Chapter 3 Comminution

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Abstract Particles with dissimilar size(s) and size distribution demonstrate diverse behaviors. Smaller particles have more surface area and their bulk density, porosity, flow, and solubility considerably vary from large particles. All these properties will infuence the formation, packaging, and processing of dosage forms. Thus, comminution is considered a key step in manufacturing of pharmaceutical products. This chapter discusses the concept of size reduction, its importance in pharmaceutical processes, mechanisms involved, and various factors that affect size reduction. It also describes different techniques of particle size analysis. Moreover, the design features and working principle of the equipments used for size reduction of solids, dispersions, and semisolids are also presented in detail.

Keywords Particle size reduction · Size distributions · Cutter mill · Hammer mill · Oscillating granulator · Fitz mill · Triple roller mill and colloid mill

3.1 Introduction

The reduction of bigger particles into smaller ones by the application of external (mechanical) force(s) is called comminution $[1]$ $[1]$.

Pharmaceutical raw material may contain lumps that cannot be processed as such. For these materials, size reduction is an inevitable step. The term comminution/milling/grinding is used in the context of size reduction of solid material, while the relevant term for size reduction of liquid material (droplets) is emulsifcation and atomization [\[2](#page-16-1)].

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3.2 Importance of Particle Size

Particle size can affect many physicochemical properties of dosage forms. As, in pharmaceutical suspensions, the rate of sedimentation and redispersion of the sediment is greatly affected by particle size. Therefore, particle size needs to be optimized for stable formulation [[3\]](#page-16-2). Similarly, in tablets and capsules, the fow, compaction, and compressibility of powder also depend on particle size [[4\]](#page-16-3). Moreover, particle size can affect texture, aesthetic appearance, and spreadability of semisolids. Particle size is also critical for irritability of ophthalmic semisolid products $[5]$ $[5]$.

3.3 Mechanism of Size Reduction

When an external mechanical force is applied to a material, so that the cohesive forces in a matter are exceeded, the material is fragmented into smaller particles [[5\]](#page-16-4). There are several mechanisms involved in size reduction, such as cutting, compression, impact, and attrition (summarized in Table [3.1\)](#page-1-0) [[1\]](#page-16-0).

3.4 Factors Affecting Size Reduction

The following are some of the important factors that affect the size reduction process.

Hardness and Toughness Hardness is the ability of the substance to withstand pressure, and toughness is the ability of a substance to resist being fractured

Mechanism of size of reduction	Diagram	Principle
Cutting		Material is cut by means of sharp blades, e.g., scissors, kitchen blender
Compression		Material is crushed by application of pressure, e.g., nut crackers
Impact		Material is forcefully hit by a moving object, or the material strikes a stationary surface at high speed, e.g., hammer
Attrition		Material is subjected to pressure as in compression, but the surfaces are moving against each other, e.g., levigation by mortar and pestle

Table 3.1 Mechanism of size reduction

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when pressure is applied. It is easy to break soft materials to small sizes than hard materials. Similarly, a tough substance is also very difficult to break [\[6](#page-16-5)].

- **Abrasiveness** is the ability of a material that causes it to be worn out when friction is applied. If the grinding material is abrasive, the chances of contamination with metal particles will be high due to worn out of metal during processing [\[7](#page-16-6)].
- **Stickiness** is the ability of a material to stick to the surfaces of the grinding mills or sieve surfaces. It causes diffculty in size reduction process. Increased stickiness causes the increased adherence of the material to the grinding mills resulting in choking of the mesh [\[7](#page-16-6)].
- **Softening with Temperature** Heat generated during the size reduction process can lead to softening of some waxy drugs or stearic acid. This can be avoided by cooling the mill [\[7](#page-16-6)].
- **Structure** Some materials have unique structures which can affect size reduction process. For instance, vegetable drugs with cellular structure often change to long fbrous materials when pressure is applied, while minerals that have lines of weakness are reduced in size, producing fake-like particles [\[8](#page-16-7)].
- **Moisture Content** The presence of moisture can affect hardness, toughness, and softness of material. The material for size reduction should either be dry or wet but should not be damp [\[9](#page-17-0)].
- **Feed Size** should be kept optimum in order to avoid choking of the mill [[7\]](#page-16-6).

