Breakthroughs in on-line process particle sizing

JASBIR SINGH

HEL Ltd
9-10 Capital Business Park
Manor Way
Borehamwood WD6 1GW, UK
www.helgroup.com

INTRODUCTION

Particle size data is important in many industrial applications; either during process development, or else for dry-product analysis. Analysis of product in dry form is in principle not difficult and many methods for sizing are available ranging from sieve trays to laser diffraction. Tracking particles on-line, while the chemistry is on-going, is much more difficult and the choice of tools is very limited.

There are several reasons why *in situ* analysis is important although the precise data required is not the same in all cases. The technically compelling case is that particles removed from the process environment are rarely the same, even before they are exposed to the external measuring technique. There are also practical limits – taking a representative sample is not always easy, assuming a sample can be taken at all. Also, samples are needed at times when important events take place and this is certainly not easy to decide in general.

APPLICATION AREAS FOR PARTICLE SIZING AND PROFILING

The ability to accurately track particle size and size-distribution during a process (i.e. on-line) can provide an understanding – and hence potentially an improvement – in product quality that is simply not possible by taking samples. Apart from the obvious advantage of time saving and convenience, the results from off-line sample analysis can often be totally different to the original material in the process vessel. The process conditions – high or low temperature and elevated pressure, for example – can also prohibit sampling.

In fermentations and other biological reactors, particle tracking can be used to monitor increase in biomass, essentially the product of the reaction. This is traditionally done by taking samples out of the reactor at frequent intervals and then using an off-line counting technique. This is not only time-consuming but presents an additional problem of losing sterility, leading to total loss of the batch. Optical density – a form of turbidity – is often used to track bio-activity but this does not always give sufficiently reliable quantitative information.

In the chemical process industry too, formation of solids is sometimes an integral part of the chemistry and the ability to monitor this on-line and use this information for feed-back control can be invaluable. Many polymerization processes – such as suspension polymerization – are examples of this.

Product blending is another application where knowledge of solids and the changes in size and number provide important information regarding the final product properties and on-line tracking can substantially reduce product waste and improve quality.

Particle monitoring is crucial also in the control of crystallisation; especially in the pharmaceutical industry where the FDA has given weight to this through the PAT initiative which encourages, more on-line and on-going product quality control. Effectiveness of drugs can be influenced by their crystalline form, and indeed different physical forms of the same chemical are listed in patents. The ability to monitor particle size is especially useful for troubleshooting in situations where filtration and drying become difficult or when product quality is a variable.

published by B5 srl
Via Cesare da Sesto, 10
20123 Milano - Italy
Tel. 0039 02 83241119
Fax 0039 02 8376457
www.b5srl.com

PROCESS TRENDING

In many research and industrial applications, it is sufficient to simply track changes in particle size or size distribution, rather than have absolute knowledge. For example in the context of crystallisation, the change in particle size profile within different process techniques could be very useful and sufficient to guide the development in the correct direction. In tracking biomass during fermentations, it is important to know that there is still activity and if it is increasing or decreasing without the need for absolute numbers.

At the simplest level, turbidity can provide this type of information and HEL have successfully used turbidity to monitor bio-activity and generate solubility data. The data in Figure 1 is typical of this – the turbidity is seen to rise and fall sharply as a solution is heated and cooled, indicating clearly points of solubility and re-crystallisation.

