



Influence of cohesive properties of micronized drug powders on particle size analysis

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Abstract: Particle size analysis results with respect to micronized, mean particle size below 10 μm , furosemide, chloramphenicol palmitate and acetaminophen particles are dealt with in this paper. Special consideration was given to the effect of the agglomeration of particles on data generated by three size measurement techniques. The physico-chemical basis for preparing sufficiently well dispersed and stable suspensions for analysis by employing mechanical methods of pretreatment are shown. Furthermore, methods to determine the state of dispersion and methods to assess the individual particle size before size analysis are described. An attempt was also made to establish the statistical confidence that can be assigned to a particular instrument and the confidence level that may be placed on comparative data obtained with the different particle size analysers. Results especially showed the impact of the agglomeration of very small furosemide particles, mean size 3 μm , on particle size analysis and the importance of controlling the cohesive properties of this drug. To overcome the problems associated with agglomeration more attention must be paid to the physical properties of the drug substance. Combining particle size analysis with bulk density, surface area and microscopical studies also helped to identify potential problems.

Keywords: *Particle size analysis; drugs; cohesive powders; micronized powders.*

Introduction

The importance of particle size to the pharmaceutical industry is widely recognized and this is reflected in that particle size analysis is a commonplace activity [1]. The size distribution of drug powders is a key property that can influence its transport, storage, reactivity and solubility [2]. In pharmacy we are mostly concerned with particles, ranging from 0.1 to 1000 μm in size, that only approximate to spheres in shape. The degree of fineness of a powder is of outmost importance since the presence of very small particles can modify the cohesive properties of the powder [3]. In practice, the primary particles of micronized powders — particle size below 20 μm — will adhere to one another due to surface forces forming secondary particles, agglomerates and aggregates [4].

There are close to 200 different methods for characterizing some size-dependent aspects of a fine particle system [5]. Recently, laser diffraction has become one of the most widely used methods for determining particle size [2]. Its popularity arises out of the apparent simplicity and because a size distribution may be obtained within minutes. Selection of a specific

size analysis method may be limited by pharmacopoeia requirements, but in general the most efficient method should be selected on particle properties, for example cohesiveness, wettability and solubility [6]. Recently the tendency is to extract information on the effect of a specific particle property from the comparison of data obtained with different particle sizing techniques [7].

An important precondition for most methods of particle size analysis is the preparation of suspensions with a defined state of dispersion [8]. The preparation of a suspension of deagglomerated particles is particularly difficult when working with micronized, cohesive powders. Dispersion is intended to counteract the forces between particles by physico-chemical and mechanical means such that the particles finally exist individually. To achieve this the following three fundamental processes must take place: (1) wetting of the solid; (2) deagglomeration of particle agglomerates; and (3) stabilization of the dispersed suspension [4]. Some mechanical means used to disperse particles include, stirring, shaking and ultrasonic treatment of the suspension [8]. Most commercially available particle size analysers employ one or the other sample

suspension and dispersion technique during analysis.

This investigation attempted to study the influence of the cohesive behaviour of micro-fine drug particles on particle size analysis. It was done by comparing the differences between particle size analysis of micronized furosemide, chloramphenicol palmitate and acetaminophen particles in the same and in different instruments. The aim was also to evaluate methods used to assess agglomeration and methods employed to disperse agglomerates before analysis.

Materials and Methods

Materials

Three micronized drugs, furosemide, chloramphenicol palmitate and acetaminophen were chosen due to differences in cohesive behaviour. The powders were supplied by Fine Chemicals (South Africa) and complied to USP standards. Larger particles (mean size approximately 20 μm) were prepared by milling large particles, recrystallized from hot saturated solutions (50°C) of the drugs in ethanol, with a Retzh high speed mill (Haan, Germany). X-ray powder diffraction analysis showed that the crystal forms of the recrystallized material were similar to that of the supplied powder. Powders were stored in desiccators over silica gel. All the solvents and chemicals were analytical grade and water fit for liquid chromatography was used.

