Int J Pharma Res Health Sci. 2020; 8 (3): 3185-91
DOI:10.21276/ijprhs.2020.03.06
Poonam *et al.*
CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

PHS Scientific House
PHARMAHEALTHSCIENCES

International Journal of Pharma Research and Health Sciences

Available online at www.pharmahealthsciences.net

Review Article

Recent Advances in Particle Characterization and its Application in Pharmaceutical Industry

Poonam Dogra[1,*], Shikha Atteri [1], Sanjay Kumar[2]

[1] Department of Pharmaceutical and Health Sciences Career Point University, Hamirpur , Himachal Pradesh, India.
[2] Gautam College of Pharmacy, Hamirpur , Himachal Pradesh, India.

ARTICLE INFO

Received: 02 Jun 2020
Accepted: 28 Jun 2020

ABSTRACT

Particle size characterization is a area of analytical chemistry which is required in a great number of industries where the product's end-use is affected by particle size distribution. The Particles can be in the form of solids, liquids, or gases or an aggregation of molecules as in the case of micelles. Particularly In some instances, especially in the area of pharmaceuticals finished forms, analyses are done to ensure the absence of particulate matter in the product. Particle size characterization helps in monitoring the environment accurately for particulate matter as well as particle size distributions, concentrations for full assessment of health hazard substances. The growing interest in particle size characterization and analysis, especially among analytical chemistry researchers, the subject is mainly emphasized on the application. The number of techniques available for particle size analysis is confounding. More than 250 methods have been reported by the analytical researchers for understanding and assessing the particle size.. Because of the broad scope of this area in terms of techniques and analytical approaches, products, and size ranges major technique areas have been discussed. which have received the most attention in recent years: radiation scattering and chromatographic techniques. The new and growing areas are rapidly becoming techniques of choice especially for the rapid analysis of submicrometer particles.

Keywords: Particle Size Characteristics, Analytical Technique, Size, Chromatographic techniques

1. INTRODUCTION

Particle size characterization techniques currently in use within pharmaceutical industry and academia. It assumes no prior knowledge of particle characterization theory or instrumentation and should be ideal for those new to particle

Corresponding author *
Poonam Dogra,
Department of Pharmaceutical and Health Sciences Career Point University Hamirpur , Himachal Pradesh, India
E-mail: poo.nu04@gmail.com

characterization, or those wishing to reinforce their knowledge in the area [1].

Earlier there were particle-sizing techniques which use manual microscopy and sieving. These methods are still used today, but both the techniques have drawbacks. If you look at microscopy is slow and manually intensive, while sieving is unsuitable for fine or cohesive materials. As such, industry has sought more advanced particle-sizing techniques came into picture. [2].

Particle can be defined as a discrete sub-portion of a substance. It includes solid particles, liquid droplets or gas bubbles with physical dimensions ranging from sub-nanometer to several millimeters in size [3]. The most common types of materials consisting of particles are:

1. Powders and granules e.g. pigments, cement, pharmaceutical ingredients
2. Suspensions, emulsions and slurries e.g. vaccines, milk, mining muds
3. Aerosols and sprays e.g. asthma inhalers, crop protection sprays.

Their main reasons why many industries routinely employ particle characterization within their core business arena is for better controlling of product quality. So that it can deliver real economic benefits to the scientific society. It mainly emphasizes on ability to charge higher premium for the finished product and helps to reduce customer rejection rates [4]. The regulatory market is enforcing it as a mandatory for compliance.

2. PARTICLE SIZE AND CHRACTERIZATION

The particle size characterization helps in better understanding of how particle properties affect products, ingredients and how the processes will allow you to improve product performance.

In addition to chemical composition, the behavior of particulate materials is often dominated by the physical properties of the constituent particles. These can influence a wide range of material properties including, for example, reaction and dissolution rates. The following physical properties will help in knowing the particle characteristics.

1. Particle size
2. Particle shape
3. Surface properties
4. Mechanical properties
5. Charge properties
6. Microstructure.

Then there are mobility techniques which can be used for characterization. The most important ones are electrozone sensing (also called coulter counting) and aerodynamic time-of-flight measurements. Electrozone sensing is performed in a liquid and the sample needs to be dispersed. Aerodynamic time-of-flight can be performed in both gas and liquid samples, but is much applied in aerosol characterization in pharmaceutics.

The most important physical property of particulate samples is particle size. Particle size measurement is routinely carried out across a wide range of industries and is often a critical parameter in the manufacture of many pharmaceutical products [6].

