WHAT IS WRONG WITH LASER DIFFRACTION?

A Critical Review of Current Laser Diffraction Methods for Particle Size Analysis

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A particle-sizing method based on laser diffraction suffers from several major pitfalls, namely:

(1) the method is based on false assumptions
(2) the reported distribution can be skewed towards the smaller range
(3) the results vary significantly with optical parameters
(4) the software used for calculation of results can not be independently validated
(5) the accuracy of measurements for non-spherical particles is unacceptable

Consequently, the results of particle-sizing analysis based on laser diffraction methods should not be trusted.

Laser difractometry is the most popular particle-sizing method today due to ease of use and proven precision. Its range of applicability includes sprays, dry powder, and suspensions. A wide dynamic range (0.02 μ to 2-3 mm) and the speed of measurements (up to 400 μs/measurement in real time) add to the popular appeal.

Numerous attempts (ISO, USP, NIST, ASTM) to standardize the laser diffraction and other particle-sizing methods were made although the USP laser diffraction standard is not finalized yet [1, 17-28, 47-50].

The laser diffraction vendors assert that the instruments require no calibration although the diffraction detectors need some initial setup and adjustments. The major claim for fame of the laser diffraction method is based on repeatability. Average of thousands of measurements can be repeated with a high degree of precision.

However, the last decade was marked by an increasing number of testimonies about the drawbacks of laser diffraction methodology for particle-sizing [3-5, 11-13, 32-34, 42, 46]. There was a growing evidence of a rather large discrepancy between laser diffraction measurements of non-spherical objects, and the results obtained by other techniques, and, especially, by image analysis.

The discontent became so deep that some laser diffraction salesmen recently felt an urge to defend their source of income [35, 36]. In the absence of scientific evidence, Paul Kippax (2005), a Malvern product manager, for example, have accused the laser diffraction critics of incompetence, improper use of refractive indices, "poor sample preparation or the incorrect selection of the range lens" [36]. Despite the obvious lack of educational credentials, a didactic attempt was made "…to encourage a more informed assessment…" of laser diffraction by teaching the "novices" the fundamentals of the method.

It is imperative, however, for any scientific discussion to rely solely on facts. In what follows, we will present the scientific evidence of pitfalls and inaccuracies associated with laser diffraction for particle size analysis.

FALSE ASSUMPTIONS

First, let us examine the basic assumptions of the laser diffraction method.

It has been postulated that scattering events are independent and that total scattering is the sum of individual events. In general, these assumptions are hard to dispute.

However, the other fundamental assumptions are not.

- *The False Assumption of Random Particle Orientation.*

  For extremely non-spherical particles, this assumption is crucial for proper analysis [9].

  It was shown that in most laser diffraction systems, the flow is not turbulent but rather laminar [3]. As a result, a phenomenon of "flow alignment" causes the non-spherical particles orient themselves in the direction of the flow.

  When aspect ratio of particles is larger than 5:1, "flow alignment" forces particles to pass the

laser at 90^o (perpendicular to the beam) and the projected surface area is measured instead of volumetric size [52]. Recent numerical simulations conducted in the Czech Republic indicate that deviations from perpendicular alignment do not have a statistically significant effect upon the results [40, 41].

Theoretically, in case of random orientation of ellipsoid particles, only a single peak at the minor diameter should appear in laser diffraction systems [38]. However, studies with LGC Promochem mono-sized fiber-analogue certified shape standards indicate that "flow alignment" is a common phenomenon, resulting in both minor and major axis being reported [34]. When the results are presented as the volume probability, practically all data was rendered bimodal for both the Mie analysis and Fraunhofer approximation (Fig. 1).

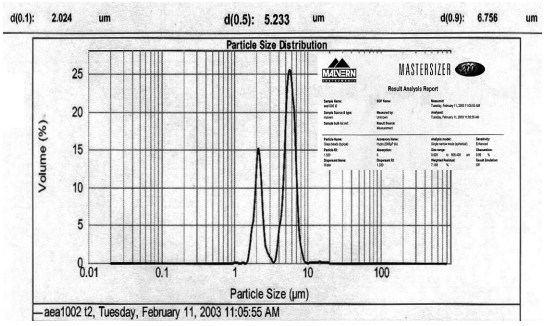

Fig. 1. Bimodal distribution corresponds to diffraction along both the minor and major chords. This response was noted regardless of the flow speed or the laser diffraction system used (Beckman-Coulter, Horiba, Malvern, and Sympatec). From Kelly, 2004.

