UNIT: 1 **(SIZE REDUCTION)**

CLASS:5

TOPIC: OBJECTIVES, MECHANISMS & LAWS GOVERNING SIZE REDUCTION

SIZE REDUCTION

Size reduction is a process of reducing large solid unit masses (vegetable or chemical substances) into small unit masses, coarse particles or fine particles.

Normally, pharmaceutical powders are polydisperse, i.e., consisting particles of different sizes. Polydisperse powders create considerable difficulties in the production of dosage forms. Particles of monosize (equal size) may be ideal for pharmaceutical purposes. In practice, powders with narrow range of size distribution can obviate the problems in processing them further. Size reduction alone is not sufficient to obtain mono-size or narrow size range powder. Therefore, size reduction and size separation should be combined to obtain powders of desired size.

Size reduction process is also termed as comminution or diminution' or pulverisation. Normally, size reduction may be achieved by two methods, namely precipitation or mechanical process.

In the *precipitation method,* the substance is dissolved in an appropriate solvent. Subsequently, it is finely precipitated by the addition of another solvent, which is miscible with the first, but in the later the substance is insoluble. This method is suitable for the production of raw materials and bulk drugs. Inorganic chemicals, such as calcium carbonate, magnesium carbonate and yellow mercuric oxide, are prepared by precipitation method.

In the *mechanical process*, the substance is subjected to mechanical forces using grinding equipment (ball mill, roller mill, colloid mill etc.). In general, dry grinding or milling is used in the production of tablets and capsules, while wet grinding is used in the preparation of suspensions, emulsions and ointments. The method of milling is applied either in the production of raw materials or as a part of the production cycle in the manufacture of dosage forms.

Advantages and objectives of size reduction

(1). Content uniformity: Mixing of different ingredients can be effective, if the particle size is uniform and small. Size reduction ensures this objective. Particles of optimum size are desirable for effective mixing.

As the size of particles is small, the number of particles per unit weight (dose) is large. The larger the number of particles, the better is the mixing. Thus, better content uniformity can be obtained for a given dose. This is particularly important in formulations containing potent and low dose drugs.

(2). Uniform flow: Smaller particle size and controlled size distribution promote the flow of the powder into dies during compression of tablets. The same principles are used in the production of capsules.

(3). Effective extraction of drugs: Smaller particles allow rapid penetration of menstruum or solvent into the tissue or cells of vegetable and animal origin (liver and pancreas). As a result, extraction or leaching of active constituents becomes effective and complete in preparation of galenicals. The time required for extraction can be shortened. For example, pancreas is subjected to grinding action for the extraction of insulin.

Normally, fine powders are preferred for compound powders, while moderately coarse powders are, used for the, preparation of tinctures. Coarse powder without fines is employed in percolation process.

(4). Effective drying: Drying of a granular mass can be rapid and effective, if the size of granules is small and uniform. Such techniques are used in the production of tablets. Similarly drying of medicinal plant parts can be quick and fast after size reduction.

(5). Improved physical stability: In case of suspensions and emulsions, the rate of sedimentation decreases to a large extent if particle size is small.

(6). Improved dissolution rate: Size reduction increases surface area, which facilitates intimate contact of solid particles and gastric or intestinal juices. Thus, the rate of dissolution enhances tools. For example, size reduction of griseofulvin led to the development of oral dosage regimen with a dose half that of the originally marketed product. In case of insufflations (preparations inhaled directly into the lungs), the drug should be usually smaller than about 5 µm. Micronized powder of aspirin is used in the preparation of tablets, microfined aspro (analgesic and anti-inflammatory agent).

(7). Improved rate of absorption: The smaller the particle size, the faster is the absorption, because of enhanced dissolution. Chloramphenicol has been shown to absorb faster when given with particle size of 50 µm compared to particle size of 400 µm. Keeping in view of the advantages, pharmacopoeia specifies particle size as a quality control. For example, griseofulvin (antifungal antibiotic) should have surface area of not less than 1300 to 1700 metre square per kilogram (as per IP). If it is less, the absorption of the drug decreases. Sulphonamides attain their antibacterial activity at powder sizes of about 1 µm or below. Increased antiseptic action has been demonstrated when the particle size of calomel has been reduced.

