Learning objectives (powder):

- Definition, classification, application and advantages
- List and describe a variety of types of powders and granules.
- Understand how to use the equations (particle size determination, Stoke's law, etc).
- Give general explanation about the instruments for particle size determination, etc (application, theory, etc)
- Give general explanation about the instruments for particle density determination, etc (application, theory, etc)
- Demonstrate knowledge about USP methods to characterize powder properties
- Know compounding techniques
- Describe appropriate uses of pharmaceutical powders and granules.

Powders

Definition:

Powders are intimate mixtures of dry, finely divided drugs and/or chemicals that may be intended for internal (Oral Powders) or external (Topical Powders) use

--USP 29

Properties of Powder

- The word "powder"refers to a chemical or mixture that is solid in physical and that is a dry substance composed of finely divided particles
- In compounding, "powder"refers to a dosage formulation that is solid in physical state
- The formulation may be composed of only the active drug or may be a mixture of the active drug and other ingredients

POWDERS as Dosage From

- Because of their greater specific surface area, powders disperse and dissolve more readily than compacted dosage forms.
- Children and those adults who experience difficulty in swallowing tablets or capsules may find powders more acceptable.

Other Uses of Powders

- Powdered drug can be blended with powdered fillers and other pharmaceutical ingredients to fabricate solid dosage forms as tablets, capsules, solutions, suspensions, semi solids.
- Because the quantity of drug formulated into tablets and capsules can be measured accurately, these systems are ideal for potent drugs
- Powders are used as primary ingredients for most other drug delivery systems

POWDERS for Reconstitution

- Immediately prior to use, oral powders are mixed in a beverage or apple sauce.
- Often, stability problems encountered in liquid dosage forms are avoided in powdered dosage forms.
- Drugs that are unstable in aqueous suspensions or solutions may be prepared in the form of granules or powders.
- Because these constituted products have limited stability, they are required to have a specified expiration date after constitution and may require storage in a refrigerator.

POWDERS

- Oral powders may be dispensed in doses premeasured by the pharmacist, i.e., divided powders, or in bulk.
- Granules for veterinary use may be administered by sprinkling the dry powder on animal feed or by mixing it with animal food.

POWDERS

- Traditionally, divided powders have been wrapped in materials such as bond paper and parchment.
  - **Bond paper** is a strong, durable paper especially suitable to electronic printing and use in office machines including copiers and desktop printers.
  - made from fine calf skin, sheep skin or goat skin
- However, the pharmacist may provide greater protection from the environment by sealing individual doses in small cellophane or polyethylene envelopes.

Classification of Powders

Divided Powders: known as Chartulae or Powder Papers, have individual doses of powder packaged in folded papers plastic bags, cellophane, metallic foil, etc.

The divided powder is a more accurate dosage form than bulk powder because the patient is not involved in measurement of the dose.

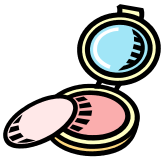
After a powder has been properly blended (using the geometric dilution method for potent substances), it may be divided into individual dosing units based on the amount to be taken or used at a single time

Hint for compounding: Prepare one extra dosage unit or some excess because some powder will be lost in the blending process

POWDERS

- Bulk oral powders are limited to relatively non-potent drugs such as laxatives, antacids, dietary supplements, and certain analgesics that the patient may safely measure by the teaspoonful or capful.
- Other bulky powders include douche powders, tooth powders, and dusting powders.

Bulk Powders



For external application

•Diluents are starch, etc.

• Container: wide-mouth jar, etc. Selected base on properties of powders (volatile, sensitive to moisture)

• Labeling: content, concentrations of active ingredients as per cent weight-weight or weight of active ingredient per gram powder

Bulk Powder

For internal application

• Select container based on the properties of powder

• Administered by teaspoonful or tablespoonful

• Labeling: the weight of active ingredient per volume to be ingested.

a. Prepare the prescription

b. Measure the volume to be taken

c. Weight this of powder

d. calculate the weights of active ingredients in the volume based the prescription

Particle size reduction

- Reducing the particle size of a powder will result in an uniform distribution of particle sizes. The process of reducing the particle size is called comminution. In extemporaneous compounding, there are three methods of comminution:

