DOI: 10.5138/09750215.2204

International Journal of Drug Delivery

2018;10(1):01-11

ORIGINAL RESEARCH ARTICLE

Particle Size Characterization- Techniques, Factors and Quality-by-design Approach

Rupinder Kaur Dhamoon[1], Harvinder Popli[1], Geeta Aggarwal[1], Madhu Gupta[1*]

Abstract

Particle size characterization is one of the key areas involved in quality assurance. The concept of particle size and size characterization acts as a foundation for all the processes involved in the production of a formulation; from manufacturing to quality control operations. Particle size characterization dictates many properties of the finished product. Particle size characterization of samples is important to make a better quality product, improve its appearance, taste, texture and shelf-life. There are many instruments for particle size characterization that are available commercially. Each instrument is based on a different technique and each technique is based on a different principle. Selecting the right particle size characterization technique for the given sample is a challenging decision. The choice of technique is made according to the sample. Sometimes even a combination of techniques is used to obtain accurate results. There are several factors upon which choice of technique depends like size range, sample quantity, cost-effectiveness etc. To ensure appropriate quality standards in the field of particle sizing and particle size characterization, ICH and US-FDA have recently insisted on including Quality-by-design approach in the pharmaceutical industry. Application of QBD approach to particle size characterization techniques ensures a resilient method which gives reproducible results. It aids in reducing result and method variations and promotes productivity and quality. The main objectives of this review are first, to understand the principle, instrumentation, and working of commercially used techniques and to compare their pros and cons; secondly, to study the factors which govern the choice of technique and lastly, to understand the concept of Quality by design and its role in particle size characterization through some example.

Keywords: Particle size characterization; techniques; factors; QBD

Introduction

Particle size and size characterization knowledge act as a prerequisite for all the processes which are involved in the production of a formulation. They influence mechanical strength, electrical and thermal properties of the finished product. Massive production losses can occur if particle sizes of the materials being used in the process are not appropriately monitored [1]. A wide range of materials starting from proteins and polymers, microemulsions, viruses, droplets, pigments up to sand and cement require particle characterization [2]. Particle size characterization is about describing particle sizes in a formulation that helps in understanding, predicting and optimizing pharmacokinetic properties of that formulation. Accurate determination of particle size is necessary for pharmaceutical industry. It is a physical parameter that must be specified, examined and managed right from the starting material to the finished product. Despite the modern instrumentation, there are some challenges faced in the field of particle size characterization-

Need for an appropriate method development specific to drug type, form, and delivery. The very minute quantity of sample available, especially, in initial stages of drug development.

Inaccuracies in data interpretation due to most of the particles being non-spherical in shape.

Correspondence: madhugupta98@gmail.com

[1]Delhi Pharmaceutical Sciences Research University, Pushpvihar, Sector-3, M.B Road,, New Delhi, 110017, India

Full list of author information is available at the end of the article.

Received: 28 Oct 2017, Accepted: 09 Jan 2018

Problems occurring during analytical measurements like agglomeration or de-stabilization [3].

For efficient particle size characterization, it is important to understand the instrumentation first. It is advised to use more than one technique to obtain accurate results. The main objectives of the present review are first, to understand the particle size characterization techniques commercially used, bycomparing their pros and cons, secondly, to study the application of Quality-by-design approach to particle size characterization and lastly, to understand its role in formulations through some examples.

Importance

The main purpose of particle size characterization in the pharmaceutical industry is to collect quantitative data on mean particle size, particle size distribution, and particle shape. The other purpose is to ensure the quality of the finished drug product. This applies to powders, suspensions, emulsions, and aerosols. Flow and compaction properties of the powders are influenced by particle size and particle shape. Smaller particles have better dissolution profile and spherical particles have better flowability [4]. Aerosols with droplets having an aerodynamic diameter of 2-5 micrometers will penetrate deeper into the lungs [3]. Particle size also greatly affects physicochemical and bio pharmaceutical properties of drug materials and final dosage forms like absorption, dissolution, bio availability, flow properties of the drug. For example, micronization of drugs like chloramphenicol, griseofulvin results in better absorption profile. But reduced particle size in case of lipophilic drugs like aspirin increases their effective surface area, thereby, decreasing their absorption manifolds. Particle size characterization in the powders ensures powder bed with appropriate and uniform particle size. It improves flow properties of the powder particles. Moreover, proper size characterization of drug materials helps in detecting contamination. Particle size characterization techniques can detect any deviations from the anticipated particle size range and hence confirm the presence of an impurity. For these reasons, particle size characterization is an important parameter in quality control of pharmaceuticals and in the improvement of particle properties [5].

Sample Presentation

Particle size characterization can be done using various commercially available instruments. Different instruments arebased on different techniques, sometimes even a combination of techniques. Generally, the sample to be introduced into the instrument is first dispersed in an appropriate medium. The dispersion can be either wet or dry. Wet dispersion involves changing the solid-air interface into a solid-liquid one, that is, the sample is first dispersed in a liquid medium. Then, agitation and mixing are done to break down the agglomerates. Lastly, the dispersion is stabilized by adding suitable surfactants. On the other hand, dry dispersion involves particles dispersed in dry form. Agglomerates in dry dispersion are broken by sheer and mechanical forces. For efficient separation, air is passed through the sample before its introduction into the instrument. There are many factors which are considered before choosing one of the two dispersions. For example, the solubility of the sample in water, agglomeration tendency, solvent compatibility, hygroscopicity, fragility and toxicity of the material [6].