3.5 Particle Size Distribution

Naturally particles exist in variable sizes and shapes. This size difference varies from smallest particles to the largest ones. There is no specifc method to describe particle size of each and every particle in a powder sample [[10\]](#page-17-1). Nevertheless, the size can be described using statistical methods that present particle size in a single dimension by different ways [\[6](#page-16-5)]. The tabular form is the most appropriate and precise method. Besides, frequency as a function of size, bar graph, histogram, etc. are also easily understandable representations of particle size distribution. An example is given in Fig. [3.1](#page-3-0) [\[11](#page-17-2)].

3.6 Particle Size Analysis

Particle size analysis is performed to determine particle size distribution in a given powder.

Fig. 3.2 Size analysis by microscopy

3.6.1 Microscopy

The direct method for size measurement is the microscopy. A Calibrated flar micrometer eyepiece is used to measure the diameter of the particles. The results are presented graphically, as shown in Fig. [3.2](#page-3-1). The lower limit of microscopy can be enhanced by using lenses of different resolutions, for instance, particles in nanometer size range can be measured using scanning electron microscopy (SEM), scanning probe microscopy (SPM), etc. [\[10](#page-17-1)].

3.6.2 Sieving

Sieving is the most economical and simplest method for measuring the particle size of a powder. However, the size measured by sieving method is not very precise [[10\]](#page-17-1). The lowest size that can be measured by this method is 50 μm, or 10 μm in case of micromesh sieves. The device comprises rack of sieve pans sequentially arranged such that sieve having smallest pores is placed on top while the sieve with largest pores is placed at the bottom. A certain amount of powder is placed over the upper pan and shaken mechanically. The residual powder left over each sieve pan is weighed [[7\]](#page-16-6).

Sieving is affected by factors, such as sieving time, the powder load, and the type of motion during shaking. Therefore, all of these factors need to be optimized.

Mesh number is a numerical number of holes per linear inch on a sieve. There are different series of mesh numbers. Table [3.2](#page-4-0) shows the standard sieve numbers and the corresponding openings expressed in microns.

3.6.3 Sedimentation

Sedimentation refers to the settling down of particles in a medium. This method can be used for particles in the size range of 1–200 μm. Moreover, it can only be applied to dilute dispersion where the solid concentration is not more than 2% w/w [[10\]](#page-17-1). The results are expressed as size weight distribution curve. It is based on the sedimentation rate which its reliant on the particle sizes, according to Stoke's equation: $d = \sqrt{\frac{(\rho_s - \rho_i)gt}}$ $\rho_{\rm s} - \rho_{\rm i}$) gt (3.1)

where *d* is the diameter of particles, *η* represents viscosity of the medium, *h* is the distance of fall in time *t*, *g* denotes gravitational constant, ρ_s is the density of particles, and ρ_i represents density of medium.

Mesh number	Sieve opening in μ m	Mesh number	Sieve opening in μ m
2.00	9500	70	212
3.5	5600	80	180
4.00	4750	100	150
8.00	2360	120	25
10	2000	200	75
20	850	230	63
30	600	270	53
40	425	325	45
50	300	400	38
60	250		

Table 3.2 Mesh number and opening of standard sieves

Source: USP 31-NF 26

This method is also called *Andreasen method*; briefy, the sample powder is dispersed in a suitable medium (1% w/v). The suspension is placed in Andreasen pipette, shown in Fig. [3.3.](#page-5-0) At fxed time points, a small portion of sample (10 mL) is withdrawn from the medium and dried without affecting the suspension. The diameter of particles is determined using Stokes equation. Particles of different sizes have different sedimentation rates, i.e., the larger particles will settle down very fast.

