Particle Size Analysis: AAPS Workshop Report, Cosponsored by the Food and Drug Administration and the United States Pharmacopeia*

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ABSTRACT

The concepts of particle engineering and dosage form design have become dominant themes in pharmaceutical manufacturing. This trend is not simply a reflection of the development of new, more sophisticated manufacturing methods of particles or dispersed systems but also recognition of the importance of quality control even in more traditional manufacturing processes. However, the diversity of particle treatments, methods of particle size analysis, expression and interpretation of data, and process applications results in complicated and sometimes confusing criteria for selection, adoption, or relevance of the available techniques.

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INTRODUCTION

A workshop on "Particle Size Analysis" was held in April of 2003 in Washington, DC. This workshop was cosponsored by the American Association of Pharmaceutical Scientists (AAPS), the Food and Drug Administration (FDA), and the United States Pharmacopeia (USP). The intent of the meeting was to provide a forum for debate and exchange of ideas among academic, industrial, and regulatory pharmaceutical scientists and equipment manufacturers. Critical process parameters and their control were identified, and particle size measurement techniques and statistical comparisons were reviewed. Particle size specifications and method validation were also discussed. Knowledge and information were shared with a view to the preparation of this report.

Pharmaceutical scientists and instrument manufacturers representing academia, the industry, and government attended the workshop. Selection of appropriate particle sizing methods and the expression of data often seem complex and apparently subjective activities. The difficulties associated with approaching particle size analysis extend from solid dosage forms to dispersed systems. This workshop covered numerous areas of analysis, from fundamentals of particle structure and morphology to the characterization and measurement of particle size. Key issues are common to a range of dosage forms including solids, aerosols, suspensions, emulsions, liposomes, microspheres, and nanoparticles. The workshop was divided into presentations on a number of key issues followed by specific case studies. A review of the meeting was conducted at its close. The attendees on a majority vote following discussion approved a bullet point list of action items. Subsequently, the views of the attendees were sought by e-mail.

The first day consisted of a review of particle manufacture, processing, structure, descriptors of shape and size, and statistical comparison of data. The day concluded with a review of methods with specific examples described in case studies. The second day involved a review of the fundamentals of particle size analysis and its role in the characterization of a variety of dosage forms, followed by the introduction of process analytical technology (PAT). On the third and final day, case studies of particularly difficult particle-sizing examples were discussed, with particular emphasis on sub-micron sizing and the influence of shape on analysis. Throughout the meeting, submitted posters were on display as were exhibits of particle-sizing instruments.

BACKGROUND

Size analysis of pharmaceutical products and their components is highly dependent on variables related to the particles themselves, the method of sampling, the technique of analysis, and the means of expressing the data. The particles are

susceptible to the influence of manufacturing, processing, compatibility, storage, and intended use variables. The scale, context, and method of sampling require consideration to minimize bias in the particle size estimates. The technique of measuring characteristic dimensions of the particles inherently dictates the nature of the data collected. In many cases statistical or mathematical distributions are fitted to the data as a means of expression, which may predispose the data to a particular interpretation. The dosage form and route of administration may necessitate the use of particles with unique characteristics and the adoption of specialized methods of analysis. The purpose of this workshop was to acknowledge the importance of each of these factors and to provide a forum for debate and discussion for individuals from all sectors of the scientific community with interest in pharmaceutical particle size analysis. This report was a planned outcome of the meeting and is intended to be a useful guide to industry and regulators in pursuit of optimal approaches to particle sizing for specific applications.

TOPICS

Particle Manufacture and Blending

The origin and history of particles plays a key role in the interpretation of their analysis. The manufacture and engineering of particles must be considered for a thorough understanding of a drug product and its performance. Successful manufacturing techniques eliminate postcrystallization operations such as drying and milling. A range of crystallization methods was outlined including (1) solvent, (2) jet, (3) emulsion, (4) supercritical fluid, and (5) spray drying. Unique dosage forms, such as inhaled aerosols, were identified as highly dependent on particle size and morphology. Blending is also highly influenced by the nature of the particles and in this context real-time analysis may be an important tool.

Crystallization of Polymorphs and Methods of Analysis

Many drugs exhibit polymorphism, which is defined as the ability to exist in 2 or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. The polymorph with the lowest thermodynamic activity is usually preferred, if bioavailable, owing to greater stability in solid pharmaceutical formulations. The relative tendencies of the competing aggregates to grow to the size of a critical nucleus and subsequently to form a crystal are determined by competing thermodynamic and kinetic factors. X-ray diffraction (XRD) is the most direct method for the quantitative and qualitative analysis of polymorphs. Spectroscopic methods that recognize the differences between intermolecular interactions among the polymorphs are also used. Solid-state nuclear magnetic resonance (NMR) spectroscopy, Fourier transform infrared (FTIR) spec-

troscopy, and FT Raman spectroscopy are among these methods. Thermal methods, such as differential scanning calorimetry (DSC) and hot-stage microscopy, are used to study phase changes during heating and cooling, while thermogravimetric analysis is used to analyze dehydration or desolvation. Solubility measurements and solution calorimetry reveal thermodynamic differences. If the various polymorphic forms can be distinguished by differences in crystal habit, optical techniques including but not necessarily limited to laser diffraction of light and image analysis (computer-assisted microscopy) may be used for quantitative analysis of polymorphs.