Based on the above studies, there is sufficient evidence that the assumption of random orientation for non-spherical particles larger than 1 μm (and with a large aspect ratio) is wrong.

- *Dubious assumption of volume (weight) based results and spherical equivalent diameter data*

  It is claimed that laser diffraction results are reflecting a volume distribution [7, 43]. In reality, they are volume-weighted as a result of a cubed radius term in the analytical equation but are best considered as surface area data. Kelly [33] showed that Coulter laser diffraction volume data practically coincides with the projected surface area. Moreover, it was shown that laser diffraction instruments do not differentiate between plates and cubes of similar linear dimensions and significantly different volumes. For irregular particles, "volume probability" laser diffraction results are mostly correlated with the projected surface area results based on image analysis or the equivalent circular area diameter of the non-spherical shape standards. An extended discussion of this phenomenon can be found in Kelly and Kazanjian [34].

  The Mie theory is expected to provide the volume of the particle as opposed to Fraunhofer approximation that is a projected area prediction.

  It is often claimed [43, 35, 36] that for particles with a constant density, laser diffractometers results represent mass (weight) distribution. This claim is based on the assumption that laser diffraction systems provide equivalent spherical volume diameter data. Since this assumption was shown to be wrong for non-spherical particles, the laser diffraction volume percent data cannot be equated with mass distribution.

Since the major assumptions of the laser diffraction technique appear to be false, or, at least, questionable, the discrepancy between the measurement results and reality may be expected.

DISTORTION OF MEASUREMENTS

Kaye [29, 31] has suggested the existence of "ghost" particles caused by sharp edges on the objects which produce high angle diffraction. These "ghosts" diffractions are interpreted by the laser diffraction instrument to be small particles.

It has been stated [33] that in a diffractometer, larger particles in a Lorenzian distribution may go undetected. The Lorentzian distribution, also called the Cauchy distribution, is a continuous distribution of horizontal distances at which a line segment tilted at a random angle cuts the *x*-axis. Laser difractometry is governed by this distribution since, by assumption, the laser beam is deflected by particles at random angles.

For acicular particles, image analysis shows much larger particle sizes compared to laser diffraction because laser diffraction undercounts events generated by larger dimensions (major chord) or rather overestimates the contribution of the minor chord data [34].

Thus, a particle size distribution as rendered by a laser diffraction instrument, may be intrinsically biased towards the smaller edge of the spectrum.

FRAUNHOFER APPROXIMATION AND MIE THEORY

Fraunhofer approximation can be used for particles significantly larger than 5λ (laser wavelength). This approximation assumes that the sample is opaque, that total diffraction is the sum of individual components, and that there are no multiple scattering events.

The Mie theory as used in laser difractometry requires refractive indices of sample and solution. It was suggested as a remedy for inability of the Fraunhofer approximation to properly report fines. In the limit of large particle size, the Mie and Fraunhofer optical models converge.

However, the Mie optical model does not fully correct for over representation of small particles associated with Fraunhofer approximation (Fig. 2).

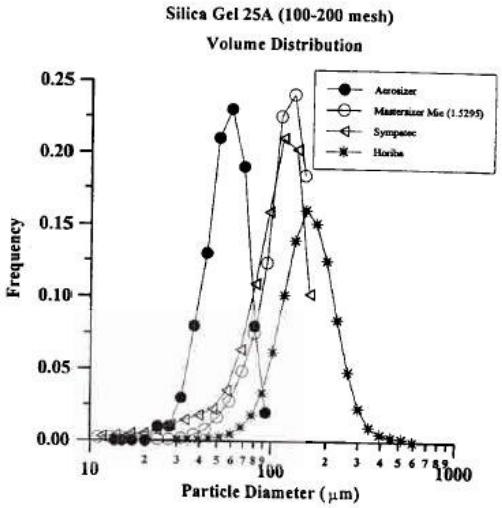

Fig. 2. An example of a discrepancy between laser diffraction analysis (using either Mie or Fraunhofer optical model) and time-of-flight technique (corroborated by image analysis). From Etzler and Deanne, 1997.