Particle size reduction

- **Trituration** is the continuous rubbing or grinding of the powder in a mortar with a pestle. This method is used when working with hard, fracturable powders.
- **Pulverization by Intervention** is used with hard crystalline powders that do not crush or triturate easily, or gummy-type substances. The first step is to use an "intervening" solvent (such as alcohol or acetone) that will dissolve the compound. The dissolved powder is then mixed in a mortar or spread on an ointment slab to enhance the evaporation of the solvent. As the solvent evaporates, the powder will recrystallize out of solution as fine particles.
- **Levigation** reduces the particle size by triturating it in a mortar or spatulating it on an ointment slab or pad with a small amount of a liquid in which the solid is not soluble. The solvent should be somewhat viscous such as mineral oil or glycerin. This method is also used to reduce the particle size of insoluble materials when compounding ointments and suspensions.

Particle size reduction

- Example cube:
- 6 surfaces each 1 mm = 6 mm^2
- Reduction to 10 um results in 600 mm^2 surface

Influences of Properties (particle size, shape etc.)

• Powders should be divided finely and uniformly (most important)

• For topical use, then be smooth to the touch and nonirritating to the skin (free-flowing and spread easily on the surface of the skin)

• For internal use, the particle size of the drug affects the rate of dissolution and bioavailability. For certain amount drug solid, the smaller the particle size, the larger the surface area and the faster the rate of dissolution

Noyes-Whitney equations:

$$\frac{dC}{dt} = KS(Cs - C)$$

dC/dt=rate of dissolution, *K*=dissolution rate constant
S=surface area of the solid, *Cs*=solubility of the solid
C=concentration of the drug in solution at time=t

•

•Compounding hint: Particles of different size of bulk powders tend to stratify on standing, resulting in inaccurate dosing (should ensure dose-to-dose content uniformity)

Powder characteristics Micromeritics

Particle size
Particle size distribution
Shape
Angle of repose
Porosity
True volume
Bulk volume
Apparent density
Bulkiness

Powder characteristics particle size

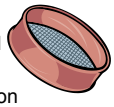
- Sieve analysis
- Microscopy (grid background)
  - Martin's, Feret's, projected area diameter
- Sedimentation rate
  - Andreasen apparatus
- Laser light scattering
- Other methods…..
  - Coulter Counter: particle volume measurements, cascade inpactor

786 PARTICLE SIZE DISTRIBUTION ESTIMATION BY ANALYTICAL SIEVING

- Sieving is one of the oldest methods of classifying powders and granules by particle size distribution.
- When using a woven sieve cloth, the sieving will essentially sort the particles by their intermediate size dimension (i.e. breadth or width).
- Mechanical sieving is most suitable where the majority of the particles are larger than about 75 µm.

786 PARTICLE SIZE DISTRIBUTION ESTIMATION BY ANALYTICAL SIEVING

- Among the limitations of the sieving method are the need for an appreciable amount of sample (normally at least 25 g, depending on the density of the powder or granule, and the diameter of test sieves) and difficulty in sieving oily or other cohesive powders or granules that tend to clog the sieve openings.
- This method is intended for estimation of the total particle size distribution of a single material.
- It is not intended for determination of the proportion of particles passing or retained on one or two sieves.



786 PARTICLE SIZE DISTRIBUTION ESTIMATION BY ANALYTICAL SIEVING

Principles of Analytical Sieving—

The basic analytical method involves stacking the sieves on top of one another in ascending degrees of coarseness, and then placing the test powder on the top sieve.

The test gives the weight percentage of powder in each sieve size range.

This sieving process for estimating the particle size distribution of a single pharmaceutical powder is generally intended for use where at least 80% of the particles are larger than 75 µm.

786 PARTICLE SIZE DISTRIBUTION ESTIMATION BY ANALYTICAL SIEVING

Agitation Methods—

- Methods using mechanical agitation or electromagnetic agitation, and that can induce either a vertical oscillation or a horizontal circular motion, or tapping or a combination of both tapping and horizontal circular motion are available.
- Entrainment of the particles in an air stream may also be used.

- Endpoint Determination— The test sieving analysis is complete when the weight on any of the test sieves does not change by more than 5% or 0.1 g (10% in the case of 76-mm sieves) of the previous weight on that sieve.

