In-Process Droplet Size Analysis of Pharmaceutical Emulsions

Emulsions are two phase systems composed of a dispersed phase (the droplets or particles) and a continuous phase (liquid diluent such as water). The size of the droplets in the dispersed phase is critically important. To date almost all droplet size measurements are made in the laboratory. Now these measurements can be measured continuously using the Entegris Mini dynamic light scattering (DLS) system.

INTRODUCTION

There are various types of emulsions including oil on water (OIW), water in oil (WIO), and complex double emulsions. Most pharmaceutical emulsions are oil in water emulsions where the active ingredient is in the oil phase and the dispersed phase is water. If the drug delivery route is internal (swallowed or injected) the product is typically called an emulsion. If the drug delivery route is topical (spread on the skin or through a patch) the product is typically called a cream or lotion.

The droplet size is important for quality and stability reasons.[1] The emulsions droplet size is sometimes categorized into three ranges:[2]

Type	Size Range
Macroemulsions	0.1 – 100 µm
Microemulsions	5 – 50 nm
Nanoemulsions	<100 nm

PROCESSES

Various types of process equipment are available for creating suspensions and emulsions at both the laboratory and commercial scale including propeller mixers, turbine mixers, homogenizers, ultrasonicators, colloid mills, microfluidizers.[3] A basic process flow chart for manufacturing a lipid emulsion is shown in Figure 1.

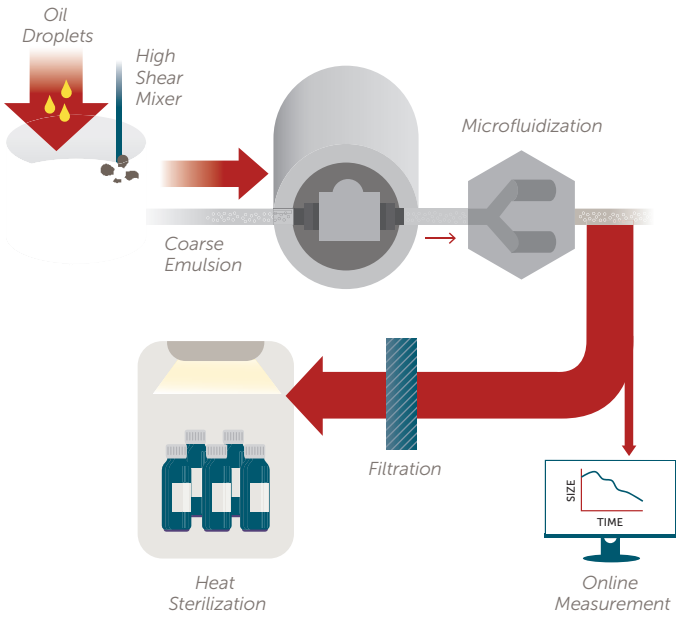

Figure 1. Emulsion process flow chart.

DLS

Laboratory DLS instruments are the most common analytical technique used to measure the droplet size of micro and nano emulsions. Testing the droplet size of lipid injectable emulsions is thoroughly described in USP 729.[4,5] DLS or laser diffraction are used to measure the mean size (Method I) and single particle optical sizing (SPOS) is used to measure the tail (Method II) of the distribution greater than 5 µm. The mean size must be below 500 nm in order to pass the Method I specification. These tests are all currently performed on lab systems such as the Entegris Nicomp system. With the Entegris Mini DLS system these measurements can now also be performed continuously in-process.

MINI DLS SYSTEM

The Mini DLS is a flexible and elegant solution that can be adapted to a wide range of nanoparticle manufacturing processes including milling, homogenizing, or microfluidizers. A pressurized stream of suspension product connects to the Mini DLS system. This sample is then automatically diluted to achieve an appropriate light scattering intensity for the measurement (Figure 2). The particle size distribution is determined and the system is automatically flushed and cleaned before the measurement sequence is repeated.

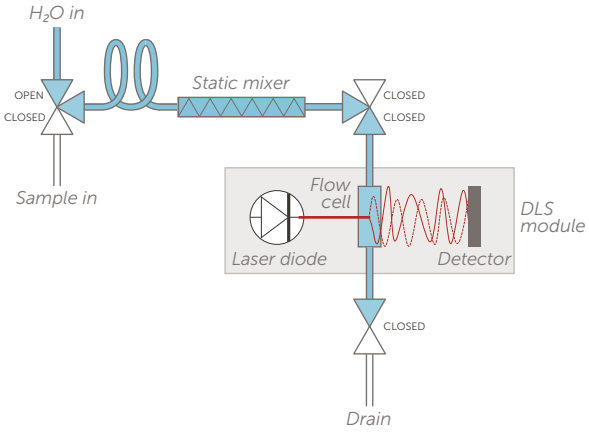

Figure 2. Mini DLS system flow chart.

The benefits of using the Mini DLS include:

- Automated sampling and measurement to eliminate operator and lab resources
- Flexible protocols to optimize measurement to application
- Continuous data to track changes in particle size distribution
- Easy data transfer to process monitoring control software

The operating screen for the Mini DLS shown in Figure 3 provides a graphical user interface to monitor the system operation.

