QbD QUANTITATIVE MEASUREMENTS OF CQAS IN SOLID DOSAGE FORM UNIT OPERATIONS

Particle Size • Material Segregation-Flow • Zeta Potential

micromeritics®

USP ‹429›	Light Diffraction Measurement of Particle Size
USP ‹811›	Powder Fineness
USP ‹1174›	Powder Flow
Ph. Eur. 2.9.31	Particle Size Analysis by Laser Light Diffraction
Ph. Eur. 2.9.36	Powder Flow
JP 10	Laser Diffraction Measurement of Particle Size

INTRODUCTION

The purpose of Quality by Design (QbD) is to design and develop formulations and manufacturing processes to ensure a predefined quality. The challenge of QbD is to accurately and quantitatively determine the functional relationship between material/physical Critical Quality Attributes (CQAs) with Unit Operation Critical Process Parameters (CPPs) and their impact on the finished dosage forms.

Particle size, material segregation-flow and water sorption can be key quantitative measures of the physical characteristics of APIs, excipients, additives, etc. used to manufacture the final dosage form. The information obtained can be correlated to control key variables within the manufacturing process, maintaining the manufacturing profile within the design space.

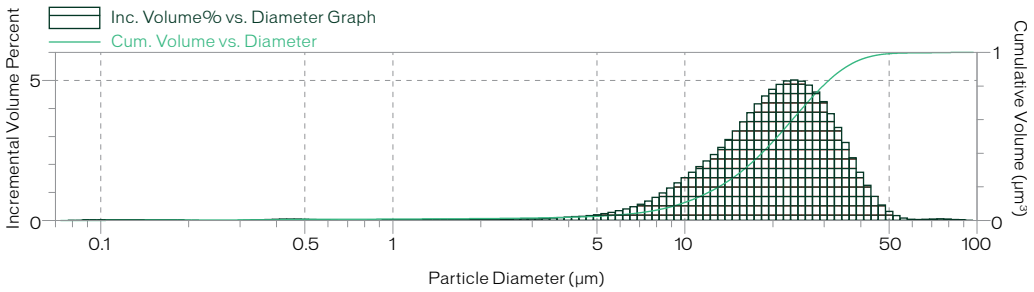
PARTICLE SIZE

Particle size distribution of APIs and excipients is an important physical characteristic of the components used to formulate final dosage forms. Milling, size reduction, or granulation is used to define the desired quality in key areas such as product uniformity, solubility, flow, hardness, and bioavailability. Particle size is also used to optimize downstream processing as it relates to blending, compression, and coating.

Mixing and blending processes are critical when a formulation combines materials where the size differences among these components have a direct influence on the homogeneity of the final blend. If the differences in particle size/shape are significant, the powder mixture may segregate which will negatively affect the desired homogeneity of the combined elements. This leads to blend and content uniformity issues and can result in sub-potent or super-potent tablets. Particle size also affects compression properties in tablet manufacturing. Particle fragmentation and tablet strength during compression can vary with differences in the particle sizes of the formulation's constituent ingredients. A processing step that causes a shift in the mean particle size may alter the predominant consolidation mechanism. Particle size has a direct effect on disintegration and dissolution performance as well as being a key control parameter for product appearance to the patient and physician.

