CHAPTER 5

SIZE REDUCTION

Author

Miss Poonam Dashrath Dighe,
Assistant professor, Dept of Pharmaceutics,
Amruthvahini College of Pharmacy, Sangamner,
Ghulewadi, Maharashtra, India

Abstract

Size reduction is a fundamental unit operation in pharmaceutical manufacturing, crucial for enhancing drug dissolution, absorption, and overall therapeutic efficacy. This process involves breaking down larger particles into smaller ones, often to achieve specific particle size distributions tailored to the needs of different dosage forms. Various mechanisms of size reduction are employed, including impact, attrition, compression, and cutting. The choice of size reduction method depends on the material properties, desired particle size, and scale of operation. Common equipment used in pharmaceutical size reduction includes ball mills, hammer mills, jet mills, and roller mills, each with its unique operating principles and applications. Factors affecting size reduction efficiency include material hardness, feed rate, and equipment design. The concept of critical size in milling is explored, along with methods for controlling and optimizing the size reduction process. Understanding particle size analysis techniques is essential for quality control and ensuring the consistency of the final product. Size reduction not only impacts the physical properties of materials but also influences their chemical and biological behavior, making it a critical consideration in drug formulation and manufacturing.

Keywords: *Comminution, Particle size distribution, Milling equipment, Process optimization, Dissolution enhancement, Quality control*

Learning Objectives

After completion of the chapter, the student should be able to:

- Define size reduction and explain its importance in pharmaceutical manufacturing.
- Describe the principles and mechanisms of size reduction.
- Identify and explain the various methods of size reduction used in pharmaceuticals.
- Compare and contrast different types of size reduction equipment.
- Discuss the factors affecting the efficiency of size reduction processes.
- Explain the concept of particle size distribution and its measurement techniques.
- Analyze the impact of size reduction on drug dissolution and bioavailability.

This process of conversion of raw material to useful product comprises many steps. Some steps are required to make raw materials ready for processing. Some steps are required to bring the final product to desired form. These unique and distinctive steps are called unit operations

Properties of unit operations:

- They are physical in nature.
- They are used invariantly in all chemical industries (approximately)
- For a specific unit operation basic concept and principle behind it as same in all industries.
- But may be differ in method of application

Unit operation may also be called separation process. The separation is generally based on any specific property called driving force.

This driving force is the deviation of that property from the equilibrium. When the driving force is high i.e. deviation from equilibrium is large separation is easy. When equilibrium achieved separation stops as equilibrium is the condition in which netflow of the property across the system is zero. For example if the separation is based on concentration and the concentration of the species is same on both the side there will no movement meaning thereby no separation.

Classification of unit operations

Heat Transfer Operation: Unit operations where temperature difference is driving force.
Mass Transfer Operations: Unit operations where concentration gradient is driving force.
Fluid Flow Operations: Unit operations where momentum gradient is driving force.
Mechanical Operations: Operations based on some external mechanical force.
Some important unit operations carried in the pharmaceutical industries are:- Distillation, Drying, Evaporation, Gas Absorption & Desorption, Liquid-Liquid Extraction, Solid-Liquid Extraction (Leaching), Crystallization, Adsorption etc

Size reduction (or Comminution)

Definition

Size reduction or *comminution* is the process of reducing substances to smaller particles.

Objectives

1. Size reduction leads to increase of surface area.

Example-I: The rate of dissolution of solid drug particles increases many folds after size reduction. Griseofulvin, an antifungal drug, when administered in its micronized form shows around five times better absorption.

Example-II: The absorptive power of charcoal and kaolin increases after size reduction due to increase in surface area.

2. Size reduction produces particles in narrow size range. Mixing of powders with narrow size range is easier.
3. Pharmaceutical suspensions require finer particle size. It reduces rate of sedimentation.
4. Pharmaceutical capsules, insufflations (i.e. powders inhaled directly into the lungs), suppositories and ointments require particles size to be below 60μm size.

Factors affecting size-reduction

The pharmaceutical industry uses a great variety of materials, including chemical substances, animal tissues and vegetable drugs.

A. Factors related to the nature of raw materials

Hard materials: Hard materials like pumice and iodine are most difficult to comminute. During size reduction these types of materials will produce abrasive wear of milling surfaces, which will then contaminate the material.

Fibrous materials: Crude drugs obtained from plants like glycyrrhiza, rauwolfia, ginger etc. are fibrous in nature and cannot be crushed by pressure. So they may be size-reduced by cutter mill.

Friable materials: Sucrose and dried filter cakes are friable (i.e. brittle) hence they are easy to comminute by hammer mill or fluid energy mill.

Plastic materials: Synthetic gums, waxes and resins become soft and plastic during milling. These low melting substances should be chilled (made cold) before milling. These types of materials are milled by using hammer mill and fluid energy mill.

