



M I C R O M E R I T I C S

P H A R M A C E U T I C A L S

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www.micromeritics.com

Micromeritics Predictive Materials Science Solutions for the Identification and Control of Critical Quality Attributes

Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Achieving QbD requires an in-depth understanding of physicochemical properties that predict processability, *in vivo*, and *in vitro* performance. Early identification of Critical Quality Attributes (CQA) of excipients and active pharmaceutical ingredients (API) and their impact on a formulation is a key component of QbD. Micromeritics' instruments and contract analytical services offer solutions for the early identification of CQA's, continuous process monitoring, and verification, which are the foundation of QbD.

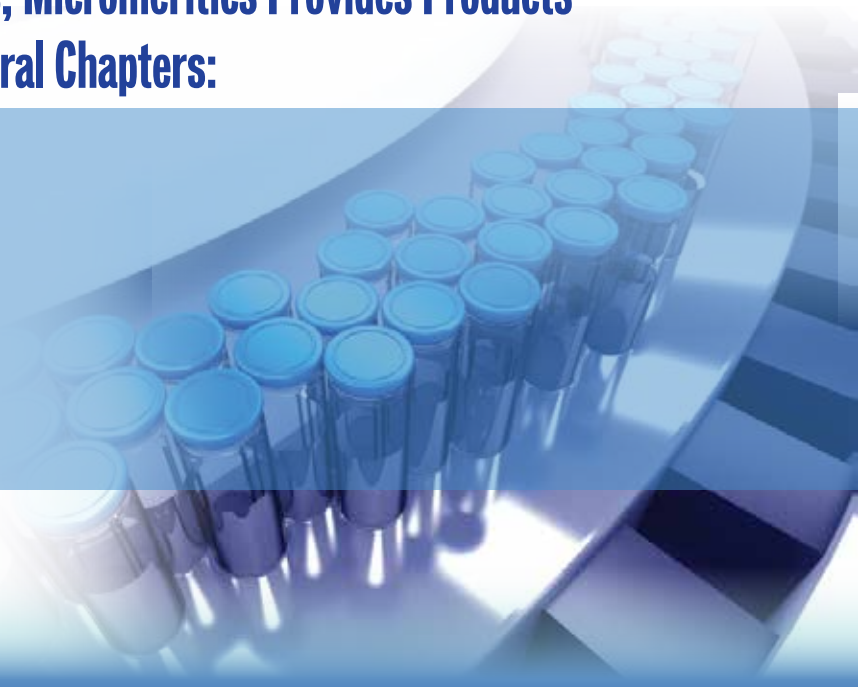
To date, chemical analysis has received the greatest level of emphasis and deployment within a QbD architecture. The need for robust product and process design to ensure lot-to-lot consistency has led to an increased focus on the importance of material characterization. Historically, particle size has been the dominant physical characteristic control parameter for release. But now, properties such as surface morphology, porosity, particle shape, density, and surface energy are additionally utilized as predictive tools to reduce possible manufacturing failures by predicting scale-up effects on the final product. This effort improves the overall efficiency of a manufacturing process and cuts the cost of waste due to batch rejection, reprocessing, or testing failures.

Micromeritics Material Science Solutions

- Streamlining Pharmaceutical Development
- Identification/Evaluation of API, Excipient, and Blended Material Critical Quality Attributes
- Providing Predictive Tools and Lab Services for Implementing QbD and PAT initiatives in line with ICH Q6A, Q8, Q9, and Q10 Guidelines
- Using Materials Science to Model and Predict Material Behavior
- Characterization Solutions for Robust Quality Control
- Raw Material Qualification
- Assessing Lot-to-Lot Variability
- Assistance in Quality Investigations and CAPAs (Corrective and Preventative Actions)

In addition to Material Science Solutions, Micromeritics Provides Products and Services for the Following USP General Chapters:

- USP <267> Porosimetry by Mercury Intrusion
- USP <429> Laser Diffraction Measurement of Particle Size
- USP <699> Density of Solids-Gas Pycnometry
- USP <788> Particulate Matter in Injections
- USP <789> Particulate Matter in Ophthalmic Solutions
- USP <846> Specific Surface Area
- USP <1174> Powder Flow
- USP <1241> Water Solid Interactions in Pharmaceutical Systems



Micromeritics Pharmaceutical Services- Material Sciences Contract Research

Understanding physicochemical properties of drug substances, excipients and finished products is crucial. In today's age of Process Analytical Technology (PAT) and Quality by Design (QbD), regulatory authorities look favorably upon drug developer partnerships with Contract Research Organizations (CROs) that have specific areas of expertise in material characterization.

Backed by Micromeritics with 50 years of experience, Micromeritics Pharmaceutical Services 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.

Early identification and understanding of Critical Quality Attributes (CQAs) are essential steps in the process. From a QbD perspective, scientists, researchers, and regulators look for consistency, both in physical and chemical attributes. MPS is here to help you define, specify, and control the critical quality attributes of your materials.

Our areas of expertise include particle size distribution analysis (micrometer and nano particles), particle shape and morphology, surface area, surface energy, vapor sorption, porosity, density, thermal analysis, and material flow properties.

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



Method Development / Validation

- Method Development Services for all analytical tests
- Method Validation Services for all analytical tests
- Method transfer documentation
- Secure Method and Validation storage for future projects

Analytical Services

- Particle Size, Particle Shape (Light Scattering, Dynamic Light Scattering, Electrical Sensing Zone, Dynamic Image Analysis, Microscopy)
- Surface Area (Gas Adsorption, BET)
- Density (True, Apparent, Bulk, TAP, Carr index)
- Porosity (Gas Adsorption, Mercury Porosimetry)
- Thermal Analysis (DSC/TGA)
- Volumetric Vapor Sorption
- Zeta Potential





Preformulations

Preformulation is a multidisciplinary development of a drug candidate. Material characterization techniques play a key role in a QbD approach during preformulation activities by determining the physical and mechanical properties of APIs, excipients, and blends. This helps to ensure stability, bioavailability, and lot-to-lot consistency of materials while beginning to define your design space and overall control strategy.

During this phase, research is directed to APIs and excipients, both as individual components and blends. Identification and evaluation through physical measurements include: particle size, particle shape, porosity, bulk powder flow, BET surface area, water vapor sorption, surface energy, and density. All can be utilized during this stage of development.

Micromeritics Material Science Solutions



Material Characteristic	Influences	Example
Particle Size pg 10, 11, 12	Solubility, Bioavailability, Powder Flow, Compaction, Compression, Dissolution, Downstream Manufacturing Efficiencies	Magnesium stearate as a lubricant in tablet production and its effective lubricity can be correlated to tablet ejection forces. Magnesium stearate batches with a smaller particle size distribution and larger surface area produces increased lubricity when compared with batches of larger particle size and smaller surface area.
Particle Shape pg 10	Bioavailability, Compaction, Powder Flow, Dissolution	The principle used by Laser Diffraction assumes all particles are spheres. In practice, when irregularly-shaped particles are present in greater degrees, the DLS particle size may be erroneous and this could prevent a proper assessment of bioavailability/dissolution downstream, as well as compaction and flow.
Surface Area pg 14	Dissolution, Solubility Compaction	Increasing surface area may improve solubility and dissolution, hence a control parameter for proper dosage/bioavailability. Surface area also plays a significant role in material flow and bonding properties.
Density pg 13	True Density, Roller Compaction-Lubrication Tableting Setting, Segregation, Compaction, Crystallinity	Knowing the density distributions in the ribbons is very important in improving the effectiveness of the roller compaction process and the granules produced for milling. Other applications include tablet void volume and predicting material segregation. Blends with varying particle densities may require special handling.
Porosity pg 13, 14	Roller Compaction, Tablet Strength (physical), Fragmentation, Compaction, Content Uniformity/Dissolution	Porosity measurement can evaluate the ability of liquids to penetrate the tablet for dissolution assessment. Can assist in parameter setting for material flow in coating operations. Predictive evaluation for pellet deformation during compression. Total pore volume and percent porosity for roller compacts.

