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Review Article

Particle Size and It's Importance in Industrial Pharmacy: A Review

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ABSTRACT

The science of small particles is known as 'micromeritics' and it is used extensively in many different industries, including pharmaceuticals. When you really think of how important the consistency of a drug is for it to work well, the relevance of micromeritics comes to the surface. The release and dissolution of a drug, absorption and therapeutic action, physical stability, dosage and many more are important parameters which are influenced by particle size. This review highlights the description of particle size, methods of particle size reduction, particle size determination and its significance.

INTRODUCTION

Particle size is very important in designing of any dosage form. Particle size can affect the process ability of powder like flow, mixing and compaction. Reduction of particle size is important to increase flow property. Some particles are larger in size in that case having problem with solubility because larger sized particle required less surface area hence required more time for dissolving. In some cases particles are not soluble in any media then required to prepare the suspension, in suspension particle size should be in same size. In absorption particle size is important because particle size decreases the surface are increases also increase the absorption.

Particle size can be reduced by using some technique like ball mill, cutter mill, colloidal mill, hammer mill, fluid energy mill and roller mill, by applying principles like attrition and impact. The principle of mill depends on direct pressure, impact from a sharp blow, attrition, or cutting. There are different methods to characterize the particle size that are: sieving, optical microscopy, sedimentation, transmission electron microscopy. In powder for reconstitution (sterile dosage form) particle size play important role[1].

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The fine particles of many finely divided materials are so small that it is impractical to make effective size separations by pneumatic methods and microscopic methods are not readily applicable[1].

Within pharmaceutical manufacturing, size reduction is one of the most extensively used and vital unit operations. Size reduction in tablet production is achieved primarily through milling procedures, which allows for attaining product uniformity, optimizing product solubility, and improving bioavailability. Additionally, powders with a narrow range of size distribution can obviate problems in downstream processing as pertains to blending, compression, and coating as well as improve drug performance. For lactose granules, data showed that fine particle sizing occurred at 9000 RPM, while only larger particles were reduced at 1000 RPM, 4000 RPM, and 6600 RPM. Large particles were reduced much more effectively as speed increased from 1000 RPM to 4000 RPM; however less change was seen from 4000 RPM and 6600 RPM. For both extrudate and granules, particle size decreased as mill speed was increased and smaller screens were utilized. [2]

Significance of particle size [3]

Suspension

When powders are suspended in liquid, the behavior and flow properties will depends on the particle size. Optimum particle sizes for any suspension are required.

Mixture of solid
Particle size has great effect on the mixing of solid substances and on the stability of the mixture.

Solid/ fluid separation
Processes for separating solid from fluid, such as filtration and sedimentation, are influenced greatly by the particle size.

Granule size in tablet
Successful tablet manufacture requires careful control of the size of the granules from which the tablets are compressed.

Surface area
As the particle size decrease, the surface area of particle is increases.

Adsorption
Adsorptive capacities should be increases as particle size decreases.

Different methods of characterize particle size

- Sieve analysis
- Optical Microscopy
- Sedimentation
- Lesser
- Scanning electron microscopy
- Transmission electron microscopy

Sieving Analysis
Sieving is the most widely used method for measuring particle size distribution because it is inexpensive, simple, rapid, with little variation between operators. Although the lower limit of application is generally considered to be 50 microns, micromesh sieves are available for extending the lower limit 10 microns.

In united state, two standards of sieves are used. In the Tyler Standards Scale, the ratio of the width of opening in successive sieve is $\sqrt{2}$. The procedure involves the mechanical shaking of sample through a series of successively smaller sieves, and the weighing of the portion of the sample retained on each sieve. [4]

Advantages
1.Easy to perform
2.Wide size range
3.Inexpensive

Disadvantages
1.Known problem of reproducibility
2.Wear/damage in use or cleaning
3.Irregular/ agglomerated particle
4.Rod shape particle
5.Laboure intensive[5]

Microscopy
Microscopy is the most direct method for size distribution measurement. Its lower limit of application is determined by the resolving power of the lens. A particle cannot be resolved if its size is close to wave length of the light source. For white light, an ordinary microscope is used to measure particle from 0.4 to 150 microns. With special lenses and ultraviolet light, the lower limit may be extended to 0.1 microns .In the ultra microscope, is from 0.01 to 0.2 micron.