Techniques of particle size characterization/ analysis

Laser diffraction technique

This technique can be more appropriately called Low Angle Laser Light Scattering (LALLS). This is now a preferred method for particle size characterization and quality control in many industries. According to ISO 13320, the particle size range where this technique is applicable is 0.1-3000 μm [7]. Laser diffraction technique by static light scattering is based upon Mie theory of light scattering which also includes Fraunhofer theory. According to Mie theory, the intensity vs angle relationship obtained from scattering of laser light, is related to sizes of the particles participating in scattering, with other variables kept constant. The variables include the wavelength of the incident laser light and relative refractive index of sample and dispersion medium [8]. The technique is based on the interaction between light and particle surface. Laser diffraction analyses particle sizes by determining angular variation in light intensity as the laser beam passes through a given sample. Bigger particles scatter light at smaller angles and smaller particles at wider angles [9]. Many particles together form a pattern of scattered light which can be converted into a particle size distribution curve. Utilizing Mie theory of light scattering, the particle size is measured as Volume-weighted distribution. This method is based on the fact that diffraction angle is inversely proportional to particle size [4]. The Fraunhofer approximation gives the following information-

Wavelength of light used is much smaller than particle

All particles disperse light with equal magnitude There is

no penetration of light

The optical model employed in Fraunhofer approximation states that particles are assumed –

To be spherical

To be non-transparent and impenetrable

To scatter light equally at wide and narrow angles

To communicate differently with light as compared to medium [9]. The above-given model restricts the choice of Fraunhofer ap- proximation for particle size characterization. But Mie theory of light scattering fulfills these drawbacks. It states that-

The particle is assumed to be spherical

The particle is present in homogeneous dispersion Refractive indices of both particle and medium are known [4].

Instrumentation

Optical bench- It is where laser beam strikes the particles. Laser source commonly employed is a He-Ne gas laser as they are temperature-stable and have a better signal-to- noise ratio [7]. Detectors are also present to analyze the intensity of light scattered by particles. Photosensitive silicon with a series of detectors is generally used [9]. There is always an optimum number of detectors which can be used, like 16-32. Increasing the numbers does not lead to a better resolution [7].

Sample dispersion units- These units analyze the samples in their dry or wet dispersions. They guarantee that the sample reaches the optical bench at an optimum concentration. Wetdis- persion of sample requires a liquid vehicle- aqueous or organic solvent whereas dry dispersions require only dry air as a dispersant. Instrument software- This consists of data controlling system which converts the pattern of scattered light into a readable particle size distribution curve.

Advantages

It has broad particle size analysis range.
It offers flexibility in sample presentation.
The whole of the sample can be analyzed and recovery is also possible.
The technique is fast and gives reproducible and reliable results.
There is no need for calibration in this technique, though validation is required.
This technique does a direct measurement of dry powders.
Laser diffraction is flexible in operations [3, 7, 10].

Disadvantages

This technique is comparatively low in resolution.
In this technique, particles with different optical properties cannot be analyzed.
This technique is not for strongly absorbing materials.
The validity of results depends upon the validity of data collected.
There is high obscuration due to the high concentration of particles analyzed.
There is over-estimation of volume diameter for non- spherical particles.
Prior knowledge of refractive index is required.
In this technique, the equivalent diameter is calculated which is not directly related to particle volume.
Formulation ingredients may affect the data in this tech- nique [3, 10].

This method is mainly applied to low concentration samples to minimize multiple random scattering of the laser beam as oth- erwise, particle size distribution data would be so difficult to in- terpret [9]. For the particles with a size below one micron, the refractive index of sample material and dispersion fluid are re- quired to make Mie theory algorithmic corrections [11].

Dynamic Light Scattering

Dynamic light scattering (DLS) is also known as Photon Correlation Spectroscopy (PCS) or Quasi-elastic Light Scattering (QELS). It measures particles in the range of 0.3nm-8μm.[10] Apart from measuring particle size, this technique also measures zeta potential and molecular weight [12]. The basic prin- ciple involved is that Brownian motion of particles in a sus- pension causes scattering of the laser beam at different intensi- ties. These fluctuations correspond to velocity of Brownian mo- tion and therefore, particle size can be determined using Stokes- Einstein equation-

$$Dh \quad \frac{k_B T}{3\pi n D}$$

Where,

D_h: hydrodynamic diameter; Dt: translational diffusion coefficient; KB: Boltzmann's constant; T: thermodynamic tempera- ture; n: dynamic viscosity [9].

When a monochromatic beam of light strikes a suspension containing the particles, the light gets scattered and spreads out in all directions. The particles in a suspension undergo Brownian motion. This motion causes changes in the distances between the particles and therefore, causes fluctuations in the phase of scat- tered light. So, the net result comes out to be fluctuating scattered intensity [13]. The larger the particle, the slower the Brownian motion. It is also used for measuring zeta potential of a parti- cle or estimating the molecular weight of organic compounds. The laser light strikes the sample in the cell and the scattered light is captured by detectors, either at 90° (a right angle) or 173°(back angle). The signal can be deciphered by auto corre- lation function [4]. The particle size is measured in terms of hy- drodynamic diameter, which is the diameter of a sphere which has same translational diffusion coefficient as the particle [12].