Particle size analysis methods

Three different particle size techniques were selected:

- (1) the electrical sensing zone technique (Coulter Counter, model ZB, England) which measured an equivalent volume diameter of particles suspended in an electrolyte solution and held in suspension by a propeller stirrer;
- (2) the laser diffraction spectrometry method (Sympatec, Germany) whose output is a volume (or mass) distribution. Powders were suspended either with the aid of a low frequency ultrasonic bath or a dry powder dispersing attachment. This attachment permits the application of laser diffraction to study dry powders with particle sizes from less than 0.5 μm ;
- (3) the dual discipline analysis technique (Galai-Cis-1, Israel), integrating diffrac-

tion and image analysis, for particle sizing whose output is also a volume (or mass) distribution. Suspended particles were measured in a small glass cuvette. A small magnetic stirrer inside the cuvette prevented sedimentation of the particles during analysis.

The criteria for the selection were to apply modern equipment commonly used for routine analysis. The operating principles of these instruments have been described in papers and textbooks and will be omitted here. It should be pointed out that they all perform fast analyses, originate highly reproducible results and are capable of handling a large variety of materials. The dry powder method, however, uses large quantities of powder.

Validation of particle size analysis

The particle size analysers were calibrated for particles in liquid analysis using polystyrene spheres of known diameter, 2 and 20 μm . Measured sizes obtained with the three instruments were not significantly different from data supplied by the manufacturer of the standard particles, with values of $2 \pm 0.3 \mu\text{m}$ and $20 \pm 2.4 \mu\text{m}$, respectively. As the dry dispersion apparatus, coupled to the Sympatec particle size analyser, requires a large volume of powder for analysis it was not possible to validate the instrument with the standards. Furthermore, to check on the dissolution of the smaller drug particles relative to the larger particles, the number of particles were counted before and 5 min after each measurement. Comparison of these counts indicated that sample dissolution was negligible.

Methods used to disperse powders

Dispersion into air was performed with a dry powder disperser, attached to the Sympatec Helos particle size analyser, using compressed air. When using the particles in liquid method, concentrated homogeneous suspensions were prepared either in an ultrasonic bath or by lightly shaking suspensions with a mechanical shaker. Suitable non-solvent dispersing liquids were chosen as a result of preliminary tests. Both membrane filtered solutions saturated with the drug and saturated solutions containing 0.011 g l^{-1} polyoxyethylene sorbitan monooleate were used as dispersing solutions [9]. For particle size analysis with the Coulter Counter a 1% calcium chloride electrolyte solution was saturated with the drug.

Microscopy

Microscopy and especially electron microscopy is the best method for determining the particle size directly because it gives additional information on particle shape and aggregates [6]. The powders were studied with a Cambridge Stereoscan 250 scanning electron microscope (SEM). Electronmicrographs and video images, taken with cameras attached to the electron microscope, were studied and the particle sizes assessed.

Surface area measurement

The surface area (A) of a powder constituted by spheres is universally related to the size of the individual particles by the following equation [10]

$$d = 6/(\rho A), \quad (1)$$

where ρ is the density of the solid and d is the mean diameter. For actual powders comprised of particles of different sizes and irregular shapes the relationship is of course more complicated but the equation still provides a rough guide to the order of magnitude of particle size [11]. The most widely applied method for surface area measurement is the BET method. A micromeritics model 2000 (Micromeritics, USA) high speed surface area analyser, designed for single point BET, using fixed pressures and variable volumes was used to measure the surface areas of the micronized powders. Results are the mean of three determinations.

Density measurement

An indirect method to measure the cohesiveness of a powder from bulk density is to calculate the percentage compressibility (C) used to evaluate the flow properties of powders [12].

$$C = (Dt - Dp)/Dt \times 100, \quad (2)$$

where Dt is the tapped density and Dp the poured or fluffed density. Powders with a compressibility of $>28\%$ have extremely poor flow properties and are classified as cohesive [13]. To measure the density change a known powder mass was placed in a calibrated glass cylinder and the cylinder mechanically tapped until no change in the volume could be detected. The true density was measured using an air comparison pycnometer (Model 930,

Beckman, USA). Presented values are the mean of five determinations.

Calculations and statistical interpretations

For fine particulate pharmaceutical powders, the volume or mass bias (identical to volume if the measured particles have equal densities) proved the most useful way of representing particle diameters of milled or micronized powders [6]. These powders usually have log-normal particle distributions that can be described completely by the geometric median or mean diameter plus geometric standard deviation. To define the size distributions and compare the characteristics of the powders measured size distributions were broken down into different size ranges and the data converted to the volume (or mass) distribution [6]. Results presented throughout are the mean of five individual measurements and particle size distributions are the relative frequency distributions by volume [6]. Mean volume particle sizes were compared according to the Newman-Keuls test (CSS: Statistica, Statsoft). A 95% confidence level ($P \leq 0.05$) was considered satisfactory for indicating significant differences in mean volume particle size.