The disadvantages of size reduction process are as follows.

(1) Drug degradation: Drug decomposition is possible due to the heat produced during milling. Thermo-labile substances are the most affected. The increased surface area also facilitates drug decomposition owing to enhanced dissolution.

Cooling support systems are provided to decrease the heat in milling equipment. Drugs containing waxy materials become soft due to heat generated during milling. Therefore, the feed is chilled before milling.

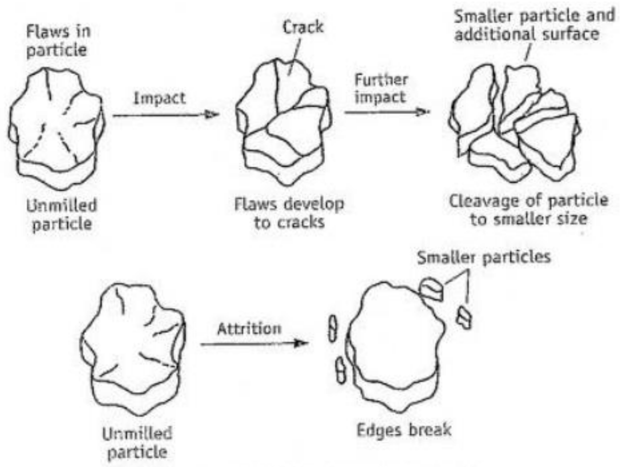
(2) Poor mixing: Normally, very small particles possess strong cohesive forces, hence, aggregation of particles is possible. Aggregation inhibits the effective blending of different additives. An increase in surface area may promote the adsorption of air, which may inhibit wettability of the drug during production. Therefore, optimum particle size is desirable to improve blending and to avoid poor mixing.

(3) Contamination: During milling and grinding, the grinding sur- faces wear off (examples are ceramic or iron equipment), the particles of which are present as impurities in the powder. Such type of mills should be avoided, when drugs of high purity are required.

The importance of size reduction is so profound that it is used in the production of all dosage forms' such as tablets, capsules, suspensions, emulsions, injections and galenicals. The principles of size reduction, construction and working of equipment are discussed in this chapter. The equipment, which are used in pharmaceutical industry, are given importance.

MECHANISMS OF SIZE REDUCTION

The mechanism of size reduction may vary with the nature of material. Therefore, each drug may require a separate treatment. However, the general mechanism may be described as follows.



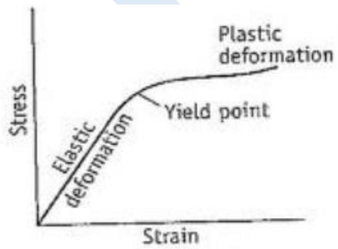
Mechanism of size reduction

Particles, be it amorphous or crystalline, will have flaws to a definite degree. These constitute weak parts in the particles. When sufficient stresses such as impact, shear and compression are applied, the weak flaws develop into cracks, which eventually lead to cleavage (Figure a). Thus, smaller particles are obtained with additional surface area. When stress in the form of attrition is applied, the particle surfaces chip and produce small particles (Figure b).

THEORIES OF COMMINUTION

Mechanical Behaviour of Solids

When various modes of stress are applied on a powder, the particles get strained. This stress-strain relationship is shown in Figure.



Stress-strain curve for a solid.

- In Figure, the initial linear portion is defined by Hooke's law. It states that stress is proportional to strain. The slope of linear portion represents *Young's modulus*. It expresses the stiffness or softness in megapascals.
- If the force of impact (stress) does not exceed the elastic limit (region of Hooke's law), the material is reversibly deformed. When the force is removed, the particle returns to original condition. The elastic limit is known as yield value. The stress energy in the deformed particle appears as heat. Example is plastic material such as polymer.