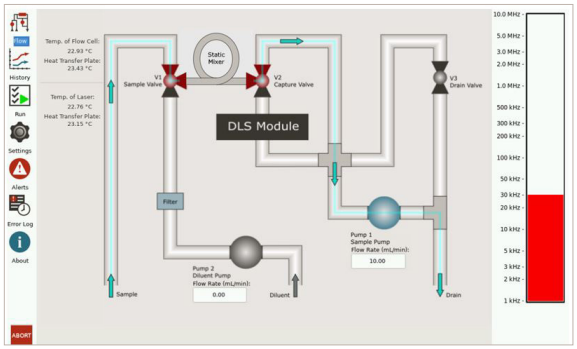

Figure 3. Mini DLS control screen.

The bar on the left side includes icons used to select which display to view. The flow diagram in the middle shows the dilution fluidics and current operating conditions. The bar graph on the right shows the current the light scattering level indicator in kHz.

A typical result for the Mini DLS system is shown in Figure 4.

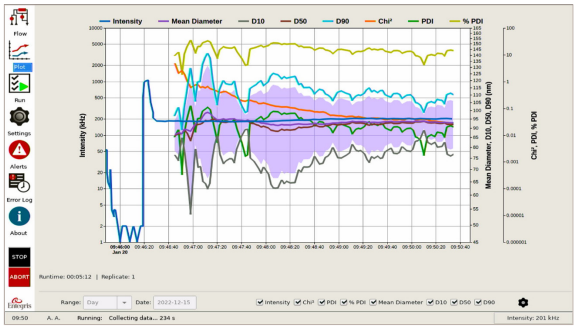

Figure 4. Size vs. time plot.

The result values plotted vs time include:

Intensity	light scattering in kHz
Mean diameter	nanometers
D10, D50, D90	key sizes in nanometers
Chi^2	goodness of fit parameter (dimensionless)
PDI	width of distribution (dimensionless)
%PDI	width of distribution as a percent

EXPERIMENTAL – SIMULATED INLINE MEASUREMENTS

The most typical samples analyzed by the Mini DLS system are pharmaceutical emulsions. The results shown here are emulsions sampled from a beaker containing the pre-diluted emulsion. The sample is pulled from the beaker by the Sample pump #1 as shown in Figure 3. For in-process pressurized lines sample pump #1 is not used.

Intralipid is a synthetic fat emulsion composed of soybean oil, glycerin, egg phospholipids, glycerol, and water. It is a source of calories and essential fatty acids used to provide calories to patients who are getting their nutrition through an injection into the vein. Figure 5 shows two measurements on the Mini DLS system of an older 10% Intralipid sample. The white space between the sample results is the cleanup time of two minutes. The intensity mean size should be less than 500 nm, and in these results lies between 360 – 380 nm. The PDI values average slightly over 0.12. Both the intensity mean and the PDI values may be higher than expected in a new batch due to the age of the sample.

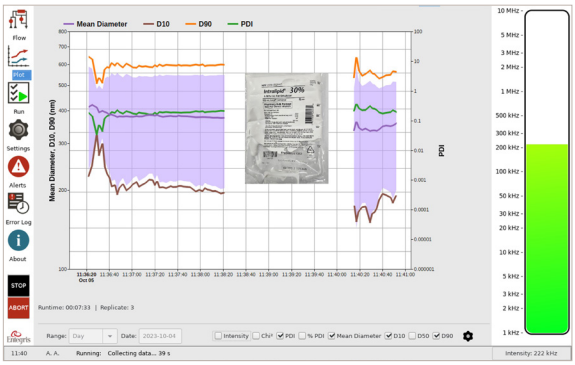

Figure 5. Intralipid size and PDI vs. time.

Propofol is a short acting medication that results in a decreased level of consciousness and lack of memory for events. It is used for general anesthesia and sedation. The intensity mean size should be between 150 – 300 nm. In the results shown in Figure 6 collected on the Mini DLS system the intensity mean results lie between 190 – 220 nm, with a PDI value of > 1. The PDI value could again be elevated due to the age of this sample. Note the intensity mean is still decreasing during the two-minute measurement, indicating that a longer analysis time would be recommended due to the polydispersity of the sample. A typical analysis time for samples with PDI > 1 would be at least five minutes.

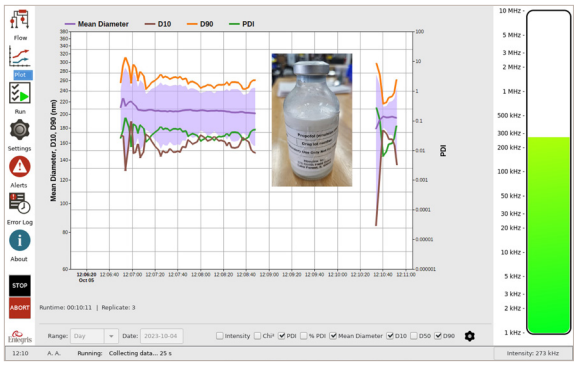

Figure 6. Propofol size and PDI vs. time.