Formulations and Drug Delivery

With physicochemical data derived from preformulation studies, the formulation scientist can leverage this information to assess initial compatibility of formulation components and begin activities surrounding process design. During this phase of the development, importance is placed on optimization of the formulation development of the final dosage form and process design. Also during this phase, consideration is given to factors affecting scale-up from bench top to pilot scale.

In QbD, this phase is focused on providing a defined design space to meet FDA and ICH guidelines. Within this area of focus, greater detail is developed for Critical Materials Attributes (CMA) and Critical Process Parameters (CPP).



Micromeritics Material Science Solutions



Material Characteristic	Influences	Example
Particle Size pg 10, 11, 12	Bioavailability, Powder Flow, Compaction, Compression, Dissolution, Blend Uniformity, Protein Aggregation	In a final crystallization step, particle size is a CQA (critical quality attribute) used to determine design space variables. Particle size distribution also has a direct impact on biologic material performance and processing. It can also be indicative of undesirable protein aggregation.
Particle Shape pg 10	Bioavailability, Compaction, Critical Element in Solid and Liquid Dispersion Processing	Product morphology in addition to size has direct influence on solubility. Inhaled products are based on less than 5 μm aerodynamic shape to be deposited in the lungs and not upper respiratory areas. Shape can be used as a PAT to define process send points and batch-to-batch variability.
Surface Area pg 14	Dissolution, Solubility Compaction, Milling, Stability, Lyophilized Products	It is apparent that the dissolution rate of a drug can be proportional to the surface area exposed to the dissolution medium. Surface area can provide critical information in lyophilization in regard to ice crystal formation.
Density pg 13	Roller Compaction-Lubrication Tableting Setting, Segregation, Compaction, Crystallinity	API and excipients are blended and typically then granulated or densified to ensure a uniform blend is delivered to the tablet press. The material is also granulated to aid in material movement as granulations move easier than powder blends. True density can be indicative of how close the material is to a crystalline state or the proportions of a binary mixture.
Porosity pg 13, 14	Roller Compaction, Tablet Shelf Life, Fragmentation, Compaction, Content Uniformity/Dissolution	Indicator for shelf life and air and moisture penetration. Porosity measurement can evaluate the ability of liquids to penetrate the tablet for dissolution assessment. Can assist in parameter setting for material flow in coating operations. Predictive evaluation for pellet deformation during compression. Tablet crushing strength influenced by pore size distribution.
Inverse Gas Chromatography pg 15	Powder Surface Energies, Acid/Base/Polar Functionality of Surfaces, Diffusion Kinetics, Solubility Parameters, Phase Transition Temperatures	Effect of manufacturing process (i.e. compaction, milling, and predictive particle interactions). Measure properties that help calculate Material Cohesivity and Hansen Solubility Parameters.



Process Design and Pilot Scale Up

During this phase of development, emphasis is placed on evaluating options available to manufacture, purify, and characterize the final formulation by focusing on how Critical Quality Attributes (CQA) can impact Critical Process Parameters (CPP). Using the principles of QbD and experimental design, a design space with proven acceptable processing ranges is created that will produce a rugged, robust control strategy to meet established Quality Target Product Profiles and may allow for parametric (real-time) product release.

Process Analytical Technology (PAT) is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality.