- The stress-strain curve becomes nonlinear at the yield point. This is a measure of the resistance to permanent deformation.
- Beyond the yield point, the region represents irreversible plastic deformation.
- The area under the curve represents the fracture toughness (or modulus of toughness). This is an approximate measure of the impact strength of the material. Fracture of a particle can be obtained when the force exceeds the elastic limit.

Theories of Size Reduction

(1) According to Griffith theory, all solids contain flaws and microscopic cracks. A *flaw* is any structural weakness that may develop into a crack under strain. The weakest flaw in a particle determines its fracture strength. It controls the number of particles produced by fracture. The particles with the weakest flaw fractures most easily and produce largest possible pieces. In the next step. another weakest flaw fractures. This process continues until all flaws are fractured. The particle size produced in this process may not be the desirable one. However. Griffith theory is simple and explains the size reduction process reasonably.

According to Griffith theory, the amount of force to be applied depends on the crack length and focus of stress at the atomic bond of the crack apex. This relationship may be mathematically expressed as:

$$T = \sqrt{\frac{Y\varepsilon}{C}} \qquad (1)$$

Where, T = tensile strength, MPa

Y = Young's modulus, MPa

ε = surface energy of the wall of crack, J/m²

C = critical crack path required for fracture, m

A linear relationship (equation 1) between the square of tensile strength of minerals and the critical height for drop weight impact suggests that the square of tensile strength is a useful criterion of impact fracture.

(2) If flaws are not present in a particle; the force of milling produces new flaws. The useful work in milling is proportional to the length of new crack formed. The mechanism of creating new flaws in a particle is as follows.

Usually, the surface of particles is irregular. The applied force is initially taken on the high portion of the surface. As a result, high stress and increased temperature may be set up locally in the particle. The bonds at this place become weak, which may be responsible for creating flaws. The particle further absorbs applied strain energy and is de- formed. The strain energy required to extend the crack to fracture is proportional to the length of the crack formed. This energy is supplied by the flow of the residual strain energy to the crack.

(3) Not all materials exhibit this type of brittle behaviour. They resist fracture even at much larger stresses, because these are tougher. They undergo plastic flow, which allows strain energy relaxation without crack propagation. When plastic flow occurs, atoms or molecules slip over one another and this process of deformation requires energy.

ENERGY FOR COMMINUTION

Size reduction begins with the opening of small flaws that were initially present. Based on the probability, larger particles may have numerous flaws and readily fracture when compared to smaller particles with fewer flaws. The supplied energy is used to:

- Increase new surface area from flaws.
- Initiate flaws or cracks in the particle.

This phenomenon is observed generally in fine grinding...

Most efficient mills utilise less than 1% of the energy input to fracture particles or create new surfaces. The rest of energy is dissipated in:

1. Elastic deformation of unfractured particles.

2. Transport of material within the milling chamber.

3. Friction between the particles.

4. Friction between the particles and mill.

5. Heat.

6. Vibration and noise.

7. Inefficiency of transmission and motor.

Energy input and utilisation are important factors to estimate, the efficiency of a mill for a given material. A number of theories has been proposed to establish a relationship between energy input and the degree of size reduction produced. The energy required to reduce the size of the particles is inversely proportional to the size raised to some power. This may be expressed mathematically as;

$$\frac{dE}{dD} = \frac{-C}{D^n} \qquad (2)$$

Where, E = amount of energy (work done) required to produce a change, kW.h

D = size of unit mass, µm

C = constant. W.h

N = constant

Equation (2) may be written (when n = 1) as:

$$E = C \, \text{Ln}\left[\frac{d_i}{d_n}\right] \qquad (3)$$

Where, d_i = size of the feed. µm

d_n = size of the product, µm

In equation (3), $(\frac{d_i}{d_n})$ is known as *reduction ratio*. The usefulness of equation (3) is that it satisfies various laws proposed. These are:

For n = 1.0. equation (3) becomes Kick's law

For n = 1.5. equation (3) becomes Bond's law

For n = 2.0. equation (3) becomes Rittinger's law

Rittinger's Theory

According to the Rittinger's hypothesis, energy, E required for size reduction of unit mass is directly proportional to the new surface area produced. It is expressed as:

$$E = K_R (S_n - S_i) \qquad (4)$$

Where, S_i = initial specific surface area, μm²/μm³

S_n = new specific surface area, μm²/μm^3

K_R = Rittinger's constant, energy per unit area, kW.h./μm³

E = amount of energy (work done), kW.h

It is mostly applicable to brittle materials undergoing fine milling. Rittinger's theory ignores particle deformation before fracture.

Bond's Theory

According to the Bond's theory, the energy used in crack, propagation is proportional to the new crack length produced. It states that the energy used for deforming or fracturing a set of particle of equivalent shape is proportional to the change in particle dimensions. According to Bond's theory, the equation can be written as:

$$E = 2\ K_B \left[\frac{1}{\sqrt{d_n}} - \frac{1}{\sqrt{d_i}}\right] \qquad (5)$$

Where, K_B = Bond's work index, energy per unit mass, kW.h .$\sqrt{\mu m}$

d_i = initial diameter of particles, μm

d_n = new diameter of particles, μm

Bond's work index is the work required to reduce a unit weight from, a theoretical infinite size to 80% passing 100 μm. According to this theory, the energy used in crack propagation is proportional to the new crack length produced. This law is useful for rough mill, sizing. The work index is useful for comparing the efficiency of milling operations.

Kick's Theory

According to the Kick's theory, the energy used in deforming or fracturing a set of particles of equivalent shape is proportional to the ratio of the change in size. It may be expressed as:

$$E = K_K \ln \frac{d_i}{d_n} \qquad (6)$$

Where, K_k = Kick's constant, energy per unit mass, kW.h

d_i = diameter of the particle in the initial stage, μm

d_n = diameter of the new particle, μm

The Kick's proposal was developed on a stress-strain diagram for cubes under compression. It assumes that the material has flaws distributed throughout its internal structure. For crushing (compression) of large particles, Kick's equation (equation 6) is more useful.

Equations (1 to 6) apply precisely only under the condition that all the energy is transferred into surface energy.

Size reduction of a material is alone not sufficient to obtain powder of desired size. It is followed by separation.

MCQ Each question carries 1marks

Which mechanism is utilized when particle concussion by a single rigid force?
a) Impact
b) Compression
c) Shear
d) Tear
Answer: a

What is the mechanism of nut cracker?
a) Impact
b) Compression
c) Shear
d) Tear
Answer: b

Why is uniform particle size important?
a) Color improvement
b) Product stability
c) Flavor improvement
d) Color and flavor improvement
Answer: b

Which of the following is a size reduction unit operation in liquids?
a) Milling
b) Mixing
c) Grinding
d) Homogenization
Answer: d

. What are the factors affecting size reduction?

a) Shape and size

b) Temperature

c) Pressure

d) Viscosity

Answer: a

Each question carries 2marks

1. It is essential to include a sieve in the size reduction equipment. Why?
2. Size reduction of vegetable matter is essential for the extraction of crude drugs. Explain.
3. It is difficult to obtain uniform sized product during milling without the use of sieves. Why?
4. Differentiate the mechanisms, attrition and impact in size reduction.
5. Size reduction of powders is not possible, if particles do not contain flaws, or cracks. Explain
6. List the areas in which size reduction equipment is used in tablet Production.
7. Differentiate dry grinding and wet grinding. State Rittinger's law.

Each question carries 5marks

1. List the laws governing size reduction. What is work index
2. How is energy utilised in size reduction accounted for?

Each question carries 10 marks

1. Explain the theories related to the size reduction of a powder.
2. Explain the advantages and disadvantages of size reduction process.
3. State and explain the laws governing size reduction.
4. Describe the mechanisms and modes of size reduction of solid drugs.