Particle size has a direct influence on material properties like:

1. Reactivity or Dissolution Rate e.g. Catalysts, Tablets
2. Stability in Suspension e.g. Sediments, Paints
3. Efficacy of Delivery e.g.. Asthma Inhalers
4. Texture and Feel e.g. Food Ingredients
5. Appearance e.g. Powder Coatings and Inks
6. Flowability and Handling e.g. Granules
7. Viscosity e.g. Nasal Sprays
8. Packing Density and Porosity e.g. Ceramics.

Measuring particle size and understanding how it affects your products and processes can be critical to the success of many manufacturing industries

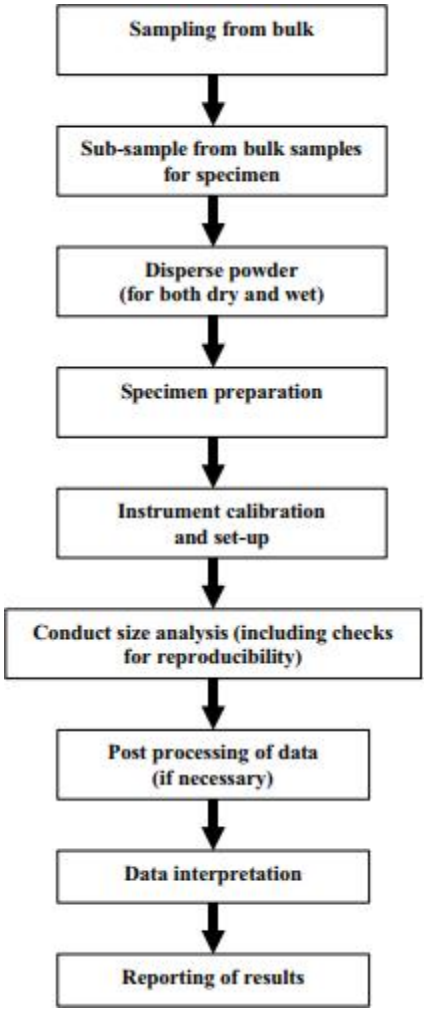


Fig 1: Procedural Flowchart for assessing Particle Size and Size Distribution Analysis [5]

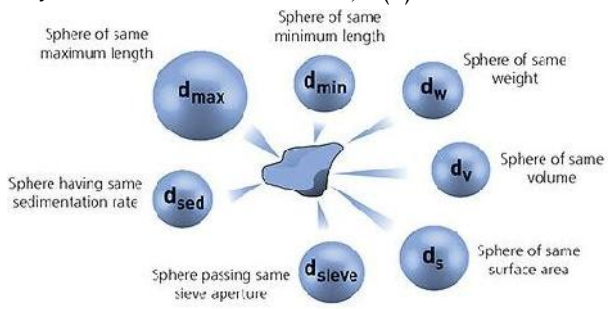


Fig 2: The different spheres of the particles for characterization

Particles are usually 3-dimensional objects and unless they are perfect spheres (e.g. emulsions or bubbles), they cannot be fully described by a single dimension such as a radius or diameter. In order to measure, it is often convenient to define the particle size using the concept of equivalent spheres (Figure 2). The particle size is actually defined by the diameter of an equivalent sphere having the same property as the actual particle such as volume or mass for example. It is important to realize that different measurement techniques use different equivalent sphere models.

Usually the interpretation of particle size distribution data, a range of statistical parameters can be calculated and reported. The choice of the most appropriate statistical parameter for any given sample will depend upon how that data will be used and what it will be compared with. For example, if you wanted to report the most common particle size in your sample you could choose between the following parameters:

1. MEAN - 'AVERAGE' SIZE OF A POPULATION
2. MEDIAN - SIZE WHERE 50% OF THE POPULATION IS BELOW/ABOVE
3. MODE - SIZE WITH HIGHEST FREQUENCY.

If suppose the shape of the particle size distribution is asymmetric, as is often the case in many samples. The best way to interpret is to measure the particle distribution (Figure 3).

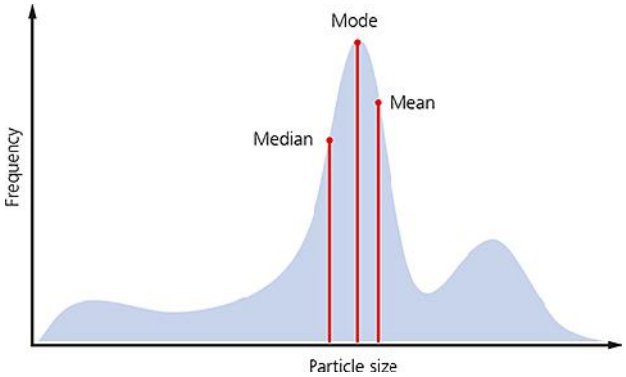


Fig 3: The particle size distribution in mean mode and median.