Figure 1 Advantages and disadvantages of dynamic light scattering

Automated Imaging

It is an automatic image capturing technique in which individual particle pictures are captured from their dispersions and are analyzed for their respective sizes, shapes or other properties. This technique is of 2 types-

Static automated imaging- in which the sample is kept stationary, as on a microscopic slide,

Dynamic automated imaging- in which the sample is in motion, as in flow through the cell [4].

It is a high-resolution technique and measures particle size in the range of 1μ to millimeters.

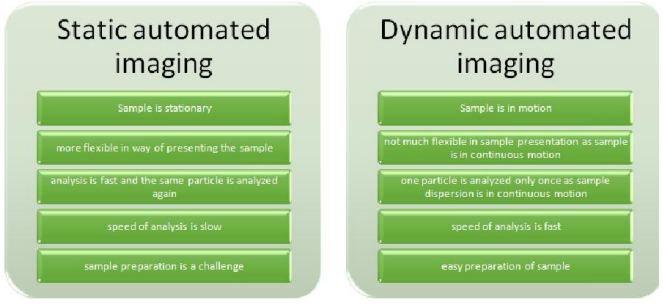


Figure 2 Differences between static and dynamic automated imaging

It employs a digital camera which clicks 2D images of sam- ple particles in the dispersion. Then particle distribution data is generated to report the results [4, 9].

This technique has an upper hand over other techniques as it can measure shape along with particle size. Particle shape measurement is important as it-

Gives idea about whether the particle under consideration is a bigger particle or an agglomerate

Shape reflects physical properties of a particle so it can be altered if required

Helps in modifying the particle so as to improve powder flow [14].

Instrumentation 1. Sample preparation and presentation- The sample is presented in the form of a dispersion with 2 techniques- static or dynamic. In static imaging, the sample is poured on a microscopic slide, a glass plate or filter membrane and then viewed whereas, in case of dynamic imaging, a flow-through cell apparatus is employed.

2. Imaging apparatus- a digital CCD camera is employed with desired magnification to capture 2D images of sample particles in the dispersion. Sample illumination is more flexible in case of static imaging as the sample is stationary and a number of techniques can be applied. On the other hand, the sample is essentially illuminated from behind in case of dynamic imaging as the particles are in motion and can only be illuminated from behind.

Data recording and interpretation- Shape and size of each particle are recorded, generally in the form of graphs and curves for easy interpretation [9].

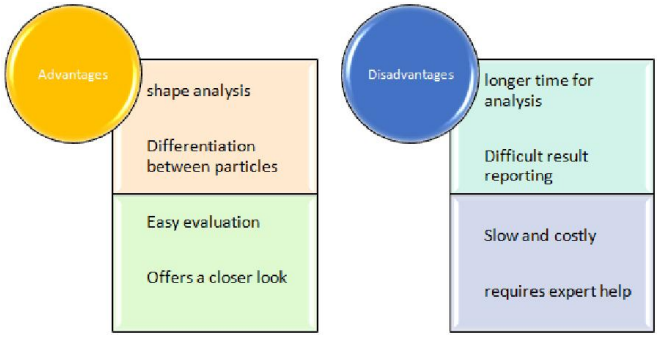


Figure 3 Advantages and disadvantages of Automated imaging

Electron Stream Sensing Zone Technique (Coulter Counter Method)

This technique was primarily invented by Wallace H. Coulter of United States Navy, to count blood cells. Its original model measured alterations in electrical conductance as each blood cell dispersed in an electrolyte solution, made way through an orifice. This original blueprint of the technique is known as the 'Coulter Principle'. This is a high-resolution particle size characterization technique as every single particle passing through the orifice is counted and measured [15]. In this, the particles to be measured for their respective size have to be dispersed in an electrolyte solution. An electrolyte solution is preferred as electrical conductivity is required. Any organic liquid with good electrical conductivity can also be used. The particles are dispersed in this electrolyte solution in low concentration. After that, the particles, essentially one-by-one, make passage through an aperture/orifice which is located in the wall of an electrical

insulator tube called the aperture tube. Electric current is applied across this aperture, thereby, creating an electrical sensing zone. When a particle enters this aperture, it displaces a volume of electrolyte equal to its own volume. This results in the generation of an electrical impulse for a short duration. In this apparatus, two electrodes are employed; one inside the aperture tube and another one outside. This creates a pathway for electrical conductance whenever an external electric field is applied. The alterations in the current are detected, often measured as impedance. From this method, particle volume is obtained, from which spherical diameter can be calculated and hence particle size distribution data can be generated. The particle size range for this technique is 0.2μm to 1600μm. If there are a variety of particles to be characterized, then two apertures instead of a single one are employed [16].

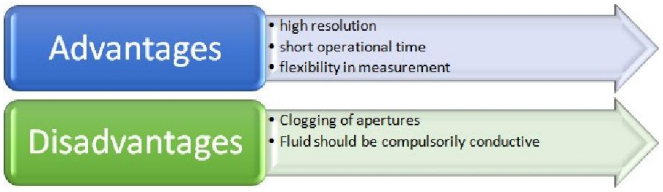


Figure 4 Advantages and disadvantages of Coulter-Counter techniques

X-Ray Sedimentation

The X-ray sedimentation technique has garnered a lot of attention and found a bunch of applications since its manifestation in 1967 [17, 18]. This technique is primarily grounded on two theories- the sedimentation theory and the X-ray absorption theory. The analytical equipment which works on this principle is called Sedi Graph [18].