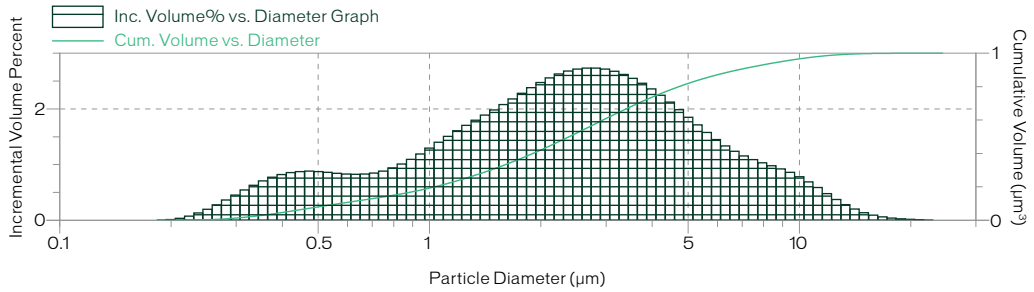
PIROXICAM RAW

Incremental Volume Percent vs. Particle Diameter Graph



PIROXICAM MICRONIZED

Incremental Volume Percent vs. Particle Diameter Graph



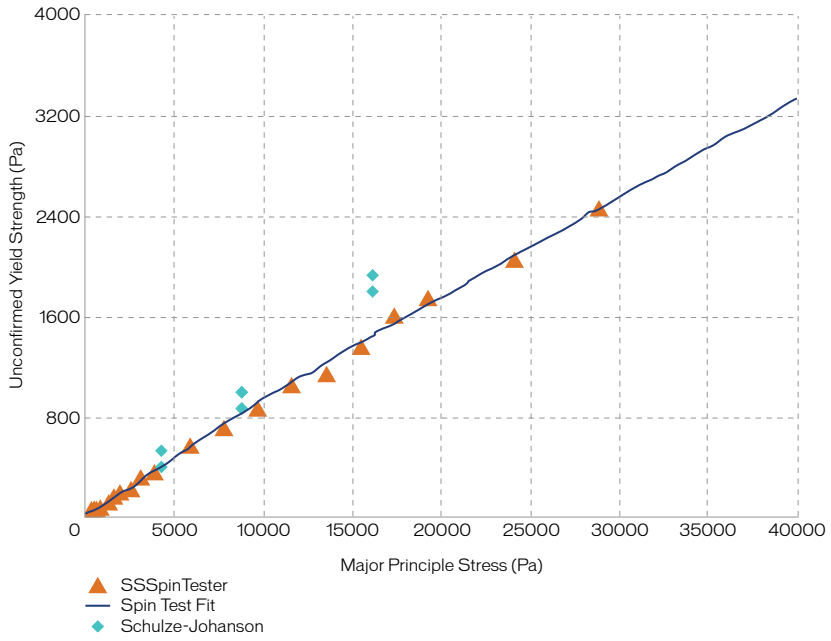
POWDER FLOW AND SHEAR

Flowability of individual components and powder blends is an influential and important property that affects several tablet manufacturing steps. During processing, flowability is instrumental in determining mixing efficiency, cohesion, and compaction. Uniformity of API concentration and tablet weight are greatly dependent on appropriate selection of production equipment and material handling processes. These parameters can be anticipated with knowledge of powder flowability and blending characteristics.

A formulation must have sufficient and consistent flow to ensure that the appropriate amount of powder flows into the dies of the tableting machine. Flow is determined by the physical properties of the powder, such as particle size, shape, particle-particle interaction, entrapment with air, fluidization, sifting, and environmental/storage factors. Segregation, ratholing, and arching could occur as a result of poor powder flow characteristics as well as the processing equipment design. Proper characterization of a flow function, a measure of the stresses that cause bulk material to flow by yielding to shear, will ensure that the manufacturing process is suitable and will achieve the desired product uniformity.

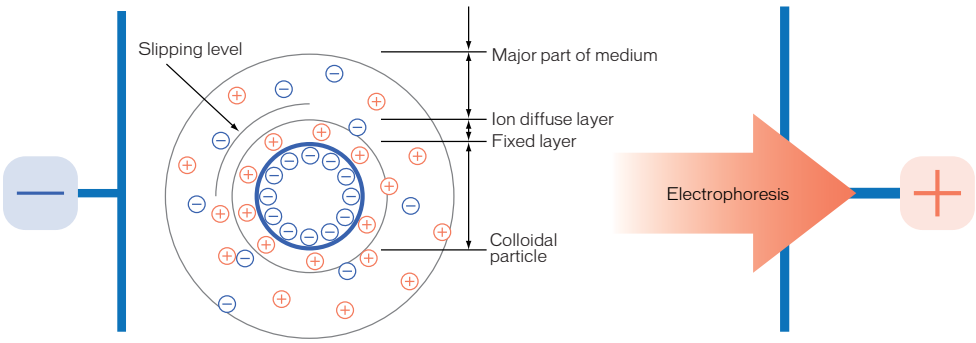
Early identification of flowability parameters through analytical testing and data generation may aid in establishing CQAs and may be used to set CPPs for the process of producing the final dosage form.

