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Henk G. Merkus
Gabriel M. H. Meesters
Wim Oostra *Editors*

Particles and Nanoparticles in Pharmaceutical Products

Design, Manufacturing, Behavior and Performance

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Preface

Pharmaceutical products occur in a wide variety of formulations, viz. powders, tablets, capsules, liposomes, extended-release formulations, crèmes, ointments, nanomedicines, coatings and theranostic particles. They are in the frontrunner group of particulate products in terms of value, both in relation to human well-being and money, despite the fact that their tonnage is relatively small in comparison to, e.g. cement and paint. Powders take a dominant position in the pharmaceutical base products, and tablets are the main final product. Formulations contain excipients in addition to the Active Pharmaceutical Ingredient (API). Both API and excipients mainly consist of particles. Their nature—particle size distribution, particle shape and morphology—is essential for adequate quality during processing (e.g. powder flowability and tablet strength) as well as for adequate functionality of the final product (e.g. efficacy, content uniformity, dissolution rate and dispersibility in air for dry powder inhalers). Pharmaceutical products based on nanoparticles are relatively new and undergo intensive R&D in view of their potential for local treatment of, e.g. cancer.

Of course, the chemical structure of the API is of prime importance for best efficacy without unwanted side effects. Therefore, much research effort is spent to find new and better APIs. Here, molecular design by computer programs shows good promise. This is, however, outside the scope of this book, which deals with the influence of particulate nature on product quality, both during processing and in the final product.

Conventionally, pharmaceutical products are manufactured following extensive research, development and testing of both intermediate products and the final product. If the final product has been proven successful, it is approved while including a description of all base materials and processing steps. This results not only in a complex and long process of testing and acquiring permission for application but also in the necessity for new tests and permission in case any process step or base material is changed. Therefore, the FDA has launched the idea of applying Quality by Design (QbD) in combination with Process Analytical Technology (PAT) to pharmaceutical products and their manufacture early in the twenty-first century to minimize the development time and costs. It means that next

to clinical aspects the decision for approval, wherever possible, is based on knowledge of the material properties and adequate control of the manufacturing process.

Pharmaceutical products are very complex due to their particulate nature. Typically, any base material contains particles of different sizes, i.e. have a size distribution. Moreover, the particles are typically not spherical but have a deviating shape, e.g. angular, elongated or flakey. Then, their measured size distribution (a distribution of equivalent sphere diameters) depends on the principle of measurement and different techniques lead to different results. And finally, the particles may have a different morphology; they may be amorphous or have one or more crystal structures, which may depend on the method of preparation. Although knowledge and measurement instrumentation have greatly improved in the last decennia, this complexity makes the design and development of pharmaceutical products still a kind of art.

This book covers all the particulate aspects that are relevant for manufacture, behaviour and performance of the various types of pharmaceutical products. Also, attention is given to the potentially harmful effects of particles in medicines. Moreover, all relevant measurement techniques and their potential for in-line measurement are shortly described. Contributors to this book are acknowledged experts in the world of pharmaceutical products coming from both industry and academia. We are indebted for their contribution in which they share their experience. Their names and affiliations have been listed separately. We hope and trust that the information provided will promote optimization in design, development and quality of pharmaceutical products.

Pijnacker, The Netherlands — Henk G. Merkus
Delft, The Netherlands — Gabriel M. H. Meesters
Hilversum, The Netherlands — Wim Oostra

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Editors and Contributors

About the Editors

Henk G. Merkus graduated in 1960 in physical organic chemistry at the University of Amsterdam. He worked several years at the Royal Dutch Shell Laboratories in Amsterdam on research in the field of detergents and industrial chemicals, followed by development work on thermal wax cracking for production of C_2–C_{14} olefins and on acid-catalyzed synthesis of carboxylic acids from C_3–C_6 olefins. Then, he made the change to analytical chemistry, involving both measurements and method development with a large variety of techniques and methods, first at Shell's process development department in Amsterdam and later in the chemical engineering department of Delft University of Technology. Gradually, his analytical horizon widened: first surface area and porosity measurements were added to chemical analysis, later followed by particle size analysis. In those areas he participated in many university, national and international courses and national and international education and research projects. He is the author of about 45 journal articles. He retired from Delft University in 2000 but remained active in the field of particle characterization. He is author of the book 'Particle Size Measurements—Fundamentals, Practice, Quality' (2009; Springer) and many journal articles, as well as co-author and co-editor of the books 'Particulate Products—Tailoring Properties for Optimal Performance' (2014; Springer) and 'Production, Handling and Characterization of Particulate Materials' (2016, Springer). Moreover, he participates since 1987 in standardization activities regarding particle size measurement, both in the Dutch standards organization NEN and the international ISO organization (TC24).

Gabriel M. H. Meesters has a B.Sc. and M.Sc. in Chemical Engineering with a major in Bio Process Technology from the Delft University of Technology. He has a Ph.D. in Particle Technology also from the Delft University of Technology. He worked at biotechnology companies like Gist-Brocades in The Netherlands, as well as for Genencor International and currently at DSM in research and development in

The Netherlands. In all these functions, he was working on formulation and product development. Since 1996 he holds a part-time position at the Delft University of Technology, as Assistant Professor at the Faculty of Applied Sciences, first in the Particle Technology group, later the Nanostructured Materials Group and currently in the Product and Process Engineering group. He supervised over 15 Ph.D. students and more than 50 M.Sc. students. He published over 70 refereed papers, holds around 15 patents and patent applications and is co-author and co-editor of the books 'Particulate Products—Tailoring Properties for Optimal Performance' (2014; Springer) and 'Production, Handling and Characterization of Particulate Materials' (2016, Springer). He (co-) organized several international conferences in the field of particle technology and was president of the World Congress on Particle Technology in 2010.

