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Topic 3 - Powders

Reference: A. J. Hickey & D. Ganderton,
Pharmaceutical Process Engineering, Chapter 5, 2nd edition, Informa Healthcare. 2010

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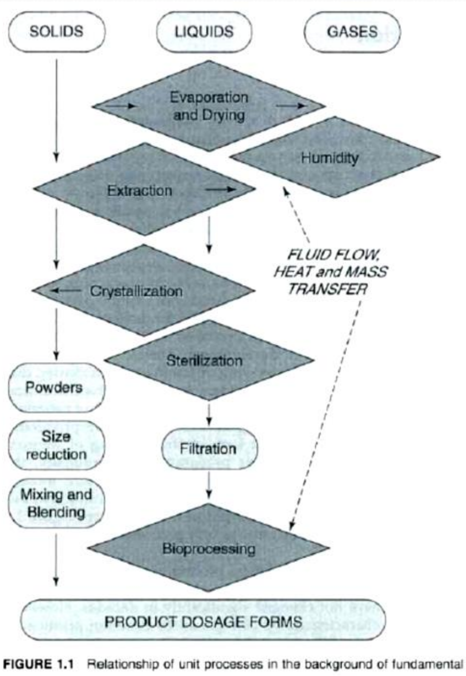

FIGURE 1.1 Relationship of unit processes in the background of fundamental principles.

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Powders

Introduction

- Powders are employed in many pharmaceutical processes.
- Powders are more difficult to handle and process than liquid and gases. **Why?**
  - Their **flow properties** are fundamentally different.
  - The manner in which the particles of a **powder pack** together to form a bed and its influence on **bulk density**.
  - In static conditions, there is no leveling at free surface of a bed of powder. Nor is pressure transmitted through the bed. Instead, the walls of containing vessel carry the weight of the bed.

Powders - Introduction

Flow Properties

- Unlike fluid:
  - A particulate mass will resist stresses less than a limiting value without continuous deformation
  - Many common powders will not flow because the stresses imposed by gravity are insufficiently high
  - Often additional processes that improve flow, such a **granulation** and **fluidization**, are adopted to facilitate powder transport and powder feeding.

Powder Packing and Bulk Density

- *Bulk density* is the ratio of the mass of the powder to its total volume, including **voids**.
- Unlike fluid:
  - Bulk density varies greatly with the **size**, **size distribution**, and **shape of the particles** because these affects the **closeness of packing** and the **fraction of the bed that is void**.
  - **Vibration** and **tapping** cause particles rearrangement and decrease in void fraction, and thus increase the bulk density.
  - These factors are important because the powder is subdivided and measured **by volume**.

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Powders - Introduction

Powder Packing and Bulk Density

- Unlike fluid:
  - Variation of bulk density causes variation of weight and dose.
  - The variation in the weight of compressed tablets is an example of this effect.
- The *manner of packing* also influence the behavior of a bed when it is compressed.

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Exercise

- Calculate the **bulk density** of a 400 cm^3 sample that weighs 575 g (oven dry weight).
  - $\rho_b = \frac{M_s}{V_s} = \frac{575\ g}{400\ cm^3} = 1.44\ g/cm^3$
- Calculate the **porosity** of a sample that has a bulk density of 1.35 g/cm^3. Assume the particle density is 2.65 g/cm^3.
  - Porosity = $\left(1 - \left(\frac{\rho_b}{\rho_d}\right)\right) \times 100$
    $= (1 - (1.35/2.65)) \times 100 = 49\%$

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PARTICLES PROPERTIES

1. Origin
2. Structure

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Particles Properties

1. Origin

- It is important to consider the particles' origin to understand their properties.
- Particles may be produced by different processes that can be regarded as **constructive** or **destructive** (increase surface area by significant input of energy).

Constructive Methods	Destructive Methods
Crystallization	Milling
Precipitation	Spray drying
Condensation	

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Particles Properties

1. Origin

- Most common methods of bulk manufacturing are crystallization and precipitation from **saturated solutions**.
- Solutions are saturated by exceeding solubility limit in one of several ways:
  - Reducing the temperature of the solution and thus reducing solubility.
  - The addition of cosolvent with different capacity to dissolve the solute and reduce solubility.