811 POWDER FINENESS

- Test procedures for sieving powder materials are described under **Particle Size Distribution Estimation by Analytical Sieving 786** , and, where practical, the particle size distribution should be estimated by this procedure.

Classification of Powders by Fineness

Classification of Powder	d_{50} Sieve Opening (µm)
Very Coarse	> 1000
Coarse	355–1000
Moderately Fine	180–355
Fine	125–180
Very Fine	90–125

- Sieving is most suitable where a majority of the particles are larger than about 75 µm, although it can be used for some powders having smaller particle sizes where the method can be validated.
- Avoid processing conditions that would alter the true particle size distribution of the powder being tested.

	Mesh Opening Size	
Mesh Size Number	Millimeters	Microns
2	9.52	9520
4	4.76	4760
8	2.38	2380
10	2	2000
20	0.84	840
30	0.59	590
40	0.42	420
50	0.297	297
60	0.25	250
70	0.21	210
80	0.177	177
100	0.149	149
120	0.125	125
200	0.074	74

Sieve analysis
see Ansel page 189

- A stack of sieves (U.S standard) is arrange in order (20/40, 40/60, etc)
- Put the powder in the top sieve, and shake the stack. Weigh the quantity of powder resting on each sieve
- Know the arithmetic mean opening (mm)
- Calculating the % retained (each sieve)
- Equation:

$$d_{av} = \sum (\%retained) X (avesize) / 100$$

Powder size definition

- Herbal drugs
  - very coarse No 8 and not more than 20% No 60,
  - coarse No20 and not more than 40% No 60,
  - moderately coarse No 40 and not more than 40% No 80,
  - Fine No 60 and not more than 40% No 100,
  - very fine No 80
- Chemicals
  - very coarse –does not exist
  - coarse No20 and not more than 60% No 40,
  - moderately coarse No 40 and not more than 60% No 60,
  - Fine No 80 no limit
  - very fine No 120 no limit

776 OPTICAL MICROSCOPY

Optical microscopy for particle characterization can generally be applied to particles 1 µm and greater.
Optical microscopy is particularly useful for characterizing particles that are not spherical.

- Apparatus— Use a microscope that is stable and protected from vibration.
- Adjustment— The precise alignment of all elements of the optical system and proper focusing are essential.
- Illumination— A requirement for good illumination is a uniform and adjustable intensity of light over the entire field of view

776 OPTICAL MICROSCOPY

Crystallinity Characterization—

- The crystallinity of a material may be characterized to determine compliance with the crystallinity requirement where stated in the individual monograph of a drug substance.
- Unless otherwise specified in the individual monograph, mount a few particles of the specimen in mineral oil on a clean glass slide.

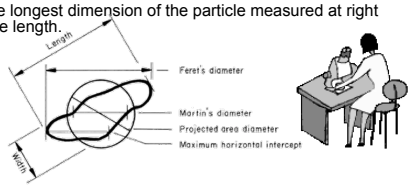
Particle Size Characterization—

- For spherical particles, size is defined by the diameter. For irregular particles, a variety of definitions of particle size exist.
- In general, for irregularly shaped particles, characterization of particle size must also include information on the type of diameter measured as well as information on particle shape.

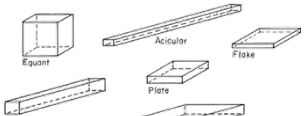
776 OPTICAL MICROSCOPY

- *Feret's Diameter*— The distance between imaginary parallel lines tangent to a randomly oriented particle and perpendicular to the ocular scale.
- *Martin's Diameter*— The diameter of the particle at the point that divides a randomly oriented particle into two equal projected areas.
- *Projected Area Diameter*— The diameter of a circle that has the same projected area as the particle.

- *Length*— The longest dimension from edge to edge of a particle oriented parallel to the ocular scale.
- *Width*— The longest dimension of the particle measured at right angles to the length.



