MICROMERITICS

Unit Objective - Student should able to understand the various aspects of formulation of solid dosage form i.e Powder.

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MICROMERITICS

Particle size studies

Rheology of powders and their significance

Definition

- The science and technology of small particles
- The name micromeritics was given by Dalla Valle

TABLE A. PARTICLE DIMENSIONS IN PHARMACEUTICAL DISPERSE SYSTEMS

Particle Size, Diameter			
Micrometers (μm)	Millimeters	Approximate Sieve Size	Examples
0.5–10	0.0005–0.010	—	Suspensions, fine emulsions
10–50	0.010–0.050	—	Upper limit of subsieve range, coarse emulsion particles; flocculated suspension particles
50–100	0.050–0.100	325–140	Lower limit of sieve range, fine powder range
150–1000	0.150–1.000	100–18	Coarse powder range
1000–		18–6	Average granule size

Powders

1. The physical form of a material

   A dry substance composed of finely divided particles

   The use of powdered substances in the preparation of other dosage forms is extensive. For example,

   a. tablets and capsules

   b. liquid dosage forms (solutions or suspensions);

   c. ointments and creams.

2. A type of pharmaceutical preparation

   a medicated powder intended for internal (i.e., oral powder) or external (i.e., topical powder) use

   The use of medicated powders in therapeutics is limited

Definition of granules

Granules are prepared agglomerates of powdered materials, and may be used for the medicinal value of their content or they may be used for pharmaceutical purposes, as in tableting.

The chemical and physical features of solid materials used in the preparation of pharmaceutical products

1. morphology
2. purity
3. solubility
4. stability
5. particle size
6. uniformity
7. compatibility with any other formulation components

↓ chemical and pharmaceutical processing

The requirements for the material of solid dosage form

- Mixing thoroughly
- Flowability
- Filling property

efficient production of a finished dosage form and optimum therapeutic efficacy

Particle size and its analysis

The particle size gradation in USP

- Very coarse
- Coarse
- Moderately coarse
- Fine
- Very fine

This gradation system is based on sieving method, and is related to the proportion of powder that is capable of passing through the opening of standardized sieves of varying dimensions in a specified time period under shaking.

Particle size and analysis

Typical particle size of granules: 4- to 12- sieve

Granules falling within the range of 12- to 20- sieve are sometimes used in tablet making.

The purpose of particle size analysis in pharmacy is to obtain quantitative data on the size, size distribution, and shapes of drug and nondrug components to be used in pharmaceutical formulations

Particle size and analysis

Particle size can influence a variety of important factors:

- Dissolution rate (particle size↓→ surface area↑)
- Suspendability (suspensions; 0.5-10 μm)
- Uniform distribution to ensure dose-to-dose content uniformity (powders, granules and tablets)
- Penetrability (inhalers; 1-5 μm, deposition deep in the respiratory tract)
- Nongrittiness (dermal ointments, creams, and ophthalmic preparations; 50-100 μm)

Particle size and analysis

The methods used for the determination of particle size

- Sieving 40 to 9500 µm
- Microscopy 0.2 to 100 µm provide information of shape also
- Sedimentation rate 0.8 to 300 µm
- Light energy diffraction or light scattering 0.2 to 500 µm laser scattering 0.02 to 2000 µm photon correlation spectrum
- Laser Holography 1.4 to 100 µm provide information on shape
- Cascade impaction

A combination of the above methods and others is often preferred to provide greater assurance of size and shape parameters.