Theory

The SediGraph works mainly on two principles. The first principle is the Sedimentation theory which is governed by Stokes'law. It states that when a particle homogeneously dispersed in a liquid experiences gravitational force which gets equally balanced by buoyant and drags force, then it achieves a velocity called terminal velocity. This velocity depends upon size (diameter) and density of the particle. So alternatively, it can be quoted that the terminal (settling) velocity is directly proportional to a particle size of the drug. The equation for Stokes' law can be written as-

$$V = \frac{g(\rho - \rho_s)d^2}{18\eta}$$

Where,

V: terminal velocity of particle; G: acceleration due to gravity; ρ: density of medium ; ρ: density of the particle; d: diameter of the particle; 6 : viscosity of medium

So, if we know the time taken by the particle to travel a known distance, then its velocity can be easily determined by dividing distance traveled by time. Finally, when velocity is known, the diameter of the particle can be easily determined.

The other theory of X-ray absorption aids in the determination of particle concentration. The X-ray absorption technique is based on Beer-Lambert law which states that when an x-ray beam passes through a given sample, its intensity reduces and this reduction in intensity is directly dependent on the concentration of the sample. Alternatively, x-ray intensity decrement is directly proportional to the mass concentration of the sample. Beer-Lambert law has following expression-

$$T\frac{I}{I_o} = e^{\in lc}$$

Where,

T: Transmittance; I: Final intensity of x-radiation; I: Initial intensity; ε: Molar extinction coefficient; l: thickness of the medium; C: concentration of the sample in solution

The value of the intensity of x-radiation is maximum with a clear solution and minimum with homogeneously dispersed particles. So during the process of sedimentation, x-ray intensity rises from minimum to maximum.

Method

In the SediGraph method, a homogeneous dispersion is prepared of particles under consideration in a suitable liq- uid medium. Agitation is done to achieve this. Then agitation is halted and all the particles are given time to settle down under gravity. The bigger particles settle first and smaller in the last. Each particle settles down with its own terminal velocity which is determined by taking the ratio of distance traveled by particle below a measurement zone to the time taken to cover this distance. When velocity is calculated, the diameter of the particle can be easily calculated from the equation of Stokes' law. Simultaneously, as the particles settle down in the medium, the intensity of x-ray beam passing through medium also increases. This is because there is no hindrance in the path as the solution above is clear. This increment in intensity relationship with the concentration of the sample can be determined from Beer-Lambert law [18–20].

Advantages

It gives reproducible results.
It allows usage of different liquid mediums.
A small quantity of sample is required.
Size determination is direct in this technique [19, 20].

Disadvantages

There are issues of sedimentation instability in this technique.

Frequent deviation from Stokes'law is also a chal- lenge [19, 20].

Selecting an appropriate particle size characterization technique out of all the available options is a challenging task. There are several techniques to choose from and also, significantattention to be paid to technique- to- technique variations. The notion that one particular technique is suitable for all the tasks is not a true one [21]. The variations may come because of differences in dynamic range, algorithmic or mechanical improvements in the instruments. Switching from older techniques like sieving to advanced ones like laser diffraction can also be the cause of variations. Data generated from sieving is comparatively smaller than that obtained by laser diffraction. Microscopic and image analysis techniques are best suited when particle shape is the main area of interest. In case of dispersions and suspensions, when particle size, as well as zeta potential, are the areas of interest, then Dynamic Light Scattering technique is the method of choice [22].

Factors to consider while selecting a particle size analyzer

Abundant particle size characterizations exist from old (sieving, sedimentation) to new (laser diffraction, dynamic light scattering). Selecting the most appropriate technique for characterization depends upon a number of variables. Some are listed below-

Understanding the existing analytical technique- This involves understanding the working and limitations of the technique. The company can reject a technique because they do not find its resolution up to the mark. Sometimes, a technique is employed because the literature backs its usefulness. Sometimes, the company aspires to establish a correlation in the results, so they use the same technique which was used earlier in the same experiment.

Size range- The choice of analyzer strongly depends upon the size range to be detected and analyzed. Different analyzers work on different size ranges. It is considered wise to select the instrument with the particle size range which encompasses the desired size in its middle.

Material to be analyzed- The technique to be chosen also depends upon the nature of the material to be analyzed. Like what type of material it is- free-flowing, dry powder, dry or wet dispersion, suspension or emulsion. For example, a material prone to agglomeration or a highly water-soluble material can be best analyzed in the form of dry powder by Static Light Scattering Technique.

Appropriate throughput- This refers to the efficiency of the whole measurement process. Analysts often consider throughput to be an indication of how fast a technique can produce a result with precision. The faster and precise the technique, the faster the analyst would know about the lapses in the experiment and the areas which need improvement. Laser diffraction is the best technique when it comes to fast analysis and throughput.

The quantity of sample- The choice of the technique also depends upon the amount of sample available for analysis. Smaller the amount, more efficient the instrument and hence more difficulties with managing cost and cleaning. In practice, with very small volumes of sample, dynamic light scattering is preferred and with relatively larger particle sizes, laser diffraction or image analysis is considered.