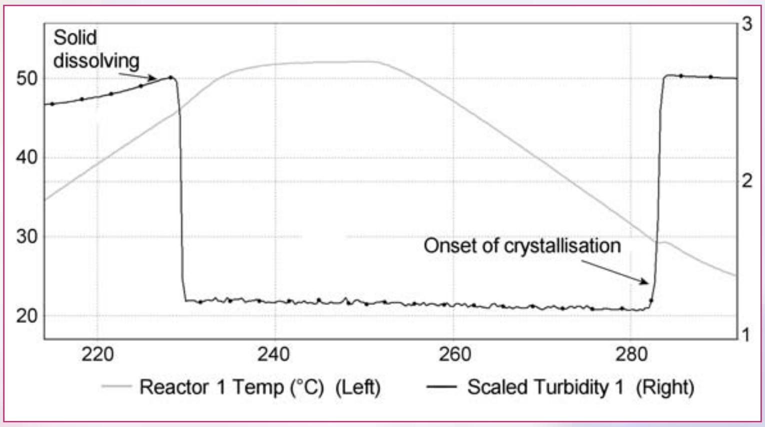

Figure 1 – Turbidity data for solubility information

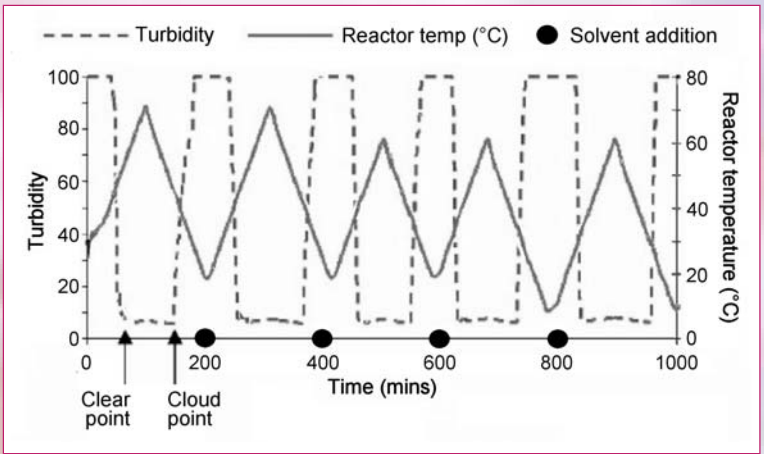

Figure 2 – Automated metastable zone width (MSZW) data reported by Astrazeneca

The difference between these two temperatures – so-called metastable zone width, MSZW – at a range of concentration can easily be generated when integrated into a computer controlled reactor platform. The data in Figure 2 was generated by Astrazeneca using the AutoLAB reactor control platform from HEL (Figure 3), whereby temperature cycling and dilution were performed through a user-defined recipe.

When more detailed information about the particles is required, laser reflection techniques are needed and one well known method is the FBRM™* (Mettler-Toledo) which is primarily a trending tool that produces statistics in real-time, based on particle size and population. Though it has being correctly described as a "sophisticated turbidity meter", it has proved very popular due to the fact that it can provide information on qualitative **changes** (ie trends) in particle size and population.

Particle sizing by laser reflection works by detection of light bounced off moving solid particles. Knowing the relative speeds of the particle and light source, and the time to pass from one solid edge to the next, allows the particle size to be calculated. FBRM™* uses a rotating laser source to increase the amount of space sampled and thus provide more reliable figures but suffers from the fact that it uses signals from a wide range of particles – many of which are not in focus and essentially contribute noise. As a result, the size information is only indicative rather than quantitative.

A device that substantially reduces the noise, by making use of reflections only from particles in focus is the **LasenTrack**™ and this has the potential to provide much more accurate numbers. In its simplest implementation, however, described as "**Fixed** Focus" (**F**F), the final result is only marginally better than FBRM™*. This is due to the fact that the sampled particle population at a fixed point can be rather small especially at dilute concentrations. The final result is that the simplest version of **LasenTrack**™ is generally also good for following trends and changes, and not to get absolute numbers, except at higher concentrations. The lack of moving parts does however have the advantage of being a much simpler and virtually maintenance free device.