COMPARISON OF THE UNCONFINED YIELD STRENGTH OF FMC PH-102 MCC MEASURED WITH THE SCHULZE DIRECT SHEAR METHOD AND THE NEW TEST TECHNIQUE (SSSPINTESTER)



ζ ZETA POTENTIAL

In most cases, colloidal particles possess a positive or negative electrostatic charge. As electrical fields are applied to the particle dispersion, the particles migrate in oppositely charged directions. As particles are irradiated in migration, scattering light causes Doppler shift depending on electrophoretic mobility. NanoPlus HD software calculates the amount of Doppler shift followed by electrophoretic mobility and zeta potential by combining a heterodyne system and photon correlation method to perform Fourier transform of obtained correlation function.



$\Delta v = 2Vn \sin(\theta/2)/\lambda$

$U = V/E$

$\zeta = \eta U/\varepsilon$… Smoluchowski equation

Δv: Doppler shift
V: Velocity of particle movement
n: Refractive index
η: Viscosity
θ: Detect angle
λ: Wavelength of incidence light
U: Electrophoretic mobility
E: Electric field
ζ: Zeta potential
ε: Permitivity

LASER DIFFRACTION PARTICLE SIZE

Saturn DigiSizer II

High-Definition Digital Particle Size Analyzer
USP <429>, Ph. Eur. 2.2.31, JP 10

Small differences between particles in a sample distribution can affect bioavailability, flowability, rheology, drug delivery, and other critical parameters. The Saturn DigiSizer II is a state-of-the-art laser particle size analyzer that utilizes advanced optics, CCD technology, and over three million detector elements to deliver a high-resolution measurement of articulations in the scattering pattern. This allows a high degree of size discrimination or resolution. Higher resolution reveals information about the material that goes undetected with other laser particle size systems, providing more accurate results.

High resolution of data permits Mie Theory to be applied directly. There are no compensation algorithms or adjustments for monomodal or multimodal samples. Direct measurement increases the reliability of your results. The Saturn DigiSizer II is fully automated including a patented liquid sample handling system which features auto-dispersion and auto-dilution with liquid level control. Software control of sample preparation, concentration, fluid levels, and cell rinsing after the analysis also limits the possibility of operator error.

Saturn DigiSizer II Specs	x_{10} @ 0.10%CV
x_{50} @ 0.07%CV	x_{90} @ 0.40%CV

"Micromeritics provided an excellent instrument (Saturn Digisizer II) which has performed as expected and has been reliable. The company provides strong support and technicians come to perform both emergency and routine service when scheduled."

R. Gary Hollenbeck, Chief Scientific Officer, UPM Pharmaceuticals, Inc.

Research by TechValidate
Nov 2014

Broad particle size range of 40 nanometers to 2.5 millimeters

Liquid sample handling unit available in both standard and low-volume configurations for automatic sampling, diluting, and dispersion

Fast, detailed results that are repeatable and reproducible between every Saturn DigiSizer II

Optional MasterTech Autosampler provides unattended analysis of up to 18 samples

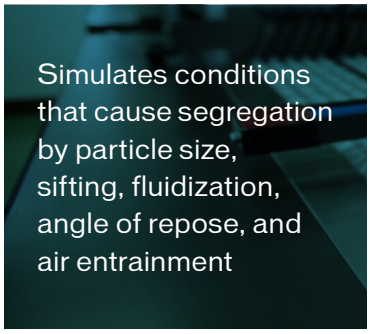
MATERIAL SEGREGATION AND POWDER SHEAR

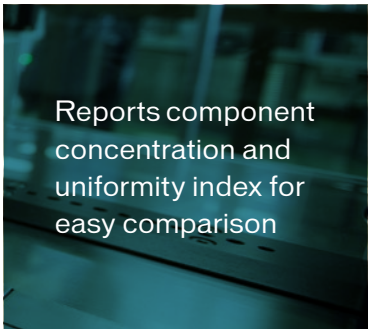
SPECTester

Segregation Tester
USP <1174>, Ph. Eur. 2.9.36, JP 18

Using an advanced spectroscopic method, the SPECTester quantifies segregation potential of powder mixtures containing up to 6 unique components. The instrument simulates a pile-formation process and then detects variation in component concentration across the radius of the simulated pile. Alternately, variations in particle size of a single component along the pile can also be measured. Reported data includes component concentration along the pile and uniformity indices which allow relative comparison of segregation potentials of each component.