Hygroscopic materials: Hygroscopic materials absorbs moisture rapidly hence they must be comminuted inside a closed equipment like ball-mill.

Thermolabile materials: Thermolabile materials like vitamins and antibiotics are milled inside chilled equipment.

Inflammable materials: Fine dust, such as dextrin, starch and sulphur, is a potential explosive mixture under certain conditions. All electrical switches should be explosive proof and the mill should be earthed properly.

Particle size of the feed: For a mill to operate satisfactorily, the feed should be of proper size.

Moisture content: Presence of more than 5% moisture hinders the milling process and produces a sticky mass.

B. Factors related to the nature of the finished product

Particle size: Moderately coarse powders may be obtained from various impact mill. If very fine particles like micronized particles of griseofulvin may be obtained from fluid energy mill.

Ease of sterilization: When preparations are intended for parenteral (injection) purpose and ophthalmic uses, size reduction must be conducted in a sterile environment. Mills should be sterilized by steam before use.

Contamination of milled materials: In case of potent drugs and low dose products, contamination of the products should be avoided. Equipment free from wearing (e.g. fluid energy mill) may be used in this case.

Laws governing energy and power requirements of mills

During size reduction energy is supplied to the equipment (mill). Very small amount of energy (less than 2%) actually produce size reduction. Rest of the energy is dissipated (wasted) in:

(i) Elastic deformation of particles
(ii) Transport of material within the milling chamber
(iii) Friction between the particles
(iv) Friction between the particles and mill

(v) Generation of heat
(vi) Vibration and noise.
(vii) Inefficiency of transmission and motor.

Theories of milling

A number of theories have been proposed to establish a relationship between energy input and the degree of size reduction produced.

Rittinger's theory

Rittinger's theory suggests that energy required in a size reduction process is proportional to the new surface area produced.

$$E = K_R (S_n - S_i)$$

where, E = energy required for size reduction
K_R = Rittinger's constant
S_i = initial specific surface area
S_n = final specific surface area

Application: It is most applicable in size reducing brittle materials undergoing fine milling.

Bond's theory

Bond's theory states that the energy used in crack propagation is proportional to the new crack length produced

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

where, E = energy required for size reduction
K_B = Bond's work index
d_i = initial diameter of particles
d_n = final diameter of particles

Application: This law is useful in rough mill sizing. The work index is useful in comparing the efficiency of milling operations.

Kick's theory

Kick's theory states that the energy used in deforming (or fracturing) a set of particles of equivalent shape is proportional to the ratio of change of size, or:

$$E = K_K \log \frac{d_i}{d_n}$$

where, E = energy required for size reduction

K_K = Kick's constant

d_i = initial diameter of particles

d_n = final diameter of particles

Application: For crushing of large particles Kick's theory most useful.

Walker's theory

Walker proposed a generalized differential form of the energy-size relationship:

$$dE = -K \frac{dD}{D^n}$$

where E = amount of energy (work done) required to produce a change

D = size of unit mass

K = Constant

n = constant

For n =1.0 Walker equation becomes Kick's theory used for coarse particles > 1 μm. For n =1.5 Walker equation becomes Bond's theory. This theory is used when neither Kick's nor Rittinger's law is applicable. For n =2.0 Walker equation becomes Rittinger's theory used for fine particles < 1 μm size.

Table: Methods of size reduction

Method	Examples
Cutting	Cutter Mill
Compression	Roller Mill
Impact	Hammer Mill
Attrition	Fluid Energy Mill

Table: Uses of size reduction methods

Degree of size reduction	Typical methods	Examples
Large pieces	Cutter or compression mills	Rhubarb
Coarse powders	Impact mills	Liquorice, cascara
Fine powders	Combined impact and attrition mills	Rhubarb, Belladonna
Very fine powders	Fluid energy mills	Vitamins and antibiotics

HAMMER MILL

Method of size reduction: Impact

Construction and working principle:

Hammer mill consists of a stout metal casing, enclosing a central shaft to which four or more *hammers* are attached. These are mounted with *swivel* joints, so that the hammers swing out to a radial position when the shaft is rotated. The lower part of the casing consists of screen through which materials can escape, when sufficiently size reduced. The material is collected in a container placed below the screen.

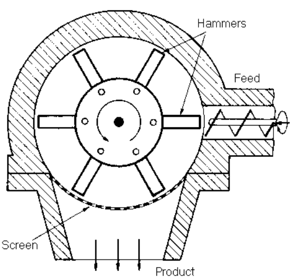

Fig. Hammer Mill

- The screen can be changed according to the particle size required.
- According to the purpose of operation the hammers may be square-faced, tapered to a cutting form or have a stepped-form.
- The interior of the casing may be undulating in shape, instead of smooth circular form for better impact.
- The rotor operates at a speed of 80cycles per second.