It is a well known fact that the success of Mie laser diffraction is predicated on the estimation of correct refractive index numbers and yet Kippax [35, 36] claims that these numbers are required only to an accuracy of ±0.2 to achieve "reliable results". However, with good precision, refractive index numbers can be far off and the resulting particle size estimates may have nothing to do with reality.

Anyway, the argument goes, there are "simple tests" such as optical index matching "to estimate refractive index to the required accuracy" [36]. Unfortunately, there is nothing simple about the optical index matching method as described by Gustafsson and Sebesta [16]. Noting that anisotropic objects (e.g. lactose crystals) have different index of refraction in different directions, they try to find the minimum and maximum refractive index "by multiple exposures of the same object, with a step by step rotation of the polarization of the illuminating light". The method (1) requires a rather sophisticated digital Fourier holographic setup; (2) requires a pre-test information about minimum and maximum refractive index of anisotropic particles for the selection of a suitable liquid, and (3) gives no indication at all of the accuracy of the results.

Thus, the need for good estimates of the refractive indices of both the sample and the solution is yet another obstacle in the "proper" use of laser diffraction.

NUMERIC ALGORITHMS AND SOFTWARE

Signal intensity in a laser diffraction instrument must undergo matrix inversion and least square fit to arrive at particle size. Different (and proprietary) algorithms are employed to either fit an assumed distribution to data or to break the model into fixed size classes corresponding to number of detectors and then vary the weight fraction of each class to minimize the fitting "error" [8].

Brian Kaye of Laurentian University in Canada has noted [30]: "Companies that have developed diffractometers do not divulge the structure of their software. The user of this equipment should be careful to obtain information on the data-processing protocol followed in any specific instrument to change the diffraction information into a size-distribution function. Some of the instruments assume a given distribution function and curve fit to accelerate the data processing. Sometimes such curve fitting can distort the data generated."

Complex proprietary numerical algorithms used for laser diffraction are usually not validated and are prone to artifacts. They vary between vendors and with time. In our age of computer system validation, the use of proprietary algorithms can be acceptable only if, in the process of "black box" validation, the input (particle size) is tightly controlled, and the predicted output (reported particle size) coincides with the expected output within the acceptance criteria (usually less than 5%). The proper validation necessarily involves tests of accuracy, and laser diffraction instruments will fail such tests for non-spherical particles with a large aspect ratio.

PRECISION vs. ACCURACY

The laser diffraction method is usually validated (and its accuracy tested) with microspheres standards or similar objects [45]. Etzler and Deanne [12] noted

that laser diffraction is accurate only for non-transparent spherical particles.

The claim that laser diffraction instruments are not accurate comes from recent comparison with other particle-sizing techniques, notably, with optical imaging. Very poor correlation between image analysis and laser diffraction exists in case of acicular particles ("shape of a needle"), rods or plates. Taking into account the fact that error functions of different measurement systems are different, nevertheless we must place more trust in direct observation rather than in the result of a convoluted calculation.

Compared with direct measurements, laser diffraction results for plates can be 31% off, and rods up to 70% wrong [14].

In tightly controlled experiments**,** Etzler and Deanne [12] have concluded that laser diffraction devices were unreliable for the determination of particle size distributions of fine pharmaceutical powders. In their experiments, several laser diffraction instruments from different vendors were used to analyze such materials as glass microspheres (10-95 μm), silica gel 100-200 mesh (irregular shape), pharmatose 200 mesh lactose, and a micronized drug compound. Since all results were reproducible, sampling issues were not relevant. No imaginary refractive index was used as "the materials are generally weakly absorbing in the visible range". The results from different laser diffraction instruments were significantly different, and had, in general, underestimated particle size as compared to image analysis results.

The FDA is aware of this limitation of laser diffraction. A study of comparability of various common particle size analysis techniques was conducted on nitrofurantoin, chosen because of its acicular morphology and also because it contained significant fines [42]. The conclusion was that the large population of fine particles was only detected by the particle counting techniques (image analysis and light obscuration) and not by the ensemble technique (laser diffraction).