Results are scalable to actual process conditions and tests are completed quickly, in as little as 10 to 30 minutes, depending on sample and application. The intuitive software graphs the presence and concentration value of the various ingredients of a mixture at specific locations within the pile to permit scale to process conditions.



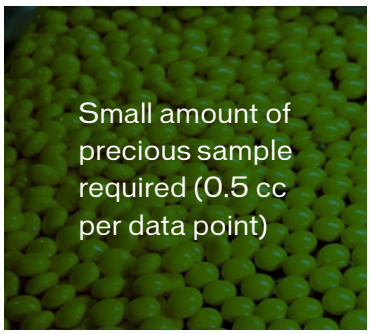


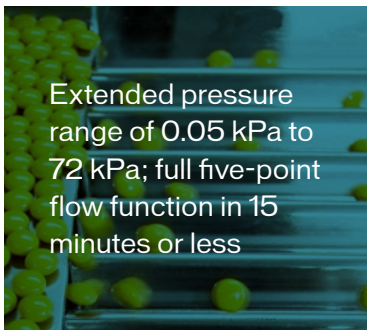
SSSpinTester

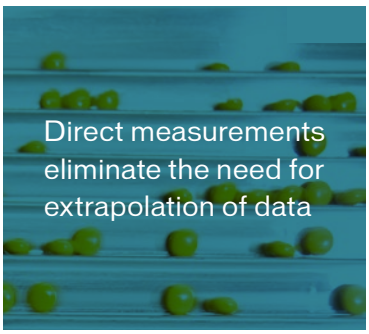
Bulk Strength Powder Analyzer
USP <1174>, Ph. Eur. 2.9.36

The SSSpinTester uses the science of centrifugal force to measure the unconfined yield strength of powders. A sample cell is mounted to a centrifuge rotor, which is rotated to create compression/consolidation force as well as the yielding stress. The rotational velocity of the rotor governs the forces on the sample. This technique allows several unique advantages to traditional testing methods including faster testing time, smaller sample size, and a wider range of consolidation pressures.

While commercially available powder strength testers are limited to a minimum 1 kPa consolidation pressure and rely on extrapolation for low pressure flowability assumptions, the SSSpinTester can determine flowability at pressures lower than 0.1 kPa. These low pressures exist in process equipment such as tablet presses, blenders, and fluidized beds. By directly measuring flowability at these pressures the SSSpinTester allows a more complete predictive model for material handling processes, while consuming much lower amounts of potentially costly sample material (experimental, preformulation compounds), utilizing a sample cell only 0.5 cc in volume. For each data point, less than half a gram of material is used, and results are available in less than 3 minutes. This means that a full five-point flow function can be obtained in only 15 minutes while expending less than 3 grams of sample.