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Particles Properties

2. Structure

- Characterization of particles structure by:
  - Crystal system
  - Crystal habit

o **Crystal system**: lattice group spacing and bond angles in three dimensions.
  - These angles and distances are determined by X-ray diffraction (XRD) utilizing **Bragg's law**.
  - Crystals may be considered as polygons wherein the number of faces, edges, and vertices are defined by **Euler's law**.

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Particles Properties

2. Structure

- Seven specific categories of crystal system:
  1. Cubic
  2. Monoclinic
  3. Triclinic
  4. Hexagonal
  5. Trigonal (or Rhombohedral)
  6. Orthorhombic
  7. Tetragonal

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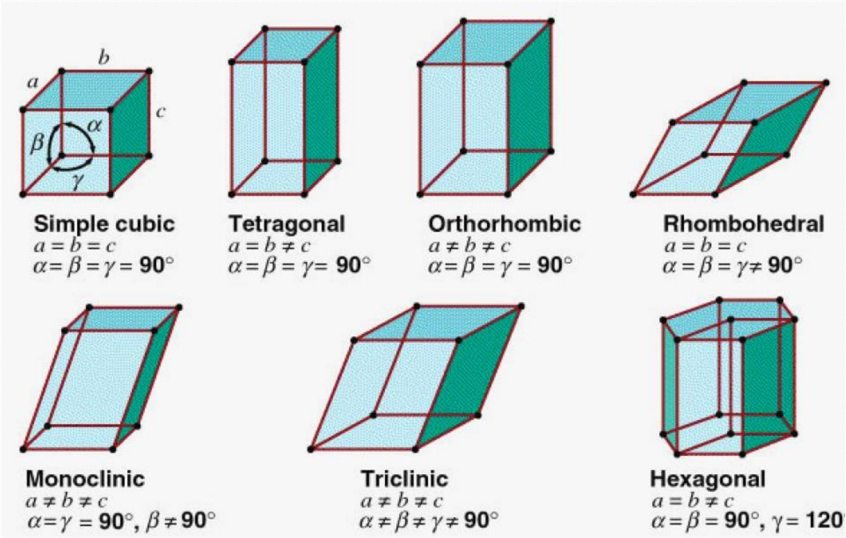
The Seven Crystal Systems



Particles Properties

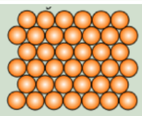
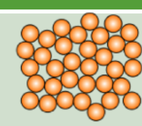
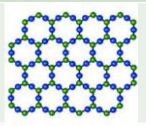
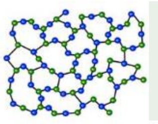
2. Structure

- Once crystal molecular structure has been established, the manner in which **crystal growth** occurs from solution is dictated by <u>inhibition</u> in any of the three dimensions.
- Inhibition of growth occurs because of differences in surface energy or surface energy density. These differences may be brought about by:
  - Regions of different polarity at the surface
  - Charge density at the surface
  - The orientation of charged side groups on the surface
  - Location of solvent at the interface
  - The adsorption of other solute molecules (surfactant)

Particles Properties

2. Structure

- Any of the production methods may result in particles that have no regular structure or specific orientation of molecules → **amorphous**.

Crystalline	Amorphous
	
	

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Particles Properties

- Properties dictated by method of manufacturing include:
  - Particle size and distribution
  - Shape
  - True density
  - Melting point
  - Specific surface area
  - Tensile strength
  - Polymorphic form
- Arising from these fundamental physicochemical properties are other properties such as:
  - Solubility
  - Dissolution rate

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Particles Properties

- **Polymorphism:**
  - the ability of crystals to exhibit different crystal lattice spacing under different conditions (temperature and moisture content)
  - can be evaluated by thermal techniques like **differential scanning calorimetry (DSC)**
- **Differential scanning calorimetry** is used to determine the energy requirements for rearranging molecules in the lattice as they convert from one form to another.
- The difference between polymorphic forms of the same substance can also be detected by assessing their **solubility characteristics**.

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PARTICLE INTERACTIONS

- Cohesion & Adhesion
- The Angle of Repose
- Tensile & Shear Stresses

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Particle Interactions

- The attraction between particles (**cohesion**) or between particles and a containing boundary (**adhesion**) influences the flow and packing of powders.
- If two particles are placed together, the cohesive bond is normally very much weaker than the mechanical strength of the particles themselves.
- This may be due to the distortion of the crystal lattice, which prevents the correct adlineation of the atoms or the adsorption of surface films.
- These prevent contact of the surfaces and usually but not always decrease cohesion.