Laser diffraction advocates suggest selecting the method "on the basis of its speed, reproducibility, and robustness" providing "precise, rapid results" [36]. Note that accuracy is not mentioned as one of the benefits. In a typical representation, under the subject heading of "method validation", laser diffraction proponents [51] are discussing sampling, specificity, robustness, linearity, reproducibility, and precision - but not accuracy. Moreover, in a failed effort to defend the laser diffraction, the arguments against it are presented as if "both the reproducibility and robustness of the technique have been called into question…" [51]. Alas, it is not the precision of laser diffraction that is questioned but rather its accuracy.

The proposed USP General Chapter <429> asserts that "mathematical analysis [of laser diffraction data] can produce an accurate, repeatable picture of the size distribution" [47-50]. Such statements are patently questionable.

A 3D shape analysis is required for calibration of laser diffraction measurements of arbitrary shaped particles, to express the results as equivalent spheres. However, a general algorithm for laser diffraction can not be developed for particles that vary in both size and shape [39].

Validation of laser diffraction methods of particle size analysis are usually stated in terms of precision rather than accuracy [37]. Accolades for laser diffraction, as a rule, are indeed focused on a potential use of its reproducibility for quality control [6]. For example, Brittain and Amidon [8] carefully worded statement reads: "When particle size measurements are made using the same laser light scattering system, following the same method of sample preparation, and obtained using the same system parameters, it is possible to obtain good information regarding the particle size differences between two lots of materials".

The choice of the most appropriate method is then presented as "largely a matter of accuracy vs. precision" [8] as if no particle-sizing method offers both. Indeed, even in case of acicular particles, laser diffraction is often chosen as the "most reproducible" [44] compared to optical microphotography.

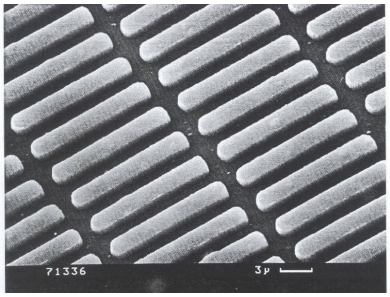

Fig. 3. LGC Promochem 12 μm long shape standards attached to a silicon substrate. From Kelly and Kazanjian, 2005.

Since laser diffraction is intrinsically not accurate, statements such as "accuracy is not applicable to particle sizes" [2] are often made with a flagrant disregard for common sense. The inadequacy of a method, via a false generalization, is extended to the measurement. In fact, any measurement technique must provide an acceptable assessment of accuracy.

How can a particle-sizing accuracy be established? Gokhale & Wright [15] suggested verifying accuracy using a reference material (e.g., starch or a control lot of drug). This approach, however, leaves open the question of validating the size of the "standard" particles.

It was claimed that for irregularly shaped particles, "no one technique provides a more real representation than any other of the true particle size" [36]. Brittain and Amidon [8] suggested that "the 'correct' (but differing) particle size results obtained using different instruments are all equally 'correct', but each may simply be expressing its 'correct' results in different terms". Indeed, for non-spherical particles, the "equivalent spherical diameter" may be calculated on the basis of mass, volume, surface, or length. However, use of mono-sized non-spherical certified standards can help differentiate between accurate and inaccurate particle size representations, and, since such standards are available (Fig. 3), they should be used for equipment validation.

In pharmaceutical applications, there are cases where the accuracy of particle-sizing is of a paramount importance. For example, clinical risks associated with the infusion of particles that exceed the internal diameter of the pulmonary capillaries can be deadly. The accuracy of the particle size analyzers used to quantify the intravenous lipid emulsions, especially for extreme sizes above 5 μm, is, therefore, very important. Studying the differences between particle-sizing instruments for analyzing the stability of lipid emulsions, Driscol et al. [10] have concluded that, unlike the light obscuration technique, the results of the laser diffraction method were non-linear. The laser diffraction instruments overestimated, were less sensitive or missed entirely, globules or particles in the large-size tail of the dispersion. Laser diffraction instruments were clearly shown to be either insensitive to the presence of large particles or overestimated it by a factor of 10.

HOW TO CHOOSE A PARTICLE SIZING METHOD

For quality control applications, any method used to determine a particle size distribution has to be judged upon the technique's ability to detect a significant change compared to previous testing.