3.6.4 Conductivity Method

Conductivity method is also known as Coulter principle and it analyze sizes of individual particles. It requires only trivial amount of sample for analysis and is one of the common method used for particle size measurement. This method relies on fuctuation in electric current caused by particles [[12\]](#page-17-3). An evenly dispersed suspension is formed in an electrolytic solution. A tube having a small orifce of squat path length is immersed in the suspension, and an electrode is placed on both sides of the orifce, as shown in Fig. [3.4.](#page-6-0) A pump creates movement of electrolyte through the orifce, giving a conductive path in between the two electrodes. A slight electrical current is established in between the electrodes. Individually, electrolyte and particle (s) pass through the orifce. The particle, being non-conductive, hinders the electrical current movement, as they move in the orifce. This generates an electrical signal proportionate to the volume of the particle. Every single particle is measured and categorized according to the volume, thus constructing a volume frequency

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Fig. 3.4 Coulter counter

distribution. The particles are considered to be spherical and a particle diameter can be determined from volume [[11\]](#page-17-2).

3.7 Equipments Used for Size Reduction

Selection of size reduction equipment depends on the nature of material to be micronized and required particle size. Each mill gives particles of different sizes and shapes. Once the size range is established (i.e. coarse, intermediate, or fne), then the method can be easily selected [[13\]](#page-17-4).

3.7.1 Size Reduction of Powder

Laboratory-scale size reduction done in pestle and mortar is called *trituration*. For industrial-scale size reduction, a variety of equipments are used, called *mills*. These mills typically consist of three basic parts, i.e., feed channel, grinding mean (rotor), and discharge channel.

Feed Channel: The material is introduced into the mill through feed channel.

Grinding Mean: The size of material is reduced by rotating blades or other means of grinding.

Discharge Channel: gives off the reduced particles.

The feed rate and discharge rate should be equal. Gravitational force is typically responsible for material to be discharged from the mill. However, for ultrafne powders, gravitational force alone is not suffcient so air or inert gas is used in order to move particles out of the mill. The milled particles are either coarse, intermediate, or fine $[12]$ $[12]$.

- **Coarse (No. 20):** All particles pass through mesh number 20 and not more than (NMT) 40% pass through mesh number 60.
- **Intermediate (No. 40):** All particles pass through mesh number 40 and NMT 40% pass through mesh number 80.
- **Fine (No. 60):** All particles pass through mesh number 60 and NMT 40% pass through mesh number 100 [[14\]](#page-17-5).

The milling process where the material is reduced to the desired size by moving once through the mill is called *open circuit milling*. Conversely, if large particles are frst reduced and then transferred to the grinding chamber it is called *closed circuit milling.*

3.7.1.1 Cutter Mill

Design Features Cutter mill has a rotor that has 2–12 knives attached to it. The speed of rotation can vary from 200–900 rpm. It also has stationary knives fxed to the wall of milling chamber. An adjustable screen is fxed at the bottom of milling chamber for controlling particle size, as shown in Fig. [3.5.](#page-7-0)

The size reduction involves the cutting mechanism. The resultant product is coarse. Particle size can be tuned by adjusting the rotor size, the distance between two adjacent knives, and by changing the screen [\[12](#page-17-3)].

Uses: It is frequently used to reduce particle size of crude drug before extraction. It is common for crushing of crude drug materials that are hard and tough in nature. Moreover, it can also be used to mill dried granules [\[15](#page-17-6)].

Advantages: It is simple and cheap mill which does not require any complex operation procedure. It can be used for materials that cannot be reduced by other methods.

Limitations: Material cannot be reduced to fne particles, and the produced particles are coarse in size. Cutter mill is diffcult to clean after use.

3.7.1.2 Hammer Mill

Design Feature It is also called impact mill, since the mechanism involved is impact. Hammer mill consists of a high-speed rotor to which swinging hammers are attached. It has a feed inlet at the top or center, through which drug material is fed into the chamber [\[16](#page-17-7)]. For particle size adjustment, there is a perforated screen above the discharge outlet as shown in Fig. [3.6.](#page-8-0)

Operation: The material is fed into the main chamber through inlet. The material is hit by swinging hammers that are attached to a shaft that rotates within the chamber at high speed (7600 rpm/min). The substance is crushed by repeated impact action of the hammers and collisions with the grooved grinding chamber walls. The perforated metal screens retain coarse materials for further grinding while smallsized particles pass through. Brittle material is best reduced by blunt hammers, whereas fibrous material by cutting edges [[15\]](#page-17-6). The final size is controlled by hammer speed and the hole size of screen.