Assuming the history and chemical composition and structure of the particles are known, other morphological features such as shape and size can be studied. The following sections outline approaches to evaluating particle shape and size.

Particle Shape Factors and Nomenclature Issues

The measurement and expression of particle size is intimately bound with the shape and morphology of the constituent units that make up the ensemble of particles. The difficulties encountered when relating empirical information derived using different methods would not exist if the component particles were spherical. In the real world of pharmaceuticals, particles are rarely (if ever) spherical, and consequently it is important to understand the importance of particle shape and morphology. An exposition on the nomenclature for particle shape and illustrations of the effect of differing types on various particle size measurements were given. Important qualitative descriptors of particle shape were outlined and empirical methods for their determination were discussed.

Statistical Analysis, Equivalence, and Inequivalence: An Overview of Data Reporting

Some particle size distribution data are mass distributions. A mass-weighted, rather than number or surface area-weighted, form is most often the most relevant descriptor of the content of active pharmaceutical ingredient as a function of particle size. The implications of defining particle size distribution in terms of mass weighting were discussed. Statistical methods of assessing differences or equivalence of mass-weighted particle size distributions were reviewed. These methods fall into the categories of stage-by-stage, multivariate, and profiles for cascade impactor data obtained when characterizing aerosol-based formulations.

Particle Size Analysis: A Comparison of Methods

The apparent simplicity of particle size analysis is deceptive. Particle sizing is a poorly posed problem. Only objects of simple geometry, namely spheres, can be unambiguously

described by a single numerical descriptor. The size of irregularly shaped particles is typically expressed in terms of equivalent spherical diameters. Particle-sizing instruments use various algorithms based on surface area, volume, or linear dimension to calculate equivalent spherical diameters. The various diameters are only identical for spherical particles. For particles that do not have shapes that significantly differ from that of a sphere (not long-needles or disks), it is nonetheless possible to achieve agreement among several methods. However, there is increasing literature on the effect of shape on size estimates.

The performance of various particle-sizing instruments was reviewed. In particular, the performance of the low angle laser light scattering or laser diffraction was examined and compared with techniques operating under other principles. Light scattering instruments may produce artifacts that are dependent on the instrument (model) and the software employed. Various number counting methods, despite using different methods of particle size, in contrast, agree substantially. The causes of artifacts, produced by the Mie-Fraunhofer instruments were explored. Assumptions of sphericity and random orientation may be sources of error for regular polygons (eg, cubes), plates, or fibers, for example. Performance verification was recommended as a step to ensure the accuracy of the measurements in the absence of artifacts. The usual verification methods often do not fully address significant issues associated with instrument performance.

Case Studies

Inhalation of Aerosols

Drug delivery via the lungs offers numerous advantages for the treatment of respiratory diseases, as the drugs are delivered directly to the site of action. The deposition pattern of drug aerosols in the lungs is controlled by 3 major factors: airway geometry, particle size distribution, and the inhalation flow rate at which the drug is inhaled. The formulation and device characteristics are the major determinants of particle size distribution of drug aerosols. Three techniques are widely employed to determine particle size distribution of inhalation products; namely, inertial diffraction, laser diffraction analysis, and time-of-flight particle sizing (TOF). Impactors have been used extensively and are the instruments of choice for the determination of aerosol mass size distribution. The impactor consists of multiple stages that are held together to prevent air leakage. Each impactor stage contains multiple precision-drilled orifices. When air is drawn through, the impactor particles are projected toward the surface of a collection plate. The range of particle sizes collected on each stage depends on the jet velocity and the cut-off diameter of the previous stage. At each subsequent stage, the orifice sizes are smaller, thereby increasing the linear velocity of parti-

cles, their inertia, and the opportunity to collect them as a function of their size. Submicron particles that pass the last stage are collected on an absolute filter. There is a link between the cut sizes of individual impactor stages and the likely deposition sites in the respiratory tract of the particles that are size-separated. However, it is important to appreciate that the constant flow rate through a cascade impactor does not simulate the continuously varying flow rate associated with the respiratory cycle. Therefore, the inertial classification method should be used for in vitro characterization of inhalation aerosols. Laser diffraction was originally employed to evaluate populations of liquid droplet sizes but is now often used for dry powder aerosol characterization. In classical laser diffraction, an expanded laser beam is used to produce a parallel beam of coherent, monochromatic light. A Fourier transform (range) lens is used to focus the diffraction pattern generated by the collection of particles entering the measurement zone onto a multi-element photodetector array located in the plane orthogonal to the incident light, at a focal distance from the range lens. The angle of scatter is a function of particle size and summing from each of the detectors allows the distribution to be reconstructed. The measurement is quick but does not employ a chemical detection method and only samples the aerosol plume. Time-of-flight instruments operate on the principle of accelerating particles in ultra-Stokesian flow. The time-of-flight of individual particles is longer than for a particle of infinitesimal mass that would move with the accelerating fluid and is related to aerodynamic particle size. The instrument provides a direct measurement of the aerodynamic size distribution. Again this method does not discriminate between particles of different composition. Co-incidence errors may occur as a result of incomplete separation of particles.