Wim Oostra obtained his Ph.D. in chemical engineering from Delft University of Technology. He works in Pharma since 1998. Originally, he started his career in formulation development, later moving to process development and upscaling. He currently works for Abbott's Established Products Division where he is a Sr. Technical Manager in the Manufacturing Science and Technology department. While working previously for Organon, Schering Plough and MSD, Wim was a member of the corresponding Quality by Design (QbD) and Process Analytical Technology (PAT) teams, and was actively involved in two QbD filings of new products, including the online control of Blend uniformity by Near-Infrared spectroscopy (NIR). Wim was a member of the International Society for Pharmaceutical Engineering (ISPE) Product Quality Lifecycle Implementation® (PQLI) initiative and is co-chair of the European Federation for Pharmaceutical Sciences (EuFEPS) PAT and QbD network.

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Chapter 1
Introduction

Henk G. Merkus

Abstract Most pharmaceutical products contain particles, as active ingredient (API) and/or as excipient. The nature of these particles—e.g. particle size distribution (PSD), particle shape, morphology and powder flowability—is generally essential for product quality, during processing of powders and liquids to tablets, capsules, suspensions, emulsions and ointments as well as for the quality of the final product in terms of content uniformity, efficacy and stability. In view of their complex and particulate nature, pharmaceutical products and their manufacturing process require careful design and control. The quality of the final products should meet various strict requirements for e.g. content uniformity, tablet strength and stability and viscosity of dispersions, as well as for patient safety. Most often, quality aspects relate to the particle size distribution, particle shape, specific surface area and particulate concentration of the base materials. Since determination of these aspects is relatively easy, optimum relevant characteristic parameters are laid down in the form of specifications. In addition, some performance aspects of powders and dispersions, such as flow and viscosity behavior, are usually specified. This chapter describes the properties and characteristic features of particles, powders and dispersions and their relevance to pharmaceutical products. Also, it gives an overview of the main measurement methods that are relevant for pharmaceutical products. At the end of this chapter, the contents of this book are summarized.

1.1 Objective of This Book

Most pharmaceutical products contain particles, both as active ingredient (API) and as excipient in formulations in the form of e.g. binder, filler, disintegrant, stabilizer, lubricant or colorant. The particles may be solid or liquid, occurring as powders in capsules or in tablets or dispersed in an immiscible liquid in the form of suspensions

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or emulsions or in air as sprays. Second to the chemical nature of the active ingredient, the nature of all of these particles—e.g. particle size distribution (PSD), particle shape, morphology and powder flowability—is essential for product quality, both during processing and for the final quality.

The objective of this book is to highlight the role of particulate nature in the wide variety of pharmaceutical products, with focus on the very large range of particle sizes involved, as well as to give guidance in the choices of particle and powder characteristics and their measurement for setting product specifications, which have an optimum relationship with product quality. A further objective is to promote the approach of Quality by Design (QbD) and Process Analytical Technology (PAT) for pharmaceutical products and processes. Expert authors have contributed to the chapters on different types of pharmaceutical products, for which we are very grateful to them.

In the next sections of this introductory chapter, particle and powder characteristics, measurement methods and their relevance for product manufacture, performance and quality are described.

1.2 Pharmaceutical Products

Pharmaceutical products occur in many forms, viz. powders, capsules, tablets, solutions, emulsions, suspensions, ointments and sprays. Their composition may be very complex. The Active Pharmaceutical Ingredient (API) is the heart of the product. It should have optimum pharmaceutical activity for curing a specified disease in given surroundings with least negative side effects. It usually is a solid material, often crystalline, having a complex organic chemical structure. Among other things, adequate bioavailability requires that the substance is sufficiently soluble in the surrounding liquid. Following synthesis and purification, the active ingredient is typically combined with other components, each with its specific function, in a pharmaceutical formulation. These formulations may contain:

- binders, to facilitate tabletting and granulation
- lubricants or glidants, to aid flow of the powder
- fillers, to give tablets the desired size, API concentration and strength
- disintegrants, to facilitate break-up and dispersion of tablets into smaller particles for quick dissolution when in contact with water
- polymer, to form a matrix for extended release of the drug
- particle coatings, to promote liberation of the API in the desired region of the gastro-intestinal system, to promote extended release and/or to mask an unwanted taste
- liquid, to form suspensions or emulsions
- surfactants, to facilitate wetting of powders
- dispersants, to stabilize particle dispersions in liquids
- antimicrobial preservatives

- antioxidants
- colorants, to give an attractive and distinctive color to tablets
- flavoring agents, to mask bad tastes and increase patient acceptance
- viscosity modifiers, to adjust the viscosity of ointments.

In addition to the pharmaceutical products for curing diseases, there are the particulate theranostics. These are particles that are useful for diagnosis of the presence of a specific, often localized disease and its therapeutic treatise (see Chap. 3).

The majority of pharmaceutical products consists of tablets and capsules. Typically, the production process of these products starts with dry powders that are stored in hoppers and must be blended to the desired, constant composition, prior to die filling for compaction into tablets or introduction into capsules. Adequate, steady flow behavior of the mixture at the exit of the blender is essential to reach a constant quality for tablets or capsules. Most often, either of three blending processes is applied:

1. Dry blending. The API and the excipients are mixed as powders and fed into capsules or into separate dies where they are compressed to tablets. The blending process can be executed in batch or continuous equipment [106].
2. Dry granulation. Here, the various powders are mixed in the dry state and immediately and continuously squeezed to form a thin 'ribbon', which is then cut into pieces [24]. Compacts, having sufficient strength, require adequate binders and lubricants. They can be produced in roller compactors.
3. Wet granulation. Here, some liquid is sprayed over the powders while they are mixed, which causes agglomeration of particles. In this process, particles having a hydrophobic surface require addition of a suitable surfactant to promote adequate wetting. There are two basic designs for granulators. Mixer granulators can be applied when small forces are necessary for mixing and granulation. They typically result in near-spherical mixed particles. When strong shear forces are required, then impellers in the granulator cause mixing as well as partial breakage of the lumps formed and, thus, re-mixing and densification of the final agglomerated product [24]. Following drying, the usually porous granules can be used as such or be milled to some extent and then pressed into more compact tablets.