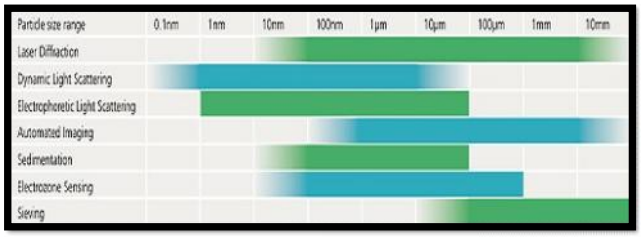
There is a wide range of commercially available particle characterization techniques in the market that can be employed to measure particulate samples. Each and every one has its relative strengths and limitations [7]. To be precise there is no universally applicable technique for all samples and at all situations.

There are number of criteria's one must be considering when they decide on what particle characterization techniques need to be used during the analysis will depend on the following criteria's.

1. Which Particle Properties Are Important To Me?
2. What Particle Size Range Do I Want To Work Over?
3. Are My Samples Polydisperse I.E. Do I Need A Wide Dynamic Range?
4. How Quickly Do I Need To Be Able To Make Measurements?
5. Do I Need To Measure At High Resolution?
6. Do I Need Good Statistical Sampling For Robust Qc Measurement?
7. Do I Need To Disperse My Sample Wet Or Dry?
8. How Much Money Am I Prepared To Spend?

The following table is designed to provide some basic guidelines which will help us to decide which of some of the commonly used techniques could be most suitable for a particular application. The particle size ranges indicated are a guide only and exact specifications may vary from one instrument to another as per the manufacturer.

Table 1: Particle size characterization and the technique used for measurement as per the standard guidelines [8]



Technique	Size	Shape	Zeta potential	Dynamic range	Rapid	Resolution	Sampling	Wet	Dry
Laser Diffraction	•			••••	•••	••	•••	•	•
Dynamic Light Scattering	•			•••	•••	••	••	•	
Electrophoretic Light Scattering			•	•••	•••	••	••	•	
Automated Imaging	•	•		••	••	•••	••	•	•
Sedimentation	•			••	•	••	••	•	
Electrozone Sensing	•			•	••	•••	•	•	
Sieving	•			•	•	•	•	•	•

Virtually all particle characterization techniques will involve a degree of sub sampling in order to make a measurement. Even particle counting applications where the entire contents of a syringe are measured, for example, will only examine a small fraction of all the syringes on a production line. It is therefore essential that the subsample measured by the instrument is as representative as possible of the whole.

Where instruments (laser diffraction for example) require presentation of the sample as a stable dispersion, the effects of any sampling issues are minimized by homogenizing,
stirring and recirculating the material. This does not, however, deal with the challenge of taking a representative 10g aliquot from a 10,000 kg batch for example. One common method that is widely used to increase the robustness of powder sampling is a device known as a spinning riffler.

As per the literature particle characterization techniques require the sample to be analyzed in some sort of dispersed form where the individually particles are spatially separated. Basically two approaches usually used. They are as follows:

1. Wet dispersion - particles dispersed in a liquid
2. Dry dispersion - particles dispersed in a gas (usually air).

The following techniques are usually used for the measurement of the particle size such as:

1. Laser Diffraction Particle Sizing
2. Dynamic Light Scattering
3. NIBS (Non-Invasive Back-scatter) technology
4. Automated Imaging

The above mentioned techniques are basically characterized based on the type of the particle that has to be determined.

Particle-characterization data is central to the development, manufacture, and quality control of pharmaceutical products. The characteristics of a pharmaceutical's composite particles can affect the product in many ways, including by influencing drug efficacy and stability, as well as how the product behaves during processing. Particle characterization uses the International Conference on Harmonization's (ICH) Q6A guideline on specifications [9] is a useful starting point because it identifies potentially important particle variables, including polymorphic form, enantiomeric purity, and particle size and distribution. Today, particle characteristics are attracting even greater focus as industry strives to increase manufacturing efficiencies. This drive has been largely influenced by the growing emphasis on quality by design (QbD).

