SEVENTH EDITION

PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS

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Physical Pharmacy Capsule 6.2

Particle Size Reduction

Comminution, the process of reducing the particle size of a solid substance to a finer state of subdivision, is used to facilitate crude drug extraction, increase the dissolution rates of a drug, aid in the formulation of pharmaceutically acceptable dosage forms, and enhance the absorption of drugs. The reduction in the particle size of a solid is accompanied by a great increase in the specific surface area of that substance. An example of the increase in the number of particles formed and the resulting surface area is as follows.

EXAMPLE

Increase in Number of Particles

If a powder consists of cubes 1 mm on edge, and it is reduced to particles 10 μ on edge, what is the number of particles produced?

1. 1 mm equals 1000 μ.
2. 1000 μ/10 μ = 100 pieces produced on each edge, i.e., if the cube is sliced into 100 pieces, each 10 μ long, 100 pieces would result.
3. If this is repeated in each of the other two dimensions, i.e., to include the x, y and z axes, then there would be 100 × 100 × 100 = 1,000,000 particles produced, each 10 μ on edge, for each original particle 1 mm on edge. This can also be written $[(10^2)^3 = 10^6]$.

Increase in Surface Area

What is the increase in the surface area of the powder by decreasing the particle size from 1 mm to 10 μ?

1. The 1 mm cube has 6 surfaces, each 1 mm on edge. Each face has a surface area of 1 mm^2. Because there are 6 faces, this is 6 mm^2 surface area for this one particle.
2. Each 10 μ cube has 6 surfaces, each 10 μ on edge. Each face has a surface area of 10 × 10 = 100 μ^2. Because there are 6 faces, this is 6 × 100 μ^2, or 600 μ^2 surface area for this one particle. Since there are 10^6 particles that resulted by comminuting the 1 mm cube into smaller cubes, each 10 μ on edge, there would be 600 $\mu^2 \times 10^6$ or 6×10^8 μ^2 surface area now.
3. To get everything in the same units for ease of comparison, we convert the 6×10^8 μ^2 into mm^2 as follows.
4. Since there are 1,000 μ/mm, there must be $1{,}000^2$, or 1,000,000 μ^2/mm^2. This is more appropriately expressed as 10^6 μ^2/mm^2,

$$\frac{6 \times 10^8 \mu^2}{10^6 \mu^2/mm^2} = 6 \times 10^2 \text{ mm}^2$$

As is evident here, the surface areas have been increased from 6 mm^2 to 600 mm^2 by the reduction in particle size of cubes 1 mm on edge to cubes 10 μ on edge (i.e., a hundred-fold increase in surface area). This can have a significant increase in the rate of dissolution of a drug product.

"figure 8" track is commonly used to incorporate the materials. Mineral oil and glycerin are commonly used levigating agents.

Blending 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 upon the nature of the ingredients, the amount of powder to prepare, and the equipment available, powders may be blended by spatulation, trituration, sifting, and tumbling.

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. The method is not suitable for large quantities of powders or for powders containing potent substances, because homogeneous blending is not as certain as through other methods. Very little compression or compacting of the

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powder results from this method. This method is especially suited to the mixing of solid substances that form eutectic mixtures (or liquify) when in close and prolonged contact with one another. Substances that form eutectic mixtures when combined include phenol, camphor, menthol, thymol, aspirin, phenylsalicylate 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 physically the troublesome agents.

Trituration may be employed both to comminute and to mix powders. If simple admixture is desired without 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 and the nonpotent ingredients are of the same color and a visible sign of mixing is lacking. By this 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. Some pharmacists add an inert colored powder to the diluent before mixing to permit visual inspection of the mixing process.

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

Another method of mixing powders is tumbling the powder enclosed in a rotating container. Special small-scale and large-scale motorized powder blenders have been developed which mix powders by a tumbling motion (Fig. 6.2). Mixing by this process is thorough, although time-consuming. Such blenders are widely employed in industry as are mixers that utilize motorized blades to blend powder contained in a large mixing vessel.

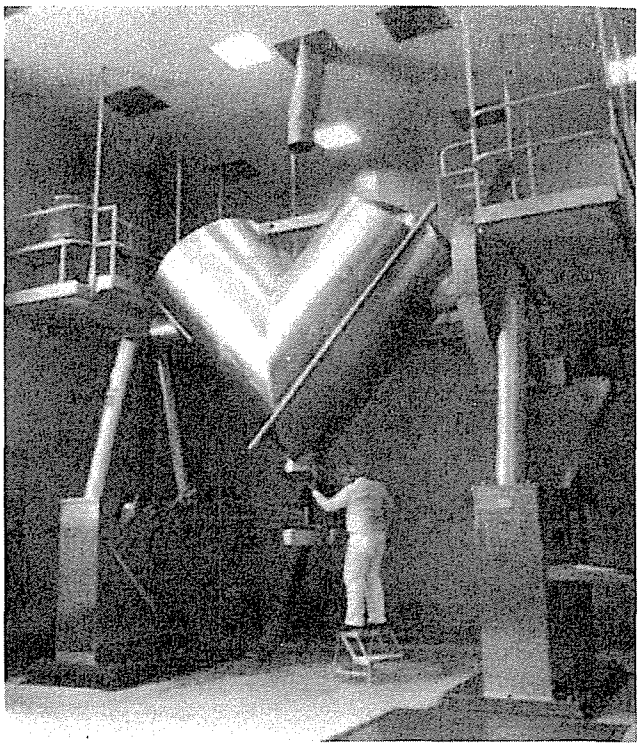

Fig. 6.2 *Industrial size solid state processor or "twin shell" blender used to mix solid particles. (Courtesy of Abbott Laboratories.)*

Medicated Powders

Some medicated powders are intended to be used internally; others externally. Most powders for internal use are taken orally after mixing with water. Some powders are intended to be inhaled into

powders are commercially packaged for constitution with a liquid solvent or vehicle, some for administration orally, others for use as an injection, and still others for use as a vaginal douche. 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 an EXTERNAL USE ONLY or a similar label.

Medicated powders for oral use may be intended for local effects (e.g., laxatives) or systemic effects (e.g., analgesics) and may be preferred over counterpart tablets and capsules by patients who have difficulty swallowing solid dosage forms. Oral powders for systemic use may be expected to result in faster rates of dissolution and absorption than solid dosage forms since there is immediate contact with the gastric fluids; however, the actual advantage in terms of therapeutic response may be negligible or only minimal depending upon the drug release characteristics of the counterpart products. A primary disadvantage to the use of oral powders is the undesirable taste of the drug.

There are some medications, notably antibiotics

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