Typically, the consistency of a product is assessed by monitoring of lot-to-lot particle size distribution. In such applications, accuracy may be irrelevant, which is a point that is often made by advocates of the laser diffraction instruments. The only concern then would be whether or not the system is sufficiently sensitive to allow the degree of change control desired. Reproducibility of the laser diffraction technique is often confused with inability to differentiate between samples with real size differences.

The limitation of laser diffraction systems with respect to the detection of significant changes in non-spherical particle systems should be always a

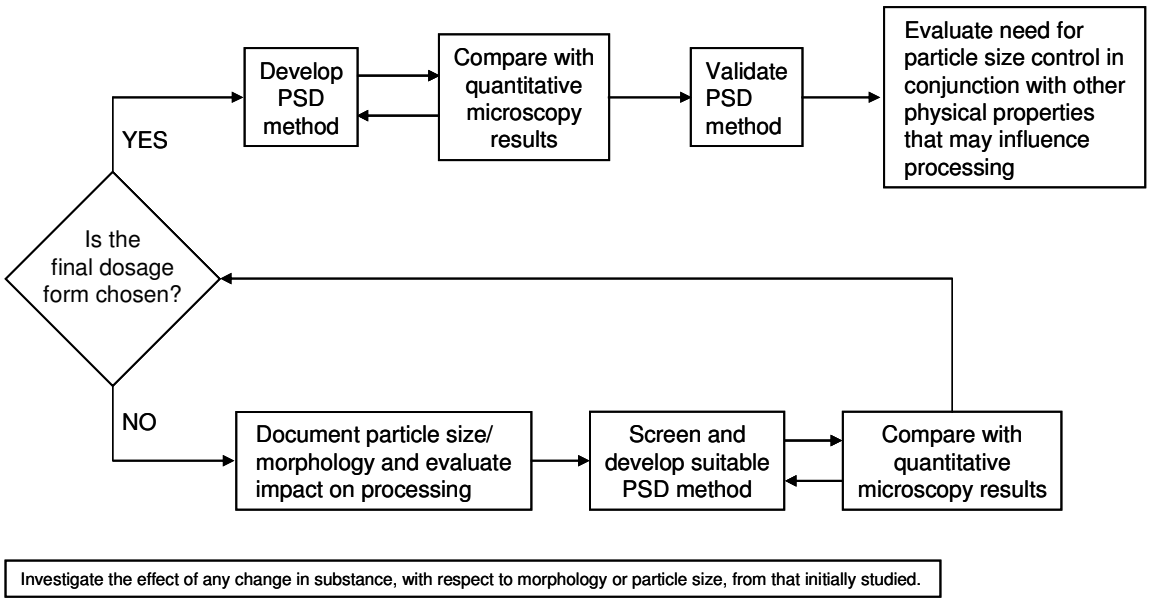

Fig. 4. The proper way of selecting and validating a particle-sizing method. From Kelly (2004).

concern. The determination of applicability of such systems to quality control applications would ideally be made by means of simulation studies in which standards would be used to model the samples of interest or by extensive corroboration of the results by image analysis.

Prior to selecting the final dosage form, a preliminary assessment of particle size and shape should be made, and then a particle-sizing method can be selected with a proper corroboration of results by image analysis (Fig. 4). Once the dosage form has been chosen, a particle-sizing method has to be developed and validated on the basis of a computer-aided image analysis before it can be used for quality control.

CONCLUSION

An urgent need exists for proper validation of particle-sizing equipment, and especially, the laser diffraction instruments. Round robin comprehensive experiments aiming to quantify both accuracy and precision of commercially available particle sizing instruments are long overdue. The alternative methods of particle sizing, such as electron microscopy, time of flight (e.g. API Aerosizer) or time of transition (e.g. Ankersmid CIS-100, described at length as a Galai instrument by Kaye [30]), deserve a closer look by anyone who understands the value of instrument accuracy.