Sieving 40 to 9500 µm

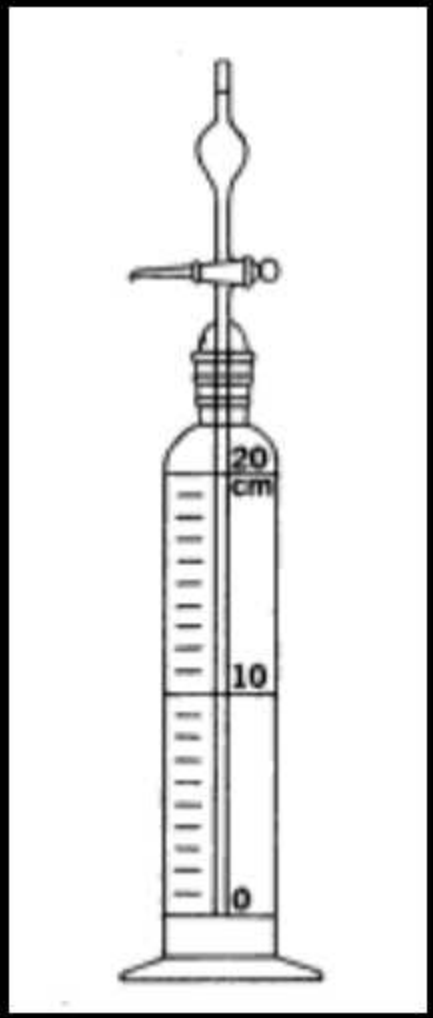
Mechanical sieve shaker

Microscopy

0.2 to 100 µm provide information of shape also

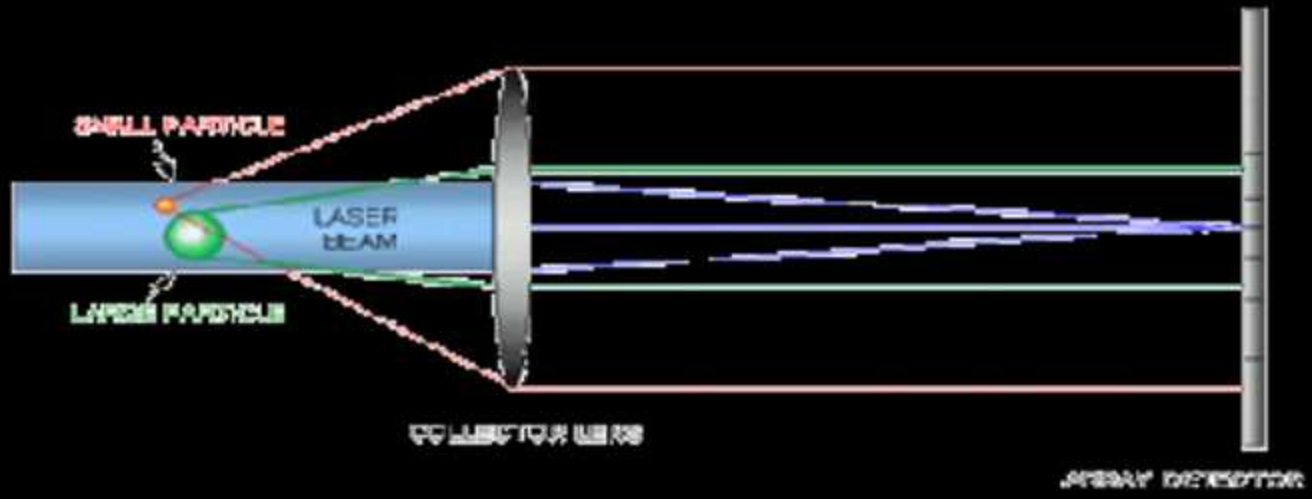
Sedimentation rate

0.8 to 300 µm



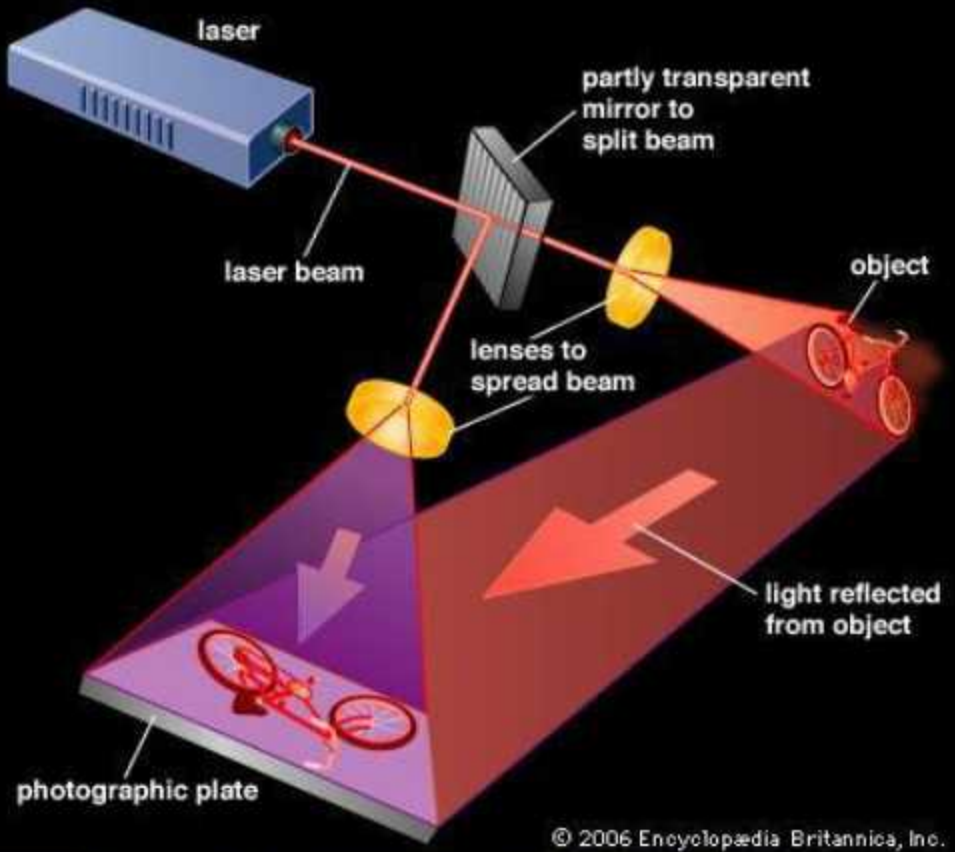
Andreasen apparatus

Light energy diffraction or light scattering



Laser Holography

1.4 to 100 µm provide information on shape



Cascade impaction

Air is drawn through a series of orifices of decreasing size; the air flow is normal to collecting surfaces on which aerosols are collected by inertial impaction. The particles, separated stepwise by their momentum differences into a number of size ranges, are collected simultaneously

Particle size and analysis

Stokes' law/relation

$$v = \frac{2r^2(d_1 - d_2)g}{9\eta} = \frac{D^2(d_1 - d_2)g}{18\eta}$$

$$D = \left(\frac{18v\eta}{(d_1 - d_2)g} \right)^{\frac{1}{2}}$$

v: velocity of the sedimentation in cm/sec

r: particle radius in cm D: particle diameter in cm

d_1: density of the particle in g/ml d_2: density of the liquid in g/ml

g=gravitational constant=980.7 $cm \cdot sec^{-2}$

η=the viscosity of the medium in poises, i.e., $g \cdot cm^{-1} \cdot sec^{-1}$ (poise) in cgs units

Incidentally, the water at 20 ℃ has a viscosity of approximately one centipoises (0.01 poise).

1 $g \cdot cm^{-1} \cdot sec^{-1}$ = 1 p = 100 cp =0.1Pa·s 1 cp =1 mPa·s

On micromeritics

Micromeritics is the science of small particles; a particle is any unit of matter having defined physical dimensions.