Uses: Hammer mill can be used for size reduction of almost all types of materials (barks, leaves, roots, crystals, flter cakes); therefore, it is widely used in pharmaceutical industry. Besides, hammer mill is also used for the size reduction of both wet and dry granulation excipients prior to formulation of compressed tablets [[16\]](#page-17-7).

Advantages: It is a rapid action mill and can be used for grinding of different types of materials. Since, no hammer surfaces move against each other, therefore, there are less chances of metal detachment from the equipment and hence less chances of contamination.

Limitations: It is not suitable for heat-sensitive materials because at high operation speed it generates heat. There is a need for optimization of the rate of feed to avoid choking of the mill [\[12](#page-17-3)].

3.7.1.3 Ball Mill

Design Feature: Ball mill has a horizontally rotating chamber whose length is rather greater than its diameter and is either flled with stainless steel or porcelain balls. The ball charge is stated as % age of the chamber flled by the balls. Normally balls cover 30–50% of the mill volume. The outlet is covered with coarse screen to prevent loss of the balls [\[12](#page-17-3)]. There are different variations of these mills. For instance,

in *pebble mill*, the grinding material is pebble. When the grinding material is rod, then it is called *rod mill*. In *tube mills* the length of balls is four times greater than its diameter [[15\]](#page-17-6).

Operation: The chamber rotates horizontally that reduces particle size by both attrition and impact. If the balls rotate at slow speed, it provides attrition effect on the powder, while at high rotation speed the ball provides impact action [[12\]](#page-17-3), as shown in Fig. [3.7](#page-9-0).

Advantages: Ball mill can provide fne grinding. It can be used for both dry and wet milling. Toxic materials can be grinded in ball mill safely because it is a closed system. It is an economical equipment and easy to install and operate. It is effective for hard and abrasive material [\[6](#page-16-5)].

Disadvantages: It produces very high noise.

3.7.1.4 Oscillating Granulator

Design Feature: It consists of a hopper, granulating rods, sieves, and oscillating rotor. All parts are made from stainless steel. It is designed such that the screen can be held and stretched through specifc arrangements and a uniform gap is maintained throughout the operation [[12\]](#page-17-3), as shown in Fig. [3.8](#page-10-0).

Operation: It has one rotor with fve rods attached that oscillates at about 180 rpm on its horizontal axis. The material is feed into the hopper which then falls on the oscillating rods. The powder passes through the sieve and is collected [\[6](#page-16-5)].

Uses: It is used for homogenization and size reduction of powders and granules in pharmaceutical industries. It is used for dry and wet granulation of pharmaceutical materials.

Advantages: It is made up of stainless steel and chances of contamination are less. Its installation is simple and it is easy to operate [[12\]](#page-17-3).

Limitations: Dust generation is common during crushing process.

Fig. 3.9 Fluid energy mill. (Courtesy: International Chemical Scientifc Co., Ltd., South Korea)

3.7.1.5 Fluid Energy Mill

Design Feature: It consists of an inlet for feed, outlet for discharge of comminuted material, loop of pipe with 20–200 mm diameter and 2 m high, and a series of nozzles for air and an inert gas, as shown in Fig. [3.9.](#page-10-1)

Operation: It involves both impact and attrition mechanisms for size reduction. The material is suspended in high velocity air that is introduced through the nozzles $(100-150 \text{ lb/Inch}^2 \text{ (psi)}).$ The particles impact the walls of the grinding chamber and other particles. The collision with the walls and the interparticle attrition breaks the particles into smaller pieces [[12\]](#page-17-3). These particles are then collected into the cyclone collector, which is attached with the discharge outlet. The large particles are centrifugated and recycled into the grinding chamber for further size reduction. The continuous particle collision can yield particles up to about 5 μm size [[6\]](#page-16-5).

