Particle Size Reduction (Lect. 6)

- **Reduction in particle size, increases the number of particles and the total surface area. The reduction in the particle size of a solid is accompanied by a great increase in the specific surface area of that substance.**

- **Comminution, reduction of the particle size of a solid substance to a finer state, is used to**

1. **facilitate crude drug extraction,**
2. **increase the dissolution rates of a drug,**
3. **aid in the formulation of pharmaceutically acceptable dosage forms, and**
4. **enhance the absorption of drugs.**

Increase in the number of particles

- **If a powder consists of cubes 1 mm on edge and it is reduced to particles 10 μm on edge, what is the number of particles produced?**
- **1 mm equals 1,000 μm.**
- **1,000/10 μm = 100 pieces produced on each edge; that is, if the cube is sliced into 100 pieces on the x-axis, each 10 μm long, 100 pieces result.**
- **If this is repeated on the y- and z-axes, the result is 100 × 100 × 100 = 1 million particles produced, each 10 μm on edge, for each original particle 1 mm on edge. This can also be written as $(10^2)^3 = 10^6$.**

Increase in surface area

- **What increase in the surface area of the powder is produced by decreasing the particle size from 1 mm to 10 μm?**
- **The 1-mm cube has six surfaces, each 1 mm on edge. Each face has a surface area of 1 mm^2. Because there are six faces, this is 6 mm^2 surface area per particle.**
- **Each 10-μm cube has six surfaces, each 10 μm on edge. Each face has a surface area of 10 × 10 = 100 μm^2. Because there are six faces, this is 6 × 100 μm^2, or 600 μm^2 surface area per particle.**
- **Since 10^6 particles resulted from comminuting the 1-mm cube, each 10 μm on edge, the surface area now is 600 μm^2 × 10^6, or 6 × 10^8 μm^2.**
- **To get every thing in the same units for ease of comparison, convert the 6 × 10^8 μm^2 into square millimeters as follows.**
- **Since there are 1,000 μm/mm, there must be $1{,}000^2$, or 1 million $\mu m^2/mm^2$. This is more appropriately expressed as 10^6 $\mu m^2/mm^2$,**

Increase in surface area

$$\frac{6\times10^{8}\,\mu m^{2}}{10^{6}\,\mu m^{2}/mm^{2}}=6\times10^{2}\,mm^{2}$$

- **The surface areas have been increased from**
- **6 mm² to 600 mm² by the reduction in particle size of cubes 1 mm on edge to cubes 10 µm on edge, a 100-fold increase in surface area. This can have a significant increase in the rate of dissolution of a drug product.**

Comminution of drugs

- **On a small scale**,
- **Trituration or comminution**
- **the pharmacist reduces the size of chemical substances by grinding with a mortar and pestle. A finer grinding action is accomplished by using a mortar with a rough surface (as a porcelain mortar) than one with a smooth surface (as a glass mortar). Grinding a drug in a mortar to reduce its particle size is termed trituration or comminution.**
- **(as a result of pressure and attrition).**

Levigation

- **Used in small-scale preparation of ointments and suspensions to reduce the particle size and grittiness of the added powders.**
- **A mortar and pestle or an ointment tile may be used.**
- **A paste is formed by combining the powder and a small amount of liquid (the levigating agent) in which the powder is insoluble.**
- **The paste is then triturated, reducing the particle size. The levigated paste may then be added to the ointment base and the mixture made uniform and smooth by rubbing them together with a spatula on the ointment tile (slab).**
- **Water, mineral oil and glycerin are commonly used levigating agents**

On a large scale

- Various types of **mills and pulverizers** may be used to reduce particle size. **Fitz Mill** comminuting machine with a product containment system. Through the grinding action of rapidly moving blades in the comminuting chamber, particles are reduced in size and passed through a screen of desired dimension to the collection container.

The collection and containment system

- protects the environment from chemical dust,
- reduces product loss, and
- prevents product contamination.