3. APPLICATIONS OF PARTICLE SIZE MEASUREMENTS

The most common applications of size exclusion chromatography is synthetic polymer, biopolymer and protein analysis, but it can also be used for nanoparticles separation. For synthetic polymers an organic mobile phase is often used. For biopolymers and proteins, an aqueous eluent is used. Hydro dynamic chromatography is a flexible technique which is suitable for quite a broad range of applications. The technique has the same advantages as SEC; it is fast, requires only low sample amounts and it can be performed on regular LC systems. One of the biggest advantages is that it is not limited to solute species but also suitable for colloids and particulates.

The present development in particle characterization by using Hydro Dynamic Chromatography is a multi-detection approach in which triple- and quadruple detector HDC is used. This is attractive because more information of the sample and analyte can be obtained in a single analysis. By Using quadruple-detector approach both size and shape of latexes could be characterized in one chromatographic run [10].

Field-flow fractionation (FFF) is knows for many applications in environmental sciences. Especially sedimentation FFF is applied in this field. A broad particle size range can be analyzed and for this reason provides a good alternative for membrane filtration which has a cutoff point. Furthermore, it is faster than microscopy which makes it an attractive new technology in the environmental field.

The other techniques which can be employed for particle size characterization includes, Electro zone Sensing [11], Aero Dynamic Time of flight analysis [12]. Techniques such as light scattering [13], dynamic scattering [14, 15], Acoustic and electroacoustic spectroscopy [16] are the latest techniques for better understanding the particle size.

4. REPORTING OF PARTICLE SIZE DATA

Reporting particle size and particle size distribution information is as critical a component as designing and conducting the experiments that generate this information. The main consideration while reporting size and size distribution data is to ensure that all pertinent information is presented, such that the experiments conducted to generate this information can be reproduced when necessary. This feature is of particular interest for comparing and communicating the particle size and size distribution data between different laboratories or between suppliers and customers. Thus, effective communication of size and size distribution data requires that pertinent information be provided in the most efficient manner.

5. DISCUSSION

There are wide ranges of analytical techniques which can be used for particle characterization. Techniques described in this report are only a fraction of all techniques available. It is not difficult to imagine that it is difficult to choose the most suitable technique for a certain application or for a specific laboratory. In order to compare these techniques, the principles, advantages and limitation should be compared. It should be stressed, that these techniques are based on the equivalent sphere theory and that this introduces inaccuracies by definition. Additionally, it should be noted that care should be taken when results of different analytical techniques are compared. This is because techniques might use different statistical means (volume, number, length, etc.). There is not one superior technique to be used for particle characterization. All have their own strengths and weaknesses. Different applications will require different measurements and techniques. In order to provide a

comparison of the techniques mentioned in this report, table 3 provides an overview of the analytical techniques which are reviewed. Different factors will be addressed for comparison purposes. Specifications of the techniques are checked with instrument manufactures.

Table 3: A comparative picture of the analytical techniques employed in determination of particle size

Analytical Technique	Size range	Sensitivity	Concentration range	Sample preparations	Sample	Sample size	Chip possibilities	Analysis time
Sedimentation	> 1 µm	Dependent on detection technique	Variable	None Dilution	Dispersion	~100 µg	No	Sample and method dependent
Sieving	> 10 µm	Low	Concentrated	Variable	Dry Dispersion	Variable	No	Few minutes
SEC	< 0.5 µm	Dependent on detection technique	< 500 µg[1]	Dilution Other[2]	Solution	< 1 mL	No	~ 30 min
HDC	0.03 – 2 µm[3], 0.02 – 50 µm	Dependent on detection technique	< 500 µg[1]	Dilution Other[2]	Solution Dispersion	< 1 mL	Yes	~ 30 min
FFF	10 nm – 10 mm	Dependent on detection technique	< 500 µg, 0.5 – 5 mg4	None Dilution	Solution Dispersion, Emulsion	< 1 mL	Yes	10 – 90
Electrozone sensizing	10 nm – 100 µm	Good[5]	Diluted	Dilution	Dispersion (aq)	< 1 mL	Yes	Few minutes
ATOF	3 nm – 3 µm[5]	Variable	< 10^{10} (particles/ m^3)	None	Aerosols Dry	Variable	No	< 1 min
RALS	Approx. < 30 nm[6]	Good	Diluted	Dilution	Solution Dispersion	> 12 µL	Yes	< 1 min
LALS	nm - mm	Low	Diluted	Dilution	Solution	> 12 µL	Yes	< 1 min
MALS	nm - mm	Good	Diluted	Dilution	Solution Dispersion	> 12 µL	Yes[7]	< 1 min
DLS	1 nm – µm	Good	Diluted	Dilution	Solution Dispersion, Emulsion	> 12 µL	Yes	< 1 min
(Electro-)Acoustic spectroscopy	10 nm - 1 mm	Good	0.1 – 50% vol.[2]	None	Solution Dispersion Emulsion	~ 1 mL	No	< 1 min