REFERENCES

1. ASTM. E1919-03 Standard Guide for Worldwide Published Standards Relating to Particle and Spray Characterization. ASTM, , 2005

2. Bell R, Dennis A, Hendriksen B, North N, Sherwood J. Position paper on particle sizing: sample preparation, method validation and data presentation. Pharm Tech Europe, November, 1999

3. Berthold C, Klein R, Luhmann J, Nickel KG. Fibers and Fibre Collectives with Common Laser Diffractometers. Part Part Syst Charact, 17:113-116, 2000

4. Bowden P. Particle Size Distribution Measurement from Millimeters to Nanometers and from Rods to Platelets. J Disp Sci Tech, 23(5):631-662, 2002

5. Brewster E, Ramsland A. Particle size determination by automated microscopical imaging analysis with comparison to laser diffraction. J Pharm Sci, 84(4):499-501, 1995

6. Brittain HG. What is the "Correct" Method to Use for Particle-Size Determination?. Pharm Tech, 7:96-98, 2001

7. Brittain HG. Representations of Particle Shape, Size, and Distribution. Pharm Tech, 12:38-45, 2001

8. Brittain HG, Amidon G. Critical Overview of the Proposed Particle Size Analysis Tests. American Pharm. Review, 6(1):68-72, 2003

9. Crompton C. Image Analysis. Why does orientation matter in particle shape and size measurements?. Pharm Form Qual, May, 81-82, 2004

10. Driscol DF, Etzler F, Barber TA, Nehne J, Niemann W, Bistrian BR. Physicochemical assessments of parenteral lipid emulsions: light obscuration versus laser diffraction. Int J Pharm, 219:21-37, 2001

11. Etzler FM. Particle-Size Analysis: A Comparison of Methods. American Pharm. Review, 7(1):104-108, 2004

12. Etzler FM, Deanne R. Particle-Size Analysis: A Comparison of Various Methods II. Part Part Syst Charact, 14(6):278-282, 1977

13. Etzler FM, Sanderson MS. Particle Size Analysis: a Comparative Study of Various Methods. Part Part Syst Charact, 12:217-224, 1995

14. Gabas N, Hiquily N, Laguuerie C. Response of Laser Diffraction Particle Sizer to Anisometric Particles. Part Part Syst Charact, 11:121-126, 1994

15. Gokhale R, Wright PB. Particle size analysis and its role in pharmaceutical development. AAPS Workshop: Particle Size Analysis, , 2003

16. Gustafsson M, Sebesta M. Refractometry of Microscopic Objects Using Digital Holography. , http://www.tde.lth.se/teorel/Publications/TEAT-7000-series/TEAT-7120.pdf, 2003

17. ISO 13320-1. Particle Size Analysis - Laser Diffraction Methods, Part 1: General Principles. ISO Standards Authority, , 1999

18. ISO 13322-1. Particle size analysis -- Image analysis methods -- Part 1: Static image analysis methods. ISO Standards Authority, , 2004

19. ISO 13323-1. Determination of particle size distribution -- Single-particle light interaction methods -- Part 1: Light interaction considerations. ISO Standards Authority, , 2000

20. ISO 9276-1. Representation of results of particle size analysis -- Part 1: Graphical representation. ISO Standards Authority, , 1998

21. ISO 9276-2. Representation of results of particle size analysis -- Part 2: Calculation of average particle sizes/diameters and moments from particle size distributions. ISO Standards Authority, , 2001

22. ISO 9276-4. Representation of results of particle size analysis -- Part 4: Characterization of a classification process. ISO Standards Authority, , 2001

23. ISO/CD 9276-3. Representation of results of particle size analysis -- Part 3: Fitting of an experimental cumulative curve to a reference model. ISO Standards Authority, in preparation,

24. ISO/DIS 13322-1. Particle size analysis -- Image analysis methods -- Part 2: Dynamic image analysis methods. ISO Standards Authority, in preparation,

25. ISO/FDIS 9276-5. Representation of results of particle size analysis -- Part 5: Methods of calculation relating to particle size analyses using logarithmic normal probability distribution. ISO Standards Authority, in preparation

26. ISO/WD 9276-6. Representation of results of particle size analysis -- Part 6: Descriptive and quantitative representation of particle shape and morphology. ISO Standards Authority, in preparation,

27. Jillavenkatesa A, Dapkunas SJ, Lum LH. Recommended Practice Guide: Particle Size Characterization. NIST, Special Publication 960-1, 2001

28. Jillavenkatesa A, Kelly J, Dapkunas SJ. Some Issues in Particle Size and Size Distribution Characterization of Powders. American Pharm. Review, Summer:98-105, 2002