Uses: Fluid energy mill is the method of choice for drugs that require high level of purity. Moreover, it is also favorable for heat-sensitive material [\[12](#page-17-3)]. Fluid energy mill is commonly used for the size reduction of alumina, kaolin, zinc, etc.

Fig. 3.10 Typical Fitz mill. (Courtesy: Pharmao Industries Co., Ltd., China)

Advantages: Fluid energy mill produces very fne powder. It has no moving parts so wearing of the parts is minimal; hence chances of contamination are less. It is suitable for thermolabile (heat-sensitive) substances [[6\]](#page-16-5). Moreover, the mill is easily cleanable.

Limitations: Particles may tend to aggregate after the size reduction. Fluid energy mill has a high energy impact so it makes amorphous content [\[15](#page-17-6)].

3.7.1.6 Fitz Mill

Design Feature: It consists of feed throat. Several designs of feed throat are available. The type, number, and design of the blade actually control the level of reduction attained. The screen and rotor speed both are adjusted according to desired particle size [[17\]](#page-17-8).

Operation: The material enters into the grinding chamber and is reduced into smaller particles by high-speed rotating blades, as shown in Fig. [3.10.](#page-11-0) Thus, it works on the principle of cutting.

Uses: Fitz mills are the standard mills for the pharmaceutical industry because of their accuracy and precision in particle size reduction. It is also used in continuous batch production and research.

Advantages: The end results of Fitz mill are accurate and predictable. The equipment is easy to clean and is simple in operation. It can be scalable to larger units (Table [3.3](#page-12-0)).

3.7.2 Size Reduction of Pharmaceutical Dispersions

Dispersion is a heterogeneous two-phase system in which internal phase is dispersed in the continuous (external) phase or vehicle. In case of emulsions/creams, two immiscible liquids are blended to disperse one into the other, while in case of suspension/pastes, solid particle (s) are dispersed in a liquid by mixing [\[18](#page-17-9)].

		Size		
Mill	Mechanism of action	(mesh) no.)	Advantages	Disadvantages
Cutter	Cutting	$20 - 80$	Used for fibrous crude animal/vegetable drugs	Cannot be used for friable materials
Revolving	Attrition and impact	$20 - 200$	Abrasive materials can be finely grinded	Cannot be used for soft materials
Hammer	Impact	$4 - 325$	Used for almost all drugs	Cannot be used for abrasive materials
Roller	Pressure	$20 - 200$	Used for soft materials	Cannot be used for abrasive materials
Attrition	Attrition	$20 - 200$	Used for soft and fibrous materials	Cannot be used for abrasive materials
Micronizer	Attrition and impact	$1-30 \mu m^a$	Used for moderately hard and friable materials	Cannot be used for soft and sticky materials

Table 3.3 Comparison of different mills in pharmaceutical particle size reduction

a Particle size expressed in micrometer

The emulsion preparation involves energy input to create a homogeneously dispersed droplets [[1\]](#page-16-0). In suspension preparation, the frst step is to get the right sized particle usually in the micrometer range. Particle size reduction of the dispersed phase is attained by dry milling prior to incorporation into the dispersion medium [\[10](#page-17-1)] or milling of the fnal product to obtain uniform size particles. Size reduction in emulsions and suspensions is accomplished by a number of different types of agitators and mills.

3.7.2.1 Agitators

Conventional shaking or agitation can effectively be used to make emulsion. The equipment is normally used for emulsifcation of easily dispersible, low-viscosity oils. It is also used for dispersion of solids in liquids. Containers using rotating impellers are employed for agitation (detailed in Sect. [2.3.1\)](https://doi.org/10.1007/978-3-030-84977-1_2#Sec4).

3.7.2.2 Mechanical Mixers

In propeller and/or impeller mixers, propeller is connected to a shaft run by an electric motor. This type of mixers can perform both functions of stirring and emulsifcation. They are used for preparing emulsions with low viscosity [[19\]](#page-17-10). Turbine mixer has additional blades (with or without a pitch) that offer more shear than propellers and is suitable for emulsion preparation of both low-viscosity and medium-viscosity consistencies [[1\]](#page-16-0) (detailed in Sect. [2.3.1](https://doi.org/10.1007/978-3-030-84977-1_2#Sec4)).