It should be considered that factors are sample and application dependent. The most distinct differences between analytical methods for particle characterization that should be noted:

1. Chromatographic techniques (SEC, HDC, FFF), have the longest analysis time
2. Sieving and (electro) acoustic spectroscopy are the only techniques which can be used for the analysis of concentrated samples.
3. Most techniques use 'wet' samples. Only few can handle powders, other dry samples or aerosols.
4. More than half of the techniques discussed in this report can be applied on-chip. This could indicate a growing interest in on-chip particle analysis, which can be interesting for in-field analysis.
5. Generally, the sample preparation for these techniques is quite simple and fast, making the techniques accessible of all sorts of laboratories.
6. Since only small sample amount are required for most techniques, it is important that attention is paid to the sampling procedures. A representative sub-sample is needed in order to assess a total sample. When only small samples are required and used for analysis, this becomes even more important.

Even though, only a fraction of all analytical technique for particle characterization is discussed in this report, it is clear that there is not one superior technique. Depending on the type of sample and information required the most suitable analytical technique should be selected. Whichever technique is chosen, the equivalent sphere theory is used and this will induce errors. Moreover, results from different techniques cannot be compared directly due to different statistical means result from different techniques. The results should be interconverted, but this will increase the error of the analytical method itself.

Sedimentation and sieving is the most simple and cheap methods for particle size analysis. However, only relatively

large particles can be sized using these methods. For particle separation, chromatographic methods such as SEC and HDC are the more advanced methods. They can separate the other side of the particle range (macromolecules and very small particles). If the molecules and particles become too large, they cannot be analyzed and may clog the system. Multiple detectors can be used to characterize the separated materials, which is a big advantage. However, analysis times are relatively long and shear forces and unwanted interactions may appear. FFF provides a more extended range for particle characterization with only limited shear forces and interactions. Furthermore, different field can be applied which extends the applicability. However, the instrumentation can be rather complex and the technique is relatively new and is still in development.

In the mobility techniques different advantages and limitations are seen. Electrozone sensing is a fast analytical technique with a wide size range. A conductive medium is required for the analysis, which does not make it suitable for samples which require organic solvents. The limitation of electrozone sensing is the trade-off between sensitivity and the chance of clogging. Aerodynamic time-of-flight analysis is one of the few methods used for aerosols and has a main application field in pharmaceutics. The technique has a high resolution and multiple detectors can be used for characterization of the particles. The limiting factor is that the concentration of the sample can limit the accuracy. High dilutions are required for accurate analysis. For light scattering there are multiple options which can be used, depending on the applications. In static light scattering the most important variants are RALS, LALS and MALS. The sensitivity of these methods depends on the measurement angle of the scattered light, as well as the size range which can be measured. For static light scattering the concentration should be known and the sample should be transparent and diluted. Dilution might change the characteristic of the particles and sample (e.g. aggregation). Dynamic light scattering has the advantage over this, because for this technique the concentration does not need to be known and the measurement is truly absolute. Only the viscosity of the sample solution needs to be known and the temperature should be controlled during the measurement. However, the resolution of the techniques is poor and consequently, less suitable for polydisperse samples.

Finally, (electro) acoustic spectroscopy can be used where the light scattering techniques fail. The results of this technique are in agreement with light scattering results. However, acoustic spectroscopic techniques can analyze the particle size in non-transparent and concentrated samples over a wide size range. The technique is sensitive to the presence of bubbles, which can be both an advantage and a disadvantage. The requirement for the analysis of concentrated samples is the absence of particle-particle interactions. As a result, knowledge of the sample characteristics and compounds should be present in order to provide accurate results.

6. CONCLUSION

It is further recommended to carefully select the most suitable analytical technique for particle characterization. It is better to use one single technique for sample comparison, since this is the most accurate. Generally every technique has its advantages and limitations and they should be considered during both the selection process and data analysis. Additionally, the use of the equivalent sphere theory (and possibly other theories depending on the analytical technique) should be considered and the meaning of this should be understood and employed in determining the particle size characteristics.

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Conflict of Interest: None
Source of Funding: Nil