The diameters of particles on the slide are measured by means of calibrated filar micrometer eyepiece. Graticules or eyepieces with grids of circles and squares are used to compare the cross-sectional area of each particle in the microscopic field with one of each particle in microscopic field with one of the numbered patterns. The magnification is determined by the use of a calibratrated stage micrometer.[4]

Electron microscopy
Advantages
1. Particles are individually examined.
2. Visual means to see sub-micron specimen Particle shape can be measured.

Disadvantages
1.Very expensive.
2.Time consuming sample preparation.
3.Materials such as emulsions difficult/ impossible to prepare
4.Low throughput - Not for routine.[5]

Laser Diffraction
Laser Diffraction Particle Size Analysis (Particle size range 0.02-2000μm/0.01-3500 μm)
Particles pass through a laser beam and the light scattered by themes collected over arrange of angles in the forward direction. The angles of diffraction are, in the simplest case inversely related to the particle size. The particles pass through an expanded and collimated laser beam in front of a lens in whose focal plane is positioned a photosensitive detector consisting of a series of concentric rings. Distribution of scattered intensity is analyzed by computer to yield the particle size distribution.

In essence, each particle scatter pattern is matched to a theoretical pattern using comprehensive mathematical solution to the scattering of incident light by spherical particles; the Mie Theory. This theory indicates the necessity for a precise knowledge of the real and imaginary components of the refractive index of the material being analyzed, to determine particle size and particle size distribution. When a good fit is obtained, then we know all of the relevant information in order to deconvolute the Miepattern into meaningful particle size information.

All laser diffraction instruments rely on three basic tenets:
1. The particles scattering the light are spherical in nature.
2. There is little to no interaction between the light scattered from different particles.
3. The scattering pattern at the detectors is the sum of the individual scattering patterns generated by each particle[7].

Advantages
1. Non- intrusive: uses a low power laser beam.
2. Fast: typically <3minutes to take a measurement and analyze.
3. Precise and wide range up to 64 size bands can be displayed covering a range of up to 100,000:1 in size. Absolute measurement: No calibration is required; the instrument is based on fundamental physical properties.
4. Simple to us
5. Highly versatile

Disadvantages
1. Expense.
2. Volume measurement all other outputs are numerical transformations of this basic output form, assuming spherical.
3. particles must be a difference in refractive indices between particles and suspending medium[6]
4. The underlying assumption in the design of laser diffraction instruments is that the scattered light pattern formed at the detector is a summation of the scattering pattern produced by each particle that is being sampled. Deconvolution of the resultant pattern generates information about the scattering pattern produced by each particle and, upon inversion, information about the size of the particle.

Sedimentation
Sedimentation method may be used over a size range from 1 to 200 microns to obtain a sieve weight distribution curve and to permit calculation of particle size. The sedimentation method based on the dependence of the rate of the sedimentation of the particle s on their size. The pipette method (Andersen) is the simplest means of incremental particle size analysis[4].

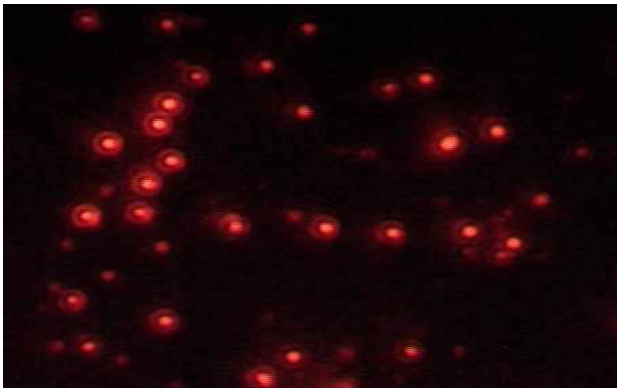

Figure 1: Light scattering patterns observed for polystyrene latex particle

NANO PARTICLE
Nanotechnology is enabling technology that deals with nano-meter sized objects. It is expected that nanotechnology will be developed at several levels: materials, devices and systems. The nonmaterial level is the most advanced at present, both in scientific knowledge and in commercial applications. A decade ago, nanoparticles were studied because of their size-dependent physical and chemical properties [8]
Living organisms are built of cells that are typically 10 μm across. However, the cell parts are much smaller and are in the sub-micron size domain. Even smaller are the proteins with a typical size of just 5 nm, which is comparable with the dimensions of smallest manmade nanoparticles. This simple size comparison gives an idea of using nanoparticles as very small probes that would allow us to spy at the cellular machinery without introducing too much interference. Understanding of biological processes on the nanoscale level is a strong driving force behind development of nanotechnology. [9]