29. Kaye BH. A Random Walk through Fractal Dimensions, 2nd ed. , VCH, Weinheim, 1994

30. Kaye BH. Particle-Size Characterization. In: M. Decker Encycl Pharm Tech, 1997-2011, 2002

31. Kaye BH, Alliet A, Switzer L, Turbitt-Daoust C. The Effect of Shape on Intermethod Correlation of Techniques for Characterizing the Size Distribution of a Powder I: Correlating the Size Distribution measured by Sieving, Image Analysis, and Diffractometer Methods. Part Part Syst Charact, 14:219-255, 1997

32. Keck C, Muller RH. Size analysis by laser diffractometry - how valid are the data?. AAPS Meeting, November, 2004

33. Kelly RN. False Assumptions: Laser Difraction PSA Systems Exposed. NJPhAST Meeting, May 13, 2004

34. Kelly RN, Kazanjian J. Use of LGC Promochem Shape Standards AEA1001-AEA1003 in the Study of the Effects of Particle Shape on the Results from Current Generation Laser Diffraction-Based Particle Size Analysis Systems. Personal Communication, in preparation, 2005

35. Kippax P. Issues in the appraisal of laser diffraction particle sizeing techniques. Pharm Tech Europe, Jan 32-39, 2005a

36. Kippax P. Appraisal of the Laser Diffraction Particle-Sizing Technique. Pharm Tech, 3:88-96, 2005b

37. Lerke SA, Adams SA. Development and Validation of a Particle Size Distribution Method for Analysis of Drug Substance. American Pharm. Review, Fall, 2002

38. Matsuyama T, Umaamoto H, Scarlett B. Theoretical prediction of effect of orientation on diffraction pattern transformation of diffraction pattern due to ellipsoids into equivalent diameter distribution for spheres. Part Part Syst Charact, 17:41-46, 2000

39. Muhlenweg H, Hirleman ED. . Part Part Syst Charact, 15:163-169, 1998

40. Pabst W, Kunes K, Gregorva E, Havrda J. Extraction of Shape Information From Particle Size Measurements. British Ceramic Trans, 100(3):106-109, 2001

41. Pabst W, Mikac J, Gregorva E, Havrda J. An Estimate of Orientation Effects on the Results of Size Distribution Measurements for Oblate Particles. Ceramics-Silikaty, 46(2):41-48, 2002

42. Prasanna HR, Jefferson EH, Taylor JS, Hussain AS, Karuhn RF, Lyon RC. Comparative Analysis of Common Particle Sizing Techniques For Pharmaceutical Powders. , FDA Science Day Poster, February, 2001

43. Rawle A. The Importance of particle sizing to the coatings industry. Part 1: Particle size measurement. Adv Pharm Sci, 5(1):1-12, 2002

44. Redkar S. Determining particle pize specification for a poorly water soluble, needle-shaped, crystalline active in oral drug product. AAPS Workshop: Particle Size Analysis, 2003

45. Schellhamer M, Bowen P, Vaussourd C, Hofmann H. Accuracy of Particle Size Distribution Measurement of Spherical Glass Beads (70-400µm) Using Laser Diffraction. Recent Progres en Genie des Procedes, 77:129-134, 2001

46. Sesholtz DA. Sizing Up… Particle size, distribution and accurate measurements. Pharm Form Qual, May 79-80, 2004

47. USP General Chapter <429>, Proposal Stage 3. Light Diffraction Measurement of Particle Size. Pharm Forum, 28(3):895-901, 2002

48. USP General Test Chapter <429>, Additional Revisions. Light Diffraction Measurement of Particle Size (1st Supp to USP 27). Pharm Forum, 29(4):1146-1153, 2003

49. USP General Test Chapter <429>, In-Process Revision. Light Diffraction Measurement of Particle Size [new] (USP 27). Pharm Forum, 29(2):484-490, 2003

50. USP General Test Chapter <429>, Preview. Light Diffraction Measurement of Particle Size [new]. Pharm Forum, 28(4):1293-1298, 2002

51. Ward-Smith RS, Gummery N, Rawle AF. Validation of wet and dry laser diffraction particle characterization methods. www.malvern.co.uk, November, 2003

52. Xu R, Di Guida A. Size and Shape Characterization of Small Particles. Powder Technol, 132:145-153, 2003