Micromeritics includes a number of characteristics including particle size, particle size distribution, particle shape, angle of repose, porosity, true volume, bulk volume, apparent density and bulkiness.

A reduction in a powder's particle size increases the number of particles and the powder's total surface area.

Particle size

Determined by microscopic method

size group of counted particles/μm	Middle value μm "d"	Number of particles per group "n"	"nd"
40-60	50	15	750
60-80	70	25	1750
80-100	90	95	8550
100-120	110	140	15400
120-140	130	80	10400
		∑n=355	∑nd=368500

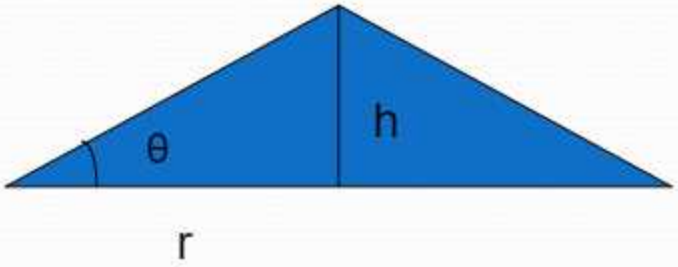
Particle size

Determined by sieving method

Sieve number	Arithmetic mean opening (mm)	Weight retained (G)	% Retained	%Retained × Mean opening
20/40	0.630	15.5	14.3	9.009
40/60	0.335	25.8	23.7	7.939
60/80	0.214	48.3	44.4	9.502
80/100	0.163	15.6	14.3	2.330
100/120	0.137	3.5	3.3	0.452
		108.7	100.0	29.232

Angle of repose

The angle of repose is a parameter used to estimate the flowability of a powder.



$$\text{tangent}\theta = \frac{h}{r} = \mu$$

The angle of repose or the critical angle of repose, of a granular material is the steepest angle of descent or dip of the slope relative to the horizontal plane when material on the slope face is on the verge of sliding. This angle is in the range 0° –90° .

Angle of repose

- Powders with low angles of repose will flow freely and powders with high angles of repose will flow poorly.
- A number of factors, including shape and size, determine the flowability of powders.
- Shape: Spherical particles flow better than needles.
- Size: Very fine particles do not flow as freely as large particles.

a) 250-2000 μm: flow freely if the shape is amenable

b) 75-250 μm: may flow freely or cause problems, depending on shape and other factors

c) less than 100 μm: Flow is problem with most substances.

- The angle of repose is sometimes used in the design of equipment for the processing of particulate solids For example, it may be used to design an appropriate hopper to store the material, to size a conveyor belt for transporting the material.
- It can also be used in determining whether or not a slope will likely collapse; the talus slope is derived from angle of repose and represents the steepest slope a pile of granular material will take. This angle of repose is also crucial in correctly calculating stability in vessels.

- Material (condition) *Angle of Repose* (degrees)
- Ashes 40°
- Asphalt (crushed) 30–45°
- Bark (wood refuse) 45
- Bran 30–45°
- Chalk 45°
- Clay (dry lump) 25–40°
- Clay (wet excavated) 15°
- Clover seed 28°

- Coconut (shredded)45°
- Coffee bean (fresh)35–45°
- Earth30–45°Flour (wheat)45°
- Granite35–40°
- Gravel (loose dry)30–45°
- Gravel (natural w/ sand)25–30°
- Malt30–45°
- Sand (dry)34°
- Sand (water filled)15–30°
- Sand (wet)45°
- Snow38°
- Wheat28°

Other characteristics of micromeritics

$$\text{Void} = \frac{V_{bulk} - V}{V_{bulk}}$$

$$\text{Porosity} = \text{Void} \times 100$$

$$\text{Porosity} = \frac{V_{bulk} - V}{V_{bulk}} \times 100$$

$$\text{apparent density}(\rho_a) = \frac{\text{weight of the sample}}{V_{bulk}}$$

$$\text{bulkiness}(B) = \frac{1}{\rho_a}$$

$$\text{true density}(\rho_t) = \frac{\text{weight of the sample}}{V}$$

Comminution of drugs

Definition:

Comminution is the process of reducing the particle size of a solid substance to a finer state of subdivisions. It is used to

a) facilitate crude drug extraction,

b) increase the dissolution rates of a drug,

c) aid in the formulation of pharmaceutically acceptable dosage forms, and

d) enhance the absorption of drugs.

Comminution of drugs

Mechanism of comminution is-

overcoming the internal adhering force with mechanical action including:

a) Cutting: Cutter mill

b) Compression: Roller mill

c) Impact: Hammer Mill

d) Attrition: Mortar-pestle, Roller mill

e) Combined Impact and attrition: Ball mill, Fluid energy mill

f) Crushing and shearing: Edge runner mill

Comminution of drugs

Trituration: the process of grinding a drug in a mortar to reduce its particle size.

Tools: mortar and pestle

Application: on a small scale

On a large scale

Tools: ball mills, colloid mills, impact mills and fluid-energy mills

Comminution of drugs

Levigation: Combining the powder material and a small amount of liquid (the levigating agent: mineral oil and glycerin) in which the powder is insoluble, then triturating the mixture to reduce the particle size and grittiness of added powders (a paste is produced), this process is termed levigation.

Tools: mortar, pestle or an ointment tile

Application: the small-scale preparation of ointments

Comminution of drugs

What is ointment tile, and how to use it?

It is a flat rectangular or square slab of glass or porcelain. It is also an excellent work surface for triturating and levitating small amounts of ointments and suppository masses. The ointment tile should never be scratched and should be cleaned and stored when not in use.