Parenterals

Stable drug nanosuspensions for intravenous (IV) injection are typically prepared using a proprietary microprecipitation and/or homogenization process. These preparations were shown to possess significantly reduced acute toxicity as compared with the commercially available IV drug solution product. In the example discussed, each nanosuspension was prepared using a proprietary technique combining comminution of solid drug raw material with particle coating. The particle coating was carried out using surface-active coating agents that consisted of a combination of conventional ionic and nonionic surfactants at low concentrations. Solvent/surfactant residue in the finished product met International Conference on Harmonization (ICH) guidelines. No wear metal contamination was detected. Representative nanosuspensions used in preclinical animal studies were tested for pyrogenicity using the standard *United States Pharmacopeia (USP)* rabbit test and were nonpyrogenic. Both thermal sterilization and aseptic processing were successfully demon-

strated. Particle size distribution is an important physical stability parameter.

Instrumental particle-sizing equipment manufacturers often recommend but do not provide specific methodology in correlating imaging and instrumental analytical results. Most often consistent results between the 2 methods can only be achieved with spherical and narrow-size distributed particles. For plate-like drug solid in nanosuspension, population instrumental analysis techniques remain the only practical option for the determination of suspension particle size distribution. However, instrumental particle sizing results can be influenced by a number of factors (eg, refractive index). A matrix approach has been initiated to correlate results from different instruments using various particle-sizing principles. In addition, an approach to use 2-dimensional scanning electron microscope (SEM) photographs of large particles for the calculation of 3-dimensional, equivalent volume sphere diameters has been performed. The combination approach has the potential to appropriately report particle size distribution using an instrumental particle-sizing method.

Perspective on Optimizing Particle Size to Improve Performance of Oral Immediate Release Tablets

A decision tree for optimization of the particle size of drug substance for an oral dosage form was outlined (see Figure 1). A discussion was then presented on the effects of particle size on absorption properties. Small particles with large surface area gave higher peak plasma concentration and bioavailability and reduced time to peak plasma concentration. There was further discussion on the effect of hydrodynamics, wetting, and the presence of surfactant on dissolution. It was concluded that particle size may significantly affect oral absorption of a compound. Dose required, solubility, and permeability are important parameters for predictions. Several factors such as fed or fasted state, gastrointestinal hydrodynamics, wetting, etc, may affect oral absorption from different particle sizes; however, more research is required and better models are needed for further study. Other particle attributes, such as density and morphology may have significant effects on material properties and tablet attributes.

Particle Size and Blending

Drug particle size has a critical effect on the content uniformity of solid dosage forms, where poor content uniformity would result if a drug powder were not dispersed evenly throughout a mixture with excipients. A leading cause of poor content uniformity is a mismatch of drug and excipient particle size and density leading to segregation during sampling and manufacture, especially for low drug to excipient ratio blends. However, the focus of this presentation was to

Figure 1. A decision tree for recommending particle size (PS) of drug substance.

discuss perhaps a less obvious cause of poor content uniformity: a particle size distribution of a drug too large to achieve content uniformity even when all of the aforementioned causes have been addressed. The concept of ideal mixing was presented to demonstrate that poor content uniformity resulted, even with ideal mixing, if the drug particle size distribution was too large. Using the ideal mixing analysis, an edge of failure between a particle size distribution that will certainly cause poor content uniformity and one that is conducive to good content uniformity can be established. Approaching the upper edge of failure in terms of drug particle size may be desirable, since reducing the particle size too dramatically can exacerbate the problems of drug agglomeration and mixing. The goal of the presentation was to provide a scientific rationale for setting a drug particle size specification that is conducive to content uniformity before expensive and time-consuming formulation development begins. Simulations of content uniformity assuming ideal mixing were compared with experimental content uniformity data as validation of analysis.

Process Analytical Technology, Specification, and Comparisons: FDA Perspectives

Initiatives from the FDA Office of Pharmaceutical Sciences were described that focus on optimizing pharmaceutical process quality. Current FDA initiatives on science and tech-

nology focus on process analytical technology (PAT). This involves process analytical chemistry, in- and on-line tools, and multivariate and pattern recognition methods. The application of these technologies provides the opportunity to move from testing to assess product quality to continuous quality assurance. Following in the footsteps of W. Edwards Deming quality systems will reduce process variability and thereby ensure product quality and performance characteristics. The development process and science behind a product are not generally shared with the FDA, therefore manufacturing processes and controls have the appearance of art and not science. Research and development is conducted in a high technology environment and manufacturing is often low tech. The barrier between the FDA and industry leads to both a poor interchange of data and a poor understanding of quality and process design. Material property characterization and process simulation encompass clear disciplines from physical chemistry to engineering physics. The PAT initiative of the FDA will advance pharmaceutical science and manufacturing efficiency. The Science Board of the FDA is very supportive of PAT. A training curriculum for FDA staff and regulatory framework are proposed. The FDA intends to improve the knowledge base for technical policy development. The overall goal of these pursuits is to develop a drug quality system for the 21st century. This requires up-to-date concepts of risk management. Submission, review and inspection should be coordinated. To define the desired state requires a shared vision from all stakeholders highlighting the science of process engineering and common good manufacturing practices (cGMPs) for the 21st century. Regulatory policies should be tailored to recognize the level of scientific knowledge of manufacturing processes. The impact on product manufacturing and performance will result in quality by design.