Cost-effectiveness- There is always conflict in industries when it comes to cost-effectiveness and efficiency. More effi- ciency and accuracy calls for a higher budget. That is where the need to find a balance between these two arise. In many cases, high initial costs reduce long time costs. For example, the instrument with highly technical and modern software will produce more accurate results and automatic nature will reduce the need for an operator and operator-related errors. Hence, there will be less investment in procedure corrections and error rectification. So, budget management is a daunting task which calls for good analytical skills [22].

Particle Size Characterization in Formulations

A wide range of particle sizes exists for particles used in the formulations in the form of active pharmaceutical ingredient and excipients such as in dry powders, suspensions, semisolid dispersions. Such particles size range from nanometers (in advanced formulations) to millimeters (in granules). A variety of properties of a dosage form depends upon their particles sizes and shapes like-

Rate of drug dissolution and the amount of drug bioavail- able
Release kinetics of the drug
Pharmacokinetic parameters, especially of novel formula- tions
Uniformity of the dose and stability of formulation
Rheological properties of the formulations, like flow abil- ity, mixing etc [3].

Some of the formulations along with their respective particle sizes and instrumentation are listed in table 2- [23–29].

Quality By Design Approach In Particle Size Characterization

The concept of quality by design (QBD) was first put forth by Dr. Joseph M. Juran who believed that quality should be instilled into a product from the very beginning as the breaches in quality arise from the way with which the product was developed in the first place [30]. Quality by design as per ICH document Q8(R2)(ICH Q8) can be explained as an "organized approach to an establishment having its foundation with already laid goals, focuses on product and process understanding, based on scientific ground and quality risk management" [31]. Pharmaceutical QBD is a systematic, scientific, risk-based and holistic approach that works as per pre-laid objectives to ensure quality in a product. QBD identifies the critical quality attributes which are critical to the quality of a product. It also decides when and how the process attributes should be varied so as to ensure maximum quality product [32].

The US-FDA also encourages inculcation of QBD principles in the development of drug product [30]. For QBD approach in particle size characterization, it will be more appropriate to quote it as 'Analytical QBD'(AQBD) as particle size characterization comes under analytical method development. Application of quality by design (QBD) to the desired particle size characterization technique guarantees a resilient method as well as assists in obtaining a quality product (in this case quality particle size) with reproducible results. The AQBD approach generally consists of six steps. These steps are explained by quoting Laser Diffraction as an example of Particle size Characterization technique. The adoption of QBD principles in the pharmaceutical industry has resulted in reduced variability within manufacturing process and hence an enhanced productivity and professionalism. Moreover, QBD approach has an upper hand over Standard Operating Procedures (SOPs) as the former is more flexible and can be adjusted to obtain desired results whereas the latter is quite rigid [31].

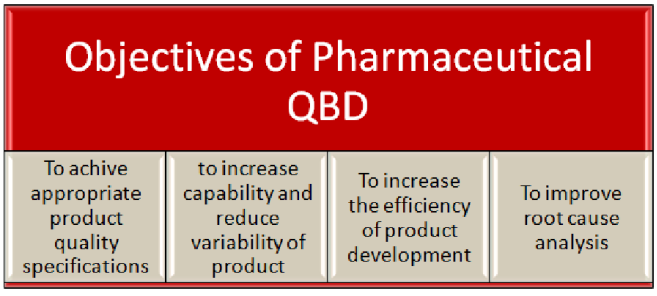


Figure 5 Objectives of Pharmaceutical quality-by-design

Step 1: Analytical Target Profile (ATP)

This is the very first step in Analytical QBD. This can be explained as laying down or defining method goals as to what exactly we expect from a method to do. ATP helps in laying down goals of the analytical method development process to achieve Quality Target Product Profile (QTPP) [33]. For example, we know that particle size directly affects dissolution and bioavailability of a drug so particle size characterization is the goal that we should work towards achieving optimum product quality. This ensures reproducibility and accuracy of results. To identify the ATP for a particle characterization technique, it is important to consider the reason why we require particle size measurement or analysis, like what exactly do we need that can be achieved from a particle size characterization technique. Is it enhanced solubility or is it improved flow properties. This is called deciding method goals or developing ATP. Moreover, not only desired characteristics but also accuracy and repeatability of results are to be considered in developing ATP. This requires consideration of an appropriate particle size characterization which will give accurate results in the desired range of particle size. For instance, laser diffraction gives most accurate results in the micron range [31].

Step 2: Identify Critical Method Attributes (CMAs)

Once a technique is finalized in the process of ATP, the Analytical QBD approach now looks into identifying critical method attributes (CMAs) which may pose a potential risk in achieving desired result and accuracy. CMAs include processes or parameters associated with particle size characterization technique which may affect results. In case of laser diffraction, the potential error sources are a dispersion, sampling, and instrumentation. Out of these three, dispersion and sampling pose a greater threat to the accuracy of results. As far as sampling is concerned, it mainly depends upon measurement time of analytical method. It decides how much sample is collected and how much is analyzed. On the other hand, when it comes to dispersion, it is good to consider the reason for particle size characterization again. If flow ability is to be checked, then analysis in agglomerated form is suggested. If their individual characteristics are to be studied, like solubility or bio availability, then analysis in original particle size is recommended, as in dispersion. For example, dry and wet dispersion are the two ways a sample can be presented for analysis in laser diffraction technique.