Blending powders

The mechanism of blending

(a) convective mixing; **convective mixing** is the vertical transport of a fluid and its properties

(b) shear mixing; A **high-shear mixer** disperses, or transports, one phase or ingredient (liquid, solid, gas) into a main continuous phase (liquid), with which it would normally be immiscible.

(c) diffusive mixing

Diffusive equilibrium is reached when the concentrations of the diffusing substance in the two compartments becomes Equal.

Itis the thermal motion of all (liquid or gas) particles at temperatures above absolute zero.

The rate of this movement is a function of temperature, viscosity of the fluid and the size (mass) of the particles.

The methods of blending:

Spatulation

Trituration

Sifting

Tumbling

Stirring

Blending powders

1. Spatulation:

Spatulation is a method by which small amounts of powders may be blended by the movement of a spatula through the powders on a sheet of paper or an ointment tile.

Features: little compression or compaction of the powder

Not suitable for: large quantities of powders or for powders containing potent substances.

Suitable for: the mixing of solid substances that form eutectic mixtures (being dampened or liquefied) when in close and prolonged contact with one another.

Blending powders

How to avoid forming eutectic mixtures?

- mixing in the presence of an inert diluent such as light magnesium oxide or magnesium carbonate (at eutectic point all the phases co-exist & eutectic point denotes a invariant system)

Substances that form eutectic mixtures when combined include chloral hydrate, phenol, camphor, menthol, thymol, aspirin, phenylsalicylate and other similar chemicals.

Blending powders

How to blend materials containing eutectic mixtures?

Method 1: avoid forming eutectic mixtures

Method 2: by forming eutectic mixtures

Take the effect of eutectic mixtures on the pharmacological action into account:

a) pharmacological action↑: method 2

b) pharmacological action↓: method 1

c) pharmacological action→: method 1 or 2

Blending powders

2. Trituration:

Features: may be employed both to comminute and to mix powders

Geometric dilution method: The potent drug is placed on an approximately equal volume of the diluent in a mortar and mixed thoroughly by trituration. Then a second portion of diluent equal in volume to the mixture is added, and the trituration repeated. This process is continued by adding equal volumes of diluent to the powder mixture and repeating until all of the diluent is incorporated.

Suitable for the mixing of a small amount of a potent drug with a large amount of diluent, in particular, the potent and the nonpotent ingredients being of the same color.

Blending powders

3. Sift---ing:

Features: resulting in a light fluffy product;

not acceptable for the incorporation of potent drugs into a diluents powder.

Blending powders

4. Tumbling:

Features: tumbling the powder enclosed in a rotating container (V-shape, cube, cylinder etc.);

motorized powder blenders (large-scale) →widely employed in industry

Mixing is thorough, although time-consuming

5. stirring:

also frequently used on large scale.

Medicated powders

Application

- Internally (with blue label)

  a. taken orally after mixing with water

  b. inhaled into the lungs

  c. packaged with a liquid solvent or vehicle for constitution (orally, as an injection, as a vaginal douche: A stream of water, often containing medicinal or cleansing agents, that is applied to a body part or cavity for hygienic or therapeutic purposes.)

  e.g., antibiotics for pediatric use

- Externally (with red label, *externally use only* or *topical*)

  a. sifter-type container

  b. a powder aerosol

Medicated powders

The advantage and disadvantage of medicated powder

- Advantages

  a. Suitable for patients who have difficulty in swallowing solid dosage forms

  b. Faster rates of dissolution and absorption than solid dosage forms (oral powders for systemic use)

- Disadvantage

  a. The undesirable taste of the drug

Aerosolized powders

Various application form

- Pressurized aerosols

  To make the powder deposit deep into the lungs, the particle size of the micronized medication is prepared in the range of 1 μm to 6 μm in diameter.

- Mechanical devices (SPINHALER)

  for the delivery of powders in a capsules

- Powder blowers or insufflators

Packaging of powders

- **Bulk powders**

  limited to nonpotent substances such as

  a) antacid powders and laxative powders

  b) douche powders

  c) medicated powders for external application anti-infectives or antifungals

  d) powder containing nutritional supplements

- **Divided powders**

  a) weigh each portion separately for potent drug

  b) block-and-divide method for nonpotent drug-approximate each portion

Granules

Preparation of granules

1. Wet methods

a) Basic wet method

a) moistening the powder mixture (paste-like mass)

b) granulation by screening (wet granules)

c) drying (dry granules)

d) sizing the granules by screening (finished granules)

b) Fluid-bed processing

Particles are vigorously dispersed and suspended while a liquid excipient is sprayed on them and the fluidized product dried, forming granules or pellets of defined particle size.

Granules

Preparation of granules

2. Dry methods

- The dry granulation process is used to form granules without using a liquid solution because the product to be granulated may be sensitive to moisture and heat.
- Forming granules without moisture requires compacting and densifying the powders.
- In this process the primary powder particles are aggregated under high pressure. Sweying granulator or high shear mixer-granulator can be used for the dry granulation.
- Dry granulation can be conducted under two processes; either a large tablet (slug) is produced in a heavy duty tabletting press or the powder is squeezed between two rollers to produce a sheet of materials

Compactor/Compression granulation

a) Roller compactor (densified sheets or forms)

b) Granulating machine

b) Slugging method

a) Compression of powder mixture into large tablets (slugs)

b) Granulated into desired particle size

Disadvantage of dry methods: the production of fines

The advantages of granules

- Flow well compared to powders
- Stable to the effects of atmospheric humidity and less likely to cake or harden upon standing
- Easily wetted by liquid
- The antibiotics that are unstable in aqueous solution are prepared as small granules for constitution prior to dispensing

Effervescent granulated salts

Features:

- Dosage form: granules or coarse to very coarse powders to decrease the rate of acid-base reaction
- Composed of sodium bicarbonate, citric acid, and tartaric acid
- The acids and base react to liberate carbon dioxide upon contacting water which masks undesirable taste and facilitates disintegration.