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Particle Interactions

- Low cohesion is also the result of small area of contact between the surfaces.
  - On a molecular scale, surfaces are very rough, and the real area of contact will be very much smaller than the apparent area.
  - Finally, the structure of the surface may differ from the interior structure of the particle.

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Particle Interactions

- Nevertheless, the cohesion and adhesion that occur with all particles are appreciable. It is normally ascribed to nonspecific Van der Waal's forces, although, in moist materials, a moisture layer can confer cohesiveness by the action of surface tension at the points of contact.
  - For this reason, an increase in humidity can produce a sudden increase in cohesiveness and the complete loss of mobility in a powder that ceases to flow and pour.
  - The acquisition of an electric charge by frictional movement between particles is another mechanism by which particles cohere together or adhere to containers.

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Particle Interactions

- These effects depend on both the chemical and physical forms of the powder.
- They normally oppose the gravitational and momentum forces acting on a particle during flow and therefore become more effective as the weight or size of the particle decreases.
- Cohesion and adhesion increase as the size decreases because the number of points in contact in a given area of apparent contact increases.
- The effects of cohesion will often predominate at sizes less than 100 μm and powders will not pass through quite large orifices, and vertical walls of a limited height appear in a free surface.
- The magnitude of cohesion also increases as the bulk density of the powder increases.

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Particle Interactions

- Cohesion also depends on the time for which contact is made.
  - This is not fully understood but may be due to the gradual squeezing of air and adsorbed gases from between the approaching surfaces.
  - The result, however, is that a system that flows under certain conditions may cease to flow when these conditions are restored after interruption.
- This is of great importance in the storage and intermittent delivery of powders.
- Fluctuating humidity can also destroy flow properties if a water-soluble component is present in the powder.
- The alternating processes of dissolution and crystallization can produce very strong bonds between particles, which cement the mass together.

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Particle Interactions

Measurement of Cohesion & Adhesion Effects

- The measurement of the cohesion between two particles or the adhesion of a particle to a boundary is difficult, although several methods can be used.
- More commonly, these effects are assessed by studying an assembly of particles in the form of a bed or a heap.
- Flow and other properties of the powder are then predicted from these studies.

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Measurement of Cohesion & Adhesion Effects

- The most commonly observed and measured property of a heap is **the angle of repose**.
- **The angle of repose:**
  - is the maximum angle at which a free powder surface can be inclined to the horizontal.
  - can be measured in a number of ways.
- The angle depends to some extent on the method chosen and the size of the heap.

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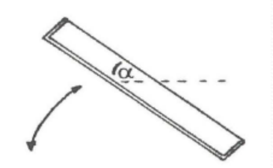
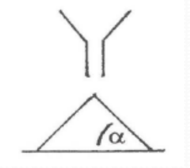
Measurement of the Angle of Repose (α)

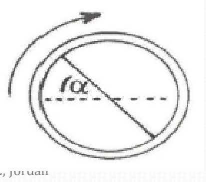
Tilting Box Method



Fixed Funnel Method



Revolving Cylinder Method



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Particle Interactions

The Angle of Repose

- Minimum angles are about 25°, and powders with repose angles of less than 40° flow well.
- If the angle is over 50°, the powder flows with difficulty or does not flow at all.
- The angle, which is related to the tensile strength of a powder bed, increases as the **particle shape** departs from sphericity and as the **bulk density** increases.
- Above 100 μm, it is independent of **particle size**, but below this value, it increases sharply.
- The effect of **humidity** on cohesion and flow is reflected in the repose angle.
  - Moist powders form an irregular heap with repose angles of up to 90°.

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Particle Interactions

Tensile Stress

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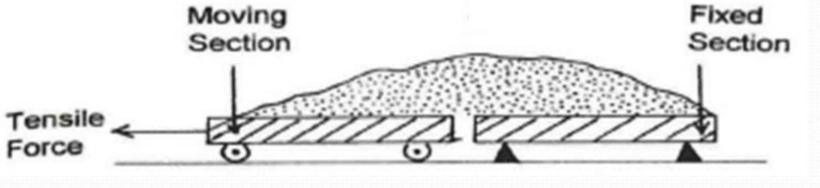
- A more fundamental measure is the **tensile stress necessary to divide a powder bed**.
- The powder may be dredged on to a split plate or, in a more refined apparatus, contained within a split cylinder and carefully consolidated.
- The stress is found from the force required to break the bed and the area of the divided surface.



