SIZE REDUCTION

- Size reduction is the process of reducing the size of a substance into smaller pieces, coarse particles (355 µm) or fine powder (125 µm).

Objective Of Size Reduction

1. To increase the rate of solution in case of chemical substances because reduction in particle size increases the surface area for the solvent action.
2. To allow the rapid penetration of the solvent in extraction process.
3. To get a uniform powder because size reduction helps in uniform mixing of drugs.
4. To increase the rate of absorption of a drug because the smaller the particle size.
5. To improve the stability of certain pharmaceutical dosage form like suspension.

Factors Affecting Size Reduction

1. Hardness

The hardness of a material affects the process of size reduction. It is easier to break a soft material to small size than a hard material.

2. Toughness

The crude drug having higher moisture content are generally tough in nature a soft but tough material may create problem in size reduction than a hard but brittle substance.

3. Stickiness

Stickiness causes a lot of difficulty in size reduction because the material adheres to the grinding surface so, such material can be reduced in size by complete dryness of the material.

4. Material Structure

- Vegetable drugs having cellular structure are slippery in nature such material act as lubricant and lower the efficiency of grinding surfaces, hence required more time for size reduction.

5. Moisture content

The material should be either dry or wet but it should not be damp. The material having 5 % moisture is required for dry grinding and 50 % moisture for wet grinding does not create any problem.

6. Temperature

- Most of the size reduction process generates heats which melt the waxy substance like stearic acid or drugs containing oils or fats. This problem can be avoided by cooling the mill.

7. **Purity Required**

Various mills used for size reduction often causes the grinding surface to wear off and thus impurities come in the powder, so if high degree of purity is required the such mills must be avoided and the mill should be thoroughly clean between batches of different materials.

8. Physiological Effect

Some drugs are very potent, during their particle size reduction in a mill, dust is produced, which is inhaled by the operator and having harmful effect on the operator, so for such drugs enclosed mill may be used.

9. **Ratio of feed size to product size**

To get a fine powder in a mill, it is required that a small feed size should be used.

10. **Bulk Density**

The capacity of most of the batch mill depends on volume, thus a batch mills can reduce more quantity of denser material as compared to lighter once.

Equipment used for Reduction

Hammer Mill

Principle

Hammer mill works on the principle of impact. In impact the material is more or less stationary and is hit by an object moving of a high speed or when the moving particle strikes a stationary surface.

Construction

It consists of a steel casing enclosing a central shaft to which 4 or more hammers are attached.

- The lower part of the casing consists of a screen through which material can pass and collected in a suitable receiver after desire degree of size reduction.

Working

- The material is put into the hopper/feed which is connected to the drum. Due to the fast rotation of the hammers, the material is powdered to the desired size and is collected under the screen.
- Hammer mill has the advantage of continuous operation, it can produce coarse to moderately fine powder.

Disadvantages

- Hammer mill produces heat during size reduction process. So it is not used for thermolabile drugs.

Use

- It is used for producing intermediate gradles of powder from all types of substance except sticky materials.

BALL MILL

Principle : -

It works on the principle of impact and attrition.

ATTRITION

In this pressure is applied on the material and the surfaces are moving relative to each other which break the particles.

CONSTRUCTION

It consists of a hollow cylinder which is mounted on a metallic frame in such a way that it can be rotated on its longitudinal axis.

- The cylinder contains balls that occupy 30 – 50 % of the mill volume.
- The cylinder and balls are made up of same materials like metals usually lined with Chrome, rubber or porcelain.

Working : -

The drug to be reduced is put into the cylinder of the mill and is rotated.

The speed of the rotation is very important.

- ❖ At low speed the mass of balls will slide or roll over each other and only very small amount of size reduction will occur.
- ❖ At a high speed the balls will be thrown out to the walls of the cylinder by centrifugal and no size reduction will occur.
- ❖ At about 2/3rd speed the centrifugal force just occurs and the balls are carried all most to the top of the mill and then fall in. By this way maximum size reduction occurs.
- ➢ After a suitable time, the material is taken out and passthrough sieve to get powder of required size.

N . B : -

In this, size reduction occurs by impact of particles and balls and by attrition between the balls.

ADVANTAGES

1. It can produce very tone powders.
2. It can grind a large variety of material.
3. It is suitable for both wet and dry grinding process.
4. Since it is an enclosed mill it can be used for size reduction of toxic materials.