776 OPTICAL MICROSCOPY



- Commonly used descriptions of particle shape.
- *Acicular*— Slender, needle-like particle of similar width and thickness.
- *Columnar*— Long, thin particle with a width and thickness that are greater than those of an acicular particle.
- *Flake*— Thin, flat particle of similar length and width.
- *Plate*— Flat particles of similar length and width but with greater thickness than flakes.
- *Lath*— Long, thin, and blade-like particle.
- *Equant*— Particles of similar length, width, and thickness; both cubical and spherical particles are included

776 OPTICAL MICROSCOPY

General Observations

A particle is generally considered to be the smallest discrete unit. A particle may be a liquid or semisolid droplet; a single crystal or polycrystalline; amorphous or an agglomerate. Particles may be associated. This degree of association may be described by the following terms:

- *Lamellar*— Stacked plates.
- *Aggregate*— Mass of adhered particles.
- *Agglomerate*— Fused or cemented particles.
- *Conglomerate*— Mixture of two or more types of particles.
- *Spherulite*— Radial cluster.
- *Drusy*— Particle covered with tiny particles.

776 OPTICAL MICROSCOPY

General Observations

Particle condition may be described by the following terms:

- *Edges*— Angular, rounded, smooth, sharp, fractured.
- *Optical*— Color (using proper color-balancing filters), transparent, translucent, opaque.
- *Defects*— Occlusions, inclusions.
- Surface characteristics may be described as:
- *Cracked*— Partial split, break, or fissure.
- *Smooth*— Free of irregularities, roughness, or projections.
- *Porous*— Having openings or passageways.
- *Rough*— Bumpy, uneven, not smooth.
- *Pitted*— Small indentations. *2S (USP28)*

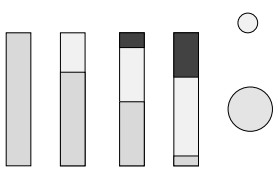
Microscopic method See Ansel p 189

- Counting not less then 200 particles in a single plane
- Calculating the average diameter of particle size
- Equation:

$$d_{av} = \sum nd / \sum n$$

- d: middle value μ
- n: No. particle per group

Sedimentation rate and Particle Radius



$$V = \frac{d^2 (\rho_1 - \rho_2) g}{18 \eta}$$

$$V = \frac{d^2 (\rho_1 - \rho_2) g}{18 \eta}$$

Sedimentation rate--Andreasen apparatus

- Equation (Stokes'law):

$$d = \sqrt{\frac{18h\eta}{(\rho_i - \rho_e) gt}}$$

- d: the diameter of the particles
- h: the height of the liquid above the sampling tube orifice
- η: the viscosity of the suspending liquid
- g: the acceleration of gravity
- ρ_i: the density of suspending liquid
- ρ_e: the density of the particles

The Coulter Principle

The Coulter Principle has become the accepted "Reference Method" throughout the world for particle size analysis and is the recommended limit test for particulate matter in large-volume parenteral solutions.

The Coulter method of sizing and counting particles is based on measurable changes in electrical resistance produced by nonconductive particles suspended in an electrolyte.

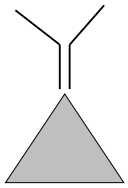
A small opening (aperture) between electrodes is the sensing zone through which suspended particles pass. In the sensing zone each particle displaces its own volume of electrolyte. Volume displaced is measured as a voltage pulse; the height of each pulse being proportional to the volume of the particle.

The quantity of suspension drawn through the aperture is precisely controlled to allow the system to count and size particles for an exact reproducible volume. Several thousand particles per second are individually counted and sized with great accuracy. This method is independent of particle shape, color and density.

Angle of Repose (the flow ability)

Equation:

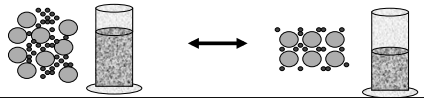
$$\tan\theta = h/r$$



- h is the height of the powder cone and r is the radius of the powder cone
- Powder with low angles of repose will flow freely

Characteristics of Powders

- True volume: the space occupied by the powder exclusive of spaces greater than the intramolecular space
- bulk volume: the volume occupied by a selected weight of a powder
- apparent density : Weight of sample/ V_{bulk}
- true density : Weight of sample/ V_{true}
- bulkiness: the reciprocal of the apparent density
- Powders with a low apparent density and a large bulk volume are light



616 BULK DENSITY AND TAPPED DENSITY

- **BULK DENSITY**
- Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder (*Method I*) or through a volume-measuring apparatus into a cup (*Method II*).