Step 3: Risk Assessment

The outlined risk in laser diffraction that can cause variation in results came out to be dispersion. The risk assessment involves assessing and analyzing the outlined risk. This involves consideration of the reasons why exactly this risk is a risk, what are

Table 1 Detailed list for various particle size characterization techniques

TECHNIQUE	PARTICLE SIZE RANGE	PARAMETERS MEASURED	PRINCIPLE	SAMPLE PRESENTATION	SAMPLE RECOV-ERY
Laser Diffraction	0.1-3000μm	Particle size	-Mie theory of light scattering -Fraunhofer theory	Wet or dry dispersion	Yes
Dynamic light scattering	0.3mm-8μm	-Particle size; -Zeta potential -Molecular weight	Brownian motion of particles	Suspension	Yes
Automated imaging/ Image analysis	1μm- mm	-Particle size -Particle shape -Particle count -Particle location -Particle transparency	Image capturing	Dispersion	Yes
Electron stream sensing zone	0.2-1600μm	-Particle size -Particle charge	Coulter principle	Dispersion in electrolyte solution	Yes
X- Ray sedimentation	0.1-300μm	Particle size	-Sediment-ation theory -X- ray absorption theory	Homogenous dispersion	Yes

Table 2 Particle size characterization of different formulations

S. no.	Formulation or carrier	Particle size	Technique used	Instrument used	Use of the formulation	
1	Niosomes	0.85-1.01 μm	Laser diffraction	Mastersizer X version 2.15, Malvern Instruments, Malvern, U.K	To enhance ribavirin liver concentration for liver targeting	[23]
2	Liposomes	110-135 nm	Dynamic light scattering	Particle size NICOMP 380 Submicron particle analyzer, Particle sizing system, CA, U.S.A	For efficient delivery of Epirubicin	[24]
3	Nanoparti-cles	186-107 nm	Laser diffraction	Malvern-Zetasizer 3000hs, Malvern, UK	Tumor targeting by enhancing concentration of doxorubicin	[25]
4	Dendrimers	534-373 nm	Dynamic light scattering	Malvern Nanosizer, ZN series, Malvern Instruments Ltd, Malvern, UK	For efficient liver cancer drug delivery and sustained kinetics	[26]
5	Micro-spheres	24.30 to 52.40 μm	Microscopic image analysis	AXIOPALN microscope	To enhance mucoadhesion and better targeting	[27]
6	Microcap-sules	100-1000 μm	Laser diffraction	Mastersizer 2000z, model Hydro 2000MU (Malvern Instruments, Malvern, UK	optimization of spray-drying process conditions	[28]
7	Ethosomes	1.112 0±053μm	Dynamic light scattering	Malvern Zetamaster ZEM 5002, Malvern, UK	To improve topical delivery of aceclofenac	[29]

various processes involved which can contribute to variability. Some of such considerations for wet dispersion are- a) the employment of a suitable liquid as a dispersant which can make the technique more challenging, b) even smallest of particle-liquid interaction can induce variation in results and affect reproducibility of laser diffraction, c) some drugs are not compatible with water, the most commonly preferred dispersant because of its non- reactivity, low cost and accessibility. On the other hand, the wet dispersion is the preferred choice for friable and breakable samples which cannot be analyzed dry. Also, the wet dispersion is used at times when contact of drug particles with the environment has to be cut. All of such considerations make up risk assessment and the areas which require attention, are outlined. Some designs of risk assessment as mentioned in ICH guideline Q9 is Failure Mode Effects Analysis (FMEA),Failure Mode, Effects and Criticality Analysis (FMECA) etc. These further assist in identification of Critical Process Parameters (CPPs) which can impact the quality of final product[34].

Step 4: Method Operable Design Region (MODR)

Once the risks are assessed, they are systematically studied and a design is created which will give reproducible results and meet target profile goals [31]. The risk assessment and MODR are based upon studies conducted with the help of Fish bone diagram (Ishikawa diagram), Failure Mode and Effects Analysis (FMEA) and a risk prioritization matrix. These are regarded as risk assessment tools [35]. The design region describes the relationship between process parameters and critical quality attributes [34]. Ishikawa diagram was first introduced by Kaoru Ishikawa in 1968. It is commonly called as Wishbone diagram

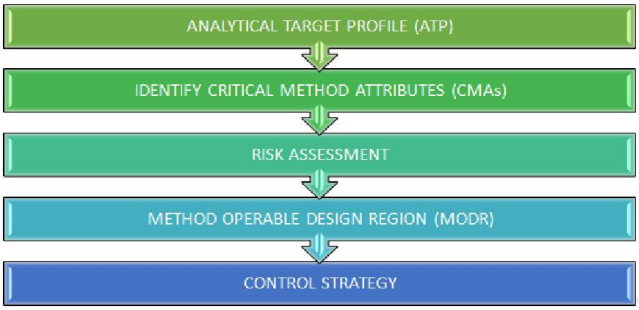
because of its resemblance to a fish's skeleton. The main purpose of Wishbone diagram is to prevent quality breaches and to identify and expose the underlying factors which can be potential threats to the quality of a product [36]. The general heading included in a Wishbone diagram are- methods, machines, personnel, material, measurement, and environment. Taking wet dispersion as an example, areas which can cause variation are- sonication time, sample quantity, agitation power and measurement time. Similarly, a Wishbone diagram for dry dispersion can also be made. Areas requiring attention, in that case, would be air pressure and feed rate. In Failure Module and Effects Analysis (FMEA), each variable shortlisted in Wishbone diagram can be studied in detail. Failure modes mean the routes by which some methods can fail and effect analysis means assessing what could be the ramifications of such a failure [37]. Each variable is assigned a number from 1 to 10 based on 3 factors- severity, probability, and detection. The Risk Priority Number (RPN) is then calculated as follows with each factor having to rate from 1 to 5-