ZETA POTENTIAL

NanoPlus HD

Zeta Potential and Nano Particle Size Analyzer
USP <729>, BP 851, JP 16

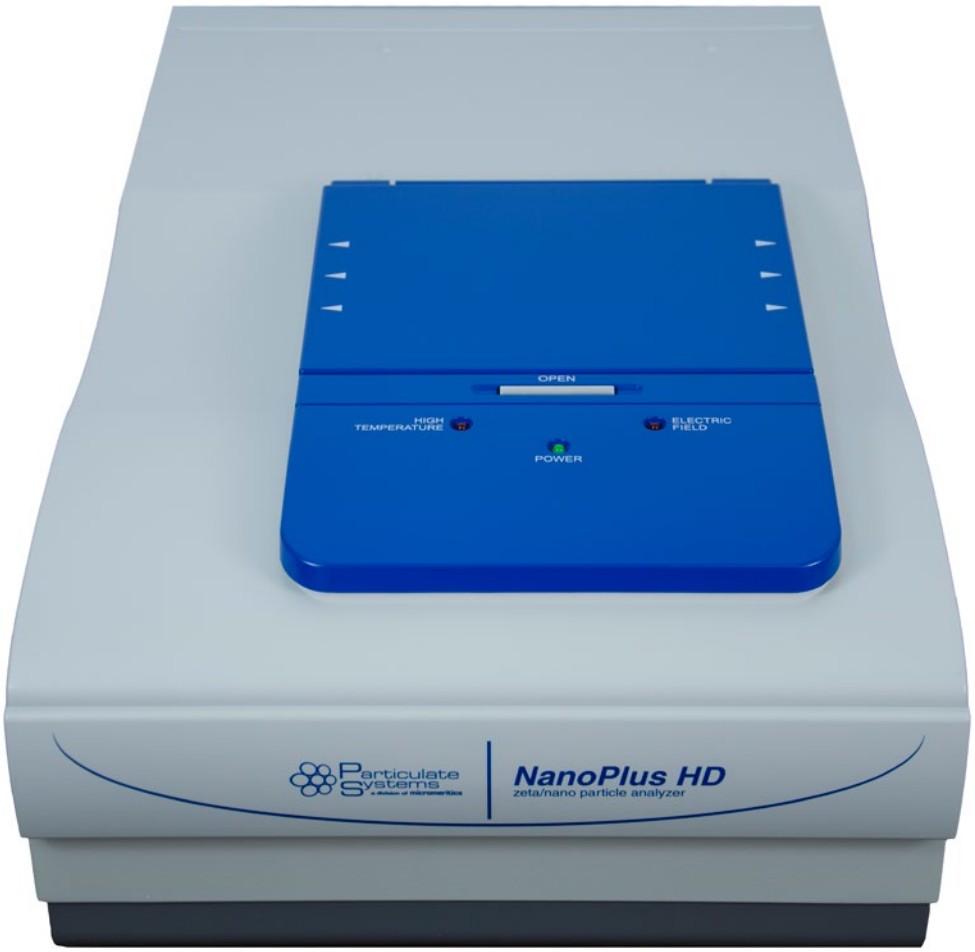
The NanoPlus HD offers high definition analysis with 70 mW of laser power and finds small volume aggregates in mixtures. Discover true zeta potential with multi-point measurement scans for isoelectric point, formulation constancy, and uniformity in colloidal systems.

The Avalanche Photodiode Detection (APD) permits high sensitivity detection of even small volume, diluted samples. It lets you successfully acquire data in valuable and challenging low volume analyses.

Generate customized 3D plots to track changes, compare lots, or see pH affects.

Exceptional multi-point electrophoretic mobility detection eliminates EOF affects. A broad range of temperature control secures sample integrity with protein and biological samples, and keeps sample bioactivity intact. Specially engineered analysis cells with parallel electrodes eliminate thermal damage to protein or biological materials.

- Colloidal solution stability in liposome and monoclonal antibody development
- Quantitative determination of oral and injectable suspension stability
- Pharmacokinetic drug delivery studies of nano-emulsions



"This instrument has solved a particle size problem that we could not solve with a different manufacturer's instrument... The NanoPlus software is easy to use and logical."

William Betz, Senior Scientist at Sigma-Aldrich

Measures zeta potential of a sample suspension in the range of -500 mV to +500 mV with concentrations from 0.001% to 40%

Measures particle size of samples suspended in liquids in the range of 0.1 nm to 12.30 µm with sample suspension concentrations from 0.00001% to 40%

Well-established photon correlation spectroscopy technique conforms to ISO 13321 and ISO 22412

The NanoPlus HD also features improved sensitivity and reduced analysis time

MICROMERITICS PHARMACEUTICAL SERVICES

Material Sciences Contract Research

Backed by Micromeritics, with over 50 years of experience, Micromeritics Pharmaceutical Services (MPS) can be trusted as your materials characterization solution for pharmaceutical materials, medical devices, nutraceuticals, and other FDA regulated products. Through the use of advanced analytical testing systems, MPS provides solutions for the optimization of your drug development and production processes.

Our areas of material characterization expertise include particle size distribution (micrometer and nano particles), particle shape and morphology, surface area, surface energy, vapor sorption, porosity, density, thermal analysis, zeta potential, and material flow properties. We have the ability to perform full method development or method validation along with the individual sample analytical testing that you require.

MPS is a DEA-licensed, FDA-registered, cGMP/GLP compliant contract lab service organization.

MICROMERITICS PHARMACEUTICAL SERVICES

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