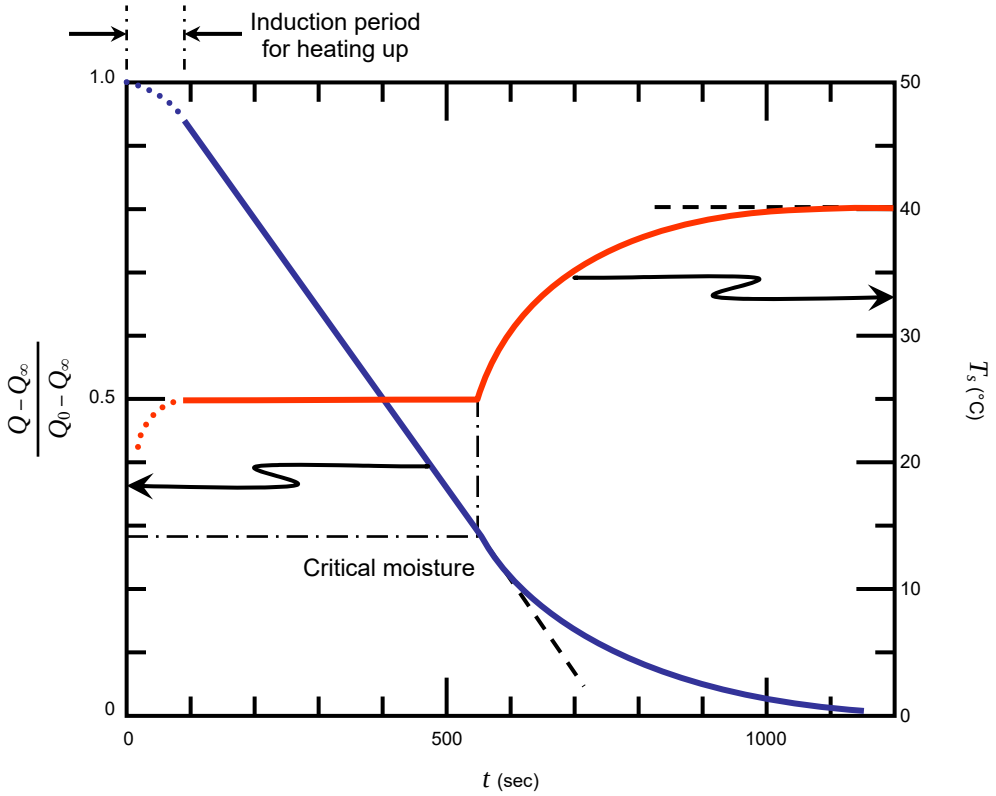

Figure 2.4 An idealized depiction of the change in exit temperature and the moisture content during drying in a fluidized bed. The left *y* axis presents the fraction of excess water remaining in the sample. The right *y* axis presents the change in temperature during the course of the drying process (Kunii & Levenspiel, 1991).

Another common technique is to determine the relative humidity of the exit air. During the initial stage of the drying process, the relative humidity of the exit air will be quite high compared to the relative humidity of the inlet air. After the critical fraction of moisture has been removed, the relative humidity of the exit air begins to decrease since there is less moisture in the particles. Near the endpoint of drying, the relative humidity of the exit air approaches the relative humidity of the inlet air.

Recently, the moisture content of fluidized bed has been assayed using near-infrared (NIR) spectrophotometric techniques. The NIR region of the electromagnetic spectrum is 780–1500 nm (12820–4000 cm^{-1}), the range between visible light and the mid-infrared region. NIR bands are due to overtones and combinations of fundamental vibrations of mainly covalent hydrogen bonds (*e.g.*, O—, N—H, and C—H). The NIR region is especially suitable for investigating water, both bulk water in moist solid samples as well as water in crystalline hydrates. Alone, or in combination with temperature and relative humidity readings, NIR can readily detect the endpoint of drying in a fluid-bed dryer.

3. Moisture Level Determination

Samples can be acquired during the drying process and analyzed with a moisture balance to determine the "loss on drying" (LOD). A moisture balance is a top-loading balance with a heat source located in the lid that covers the weighing pan. A moist sample is placed in a thin aluminum weighing pan and evenly distributed over the surface of the pan. The pan is placed on the balance and the lid is closed. Heating source, usually a heating element or a quartz lamp, can be adjusted to a specific temperature. The sample is heated until the difference in weight detected by the balance has reached the ascribed set point. The moisture content of the sample (in percent weight loss) is then shown on a LED display and printed a ribbon printer. The moisture content can be determined to within a tenth of a percent using this method. This technique is not limited to water content but can also be used to indiscriminately determine any volatile component in a sample. This technique is generally not suitable for samples containing components that may sublime since the acquired data will be confounded with the loss of solid material as well as moisture and other volatile components.

A more accurate technique used to determine the amount of water in a sample is the Karl Fischer (KF) technique, which utilizes the reaction among iodine, water, and a reagent in a titrimetric analysis. There are two types of KF methods: volumetric and coulometric. The volumetric method is used for samples containing large amounts of water (> 1% water). The coulometric method measures the amount of current generated during the titration and can determine moisture levels in the parts per million level (0.0001%). Both of these analyzes can be used on small amounts of sample (1–5 mg) and are tedious but are easily automated.

REFERENCES

Daizo Kunii & Octave Levenspiel (1991) *Fludization Engineering*, 2nd ed., John Wiley & Sons: New York, NY.