Contact angle measurement

To lower the interfacial tension surfactants (wetting agents) are used [14]. The most popular approach to obtain an indirect contact angle for powders is to prepare a compressed disc and to observe a small drop of liquid on the surface. Powder discs were compressed on a RIIC ring press used for compressing discs for infrared spectroscopy. For each powder three discs were prepared and the contact angle of the dispersing solutions measured. Results are the mean of 15 measurements per disc.

Results and Discussion

No uniform behaviour of the powders could be detected when examining the appearance of the micronized, and recrystallized, milled, furosemide, chloramphenicol palmitate and acetaminophen powders. Estimation of the cohesive properties of the powders, indicated by a percentage compressibility, equation 2, larger than 28%, showed that the micronized furosemide powder was extremely cohesive ($C = 42\%$). Micronized chloramphenicol

palmitate ($C = 30\%$) and acetaminophen ($C = 26\%$) powders were also cohesive. The larger recrystallized, milled powders could all be classified as fair to free flowing powders. $C = 21\%$ for furosemide, $C = 11\%$ for chloramphenicol palmitate and $C = 7\%$ for acetaminophen.

The scanning electronmicrographs of the micronized furosemide powder, Fig. 1, show that the powder contained agglomerates of particles with varying sizes. Such electronmicrographs and video images taken of all the powders, were used to estimate the microscopical mean length of the powders, listed in Table 1. However, microscopical examination was necessarily confined to a minute sample of the material, so that large numbers of such samples had to be examined to obtain meaningful results. Notwithstanding highly accurate

values for particle size not being attainable the particle size assessed from carefully studied micrographs proved an ideal tool for assessing the mean particle size before analysis with a dedicated particle size analysis instrument. Particle sizes were also estimated from surface area measurements, equation 1. When a solid is cohesive, the particle size calculated from the external surface area, may be smaller by several orders of magnitude than the particle size measured without dispersion of agglomerates. Surface area calculated mean sizes for the three micronized powders are listed in Table 1. Despite the arbitrariness of the correlation between surface area and particle size it also indicated primary particle size. For practical reasons the application of the BET method to the study of surface area had to be limited to particles that were extremely finely divided.

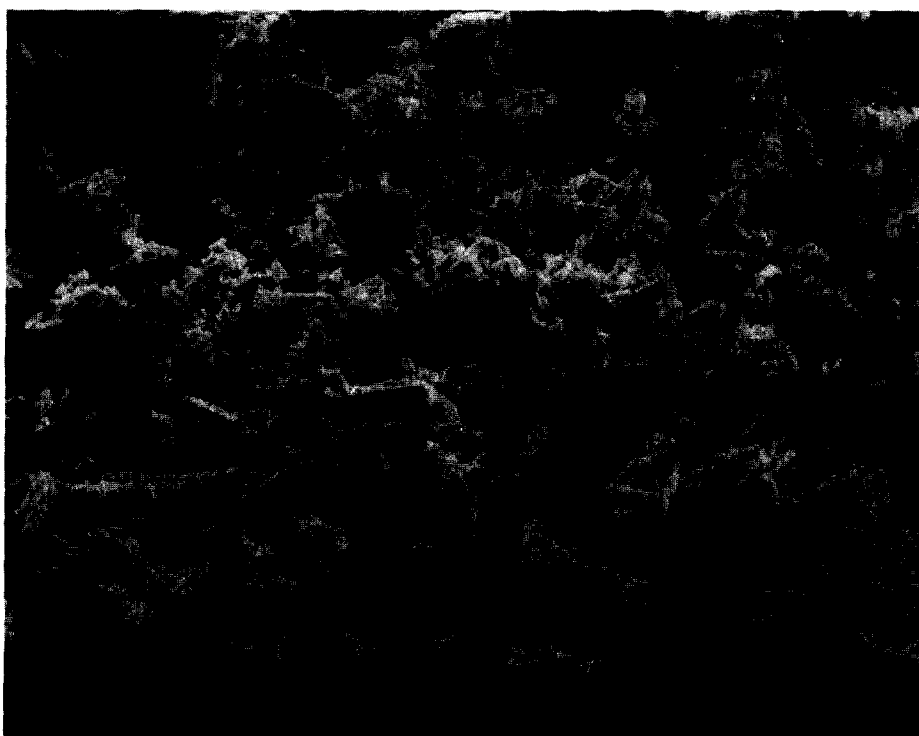


Figure 1
Scanning electronmicrograph of agglomerated, micronized furosemide particles with a mean volume particle size of $3\ \mu\text{m}$.