Dry processes are favorable as they avoid the use of a liquid and related extra processing steps. However, they are very sensitive to adequate flow behavior of the particles and to segregation, and, thus, require careful design and control to reach a homogeneous composition of the product. This sensitivity to particle flow behavior is much less in wet granulation due to the increased cohesivity of wetted particles and the intermediate break-ups of lumps, followed by re-agglomeration, which improves the mixing process. On the other hand, at least an additional drying step is required to reach the final product.

Typically, particle size applied for manufacture of tablets is in the range of 10–300 μm. But particle sizes in pharmaceutical products can be much smaller. For example, medical inhalers require an aerodynamic size of about 1–5 μm for particles to reach the lungs, (micro-) emulsions contain liquid and/or solid particles in a size range of about 10 nm–100 μm (the exact range depending upon way of preparation and type of application) and nanoparticles have a size range of about 1–100 nm. These latter particles are subject of much research directed towards diagnostic purposes (e.g. for cancer cells), antibacterial applications, or as carriers for delivery of substrates (e.g. drug molecules) to specific targets. The advantages of nanoparticles are their large surface area for encapsulation to enhance stability, their potential for good access to specific cells and tissues, and their possibility for being triggered from the outside or for acting as contrast agent. This offers possibilities to target drug delivery to diseased cells and tissues, and to regulate drug release, while minimizing side effects and improving therapeutic efficacy.

The complex nature of pharmaceutical products requires extensive research and development of all composing materials, their processing and process control, designed to reach optimum, constant product quality. This complex nature and the long process of R&D, testing and acquiring permission for application ask for a good design and planning of activities. Various design methods exist. In Chap. 2, the method of Quality by Design (QbD; for products and processes) in a Process Analytical Technological (PAT; for process monitoring and control) framework is discussed. This approach has been launched in the first decennium of the 21st century by the US Food and Drug Administration (FDA) for the development and manufacture of pharmaceutical products and adopted by its European counterpart EMA and other national regulatory agencies. It promotes that the desired good quality of pharmaceutical products in combination with an improved efficiency of its manufacturing process be reached by design on the basis of (available) knowledge and understanding of the product, its processing steps and their control, rather than by trial and error and analysis of the final product alone. In an earlier book, I described the basic steps in a general method with similar goals named Quality Function Deployment (QFD) or House of Quality (HoQ), which also can be applied for both products and processes [55, 59].

Both methods aim at optimum product quality at minimum costs and time. Their guidelines agree on the importance of defining explicit targets for the desired product (a ***Quality Target Product Profile***), collecting all relevant information, selecting the ***critical quality attributes*** of final products, components and manufacturing process steps and of adequate reporting. However, also differences exist. For example, the QFD/HoQ approach also emphasizes the necessity of making a realistic planning scheme for all activities, including research and development and decision moments, whereas the QbD/PAT approach is more specific on the quality attributes for the drug products, their components and their manufacturing process steps as well as on process monitoring and control issues for application by regulatory agencies.

1.3 Relevance of Particle and Powder Characteristics for Product Quality

Product quality can be defined as '*The totality of features and characteristics of a product that bear on its ability to satisfy stated or implied expectations, needs and requirements in exchange for monetary considerations*'. A more simple definition is '*Conformance to product specifications*'. This simple definition implies, of course, that all product performance properties are covered by the specifications.

The characteristic features of the final product typically do not only depend upon the characteristics of the active material but also upon those of its components and the processing steps. Important quality attributes for pharmaceutical products and components are:

- pharmaceutical efficacy and potential side effects, in relation to:
  - content uniformity in dose quantities
  - product stability in dispersions
  - dissolution properties of solid particles, without or with a coating
  - dispersability of the product in air
  - rheological properties of emulsions, suspensions and ointments
  - safety for patients.

Additional characteristics are often to be addressed in relation to product processing steps, for example

- flowability of powders
- segregation behavior of the particles in powders during transport and storage
- tendency of particles to form agglomerates
- ability to compact particles into tablets having sufficient strength
- dusting behavior during transport and processing, which may lead to health hazards
- safety, toxicity and explosion sensitivity when processing
- ability to sufficiently break up agglomerates or aggregates
- vulnerability to breakage and attrition of particles and tablets
- potential to optimize API particle shape during production
- drying rate of solid particles coming from liquid dispersions
- influence of moisture in these behavioral aspects
- absence of unwanted pollutants.

In relation to performance characteristics, component and product specifications must be set, process equipment chosen and process conditions defined in order to make the products conform to the specified quality. First, requirements are set for the performance properties that are listed above. Many of them are subsequently transformed into specifications for particles, powders and dispersions, as well as into process conditions. These specifications require availability of adequate analytical methods and techniques. Typically, a variety of specifications is necessary

since different performance aspects relate to different characteristics of particles, powders and dispersions. Note that, sometimes, different performance characteristics ask for contradictory particle characteristics. Then, an optimum has to be found. As stated in Sect. 1.2, often additional, non-particulate components are necessary to reach optimum product quality, such as particle coatings, surfactants, dispersants and viscosity modifiers.