DISADVANTAGES

1. It is a very noisy machine.
2. Contamination of the product may occur.

FLUID ENERGY MILL

Principle

It works on the principle of impact and attrition.

Construction

It consists of loop of pope which has a diameter of 20 – 200 mm and height is upto about 2m.

- ➢ There is an inlet for the feed of the material.
- ➢ There is a series of nozzles for inlet of fluid i.e. air or an inert gas.
- ➢ It has an outlet with a classifier.

Working

The air or inert gas is introduced with a high pressure through the nozzles. Solids (drugs) are introduced into the air stream through feed inlet. Due to high degree turbulence, impact and attritional forces occurs between the particles and size reduction of the material occurs. The tone particles are collected through a classifier.

Uses :

1. This is used for size reduction of heat sensitive material like sulphonamide, vitamins and antibiotics.
2. Used for those drugs on which high degree of purity is required.

ADVANTAGES

1. There is no wear of the mill, hence there is not contamination of the product.
2. The particle size of powder can be controlled due to use of a classifier.

DISINTEGRATOR

Principle :

It works on the principle of impact.

Construction : -

- It consists of a still drum having a shaft at the centre.
- The shaft contains a disc, on which tear beaters are foxed.
- The shaft rotates with a speed of 5000 – 7000 rev/min.
- The sidle and upper inner surface of the drum is rough and undulation (Rough surface).
- The lower part of the drum has detachable screen or sieve.

Working

- The material is fed to beaters through hopper which is fitted to the drum. The material is broken into small particles by the beaters and also are helped undulation of the inner surface and roughness of drum.
- The air is allowed to pass through an outlet on which dust bag is tied, which retains the fine particles.

Uses

It can be used for all types of drug including very hard drugs.

SIZE SEPARATION

Size separation is defined as the process to separate particles of specified size so that the particles of uniform size can be obtained.

OFFICIAL STANDARDS FOR POWDERS

The Indian Pharmacopeia specified seven grades of powder such as :

a. Coarse Powder
b. Moderately Coarse Powder
c. Moderately fine Powder
d. Fine Powder
e. Very fine Powder
f. Microfine Powder
g. Superfine Powder

1. **Coarse powder (10/44)** : A powder of which all the particles pass through a sieve with nominal mesh aperture of 1.70 mm (No. 10 sieve) and not more than 40 % through a sieve no.44 having nominal mesh aperture of 355 urn (No. 44 sieve) is called coarse powder.
2. **Moderately coarse powder (22/60)**: A powder of which all the particles pass through a sieve no 22 having nominal mesh aperture of 710 micrometre and not more than 40% through a sieve no 60 having nominal mesh aperture of 250 urn (No. 60 sieve) is called moderately coarse powder.
3. **Moderately fine powder** (44/85): A powder of which all the particle passes through a sieve no 44 having nominal mesh aperture of 355 micrometre and not more than 40% through a sieve no 85 having nominal mesh aperture of 180 micrometre is called Moderately fine Powder
4. **Fine powder (85/120)**: A powder of which all the particles passes through a sieve no 85 having nominal mesh aperture of 180 micrometre and not more than 40% through a sieve no 120 having nominal mesh aperture of 125 micrometre is called fine Powder.
5. **Very fine powder(120/350)** : A powder of which all the particles passes through a sieve no 120 having nominal mesh aperture of 125 micrometre and not more than 40% through a sieve no 350 having nominal mesh aperture of 45 micrometre is called Very fine powder.
6. **Microfine powder** : A powder of which not less than 90% of the particles passes through a sieve no 350 having nominal mesh aperture of 45 micrometre is called Microfine powder.
7. **Superfine powder(120/350)** : A powder of which not less than 90% of the particles are less than 10 micrometre in size.

Sieve No	Nominal Mesh aperture
10	1.70 micrometre
44	355 micrometre
22	710 micrometre
60	250 micrometre
85	180 micrometre

120	125 micrometre
350	45 micrometre

SIEVES:

- The sieves are constructed from wire of brass, bronze, stainless steel or any other suitable material, with square meshes.
- The wires should be uniform cross section (circular) and should not be coated or plated.
- They should not be any reaction between the material of sieve and the substance being shifted from it.

Standards of Sieves

- Sieves used for pharmaceutical testing must specify the following standards:

1. No. of sieve:

- Sieve no. indicates the number of meshes in a length of 2.54 cm in each transverse directionparallel to the wires.

2. Nominal Size of Aperture

- Nominal size of Aperture indicates the distance between the wires. It is generally expressed with the unit millimeter or micrometer.

3. Nominal Diameter of the wire

- Wire mesh sieve are made from the wire having the specific diameter. So that a suitable aperture size and sufficient strength of the sieve can be obtained.

4. Approximate percentage sieving area

- This standard expresses the area of the meshes as a percentage of the total area of the sieve.
- Generally the sieving area is kept with in the range of 35-40%.

PROCESS OF SIZE SEPARATION:

The various methods used for size separation are:

1. Sieving
2. Cyclone Separator
3. Sedimentation method

1. SIEVING

By this method fine powder is separated from the coarse powder by using the sieves of desired numbers. The degree of fineness of powder is known with the help of sieve through which the powder material is passed.

METHOD

In this method the sieves are arranged in descending order i.e., the sieve of larger size is at the top and the smallest one is at the bottom. The bottom sieve is attached to receiving pan.

The material is placed in the uppermost sieves are shaken with the help of mechanical sieve shaker. It helps the particles to pass through the sieves. After shaking the powder material, the weight of powder retained on each sieve is determined and the percentage of each fraction is then calculated.

WORKING METHOD

The sieving are based on 3 methods, such as

1. Agitation
2. Brushing
3. Centrifugal

Agitation Methods:

Agitation methods sieves may be agitated in a number of different ways such as

1. Oscillation : The sieve is mounted in a frame that oscillates back and forth. It is a simple method but the material roll on the surface of the sieve.
2. Vibration : The sieve is vibrated at high speed by means of an electric device. The rapid vibration is imparted the particles on the sieve which helps to pass the powdered material through it.
3. Gyration: In this method, a system is made so that sieve is on rubber mounting and connected to an eccentric fly wheel. This gives a rotary movement of small amplitude to sieve which in turn gives spinning motion to the particles that helps to pass them through a sieve.

Agitation methods are not continuous methods but can be made so by inclination of the sieve and the provision of separate outlets for undersize and oversize particles.

Brushing Methods In this case, a brush is used to move the particles on the surface of the sieve and to keep the meshes clear. The brush is rotated in the middle in the case of a circular sieve but spiral brush is rotated on the longitudinal axis in case of a horizontal cylindrical sieve.

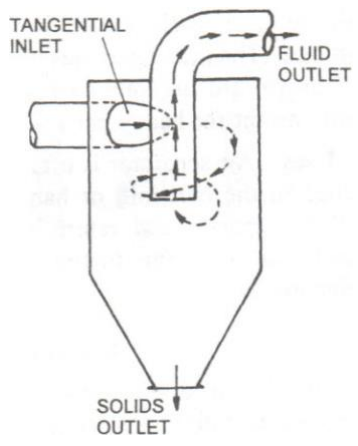
Centrifugal Methods In this method, a high speed rotor is fixed inside the vertical cylindrical sieve, So that on rotation of rotor the particles are thrown outwards by centrifugal force. The current of air which is produced due to high speed of rotor helps in sieving the powder.

On sieving the powdered material in a mechanical or electromagnetic device using any of the above methods, the weight of powder retained on each sieve is determined. The percentage of each fraction is then calculated.

Sieving method is a rapid process and it requires very little skill. The equipment used for sieving is not expensive.

ADVANTAGES:

1. It is a rapid process.
2. Equipment is not expensive.
3. Very little skill is required.
4. It can be used for separation of wide ranges of powders.



2. CYCLONE SEPARATOR

Principle It is based on the principle of centrifugation and sedimentation. The separation of the particles depends upon the particle size and also the density of the particles.

Construction It consists of a cylindrical vessel with a conical base. In the

upper part of the vessel there is a tangential inlet for the particle suspension. The bottom of the apparatus has a particle or solid outlet.

Working The suspension of a solid in gas (usually air) is introduced tangential1y at a very high velocity, so that rotary movement takes place within the vessel. This rotary flow causes the particle to be act by centrifugal force. The solids are thrown out to the wall and it falls to the conical base and discharged out through solids outlet. The fluid is removed at the top.

Uses Cyclone separators are used to separate the suspension of a solid in a gas (air). It can be used with liquid suspensions of solids.
Advantages : This is a fast and efficient process.

Disadvantages: Special equipment is required.

Size Separation by Sedimentation Method (Elutridtion method)

PRINCIPLE : The rate of sedimentation is directly proportional to their particle size i.e., bigger particle settle down faster than the smaller ones.

Construction:

It consists a chamber fitted with pipette at different heights.

Working:

The powder to be separated is fast suspended in a suitable liquid i.e., water. The suspension is filled into the chamber and allow to rest where by the particles begin to settle.

After predetermined time the particles less than a given diameter and recovered from the pipettes fixed at different heights on the chamber.

Although it is a batch process, it can make continuous operation by utilizing of a pump mechanism instead of pipette for particle recovery.

Mixing and Homogenisation

Definition : Mixing may be defined as the process, in which two or more substances are combined in such a manner that it results in a state where each particle of one substance lies as close as possible to a particle of the other substance.

Objectives:

1. Simple physical mixing of materials to form a uniform mixture.
2. To promote the chemical reaction to get uniform product e.g., Addition of a buffering agent to adjust the point of a solution.
3. Dispersion of solid in liquid to form suspension or paste.
4. Dispersion of two immiscible liquids to form an emulsion.
5. For changing the physical state of a substance by mixing it with a substance of the other state. e.g., Addition of a solid to a liquid to form a simple solution.

Types of Mixture:

There are three types of mixtures:

- Positive mixture
- Negative mixture
- Neutral mixture

POSITIVE MIXTURE:

When two or more than two miscible liquids are mixed or soluble solid is dissolved in water, the mixtures are called positive mixture.

- The mixture formed is irreversible.
- These mixtures do not present any problems in mixing.
  e.g., Mixture of alcohol and water.

NEGATIVE MIXTURE:

When two immiscible liquids are mixed or insoluble solids are mixed with water, it forms negative mixtures.

- The mixture formed is a reversible mixture.
- For preparing such mixture, a higher degree of mixing of materials is required.
  e.g., Emulsion, Suspension

NEUTRAL MIXTURES:

These substances do not have tendency to mix with each other immediately, but once mixed they do not separable after mixing.
Ex: ointments and paste

MIXING OF POWDERS:

Powder mixing may be regarded as an operation in which two or more than two solid substances in particulate form are intermingled randomly in particles.

MECHANISM OF MIXING :

The solid mixing takes place by a combination of one or more mechanisms given below:

(i) Convective mixing:
In this, there is bulk movement of groups of particles from one part of the powder bed to another, by means of blades or paddles of the equipment.

(ii) Shear mixing:
This type of mixing takes place due to setting up of slip planes with in the mass of the material. When shear force occurs, it reduces the scale of segmentation by thinning

(iii) Diffusion mixing :
It occurs when random motion of particles within a powder bed causes them to change position relative to one another. It is produced by any form of agitation of powder.

FACTORS AFFECTING MIXING OF POWDERS

1. PARTICLE SIZE
   Difference in particle size can lead to segregation because the small particles move downward through the space between the bigger particles. Hence it is easy to mix two powders having approximate the same particle size.
2. PARTICLE SHAPE
   Spherical particles are easier to mix than irregular shaped particles. But in case of irregular shape there is less chance of separation if particles, once these are mixed together due to there interlocking properies.
3. PARTICLE ATTRACTION
   Some particles exert attractive forces due to electrostatic charges on them, leading to aggregation of powders. But this can lead to the segregation (separation) of materials with different surface charges.
4. MATERIAL DENSITY
   It is difficult to mix two powders having different density. Because dense material (heavier particles) always moves downward and settle down at the bottom. So, the material being mixed be of as close the density as possible.
5. PROPORTIONS OF MATERIALS
   It is easier to mix, two powders in equal proportions by weight or by volume. When there is large difference in the proportions of two powders to be mixed in the mixing of powders is always done in the ascending order of their weights.
6. PRESENCE OF MOISTURE
   Presence of mixture in the powder may cause its surface to become sticky and lead to aggregation. It is therefore, essential that the powders should be properly dried before mixing.

EQUIPMENT USED FOR MIXING OF POWDERS

AGITATED POWDER MIXER

CONSTRUCTION

It consists of a stationary vessel or a through in which a central shaft with helical blades is fitted. The shaft is rotated by means of an electric motor.
Fig-

WORKING:
The material to be mixed is loaded into the vessel and the blades are allowed to rotate at a slow speed. The blade produce a continuous cutting and shuttling motion and cause the powder material to flow in rotational as well as transverse direction. Any powder agglomerates in the material are broken down by the shearing action that develops between the moving blade and through.
APPLICATION: Used for mixing free flowing powdered materials having uniform particle size and density.

MIXING OF LIQUIDS:

Mixing of liquids is done to prepare true solution or emulsions.
Liquid mixing may be divided into the following categories:

(i) Mixing of liquids and liquids
- Mixing of two miscible liquids
- Mixing of two immiscible liquids

(ii) Mixing of liquids and solids
- Mixing of liquids and and soluble solids
- Mixing of liquids and and insoluble solids

EQUIPMENT USED FOR MIXING OF LIQUIDS

On large scale, the following equipments are used-

1. Propeller mixer
2. Turbine mixer
3. Paddle mixer

Propeller Mixers

CONSTRUCTION:
It consists of a vessel and a propeller. The propellers used for liquid mixing consist of angled blades attached to the end of a shaft which is rotated by means of a motor. Although any number of blades may be used the three blades design is the most common for use with liquids, The propeller is usually quite small as compared to the size of the vessel but its high operational speed (upto 800-8000 r.p.m.) compensate for the size and produce efficient mixing specially in case of low viscosity liquids.
WORKING:
The materials to be mixed are taken in a vessel and the propeller bearing shaft inserted into the liquids. The angled blades of the propeller cause circulation of the liquids in both arial and radial direction ensuring good bulk transport but low shearing force.
The propeller may be instilled in a number of ways. The centrally mounted vertical propeller is however not consedered good as it produces pure rotary motion and draws a vortex which may result in air entrapment in the product. This can be avoided by making the following changes in the position of the propeller shaft.

a. offset from the centre.
b. Mounted at angle
c. Enter the side of the vessel
d. Using push pull propeller
e. By the use of battles

Fig

- The offset and angled mounting i.e., (a) & (b) discourage the vortex formation and air entrapment.
- For very large tanks, the side entering propellers i.e., are often used.
- (d) is an alternate arrangement for prevention of air entrapment is a push-pull propellers of opposite angle or pitch are mounted on the same shaft. So that the rotary effects are in opposite directions and cancel each other.
- (e) & f : One or more vertical baffles are fitted into the vessel. The baffles are usually $\frac{1}{10}$th to $\frac{1}{20}$th of the vessel diameter and prevent vortex formation by diverting the centre of the vessel.

MIXING OF SEMI SOLIDS

The mixing of semi soilds is done for preparing ointments, creams, pills masses and wetness for making granules etc. Because of poor flow characteristics of semi solids, mixer with high mixing are generally employed for mixing of semi solids.

EQUIPMENTS USED FOR MIXING OF SEMI-SOLIDS

In large scale, the following equipments are used-

1. Triple Roller Mixer
2. Agitator Mixer
3. Planetary Mixer

1. Triple Roller Mixer:

This consists of three Rollers which are made of a hard-abrasion-resistant material like metal or porcelain. These rollers are arranged very close to each other. Depending upon the requirement. The gap between the rollers can be adjusted. These rollers are rotated at different rates of speed, by means of a motor.

The material coming between the rollers is crushed depending on the gap between them and the difference in rates of movement of the two surfaces. One scrapper is arranged with the roller 3.

Fig

WORKING

- Materials to be mixed are fed in the hopper which pass on to the gap between the first two rollers i.e., Roller no. 1 & 2 and are crushed during the process.
- The gap between Roller 2 and 3 is usually less than that between 1 & 2. The speed of the second roller is greater than Roller 1 & Roller 3 speed is more than roller 2.
- Material from the first two rollers passes on to the gap between the second and third roller, where it gets further crushed and smoothens the mixture which adheres to roller 2.
- The materials adheres to the 3rd roller, is removed by a scrapper.
- The arrangement of scrapper is done in such a way that, no material passes on to the scraper before it has passed between both sets of rollers.

USE : Used for mixing solid powder in ointment base.

3. Planetary Mixer:

CONSTRUCTION:

It consists of a stationary vessel which is made up of stainless steel. The mixing blade is mounted from the top of the vessel, on the rotating arm. The rotating arm rotates about it's own axis and also travels in a circular path around the mixing vessel. This arm connected to a electric motor. The behaviour of this mixer is analogous to that of planets, the mixer is known as planetary mixer.

- N.B. : The vessels can be removed by lowering it beneath the mixing blade or raising the blades above the vessel.
- Mixing blades or paddles of varying sizes and shapes are available depending on the requirements.

HOMOGENISATION :

- Homogenisation is defined as the presence of rendering a material to a uniform quality, consistency and structure.
- This process is commonly employed for preparing a fine emulsion from a coarse one by converting the large globules to small globules.
- Homogenisation is done in an apparatus called "Homogeniser".

EQUIPMENTS USED FOR HOMOGENISATION:

1. Hand homogeniser
2. Silverson mixer homoeniser
3. Colloidal mill

Principle:

These are based on the principle that the large globules in a coarse emulsion are broken into smaller globules by passing them under pressure through a narrow orifice.

1. **Hand Homogeniser**

WORKING:
The materials to be mixed are loaded into the mixing vessel. The mixing blade is rotated at a slow speed initially with any additional material required being added gradually to the vessel during the operation. Finally the speed is increased for active mixing. The small clearance between the mixing vessel and blade provides a kneading and shearing action for through mixing. However intermittent scrapping of the material during the operation may be required to ensure proper mixing of the contents as some materials are forced to the top of the bowl.
USE: Used for wet granulation

- Mixing of powdered drug with an ointment base.

CONSTRUCTION :
This equipment is used in the laboratory or for small scale work, consists of a hopper, a valve and a handle.
WORKING:
The dispersion to be homogenised is placed in the hopper and the handle is operated in up and down positions. This forces the preparation to enter into the value and come out from a fine orifice in the form of a fine jet, with a great force. When this jet hits the baffles, it reduces the size of the dispersed particles of globules.
The reduction in size depends upon the diameter of the orifice and the speed of pumping. After homogenisation, a fine dispersion comes out of the homogeniser.
2. **Colloid Mill** :
Principle:
The size reduction is affected due to shearing when the material is passed between the narrow gap of mixing surfaces of rotor and stator.
Fig:

CONSTRUCTION:
The colloid mill basically consists of a rotor and a stator having conical milling surfaces. The rotor rotates at a speed of 3000 to 20000r.p.m. by means of an electric motor. The gap between the rotor and stator is of the order of a fraction of a millimetre. i.e, 002 to 0.03 inches. The rotor is placed at the base of the hopper through which the material to be homogenised is fed. The hopper as well as the grinding surfaces are usually made up of stainless steel.
WORKING:
The material e.g. emulsion and suspensiom is placed into the hopper of the mill. It is then passed through a narrow gap between the rotor and stator and thus reduces to fine particle size. The fine material is then either collected from the outlet or is recirculated till desired degree of homogenisation is achieved.
USE : Used to prepare pharmaceutical suspensions and emulsion cream, ointments etc having particle size less than 1 micron.

3. SILVERSON MIXER EMULSIFIER:

CONSTRUCTION
The silverson mixer emulsifier consists of an emulsifier head containing a number of sharp blades. The blades are surrounded by a stainless steel mesh having fine holes and are attached to a central shaft, the other end of which is connected with a motor at the top.

Fig.:

WORKING

The emulsifier head is placed in the vessel containing immiscible liquids, in such a way that it should get dipped into it. When the motor is started, the liquids are sucked through the fine holes and the oil is reduced into fine globules due to the rotation of the blades.
So a fine emulsion which is produced is then expelled out. The intake and expulsion of the mixture set up a pattern of circulation.

DOUBLE CONE MIXER:

CONSTRUCTION:

It is made up of stainless steel and is available in different capacity ranging from 5kg to 200kg. or even more. The efficiency of the mixer depends on the size and shape of the tumbler and the nature of material to be mixed. The common range is 30-100 r.p.m.

WORKING

The material to be blended is loaded approximately 50-60% of the total capacity of the blender. As the blenders rotates the material undergoes tumbling motion and mixes the material thoroughly. Agitator blades can also be fixed in order to produce shearing action.
USE: For powder mixing of small quantity.