Particles, crystals, and droplets are present in many manufacturing processes and products, and often pose challenges for the engineers who must optimize product quality and process efficiency. The proper control of particle size, shape, and count is often a critical factor in final product quality, and can greatly influence process efficiency (Figure 1).

For example, the effectiveness of medicines used to treat lung diseases depends heavily on particle size; small particles penetrate into the airways faster than large particles (1). Particulate processes take longer to optimize and scale up than other unit operations and require continuous troubleshooting to operate effectively (2).

The optimization of process parameters is critical to consistently obtain the desired particle attributes. For instance, in crystallization, the cooling rate directly influences final crystal size — faster cooling rates typically produce smaller crystals (3). In emulsification processes, mixing intensity must be controlled to obtain the desired droplet size distribution (4). In the flocculation of fiber cement particles, high-molecular-weight polymer flocculants increase aggregation and produce larger and stronger flocs (5).

Multiphase systems involving combinations of particles, droplets, and bubbles add complexity to the challenge of understanding, optimizing, and controlling the processes used to produce, modify, or separate them.

Understanding how process parameters affect particle properties and characterizing particle properties effectively, particularly particle size and count, enables engineers to solve processing problems and improve product quality. Historically, particle characterization was performed by offline particle size analyzers, such as laser diffraction or sieving. In recent years, newer technologies have emerged...

**Figure 1.** Particle size and count can influence product quality, as well as process efficiency. (a) Small droplets (front) deliver medicine in an ointment faster than larger droplets (back). (b) Separation times are longer when small crystals (front) block filters.
that describe particle size and count in real time, as particles naturally exist in the process.

This article introduces some of the most common in-process particle measurement approaches, and explains how they can be deployed for the effective delivery of high-quality particle products.

**Traditional particle size analyzers**

Traditional particle size analysis (PSA) using an offline analyzer is a powerful and widely used technique for the measurement of particle size in quality control (QC) labs. Examples of traditional PSA techniques include sieving, laser diffraction, dynamic light scattering, electrozone sensing, and image analysis. Because these techniques employ different methods of measurement, different techniques might report different particle size distributions for the same system (6). Some techniques, such as electrozone sensing, can report particle count and size in the same measurement. Other techniques are ensemble methods that can report only particle size. Offline particle size analysis allows QC laboratories to check the physical properties of particles at the end of a process, and identify deviations from the targeted particle system specifications. To obtain useful results from traditional particle size analyzers, consider the following points.

**Sampling and sample preparation.** A successful laboratory analysis of particle and droplet systems requires the removal of a representative sample from the process and the preparation of the sample for analysis. Most PSA techniques have strict constraints on the range of concentration, size, and shape of particles that can be measured accurately. Sample preparation often involves multiple steps to meet those measurement constraints, and can include methods such as filtration, rinsing, drying, subsampling, resuspension, surfactant addition, dilution, and sonication. However, it is quite possible that these steps may significantly alter the particles or droplets of interest.

Even with the utmost care and precision in the sampling and sample preparation methods, the actual particles that are analyzed may be significantly different from the particles that were initially present in the process (Figure 2). Thus, particles must be sampled in a way that minimizes the possibility that change might occur during the removal, preparation, or measurement phases of the procedure (6).

Droplets and bubbles are particularly prone to change upon sampling. The interfacial forces present in the process stream that dictate the droplet or bubble size distribution are changed completely when a sample is taken and exposed to ambient conditions. This makes these delicate systems difficult or even impossible to sample effectively.

**Particle shape.** In order to report consistent results, many particle size analyzers employ simplified models that assume particles are spherical (7). A sphere is the simplest particle shape in the sense that one number, the diameter, describes the particle size completely.

Often, however, particles are nonspherical (Figure 3), and particle shape can be even more important than size in determining bulk solids properties, such as flowability (8) and filterability (9). Engineers must understand how particle shape influences a traditional PSA technique, and in cases where particles are known to be nonspherical, take this into account when analyzing results.

Furthermore, particle systems consist of a population of particles of different sizes and shapes. Many traditional particle size analyzers calculate the particle size distribution according to a theoretical model that calculates an average, typically a mean or median. Particle count at the fine and coarse tails of such a distribution might be influenced by...
the method of measurement and the mathematical treatments of the reported measurement.

**Time delay.** Most particle process streams operate at a solids loading much higher than anything traditional particle size analyzers can handle. Thus, careful sample preparation is needed for accurate measurement. It is virtually impossible to apply traditional offline PSA measurements directly in a process. In order to obtain continuous information relating particle size to process parameters, samples would have to be manually extracted and analyzed immediately, without interruption. This approach is challenging from a cost perspective, and may expose operators to an unacceptable level of risk, especially for processes that operate at high temperatures and pressures or that contain toxic or explosive slurries and solvents. The inevitable time delay between sampling and receipt of results makes it extremely difficult to implement traditional PSA for real-time measurement. These analyzers, therefore, are unsuitable for monitoring processes continuously as they change over time.

**Traditional PSA for QC.** Offline PSA is a powerful and widely used quality control technique for the measurement of particle size, and for comparison with a specification. With care, traditional PSA can be used to identify variations in product quality and to ensure that products meet the specifications required by producers, their customers, and regulators who oversee the quality of products reaching the public.

**Particle size analysis for process optimization**

Traditional PSA, however, does not lend itself to characterizing particles continuously as process parameters change, and for this reason it is not well-suited to the task of process optimization. It is extremely difficult to rely on a single offline sample, no matter how reliable the data obtained, to completely understand particle behavior from the beginning until the end of a process. To develop a truly effective process understanding and to translate this into meaningful improvements for the process, continuous measurements are needed that characterize particles in real time as they naturally exist in the process. This information enables you to directly observe particle mechanisms such as growth, breakage, and agglomeration, determine the influence of process parameters on the system, and identify and quickly implement an optimum route to the desired particle properties.

Figure 4 illustrates some common techniques to obtain real-time information about particle systems under dynamic process conditions. At-line, online, and inline approaches are used for different purposes, and the choice of method depends on the process objective. At-line measurement techniques are typically used to obtain traditional PSA information with minimal time delay. Online analysis is used to increase data density and enable the near-real-time measurement of attributes critical for quality control. Inline analysis is commonly used in laboratory and production environments to obtain fast representative information that allows engineers to directly relate particle system behavior to the prevailing process conditions.

**At-line analysis**

At-line analysis involves relocating offline PSA equipment to the immediate vicinity of the process so that samples can be taken from the process and analyzed immediately. PSA equipment must be available close to the reactor or pipeline where the process is running. In manufacturing environments, this often means the equipment must be rated for use in hazardous locations, or it must be located outside the hazardous area. In process development laboratories, there is a trend to co-locate process development and QC laboratories so that fast and accurate measurements can be made at-line for important projects.

A significant advantage of the at-line approach is that it can mitigate the time delay associated with traditional offline PSA methods, allowing results to be obtained
quickly and immediate adjustments made to the process to improve the outcome. However, obtaining enough samples to provide the data density needed to understand process kinetics remains challenging, and ensuring the information is representative is still a concern.

Online analysis

Online analysis refers to the use of an automated system for sample preparation and analysis of particle processes. The system performs automated sampling, dilution, and preparation followed by injection into a traditional particle size analyzer.

One common approach employs a recirculation or bypass loop to continuously remove particles from the process. The pump used to move the particles must be selected carefully so as to not introduce unnecessary shear, which can break particles and lead to an unrepresentative measurement. Conditions in the loop must also be carefully controlled to ensure that they quickly mimic the actual process conditions. For example, poor temperature control in a recirculation loop can cause nucleation or dissolution to occur prior to measurement in a crystallization process.

Implementing a successful online monitoring system is time-intensive, but if successful, opportunities for real-time quality control become available and the burden on analytical laboratories can be reduced.

Inline analysis

Inline particle measurement techniques such as focused-beam reflectance measurement (FBRM) (10) and real-time microscopy techniques such as particle vision and measurement (PVM) (11) involve inserting a probe-based instrument into a process stream for direct measurement of particles as they naturally exist in the process (see sidebars). This type of measurement occurs at full process concentrations, and does not require sampling. Measurement at full concentration is possible because these techniques measure light reflectance rather than transmission. Transmission-based methods saturate at low to moderate solids concentrations, whereas reflectance-based techniques do not. (Transmission-based methods shine light through a sample and measure, for example, the diffraction pattern that is

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**Focused-Beam Reflectance Measurement (FBRM)**

In focused-beam reflectance measurement (FBRM), a probe (a) is inserted directly into a process stream at an angle to ensure particles can flow easily across the probe window where the measurement takes place. A laser beam travels down the probe tube through a set of optics and is focused to a tight beam spot at the sapphire window. The optics rotate at a fixed speed (typically 2 m/sec), causing the beam spot to rapidly scan across particles as they flow past the window.

As the focused beam scans across the particle system, individual particles or particle structures (i.e., larger structures formed when multiple particles come together, such as aggregates or agglomerates) backscatter the laser light to the detector. These pulses of backscattered light are detected and counted, and the duration of each pulse is multiplied by the scan speed to calculate the distance across each particle (b).

This distance, known as the chord length, is defined as the straight-line distance from one edge of a particle to another edge. Typically, thousands of particles are counted and measured per second to produce a precise and highly sensitive chord length distribution (CLD) (c).

The chord length distribution tracks how particle size and count change from the beginning until the end of a process. Statistics from each chord length distribution, such as counts in fine and coarse size classes, can be trended over time (d).

Unlike other particle analysis techniques, FBRM does not assume any specific particle shape. Instead, the CLD serves as a fingerprint of the particle system, providing statistics to detect and monitor changes in particle dimension and count in real time.
produced. As concentration increases, it becomes more and more difficult for the light to pass through the sample and reach the detector. At some point, called the saturation limit, the concentration is too high to measure anything. This is why dilution is needed to measure systems using transmission based methods.)

Probes can typically be applied across a range of scales and installation environments, from small-scale laboratory reactors to full-scale production pipelines (Figure 5). Inline analysis offers many benefits for engineers engaged in developing and producing particles and complements offline PSA techniques, which are traditionally used exclusively for quality control. With any inline particle analysis method, care must be taken to ensure the data collected are representative and can be interpreted effectively.

**Particle Vision and Measurement (PVM)**

Particle vision and measurement (PVM) employs a probe-based real-time microscope with a high-resolution camera and an internal illumination source to obtain images in dark and concentrated suspensions or emulsions. Information from every image is used to calculate a process analytical trend called the relative backscatter index (RBI). RBI is a measure of the overall reflectivity of a particle system and indicates how particle size, shape, and concentration are changing over time.

![Diagram of PVM](image)

**Figure 5.** Focused-beam reflectance measurement (FBRM) instruments can perform in-process particle measurement in (a) laboratory and (b) production settings.

**Figure 6.** (a) Discrete distributions obtained by FBRM can be recorded in real time at user-defined intervals. (b) Statistics such as particle count in individual sizes classes (e.g., particle count 0.5–50 µm or 50–1,000 µm) can be trended continuously in real time. (c) Statistical trends provide key information regarding changes to particle size and count.

*Article continues on next page*
Functions of inline analysis

Study particle size and count over time (Figure 6). Inline particle measurements are typically taken every few seconds, allowing discrete distributions to be recorded at user-defined intervals. Engineers can analyze statistical trends of each distribution over time to monitor the trajectory of the process in real time. By monitoring particles in-line and in real time, it is straightforward to determine:

- when particle size and count start changing (Point 1 in Figure 6c)
- the rate at which particles change (Line 2)
- when particle size and count stop changing (Point 3)
- the degree to which particles change (Line 4).

With this information, engineers can develop a much deeper understanding of their processes than they could if they had to rely on a single traditional PSA result taken at a single point in time at the end of a process.

Understand the impact of process parameters on particles. Inline particle measurement differs significantly from the role traditional PSA plays in the characterization of particles. In-process measurement takes place directly in the vessel or pipeline, while the particles are changing, rather than in the QC laboratory, and results are immediately related to dynamic process conditions, rather than to a predetermined particle size specification. By combining relevant process parameter information with in-process particle measurements, engineers can quickly obtain evidence to optimize processes with scientific rigor.

In Figure 7, the fine-particle count is plotted over time together with the process temperature for a crystallization unit operation. Notice that the rate of fine particle formation increases when the cooling rate is increased near the end of the batch (at time \( t \)). A secondary nucleation event has occurred, which may influence filtration and drying performance downstream. With the evidence presented in Figure 7, the engineer can develop strategies to optimize the cooling profile so as to produce crystals with the desired attributes.

Choose parameters to produce the correct particles. By directly monitoring the impact of process parameters on particle size and count, it is possible to reliably determine the process parameters needed to target a specific set of particle attributes.

Figure 8 illustrates the impact of agitation rate on droplet size — as the agitation rate increases, droplet size decreases. Droplet size can be very difficult to effectively measure using offline techniques, because droplets tend to break or coalesce easily outside the process environment. Inline particle analysis and microscopy can provide a comprehensive picture of the effect of shear rate on droplet size so process conditions can be optimized.

Monitor and correct process deviations. Monitoring particle size in real time during manufacturing reveals deviations and enables operators to take corrective action to minimize the impact of the upset.

Consider the continuous process depicted by the control chart in Figure 9. The process must be operated so that the mean particle size meets a tight specification. (Note that
the specification for the in-process instrument is not necessarily the same as the specification for a traditional particle size analyzer in the QC lab. This is because inline and offline instruments employ different measurement techniques that may report somewhat different absolute mean particle sizes.) Here, the in-process particle measurement instrument is used to identify a process upset in real time, which can be confirmed by pulling a sample and analyzing it in the QC laboratory.

A combination of inline and offline analysis can support troubleshooting the problem before implementing a corrective action to bring the process back into specification. Ultimately, the inline measurement could be used for real-time feedback control, rejecting process disturbances and minimizing process deviations.

**Challenges measuring particles inline**

Inline particle analysis is intended to provide real-time measurements of critical process and product parameters, and can be used together with offline QC information to improve process understanding and control. Inline and offline techniques require sound method development, and care must be taken to ensure the data obtained from either technique is representative and valuable for the engineer.

*Probe location and orientation.* Two important factors to consider when applying inline particle analysis are:

- proper instrument orientation — *i.e.*, a representative sample of the process material is presented to the analytical instrument
- proper instrument location — *i.e.*, the instrument or sample probe is located at a point in the process where the product or process parameter of interest can be measured.

Probe-based instruments should be placed in a well-mixed area of the process at an angle to the process flow to allow particles to impinge on the probe window and pass by unrestricted. Figure 10 shows four different probe orientations. In Figures 10a, 10b, and 10c, the particles are not able to directly impinge upon the probe window. Positioning the probe at an angle of 45 deg. into the process flow (Figure 10d) is optimal and allows for the best measurement.

Probes should also be positioned so they can measure the particles of interest in the process. For example, in a poorly mixed tank, coarse particles can settle closer to the bottom of the vessel and fine particles can float to the top.
Depending on the objective of the inline analysis, the probe should be positioned so as to effectively measure fine or coarse particles. Depending on the objective of the inline analysis, the probe should be positioned so as to effectively measure fine or coarse particles.

**Probe fouling and coating.** Most installations of probe-based instrumentation for inline particle measurement remain clean and unobstructed. However, any probe that is placed directly into a real process environment is susceptible to window fouling or coating by the process material. This can be mitigated by positioning the probe so that it is not located in a dead zone where process material can build up and cause fouling. A well-mixed region can also have a cleaning effect, whereby the constant stream of particles hitting the probe window removes any minor buildup that might occur.

Sometimes a probe can act as a “cold finger” in a hot process, allowing local formation of particles on the probe and window. This can be addressed by supplying a warm purge to the instrument or by wrapping heating tape on the probe. In most cases, well-designed processes do not experience major fouling. However, in some processes fouling is inevitable, making an at-line or possibly online approach more suitable than inline analysis.

**Understanding precision, sensitivity, and accuracy.** Offline particle size analyzers are designed to provide extremely accurate measurements of particle attributes. If sampling is representative and the particles do not change during sample preparation, offline analytics provide accurate results suitable for quality control. For inline analysis, precision is often favored at the expense of some accuracy in the measurement. In an ideal world, both accuracy and precision would be preferred, but limitations in measurement technology make trade-offs inevitable.

In Figure 11, accuracy is represented by the center of the dartboard, and individual dots represent separate measurements of particle size. In Figure 11a, there is significant variability (random error) in the measurements. This random error can be reduced by averaging enough measurements together over a large enough sample size, and the average value may provide an accurate measurement. However, each individual measurement has significant uncertainty — that is, the overall measurement has poor precision.

In Figure 11b, the darts are highly consistent, with significantly better measurement precision. However, the average value is offset from the true value, which is referred to as measurement bias.

The precision of a measurement can be improved by increasing the number of samples and averaging multiple measurements. Measurement accuracy can be improved by using a model that eliminates measurement bias.

In order for an inline particle analyzer to be sensitive to a change in the process, the change must be larger in magnitude than the random error present in the measurement. In this context, precision is often preferred, even at the expense of some accuracy. With highly precise instrumentation, it is possible to monitor small deviations in the process as they relate to changes in the process parameters. This degree of precision and sensitivity can be complemented with highly accurate offline methods to provide a complete picture of the process. As measurement techniques evolve and new technologies become available, the degree of accuracy in inline particle analysis will gradually improve and catch up with that of offline analyzers.

### Selecting an inline particle size analyzer

Selecting an inline measurement to be used as the basis for process understanding, optimization, and control requires consideration of several issues related to measurement and instrument precision and sensitivity. These can be described as follows.

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<thead>
<tr>
<th>Increase Understanding and Control</th>
<th>Improve Safety</th>
<th>Increase Throughput in Process Development</th>
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<tbody>
<tr>
<td>Understand how particles change under different conditions</td>
<td>Design processes with optimum conditions that proceed within specified limits</td>
<td>Obtain process information faster than by traditional offline methods</td>
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<tr>
<td>Study the effect of mixing and scale on particle mechanisms</td>
<td>Minimize worker exposure to hazardous materials</td>
<td>Improve data reliability by reducing potentially error-prone sampling</td>
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<tr>
<td>Monitor and control for optimized and repeatable product quality or process performance (e.g., downstream cycle time)</td>
<td>Study toxic, pressurized, energetic, and corrosive processes more easily</td>
<td>Maximize the efficiency and effectiveness of staff and equipment</td>
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in terms of robustness, repeatability, and reproducibility.

**Instrument robustness.** Instrumentation for inline particle analysis is considered robust if it is constructed to operate reliably under expected process conditions in laboratory or manufacturing environments. Inline analyzers that rely on the same underlying measurement technique can have different mechanical packages and thus operate effectively in different environments. Instruments should be designed to be compatible with common process streams and solvents, and must be able to withstand exposure to dust, solvent vapors, and vibration. Instruments should also be able to operate in hazardous environments and meet area classifications such as Class I, Div 1, or ATEX.

**Measurement repeatability.** Repeatability is a measure of an instrument’s ability to provide the same result for the same system over and over again. This is often proven with calibration of an instrument’s ability to provide the same result for the same system over and over again. This is often proven with calibration over and over again. This is often proven with calibration over and over again. This is often proven with calibration.

**Instrument-to-instrument reproducibility.** Processes are often developed across different scales and in different locations. It is important to minimize the difference in measurement between instruments to ensure that differences in results can be attributed exclusively to differences in the processing conditions, and not stemming from differences between two analyzers used at two different locations or scales.

**Return on investment for inline particle analysis**

Inline particle size analyzers typically cost more than offline instruments, because they must have a robust design, must be built with materials that are compatible with the process itself, and generally utilize sophisticated technology to provide a valuable measurement under difficult process conditions. A return on investment calculation for inline particle analysis should include the cost of personnel to operate offline or at-line equipment, as well as the cost of sampling and sample preparation equipment. The benefits of inline analysis should also be articulated clearly. Generally speaking, inline analysis offers return on investment in three areas, as summarized in Table 1.

The complementary use of in-process particle measurement for understanding, optimizing, and troubleshooting processes, along with traditional offline PSA for quality control, empowers engineers to develop more robust processes that produce higher-quality products in less time and at a lower total cost.