Application
A list of some of the applications of nanomaterials to biology or medicine is given below:
1. Fluorescent biological labels [10-12]
2. Drug and gene delivery[13, 14]
3. Bio detection of pathogens [15]
4. Detection of proteins [16]
5. Probing of DNA structure [17]
6. Tissue engineering
7. Tumor destruction via heating (hyperthermia)

8. Separation and purification of biological molecules and cells [18]
9. MRI contrast enhancement[19]
10. Pharmacokinetic studies

Method to reduce particle size
Type of mill

1. Hammer mill
2. Ball mill
3. Fluid energy mill
4. Cutting mill
5. Roller mill
6. Colloid mill

A mill consist of three basic part

1. Feed chute, which delivers the material
2. Grinding mechanism, usually consisting of rotor and stator
3. A discharge chute

Principle of mills

The principle of mill depends on direct pressure, impact from a sharp blow, attrition, or cutting [4].

Hammer mill

The hammer mill is an impact mill using a high speed rotor (up to 10000 rpm) to which a number of swinging hammers are fixed. The material is fed at the top or center, thrown out centrifugally, and ground by impact of hammer or against the plates around the periphery of the casing. The material is retained until it is small enough to fall through the screen that forms the lower portion of the casing. The speed of hammer mill up to 7600 meter per minute, at which speed most material behave as if they were brittle. Brittle material is best fractured by impact from a blunt hammer. In the preparation of wet granulation for compressed tablet, a hammer mill is operated at 2450 rpm with knife edges. In the milling the dried granulation, the mill is operated at 1000 – 2450 rpm. The size of product is controlled by the selecting the speed of the hammers and the size and the type of the screen[4].

Uses

1. The hammer mill can be used almost any type of size reduction.
2. Its versatility makes it popular in the pharmaceutical industry, where it is used to mill dry material, wet filter-press cake, ointment, and slurries.
3. A hammer mill can be used for granulation and close control of particle size of powder[1].

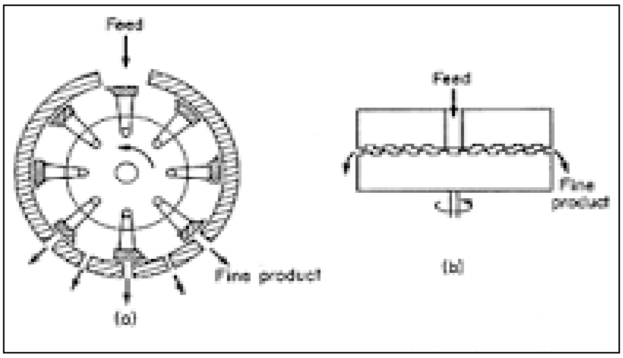

Figure 2: Hammer mill

Ball mill

The ball mill consists of horizontally rotating hollow vessel of cylinder like shape with length slightly greater than its diameter. The mill is partially filled with the ball of steel or pebbles, which act as grinding medium. If pebbles are used, it is known as pebbles mill. If rod or bars are used, it is knows as rod mill. The rod mill is particularly useful with sticky material that would hold the balls together, because the greater weight of rods causes them to pull apart. The tube mill is a modified ball mill in which the length of about four times that of diameter and which the balls are somewhat smaller than in ball mill.

The ball mill may be modified to a conical shape and tapered at the discharge end. In ball mill, rotating at a slow speed, the balls and cascade over one another, providing an attrition action. As the speed is increased, the balls are carried up the sides of the mill and fall freely onto with an impact action , which is responsible for most size reduction . the ball mill is a combination of impact and attrition. If the speed is increased sufficiently, the balls are held against the mill casing by centrifugal force and resolve with the mill.

The amount of material to be milled in a ball mill may be expressed as a material–to-void ratio. The efficacy of a ball is increased as the amount of material is increased until the void space in the bulk volume of ball charge is filled; then, the efficiency of milling is decreased by the further addition of material. Increasing the total weight of ball of a given size increases the fineness of the powder. The weight of the ball charge can be increased by increasing the number of balls or by using a ball composed of a material with the higher density. In the dry milling moisture should be less than 2 %. In the batch processing, dry ball milling produces a very fine particle size.

