QbD QUANTITATIVE MEASUREMENTS OF CQAS IN SOLID DOSAGE FORM UNIT OPERATIONS

Porosity • Density • Surface Area

micromeritics®

USP ‹267›	Porosimetry by Mercury Intrusion
USP ‹699›	Density of Solids - Gas Pycnometry
USP ‹846›	Specific Surface Area
Ph. Eur. 2.9.32	Porosity & Pore Size Distribution of Solids by Mercury Porosimetry
Ph. Eur. 2.2.42	Density of Solids
Ph. Eur. 2.9.26	Specific Surface Area by Gas Adsorption
JP 3.02	Specific Surface Area by Gas Adsorption
JP 3.03	Powder Particle Density Determinations

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) and Unit Operation Critical Process Parameters (CPPs) and their impact on the finished dosage forms.

Density, porosity, and surface area can be quantitatively correlated to the mechanical properties of the tablet/capsule and used to control key variables within the manufacturing process, as well as being an indicator of content uniformity and dissolution profile performance.

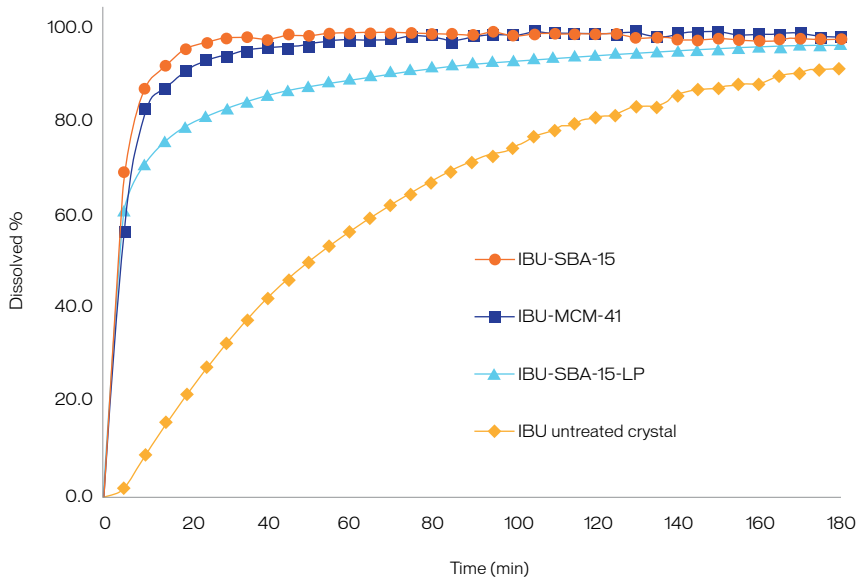
POROSITY

Tablet properties (friability, hardness, and disintegration) are principally reliant on the compact structure, which is affected by excipients used in the formulation and their compaction behavior during compression. These mechanical properties may be altered with changes in porosity. Increasing the compaction pressure brings the particles into closer proximity to one another, resulting in a reduction in tablet porosity. Knowledge of pore size and pore size distribution of tablets may provide essential information for compression settings when establishing a design space. Tablet porosity is also important as a CQA for disintegration and bioavailability behavior. These measurements also provide useful information when characterizing the API and excipients to help predict their behavior in the formulation.

In terms of the physical properties of granules, porosity along with compression shear strength are important influencers of compactibility that can be adjusted during the manufacturing process by altering granulation parameters or by altering the formulation. Changes in porosity or compression shear strength can alter the compaction characteristics of the granules. Evaluation of the porosity of the finished dosage form can be a good indicator of dissolution rate, as can pore size distribution and surface area. All of these factors can influence solvent penetration rates into a tablet.

The mercury porosimetry analysis technique is based on the intrusion of mercury into a porous structure under stringently controlled pressures. Besides offering speed, accuracy, and a wide measurement range, mercury porosimetry permits you to calculate numerous sample properties such as pore size distributions, total pore volume, total pore surface area, median pore diameter, and sample densities (bulk and skeletal).