616 BULK DENSITY AND TAPPED DENSITY

- **BULK DENSITY**
- Method I—Measurement in a Graduated Cylinder
- Select a sample mass having an untapped apparent volume of 150 to 250 mL.
- A 100-mL cylinder is used for apparent volumes between 50 mL and 100 mL.
- Carefully level the powder without compacting, and read the unsettled apparent volume, *Vo*, to the nearest graduated unit. Calculate the bulk density, in g per mL, by the formula:
- (*M*) / (*Vo*).

616 BULK DENSITY AND TAPPED DENSITY

- **TAPPED DENSITY**
- Mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using a suitable mechanical tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute.
- Unless otherwise specified, tap the cylinder 500 times initially and measure the tapped volume, *Va*, to the nearest graduated unit. Repeat the tapping an additional 750 times and measure the tapped volume, *Vb*, to the nearest graduated unit.
- If the difference between the two volumes is less than 2%, *Vb* is the final tapped volume, *Vf* .
- Repeat in increments of 1250 taps, as needed, until the difference between succeeding measurements is less than 2%.
- Calculate the tapped density, in g per mL, by the formula:

»(*M*) / (*Vf*)

616 BULK DENSITY AND TAPPED DENSITY

- **MEASURES OF POWDER COMPRESSIBILITY**
- The bulk and tapped densities are reflected in the *Compressibility Index* and the *Hausner Ratio.*
- Compressibility Index— Calculate by the formula:

$$\frac{100(V_o - V_f)}{V_o}.$$

- The *Compressibility Index* and *Hausner Ratio* are measures of the propensity (tendency) of a powder to be compressed.
- In a free-flowing powder interactions between particles are generally less significant, and the bulk and tapped densities will be closer in value.
- For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the values

616 BULK DENSITY AND TAPPED DENSITY

- Hausner Ratio— Calculate by the formula:

$$\frac{V_o}{V_f}.$$

699 DENSITY OF SOLIDS

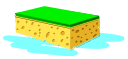
TERMS AND DEFINITIONS

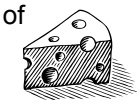
- Density refers to the average spatial distribution of mass in a material. The density of solids typically is expressed in g per cm^3, in contrast to fluids, where the density is commonly expressed in g per mL at a stated reference temperature.
- The density of a solid particle can assume different values depending on the method used to measure the volume of the particle. It is useful to distinguish among three different possibilities.

699 DENSITY OF SOLIDS

TERMS AND DEFINITIONS

- The *true density* of a substance is the average mass per unit volume, exclusive of all voids that are not a fundamental part of the molecular packing arrangement. It is a property of a particular material, and hence should be independent of the method of determination.





699 DENSITY OF SOLIDS

TERMS AND DEFINITIONS

- The *pycnometric density*, as measured by gas pycnometry, is a convenient density measurement for pharmaceutical powders.
- In a gas pycnometer, the volume occupied by a known mass of powder is determined by measuring the volume of gas displaced by the powder.
- The quotient of the mass and volume is the pycnometric density.
- The pycnometric density equals the true density unless the material contains impenetrable voids, or sealed pores, that are inaccessible to the gas used in the pycnometer.

699 DENSITY OF SOLIDS

TERMS AND DEFINITIONS

- The *granular density* includes contributions to particle volume from open pores smaller than some limiting size. The size limit depends on the method of measurement.
- A common measurement technique is mercury porosimetry, where the limiting pore size depends upon the maximum intrusion pressure.
- Because of the additional contribution from pore volume, the granular density will never be greater than the true density.

699 DENSITY OF SOLIDS

- **GAS PYCNOMETRY FOR THE MEASUREMENT OF DENSITY**
- Gas pycnometry is a convenient and suitable method for the measurement of the density of powder particles.
- A simple schematic of one type of gas pycnometer is shown in *Figure.*
- The sample, with mass *w* and volume *Vs*, is placed inside a sealed test cell with an empty cell volume of *Vc*.
- The system reference pressure, *Pr*, is determined at the manometer while the valve that connects the reference volume with the test cell is open.
- The valve is closed to separate the reference volume, *Vr*, from the test cell.
- The test cell is pressurized with the measurement gas to an initial pressure, *Pi*.
- Then the valve is opened to connect the reference volume, *V r*, with the test cell, and the pressure drops to the final pressure, *Pf*.
- If the measurement gas behaves ideally under the conditions of measurement, the sample volume, *Vs*, is given by the following expression (1):