- **Pulverization by intervention**
- **is reduction of particle size with the aid of a second agent which can be readily removed from the pulverized product. This term applies to particle size reduction of camphor, which is otherwise difficult to triturate. It may be readily triturated when a few drops of alcohol or other volatile solvent are added. The pulverized camphor is readily recovered as the solvent evaporates.**

- **Special processes of particle size reduction**
- **These processes may be used to prepare powders for dosage forms include sublimation, freeze drying and spray drying.**
- **Freeze Drying:(Drying by sublimation, lyophillization)**
- **It refers to the removal of water by sublimation from frozen products at low temperatures.**
- **Freeze drying is usually carried out in temperature range of –10 to – 40ºC. It is used to dry biological products such as blood serum, plasma, certain antibiotics such as penicillin, and other substances that are heat-labile and cannot be dried by the usual application of heat.**

- **Spray drying:**
- **Is a process for converting solution or suspensions into dry, free-flowing powders in a single drying step. The solution or suspension is atomized or sprayed into an enclosed chamber into which heated air is also introduced. The atomization process produces very fine, generally spherical droplets with large surface areas that dry almost instantaneously.**
- **Materials sensitive to heat and/ or oxidation can be spray dried without degradation. These include heat-sensitive materials such as pepsin and vitamins A and D, and easily oxidized materials such as epinephrine and ascorbic acid.**

Blending of powders

- **When two or more powdered substances are to be combined to form a uniform mixture, it is best to reduce the particle size of each powder individually before weighing and blending.**
- **Depending on the *nature of the ingredients, the *amount of powder, and the *equipments, powders may be blended by**