1.4 Particle, Powder and Liquid Dispersion Characteristics [54–56, 58]

Relevant performance characteristics of products and their processing may be related to chemical composition as well as to characteristics of the individual particles, of the powders and of the liquid dispersions. An overview of identifiers follows below. Measurement methods and techniques are described in Sect. 1.5.

1.4.1 Composition

Adequate product composition is of prime importance for pharmaceutical products. This holds primarily for the active ingredient (API) where each dose should contain the targeted amount within narrow limits. It requires that the composing components are well mixed and segregation in the manufacturing process is suppressed. But also the concentration of unwanted impurities and contaminants below a stated level should be guaranteed.

The concentration of API in a dose is often determined through infrared (IR, in the form of Fourier transform, FTIR, or of attenuated total reflection, ATR-IR), or Raman spectroscopy, or by dissolving samples followed by liquid chromatography (HPLC), ultraviolet (UV) spectrometry or mass spectrometry (MS).

A fairly new method for control and monitoring of pharmaceutical processes and for analysis of tablets uses near-infrared (NIR) analysis through application of chemometric data analysis and multivariate calibration. A major advantage of this technique is that the analysis no longer requires dissolution but can be done directly on powders and tablets. In addition to API concentration, typically also that of other components can be measured. Another new technique for determination of e.g. the content and dispersion of water and various APIs, the morphology of crystals as well as thickness of the coating layer of tablets is terahertz (THz) spectroscopy. An in-line application for this latter process has been reported by May et al. [51].

Presence, identity and concentration of metallic elements and anions in powders and solutions can be measured by energy-dispersive spectroscopy (EDS), atomic absorption spectroscopy (AAS) or atomic emission spectroscopy (AES).

See Sect. 1.5.3 for further explanation of the analysis techniques.

1.4.2 Particle Size and Particle Size Distribution (PSD)

Particle size is an important parameter for the properties of the final product as well as in the unit operations during its production and handling. For example, it has a strong influence on solubility, dissolution rate, flowability of powders and the intrinsic stability of suspensions. It has the advantage that many different techniques and instruments are available for easy measurement. Moreover, milling techniques are available for size reduction, and specific methods for particle preparation in the nanometer size range.

Homogeneous spheres are the ideal particles for characterization since their size can be described by a single parameter, the diameter (or, in some areas of scientific work, the radius). Surface area and volume of a sphere can be easily calculated from its diameter D through πD^2 and $1/6\pi D^3$, respectively; specific surface area is $6/D\rho$ (where ρ is particle density). Moreover, all particle sizing techniques yield the same size result, regardless of the measurement principle. In the world of particulate materials, however, spherical particles are very rare in comparison to other shapes.

Particles having a regular but non-spherical shape occur more often, especially at sizes below 1 μm, but are still fairly rare for larger sizes; e.g. crystals may have a regular shape, like cubic sugar crystals. Here, full description of size requires at least the size of the ribs and the angles between them, or any other typical feature. Also, calculation of surface area and volume is more difficult.

Particles having an irregular shape are the normal case for particulate materials, especially in the above-micrometre size range. Now, adequate characterization of individual particles requires many descriptors, such as Feret diameter, length, breadth, thickness and angularity. Unfortunately, many descriptors are usually dependent on particle size as well as on particle orientation during measurement. For full description of collections of non-spherical particles having different sizes and shapes this would lead to an excessively large number of descriptors, which would make setting relationships with product properties impossible.

In order to avoid such excessive numbers and to find relation to measurement techniques, the concept of equivalent spheres has been introduced. Here, an arbitrary particle and its equivalent sphere have the same property in relation to a given measurement principle. Again, the diameter of the equivalent sphere characterizes the size[1] of the particle. The nice consequence of this concept is that an arbitrary particle can still be characterized by a single parameter, the equivalent sphere diameter. Note, however, that such diameters often differ when different measurement principles are applied. This holds especially when length, breadth and thickness of the particle are very different and different particle cross sections are offered in instruments for measurement. It must be clear that also conversion of these diameters to surface area and volume may yield different results, and vice versa. Because the characterization as equivalent spheres includes both different sizes and different shapes in a distribution, derivation of particle volume from

[1] I have chosen symbol D to represent particle size (equivalent diameter).

equivalent size becomes especially problematic for e.g. acicular, fibrous and flaky particles, for which length, breadth and thickness are largely different. Then, a decision has to be made for best possibilities to adequately describe the particle characteristics with respect to performance.

Some examples of equivalent sphere diameters are:

- Equivalent projected area diameter, i.e. diameter of a circle having the same area as the particle's projection
- Equivalent surface area diameter, i.e. diameter of a sphere having the same surface area as the particle
- Equivalent volume diameter, i.e. diameter of a sphere having the same volume as the particle
- Equivalent sieve diameter, i.e. diameter of a particle that just passes through the apertures of a sieving medium
- Stokes' diameter or equivalent settling diameter, i.e. diameter of a sphere having the same settling rate as the particle under conditions of Stokes' law (low Reynolds number)
- Equivalent laser diffraction diameter, i.e. diameter of a sphere having the same scattering pattern as the particle
- Aerodynamic diameter, i.e. diameter of a sphere with density 1000 kg/m^3 having the same aerodynamic property as the particle (especially used for aerosols).

The potential differences between the different equivalent sphere diameters necessitates that their measurement technique is stated in the measurement results.

Typically, the particles in particulate materials do not have the same size but show a distribution of different sizes. These distributions are usually presented in the form of numbers or volumes of particles in given size classes, in relation to the measurement method. In graphical form the histogram curves are usually smoothened to continuous, differential or cumulative, curves [32, 54]. An example is given in Fig. 1.1.