Heavy-duty mixers are used for high-viscosity emulsions, where the mixing regime changes from turbulence (as in agitators) to one wherein viscid drag forces dominate. Also, some mixtures display non-Newtonian behavior (fuids whose fow

is not defned by a single constant viscosity value), and mixing of such mixture demands superior heavy-duty mixers like double arm, planetary, and dual and triple shaft mixers [[17\]](#page-17-8).

3.7.2.3 Colloidal Mill

Colloidal mill is often used for manufacture of colloidal solutions or very fne emulsions and suspensions. It also gives smooth texture to semisolid fnal product when used as a fnal step.

Design Feature: It consists of cone-shaped rotor and stator that are 0.005–0.075 cm apart from each other. The rotor is coupled with the motor which rotates at high speed (3000–20,000 rpm). The rotor/stator is cone-shaped and has three stages of increasing grooves that changes direction in each stage for increased turbulence. A hopper and a discharge chamber are also part of colloid mill. The stator is adjusted to get the desired gap with the rotor, as shown in Fig. [3.11](#page-13-0).

Operation: The material is introduced into the rotor through hopper which is then thrown onto the stator by centrifugal force. The rotor operates at a very high speed that generates hydraulic shear force that cuts the particles to smaller size. The product is cleared through an outlet and may be recirculated.

Uses: It is used for the size reduction of dry materials. It is also used to reduce particle size of suspension and the globule size of emulsion [[12\]](#page-17-3).

Advantages: Colloidal mill can reduce the particle size to 1 μm or less. It can reduce particles in the presence of liquid. The particles reduced are used in preparation of suspension, ointment, cream, and lotion [[6\]](#page-16-5).

Limitations: Liquid is used in colloid mill so there is chance of contamination of the product. It cannot be operated continuously because it requires a lot of energy to operate [\[12](#page-17-3)].

Fig. 3.11 Colloid mill used for size reduction of suspensions and emulsions

3.7.2.4 Homogenizers

Homogenization simply refers to reduction of globules size in emulsion or particle size in suspension, so that each dose has uniform composition [\[1](#page-16-0)].

Design Feature and operation: Simple homogenizer has a pump to rise the pressure of the dispersion (500–5000 psi) and an orifce through which the fuid strikes upon the homogenizing "valve," which is held on valve seat by strong spring, as shown in Fig. [3.12](#page-14-0). When the pressure rises, some of the dispersion leaks between valve and valve seat, and this subjects the product to extreme turbulence and hydraulic shear [\[1](#page-16-0)]. For best emulsifcation, two-stage homogenizers are built, where emulsions receive second treatment directly after frst run [[15\]](#page-17-6). *Silverson mixer* (rotor/stator mixer) is often classifed as a homogenizer; it can produce droplet size of 2–5 μm [[20\]](#page-17-11). *High-pressure homogenizer* (HP) is comprised of a displacement pump that pumps liquid into the valve area at great pressure (50–500 Mpa) and an adjustable gap width that is kept $5-20 \mu m$ [\[21](#page-17-12)]. When a dispersion is passed under tremendous pressure through a narrow orifce, the size of dispersed phase is reduced [\[20](#page-17-11)]. *Piston homogenizer* (PH) has a powerful positive displacement piston-type pump to yield high pressure (3000–10,000 psig) to force the coarse mass through a designed restricting wall, where very high shear loads are applied. Here both *turbulence* and *high shear* forces are the key factors for reducing sizes of globules. It has continuous yield capacity of 2500 Lh⁻¹ at 15 hp to 50,000 Lh⁻¹ at 150 hp [\[21](#page-17-12)].

Uses: APV Gaulin homogenizer (a simple homogenizer) is most frequently used in liquid emulsion preparation. The HP homogenizer is used in the manufacture of emulsion preparation, microemulsions, and particle size reduction [[20\]](#page-17-11). HP type is now considered the most powerful homogenizer for making emulsions and suspensions [\[11](#page-17-2), [21](#page-17-12)].

Advantages: A homogenizer does not permit air entry into the fnal product.