Impact of Particle Size on Product Performance: Chemistry, Manufacturing, and Controls (CMC Issues)

Particle size derives from physical properties, manufacturing, processability, and quality attributes. These factors determine in vitro and in vivo performance.

A number of examples were given including controlling extended release in tablets through sieving, which failed due to particle size effects. Dissolution would have predicted this phenomenon. The importance of particle size in the therapeutic effect of inhalation products renders clinical bioavailability and bioequivalence potentially irrelevant. Liposomes require control of vesicle size to ensure predictable therapeutic targeting, dose delivery, pharmacokinetics, and pharmacodynamics.

The regulatory considerations of importance are the factors controlling particle size. Management of stages at which testing is required and establishing targets and specifications on particle size should be a priority. The methods employed include

validated sampling techniques with instruments/detectors selected for the application with a relevant detection/measurement range and establishment of acceptance criteria. On-line determinations are desirable (eg, near infrared or Raman spectroscopy).

It is prudent to understand the principles effecting performance, which can be viewed in terms of quality, safety, and efficacy as depicted in a triangle or Venn diagram.

Measurement and Interpretation of Particle Size Distribution

Particle size determination involves both measurement and modeling in the context of process engineering. A matrix approach is required, which encompasses process, product, design, and control.

Sampling continues to be a source of error and concern in pharmaceutical processes. However, in the broader field of powder handling and production this may be a thing of the past. Most techniques are considered for their value off-line, on-line, in-line, or in situ with a view to continuous process control. The specifications (acceptance criteria) should dictate process control or the manner in which the particle size distribution curve is interpreted.

Particle sizes are usually viewed in terms of geometrical (eg, spherical surface, volume, etc) or behavioral (eg, sedimentation) equivalence. There is a need for written and physical standards for calibration of all particle-sizing methods. This includes size (monodisperse, polydisperse) and refractive index (eg, Japanese, International Fine Particle Research Institute [IFPRI]) standards. These standards should be reproducible, sensitive (for product control), and accurate, if absolute particle size is important. Shape is a factor that also influences calibration of almost all particle-sizing instruments and should also be the subject of investigation.

Light-scattering methods may be divided into single particle versus population analysis methods. The point was made that 5 instruments may give the same distribution but will appear different based on the algorithm used for normalization. In effect, current instruments can “iron out” differences. Since image analysis and light scattering are complementary methods, it was suggested that they could be combined into a single instrument.

Analysts were exhorted to define the question they wish to have answered. It was suggested that manufacturers are in a position to produce instruments that are capable of addressing the question once it is posed.

Parenterals: Methods of Analysis and Data Interpretation

The history and standards for foreign particulate matter in injectable products were reviewed. In 1963, Garvan and

Gunner published an article on extraneous particulate matter in injectable products that got the attention of regulators and industry. Industry practices have steadily improved since the late 1960s. In concert, compendial and regulatory standards have also been tightened and harmonized. Methodology has also improved over the years. Foreign particulate matter in parenterals comes from both intrinsic and extrinsic sources. Detection of particles is normally achieved by visual, microscopic, electrical resistance, or light obscuration techniques. Compendial methods and standards have existed since 1973 (British Pharmacopeia [BP]) and 1975 (USP). Standards were harmonized among the United States, Japanese, and European Pharmacopeias in 1998 for both small and large volume parenterals. Working with Pharmaceutical Research and Manufacturers of America (PhRMA), USP is also developing foreign particulate standards for ophthalmic solutions.

Particle Size Analysis and Its Role in Pharmaceutical Development

Aerosols

Delivery of medications as aerosols to the lungs is an excellent route of administering topical treatment as well as targeting other organs via the blood circulation. However, the respiratory tract is size-selective, in that larger particles are progressively removed from the inhaled air stream as they pass via the mouth, larynx, and bronchial airways toward the alveolar spaces in the lungs. The need to use techniques in the laboratory that measure the particle size of inhaled aerosols is therefore self-evident. Two distinct pathways for the use of the data are apparent when evaluating methods for particle size analysis. On the one hand, the manufacturer of the formulation needs to have reliable, accurate, and reproducible methods that meet the needs for product development and quality control. It is also important to understand how the aerosol is likely to behave in the respiratory tract. This pathway has resulted in developments in laboratory-based measurements that attempt to provide greater predictability for deposition behavior. Reference methods defined in the Pharmacopeias are based on inertial impaction; although often time-consuming, these methods have the advantage of having been validated successfully in many laboratories. They are also based on direct chemical assay for the mass of active ingredient (API). Aerodynamic particle size distribution data are determined, taking into account both particle shape and density, and therefore predictive of transport through the respiratory tract. Recent developments have included the integration of impactors and breathing simulators as well as the development of entry geometries that more closely simulate the upper respiratory tract. Newer techniques that incorporate optical-based particle sizing have the potential to enhance productivity greatly, since measurements are often made in real-time and may not require the

aerosol to be sampled. However, since direct assay for API is not performed, these measurements should ideally be supported by data from more traditional methods.