With wet milling produce 200 mesh particles from slurries containing 30 to 60 % solid. [4]

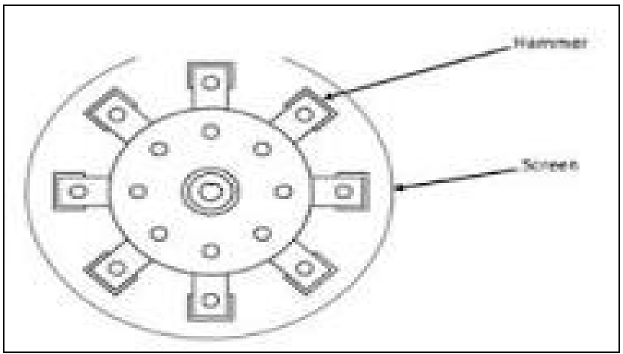

Figure 3: Ball mill

Application of Ball Mill

The ball mill is often key equipment for regrinding. It\'s widely used for the cement, the silicate product, new sort creating material, fire-proof material, chemical fertilizer, black and non-ferrous metal, glass, ceramics and etc. A ball mill can grind ore or other materials that could be grinded either by wet process or by dry process.

The Working principle of ball mill

The ball mill can be a skeleton pattern ball mill with horizontal cylindrical turning gear, drive by outer gear and two hoppers. The information visits the 1st hopper after the spiraling through the quill shaft from the feeding equipment. The hopper has ladder sheathing or corrugated sheathing with steel balls inside, which will fall under the effects of centrifugal force by barrel embracing ram tough and grind material. Following the kibbling inside 1st hopper, by monolayer partition panel, the pad will type in the second hopper, containing plane scale board with steel ball inside to grind materials. The powder material will be discharged from the grid plate to finish the grinding.

Fluid energy mill

In the fluid-energy mill or micronizer the material is suspended and conveyed at high velocity by air or steam, which is passed through nozzles at 100 to 150 pounds per square inch (psi). The violence turbulence of the air and steam reduces the particle size chiefly by interparticular attrition. Air is usually used because most pharmaceuticals have low melting point or are thermolabile . As the compressed air expands at the orifice, the cooling effect counteracts the heat generated by the milling. The fluid energy mill reduces the particle to 1 to 20 microns. [4]

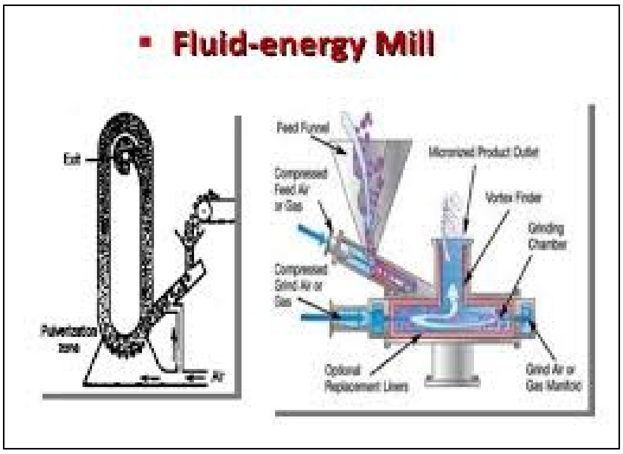

Figure 4: Fluid energy mill

Cutting mill

Cutting mills are used for tough, fibrous material and provide a successive cutting or shearing action rather than attrition or impact. The rotary knife cutter has a horizontal rotor with 2 to 12 knives spaced uniformly on its periphery turning from 200 – 900 rpm and a cylindric casing having several stationary knives. The bottom of the casing holds a screen that control the size of material discharged from the milling zone. The feed size should less than 1 inch thick and should not exceed the length of the cutting knife. [4]

Cutter mill is size reduction equipment consisting of a series of uniformly spaced knives (2 to 12 in number) attached to a horizontal rotor (rotating knives) which act against a series of stationary knives attached to the mill casing. The bottom of the mill has a screen attached to control the residence time of the particles inside the mill head. Size reduction process involves successive mechanical sheering of the feed material with the help of sharp knife.

