Application note 2017.04

Studying dynamic processes using particle size analysis

Gaining a complete understanding of a process is essential for effective process control and to consistently deliver a product of the correct specification and quality. It is therefore useful to visualize and evaluate processes in realtime in the laboratory. This application note provides illustrative examples of how particle size analysis using two technologies can be used to monitor the dissolution of solid dispersions. Crystallization processes can also be studied and an example of this type of study is described in Reference 1.

The work detailed in this note was conducted using the EyeTech particle size and shape analyzer which comprises two measurement channels, laser obscuration time (LOT) and image analysis. The Laser Obscuration technique[1] is ideally suited to making process measurements as the measurement is not influenced by temperature or changes in the composition of the suspending medium. It is also not necessary to provide information on the optical properties of the particles. Video capability enables the particle dispersion to be monitored continuously during the process and image analysis provides specific size and shape information as the process progresses.

Dissolution of solid dispersions

The preparation of solid dispersions is one way to improve the bioavailability of poorly soluble drugs. In this study we monitored the dissolution behaviour of batches of solid dispersions prepared using HPMCAS and felodipine (3:1 ratio) using image analysis and LOT. The dissolution behaviour was studied in pH7 buffer. Both image analysis and LOT measurements were made in a stirred 1cm cuvette. Data were acquired over 20 minutes in 60s cycles. The first experiment monitored the size of the particles using image analysis and the data are shown in Figure 1. The reduction in particle size can clearly be seen over the course of the dissolution process by plotting the D10, D50 and D90 percentiles. A complete particle size and shape distribution was acquired every 60s and Figure 2 shows the total number of particles detected in each measurement cycle together with the examples of frequency distributions at selected time points.

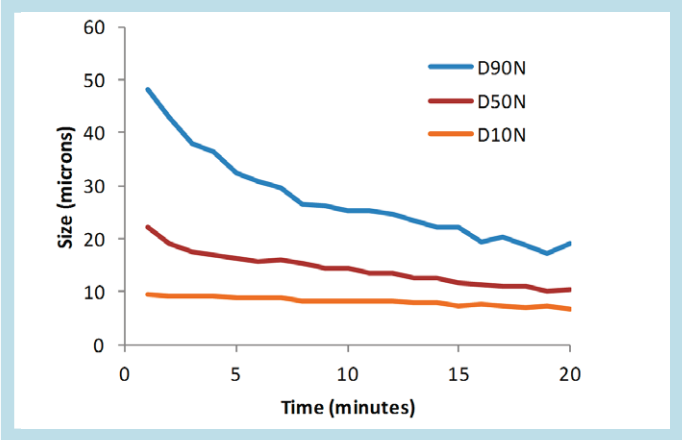

Figure 1. D10, D50 and D90 values obtained from image analysis for the dissolution of one HPMCAS and felodipine solid dispersion (SD8). The values refer to equivalent area diameters presented as a number distribution.

The reduction in the number of large particles is observed in the frequency distributions. Images of the dispersion acquired during the dissolution process support this trend (Figure 3) and they also provide an interesting observation: after approximately 5 minutes, the solid dispersion particles began to swell. This swelling is not detected by image analysis as the image processing parameters were configured only to describe the outlines of high-contrast particles. The swelling of particles is exhibited by areas of low contrast. However, this phenomenon can be seen in the particle size data determined using a different measurement technology, LOT, as shown in Figure 4. The increase in particle size seen at approximately five minutes was consistently observed and aligned with visual observations.

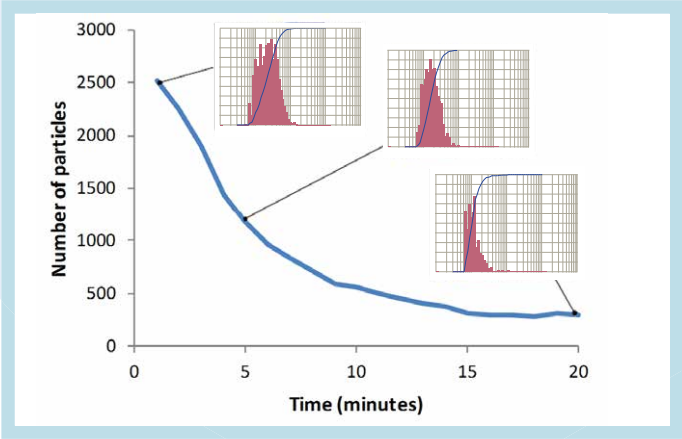

Figure 2. The total number of particles over the course of the dissolution experiment determined by image analysis together with frequency distributions of equivalent area diameter.