Micromeritics Material Science Solutions

Material Characteristic	Influences	Example
Particle Size pg 10, 11, 12	Powder Flow, Compaction, Compression, Blend Uniformity, Protein Aggregation, Fines Production	API particles are of varying sizes and distribution and can potentially affect stability, solubility, and efficacy. PAT Compatible at line
Particle Shape pg 10	Bioavailability, Compaction, Critical Element in Solid and Liquid Dispersion Processing	Product morphology in addition to size has a direct influence on solubility. Shape can be used as a PAT to define process end points and batch-to-batch variability. Fragmentation can indicate the robustness of a process from unit to unit. PAT Compatible at line
Surface Area pg 14	Critical Quality Attribute of API and Excipients Solubility Compaction, Milling, Stability, Lyophilized Products	Surface area can provide critical information in lyophilization in regard to ice crystal formation.
Density pg 13	Roller Compaction-Lubrication Tableting Setting, Segregation, Compaction	Can be utilized as a control parameter for solid dosage tableting uniformity using various tablet presses. PAT Compatible at line
Porosity pg 13, 14	Roller Compaction, Fragmentation, Compaction, Scoring Tablets for Half Dosages	Indicator for shelf life and air and moisture penetration. Tablet crushing strength, ability to withstand coating processes, and tablet robustness is influenced by pore size distribution.
Inverse Gas Chromatography pg 15	Powder Surface Energies, Acid/Base/Polar Functionality of Surfaces, Diffusion Kinetics, Solubility Parameters, Phase Transition Temperatures	Effect of manufacturing process (i.e. compaction, milling, and predictive particle interactions).
Materials Segregation pg 15	Segregation Mechanisms to Determine Sifting, Angle of Repose, Air Entrapment, Fluidization	Provides uniformity index for sample and segregation variance data. PAT Compatible at line
Yield Strength of Powders pg 15	Flowability Characteristics of Powdered or Granular Materials	Sample material will flow as long as the force acting upon the sample to cause the flow of the material is higher than the sample's yield strength. PAT Compatible at line

Particle Insight

The Particle Insight Dynamic Image / Particle Shape Analyzer is ideal for applications where the particle shape, not just the diameter, is critical information. For many years, particle size analyzers have rendered results with the assumption that all particles are spherical. However, not all particles are spherical. Particle shape information about raw materials enables manufacturers to control their process with a much higher level of sensitivity.

- Three size range model options – 1 to 150 μm , 3 to 300 μm , and 10 to 800 μm
- A camera with unique optics, high frame rate, and high resolution enables the analysis of tens of thousands of particles displayed in real time
- Select from 28 size/shape parameters for the best match to the particles being analyzed
- All analyzed particles have thumbnail images saved for post-run viewing and shape filtering to view only a specific selection of particle types

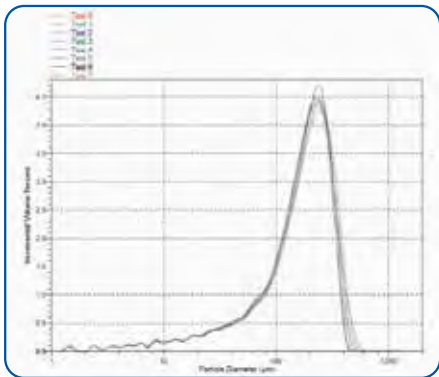
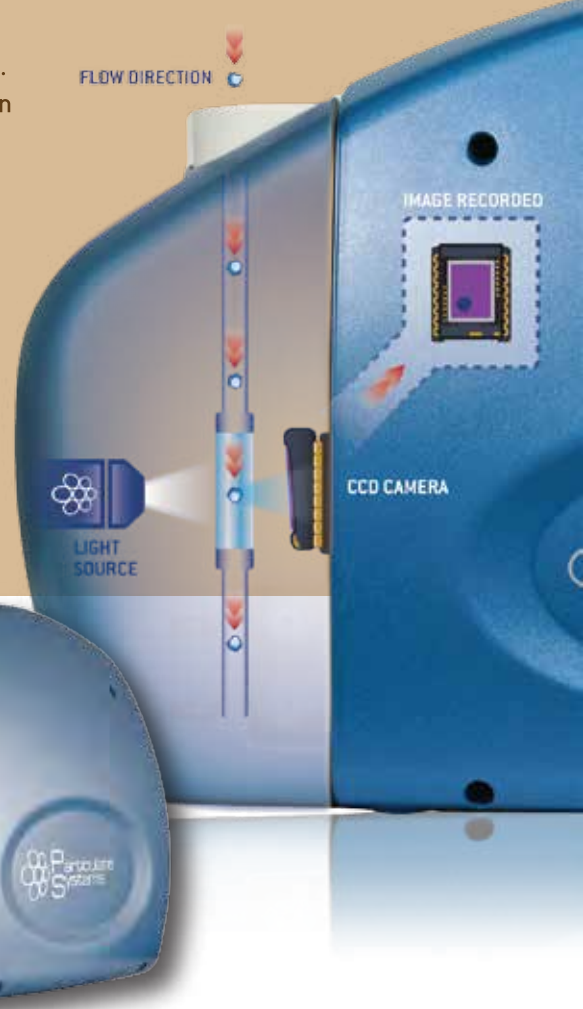


Figure 1. Static light scattering data that shows little change in particle size over time.

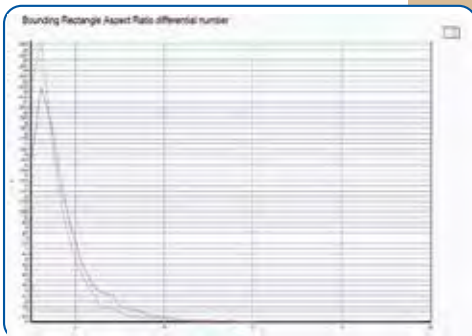


Figure 2. Test 2 (red) shows a larger population of high aspect ratio particles 10 minutes after dissolution commences.

If only represented as a round particle, as with most instruments, very limited information can be extracted.



Represented as a circular 100.1 μm particle



Particle Bounding Rectangle Width of 82 μm ; Length is 193.2 μm and BR Aspect Ratio is 2.36



Circularity of 0.321



Smoothness of 0.509 where "1" would be a perfectly smooth particle

Using particle shape analysis, more valuable information can be obtained from particles which can allow a better understanding of how this particle will flow in a process and perform in its final product.

NanoPlus

The NanoPlus Zeta Potential and Particle Size Analyzer is a unique instrument that utilizes photon correlation spectroscopy and electrophoretic light scattering techniques to determine particle size and zeta potential. The instrument is compact and easy to use with an extended analysis range, intuitive software, and multiple sample cells to fit the user's application.

- Measures particle size of samples suspended in liquids in the range of 0.1 nm to 12.3 μm with sample suspension concentrations from 0.00001% to 40%
- Measures zeta potential of a sample suspension in the range of -500 mV to +500 mV with concentrations from 0.001% to 40%
- The NanoPlus AT Auto-Titrator accessory controls the pH of suspensions in a range from 1 to 13 and conducts titrations during zeta potential or nano particle size analysis

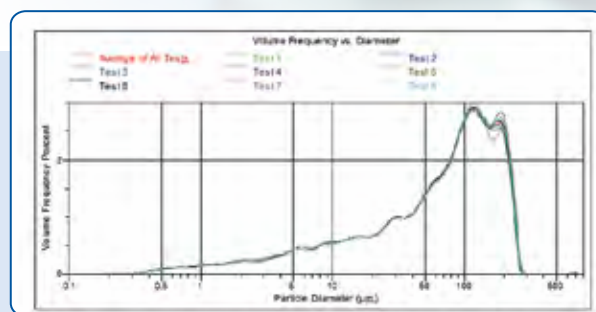


Particle Size, Particle Count

Saturn DigiSizer® II

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 size resolution reveals information about the material that goes undetected with other laser particle sizing systems, providing more accurate results.

- Range of 40 nanometers to 2.5 millimeters
- Fast, detailed results that are repeatable and reproducible between every Saturn DigiSizer
- Liquid sample handling unit available in both standard and low-volume configurations for automatic sampling, diluting, and dispersion



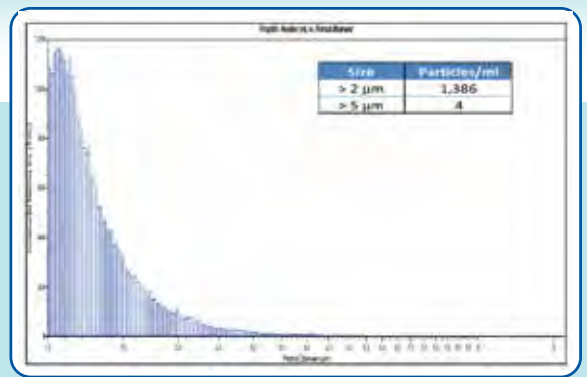
Overlay of 8 individual tests of one packet of BC powder, along with the average result of the 8 tests.



Elzone® II



The Elzone II utilizes the electrical sensing zone technique to size and count particles. Particle-by-particle sizing techniques, such as electrical sensing zone, provide the highest resolution available. The Elzone II can size samples that have assorted optical properties, densities, colors, and shapes. It can determine the size, number, and concentration of a wide variety of organic and inorganic materials.



Propofol (2,6-diisopropylphenol) is a short-acting, intravenously administered hypnotic agent. The British Pharmacopoeia specifies that no more than 5,000 particles be allowed above 2 μm in a 0.01% v/v solution of the sample in a 0.9% saline solution electrolyte using a 50 μm orifice tube.

- Sizes and counts both organic and inorganic materials down to 0.4 μm
- Single-particle measurement permits the discovery of low numbers of particles (outliers) larger than the main population
- Automated features include: start-up, run, and shut-down routines; blockage detection and clearing; flushing/rinsing; and calibration

SediGraph® III PLUS

The SediGraph III analyzer combines the proven SediGraph analytical technique with advanced instrumentation features to provide superior repeatability, accuracy, and reproducibility. The SediGraph III uses x-ray absorption to measure mass concentration and Stokes' Law to determine particle size.

- Range of 0.1 to 300 μm
- Complete sample mass accountability – accounts for material outside the measurement range
- Direct measurement of mass fraction
- Reports mass distribution by particle size and settling velocity
- High-precision x-ray tube with a lifetime warranty (Seven Years)



AccuPyc® II

The AccuPyc II is a fully automatic helium displacement pycnometer that produces high-speed, high-precision volume measurements and density determinations of powders, solids, and slurries having volumes of 0.01 to 350 cm³. Helium pycnometry is recognized as one of the most reliable techniques for obtaining skeletal volume and density

- Capable of measuring volume (and therefore density) to four decimal places
- Integrated control and analysis module can operate up to five additional external analysis modules
- Custom-sized modules can be configured to suit unique applications
- MultiVolume Option allows analyses of a variety of sample sizes in one analysis module



GeoPyc®

The GeoPyc utilizes a quasi-fluid displacement medium composed of non-hazardous microspheres having a high degree of flowability that do not wet the sample or fill its pores.

- Determines envelope volume and density of monolithic samples as well as the bulk volume and density of powdered materials
- A variety of sample chambers is available to accommodate a wide range of sample sizes
- T.A.P. Density option – measures the packing volume and calculates the bulk density of granular and powdered samples

Material	Historical Tap Density	GeoPyc Bulk Density at Consolidation Forces of					
		5N	10N	15N	20N	30N	50N
Calcium Carbonate (H)	0.83	0.8100	0.8425	0.8658	0.8872	—	—
Calcium Carbonate (L)	0.52	0.5017	0.5283	0.5433	0.5566	—	—

* Applied to a plunger of 5.07 cm²



AutoPore® IV Series

The AutoPore IV series uses mercury intrusion and extrusion to determine total pore volume, pore size distribution, percent porosity, density, compaction/compression and fluid transport properties.

- Available with two low-pressure ports and one high-pressure port or four low-pressure ports and two high-pressure ports for increased sample throughput
- Enhanced data reduction package includes tortuosity, permeability, compressibility, pore-throat ratio, fractal dimension, Mayer-Stowe particle size distribution, and more
- Operates in scanning, rate-of-intrusion equilibration, or time equilibration modes
- Enclosed mercury system to prevent mercury exposure to the environment – low-volume mercury usage





3Flex™

The 3Flex is a fully automated, three-station instrument capable of high-throughput surface area, mesopore, and micropore analyses with superior accuracy, resolution, and data reduction and reporting versatility. Each analysis station is upgradeable from mesopore to micropore with its own set of pressure transducers.

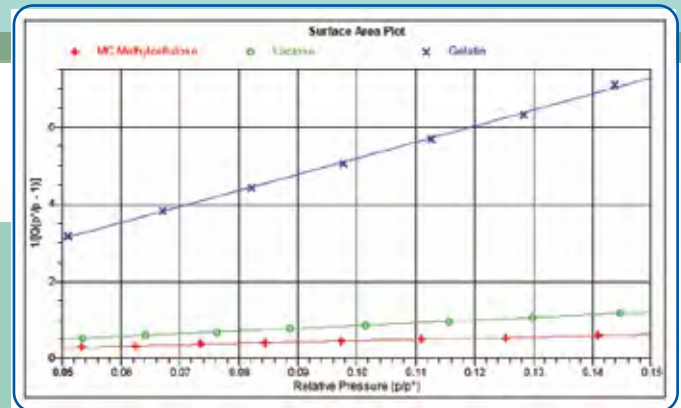
- Three independently configurable analysis stations
- Micropore stations include krypton capability for low surface area materials – vapor is standard and an extended-range vapor option is available
- Interactively evaluate isotherm data with MicroActive software and user-defined reporting options – reduces time required to obtain surface area and porosity results
- Innovative dashboard monitors and provides convenient access to real-time performance indicators and maintenance scheduling information

TriStar® II

The TriStar II is an automated, three-station, surface area and porosity analyzer capable of increasing the speed of quality control analyses with the accuracy, resolution, and data reduction features to meet most research requirements.

Simultaneous and independent analysis of up to three samples – four TriStars can be operated from a single computer.

- The standard nitrogen system can also accommodate the use of argon, carbon dioxide, and other non-corrosive gases. A krypton option allows measurements in the very low surface area range
- A dedicated Po port with transducer is standard, allowing the measurement of saturation pressure on a continuous basis. Saturation pressure can be entered manually, measured continuously, or collected over the sample
- Free space can be measured, calculated, or manually entered



Surface area for the three samples was determined using BET multipoint analysis





SPECTester

The SPECTester uses state-of-the-art spectroscopic technology to provide data about component concentrations, particle size differences, and product uniformity. The instrument is capable of identifying both primary and secondary segregation mechanisms. It can be used in R&D facilities as well as in production plants for on-the-spot, mid-stream quality control. Results are scalable to mimic actual process conditions.

- Capable of measuring segregation by particle size, sifting, fluidization, angle of repose, chemical component, and air entrainment
- Measures mixtures with up to six components reporting why and how much the material mixture is segregating
- Two models – one with visible light detection, one with NIR detection



SSSpin Tester

The SSSpinTester uses the science of centrifugal force to measure the unconfined yield strength of fine powders. When determining flowability characteristics of fine powders, the yield strength of the material is very important. The sample material will flow when the force acting upon the sample is higher than the sample's yield strength value.

- Fast analysis – results in less than five minutes
- Small amount of sample required – 0.06 to 1.00 gram
- One test acquires full data set – no multiple measurements required
- Direct measurement eliminates the need for extrapolation of data





HEADQUARTERS

Micromeritics Instrument Corporation

4356 Communications Drive

Norcross, GA 30093, U.S.A.

Telephone: (770) 662-3636

Fax: (770) 662-3696