Parenterals and Extrinsic Contamination: Quantifying Instability and Incompatibility

The extemporaneous preparation of intravenous dosage forms is a difficult task and should ideally be performed by qualified pharmacy personnel under laminar airflow conditions, and in a dedicated compounding environment to ensure the sterility and integrity of the final parenteral admixture. Although sterility may be achieved under these conditions, the introduction or generation of rigid particulates (crystals, fibers, glass, elastomeric enclosures, coprecipitates, etc), or the production of abnormal dispersions, containing enlarged fat globules from the coalescence of lipid emulsions, must also be avoided whenever possible. A prime example of the most complex intravenous dosage form extemporaneously prepared on a daily basis that poses such risks is a parenteral nutrition (PN) admixture. As many as 50 or more chemical entities comprise the typical PN formulation, which are often made with the aid of an automated compounding device that may be a significant source of particulate contamination. In addition, PN admixtures contain potentially incompatible combinations of electrolytes routinely prescribed such as calcium and phosphate salts. Lipid emulsions may also be added that may become unstable during the period of infusion. The use of inline filters will reduce the exposure of both rigid and flexible particles entering the bloodstream and are recommended for all PN admixtures. Other filtration devices, such as filter needles, will also reduce exposure to glass fragments when ampoules are used. Evidence supporting these claims has been quantified by measuring the presence of particulates or unstable fat globules using light obscuration that has been almost exclusively applied to pharmaceutical manufacturers in accordance with the *USP* chapter 788 entitled "Particulate Matter in Injections."

Case Studies

Aerosols

A historical perspective on aerosol testing and the perceived limitations were reviewed. A summary was given of the FDA Draft Guidance for use of impactors, particle size distribution (PSD), drug recovery, minimum number of actuations, characterization of PSD, and expectation of width of stage groupings were discussed. It was concluded that specifications for particle size distributions are set around groupings of size fractions. Groupings are product specific and strength specific. Stage deposition remains the most desirable method of defining sampling data. Variability in critical dimensions (principally stage nozzle diameter) in cascade impactors is a

significant source of variation in PSD measurement. Initiatives to understand the effect of stage nozzle diameter variation on impactor-measured size distribution data are being considered by expert groups, such as the European Pharmaceutical Aerosol Group (EPAG).

Nasal

While particle size must be controlled to a narrow size range for optimal targeted deposition in the lower respiratory tract, the particle size requirements for nasal deposition are far less stringent. One of the primary physiologic functions of the nose is to clean inspired air. As a result, most particles larger than 0.5 μm have a probability of depositing within the nasal cavity following inhalation through the nostrils. In general, particles larger than 10 μm are collected with greatest efficiency in the nose. The anatomical arrangement of the nasal cavity is designed to trap particulate matter to limit its entry into the lungs. The airways in the nasal cavity are narrow spaces that pass between several scrolls of mucosal tissue extending into the cavity from the lateral walls or between the surface of these extensions (turbinates) and the nasal septum. The narrow air spaces, along with the turbulent air flow patterns result in the inertial impaction of most particles that enter the nose. In addition to the narrow airspaces within the nasal cavity, the physical narrowing of the airway posterior to the nostrils, a region referred to as the nasal valve, results in most of the particulate impaction occurring within the lower one third of the nose. Because of these anatomical barriers, a major challenge in drug delivery to the nasal cavity is designing spray, aerosol, or powder systems whose particles remain in the air stream, pass through the nasal valve, and subsequently deposit within the main nasal cavity. Important parameters to consider include particle size, density, particle and inspiratory air stream velocity, nasal cavity resistance, and the shape of the spray emitted from the delivery device. Studies using an in vitro model of the nasal cavity have shown that spray angles in the range of 20° to 30° result in the maximum deposition of a spray beyond the nasal valve.

Solids

Powder flow depends directly on cohesive strength of the mixture, which is a nonlinear function of particle size and blend density. Blend bulk density is directly affected by cohesion. Hardness is a function of the number of interparticle contacts. Compressibility is a direct function of bulk density. Disintegration by capillary wetting is affected by pore size, which is directly related to particle size. Dissolution is enormously dependent on surface area. Content uniformity is affected by particle size in many ways. In the context of process analytical technology it is necessary to first understand materials, products, and processes, and then design the monitoring method. The present approach (ie, place the sen-

sor in the process, collect data, and then maintain “consistency”) raises a number of questions, such as the following:

- What should be measured?
- How should it be measured (with what error)?
- How will the data be interpreted (what do they mean)?
- What is their statistical significance?
- How can the data be applied?

Finally, how is the calibration affected by the analytical method? Most spectroscopic techniques require calibration, which is typically performed on fresh material. However, conventional pharmaceutical processes deeply affect the materials being examined.