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Particle Interactions

Tensile Stress

- Stresses of up to 100 N/m^2 are necessary to divide a bed of fine powders.
- Values increase as the **bulk density** increases.
- Changes in cohesiveness with time and the severe changes in the flow properties of some powders that occur when the relative humidity exceeds 80% can be assessed with this apparatus.

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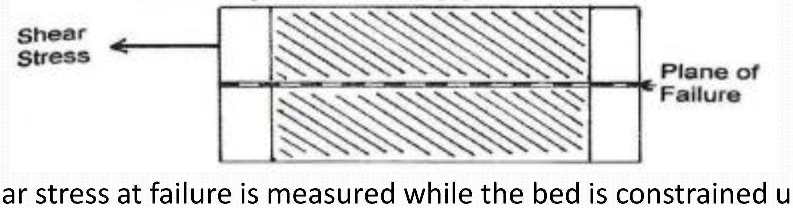
Particle Interactions

Shear Stress



- The shear stress at failure is measured while the bed is constrained under a normal stress.
- The relation between these stresses, a subject fully explored in the science of soil mechanics, is used in the design of bins and hoppers for the storage and delivery of powders.

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Particle Interactions

- The adhesion of particles to surfaces can be studied in a number of ways.
- Measurement of the size of the particles retained on an upturned plate is a useful qualitative test.
  - A common method measures the angle of inclination at which a powder bed slides on a surface, the bed itself remaining coherent.

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FLOW OF POWDERS

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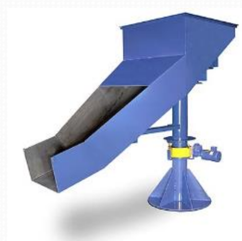
Flow Of Powders

- The gravity flow of powders in chutes and hoppers and the movement of powders through a constriction occur in tableting, encapsulation, and many processes in which a powder is subdivided for packing into final containers.



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Flow Of Powders

- In many cases, the accuracy of weight and dose depends on the ***regularity of flow***.
- The flow of powders is extremely complex and is influenced by many factors:
  - Orifice diameter
  - Particle size
  - Particle size distribution
  - Vibration and tapping

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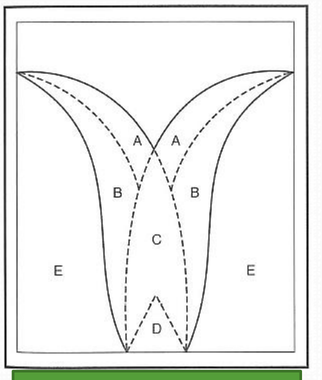
Flow Profile

- Particles slide over A while A itself slides over B.
- B moves slowly over the stationary region E.
- Material is fed into zone C and moves downward and inward to a tongue D.
- Here, in D, packing is less dense, particles move more quickly, and bridges and arches formed in the powder collapse.



Flow profile of granular solids through an aperture

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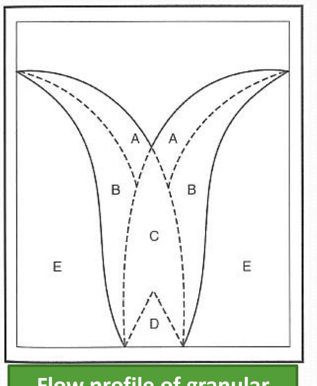
Flow Profile

- Unless the structure is completely emptied, powder in region E never flows through the aperture.
- If, in use, a container is partially emptied and partially filled, this material may spoil.
- If the container is narrow, region E is absent and the whole mass moves downward, and the central part of region C occupies the entire tube.



Flow profile of granular solids through an aperture

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Orifice Diameter

- For granular solids, the relation between mass flow rate, G, and the diameter of a circular orifice, D_o, is expressed by the equation

$$G = constant\ D_o^a H^b$$

where *H* is the height of the bed,
a & *b* are constants.

- For a wide variety of powders, the constant *a* lies between 2.5 and 3.0.
- If the height of the bed is several times that of the orifice, *H* lies between 0 and 0.05.
- The absence of a pressure-depth relation, already observed in a static bed, therefore, seems to persist in dynamic conditions.