PROCESS QUANTIFICATION

There are many applications where simply trending is not acceptable and greater precision is essential. Fortunately a solution is available and involves adding two extra features to the FF version. The **M**F (**Moving** Focus) version of **LasenTrack**™ does exactly this. Firstly, the laser source is not static

Figure 3 – AutoLAB reactor system for on-line particle tracking

* FBRM(R) is a Registered Trade Mark of Mettler Toledo International, Inc

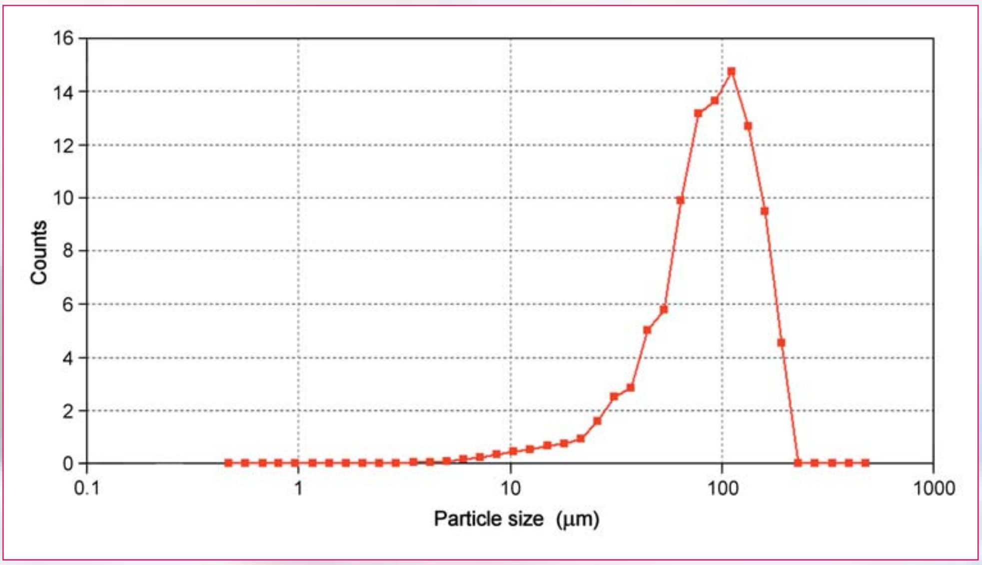

Figure 4 – Particle size data from LasenTrack™

Figure 5 – LasenTrack™ particle sizing probes for different sample sizes

but rotates at high speed and thus a larger number of particles are sampled. Secondly, the moving focus enables the depth of focus to be changed, giving 3-dimensional movement and the ability to measure a wider particle size range. For example, particles below 0.5 micron can be measured and counted, allowing crystallisation kinetics to be tracked from the nucleation stage to final product formation.

The 32-bit processor, used for data handling in all versions of **LasenTrack™**, also helps by enabling the data to be separated into discrete sizes rather than being forced to lump them into broad bands where important detail can be lost.

The availability of accurate particle size information on-line is rather like putting a microscope inside a process vessel – indeed the results have been confirmed by cross-checking with figures from both particle image analysers and microscopes. This is invaluable in situations where particle size is an important part of the process or product and also if the particle size gives important information about other properties that cannot directly be monitored. For example different polymorphs can have different sizes or shapes and this can be more reliably detected by a correctly configured **LasenTrack™**.

There remains one further limitation in laser reflection instruments and this is related to the fact that the depth of focus is fixed; as a consequence only a limited range of particle size can be measured – with a defined set up of the instruments. This final hurdle has been overcome by the **MM** (**Moving** focus, **Moving** laser) configuration of **LasenTrack™**. As a result, particles below 0.5 micron can be measured and counted – allowing for example a crystallisation to be tracked from the nucleation stage to final crystal formation.

CONCLUSIONS

The science of on-line particle measurement has progressed rapidly in recent years and it is now possible to get exactly the tools needed for an application. Conventional turbidity still has a role to play in qualitative monitoring of gross process changes but this can be improved substantially by different forms of laser reflection instruments. The most common – and simplest – forms are widely used to track changes in behaviour and this is adequate in many applications. However, more recent designs of laser reflection probes can be described as "process microscopes" because they now can report the true size of particles on-line and do this over a wide range of sizes, fully integrated into process equipment.