a) **spatulation,**
b) **trituration,**
c) **sifting, and**
d) **tumbling.**

A- Spatulation

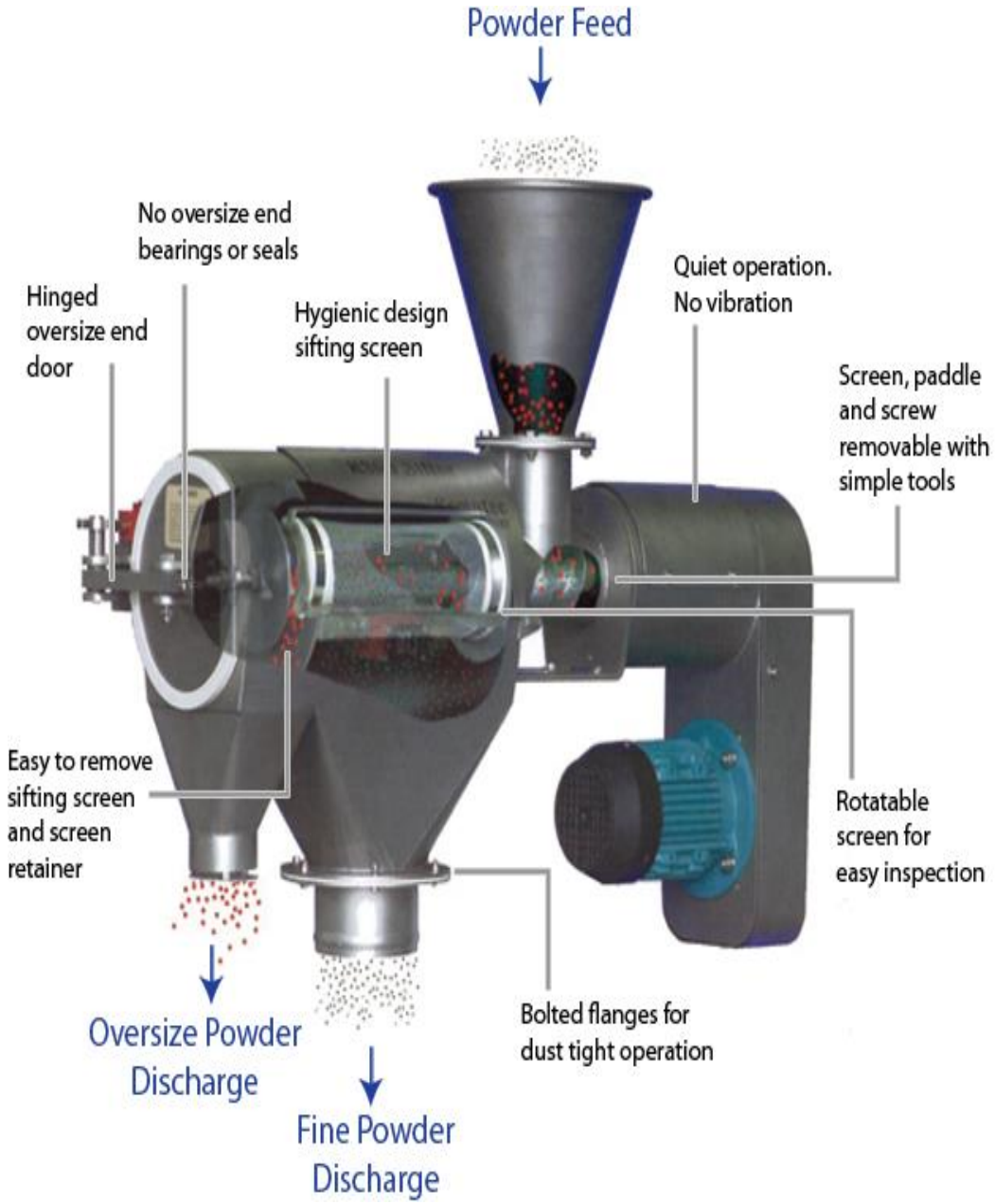
- Spatulation is blending small amounts of powders by movement of a spatula through them on a sheet of paper or an ointment tile.
- It is not suitable for large quantities of powders or for powders containing potent substances, because homogeneous blending is not as certain as other methods.
- Very little compression or compacting of the powder results from spatulation, which is especially suited to mixing solid substances that form eutectic mixtures (or liquefy) when in close and prolonged contact with one another.
- Substances that form eutectic mixtures when combined include phenol, camphor, menthol, thymol, aspirin, phenyl salicylate, and other similar chemicals. To diminish contact, a powder prepared from such substances is commonly mixed in the presence of an inert diluent, such as light magnesium oxide or magnesium carbonate, to separate the troublesome agents physically.

B- Trituration

- **Trituration may be employed both to comminute and to mix powders.**
- **If simple admixture is desired without the special need for comminution, the glass mortar is usually preferred.**
- **When a small amount of a potent substance is to be mixed with a large amount of diluent, the geometric dilution method is used to ensure the uniform distribution of the potent drug. This method is especially indicated when the potent substance and other ingredients are the same color and a visible sign of mixing is lacking. By this method, the potent drug is placed with an approximately equal volume of the diluent in a mortar and is 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 an equal volume of diluent to the powder mixture and repeating this until all of the diluent is incorporated. Some pharmacists add an inert colored powder to the diluent before mixing to permit visual inspection of the mixing process. (to ensure uniform distribution).**

C- sifting

- **Powders may also be mixed by passing them through sifters like those used in the kitchen to sift flour.**
- **Sifting (sieving) results in a light, fluffy product.**
- **This process is not acceptable for the incorporation of potent drugs into a diluent powder.**



D-Tumbling

- **Another method of mixing powders is tumbling the powder in a rotating chamber.**
- **Special small-scale and large-scale motorized powder blenders mix powders by tumbling them**
- **Mixing by this process is thorough but time consuming. Such blenders are widely employed in industry, as are mixers that use motorized blades to blend powders in a large vessel.**

Problems associated with particle size reduction

Segregation: is an undesirable separation of the different components of the powder mixture (blend) due to differences in density and size.

- Segregation may occur by:
- Sifting or percolation

Fine particles tend to sift or percolate through coarse particles and end up at the bottom of the container and actually "lift" the larger particles to the surface.