$$Severity \times Probability \times Detection$$

Greater the RPN, greater will be the failure effects and hence greater variability. [38]. The goal of FMEA is to identify the areas requiring attention and doing extra experiments to establish their significance in product quality. Now all the outlined factors or variables are analyzed with the help of risk prioritization matrix. The variables which receive the highest ratings are then grouped into two categories. For example, in Laser diffraction, factors affecting particle size and factors affecting the measurement. Then separate two designs of the experiment are drafted for these groups. The DoE approach offers two privileges- first, it upgrades the efficiency of data compilation and secondly, cuts down a number of experiments to be done, thereby, directly saving cost also.[35].

Step 5: Control Strategy

This is the last step in Analytical QbD. The concept of control strategy was introduced by ICH Q8(R2)4 guideline. The ICH Q10 guideline describes control strategy as an organized set of controls which are obtained from the understanding of the current product and helps in maintaining product quality. It includes various controls like in-process testing, end- process testing. A control strategy can encompass any attributes affecting drug product, equipment, materials, methods etc. It helps in ensuring quality, safety, and efficacy of drug product. Control strategy focuses on the components which could have an impact on Critical Quality Attributes (CQAs). The control strategy is a way to demonstrate to the regulatory authorities how errors and variations are handled. [39]. Control strategy ensures quality assurance and method validation. [31]. The control strategy includes method parameters that can cause variability and need to be overhauled [35]. Control strategy depends upon the nature of formulation to be characterized and MODR. Method control strategy can be manipulated based on the information obtained from Design of Experiment and MODR [31]. The main aim of control strategy and method validation is to ensure that the method is appropriate for use or 'fit for purpose [31, 40]. Preset criteria can be standardized in the form of ATP. The ATP defines suitable performance indicator for the appropriate analytical result. In a QbD, two points need to be well-defined, first, what analytical methods need to be employed and second, where do they need to be employed [40]. According to USP and FDA's latest Guidance for Industry for Analytical Procedures and Method Validation, accuracy, precision and concentration range need to be assessed. The decision on concentration range depends upon the nature of analyte and type of method being validated. Apart from these three attributes, calibration, robustness, and reproducibility must also be assessed [31].



Conclusions

It is usually recommended that a particular sample should be characterized by at least two different techniques to develop a cross-correlation and obtain a better idea about the particle properties. Further development in the design and technology of particle size characterization instruments is anticipated in near future. The dispersion methods need to be revised and modified. Newer and better computer software is required for better analysis of the compound and equivalent particle diameter calculations. Nowadays, scientists prefer to describe whole particle size distribution range instead of just mentioning a single value. Sources of errors associated with instruments must be looked into and mentioned in the final specifications. Also, there is a need for acceptance of various particle size characterization techniques in Pharmacopoeias and Regulatory agencies, thereby, promoting their applications in pharmaceutical industry.

References

[1] Jillavenkatesa A, Dapkunas SJ, Lum L-SH. practice guide Particle size caracterization, Nist. Special pu .2001;164. doi:Particle size characterization.

[2] Informatics H. Course # Course #.2011;4–5.

[3] Shekunov BY, Chattopadhyay P, Tong HHY, Chow AHL. Particle size analysis in pharmaceutics: Principles, methods and applications, Pharm. Res. 2007;24:203–227. doi:10.1007/s11095-006-9146-7.

[4] Scientific H. a Guidebook To Particle Size Analysis, Distribution. 2010;1–17.

[5] Brummer H. Particle characterisation in excipients, drug products and drug substances. Pharma Times.2010;42:24–26.

[6] Choosing between wet and dry dispersion,(n.d.).

[7] Rawle A. Basic principles of particle size analysis. 1993;44:1-8.

[8] Light L. Technique S, What can Micromeritics Analytical Services (MAS) do to help me?, Statistics (Ber).(nd.)1-9.

[9] Malvern Ltd. A basic guide to particle characterization.2015. http://www.malvern.com.

[10] Europe CPSI. Comparison of Particle Sizing Methods.Availablefrom://www.cpsinstruments.eu/pdf/Compare%20Sizing%20Methods.pdf. 31 (n.d.) 1–18.

[11] David BF, Weiner. A Guide to Determination of Particle Size – Making an Effective and Reliable Measurement, Brookhaven Instruments. 2017;1:1–3. http://bic.com/pdf/theory/Determination of Particle Size.pdf.

[12] Spectroscopy PC. Scattering QL, Motion B. Dynamic Light Scattering.(DLS) DLS Measurement – Scattered Light Intensity Fluctuation, Malvern Guid. (2011).

[13] Malvern Instruments Ltd. Dynamic Light Scattering (DLS),Malvern.com.(n.d.).http://www.malvern.com/en/products/technology/dynamic-light-scattering/.