Lipomed 20% is administered as part of a total parenteral nutrition (TPN) regimen. The sample is composed of soya oil, medium-chain triglycerides, egg lecithin, tocopherol, sodium oleate, sodium hydroxide and water for injection. Figure 8 shows the mean size and PDI vs. time results for an older Lipomed sample. The intensity mean size averages around 290 nm and the PDI values is just below 0.1.

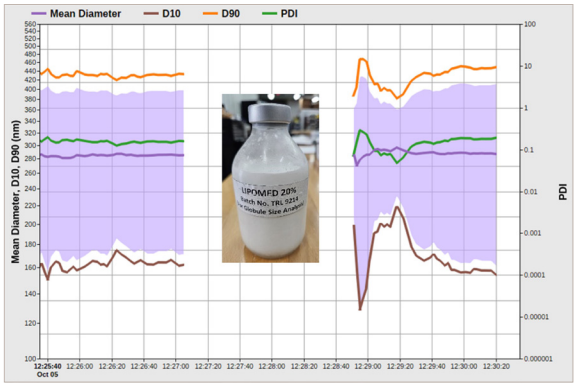

Figure 7. Lipomed size and PDI vs. time.

EXPERIMENTAL – IN PROCESS

The Entegris inline DLS system was installed downstream of a high-pressure homogenizer and set up such that it can grab an emulsion sample from the process stream every ~2 minutes. The emulsion sample is diluted in a buffer similar to the process fluid, and autodiluted to a concentration that produces ideal light scattering intensity. An initial experiment established the relationship between homogenizer pressure and produced droplet size – the response of size-to-pressure is ~9 nm per 1,000 psig, see Figure 8.

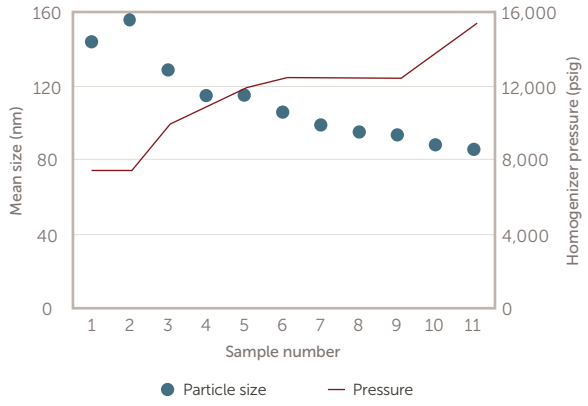

Figure 8. Size vs. pressure response.

Next a product batch made with slightly different process conditions that resulted in slightly smaller than target size for the first two in process samples. After adjusting the pressure, the size was brought back to target for the final four samples, see Figure 9.

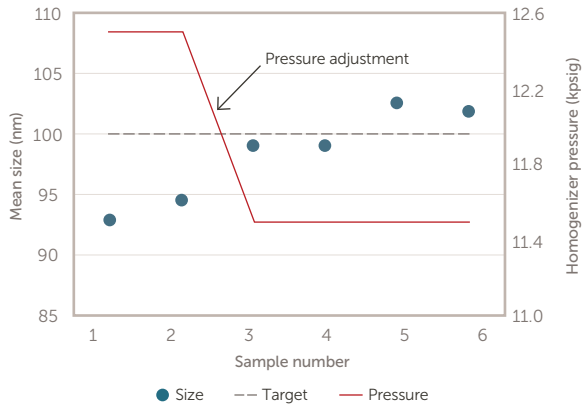

Figure 9. Size vs. pressure for production batch.

CONCLUSION

Emulsion droplet/particle size can be continuously monitored with the Mini DLS system, providing process control and ensuring product quality. The easy user interface and touchscreen makes creating protocols and conducting measurements straight forward. Results are available as a function of time, or detailed information can be displayed for individual measurements. Results can be exported in JSON standard file format into data acquisition systems.

References

[1] Entegris application note, "Emulsion Stability", https://www.entegris.com/content/dam/shared-product-assets/sensing-and-control/appnote-emulsion-stability-10544.pdf

[2] McClements, D.J., "Nanoemulsions versus microemulsions: terminology, differences, and similarities", Soft Matter, 2012, 8, 1719–1729 | 1719

[3] Entegris application note, "Size Reduction by a Microfluidizer", https://www.entegris.com/content/dam/product-assets/nicompnanodlszlssystems/appnote-size-reduction-by-microfluidizer-10541.pdf

[4] USP <729> "Globule Size Distribution in Lipid Injectable Emulsions"

[5] Entegris application note, "Globule Size Distribution in Lipid Injectable Emulsions", https://www.entegris.com/content/dam/product-assets/accusizerspossystems/appnote-usp-729-globule-size-distribution-lipid-injectable-emulsions-10537.pdf

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