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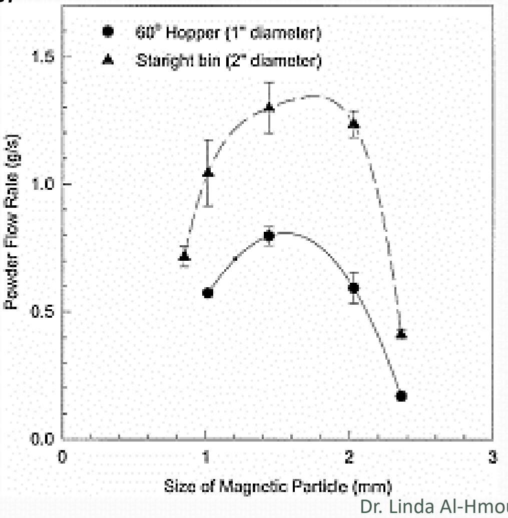
Particle Size

- The relation between mass flow rate and particle size is more complex.
- With an orifice of given size and shape. **the flow increases as the particle size decreases** until a maximum rate is reached.
- With further decrease in size and increase in cohesiveness, flow decreases and becomes irregular. **Arches and bridges** form above the aperture, and flow stops.
- The determination of the minimum aperture through which a powder will flow without assistance is a useful laboratory exercise.



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Flow Of Powders

Particle Size Distribution

- The distribution of particle sizes also affects the flow in a given system.
- Often, the removal of the finest fraction will greatly improve flow.
- On the other hand, the addition of very small quantities of fine powder can, in some circumstances, improve flow.
  - This is probably due to adsorption of these particles onto the original material, preventing close approach and the development of strong cohesional bonds.

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Flow Of Powders

Particle Size Distribution

- Magnesia and talc, for example, promote the flow of many cohesive powders.
  - These materials, which can be called **glidants**, are useful additives when good flow properties of a powder are required.

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Vibration and Tapping

- Vibration and tapping may maintain or improve the flow of cohesive powders by preventing or destroying the bridges and arches responsible for irregular movement or blockage.
- Vibration and tapping to initiate flow are less satisfactory because the associated increase in bulk density due to closer packing renders the powder more cohesive.

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Test Your Knowledge

- Intimate mixture of dry, finely divided drugs and/or chemicals that may be intended for internal or external use is called _______________.
- More spherical, larger, and denser particles have better ______.
- Flow is improved by _____ or adding ______.
- Flowability is estimated based upon a powder's _________.
- Porosity is an important determinant of ______.
- Examples of glidants to improve powder flowability include: __________________

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Test Your Knowledge

- Intimate mixture of dry, finely divided drugs and/or chemicals that may be intended for internal or external use is called **powder**.
- More spherical, larger, and denser particles have better **flowability**.
- Flow is improved by **granulation** or adding **glidants**.
- Flowability is estimated based upon a powder's **angle of repose**.
- Porosity is an important determinant of **bulk density**.
- Examples of glidants to improve powder flowability include: **talc and magnesia**.

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PACKING OF POWDERS

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Packing Of Powders

- Bulk density and porosity are terms used to describe the **degree of consolidation** in a powder.
- The porosity, ε, is the fraction of the total volume that is void, often expressed as a percentage. It is related to the bulk density, ρ_b, by the equation

$$\varepsilon = 1 - \frac{\rho_b}{\rho}$$

where ρ is the true density of the powder.

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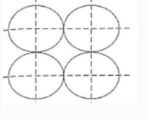
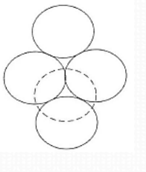
Packing Of Powders

- When spheres of equal size are packed in a regular manner, the porosity can vary from:
  - a **maximum of 46%** for a *cubical (open) arrangement*, to



  - a **minimum of 26%** for a *rhombohedral (closed) array*.



- For ideal systems of this type, the porosity is not dependent on the particle size.
- In practice, of course, packing is not regular.

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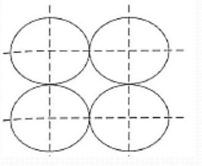
Packing Of Powders

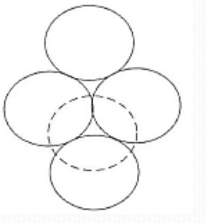
- **Cubic packing**, obtained when the next layer is placed directly on top of the four spheres above, is the ***most open packing***.