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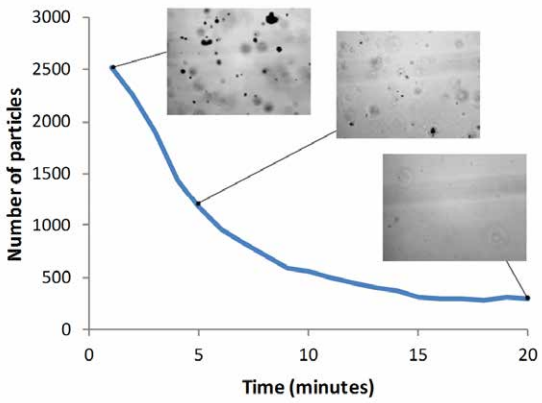

Figure 3. The total number of particles determined by image analysis together with images of the sample dispersion for the dissolution of HPMCAS/felodipine solid dispersions in pH7 buffer. Swelling of particles was observed after approximately five minutes and is shown in the images acquired during sample dissolution.

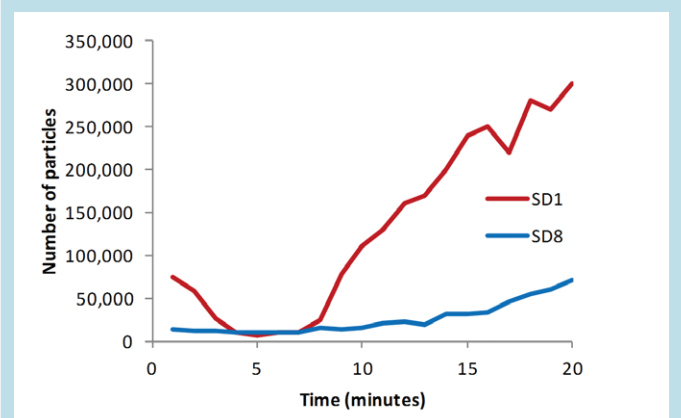

Figure 5. LOT data for two batches of HPMCAS/felodipine solid dispersions in pH7 buffer. The graph shows that the number particles increases either as a result of fragmentation of solid dispersion particles or precipitation of drug substance.

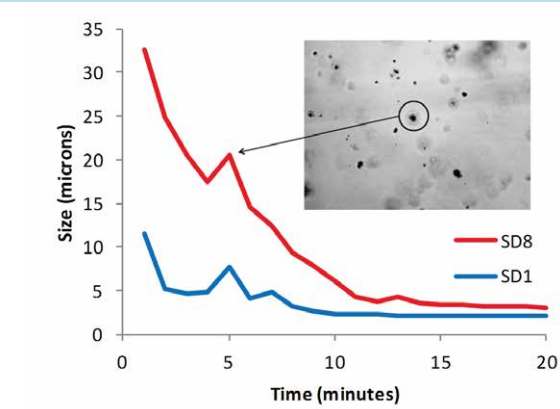

Figure 4. LOT (number distribution) data for dissolution of two HPMCAS/felodipine solid dispersions in pH7 buffer (SD1 and SD8). The swelling of particles is observed after approximately five minutes in both batches tested.

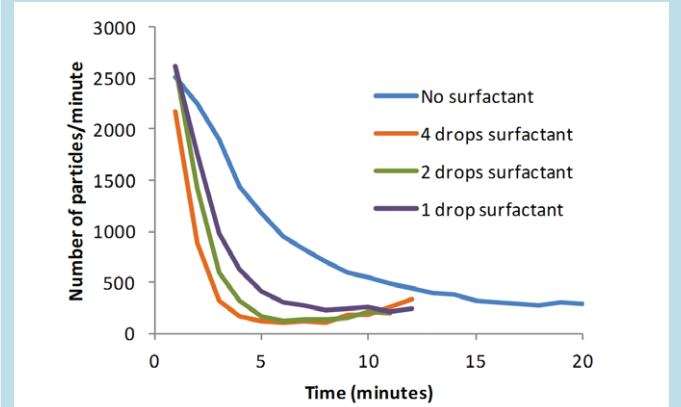

Figure 6. The total number of particles determined by image analysis for the dissolution of HPMCAS/felodipine solid dispersions in pH7 buffer with varying amounts of Triton X solution 0.5%.

The LOT data also show another interesting trend: the number of particles in suspension increases as the dissolution process progresses (Figure 5). This phenomenon, which requires further investigation, can be rationalized as an increasing number of very small particles arising from the fragmenting and dissolving solid dispersion or precipitation of drug substance. These particles were too small for detection using image analysis with the instrument configuration used for the experiment.

It is also possible to investigate the effect of additives such as surfactants on the dissolution behaviour and Figure 6 shows how the surfactant Triton X influences the dissolution by increasing the rate at which the particles dissolve. Plotting the number of particles shows that the dissolution rate increases with increasing amounts of surfactant.

Summary

The use of both imaging techniques and LOT provides a useful and flexible tool for investigating dissolution phenomena, enabling quantitative measurements to be correlated with visual observations.

References

1. AmbiValue application note, 2017.01 Particle size analysis related to dissolution and crystallization studies.