International Journal of Pharmaceutical Research and Development

ISSN Print: 2664-6862
ISSN Online: 2664-6870
Impact Factor: RJIF 8
IJPRD 2024; 6(1): 01-05
www.pharmaceuticaljournal.net
Received: 03-11-2023
Accepted: 04-12-2023

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A comprehensive review of particle size analysis techniques

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DOI: https://doi.org/10.33545/26646862.2024.v6.i1a.37

Abstract
In this review, we will discuss particle size analysis as it relates to specific pharmaceutical applications and regulatory aspects, fundamental principles, measurement techniques, and instrumentation types. We will cover the different types of measurement techniques that are commonly used in the pharmaceutical industry. This analysis is highly informative and will have a positive impact on the pharmaceutical field. Readers will gain a lot of knowledge from this review. Particle size is a critical process parameter in pharmaceutical production, as it can greatly affect the physical and chemical properties of drug substances and dosage forms. Particle size distribution (PSD) is one of the most important parameters to check when evaluating a new drug. Size reduction is a vital unit operation that is extensively used in pharmaceutical manufacturing. This process involves reducing large solid unit masses into small unit masses, coarse particles, or fine particles. Size reduction is also known as comminution, diminution, or pulverization.

Keywords: Particle size distribution (PSD), size reduction, comminution, diminution

Introduction
The investigation of particle size has significant significance in several technological domains. The majority of solid materials commonly used undergo a transformation into a powdered or granulated state at some stage. Illustrative instances may readily be identified within the realm of medicines, including both medications and excipients. Similarly, within the domain of foods, notable illustrations can be seen about grain, flour, and sugar. Furthermore, materials technology offers compelling examples, particularly in ceramics and abrasives. The primary motivation for studying the dimensions of these particles is their impact on their physical characteristics and their behavior throughout different manufacturing procedures. Most pharmaceutical products include particles of active and non-active medicinal substances in various forms, such as dry powders, liquids, and semisolid dispersions. These particles may range in size from nano-colloids to millimeter-sized granules, depending on the specific dosage form and route of administration [1].

Objectives
The dissolution rate and bioavailability of active pharmaceutical components are only two examples of how particle size and shape may impact these and other crucial physical qualities, manufacturing process abilities, and quality features. The pace at which a drug in a sustained or controlled release formulation begins to work. The in vivo particle dispersion and deposition, absorption rate, and clearance time are particularly relevant for aerosols and other colloid systems developed for targeted drug administration. Particle size analysis is also necessary to ensure the quality of the finished dosage forms and drug delivery systems [2].

Methodology
In identifying sources for this literature review, multiple databases were used. The data was collected from the online research paper, journal books which were published in different search websites such as Google, Google Scholar, PubMed, Research gate etc. and other collection were utilized in this review to obtain information. A massive amount of recently published articles from 2000 to 2020 were analyzed.

Particle size and shape may significantly impact a wide range of beneficial physical qualities, processing capabilities, and quality characteristics. The goals of particle size analysis are measurements of the average particle size, particle size distribution (PSD), and shape of substances for use in pharmaceutical formulation. Particle size analysis is also necessary to ensure the quality of the finished dosage forms and drug delivery systems. After reviewing the studies above and journals, we now know that the particle size range for various dosage forms and routes of administration (Suspension 1-50 nm, emulsion 0.2-100 nm, aerosol 1-10 nm, nasal 8-20 nm, intravenous 200-2000 nm, transdermal 10-600 nm) and the significance of particle size a) can vary greatly depending on the method of measurement used (Stream scanning, Field scanning, Sieving, Microscopy, Electrical sensing Nano sizing methods of varying complexity and statistical comparison are also discussed.

Application of particle size analysis

The size reduction process is beneficial in facilitating the quick development of solutions in chemical substances, as it effectively enhances the surface area of drugs.

The increased surface area makes the extraction of active ingredients from animal glands (such as the liver and pancreas) and crude vegetable pharmaceuticals easier, allowing solvents to readily permeate the tissues and aid fast extraction [3].

The therapeutic efficacy of particular drugs may be enhanced by reducing particle size. The decrease in size is of significant importance when considering suspensions. The formation of a cake, which may provide challenges for re-dispersion, may occur when particle size is too tiny. Therefore, it is crucial to consider and choose an appropriate particle size.

The optimum particle size is of utmost importance when considering inhalers. Tiny particles may be expelled from the bronchioles along with air without causing any noticeable impact, whereas much larger particles may fail to reach the alveoli and be absorbed into the bloodstream [4].

Limitation of size reduction analysis

Not suitable for all drugs containing volatile oils (Cinnamon, clove) must not be subjected to heavy grinding to prevent the loss of volatile oils. Due to the increase in surface area, oxidation and hydrolysis may occur when exposed to atmospheric conditions. Therefore, these drugs must be stored in a well-closed container and in a cool place [4].