Limitations: PH cannot handle the feed mixture over 200 cps. It has high maintenance cost and the product lacks consistency and has batch-to-batch variability [\[20](#page-17-11)].

Inline Mixers: Many mixers, such as Silverson mixer, colloidal mill, piston homogenizer, and ultrasonic vibrating homogenizer are now designed to offer a range of in-tank and inline mixing, and are extensively used for preparation of emulsions, from pilot scale to bulk production units.

3.7.2.5 Ultrasonic Devices

For low-viscosity emulsions use of ultrasonic vibration has been reported that causes compression and refraction in different regions of liquid that result in high shear. These devices are not practical for bulk-scale production of emulsions [\[1](#page-16-0)].

3.7.3 Size Reduction in Semisolids

Semisolids as a dosage form include creams, gels, pastes, and ointments. Their industrial processing is very similar; hence this topic will cover all semisolids collectively [\[1](#page-16-0)]. Equipment for semisolids is built to perform certain unit tasks, such as milling, separation, mixing, emulsifcation, and deaeration. *Separators* are used to separate materials of different sizes, shapes, and densities, e.g., centrifugal separators or vibratory shakers [[11\]](#page-17-2). Mixing of the active constituents and other formulation ingredients with the ointment base is achieved by different types of agitator mixers and high-shear mixers. Mixers with heating supplies are also used to help in the melting of bases and mixing of constituents [[12\]](#page-17-3).

3.7.3.1 Agitators

In manufacture of semisolids, different types of agitator mixers are used, for instance, sigma blade mixers and planetary mixers. The agitator arms are so built to offer a pulling and kneading action and the design and drive is such that content is cleaned from all sides and corners of the container [[1\]](#page-16-0). Planetary mixer is an example of agitator mixer used for semisolids (see Chapter [2,](https://doi.org/10.1007/978-3-030-84977-1_2) Section [2.4.7.1\)](https://doi.org/10.1007/978-3-030-84977-1_2).

3.7.3.2 Triple Roller Mill

Design Features: Triple roller mill is fxed with three rollers which are built from a rigid abrasion-resistant material. They are mounted in such a way that they lie in close interaction with each other and revolve at dissimilar speeds [\[6](#page-16-5)]. The material placed in between the rollers is crushed and the particle size is reduced. The decrease in particle size is infuenced by the gap and variation in roller speeds. Material is passed through hopper A, between the rollers B and C where it is comminuted. Then the material is passed between the rollers C and D where it is further homogenized to obtain a smooth mixture.

Advantages: Triple roller mill offers possibility of continuous operation. Mixing effciency achieved is very high in terms of content uniformity. Moreover, it provides excellent control of the product temperature [[15\]](#page-17-6).

Limitations: Washing of the mill after use is difficult. Overall cost is very high. Chances of contamination of the fnal product are maximum [[6\]](#page-16-5).

3.7.3.3 Vacuum Emulsifying Mixers

It is the most common and extensively used emulsifying mixer nowadays.

Design Feature: Vacuum emulsifying mixer has three distinct mixers, a central emulsifying pot, pre-treating oil pot, water pot, and work frame [\[22](#page-17-13)].

Operation: The oil-phase constituents in oil pot and the water-phase constituents in water pot are vigorously mixed before being dropped in the central emulsifying mixer. This central pot also has a rotor/stator that pulls, mixes, shears, and forces the constituents together. After thorough mixing in central pot, the temperature is raised to promote further solubility. This mixture is then removed with hydraulic pumps and cooled [\[22](#page-17-13)].

Uses: It is the best emulsifer for emulsifcation of viscous materials with high solid content like cream, ointment, lotions, and gels [\[22](#page-17-13)].