[14] Malvern Instruments Limited, Automated Imaging, 2017. http://www.malvern.com/de/products/product-range/morphologi-range/morphologi-g3-id/default.aspx.

[15] Behind the Coulter Principle,(n.d.).

[16] Saleh OA, Sohn. LL, Introduction I, Coulter counter, Rev. Sci Instrum.2001;72:4449–4452 doi:10.1063/1.1419224.

[17] Plain MP. Advantages and Disadvantages of Different Laxatives.(n.d.)2-3.

[18] Law B. The Sedi Graph Method of Particle Sizing. 1877;42901.

[19] Ceramic Industry, Sizing Particles with X-Ray Sedimentation, 2004. http://www.ceramicindustry.com/articles/86703-sizing-particles-with-x-ray-sedimentation.

[20] Laidlaw I, Steinmetz M. Introduction to Differen- tial Sedimentation, Anal. Ultracentrifugation Tech Methods.2005;31:270–290. doi:10.1039/9781847552617-00270.

[21] Bruce B, Ph. BW. A Guide to Choosing a Particle Sizer ©, Brookhaven Instruments Corp. White Pap.(n.d.).1–9.

[22] How To Select A Particle Size Analyzer – HORIBA,(n.d.).http://www.horiba.com/scientific/products/particle-characterization/particle-size-analysis/select-a-particle-size-analyzer/.

[23] Nidhi K. Indrajeet S, Khushboo M, Gauri K, Sen DJ. Hydrotropy: A promising tool for solubility enhancement: A review, Int. J Drug Dev Res;2011;3:26–33. doi:10.1002/jps.

[24] Zhang T, Zhou S. Hu L, Peng B, Liu Y, Luo X, Song Y, Liu X, Deng Y. Polysialic acid-modifying liposomes for efficient delivery of epirubicin, in-vitro characterization and in-vivo evaluation, Int. J Pharm.2016;515:449–459. doi:10.1016/j.ijpharm.2016.10.051.

[25] Yadav AK, Mishra P, Mishra AK, Mishra P, Jain S, Agrawal GP. Development and characterization of hyaluronic acid-anchored PLGA nanoparticulate carriers of doxorubicin, Nanomedicine Nanotechnology, Biol. Med.2007;3:246–257 doi:10.1016/j.nano.2007.09.004.

[26] Nomani A. Haririan I, Rahimnia R, Fouladdel S, Gazori T, Dinarvand R, Omidi E, Azizi Y. Physicochemical and biological properties of self-assembled antisense / poly. J Nanomedicine.2010;–359-369.

[27] Maddiboyina B. Asthana A, Asthana GS, Singh S, Ramya M, Sunnapu O, Kotla N. Formulation and characterization of polycarbophil coated mucoadhesive microspheres of repaglinide. J Pharm Sci Res.2015;7:972–977.

[28] Baranauskaite J. Ivanauskas L, Masteikova R, Kopustinskiene D, Baranauskas A, Bernatoniene J. Formulation and characterization of Turkish oregano microcapsules prepared by spray-drying technology, Pharm. Dev Technol.2016;7450:1–12.doi:10.1080/10837450.2016.1189934.

[29] Barupal AK, Gupta V, Ramteke S. Preparation and Characterization of Ethosomes for Topical delivery of. Aceclofenac, Indian J Pharm Sci.2010;72:582–586. doi:10.4103/0250-474X.78524

[30] Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, Woodcock J. Understanding Pharmaceutical Quality by Design. AAPS J. 2014;16:771–783. doi:10.1208/s12248-014-9598-3

[31] Kippax AP, Manager GP. Beyond SOPs – Exploring the rigor and requirements of. Analytical QbD.2015;8:1-19.

[32] Patil AS. Pethe AM. Quality by design (QbD): A new concept for development of quality pharmaceuticals, Int. J Pharm Qual Assur.2013;4:13–19. doi:10.1007/s11095-007-9511-1.

[33] Peraman R, Bhadraya K, Padmanabha Reddy Y. Analytical quality by design: A tool for regulatory flexibility and robust analytics, Int. J. Anal. Chem. 2015. doi:10.1155/2015/868727.

[34] Patel M, Sawant K. A Quality by Design Concept on Lipid Based Nanoformulation Containing Antipsychotic Drug: Screening Design and Optimization using Response Sur-face Methodology. J Text Sci Eng;2017;8. doi:10.4172/2157-7439.1000442.

[35] Adamson JT. A Quality by Design Approach for Parti- cle Size Analysis of an Active Pharmaceutical Ingredient. 2013.

[36] Wikipedia, Ishikawa diagram, Wikipedia. 2013;1–4. http://en.wikipedia.org/w/index.php?oldid=575668016

[37] Tague NR. Fishbone Diagram (Ishikawa) - Cause & Effect Diagram, Qual. Toolbox.2005:247–249. http://asq.org/learn-about-quality/cause-analysis-tools/overview/fishbone.html

[38] Quality Risk Management Application in Quality System.2011.

[39] Piriou J. Elissondo B, Hertschuh M, Ollivier R. Control Strategy as the Keystone of the Product Lifecycle , from Product / Process Understanding to Continuous Process Verification and Improvement, Pharm. Eng.2012;32.

[40] Chorghade MS. Pharma outsourcing, Chim. Oggi. 2003.