Table 1
Powder and particle properties of the drug powders

Drug powder	Contact angle ($^{\circ}$)	Powder density (g cm^{-3})	Surface area ($\text{cm}^2 \text{g}^{-1}$)	Mean size surface area (μm)	Microscopical mean length (μm)
Furosemide	81	1.63	11200	3	5
Chloramphenicol palmitate	122	1.25	6300	8	8
Acetaminophen	69	1.25	7600	6	6

Taking into account the cohesive behaviour of the micronized powders, it was, therefore, essential that these powders were completely dispersed before particle size analysis with the dedicated particle size analysers. To obtain and maintain a high degree of dispersion of the powders in the dispersing liquids the solid had to be wet by the dispersing liquid as spontaneously and completely as possible. Furthermore, the forces of repulsion had to be as high and Van der Waals energies of attraction as low as possible. For the characterization of the state of dispersion a number of methods were used including measurement of wettability from contact angle measurements, microscopical determination and comparison of the difference in particle size measured before and after dispersion.

The contact angles of saturated aqueous solutions on compressed discs of the three drugs, listed in Table 1, showed that the drugs were not easily wet by water but completely wet by saturated solutions containing a surfactant, polyoxyethylene sorbitan monooleate, below the critical micelle concentration. Contact angles could not be measured because the dispersing solutions spread over the disc surfaces. To enhance and increase dispersion, suspended powders were subjected to sonication. Ultrasonic treatment of suspensions is presently the most common and the most effective method used for agglomerate breakdown [8]. The effect of sonication time on the mean volume particle size of the agglomerated, micronized powders, measured with the Galai-

Cis-1 instrument, is illustrated in Fig. 2. The mean volume particle diameter of all the powders decreased with increased sonication time. This decrease in size was especially significant for the agglomerated furosemide powder shown in Fig. 1. When agglomerates of furosemide particles were not fully disintegrated into constituent particles, big loose aggregates were observed in the samples and the particle size distributions were multi-modal with an average size above 100 μm . After 12 min of sonication for the furosemide, 4 min for the chloramphenicol palmitate and one minute for the acetaminophen micronized powders the mean volume particle size and distribution remained constant. These times were considered as the minimum time necessary to ensure the optimum degree of disintegration and dispersion before size analysis. The larger size powders were all dispersed after one minute sonication in the surfactant dispersing solutions. The degree of sample dispersion was confirmed by microscopical evaluation of suspensions.

The results obtained from dispersion evaluation confirm that except for micronized furosemide particles and large acetaminophen particles, sample sonication in a surfactant dispersing solution disperses the agglomerates into single particles available for counting and sizing. Sonication was not sufficient to completely disperse furosemide agglomerates because even after 16 min the particle size distribution was bi-modal with a mean size of 4 μm , compared to the single population with

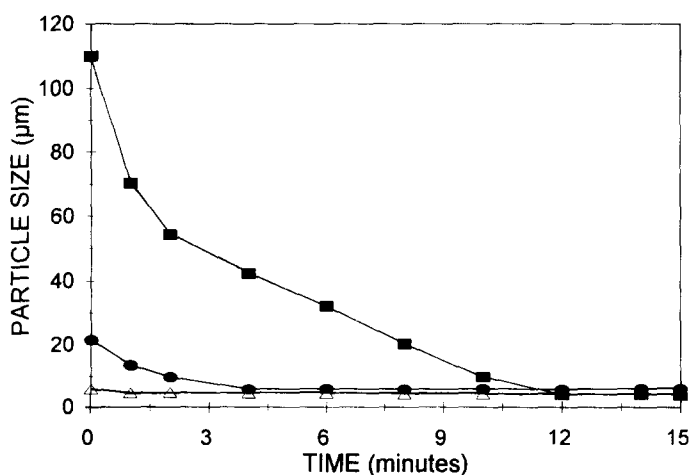


Figure 2

Effect of sonication on the mean volume particle size, measured with the Galai-Cis-1 particle size analyser, of micronized (■) furosemide, (●) chloramphenicol palmitate and (△) acetaminophen powders and suspended in saturated aqueous drug solutions containing a surfactant.

a significantly smaller mean volume particle size, 3 μm , measured after dry powder dispersion, Fig. 3. The observed decrease in particle size of the acetaminophen after sonication for longer than 2 min, and because sonication is known to fracture particles, implicated that sonication resulted in primary particle breakdown of particularly larger acetaminophen particles. Dry powder dispersion also led to primary breakdown of the larger sized acetaminophen particles.