Parenterals

In research, development, and manufacture it is important to determine not only the mean or average particle size but also the entire size distribution in order to fully understand the system. A case was presented on emulsion systems that have undergone accelerated stability testing to show how particle size distribution can be used as a predictor of accelerated stability, as well as an indicator of the destabilization mechanism. Oil-in-water emulsions were subjected to elevated temperatures. There was no significant change in the mean particle size of these emulsions; however, the particle size distribution changed with time, indicating that Ostwald Ripening was occurring. The data were analyzed according to the Lifschitz, Slezov, and Wagner (LSW) theory, which confirmed that Ostwald Ripening or coalescence was the dominant emulsion destabilization mechanism.

Challenges in Particle Sizing of Submicron Dispersions

Nanocrystal technology is a formulation and manufacturing approach used to enhance the performance of poorly water soluble drugs. One element of the technology involves milling dispersions into submicron-sized colloidal suspensions, typically in the range of 100 to 400 nm. The ability to accurately determine the particle size distribution of these suspensions is essential in order to understand their physicochemical behavior as well as to control and transfer the manufacturing process. Light scattering was the method of choice for reasons of expediency and ease of measurements. While modern instrumentation has greatly simplified the task of measuring particle size distributions, it is still important to critically evaluate both accuracy and precision of the results. The same sample analyzed on different instruments more often than not produces different results. Several examples of variability between different brands and models as well as between individual units of the same brand were presented.

In addition, a comparison between static and dynamic light scattering as it pertained to their individual formulations was presented.

Size Characterization of Submicron Suspensions

Nanosuspensions, such as those prepared by precipitation or processing, present technical challenges to those seeking to characterize the resulting size distributions and/or the particles themselves. While the small dimensions involved form one aspect of the problem, another arises from the fact that frequently there is as much interest in the low number population present at diameters greater than 1 μm as there is in the rest of the distribution. The interest in this form of polydispersity can be due to concerns of safety or in vivo performance, or from the mechanistic information that their presence tells the investigator about the process by which the nanosuspension was formed. Technical concerns result from the fact that many of the available methods do not always successfully span size distributions straddling the interval near 1 μm either because this value represents a limit to the range of the method, such as Fraunhofer diffraction or dynamic light scattering, or because of limitations in dynamic range, as is the case with counting techniques. This is in addition to the difficulty of observing a small number of larger particles in the presence of a much greater quantity of smaller particles. Multiple techniques, based upon different physical phenomena, are thus required if the desired understanding is to be obtained. Almost invariably, the situation is vastly simplified when project-specific needs and goals are detailed and understood before the analytical solution is designed. Illustrative examples in which methods based on counting (eg, single-particle counting, microscopy), spectroscopy (eg, light scattering, turbidity), and visual assessment were used to answer specific questions regarding processed and precipitated nanoparticles. In one example, these approaches were used to elucidate the relationship between processing and oral absorption, and in another, they were used to determine the suitability of a nanosuspension to intravenous or ophthalmic administration. A third example demonstrated the feedback that size characterization provides to the production of polymeric nanoparticles. Novel enhancements to measurement science such as the use of fiber-optic probes in light scattering were also discussed.

Determining Particle Size Specification for a Poorly Water Soluble, Needle-Shaped, Crystalline Active in an Oral Product

Setting a particle size specification for the active ingredient is necessary for oral drugs with poor aqueous solubility. Most particle size analysis techniques are accurate in determining the “representative diameter” of a population of relatively spherical particles. For nonspherical particles, accurate deter-

mination of a single “representative diameter” is a luxury. Rather, an analysis technique that gives reproducible “representative diameter” should be selected. The drug described was poorly water-soluble with needle-shaped crystals. The drug product was an immediate-release oral capsule. The objective was to determine the drug particle size specification that resulted in a desirable dissolution profile range. Different particle size analysis techniques were evaluated and a laser light scattering (LLS) technique was selected to measure volume-averaged diameter, the most relevant “representative diameter” for this type of drug. Three diameters were used to characterize the particle population: $d(v,0.1)$ 10th percentile diameter; $d(v,0.5)$ 50th percentile diameter; and $d(v,0.9)$ 90th percentile diameter. Since the active is needle shaped with a broad size distribution, all 3 particle diameters were evaluated for their effect on in vitro dissolution rate. Active ingredients with $d(v,0.5)$ ranging from 2 to 75 μm were prepared and in vitro dissolution of the corresponding drug product tested. The dissolution test was a *USP* basket method using surfactant in the medium with 15, 30, 45, and 60 minute test points. Dissolution specification for the drug product is set on the percentage of drug dissolved at 60 minutes. A plot of particle size with percentage drug dissolved at 60 minutes indicates a very high linear correlation between dissolution and 2 of the diameters at the 15th and 19th percentile. Correlation between drug dissolution at 60 minutes and $d(v,0.1)$ was very poor. Based on the linear correlation and the desired range of percentage of drug dissolved at 60 minutes, the active ingredient particle size specification was set on the 2 diameters of most significance: $d(v,0.5)$ and $d(v,0.9)$.