Effervescent granulated salts

The choosing of acids

- **Tartaric acid alone:** the resulting granules lose their firmness readily and crumble
- **Citric acid alone:** a sticky mixture difficult to granulate
- **The combination of citric and tartaric acids is preferable.**

The preparation method:

1. fusion/dry method,
2. wet method

The preparation of effervescent granules——
1. fusion/dry method

The one molecule of water of crystallization present in each molecule of citric acid acts as the binding agent for the powder mixture.

Mixing of powders: rapidly; in a low humidity environment → to avoid the absorption of moisture and a premature chemical reaction.

The granules are dried at a temperature not exceeding 54°C and immediately placed in containers and tightly sealed.

2. wet method

The binding agent is the water added to alcohol as the moistening agent- forming the pliable mass for granulation.

All of the powders may be anhydrous as long as water is added to the moistening liquid.

RHEOLOGY

of

POWDERS

POWDER FLOW

- Is powder free flowing?

PARTICLE PROPERTIES:

- Cohesion-between like surfaces
- Adhesion-between unlike surfaces

POWDER FLOW

PARTICLE PROPERTIES & FLOW:

- **Particle size** - Larger than 250µ are free flowing but as size falls below 100µ it is cohesive; collection of powder will be either-
  - A. Monodisperse (having particles of same size) or
  - B. Polydisperse (having particles of more than one size).
- **Particle shape -** Spheres have minimum contact & hence optimal flow; particle flakes have high surface to volume ratio & poor flow
- **Packing geometry–**
  - Characterization by porosity & bulk density
  - Bulk density is always less than true density- due to interparticle pores/voids
  - Particle can have single true density but different bulk densities

Derived properties of powders :

Apart from fundamental properties, there are derived properties. These are based on fundamental properties. These are :

1. **Porosity,**
2. **Packing arrangements,**
3. **Densities of particles:** Bulk density, Tap density, Granule density. Dense particles are less cohesive than less dense particles of the same size & shape.
4. **Particle volume:** Bulk volume, Tap volume, Void volume. Instrument used for measurement is **coulter counter**. Dilute suspension is passed through a small orifice and change in electric resistance is measured.

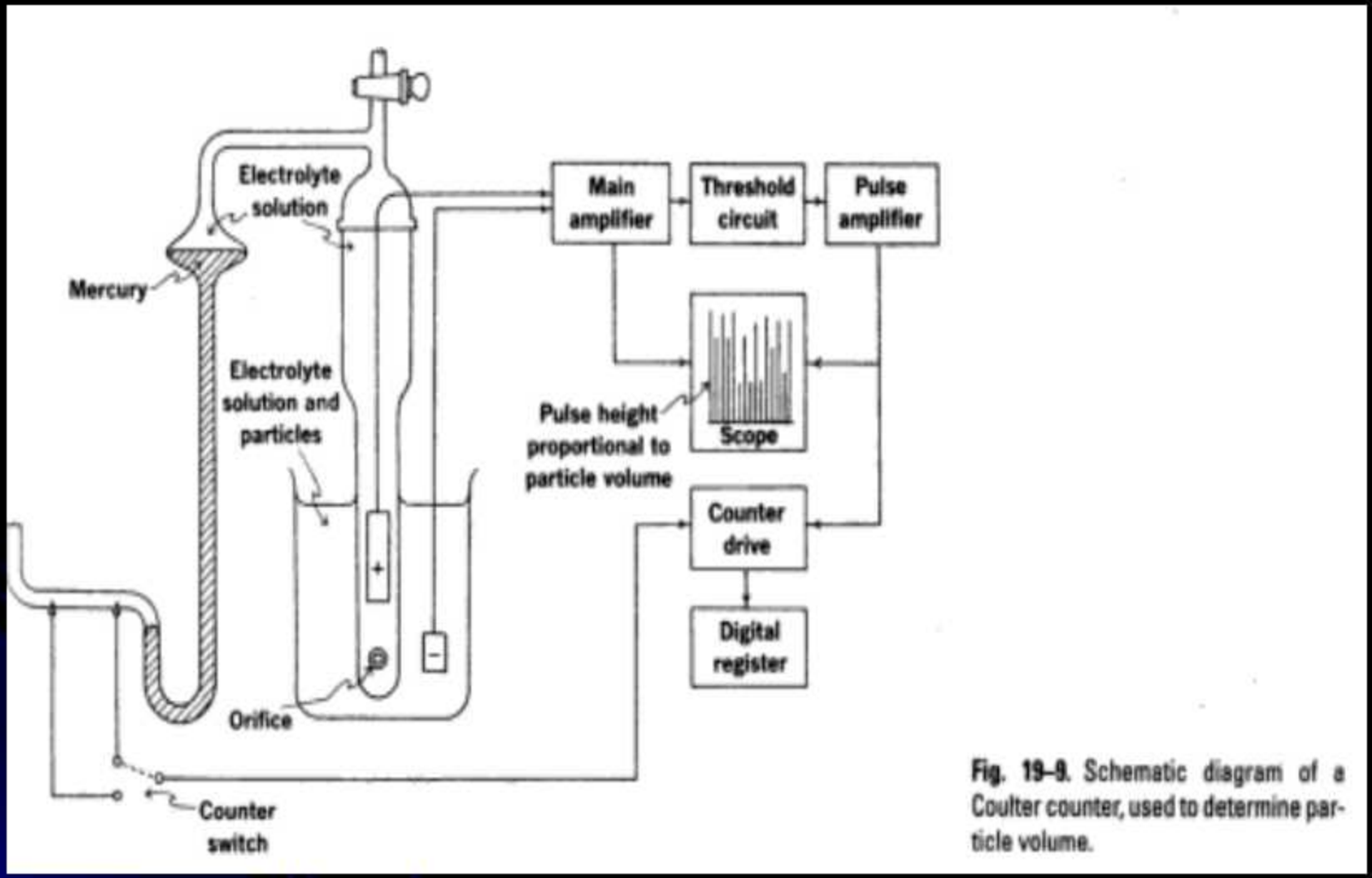


Fig. 19–9. Schematic diagram of a Coulter counter, used to determine particle volume.