Subsequently, the mean volume particle size distribution of each of the six powders was measured without dispersion and after dispersion in surfactant solutions with sonication, using each of the three selected particle size analysers. The particle size of powders measured after being suspended in drug saturated aqueous solutions and dispersed by shaking the suspension for 1 min with a low intensity mechanical shaker were regarded as representing the particle size of the powders when not dispersed. Results are listed in Table 2 for the small sized micronized powders and Table 3 for the larger recrystallized, milled particles. For all the micronized powders the sizes measured without dispersion were significantly larger than after dispersion irrespective of the method of analysis used, Table 2. This was also true for the larger furosemide particles, Table 3.

The particle size of the micronized furosemide powder after dispersion, Table 2, depended on the method used for analysis. The mean size measured with the electrical sensing

zone technique was significantly larger, 12 μm , than obtained with the laser light scattering and light blockage instruments, average 4 μm ($p = 0.046$). The smallest mean volume size, 3 μm , was measured with the laser light scattering instrument after dry dispersion. This size, although smaller, did not differ significantly from the sizes obtained with the particle in liquid methods, average size 3 μm , but differed significantly from that measured with the electrical sensing zone technique, 12 μm . The size distribution obtained after dry dispersion was also the only uni-modal dispersion, Fig. 3, measured for the micronized furosemide powder. In comparison bi-modal and multi-modal distributions, Fig. 3, were obtained with the other methods. According to its compressibility, Table 1, the larger furosemide particles were also cohesive and once again the particle size measured before dispersion was significantly larger than after dispersion.

Micronized chloramphenicol palmitate powder was not as cohesive as the furosemide powder and, therefore, provided to be less sensitive to changes in the particle size analysis methods. After dispersion the particle sizes measured with the different methods were similar. The difference between the size measured before, average ± 20 μm , and after dispersion, average ± 6 μm , is not as significant as for the furosemide powder. The larger particle size chloramphenicol palmitate powder, Table 3, was not cohesive and the size measured after dispersion was not significantly

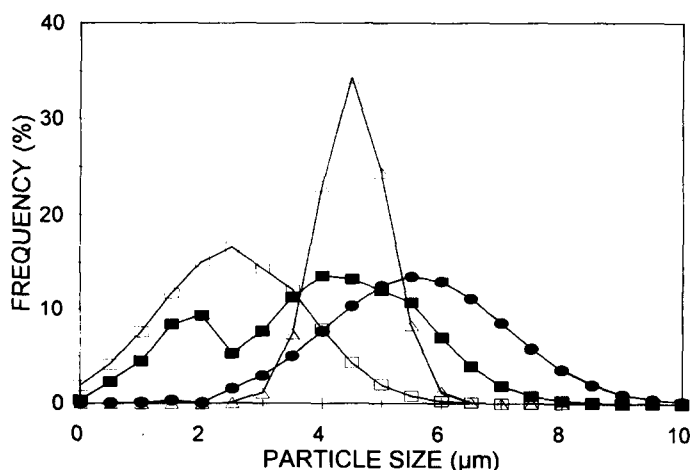


Figure 3

Relative percentage frequency particle size distribution by volume of the micronized (■) furosemide (●) chloramphenicol palmitate and (△) acetaminophen powders measured with the laser light scattering instrument and suspended in surfactant solutions plus the distribution of the furosemide powder after dry dispersion (□).