SUMMARY OF DISCUSSION AND RECOMMENDATIONS

NIST Standards

Physical

1.1.1 Shape

Silicon micromachined cube/cuboid particles were developed by Professor Paul Kaye (University of Hertfordshire, UK) and 3 shapes were certified as standards by AEA Technology (Dorchester, UK) in the mid 1990s as part of the UK Valid Analytical Measurement (VAM) program. In 2000, they were available as certified reference materials (CRMs) as AEA-1001, AEA-1002, and AEA-1003 through the Office of Reference Materials, Laboratory of the Government Chemist, Teddington, UK. The AEA 1001-1003 standards can be purchased from LGC Promochem, Teddington, UK (www.lgcpromochem.com). Other particle shapes have been made by controlled crystal growth following techniques developed by Egon Matijevic and coworkers in the 1980s; however, to date no CRMs or standard reference materials (SRMs) have been developed. The lack of standard reference materials has been

discussed elsewhere.¹

1.1.2 Refractive Index

IFPRI standards have well-defined, real, and imaginary (absorption) components of refractive index and are manufactured in different size ranges. Whitehouse Scientific (Chester, UK) [<http://www.whitehousescientific.com/>] has manufactured so-called “mirror” standards of the nonabsorbing particles. These have the same size ranges and were size characterized by several laboratories using a range of traceable methods in a consensus-based exercise in preparation for certifying the IFPRI materials. These mirror standards are readily available but would need to be adopted by a national standards body to officially reach CRM/SRM status. (IFPRI, Dr. Brian Scarlett, University of Florida, Gainesville, FL has these standards.)

1.1.3 Nanoparticles – Need standards for these – ie, physical particles

NIST already has a monodisperse 100 nm SRM available (SRM 1693, 101 ± 2 nm). It would be desirable to obtain other nanoparticle standards, eg, 20 and 50 nm SRMs.

1.1.4 Multimodal – Use 2 or 3 standards to show instrument discriminates – include uniform polydisperse distribution

So-called “cocktail” mixtures containing 3 monodisperse subfractions in well-defined proportion were produced as CRMs by AEA Technology in the mid 1990s as part of the VAM program (see 1.1.1). The sizes, based on volume equivalent diameter were: AEA-1004 : 0.1, 0.2, 0.5 μm ; AEA-1005 : 0.2, 0.5, 1.0 μm ; AEA-1006 : 0.5, 1.0, 2.0 μm ; AEA-1007 : 1.0, 2.0, 5.0 μm . Again, their current status is uncertain, but the technology has been proven, should there be a desire to remake these materials.

1.1.5 Recommendation – Formal request to National Institute of Standards and Technology (NIST) and include other potential users

The meeting indicated that any request to NIST will need to indicate broad-based consensus for particular SRMs across industry sectors. In the opinion of some, given that IFPRI already has broad-based support, the development of SRMs based on their refractive index (RI) standards would seem to have the greatest chance of success. There is a perceived need to bring together a group of opinion leaders within industries in which particle sizing is important (fine chemicals, pigments, foodstuffs, etc) as well as the pharmaceutical sector, to promote the development of the most needed CRMs/SRMs.

1.2 Written Standards (American Society for Testing

and Materials [ASTM], International Organization for Standardization [ISO])

Include European Committee for Standardization (CEN) and National Standards (eg, Canadian Standards Association). A strong desire was expressed to have International Organization for Standardization (ISO) standards eventually supersede national written standards.

2 Shape

2.1 Instrumentation – Appropriate instrumentation (eg, SEM or microscopy) allows you to choose appropriate instrument. Get data and how do we turn that into a shape (algorithm). Since shape-related effects may bias many particle size analysis techniques, microscopy should always be used as a check for particle size. Combined with automated image analysis, microscopy can give an idea of the size distribution based on appropriately chosen projected dimensions that take into account particle shape.

2.2 Error – Some techniques (eg, if calculated, equivalent spheres will give inherent error in measurement) need complementary method(s) to deconvolute shape factors. Also, real time aerodynamic particle size analysis by methods based on the time-of-flight principle are known to have a significant shape-related bias that is not apparent in the reported data that is scaled to aerodynamic diameter.

3 Sampling and Sample Preparation

3.1 Can we make on-line methods available – Samples in motion (minimizes discrete sampling inadequacies), process control (PAT). How to do particle sizing and particle characterization on-line (near infrared [NIR], etc)?

3.2 Need recommendation on best thief and sampling practices – Sampling should ideally be from a moving stream. Recognizing that this is not always possible: what methods for the use of thieves should be adopted?

3.3 Process control endpoints – eg, blending until analytically determined endpoint

3.4 If not bolus sampling, use isokinetic methods – Recommend use of bolus sampling

4 Understanding/Definition/Calculation of the 3 “A”s –Aggregation/Agglomeration/Adhesion

4.1 Blend uniformity

4.2 Sample preparation

4.2.2 How to determine degree of agglomeration and techniques to disperse

5 Similarity – The Need to Understand Materials

5.1 How do characteristics affect performance?

5.2 History of product

5.3 Address how specs are set when vendor and manufacturer have different methods

6 Comparability “Complementarity” of Methods – How you choose to express the data: all relevant data should be presented

6.1 Product specificity – method selection/method suitability

6.2 Describe how calculations are performed

6.3 Know the limitations of your instrument

7 Expression of Data – What are the methods detecting?

7.1 Needs, complete information

7.1.2 All methods

7.1.3 Complete size distribution

7.1.4 Multivariate analysis may be preferable

7.2 Definitions for expressing data

There is a need for a standardized set of definitions to express particle size data and the parameters that are derived to describe central tendency, spread, and so on, of the distribution data. The present situation is highly confusing, given both the differences in weighting that are obtained from different techniques and the multiplicity of size distribution parameters that exist.