5. **Particle surface area:** Surface area is important characteristic for understanding surface adsorption and dissolution rate studies.
Methods for determining surface area:

A. Adsorption method,

B. Air permeability method

A. Adsorption method:

An instrument used to obtain data for calculation of surface area is Quantasorb . the absorption and desorption is measured with thermal conductivity detector, when a mixture of helium and nitrogen is passed through the cell, containing powder. Here nitrogen is absorbate gas and helium is inert and is not adsorbed on surface.

With the help of mathematical calculations and graph studies , nitrogen adsorbed and area are calculated.

B. Air permeability method:

- Here the principle is "resistance to the flow of a fluid through a plug of powder is the surface area of powder. "Greater the surface area, the greater will be the resistance to flow."

The instrument used is Fisher subsieve sizer.

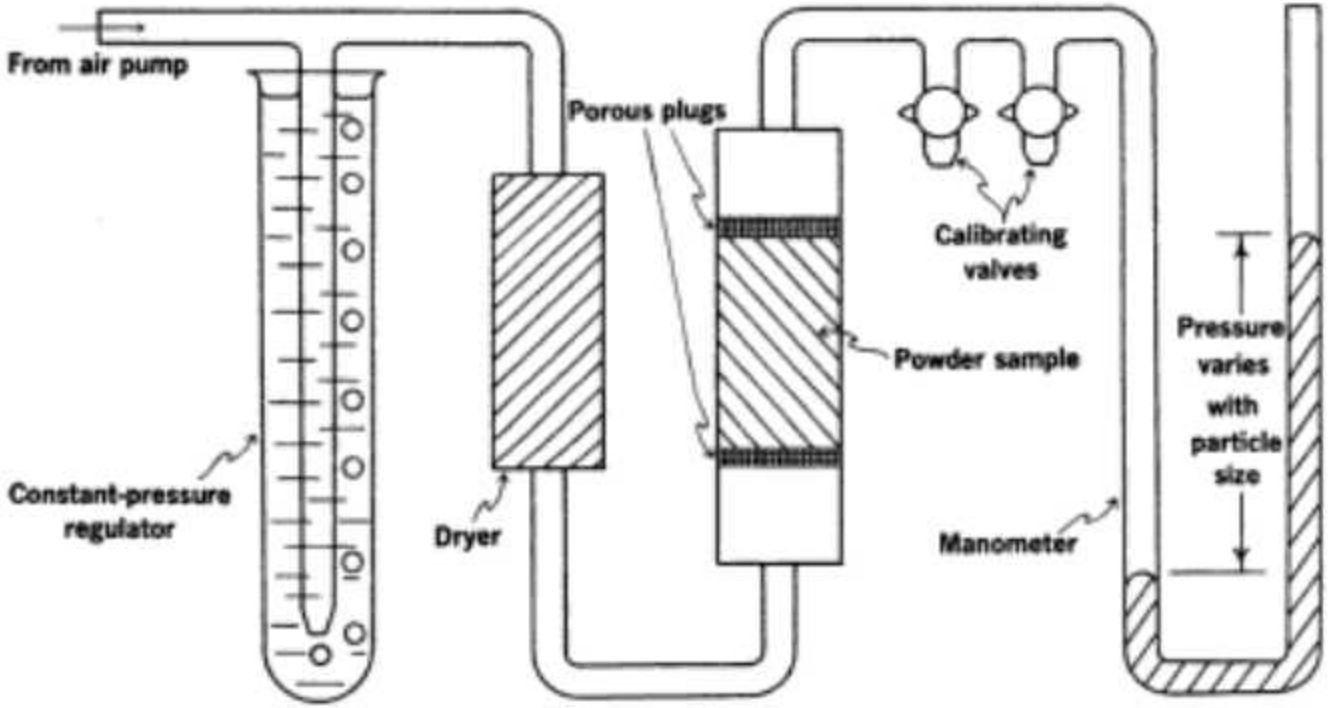


Fig. 19–12. The Fisher subsieve sizer. An air pump generates air pressure to a constant head by means of the pressure regulator. Under this head, the air is dried and conducted to the powder sample packed in the tube. The flow of air through the powder bed is measured by means of a calibrated manometer and is proportional to the surface area or the average particle diameter.

6. **Bulkiness-** Reciprocal of bulk density,

7. **Flow properties:** Powders may be free-flowing or cohesive.

   Factors those affect flow properties are

   a) particle size, b) shape, c) porosity,

   d) density, e) texture.

   Flow rate is expressed by Pressibility Index (I)=$[1-v/v_o]100$

8. **Compaction**

9. **Angle of repose**

10. **Carr's Index:** $\frac{\text{(Tapped density - Poured density) x 100}}{\text{Tapped density}}$

11. **Hausner's ratio:** $\frac{\text{Tapped density x 100}}{\text{Poured density}}$

POWDER FLOW

Factors affecting packing geometry:

- Particle size & size distribution- void spaces in between can be filled with fine particles
- Particle shape & texture-open structure vs. tight packing
- Surface properties-electrostatic forces
- Handling & processing conditions-prior to flow

FLOW through orifice

- Factors:

1. ORIFICE DIAMETER:

- Powder flows proportional to orifice diameter provided that powder head remains considerably greater than orifice diameter.