Table 2

Mean volume particle size and standard deviation of micronized drug particles measured before and after dispersion using different particle size analysis techniques. Results are the mean of five measurements

Size analysis method	Furosemide		Chloramphenicol palmitate		Acetaminophen	
	Not dispersed ($\mu\text{m} \pm \text{SD}$)	Dispersed ($\mu\text{m} \pm \text{SD}$)	Not dispersed ($\mu\text{m} \pm \text{SD}$)	Dispersed ($\mu\text{m} \pm \text{SD}$)	Not dispersed ($\mu\text{m} \pm \text{SD}$)	Dispersed ($\mu\text{m} \pm \text{SD}$)
Electric sensing zone*	126 \pm 23.3	12 \pm 4.2	25 \pm 6.3	6 \pm 1.6	8 \pm 2.0	5 \pm 0.5
Light blockage†	110 \pm 26.3	4 \pm 1.5	22 \pm 5.5	6 \pm 1.5	6 \pm 1.5	5 \pm 0.5
Laser light scattering‡	94 \pm 19.0	3 \pm 1.3	19 \pm 5.3	6 \pm 1.5	5 \pm 1.5	5 \pm 1.6
Dry powder analysis§		3 \pm 1.2		5 \pm 0.4		4 \pm 1.4

* Coulter Counter.

† Galai-Cis-1.

‡ Sympatec Helos.

§ Sympatec Helos plus Rodos dry disperser.

Table 3

Mean volume particle size and standard deviation of larger drug particles measured before and after dispersion using different particle size analysis techniques. Results are the mean of five measurements

Size analysis method	Furosemide		Chloramphenicol palmitate		Acetaminophen	
	Not dispersed ($\mu\text{m} \pm \text{SD}$)	Dispersed ($\mu\text{m} \pm \text{SD}$)	Not dispersed ($\mu\text{m} \pm \text{SD}$)	Dispersed ($\mu\text{m} \pm \text{SD}$)	Not dispersed ($\mu\text{m} \pm \text{SD}$)	Dispersed ($\mu\text{m} \pm \text{SD}$)
Electric sensing zone*	42 \pm 11.5	23 \pm 5.1	22 \pm 6.4	22 \pm 5.9	25 \pm 6.5	19 \pm 5.5
Light blockage†	33 \pm 7.7	21 \pm 4.6	24 \pm 6.0	20 \pm 5.2	26 \pm 6.2	16 \pm 5.2
Laser light scattering‡	30 \pm 10.9	20 \pm 4.4	21 \pm 5.6	20 \pm 5.3	19 \pm 6.1	16 \pm 4.1

* Coulter Counter.

† Galai-Cis-1.

‡ Sympatec Helos.

different from that measured before dispersion. According to differences in particle size measured before and after dispersion, listed in Table 2 and 3, the acetaminophen powders were apparently not cohesive. However, microscopical evaluation, did show that a slight decrease in particle size after sonication and dry powder dispersion could be the result of primary particle fracture. The breakdown of primary particles by sonication was especially significant for the larger acetaminophen particles, Table 3.

Throughout the particle size distributions obtained with different size analysers showed dispersion of cohesive particles before analysis affected the measured mean size and distribution. The mean particle size and distribution of the cohesive, poorly wetttable powder, furosemide, in particular varied considerably depending on the method used for particle size analysis, especially the method used to disperse agglomerates before measurements. This variation was not as significant for less cohesive chloramphenicol palmitate powder and was almost non existent for the free flowing acetaminophen particles.

Conclusions

This investigation attempted to study the influence of the cohesive behaviour of micro-fine particles on particle size analysis. It was done by comparing the differences between analysis of different materials in the same instrument and the same material in different instruments. Results illustrated the sensitivities of the different sizing techniques to the presence of particle agglomerates or floculates and demonstrated the effects of improper dispersion on particle size distribution results. It showed that more attention should be paid to physical properties of the drug substance and that the combination of particle size analysis with bulk density, surface area and scanning electron microscopy studies helped to identify potential problems. To be able to determine the particle size distribution of a cohesive powder the particle size and distribution of the individual particles had to be known because when a powder with fine particles of unknown size was considered, then many distributions composed of both separated particles and/or agglomerates with different sizes could not be identified.

Throughout the study particle size control proved only truly effective when the following was achieved: an easily standardized analysis method and dispersion technique was used; the method was applicable to primary particle size assessment and sensible interpretation, presentation and comparison of particle size data were possible. For cohesive powders the question also arises: which dispersing state of the system must be reached with respect to the measuring aim? The fulfilment of the following requirement proved to be ideal: the solid particles should be contained in the suspension as individual particles, the dispersing state must not change during particle size analysis and the individual particle properties must not be altered during dispersion or analysis.

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