References

- 1. Wang YB, Williams RO. Powders. Remington Essentials of Pharmaceutics. London : Pharmaceutical Press. 2013: 411–432.
- 2. Loh ZH, Samanta AK, Sia Heng PW. Overview of milling techniques for improving the solubility of poorly water-soluble drugs. Asian Journal of Pharmaceutical Sciences. 2015;10(4):255–74.
- 3. Papuga K, Kaszubkiewicz J, Kawałko D. Do we have to use suspensions with low concentrations in determination of particle size distribution by sedimentation methods? Powder Technology. 2021;389:507–521.
- 4. Chang S-Y, Sun CC. Effect of particle size on interfacial bonding strength of bilayer tablets. Journal of Powder Technology. 2019;356:97–101.
- 5. Kulkarni V, Shaw C. Particle size analysis: an overview of commonly applied methods for drug materials and products. Essential Chemistry for Formulators of Semisolid Liquid Dosages. 2016: 137–44.
- 6. Kumar R, Thakur AK, Chaudhari P, Banerjee N. Particle Size Reduction Techniques of Pharmaceutical Compounds for the Enhancement of Their Dissolution Rate and Bioavailability. Journal of Pharmaceutical Innovation. 2021:1–20.
- 7. Sushant S, Archana K. Methods of size reduction and factors affecting size reduction in pharmaceutics. International Research Journal of Pharmacy. 2013;4(8):57–64.
- 8. Opatová K, Zetková I, Kučerová L. Relationship between the Size and Inner Structure of AM Powder Particles. 2018. doi:10.20944/preprints201811.0453.v1.
- 9. Ahlneck C, Zograf G. The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. International Journal of Pharmaceutics. 1990;62(2–3):87–95. DOI:10.1016/0378-5173(90)90221-O
- 10. Buanz A. Powder characterization. In: Adejare A., (Ed), Remington the Science and Practice of Pharmacy, Elsevier, Amsterdam, Netherlands. 2021: 295–305.
- 11. Yadav KS, Kale K. High pressure homogenizer in pharmaceuticals: understanding its critical processing parameters and applications. Journal of Pharmaceutical Innovation. 2019:1–12.
- 12. Aulton ME, Staniforth JN. Particle size reduction and size separation. Aulton's Pharmaceutics E-BOOK: The design and manufacture of medicines, 4th edition, 2013. 156–169.
- 13. Duroudier J-P. Grinding: Principles and Theories. Size Reduction of Divided Solids, 1st edition, Elsevier; 2016.
- 14. Brown W, Marques MR. The United States Pharmacopeia/National Formulary 2013: 319.
- 15. Seibert KD, Collins PC, Luciani CV, Fisher ES. Milling operations in the pharmaceutical industry. Chemical Engineering in the Pharmaceutical Industry: Active Pharmaceutical Ingredients. 2019: 861–879.
- 16. Su D, Yu M, Study of Corn Stover Particle Size Distribution Characteristics for Knife Mill and Hammer Mill. IOP Conference Series: Earth and Environmental Science. 2019; 358(5):052060.
- 17. Cullen PJ, Romañach RJ, Abatzoglou N, Rielly CD. Pharmaceutical Blending and Mixing. John Wiley & Sons, Inc., Hoboken, New Jersey. 2015: 25–78.
- 18. Anger CB, Rupp D, Lo P, Takruri H. Preservation of dispersed systems. Pharmaceutical Dosage forms, CRC Press, Boca Raton, Florida. 2020: 377–436.
- 19. Torotwa I, Changying J. A Study of the Mixing Performance of Different Impeller Designs in Stirred Vessels Using Computational Fluid Dynamics. Designs 2018:2;10. [https://doi.](https://doi.org/10.3390/designs2010010) [org/10.3390/designs2010010](https://doi.org/10.3390/designs2010010)
- 20. Singh SK, Naini V. Homogenization and homogenizers. In: Encyclopedia of Pharmaceutical Science and Technology, Fourth Edition, CRC press, Boca Raton, Florida. 2013: 1848–1854.
- 21. Yadav KS, Kale KJ JoPI. High pressure homogenizer in pharmaceuticals: understanding its critical processing parameters and applications. Journal of Pharmaceutical Innovation, 2020;15(4):690–701.
- 22. Garcia EE, Kimura C, Martins AC, Rocha GO, Nozaki J JBAoB, Technology. 2017 High Quality Perforated Panel for Metal Mesh Curtain Wall. Brazilian Archives of Biology and Technology. 1999;42(3):281–90.