2. HOPPER WIDTH:

- Make adjustments so that minimum hopper widths are large enough to produce arch stresses greater than arch strength.

3. HEAD SIZE:

- Pressure changes with powder head size.

4. HOPPER WALL ANGLE:

- Powders with low wall friction angles will empty freely

5. MASS FLOW:

- First in first out

6. FUNNEL FLOW:

- "Rat hole"

CHARACTERIZATION OF POWDER FLOW

- Indirect Methods:

1. Angle of repose
2. Shear cell determinations which gives relationship between flow factors & powder flowability
3. Bulk density measurements-% compressibility & flow, Carr method
4. Critical orifice diameter-direct measure of powder cohesion & arch strength

POWDER FLOW

- **Direct Methods:**

1. Hopper flow rate
2. Recording with flowmeter

HOW TO IMPROVE FLOW

1. Alter particle size & size distribution
2. Alter particle shape or texture
3. Alter surface forces
4. Formulation additives
5. Vibration assisted hoppers
6. Force feeders

The definition of aerosols

Definition

An aerosol is defined as a system that depend on the power of a **compressed** or **liquefied** gas to expel the contents from the container with special valve system.

An aerosol product consists of the following component parts:

a. propellants

b. container

c. valve and actuator

d. therapeutic agent and pharmaceutical excipients

Advantages of aerosols

Advantages over other dosage forms

a. contamination
b. Stability
c. Sterility
d. delivered in a desired form
e. Irritation
f. ease and convenience of application
g. application of medication in a thin layer

The classification of aerosols

1. **According to administration route**
   1)inhalation aerosols
   2)non-inhalation aerosols:
   3)topical aerosols:
2. **According to the working way of valve**
   1)metered dose aerosols
   2)non-metered dose aerosols

The classification of aerosols (continued)

3. According to dispersion system
   1)solution aerosols:
   2)emulsion aerosols:
   3)suspension aerosols:
4. According to the number of phases
   1)two phases aerosols
   2)three phases aerosols

The components of aerosols

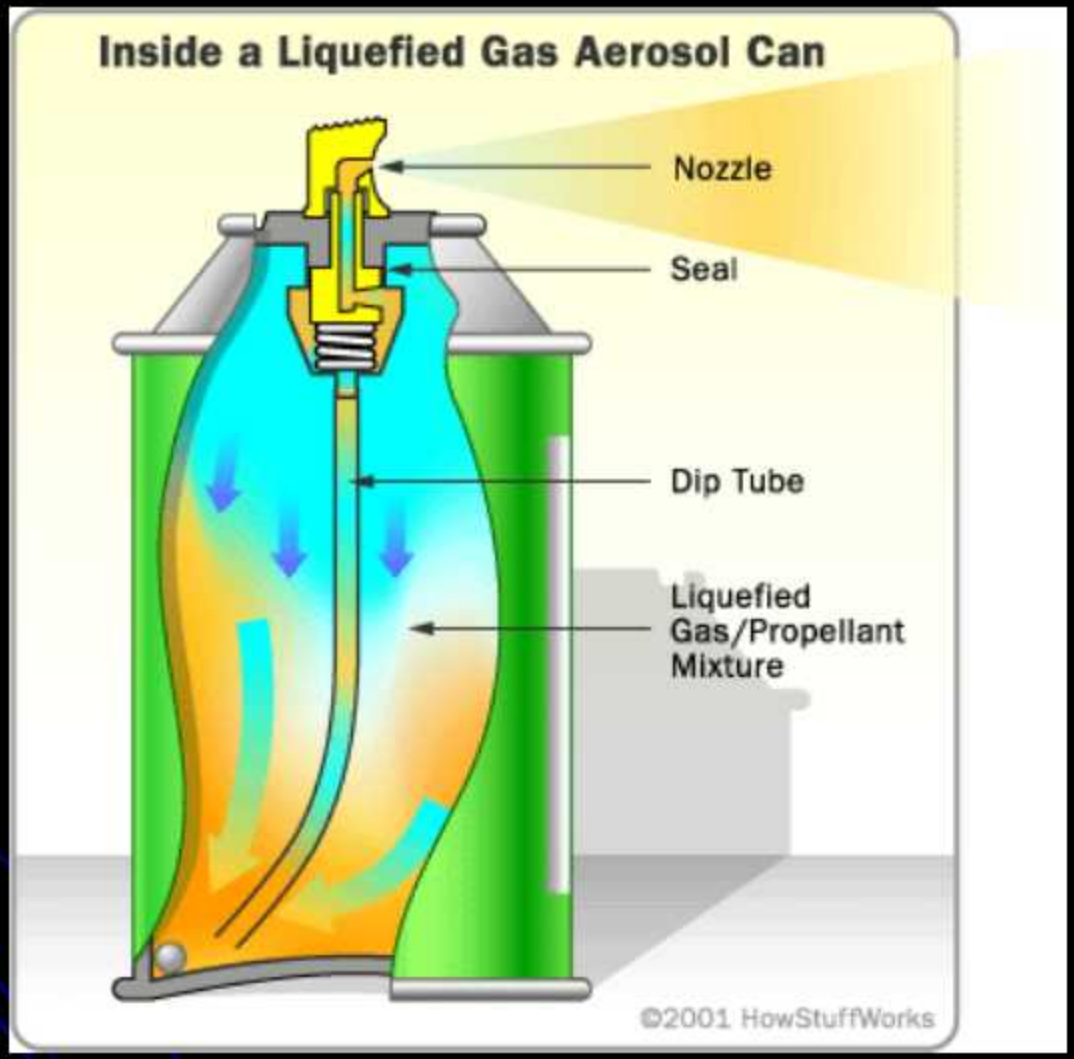
An aerosol product consists of the following component parts:

a. propellants (The fluorinated hydrocarbons find widespread use in most aerosols. Other propellants includes hydrocarbons including propane, butane, and isobutane, and compressed gases such as nitrogen, carbon dioxide, and nitrous oxide(N_2O).)