8 Validation

8.1 Alternative approaches needed if you cannot calibrate (eg, if using spheres to calibrate and they are not relevant to the particle shape).

8.2 Cascade impactor calibration is particularly important.

Recognizing that it is not current practice to calibrate impactors with monodisperse particles on a routine basis, the US compendia allows a procedure called “stage mensuration,” whereby the critical stage nozzle diameter(s) are measured at user-defined periods of time, to identify wear and/or corrosion. Cascade impactor performance verification is particularly important in relation to measurement of aerosol particle size distributions. Currently, there is no established relationship between stage nozzle diameter (mean diameter for multi-nozzle stages) and stage cut size. Stage mensuration,

recommended in the US compendia, thus provides data that cannot be readily related to changes in impactor performance. Calibration with monodisperse particles provides a direct indication of changes to stage cut sizes with use but is extremely time consuming and labor intensive to perform. There is, therefore, a need to develop a more suitable approach for routine performance verification, and methods that are based on measurement of pressure drop at a fixed flow rate may offer some potential in this respect and should be explored with urgency.

9 Suitability of Methods for Different Systems (dosage forms, particles versus emulsions)

9.1 Some methods may distort data for certain systems; for example, using liquids with microscopy.

10 Absolute Particle Size Versus Something Relevant for Quality Control (impaction-mass on stages)

10.1 Complete understanding of your instrument is important

10.2 Instrument comparison of data output is needed (signal output)

There may be some caveats with regard to the importance of these items. In the aerosol measurement field, combination of cascade impactor stages to provide an indication of total mass contained in the therapeutically relevant portion of the emitted mass from the inhaler is routinely undertaken by several organizations, particularly for quality control purposes. It is not clear that all of the meeting attendees would regard this issue as low priority. The development of robust approaches that reduce the number of samples required for assay is a significant advantage in this context, which may also be the case for other dosage forms where multi-stage particle size analysis is necessary.

11 Statistical Considerations for Data Interpretation

11.1 Sameness

The development of criteria for defining product similarity based on particle size analyses will necessitate agreeing methodology for both the measurement and interpretation of size distribution data.

11.2 Use statistical approaches for instrument data output comparisons – Permits removal of algorithms.

12 Prospective Versus Retrospective Analysis

12.1 Since we know the characteristics, we can predict

performance.

ACTION ITEMS

- Recommend FDA consider – Guidance, PAT
- USP consideration – Written standards
- Note – USP currently preparing monograph on laser diffraction
- NIST – Development of SRMs for verifying laser diffractometry-based techniques
- Workshop/Symposia/Roundtable topic(s)
 - Sampling
 - Sample preparation
 - Setting specifications
 - Image analysis
 - Milling
 - Impact of particle size on stability
 - Impact on bioavailability
 - Other ideas?
- Working group: Product Quality Research Institute (PQRI), IPAC, European Pharmaceutical Aerosol Group (EPAG), AAPS Focus Group should be formed, etc.

Attendees should consider other relevant groups that might consider issues raised at the workshop. PQRI has issued one report on aerosol testing and commentaries have also appeared.^{2,3}

- Research
 - Experimental
 - Theoretical
 - Literature-based
- Are there other industry models for these activities?
- Continued participation by attendees is expected.

CONCLUSION

The improvement of currently accepted methods for particle size analysis of pharmaceutical products will require ongoing participation by those involved with this activity. The meeting participants identified many groups whose primary activity is to review and to develop relevant methods and standards for particle size analysis for pharmaceutical products. Recognizing this ongoing effort, many of the action items involve bringing the opinions of the group to the relevant agencies. A second meeting was proposed that would occur at a defined period following the first meeting (2 years) to review the effect of the action items, and the passage of time, on industry and regulatory practice. At that time (spring 2005), we encourage the AAPS to consider setting up a Focus Group to act as a vehicle for those interest-

ed to follow up on the action items identified by this Workshop. Currently, particle-sizing issues are discussed with respect to the relevant dosage form in the various currently standing AAPS Focus Groups, but as was clear from this meeting many of the issues are common to several if not all dosage forms. Serious consideration should be given to this or a similar initiative, if the outcomes from the Workshop are not to be dissipated when other priorities take precedence in the activities of the attendees and their sponsoring organizations.

REFERENCES

1. Mitchell JP. Particle size analysis of aerosols from medicinal inhalers. *KONA-Powder and Particle*. 2000;18:41-59.
2. Christopher D, Curry P, Doub W, Furnkranz K, Lavery M, Lin K, et al, for the PQRI Particle Size Distribution Mass Balance Working Group. Considerations for the development and practice of cascade impaction testing including a mass balance failure investigation tree. *J Aerosol Med*. 2003;16(3):235-247.
3. Mitchell JP. Regarding the development and practice of cascade impaction testing, including a mass balance failure investigation tree. *J Aerosol Med*. 2003;16(4):433.