The figure clearly illustrates that presence of small amounts of e.g. large particles in a distribution, such as agglomerates, is more easily visible in the differential presentation where they may appear as shoulders on the main peak, or even as a separate peak. On the other hand, PSD characteristics relating to the amounts of material smaller or greater than a stated size and quantile values such as the D_{10}, D_{50} and D_{90} are more easily derived from the cumulative curve.

A point of attention is that different size measurement techniques yield the amount of particles in the size classes in a different manner. For example, particles are recorded by number in e.g. microscopy, whereas e.g. laser diffraction reports them by volume. This also may lead, depending upon PSD width, to considerable differences as is shown in Fig. 1.2.

For conversion of one distribution into the other, the volume of the number of particles in each size class can be calculated by assuming spheres, when errors due to particle shape are acceptable. It will be clear that small volumes of particles in the

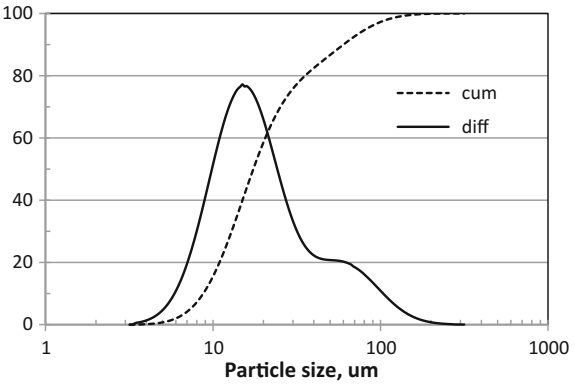

Fig. 1.1 Example of a size distribution as differential and cumulative curve

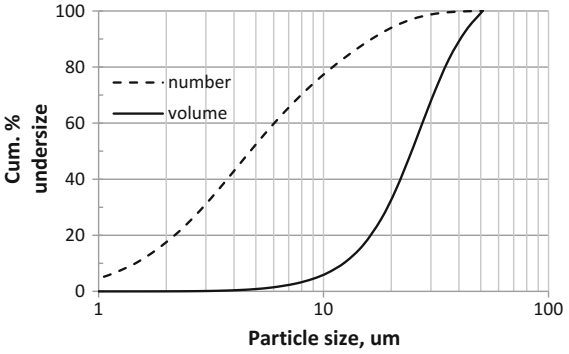

Fig. 1.2 Differences between a number-based and a volume-based size distribution

low size end of a distribution relate to a large number and are more easily visible in number-based distributions, whereas small numbers of large particles, corresponding to a large volume, are more easily seen in volume-based distributions. In relation, the uncertainty in measured results at both ends of the size distribution after transformation from number to volume or vice versa may be easily underestimated. Since the relative errors in the measured percentages remain the same in these transformations, this holds especially if the amount of sample in terms of total number or mass of particles is not considered. We take Fig. 1.2 as the example, while assuming perfect spheres. In case a microscopic measurement would include few, e.g. 500 particles in total, about 5% n/n above 20 µm would relate to 25 particles This corresponds to a relative standard deviation (RSD) of 20%, which would also mean 20% RSD in about 70% v/v of the upper side of the distribution, i.e. a RSD of about 14% v/v. The same can be said when a volume- (or mass-) based technique would only measure the 5% v/v of particles below 8 µm with a standard deviation of 1% v/v, or 20% RSD. When this 5% v/v corresponds to about 70% n/n, this 20% relative would mean a RSD of about 14% n/n for the lower size part. The differences between number- and volume-based distributions must

especially be considered if an instrument is only capable of measuring part of the total size range of the particles.

Industrial particulate products typically have a fairly wide size distribution that is composed of amounts of material of many sizes. Therefore, it is usually required to compress the data into some kind of summary for an easier translation to quality parameters. For such a summarized representation, following PSD parameters seem logical choices from the product point of view for the cases of equant particles:

- Mean size of the distribution, weighted according to number, area, volume, etc., depending on application and theoretical background. The mean values have the advantage that the contribution of all particles to the performance is taken into account. For example, the arithmetic, number-weighted mean size $\left(\left\langle D_{1,0}\right\rangle\right)$ is important e.g. in number-based health effects. The surface area-weighted Sauter mean diameter $\left(\left\langle D_{3,2}\right\rangle\right)$ is important in the rate of dissolution and evaporation as well as in explosion behavior. The mean volume diameter $\left(\left\langle D_{3,0}\right\rangle\right)$ is important for e.g. dose effects. Content uniformity has been found to relate to the volume-weighted mean volume diameter $\left(\left\langle D_{6,3}\right\rangle\right)$ (see Chap. 7).
- Size of the largest particle if this value is relevant to product quality. Often, the fraction of particles larger than a stated size or the quantile value D_{90} is used instead, in view of easier determination.[2] This parameter is important when large particles have a strong impact on dose uniformity or when they are harmful, such as in e.g. pastes or polishing powders, which should have a smooth appearance and should not cause scratches. As shown above, here the $D_{90;3}$ is a good choice for precision.
- Fraction of particles smaller than a stated size (e.g. 45 μm) or the quantile value D_{10} if these smaller particles are relevant to product quality.[2] This parameter may be important for e.g. filtration, powder dusting or powder flow properties. As shown above, here the $D_{10;0}$ is a good choice for precision.
- The width of the size distribution, in addition to one or some PSD parameters chosen, expressed as ratio D_{90}/D_{10}, D_{84}/D_{16} or the width parameter of a modeled distribution (see Footnote 2), such as the log-normal or Rosin-Rammler distribution. This parameter may be important for use in process control when narrow size distributions are desired.
- Stated volume fractions in given size classes of the distribution, e.g. to minimize voids in compacts such as tablets.