Cutter mills produce coarse particles from:

- Dried granulations before tableting and
- Fibrous crude medicinal/roots, barks prior to extraction

Particles size are determined by

- Rotor size
- The gap between the two (2) sets of knives
- Screen/sieve

Although cutter mill may differ from one another in whether the knives are movable or fixed and in classifier's configuration, two cutting mill subclasses have been identified

- Double runner disc mill
- Single runner disc mill

Table 1: General characterization of various type of mill [4]

Type of mill	Action	Product size	Used for	Not used for
Cutter	cutting	20 -80 mesh	Fibrous, crude, animal and vegetable drugs	Friable material
Revolving	Attrition and impact	20-80 mesh	Fine grinding of abrasive material	Soft material
Hammer	impact	4-325 mesh	Almost all drug	Abrasive material
Roller	pressure	20-200 mesh	Soft material	Abrasive material
Fluid energy	Attrition and impact	1-30 μm	Moderately hard , friable material	Soft and sticky material

Pharmaceutical uses of Cutter Mill

- It is It is used to mill fibrous materials prior to extraction
- used for milling tough materials
- It is also used to produce coarse particles from dried granulations before tableting.

Advantages of Cutter Mill

- It is the best option of size reduction when impaction, attrition or compaction type milling is not effective especially for tough, fibrous or resilient materials.
- It is easy to install, operate and maintain.
- The equipment is not expensive

Disadvantages of Cutter Mill

1. Cutter mill is not suitable for most pharmaceutical applications due to the formation of wide particles size.
2. It is not easy to clean after use[20, 21]

Figure 5: Cutter Mill

Roller Mill

Mills consist of 2 to 5 smooth rollers operating at different speed; thus, size reduction is effected by a combination of compression and shearing action[4, 22].

Colloid mill

A colloid mill consists of a high a speed rotor (3000 to 20000 rpm) and stator with conical milling surfaces between which is an adjustable clearance ranging from 0.002 to 0.03 inches. In pharmacy, the colloid mill is used to process dry materials. The premilled solid are mixed with the liquid vehicle before being introduced into the colloid mill.

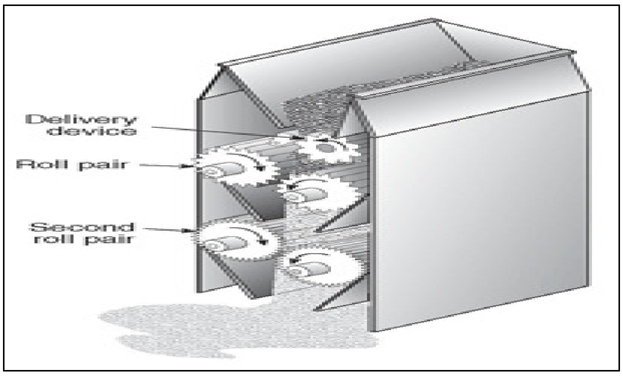

Figure 6: roller mill

A colloidal mill tends to incorporate air into a suspension. [4]

Application of particle size [22]

On-line measurement of the size of silicon carbide (SiC) nanoparticles

The synthesis of Silicon Carbide nanoparticals by laser pyroly is a route that creates aggregated nano-objects. The online particle size determination permits to limit the nanoparticles exposure and to control the process and avoid a particle size deviation.

Choosing the most Suitable theory in laser diffraction - Mie or Fraunhofer

It is possible to use two different theories adapted to the nature of particles. This application note is a quick guide to know model limits and consequences of their using on calculated particle size distributions.

Choosing the most suitable shape parameter in morphological analysis

In the literature, tens of shape parameters enable the morphology of particles to be characterized. This application note is a quick guide to choose the most suitable shape parameter.

Combined analysis of the size and shape of particles in the pharmaceutical industry

Many analytical methods exist for the characterization of products manufactured in the pharmaceutical industry. Measuring the size and shape of particles or emulsions is undoubtedly one of the simplest and quickest methods, but provides indispensable qualitative data to assess the feasibility of a manufacturing process or the final effectiveness of a formulation. Measuring size and shape is part of the precise requirements of the standards taken as the basis for the assessment of the possibilities for particle size analysis techniques and the benefits of morphological analysis for this application.

Characterization of a water/oil emulsion by laser diffraction

Emulsions are mixtures of non-miscible liquids that form a dispersion of fine droplets in a continuous phase. Such biphasic systems are very extensively used in a wide range of industrial sectors, such as the pharmaceutical and cosmetics industries, agro-foods or petrochemicals, for example. The particle size analysis of the droplets enables us to fix.

The importance of quality methods in the precise sizing of microsphere's diameter

Different characterization principles are used to measure the size of polymetric microspheres. Taking into account the number of size measurements made daily in the ESTAPOR laboratory, CILAS particle size analyzer is used in regular metrological controls by MERCK, assure a standardized product at the end.

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