46%



- **Rhombohedral packing**, obtained when the next layer is built around the sphere shown in a broken line, is the ***closest packing***.

26%



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Packing Of Powders

- For coarse isodiametric particles with a narrow range of sizes, the porosity is remarkably constant at between 37% and 40%.
- With wider size distributions, the porosity decreases because some packing of fine particles in the interstices between the coarsest particles becomes possible.
- These effects are absent in fine powders.
  - Because of their more cohesive nature, the porosity increases as the particles become finer and variation in the size distribution has little effect.

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Packing Of Powders

- In any irregular array, the porosity increases as particle shape departs from sphericity because open packing and bridging become more common.
- A flaky material, such as crushed mica, packs with a porosity of about 90%.
- Roughness of the surface of the particles will increase porosity.

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Packing Of Powders

- In operations in which powders are poured, chance packing occurs and the porosity is subject to the **speed of the operation** and the **degree of agitation**.
- If the powder is **poured slowly**, each particle can find a stable position in the developing surface. Interstitial volumes will be small, the number of contacts with neighboring particles will be high, and the porosity will be low.
- If **pouring is quick**, there is insufficient time for stable packing, bridges are created as particles fall together, and a bed of higher porosity is formed.

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Packing Of Powders

- **Vibration** opposes open packing and the formation of bridges. It is often deliberately applied when closely packed powder beds are required.
- Packing at a **boundary** differs from packing in the bulk of a powder.
- The boundary normally creates a region of more open packing, several particle layers in extent. This is important when particles are packed into small volumes.

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Packing Of Powders

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- If the particles are relatively large, the region of expanded packing and low bulk density will be extensive, and for these conditions, the weight of material that fills the volume will decrease as the particle size increases.
- With finer powders, the opposite is true and cohesiveness causes the weight of powder that fills a volume to decrease as the particle size decreases.
- There is, therefore, some size of particle for which the capacity of a small volume is a maximum.
- This depends on the dimensions of the space into which the particles are packed.

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GRANULATION

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Granulation

- Granulation is a term given to a number of processes used to produce materials in the form of coarse particles.
- Granulation (*Aggregation*) is a process whereby powder materials are made into larger particles (*agglomerates* or *granules*).
- In pharmacy, it is closely associated with the preparation of compressed tablets.
- Ideally, granulation yields coarse isodiametric particles with a very narrow size distribution.

What are the advantages of this form?

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Advantages of Granules Form

1. Granules flow well.
2. They will feed evenly from chutes and hoppers.
3. They will pack into small volumes without great variation of weight.
4. Segregation in a mixture of powders is prevented if the mixture of powders is granulated.
5. Each granule contains the correct proportions of the components so that segregation of granules cannot cause inhomogeneity in the mixture.
6. The hazards of dust are eliminated, and granules are less susceptible to lumping and caking.
7. Finally, granular materials fluidize well and a material may be granulated to gain the advantages of this process.

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Granulation

- The starting materials for granulation vary from fine powders to solutions.
- Methods can be classified as either *wet* or *dry* granulation.
- In **dry granulation**, a very coarse material is comminuted and classified.
  - If the basic material is a fine powder, it is first aggregated by pressure with punches and dies to give tablets or briquettes, or by passage through rollers to give a sheet that is then broken.

Granulation

- In **wet methods**, a liquid binder is added to a fine powder.
  - If the proportion added converts the powder to a crumbly, adhesive mass, it can be granulated by forcing it through a screen with an impeller. The wet granules are then dried and classified.
  - If a wetter mass is made, it can be granulated by extrusion.
  - Alternatively, the powder can be rotated in a pan and granulating fluid is added until agglomeration occurs.
  - *Granule growth* depends critically on the amount of fluid added, and other variables, such as particle size, pan speed, and the surface tension of the granulating fluid, must be closely controlled.
- Granular materials are also prepared by *spray drying* and by *crystallization*.

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Granulation Methods

	Wet Granulation	Dry Granulation
Method Description	The powder formulation is mixed with water to cause particle adhesion, the resulting granules are then dried in the oven; binders may also be included to facilitate particle adhesion.	The powder formulation is compressed into pellets, slugs, or sheets that are milled, or broken down, to the appropriate particle size.
Method Disadvantages	cannot use water or heat sensitive powders	the granules are "weak" and have a wide size distribution that can be uneven.