The choice of PSD parameters for representation of the distribution is far from arbitrary. Figure 1.3 and Table 1.1 illustrate, as an example, similarities and differences between three types of volume-based size distributions and some of their characteristic parameters. Distribution #1 is a monomodal, lognormal distribution

[2]In all cases an indication in the form of a second subscript has to be given for the type of weighting of the value, viz. by number (0), area (2) or volume (3), etc. and for the measurement technique.

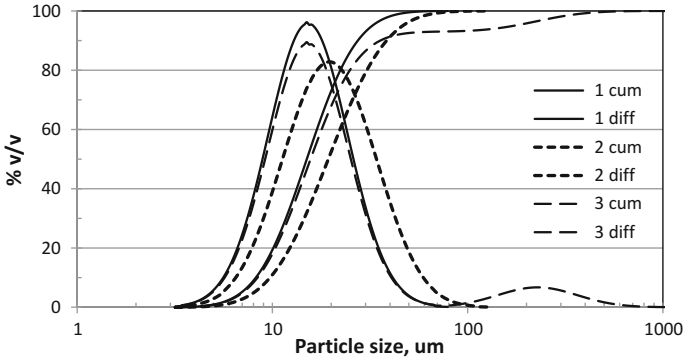

Fig. 1.3 Three cumulative and differential volumetric size distributions: #1 = distributions of $D_{50;3}$ = 15 µm and s_g = 1.6; #2 = mixture of $D_{50;3}$ = 15 µm and s_g = 1.6 (50%) and $D_{50;3}$ = 25 µm and s_g = 1.6 (50%); #3 = mixture of $D_{50;3}$ = 15 µm and s_g = 1.6 (93%) and $D_{50;3}$ = 225 µm and s_g = 1.6 (7%)

around a geometric mean size of 15 µm. Distribution #2 is a 50/50 combination of #1 with a close and similar neighbor (geometric mean size 25 µm); it looks still monomodal. Distribution #3 is a combination of #1 with a small amount (7% v/v) of much larger particles (geometric mean size 225 µm) and is clearly bimodal.

The changes in the distribution of #2 in comparison with #1 are visible in all PSD parameters, although differences are more pronounced for the parameters that relate to the higher size end (where the change occurred). For these monomodal distributions, mean values and statistical parameters show similar trends. However, for bimodal mixture #3, containing a small amount of large particles, the mean values $\langle D_{6,3} \rangle$, $\langle D_{4,3} \rangle$, $\langle D_{3,2} \rangle$ and $\langle D_{3,0} \rangle$ give a much better indication than the quantile PSD parameters $D_{50;3}$ and $D_{90;3}$. The $D_{95;3}$ also indicates the difference between #1 and #3 well; the reason is that it lies in the PSD region of the 7% large particles. Note, however, that the precision of measured $D_{95;3}$ values is much worse than that of mean sizes since it involves only few particles.

In the application of PSD parameters, two types must be discriminated, viz. application for instrument testing and representation for properties of product performance and process control.

Certified standard reference materials for ***instrument testing*** are usually monomodal (see also Chap. 2). Their values have been certified by governmental institutes or commercial manufacturers with a stated accuracy. Most often, precision, accuracy and stability of instruments are tested through repeated measurements of D_{10}, D_{50} and D_{90}, which can be derived directly from the cumulative distributions. Testing results can be set for monitoring and control over long periods of time in quality control charts, such as the as the Shewhart chart (cf. Sect. 2.5) [54]. These reference materials are often quite different from own products and, thus, the methods for sampling and dispersion may be quite different. Instead of certified

standard reference materials, a standard own in-house product can also be taken as a reference material within a company, provided that it is sufficiently stable, and reference values and their tolerances have been characterized adequately. The advantage is that the influence of the full analytical method (sampling, dispersion and dilution in addition to the instrument) and of the analyst can be included in the quality testing.

If also resolution and sensitivity of an instrument are at stake, then reference materials containing two or more modes are required. For testing of resolution, typically peak width of and distances between the differential peaks are checked, and for sensitivity, the determination limits for small amounts of material as well as sensitivity to changes in their concentration.

For relationships of PSD parameters with ***product performance*** and ***process control*** it is important to know whether the size distribution of the product is monomodal or contains more modes. Monomodal distributions are the normal case in industrial particulate products. Sometimes, the distributions are reported as parameters of a model distribution. For example, those of normal (Gaussian) distributions for narrow size distributions, which relates to small deviations during preparation. For wider distributions, the parameters of lognormal, Rosin-Rammler or other model distributions are sometimes applied. The advantage of these model

Table 1.1 Some characteristic parameters of the size distributions presented in Fig. 1.3

Parameter	#1 $D_{50;3}$ = 15; s_g = 1.6	#2 50% $D_{50;3}$ = 15; s_g = 1.6 + 50% $D_{50;3}$ = 25; s_g = 1.6	#3 93% $D_{50;3}$ = 15; s_g = 1.6 + 7% $D_{50;3}$ = 225; s_g = 1.6
$D_{10;0}$ (μm)	4.6	5.4	4.6
$D_{50;0}$ (μm)	7.9	10.2	8.2
$D_{90;0}$ (μm)	14.1	20.1	18.6
$D_{95;0}$ (μm)	16.7	24.2	91.8
$D_{10;3}$ (μm)	8.2	9.7	8.4
$D_{50;3}$ (μm)	15.0	19.3	15.7
$D_{90;3}$ (μm)	27.4	38.5	35.7
$D_{95;3}$ (μm)	32.5	46.5	172.3
$\langle D_{1,0} \rangle$ (μm)	8.8	11.7	17.5
$\langle D_{3,0} \rangle$ (μm)	10.9	15.0	67.3
$\langle D_{3,2} \rangle$ (μm)	13.5	19.1	191.1
$\langle D_{4,3} \rangle$ (μm)	16.7	23.3	249.8
$\langle D_{6,3} \rangle$ (μm)	20.7	26.9	310.0
$D_{90;3}/D_{10;3}$	3.3	4.0	4.3
>50 μm (%v/v)	0.5	3.6	7.4
>80 μm (%v/v)	0.0	0.3	6.2

distributions is that they can be characterized by two parameters, a size location parameter and a distribution width parameter [54]. A drawback is that the model most often corresponds with only a part of the actual distribution. Still, if a proper model is chosen in relation to the size region of interest, its parameters can be attractive for process control.