DISSOLUTION PROFILES VERSUS PORE SIZE



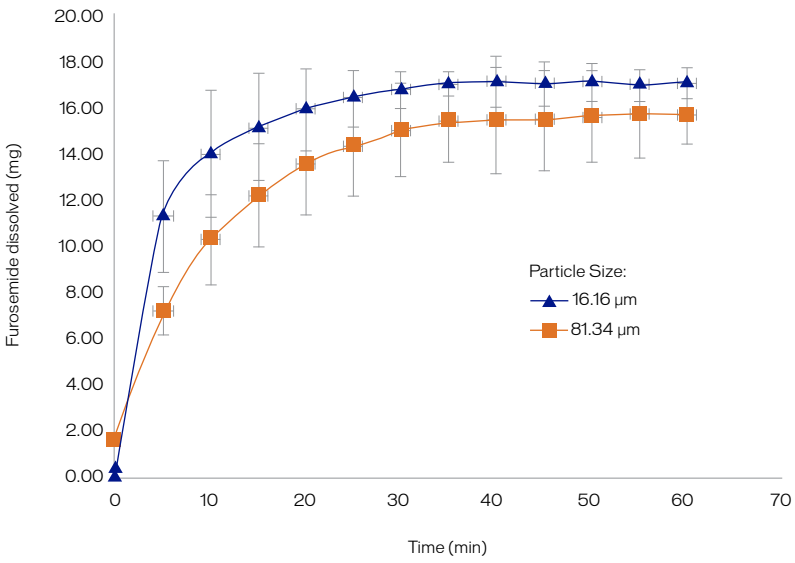
SURFACE AREA

Once powders are compacted, particle size becomes less influential. The resultant change in surface area after compression becomes of greater importance to physiochemical and mechanical properties of drug product performance. Milling and compaction will cause a change to particle size, which directly affects surface area. Surface area is a viable and important parameter to predict mechanical and processing behavior, especially in material handling, compaction, and fragmentation.

Specific surface area provides data about the surface making up the powder/solid which may include imperfections or void spaces. These void spaces are present in crystalline materials and can also be present in amorphous regions. During roller compaction the variability (batch-to-batch) of a change in the ratio of amorphous to crystalline content can produce erratic mechanical and physiochemical behavior.

Knowing the surface area can be helpful in optimizing powder flow characteristics. By reducing the specific surface area, you can prevent or control inter-particulate interaction and the resultant cohesion to improve flow. Surface area by gas adsorption is the preferred measurement technique. When coupled with mercury porosimetry, this provides two complimentary techniques for pore size, pore size distribution, and surface area.

DISSOLUTION OF FUROSEMIDE PARTICLES



Suresh Potharaju (2012). Effect of Compression Force on Agglomeration of Micronized Active Pharmaceutical Ingredients: Techniques to Prevent API Agglomeration during Compression. (Doctoral Dissertation)

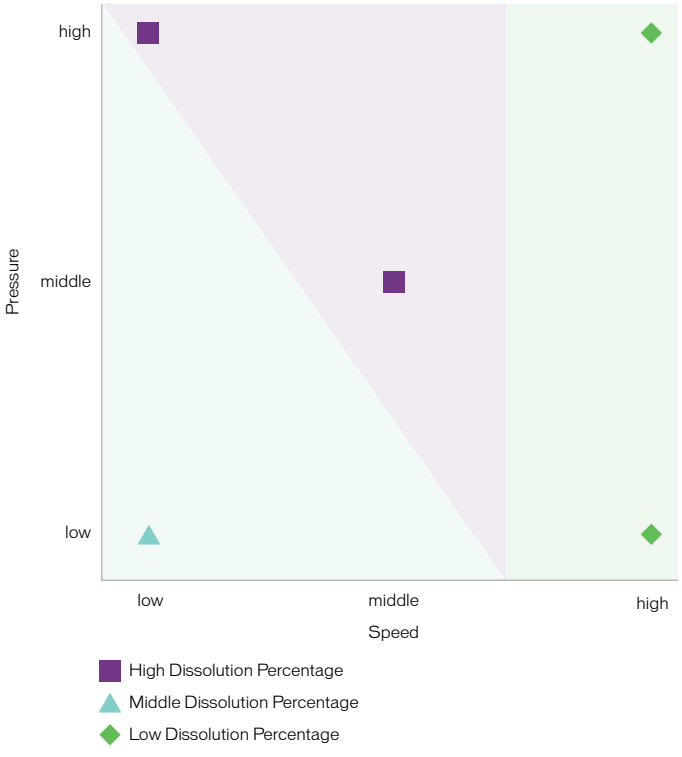
DENSITY

Roller compaction is a dry, continuous technique that densifies powders into a solid mass (compacted ribbons) which is then milled into granules of a desired size prior to compression or encapsulation. Several mechanisms are at work within this process that have material effect on the final dosage form, including content uniformity. These include material flow properties, compactibility, compressibility, roll pressure, roll speed, and hopper feeding dynamics.

One of the key elements in roller compaction is roll pressure. Several studies show that this parameter has a direct effect on tablet dissolution performance. Utilizing density measurements (true and apparent/envelope) within pre-blend and on the compacted ribbon, ribbons with suitable solid fraction can be determined. This solid fraction information can provide the necessary insight to optimize granules and establish controlled roll pressures. This data will be the basis for robust CPPs where the CQAs for final dosage are maintained with the DOE parameters.