Factors affecting size reduction

Hardness

The surface property of the material is a significant characteristic. Therefore, it is conceivable for a substance to possess hardness; nevertheless, if it also exhibits brittleness, reducing its size may not pose any significant challenges. The Mohs scale is a subjective scale used to measure the relative hardness of mineral substances, with values ranging from 1 to 10. Minerals with a hardness level below three are considered soft, while those with a hardness level beyond seven are classified as complex. In general, reducing material size becomes more challenging as the complexity of the material increases [5].

Toughness

In terms of practical importance, toughness trumps hardness since it is more challenging to decrease the size of a soft but robust material than a hard but fragile one. Liquefied gas treatment (Nitrogen, for example) might lessen the material's toughness. Even rubber gets brittle and breaks when the temperature drops below -1000 C to - 1500 C. This is not often done since the medicine might be ruined, and the equipment could break if subjected to such low temperatures.

Abrasiveness

Abrasiveness refers to the characteristics of hard materials, especially those derived from minerals, which might impose limitations on the equipment used for grinding purposes. This is because the material being ground can get contaminated with the worn-out particles from the machinery, owing to the high level of abrasiveness shown by the material. Stickiness- Adhesion of gummy substances to grinding surfaces may occur, mainly when the size reduction process involves generating heat. The use of complete dryness may potentially have beneficial outcomes. The inverse of this phenomenon, namely slipperiness, may also present challenges in size reduction since the substance functions as a lubricant and diminishes efficiency.

Softening temperature

The softening temperature of waxy substances may be attributed to the thermal energy produced during the grinding process.

Material structure

The material structure of minerals may exhibit lines of weakness similar to the cellular structure seen in vegetal medicines [4].

Particle size distribution

The particle size distribution (PSD) of a powder, granular material, or particles distributed in a fluid is a set of numbers or a mathematical function that characterizes the distribution of particle numbers throughout a range of sizes. Grain size distribution refers to the distribution of grains rather than individual grains. A substance's particle size distribution (PSD) is often relevant to deducing its physical and chemical characteristics [6].

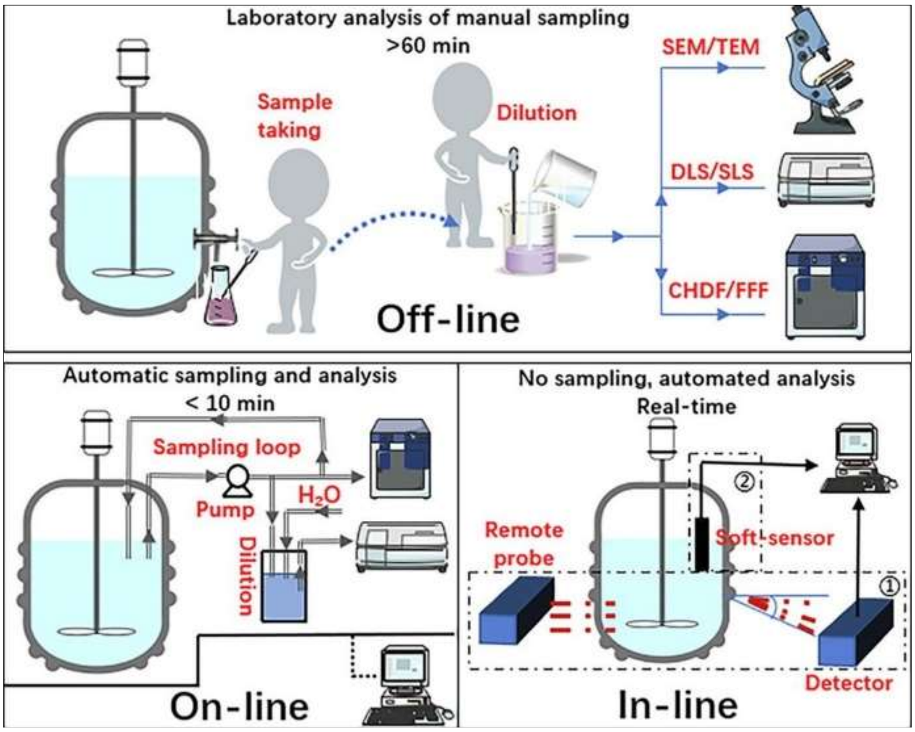

Fig 1: Measurement methods of PSD [7].

Particle size measurements

There are two primary types of scaling procedures used: stream-scanning and field-scanning. In the former, particles are measured or counted individually and then sorted into size bins. In contrast, in the latter, the particle assembly as a whole is measured at once, and the PSD is calculated from the integral field's response. There are benefits and drawbacks to both types. Stream scanning often provides better resolution, lower quantification limits, and easier data interpretation since it supplies an extra experimental parameter, the number of particles observed. On the other hand, field scanning techniques are often more rapid, reliable, and amenable to online/in-line implementations [8].