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FLUIDIZATION

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Fluidization

- It occurs by moving fluid through a bed of particles.
- If the fluid velocity is low, the same situation is found when fluid is driven upward through a loose particulate (fixed) bed.
- At higher velocities, however, frictional drag causes the particles to move into a more expanded packing, which offers less resistance to flow.
- At some critical velocity, the particles are just touching and the pressure drop across the bed just balances its weight.
- This is the point of incipient fluidization, and beyond it true fluidization occurs, the bed acquiring the properties of surface leveling and flow.

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Fluidization

- If the fluid is a **liquid**,
  - increase in velocity causes the quiescent bed to rock and break, allowing individual particles to move randomly in all directions.
  - increase in velocity causes progressive thinning of this system.

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Fluidization

- In fluidization by **gases**, the behavior of the bed is quite different.
  - Although much of the gas passes between individual particles in the manner already described, the remainder passes in the form of bubbles so that the bed looks like a boiling liquid.
  - Bubbles rise through the bed, producing an extensive wake from which material is continually lost and gained, and breaking at the surface distributes powder widely.
  - This is an effective mixing mechanism, and any nonhomogeneity in the bed is quickly destroyed.
  - Rates of heat and mass transfer in the bed are therefore high.

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Fluidization

- **Bubble size** and **movement** vary in different systems.
- In general, both decrease as the particle size decreases.
- As the size decreases and the powder becomes more cohesive, fluidization becomes more difficult.
- Eventually, bubbles do not form and very fine powders cannot be fluidized in this way.
- The final stage of fluidization occurs at very high velocities when, in both liquid and gaseous systems, the particles become entrained in the fluid and are carried along with it.
- These conditions are used to **convey** particulate solids from one place to another.

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MIXING AND BLENDING

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Mixing and Blending

- **Blending** is *mixing* two or more powders until uniform.
- Mixing and blending may be achieved by rotating or shearing the powder bed.
- Mixing two or more components that may differ in composition, particle size, or some other physicochemical property is brought about through a sequence of events.
- Most powders at rest occupy a small volume such that it would be difficult to force two static powder beds to mix.

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Mixing and Blending

- **Mixing** Process Steps:
  1. The first is to **dilate** the powder bed.
  2. The second step, which may be concurrent with the first, is to **shear** the powder bed.
  - Ideally, shearing occurs at the level of planes separated by individual particles.
  - The introduction of large interparticulate spaces is achieved by rotating the bed.

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Mixing and Blending

Batch Mixers

- A V-blender or barrel roller are classical examples of systems which, by rotating through 360°, dilate the powder bed while, through the influence of gravity, shear planes of particles.

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Mixing and Blending

Batch Mixers

- A planetary mixer uses blades to mechanically dilate and shear the powder.

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Mixing and Blending

Continuous Mixer

- A *ribbon blender* uses a screw action to rotate and shear the bed from one location to another in a continuous process.

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Mixing and Blending

- Since the shearing of particles in a bed to achieve a uniform mix of blend is a statistical process, it must be monitored for efficiency.
- Sample thieves are employed to probe the powder bed, with minimal disturbance, and draw samples for analysis.
- These samples are then analyzed for the relevant dimension for mixing, for example, particle size, drug, or excipient content.
- Statistical mixing parameters have been derived based on the mean and standard deviation of samples taken from various locations in a blend at various times during processing.

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Mixing and Blending

- In large-scale mixers random number tables may be employed to dictate sample sites.
- There is a considerable science of sampling that can be brought to bear on this problem.
- The sample size for pharmaceutical products is ideally of the scale of the unit dose.
- This is relevant as it relates to the likely variability in the dose that in turn relates to the therapeutic effect.
- In the case of small unit doses, the goal should be to sample at a size within the resolution of the sample thief.

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Conclusion

- The origins, structure, and properties of particles within a powder dictate their dynamic performance.
- Gathering information on the physicochemical properties of the powders is a prerequisite for interpreting and manipulating their flow and mixing properties.
- Flow properties are important to many unit processes in pharmacy, including transport and movement through hoppers, along conveyor belts, in granulators, and in mixers.
- Ultimately, the packing and flow properties can be directly correlated with the performance of the unit dose.
- Filling of capsules, blisters, or tablet dies; compression of tablets; and dispersion of powder aerosols all relate to powder properties.

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