Imaging Technology: New Solutions

How to increase yield in crystallization and Nutsche filtering

By Keith DeMonstoy

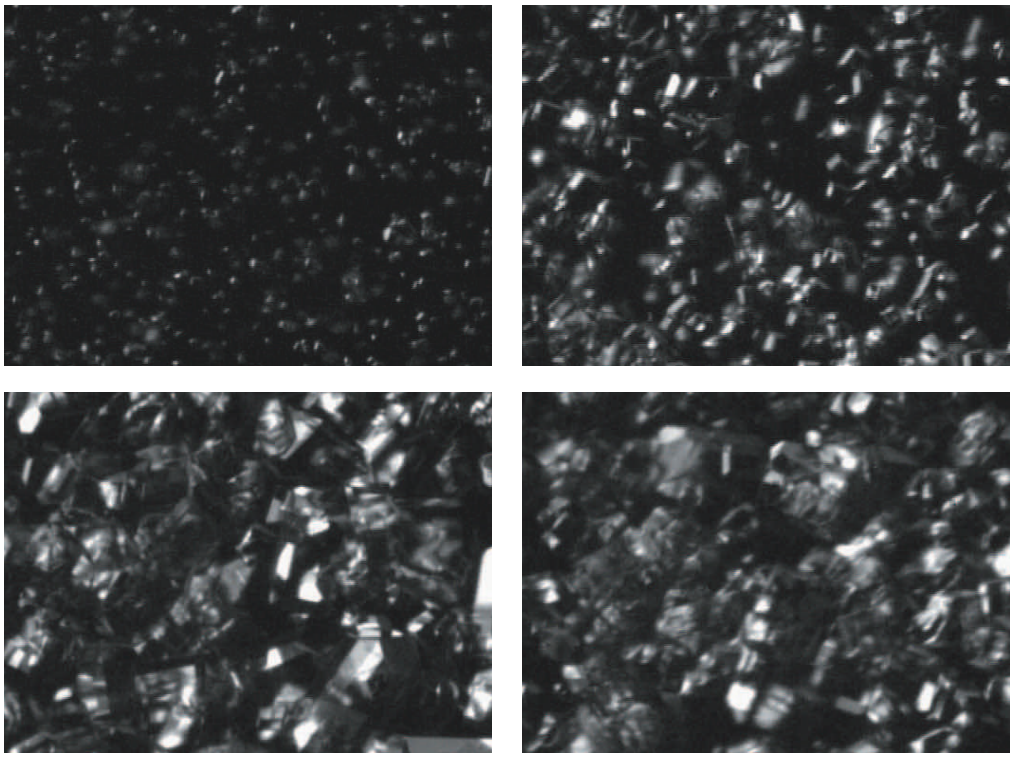
Following the introduction of the PAT initiative and the push from the FDA for process control, the pharmaceutical industry's search for PAT has never been so intense. With the high demand for advanced process technology from the pharmaceutical industry, process engineering has also increased. Two of the process applications that have advanced due to visual imaging technology are online microscopy technology and filter/dryer. Control of these areas has a major effect on the yield and, therefore, the profit of the operation.

During the Seeding Process

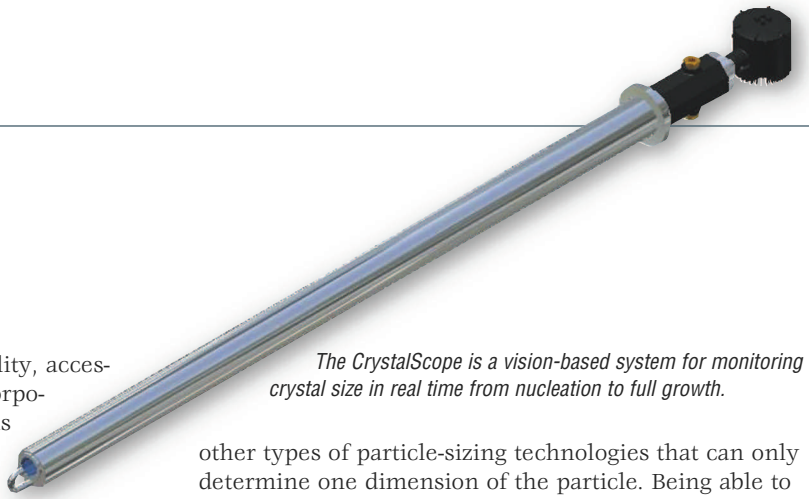
The seeding process is very important to the pharmaceutical industry. With image technology, seed growth can be monitored by measuring the size and concentration of the crystals in the nucleation stage. Monitoring crystallization has not been possible with laser system technology because the cord or equivalent sphere diameter that is given is only a one-dimensional measurement. Knowing the precise concentration of seeds is important for the filtering process. An increased number of seeds, or fines, will create a very slow, time-delaying filtration process when the liquor is drained from the batch, while too many coarse seeds will cause agglomeration. A vision-based system makes it possible to analyze and monitor crystal size from the nucleation stage to full growth.

An online microscope should include an Ethernet high-speed camera with adjustable shutter speed, combined with a lens configuration that uses dynamic Ethernet control of calibration, magnification and focus settings. Using fiber-optic backlighting allows for true shape analysis of the crystals as they flow in front of the microscopic lens. The high-speed shutter and intense light allow for a high-quality image to be captured.

Hardware advancement in the area of networking has grown in the last 10 years, leading to an increased availability of online process technology. Process control and detection devices can now be connected efficiently and at minimal cost with the use of Ethernet technology. Process personnel wanting increased speed and accuracy in their process have looked to Ethernet technology. Some advantages of using network technology as the



These images show crystal growth from nucleation to maturity, which is essential to obtain optimal product yield.



The CrystalScope is a vision-based system for monitoring crystal size in real time from nucleation to full growth.

means for connectivity are its speed, reliability, accessibility and familiarity. IT professionals incorporated in the business can now use their skills to connect and install Ethernet devices in their facility.

One specific device that has emerged with the growth of Ethernet technology is the Ethernet camera. Ethernet cameras are now packaged with 1-GB network interface cards to allow for connectivity to any 1-GB compatible LAN network. These cameras can then be placed onto vessels far away from a control room and used to monitor the crystallization process. This is essential in creating consistent and quality crystals for the pharmaceutical industry during the seeding process.

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Lighting Is Key

Lighting is an essential part of process control, especially in vision-based particle sizing. Engineers have focused much attention to ensure that lighting does not affect the outcome of the process. One such key component of fiber-optic lighting used in process control is the use of a "cold" light, or light that does not transmit heat. Cold light is accomplished by using IR filters and fiber-optic light bundles to create a barrier between the light source and the process interface. Using cool light also eliminates sight glass bake-on, allowing all available light to be used to its full potential.

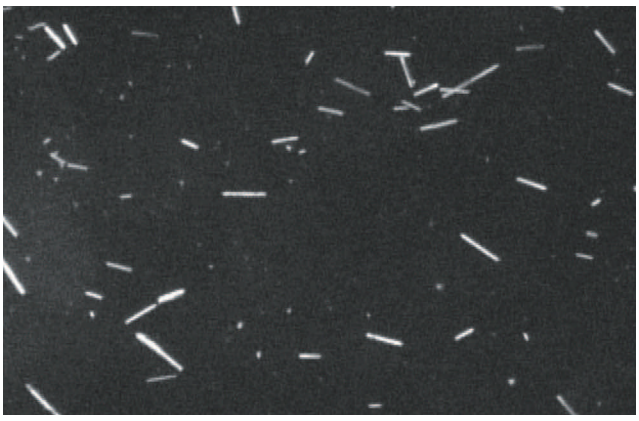
Once the lighting source is configured, an optimal digital image can be created by the Ethernet camera system. The two-dimensional digital image captured by the Ethernet would then be transmitted across a WIFI or direct Cat5 or Cat6 connection to a computer system with installed image-analyzing software. The vision-based software determines the size and shape of a particle by analyzing each particle's RGB scale. The software then throws out the background image, allowing the software to see each particle's shape and size. The remaining image is then analyzed further to determine the particle's parameter, major axis, minor axis, aspect ratio and area.

Using two-dimensional image-analyzing software provides valuable and accurate information, compared to other types of particle-sizing technologies that can only determine one dimension of the particle. Being able to record video and capture live images as the process is performed allows for visual reassurance by process personnel. With the particle's size and shape determined, the image-analyzing software can determine if the crystallization process is within the control limits or if there is a fines or agglomeration problem. Various outputs, such as 4-20 mA or OPC interface, can then be sent by the software to allow for automated control of vacuum and temperature at key times during the crystallization process. Better ability to control crystallization will increase the efficiency during the filtration stage.

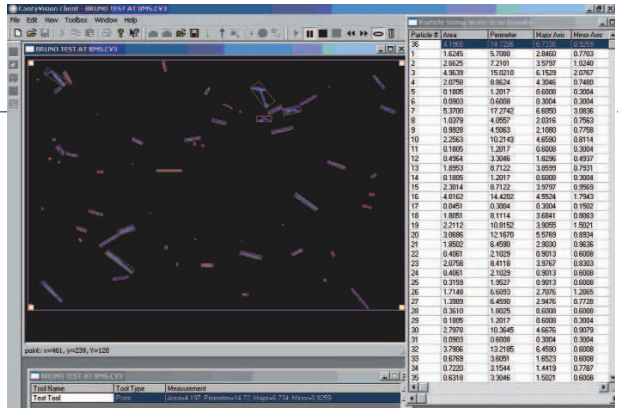
The second biggest payback of using imaging technology is the ability to keep from cracking the filter cake in a filter dryer system (Nutsche filter) or centrifuge. Cracking is when the product in a Nutsche filter becomes dry and cracks. Cracking of cake causes costly product to wash away during the filtration process. Using a visual-based system to view and analyze the filtration process allows for a non-contact means to determine if cracking of the cake is occurring. Using cake detection, determining the transition from liquid slurry to solid cake, is essential for an efficient filtration process.

Saving the Cake

Cake detection with an image-based system uses similar technology to that of a system for crystallization. Instead of an insertion-type camera, the camera is flush-mounted to the top of the vessel so that it can look down at the liquid and cake at the bottom. A light at the top of the vessel, also using the same port as the camera, shines down on the product as it is being filtered. The camera then



This digital image shows how crystals look before their evaluation with image-analysis software.



In this analyzed image of particles, the image has been reduced to black and white pixels, called binarizing, to allow the software to determine the particles' true size and shape.

focuses on the size and shape of the reflection of light on the liquid product. As the liquor lowers in the vessel and the product is filtered, the camera sends the digital image to the image-analyzing software. The software then analyzes the shape and size of the fixed reflected light off of the liquid. The software can then determine the height of the liquid and send an output signal, 4-20 mA or OPC, to control the level. Once the level reaches the cake, the software outputs the shutoff signal to the appropriate controllers, saving the cake. When a pharmaceutical company can produce a product that will create a profit of $5 million a batch and 5 percent of that product is lost due to cracks in the cake, saving 3 percent of the yield can increase profit over $150,000.

The ability to have real-time crystal size analysis during the crystal growth phase, along with cake detection, allows process technicians to constantly monitor the seeding process and aid in automation. Using previously captured images, a process technician can also look at previous batch stages to compare and achieve consistent crystal results, a fundamental standard for the FDA and the PAT initiative.

The economic advantages of using visual-based crystallization monitoring and cake detection are immense. When wasted batches are saved and consistent batches are prepared, money is saved. Consistent and reliable batches also include many opportunities for cost benefits, whether it is company time, energy resources or company manpower. With so many benefits with two-dimensional imaging analysis, the technology is sure to grow and be seen everywhere in process technology.

Keith DeMonstoy is an applications engineer with J.M. Canty Inc., 6100 Donner Rd., Lockport, NY 14094, an engineering firm with a focus in process technology. Its image-based systems offer on-line and lab-particle sizing for solids and slurries from one-micron size with no upper limit. Process vision and lighting systems handle level, foam detection and turbidity. Additional information is available at www.jmcanty.com.