Sampling

The primary objective of sampling is to collect the minimum amount of the bulk material necessary to provide a reliable PSD. Particle segregation and inadequate sample weight are the most common causes of sampling errors when working with pharmaceutical powders. Coarse-fine particle fractions may percolate apart from one another, and different species in multicomponent mixtures can agglomerate into distinct clusters [9].

Different techniques of sampling

Grabbing

It is possible to mix powder that has been kept in a container by rolling and tossing the container. The capacity of the container should not exceed fifty to sixty-six percent of its total volume. It is essential to do this procedure before manipulating a sample with a spatula. Next, extract a sample using a spatula.

Chute Riffling

Vibrating a sample as it travels down a chute splits the material into two halves using vanes. There are four pieces since each has moved forward and been split into half again. You may keep going until you have enough for eight or sixteen servings.

Rotary Riffling

The most effective technique for dividing powders in a representative manner is the rotary riffler. The whole sample that is to be divided is sent downwards down a chute and into receptacles that are not enclosed. Each container will be allocated a sample that is indicative of the original bulk material since the distribution of material is averaged over some time. It is essential to ingest the whole of the initial bulk sample fully.

Coning & Quartering

The powder is partitioned into four distinct portions. Two diagonal parts are excluded, while two are preserved and then combined. The mixture is further partitioned into four distinct pieces, and the two diagonal sections are combined. The procedure above is iterated until the leftover sample reaches the appropriate quantity required for analysis. The experiment may be conducted using either a minimal or much larger sample size [10].

Stream Scanning and Field Scanning

Stream scanning and field scanning are two methods for determining particle size, including the particles' interaction with an external field. The size of particles is determined by measuring their interactions, which is done one at a time in stream scanning. For the most part, electrical interrogation fields are employed for stream scanning, with the Coulter principle dictating that particle size is proportional to the change in electrical impedance as it passes through the area. Interferometers can calculate particle size by measuring the phase difference between a laser beam divided in two and now traveling through the particle and the surrounding liquid. Particle size is calculated using the interference pattern created when a particle travels across the overlap of two laser beams in the phase Doppler technique.

Aerometrics, canty vision, the climate elliptical mirror optical system, AWK analyzers for contamination management, and the Kratel partascope are only some of the commercial equipment discussed in this chapter [11].

Microscopy

Microscopy is widely employed as an absolute particle sizing method in pharmaceutical R&D since it is the sole technology that allows for the direct observation, measurement, and determination of the form of individual particles. Microscopy, which allows for the inspection of individual particles, is now generally accepted as an absolute assessment of particle size. Capable of telling clusters of particles apart from individual ones. Using computers for image analysis, we can look at each field individually and determine its distribution. The depth of focus of optical microscopy is only roughly 10 m at 100 and only 0.5 m at. As particle size decreases, diffraction effects rise, blurring at the edge, making particle detection less precise [12].

Sieving

Although this method has been around for a while, it still serves a use in measuring big particles and is relatively inexpensive. This is often put to good use in the mining industry. The particle size distribution of a granular material may be evaluated using a method or process known as sieve analysis. The size distribution may have a significant impact on the material's performance. Granular materials, whether organic or inorganic, may be sieved for examination. Due to its ease of use, this method of particle size is perhaps the most widespread. When doing a sieve analysis, a stack or nest of sieves is used, with each successive sieve having an aperture size the same as the one above. Sieves may be referred to either by their aperture or mass size. Despite its antiquity, this method is low-cost and highly applicable for estimating oversized particles. This is often put to good use in the mining industry. The particle size distribution of a granular material may be evaluated using a method or process known as sieve analysis. The size distribution may have a significant impact on the material's performance. Granular materials, whether organic or inorganic, may be sieved for examination. Due to its ease of use, this method of particle size is perhaps the most widespread. When doing a sieve analysis, a stack or nest of sieves is used, with each successive sieve having an aperture size the same as the one above. Sieves may be referred to either by their aperture or mass size [12].

Electrical sensing zone method, coulter counter

The instrument quantifies particle volume using dv, representing the diameter of a sphere with an equivalent volume to that of the particle. Determining the quantity and dimensions of particles suspended in an electrolyte involves their passage through an aperture, with an electrode submerged on either side of the opening. The voltage pulses produced by the variations in electric impedance as particles traverse the orifice have an amplitude that is directly proportional to the volume of the particles [12].