- Air entrapment (fluidization),

Fine, aerated powders with differences in particle size or density may result in a striation pattern and may occur during powder transfer.

- Particle entrapment (dusting).

Dusting occurs when the finer, lighter particles remain suspended in air longer and do not settle as quickly as the larger or denser particles.

MEDICATED POWDERS

- **Some medicated powders are intended to be used**

1- Internally Most powders for internal use .

- **Some powders are intended to be inhaled for local and systemic effects.**
- **Other dry powders are commercially packaged for constitution with a liquid solvent or vehicle,**

some for administration orally, are taken orally after mixing with water or in the case of infants in their infant formulas

others for use as an injection,

others for use as a vaginal douche,

2-Externally

Medicated powders for external use are dusted on the affected area from a sifter-type container or applied from a powder aerosol. Powders intended for external use should bear a label marked EXTERNAL USE ONLY or a similar label.

Medicated powders for oral use

1. Medicated powders for oral use may be intended for local effects (e.g., laxatives) or systemic effects (e.g., analgesics)
2. and may be preferred to counterpart tablets and capsules by patients who have difficulty swallowing solid dosage forms.
3. The doses of some drugs are too bulky to be formed into tablets or capsules of convenient size, so they may be administered as powders. For administration, they can be mixed with a liquid or soft food.
4. Powders taken orally for systemic use may be expected to result in faster rates of dissolution and absorption than solid dosage forms, because there is immediate contact with the gastric fluids; however, the actual advantage in terms of therapeutic response may be negligible or only minimal, depending on the drug release characteristics of the counterpart products.

Medicated powders for oral use

5. Some medications, notably antibiotics for children, are intended for oral administration as liquids but are relatively unstable in liquid form. They are provided to the pharmacist by the manufacturer as a dry powder or granule for constitution with a specified quantity of purified water at the time of dispensing. Under labeled conditions of storage, the resultant product remains stable for the prescribed period of use, generally up to 2 weeks.

A primary disadvantage of the use of oral powders is the undesirable taste of the drug.

Aerosol powders

- Some medicated powders are **administered by inhalation with the aid of dry-powder inhalers**, which deliver **micronized particles** of medication in **metered quantities**
- Most of these products are used in the treatment of **asthma** and other bronchial disorders that require distribution of medication **deep in the lung**. To accomplish this, the particle size of the micronized medication is prepared in the range of **1 to 6 µm in diameter.**

- In addition to the therapeutic agent, these products contain inert propellants and pharmaceutical diluents, such as crystalline alpha-lactose monohydrate, to aid the formulation's flow properties and metering uniformity and to protect the powder from humidity.

- They administered in a metered-valve container that apply a specific dose (Each dose is delivered through the mouthpiece upon activation of the aerosol unit's valve) or can use a powder blowers or insufflators

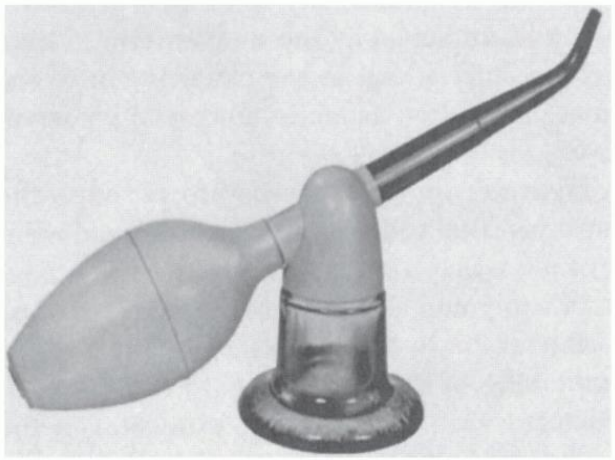
Powder blowers or insufflators

Powder blowers or insufflators may be used to deliver dry powders to various parts of the body, e.g., nose, throat, lung, vagina.

***Depression of the device's rubber bulb causes**

***turbulence of the powder in the vessel,**

***forcing it out through the orifice in the tip**



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