Reasons for extra modes may be intentional e.g. by additions in a given size class to improve product quality, or unintentional by abrasion causing the presence of fines, or by agglomeration of particles. Sometimes the different modes are even clearly visible in the analytical results or microscopic images. Alderliesten recently described a program for fitting distributions to combinations of lognormal distributions [2].

For selection of appropriate PSD parameters in relation to product performance, it is important to know in which performance aspects all particles play a role and in which aspects smaller or larger particles have a more dominant influence. In the general case of product specification, it deserves preference to use some weighted mean size that can be reasoned from theory or has been found empirically to relate most significantly to a performance property, and can be measured with sufficient precision. For monomodal size distributions also an appropriate quantile parameter might be used, as can be seen in the above discussion on the three PSDs in Fig. 1.3 and Table 1.1. However, caution is required since quantile parameters have a statistical nature and do not have an intrinsic relationship with product performance properties. Moreover, the median size D_{50} alone gives no indication of the distribution width, whereas size changes in the lower and upper 10% of the PSD will not show up in the D_{10} and D_{90}, respectively, as is shown in the difference between $D_{90;3}$ and $D_{95;3}$ for sample #3.

Parameters applied for process control require above all good precision, stability and sensitivity for process changes. Here, the quantile values D_{10}, D_{50} and D_{90} and the ratio D_{90}/D_{10} usually suffice.

For best understanding of the behavior of products containing polymodal size distributions, it can be beneficial for understanding to fit the distribution to a combination of lognormal distributions and use the corresponding parameters.

In general, the choice of PSD parameters for representation of product performance should be based on theoretical considerations, literature or sound investigation as well as on best measurability to reach optimum correlation. Their measurement should be done through using an optimized, written measurement method, including sampling and dispersion—i.e. a standard operating procedure (SOP)—in instruments having optimum quality for the defined parameters. An overview of techniques is presented in Sect. 1.5.4.4 and [54]. Note that different product properties may require different PSD parameters, which may have a contradictory correlation with particle size. On the other hand, the number of parameters taken for product specification should be minimized in view of measurement costs.

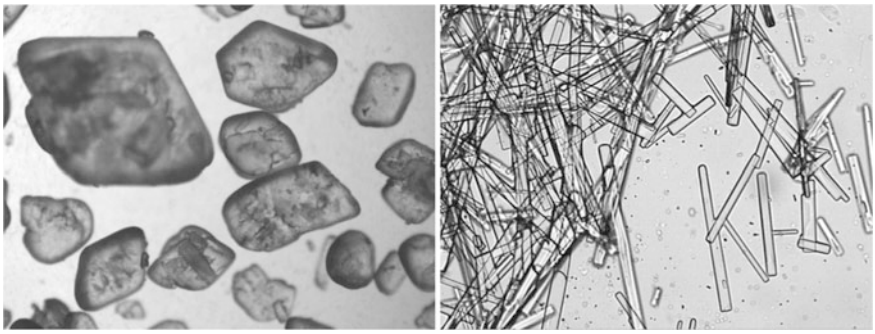

Fig. 1.4 Images of Succinic acid particles (left) and Almorexant. HCl needles (right) [105]; copyright Springer, reproduced with permission

1.4.3 Particle Shape

Although particle size is usually given first attention in relation to the properties of particulate materials, particle shape can have a significant or even dominant effect on product performance. This is especially the case for needles and flakes, having a small aspect ratio, i.e. large length to breadth ratio, which makes them vulnerable to breakage and gives them very poor flow properties, in contrast to rounded equant particles. Two examples of particle shapes are given in Fig. 1.4.

Conceptually, particle shape is the pattern of all points on the boundary of a particle [54]. Thus, it includes every aspect of external morphology of the particle. Three scales can be discriminated, viz.:

- macroscale, related to the general 3-dimensional form of particles, for example the ratio of their main three dimensions
- mesoscale, which relates to the general aspects of roundness and angularity of the particle's contour
- microscale, which involves surface roughness and porosity.

Often, only the dominant particle shape in a collection of particles is described in a qualitative manner in addition to the PSD [80]. This is due to the fact that the description of both size and shape distributions yields too many parameters for application at the present time. An example of such qualitative shape descriptors is given in Fig. 1.5.

Automated microscopy techniques (light, SEM, TEM) in combination with image analysis offer good possibilities for quantitative measurement (see Sect. 1.5.4.5).

By looking at the vast differences between some of the above shapes and spheres it will be clear that application of the equivalent sphere concept in some cases can be of little value to a proper description of the particle. This is the more true when a preferred particle projection is measured by the sizing technique. Then, a choice is

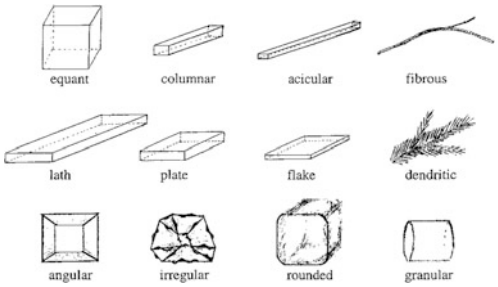

Fig. 1.5 Qualitative descriptors for particle shape [54]; copyright Springer, reproduced with permission

to be made for using e.g. (distributions of) particle length or breadth or aspect ratio to represent the particles instead of or in combination with equivalent sphere diameter.