Laser Light Scattering Techniques

Particle size measurement using laser light scattering methods has gained prominence in several fields, including combustion research. Current research and industrial applications place stringent demands on the geometry, accuracy, and other characteristics of the instruments used in these fields. In this article, we look at some of the methods now in use, both those already on the market and others still in the conceptualization stage. Amplitude-dependent approaches and amplitude-independent methods are distinguished. Principles of operation and challenges in utilizing laser-based approaches for particle-size instrumentation are reviewed. Some methodologies and their research and industrial applications are also discussed. Anyone just starting to learn about or use a laser-illuminated particle-sizing technique will find this paper invaluable. Quantifying Particle Size by Laser Diffraction Particle Size Analysis using Photon Correlation Spectroscopy [12].

Laser diffraction

Light dispersed by particles traveling via a laser beam is gathered as it enters the detector from different angles. In the most straightforward instance, the particle size has a negative correlation with the diffraction angles. Particles go via a focused laser beam that has been magnified and collimated by a lens, and a photosensitive detector made out of a stack of rings is located in the lens's focal plane. The particle size distribution may be calculated by analyzing the scattering intensity distribution using a computer [12].

Permeametry Technique

The permeametry method measures the pressure drop and flow rate through a powder bed of specified dimensions to calculate the average particle size of a gas or liquid. Some coarse particulate solids with different particle sizes and shape properties were used to assess the air permeametry of powder beds. Each powder's specific surface area was determined using the kozney-carman equation. The Reynolds number was used to analyze the airflow conditions in the powder bed. Powder surface areas were determined after microscopic analysis of the materials revealed the sizes and shapes of the particles. Powder bed height and packing density did not affect permeametry surface area, it was observed. The Reynolds value showed that the Koeny-Carman equation could be used for the flow situation. In general, permeametry yielded larger surface area measurements than microscopy, although the two methods showed a strong correlation. Finally, the exterior surface area of coarse particulate materials may be measured using the air permeametry technique. When determining the surface area of a porous material, it is more accurate to utilize the granule density rather than the actual density. The methods section comes up next. Here, I will learn about the several methods for determining particle size and the specifications that must be met [12].

Discussions

Nanosizing is a technique used in the pharmaceutical industry to reduce the size of a medicine to the sub-micron range to improve its solubility and bioavailability. The term "nano sizing" refers to a procedure used in the pharmaceutical industry to reduce the particle size of the active medicinal component to the nanometer range. This is defined as a particle size of less than one micrometer. Nanosizing methods have gained popularity because they may be used with a wide variety of chemicals, including those with low solubility. Improving the bioavailability of poorly soluble medications using these methods is called "non-specific techniques." The Noyes-Whitney equation states that poorly soluble medications may be absorbed more effectively by decreasing their particle size since this increases their surface area and dissolving rate. Nano-sizing methods have recently advanced, allowing the pharmaceutical sector and researchers to manufacture particles in the 100-200 nm range reliably. Top-down, bottom-up, and hybrid strategies are the three main categories of Nano sizing pharmaceuticals. Top-down methods use high-energy processes like media milling and high-pressure homogenization to reduce particle size. The FDA has authorized six top-down-prepared Nano crystal medications available today. Since these operations occur in liquids, the resulting Nano suspensions may be turned into pills or sold directly to consumers. Concerning active pharmaceutical ingredients (APIs), solid oral medication formulations, semi-solids, and sterile liquids, particle size is a significant quality factor. Due to the tiny sample sizes and probable settling of the sample, etc., it is crucial to ensure representative sampling, sample homogeneity, and particle morphology. Particle size may be determined using several methods, including stream scanning, field scanning, sieving, microscopy, the electrical sensing zone method, laser light scattering, laser diffraction, and permeametry. However, laser diffraction is the method that has seen the most widespread application. Measurements may be exact and reproducible, but knowing the method's limitations is essential for gathering valuable data. When it comes to the development and production of numerous pharmacological dosage forms, particle size analysis is crucial. When developing pharmaceutical drugs, it is crucial to maintain strict control over particle size distributions. The particle size distribution of a powder is a useful performance and quality metric. Research and development of a novel pharmaceutical medicine is followed by determining the most efficient means of transforming the drug's active pharmaceutical ingredients (API) into a usable dosage form for human consumption. Critical criteria for the medication formulation are the API and excipients' (Fillers and lubricants) flowability and simplicity of handling. The most crucial factors in determining a medicine's efficacy, quality, and bioavailability are its dissolution rate and its homogeneity and consistency of drug content. In pharmacology, "bioavailability" describes how well and quickly a medicine enters the bloodstream after being taken orally. At various points, all pharmaceuticals undergo testing and evaluation to see how pharmaceutical particles and powders affect bioavailability and performance. Target particle size distribution parameters are defined to manage manufacturing uniformity and medication product quality after the effect has been studied during the final stage of development. Formulations are crucial in medication development because they guarantee that the drug's active ingredient is taken at the proper dose and administered at the right time (Not too quickly or slowly).

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