Micromeritics offers a Density Solution bundle that accurately and non-destructively measures true, apparent, and envelope densities. These tests can be done in the laboratory or performed at-line. The procedure is simple, accurate, and highly repeatable. Obtain sample evaluation results in minutes.

PERCENT DISSOLVED BASED ON PRESSURE VERSUS ROLL SPEED



POROSITY AND PORE SIZE DISTRIBUTION INSTRUMENTS

AutoPore V

Mercury Intrusion Porosimetry
USP <267>, Ph. Eur. 2.9.32

The AutoPore V Series Mercury Porosimeters can determine a broader pore size distribution more quickly and accurately than other methods. This instrument also features enhanced safety features and data reduction/reporting choices that provide more information about pore geometry and the fluid transport characteristics of your material. Based on the principle of mercury intrusion, the AutoPore V has the ability to measure pore diameters from 0.003 to 1100 µm.

Controlled pressure can increase in increments as fine as 0.05 psi from 0.2 to 50 psia. This allows detailed data to be collected in the macropore region. High-resolution (sub-microliter) measurement of intrusion/extrusion volumes produces extraordinary precision allowing the development of tighter sample specifications, improved production processes, and high-quality research data.

Available with four low- and two high-pressure ports for high throughput analyses

Choice of pressure ramping methods for high-speed, on-demand results or equilibration mode for high accuracy and detail

Available in 33,000 psia or 60,000 psia models

"Pfizer Inc.'s experience with Micromeritics has been outstanding."

George Sienkiewicz, Sr. Mgr., Pfizer Inc.

Research by TechValidate
Nov 2014

SURFACE AREA AND POROSITY INSTRUMENTS

TriStar II Plus

Surface Area/Porosity Analyzer
USP <846>, Ph. Eur. 2.9.26, JP 3.02

The TriStar II Plus is a fully automated, three-station, surface area and porosity analyzer that delivers high-quality data at an affordable price. It is capable of increasing the speed and efficiency of routine quality control analyses, yet has the accuracy, resolution, and data reduction capability to meet most research requirements. The TriStar II also features a Krypton Option, allowing measurements in a very low surface area range. The instrument combines versatility in analysis methods and data reduction to allow the user to optimize analyses to specific applications.

- In many cases, high-throughput analysis results in 15 minutes
- Enhanced software for data reduction and performance monitoring
- Ability to overlay up to 25 files, including mercury porosimetry data
- Powerful Python scripting language permits user to develop custom reports

3Flex

Surface Characterization Analyzer
USP <846>, Ph. Eur. 2.9.26, JP 3.02

Micromeritics 3Flex Surface Characterization Analyzer is a fully automated, research grade, three-station instrument capable of high-performance physisorption, mesopore, and micropore analyses with superior accuracy, resolution, and data reduction. Each analysis station is upgradeable from mesopore to micropore. All analysis stations can be configured for krypton analysis of low surface area materials.

The 3Flex is capable of analyzing three samples in parallel so that three complete isotherms are collected in the time required for one analysis. Each of the analysis ports is capable of achieving very low absolute pressures as a direct result of our innovative design. Since smaller pore sizes are measured at lower relative pressures, micropore data are more accurately measured.

- Research grade instrument for superior meso and micropore physisorption analyses (including the measurement of low surface area powders or granules)
- MicroActive data reduction software provides powerful, intuitive data analysis with pre-configured or user-defined reporting options
- Three configurable analysis ports adapt to the specific needs of your work-flow

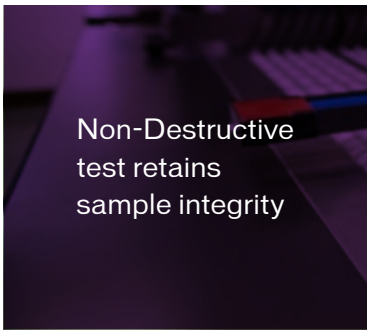
DENSITY MEASUREMENT INSTRUMENTS

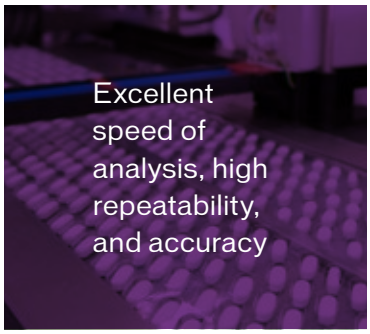
AccuPyc II

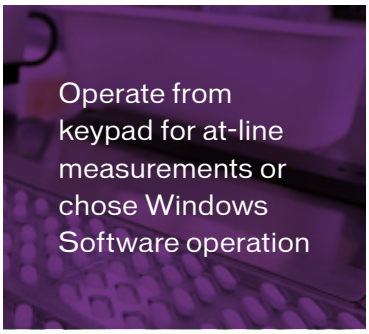
Gas Displacement Pycnometry System
USP <669>, Ph. Eur. 2.2.42, JP 3.02

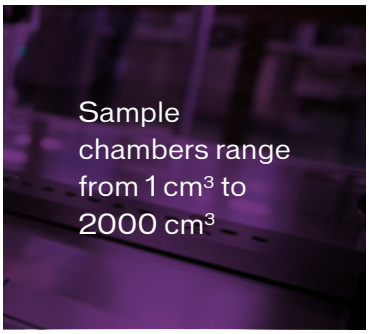
Gas pycnometry is recognized as one of the most reliable techniques for obtaining skeletal volume and true/apparent density. This technique is non-destructive as it uses the gas displacement method to measure volume. Inert gases, such as helium or nitrogen, are used as the displacement medium. Density calculations using the gas displacement method are much more accurate and reproducible than the traditional Archimedes water displacement method.

The AccuPyc II Series Pycnometers are fast, fully automatic pycnometers that provide high-speed, high-precision volume measurements and true density calculations on a wide variety of powders, solids, and slurries. The instrument completes most sample analyses in less than three minutes without sacrificing accuracy. After analyses are started with a few keystrokes, data are collected, calculations are performed, and results displayed. The AccuPyc can be used at-line in a production environment or within the laboratory.



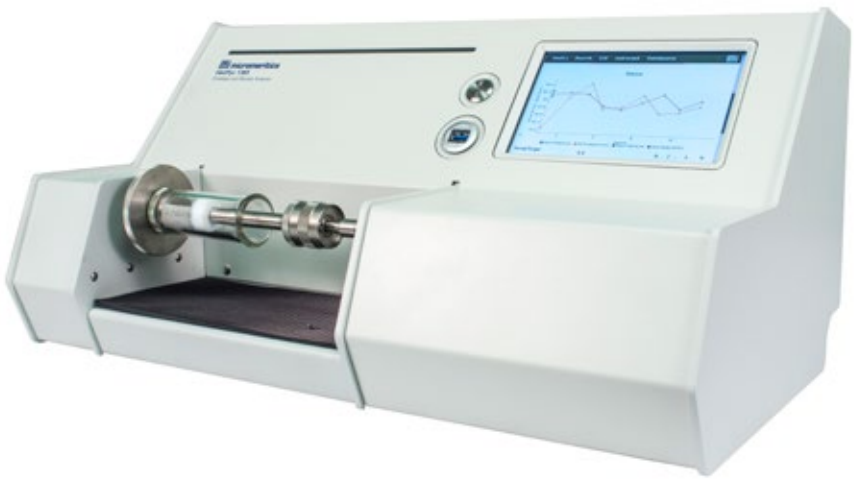




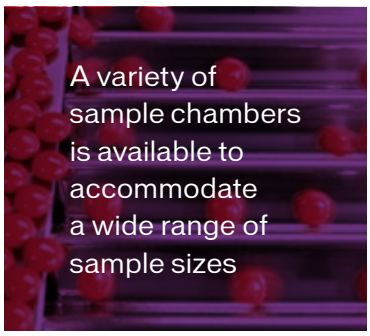


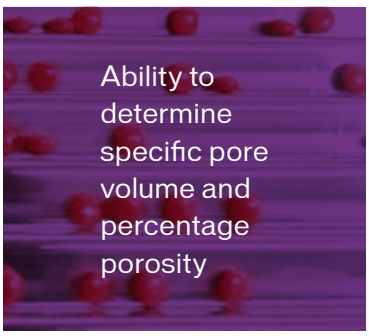
GeoPyc 1365

Bulk/Envelope Density Analyzer
USP <616>, Ph. Eur. 2.9.34, JP 3.01



The GeoPyc employs a unique displacement measurement technique that uses Dry Flo, a quasi-fluid composed of small, rigid spheres having a high degree of flow-ability. The sample is placed in a bed of Dry Flo which is agitated and gently consolidated about the sample. The GeoPyc collects the displacement data, performs the calculations, and displays or prints the results. The unit also reports percentage porosity and specific pore volume when absolute density information (density excluding pore and small cavity volume obtained from a Micromeritics AccuPyc II pycnometer) is entered.





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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.

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