

USP <729> Globule Size Distribution in Lipid Injectable Emulsions

Nicomp[®] and AccuSizer[®]

The size of the lipid droplets is critical because larger size fat globules (>5 μm) can be trapped in the lungs, and are also an indicator that the emulsion is destabilizing. The USP <729> test requires two analytical techniques: DLS, or laser diffraction, to measure the mean and standard deviation of the distribution, and light obscuration to measure the large tails >5 μm . The Entegris Nicomp[®] can be used to measure the mean size, and the AccuSizer[®] is the preferred method to measure the tails >5 μm .

INTRODUCTION

Injectable lipid emulsions (Figure 1) have been clinically used for decades as an energy source for hospitalized patients by providing essential fatty acids and vitamins. Intralipid, and other balanced lipid emulsions, provide essential fatty acids, linoleic acid (LA), an omega-6 fatty acid, alpha-linolenic acid (ALA), an omega-3 fatty acid.

The critical size characteristics of lipid injectable emulsions include the mean droplet size and the large diameter tail >5 μm . No single technique, or test, can adequately measure both parameters so two methods exist in USP <729>:

Method I—Light scattering method

Either dynamic light scattering (DLS), or laser diffraction (referred to as classic light scattering in the method), is used to measure the mean size. The intensity weighted mean diameter must be <0.5 μm , and the chi square parameter must be acceptably low.



Figure 1.

Method II—Light obscuration method

Measurement of large globule content by single particle optical sizing (SPOS) employing light obscuration or extinction method. The volume weighted percent above 5 μm must not exceed 0.05%.

Method I

The Nicomp DLS system (Figure 2) is the ideal system to use for Method I testing to determine the mean droplet size. Follow these steps to comply with the requirements set in USP <729>:

- Verify system performance with PSL standards at 100, 250 and 400 nm.
- The coefficient of variation (COV) must be <10% of the reference values.
- Dilute the sample to an appropriate concentration and measure the size at 90°. Check that the chi square error calculation is acceptably low, and record the intensity weighted mean diameter. This value must be <0.5 μm (500 nm).



Figure 2. The Nicomp DLS system

Method II

The large diameter droplet tails is measured using a light obscuration/extinction liquid particle counter that employs the single particle optical sizing (SPOS) technique, such as the AccuSizer (Figure 3). Additional guidance on using this technique can be found in USP<788> and USP <1788>.



Figure 3. AccuSizer APS

Checking the sizing and counting accuracy of the light obscuration instrument should be performed using two different size standards of ~5 and 10 μm (triplicate analyses per size). The average mean diameter on a number weighted basis should be within 10% of the expected value.

Set the lower size limit at 1.8 μm , and upper limit at 50 μm . Vary the measurement time so that there is a factor of two difference >5 μm between two runs. The volume-weighted result >5 μm (PFAT5) must be <0.05%.

TYPICAL RESULTS

A typical Nicomp DLS Method I result is shown in Figure 4. Notice that the chi square calculation is acceptably low at 0.43 and the mean diameter is 313.2 nm, well below the 500 nm limit.

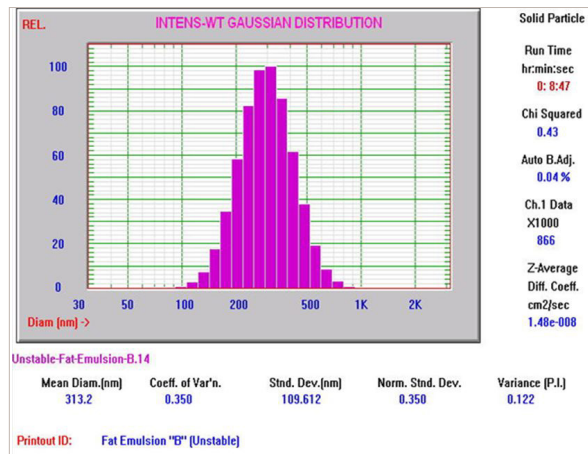


Figure 4. Nicomp DLS Method I result

Typical AccuSizer Method II results are shown in Figures 5 and 6. Notice how the >0.5 μm is considerably larger in the bad result, see Figure 6.

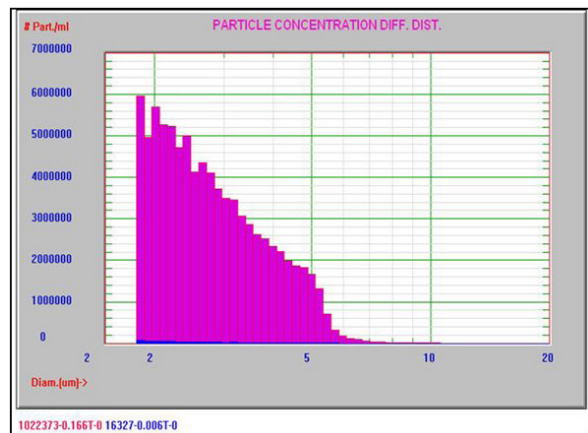


Figure 5. AccuSizer Method II good result

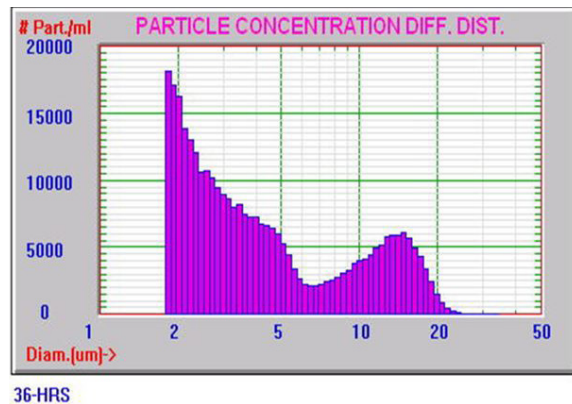


Figure 6. AccuSizer Method II bad result

CONCLUSIONS

Entegris provides ideal solutions for both Method I, with the Nicomp DLS system, and Method II, with the AccuSizer SPOS system. The AccuSizer has become the industry standard for Method II tests for the PFAT 5 due to the highest resolution and best autodilution features available.

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