699 DENSITY OF SOLIDS

GAS PYCNOMETRY FOR THE MEASUREMENT OF DENSITY

- The density, , is given by the equation (2)
- The measured density is a volume-weighted average of the densities of individual powder particles.
- Helium is the common choice.
- Because volatiles may be evolved during the measurement, the weight of the sample should be taken after the pycnometric measurement of volume.

$$\rho = \frac{w}{V_s} \quad (2)$$

731 LOSS ON DRYING

- The procedure set forth in this chapter determines the amount of volatile matter of any kind that is driven off under the conditions specified. For substances appearing to contain water as the only volatile constituent, the procedure given in the chapter, ***Water Determination*** **921** , is appropriate, and is specified in the individual monograph.
- Mix and accurately weigh the substance to be tested, and, unless otherwise directed in the individual monograph, conduct the determination on 1 to 2 g. If the test specimen is in the form of large crystals, reduce the particle size to about 2 mm by quickly crushing.

731 LOSS ON DRYING

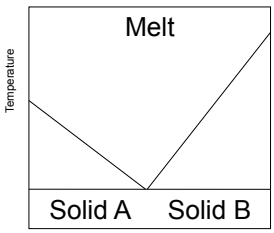
- Where the specimen under test is Capsules, use a portion of the mixed contents of not fewer than 4 capsules.
- Where the specimen under test is Tablets, use powder from not fewer than 4 tablets ground to a fine powder.
- Where the individual monograph directs that loss on drying be determined by thermogravimetric analysis, a sensitive electrobalance is to be used.

731 LOSS ON DRYING

- Example: Lactose
- Dry it at 80 for 2 hours: the monohydrate form loses not more than 0.5% of its weight, and the modified monohydrate form loses not more than 1.0% of its weight.

Other Powder Characteristics

- Melting point (QC of powders)
- Eutectic mixtures



Examples:

Aspirin	Acetaminophen
Lidocaine	Acetaminophen
Acetanilid	Menthol
Aminopyrine	Phenol
Aspirin	Phenylsalicylate
Benzocaine	Prilocaine
Betanaphthol	Resorcineol
Camphor	Salicylic Acid
Chloral hydrate	Thymol

Compounding for powders

- Powders need to be in a fine state of subdivision and particle size deduction required
- Understand the properties of a given solid in order to properly handle and manipulate the material when fabricating it into a solid dosage form or another drug delivery system (select suitable compounding technique)
- homogeneous blending of the powders is needed when several solids are being combined

Blending of Powders

Goal: to create a homogeneous mixture

1.Spatulation: Mixing of powders on an ointment slab or pad using a spatula

• powders must be fine and uniform (no particle size reduction)

• suitable for the coated powder which should avoid hard trituration

• resulting light and not compacted uniform powder

Blending of Powders

Goal: to create a homogeneous mixture

2. Trituration:

• Preferred method for mixtures that contain small quantities of potent drug and unequal size powders combined

• Two steps at the same time: particle size reduction and blending

Geometric dilution

•blending two or more powders of unequal amounts

• ensure that small quantities of ingredients such as potent drug are uniformly distributed in the mixture

• trituration method

Main principle:

Adding equal volume of powder into mortar then trituration until a uniform mixture is achieved (Smallest amount powder first)

1191 STABILITY CONSIDERATIONS IN DISPENSING PRACTICE

- DRY POWDERS AND GRANULES— Dry powders and granules that are not intended for constitution into a liquid form in the original container may cake into hard masses or change color, which may render them unacceptable.
- POWDERS AND GRANULES INTENDED FOR CONSTITUTION AS SUSPENSIONS— Dry powders and granules intended for constitution into solutions or suspensions require special attention. Usually such forms are antibiotics or vitamins that are particularly sensitive to moisture. Since they are always dispensed in the original container, they generally are not subject to contamination by moisture. However, an unusual caked appearance necessitates careful evaluation, and the presence of a fog or liquid droplets inside the container generally renders the preparation unfit for use. Presence of an objectionable odor also may be evidence of instability.