1.4.4 Particle Morphology

The morphology of API particles is also important with regard to product quality, both during processing and of the final product.

Simple solid particles can be amorphous or crystalline. Moreover, many materials can crystallize in different crystal structures (polymorphs) depending upon the type and conditions of the crystallization process. The degree of crystallinity and the crystal structure of a solid material are important for two reasons: (a) solubility and dissolution rate may be different, (b) different crystal structures often lead to different particle shapes and different strengths with respect to breakage and attrition.

For complex particles, however, there is more. Liposomes containing a particulate pharmaceutical product exemplify such complex product (see Fig. 1.6). Complex liposomes may contain:

- an aqueous core that can contain an API
- one or more (phospho-) lipid bilayers containing hydrophilic heads and hydrophobic tails, which restrain the transport of pharmaceutical product from the core to the outside and may also contain API for direct dissolution and specific colorants or elements for imaging
- a protective layer of a polyethylene-glycol derivative, to which specific targeting agents may have been added.

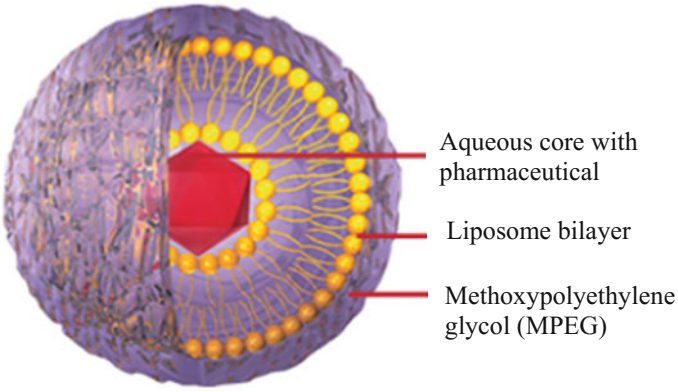

Fig. 1.6 Schematic composition of a pharmaceutical liposome

Their size is typically in the order of 100 nm, leaving a maximum size of about 80 nm for the core. It should be noted that crystalline pharmaceuticals for which the length exceeds the size of the core may change the spherical form of the liposome, or even disrupt it. This may have severe consequences its release rate. Cryogenic transmission electron microscopy (cryo-TEM), where the samples are quickly and deeply frozen before analysis, seems to be the only technique for characterization to a resolution of about 1 nm. Its rapid development in the last decades has enabled detailed characterization of these complex nanostructures.

Crystallinity and crystal type are usually determined by means of X-ray diffraction and differential scanning calorimetry (DSC), crystal shape by microscopy (optical, SEM or TEM). Infrared, (Terahertz-) Raman or Terahertz spectroscopy can be applied to identify the structure. See further Sects. 1.5.4.2 and 1.5.4.5.

1.4.5 Particle Density and Porosity

The density of particles is important as it relates volume to mass. Pharmaceutical particles are usually non-porous; mesoporous (nano-) particles are the exception. Then, particle density means skeleton density. For porous particles, the 'effective' density is smaller than the true skeleton density if closed pores are present, since their volume is incorporated in the measured density. This is also the case for the 'apparent' density coming from measurements where some part of the open pores has not been entered by the liquid used. Porosity of particles is important when sorption of components from the surrounding medium (gas or liquid) plays a role as it greatly increases particulate surface area. It can also influence PSD analysis, e.g. in laser diffraction, where scattering at the pore walls contributes to the total scattering pattern, which leads to the artificial presence of small particles.

The porosity of a pharmaceutical tablet usually mainly consists of voids in between the particles, but also porosity of the particles themselves, if present, contributes. Porosity of tablets can be important since it may facilitate, for example, access of water for easy disintegration.

Pore sizes in particles are classified in three categories, viz.:

- *macropores*, with pore diameters larger than 50 nm
- *mesopores*, with pore diameters in the range 2–50 nm
- *micropores*, with pore diameters smaller than 2 nm.

Voids in between particles in a powder or in agglomerates depend upon particle size and are generally larger than 50 nm. Thus, they may overlap with macropores.

1.4.6 Surface Area

The (external) surface area of particles is important in relation to the dissolution rate of solids and evaporation properties of droplets as well as for stabilization of suspended particles and for explosion behavior of air dispersed dry particles or small droplets. Note that dust and mist explosions require very little ignition energy if particle size drops below about 50 μm and may have very severe consequences of casualties and destruction of equipment [47, 49].

When particles or tablets contain accessible pores, then the total surface area often is greatly magnified. Surface area can be directly measured (see Sect. 1.5.4.6) or be derived from the particle size distribution. Note that the latter calculation only yields the external particle surface area, since the area of pores is not taken into regard. Moreover, it only gives a rough estimate for non-spherical particles, since equivalent sphere diameters are used in the calculation.

The internal surface area is relevant for cases where adsorption properties are required.

1.4.7 Wettability

The wetting properties of particulate surfaces—of both particles and compacts—determines to what extent a surface is wetted by a liquid. This property is important since adequate wetting of powders is required in wet granulation and wetting of the final product precedes its dissolution. Wetting occurs when the surface energy of the solid (S) exposed to the atmosphere (V) is greater than that of the liquid (L), that is if the surface (interface) tension $\gamma_{SV} > \gamma_{SL} > \gamma_{LV}$. The driving force for wetting is $\gamma_{SV} - \gamma_{SL}$. The resisting force is the energy required for increasing the surface area of the liquid drop. The Young-Dupré equation presents the balance of these forces [58]: