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Optimization of particulate and droplet processes using FBRM® and PVM® technologies

Introduction

Particles and droplets are pervasive in the chemical, consumer products, and biopharmaceutical industries. Particles grow, agglomerate, break, dissolve and change shape – all of which can have an impact on process performance and product quality. To be successful, chemists and engineers must understand and optimize particle distributions to control process efficiency such as filtration rates, flow properties, or dissolution rates. In addition, particle distributions must be well controlled to ensure repeatable product yield, purity, and bulk density.

One of the most fundamental unit operations in most chemical processes is that of crystallization. As many chemical products are produced as a solid in the final product, most chemical processes go through at least one crystallization step. One of the critical advantages of crystallization is that it is both a separation and a purification technique, there-by enabling one to achieve a final solid product with the desired physical properties as well as the necessary purity. However, for many, crystallization is still somewhat of an 'art' as opposed to a science and is often treated as a black box process. However, with the development of advanced *in situ* process analyzers such as the FBRM® and PVM® technologies from *Mettler-Toledo*, the behavior of crystallization processes can now be fully understood. The use of these technologies from laboratory to manufacturing scale is resulting in the development of highly robust crystallization processes that are well defined and understood. This of course consequently has the benefit of achieving right first time manufacturing, reduction in the number of failed batches and significant improvement in downstream processing of the solid product such as filtration, powder flowability, bulk density and particle size.

Figure 1 shows the end point distributions as measured by in situ FBRM for both a fast and slow anti-solvent addition crysallization process. As can be seen, for the fast addition, more particles have been crystallized that are smaller in size when compared to the slow addition process. This is attributed to the much higher levels of supersaturation that are achieved in the fast addition process, resulting in excessive nucleation and consequently smaller particles.

The PVM images shown in Figure 2, clearly identify the difference in the final product size and shape. The fast addition process has produced significantly smaller needle shaped particles, which have a tendency to agglomerate together. Such fine agglomerated needles often cause downstream processing issues especially during filtration where they can take excessively long times to filter and often require multiple washes. On the other-hand, by changing the rate of anti-solvent addition crystals much larger in size can be produced which will have significantly improved downstream processing characteristics.

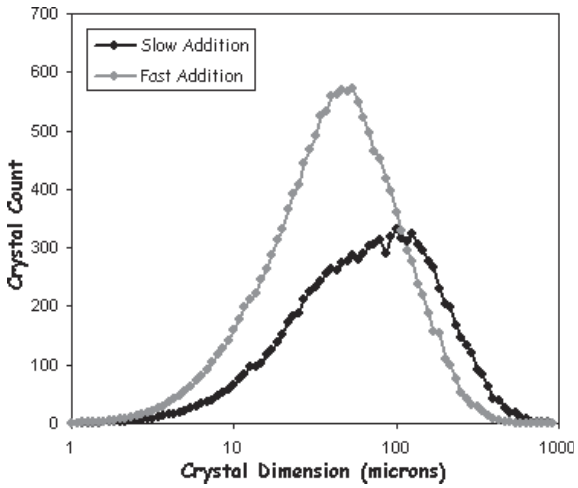

Fig. 1. End point distribution comparison for a fast and slow anti-solvent addition crystallization [1]

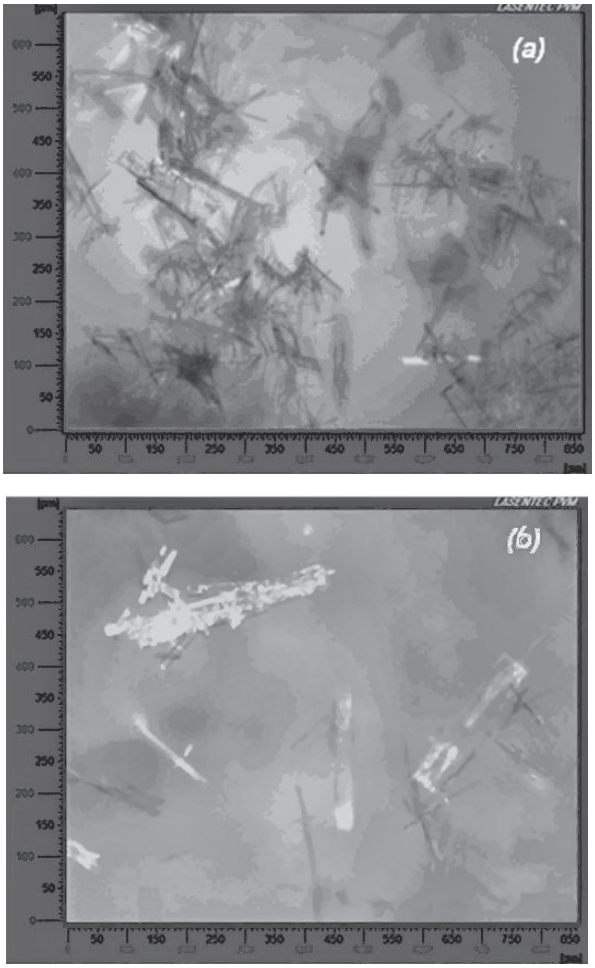

Fig. 2. PVM images of the crystals produced at the end for a fast (a) and slow (b) anti-solvent addition crystallization [1]

The FBRM® and PVM® can also be used in the design, optimization and control of droplet processes such as emulsion preparations and polymerization. Similar to crystallization processes, the ability to measure *in situ* during processing provides a unique understanding of the impact of critical process parameters on the behavior of the droplet/particulate system and this is a fundamental requirement in the efficient development of such processes. Again, through real time, *in situ* measurements, one can quickly correlate droplet system dynamics with process parameters while running fewer experiments than that required using traditional methods. One can also quickly troubleshoot un-expected process changes there-by minimizing failures, improving product yield and ensuring consistent product quality.

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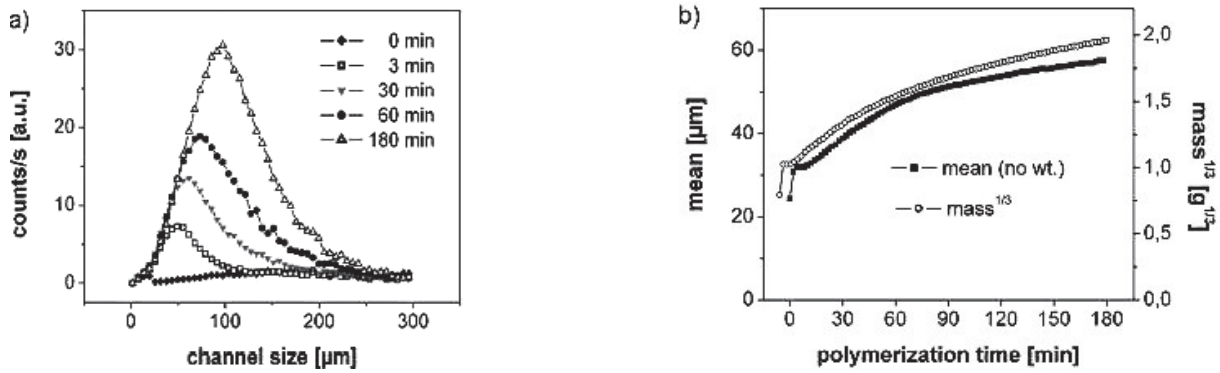

Fig. 3. Graphs taken from *Xalter* et al. [6], showing (a) square weighted CLDs (in the size range 1–300 mm) with on going polymerization for the ethylene polymerization with catalyst 1 and (b) comparison of the trend of the mean of the non-weighted CLDs and the cube root of the mass consumption

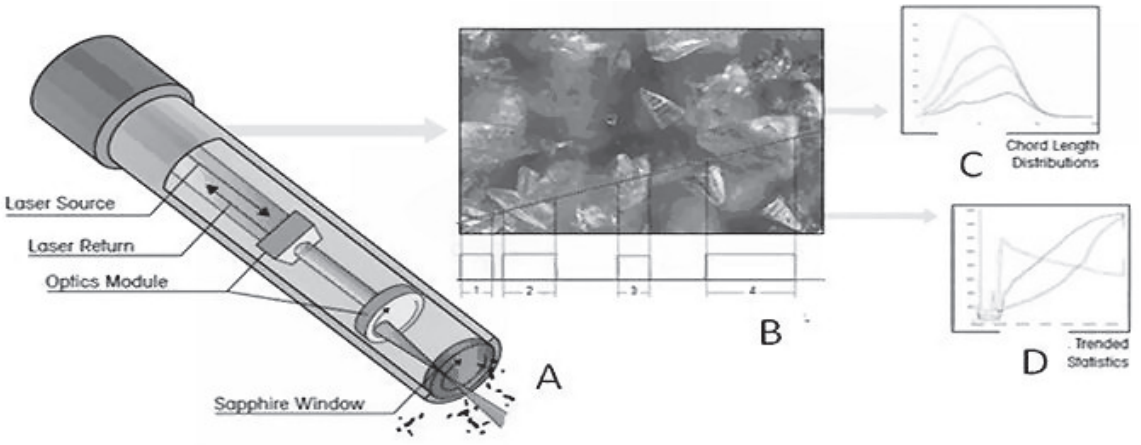

Fig. 4. Schematic describing the working principle of the FBRM technology

FBRM & PVM Technologies

METTLER TOLEDO FBRM® and PVM® technologies and expertise, enable scientists and engineers to use real-time particle and droplet distribution measurements to make more informed, faster decisions. Knowledge of the particle performance gained through FBRM® and PVM® technologies can cut months from development times, maximize process throughput, and optimize product quality. The application of FBRM® and PVM® ensures targeted particle distributions are achieved, robust repeatable processes are designed, downstream cycle times are maximized, and failures at the pilot and manufacturing scale are reduced.

PVM® is a real-time probe based vision tool which provides instant critical insight into crystal (Figure 4), particle, and droplet systems. PVM® enables chemists and engineers to detect and understand process changes that could take months to discover with traditional offline microscopy techniques. PVM® uses a high resolution CCD camera and internal illumination source to obtain high quality images even in dark and concentrated suspensions or emulsions. With no calibration needed and easy data interpretation, PVM®quickly provides critical knowledge of crystal, particle, and droplet behavior.

FBRM® is a highly precise and sensitive technology which tracks changes to particle dimension, particle shape, and particle count. Over a wide detection range, from 500 nm to 3 mm, measurements are acquired in real time while particles are forming and can still be modified enabling process optimization and control. No sampling or sample preparation is required – even in highly concentrated (70% and higher) and opaque suspensions. The FBRM® probe is immersed into a dilute or concentrated flowing slurry, droplet emulsion, or fluidized particle system (Figure 4).

A laser is focused to a fine spot at the sapphire window interface (A). A magnified view shows individual particle structures will backscatter the laser light back to the probe (B). These pulses of backscattered light are detected by the probe and translated into Chord Lengths based on the simple calculation of the scan speed (velocity) multiplied by the pulse width (time). A chord length (a fundamental measurement of particle dimension) is simply defined as the straight line distance from one edge of a particle or particle structure to another edge. Thousands of individual chord lengths are typically measured each second to produce the Chord Length Distribution (C).

The Chord Length Distribution is a ”fingerprint” of the particle system, and provides statistics to detect and monitor changes in particle dimension and particle count in real time (D). Unlike other particle analysis techniques, with FBRM® measurement there is no assumption of particle shape. This allows the fundamental measurement to be used to directly track changes in the particle dimension, shape, and count.

A series of industrial case studies focusing on both particulate and droplet processes such as crystallization, flocculation and polymerization will be presented and discussed in detail. These case studies will highlight the unique information and process understanding that these technologies provide and how this information is then quickly used to improve, optimize and ultimately control the processes under investigation.

LITERATURE

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