b. container (tinplate, aluminum, stainless steel, glass)

c. valve and actuator

d. therapeutic agent and pharmaceutical excipients including diluents, antioxidants and suspending agents


Inside a Liquefied Gas Aerosol Can
Nozzle
Seal
Dip Tube
Liquefied Gas/Propellant Mixture
©2001 HowStuffWorks

The components of aerosols (continued)

c. valve and actuator

c1. continuous spray valves

c2. metering valves

The valves consist of the following parts:

1) ferrule or mounting cup

2) stem

3) valve body or housing

4) gasket

5) spring

6) dip tube

Actuator

The formulation of aerosols

Types of pharmaceutical aerosols

- Solution system (two-phase system)
- Suspension systems
- Foam/emulsion systems

a. aqueous stable foams

b. nonaqueous stable foams

c. quick-breaking foams

d. thermal foams

The formulation of aerosols

Types of pharmaceutical aerosols——Solution system (two-phase system: consists of a vapor and liquid phase)

Example1:	weight/%
isoproterenol HCl	0.25
ascorbic acid(Vc)	0.10
ethanol	35.75
propellant 12	63.90

In order to reduce the pressure, the addition of propellant 114 is recommended. Ethanol is a cosolvent. Ascorbic acid is antioxidant.

The formulation of aerosols

Types of pharmaceutical aerosols——Solution system

Example2:

	weight/%
active ingredients	up to 10-15
solvents (ethanol etc.)	up to 10-15
distilled water	10-15
hydrocarbon propellant A-46	55-70

Hydrocarbons are often used in topical aerosol.

Depending on the amount of **water** present, the final product may be a solution or a **three-phase** system.

The formulation of aerosols

Types of pharmaceutical aerosols——Suspension systems

Example3	weight/%
epinephrine bitartrate (within 1 to 5 microns)	0.50
sorbitan trioleate(spans-85)	0.50
propellant 114	49.50
propellant 12	49.50

sorbitan trioleate: surfactants/suspending agents, to decrease the rate of settling of the dispersed particles.

The epinephrine bitartrate has a minimum solubility in the propellant system, but is sufficiently soluble in the fluids in the lungs to exert a therapeutic activity.

The formulation of aerosols

Types of pharmaceutical aerosols——Suspension systems

The physical stability of an aerosol dispersion can be increased by

a) control of moisture content,

b) use of derivatives of active ingredients having minimum solubility in propellant system,

c) reduction of initial particle size to less than 5 microns,

d) adjustment of density of propellant and/or suspensoid(悬胶体) so that they are equalized, and

e) use of dispersing agents.

The formulation of aerosols

Types of pharmaceutical aerosols——

Foam/emulsion systems

a. aqueous stable foams

b. nonaqueous stable foams (using various glycols, such as PEG)

c. quick-breaking foams

d. thermal foams

The formulation of aerosols

a. aqueous stable foams
can be formulated as follows:

	% w/w
Active ingredients Oil-waxes o/w surfactant Water	95.0-96.5
Hydrocarbon propellant	3.5-5.0

1) Oil-waxes: myristic acid, stearic acid, cetyl alcohol, lanolin, etc.

2) Hydrocarbon propellant can be replaced by compressed gas.

3) As the amount of propellant increases, a stiffer and dryer foam is produced. Lower propellant concentrations yield wetter foams.

4) Surfactants that showed some solubility in the propellants are preferable.

The formulation of aerosols

a. nonaqueous stable foams
can be formulated as follows:

	% w/w
Glycol	91.0~92.5
Emulsifying agent	4.0
Hydrocarbon propellant	3.5~5.0

1) The most effective emulsifying agents are glycol esters, namely, myrijs.

Manufacture of pharmaceutical aerosols

Step1: manufacture of concentrate (general procedure and condition)

Step2: addition of propellant

The filling methods:

cold filling: -40° F; restricted to nonaqueous products and to those products not adversely affected by low temperatures

pressure filling: preferable for solution, emulsions, suspensions; less danger of contamination of the product with moisture; high production speeds; less propellant loss.

Testing of pharmaceutical aerosols

A. Flammability and combustibility

1. Flash point of limited value
2. Flame extension, including flashback

B. Physicochemical characteristics

1. vapor pressure: pressure gauge, water bath, pressure variation from container to container;
2. density: hydrometer
3. moisture content: Karl Fisher method, GC
4. identification of propellants: GC, IR
5. concentrate-propellant ratio: GC

Testing of pharmaceutical aerosols (continued)

C. Performance

1. Aerosol valve discharge rate: W_1-W_0 g/s
2. spray pattern spray on a paper treated with a dye-talc mixture
3. dosage with metered valves:

   1)reproducibility of dosage each time the valve is depressed:a) one or two doses of discharge; b) left amount.

   2)amount of medication actually received by the patient:a) hard to determine; b)artificial respiratory system
4. net contents: W_{total}-$W_{container}$
5. foam stability: visual evaluation, rotational viscometer, rod falling, mass penetration

Testing of pharmaceutical aerosols (continued)

6. particle size determination:
   cascade impactor 0.1~30 microns
   light scatter decay: Tyndall beam
7. leakage

D. biologic characteristics
   1. therapeutic effect
   2. toxicity

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