Effect of Silicone Oil Droplets in Pre-Filled Syringes

AccuSizer® SIS

USP tests <787>[1] and <788>[2] describe how to measure subvisible particulate matter in therapeutic proteins and parenteral drugs. Many of these drug products are packaged in prefilled syringes, that may contain silicone oil, to reduce the force required to administer the drug. This silicone oil can form emulsion droplets that will be counted as subvisible particles. This application note investigates the effect silicone oil droplets have on the particle counts reported using the AccuSizer® liquid particle counter.

INTRODUCTION

Particulate matter in injectable drugs is measured in both the visible and subvisible ranges. Measurements in the subvisible range are typically made by liquid particle counter, or by microscopic analysis of the sample trapped on a filter. The filter test method was introduced as an alternative methodology to remove the subvisible particle counts due to the presence of silicone oil droplets introduced by stoppers, barrels, and plungers of prefilled syringes. While the intrinsic silicone oil droplets may be less of a health hazard than extrinsic contaminants like fibers or metal shards, they will be detected by liquid particle counters. Prefilled saline syringes with silicone oil on and/or in the barrel, will generate a wide variety of additional particle counts due to the silicone oil emulsion droplets.

MATERIALS

The syringes used in this study were BD PosiFlush Normal Saline Syringe, 10 mL, Ref no. 306546, see Figure 1. Medical grade silicone oil is applied to the stopper and to the inside wall of the syringe barrel, which facilitates consistently smooth stopper actions and predictable flush installations.

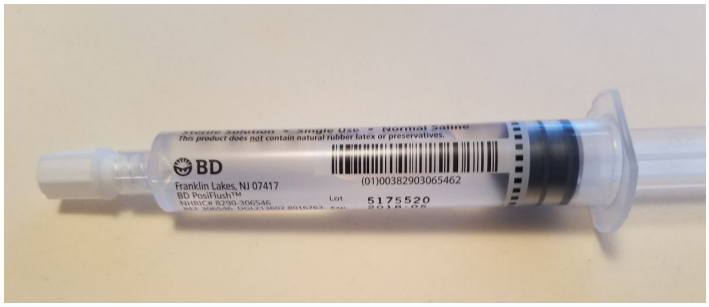

Figure 1.

Measurements were made of the saline alone present in the syringes and saline mixed with protein. The protein used was Athens Research & Technology, Immunoglobin G, Human Plasma, Lot no. IG2014-02, Cat no. 16-16-090707, lyophilized from 22.4 mL 20 mM phosphate buffer, pH 7.4, w/150 mM NaCal & 0.05% sodium azide. The protein was dispersed in filtered Phosphate buffered saline (PBS) tablet, Sigma Aldrich P4417-50TAB.

METHODOLOGY

The particle counts from the syringes were first taken directly from the syringe without activation, either by inserting a sample tube through the outlet for the AccuSizer, by removing the barrel and pouring the sample into a clean beaker, or with activation by pushing the plunger driving the sample into a clean beaker.

The IgG was prepared at 0.1 mg/mL in filtered PBS and analyzed. Then 0.5 mL IgG was pipetted into 10 mL of either filtered PBS or saline from a prefilled syringe. Measurements were made on the AccuSizer without dilution using 1 mL of sample, measured three times to check repeatability.

INSTRUMENTATION

The AccuSizer FX Nano SIS system equipped with two sensors: LE-400; 0.5 – 100 µm and FX Nano; 0.15 – 10 µm, see Figure 2. The SIS sampler provides accurate sample volume down to 100 µL with sample recovery.

Figure 2. The AccuSizer FX Nano SIS system

Note: Showing only the syringe sampler and two sensors, not the pulse height analyzer/counter or computer

RESULTS

Eight syringes were chosen at random from the box of twenty four. Four were analyzed using only the LE400 sensor without activating the plunger, see Figure 3, and four were measured after activating the plunger to drive the sample into a clean beaker, see Figure 4. Particle size in µm is plotted on the x axis and concentration in particles/mL is plotted on the y axis.

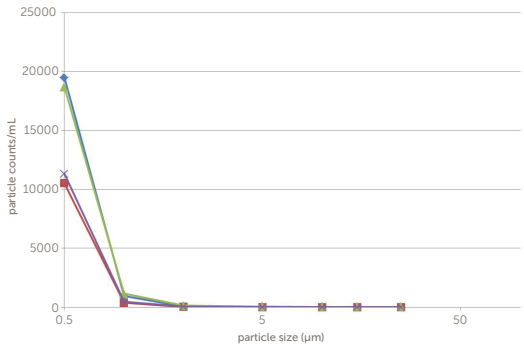

Figure 3. Without activation, sampled directly from the syringe

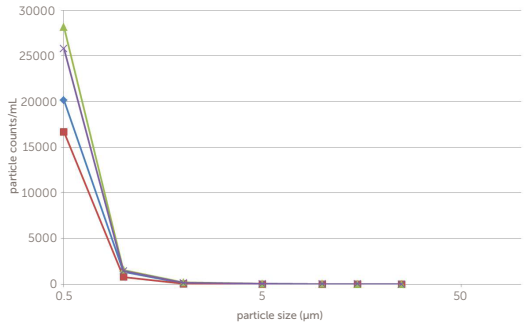

Figure 4. With activation, after extracting the sample by pushing the plunger

DISCUSSION

This experiment was designed expecting that activating the plunger would create a dramatic increase in particle concentration that could be attributed directly to the creation of additional silicone oil emulsion droplets. Instead, the syringe-to-syringe variation reported particle concentration was on par with the variation between activated vs. not activated samples. Two not activated results in Figure 3, have ~10,000 particles/mL >0.5 µm while the other two have ~20,000 particles/mL >0.5 µm. The activated results vary from ~16,000 particles/mL >0.5 µm to 28,000 particles/mL >0.5 µm.

PROTEIN RESULTS

USP <787> was written for therapeutic proteins and while the pass/fail criteria are set at 10 and 25 µm, identical to USP <788>, the FDA suggests measuring at smaller particle sizes to better understand which formulations lead to more or less aggregation.

The saline from three activated syringes and the IgG protein in filtered PBS were measured on the AccuSizer FX Nano SIS system using both sensors, see Figure 5 and Figure 6. Then the protein was diluted 2:1 using filtered PBS (blue) and saline from the activated syringes, see Figure 7.

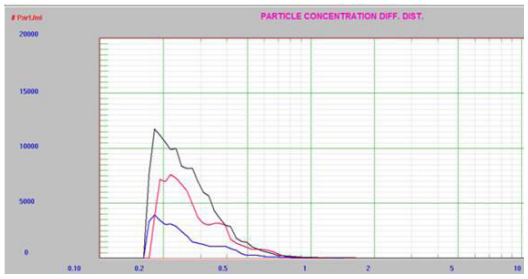

Figure 5. Saline (and silicone oil droplets) from three activated syringes

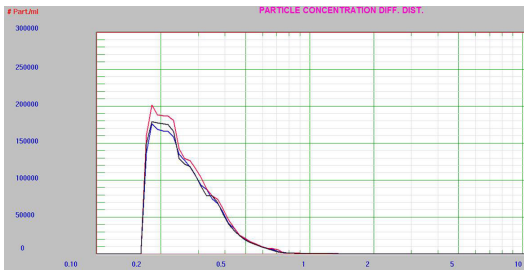

Figure 6. IgG protein in filtered PBS

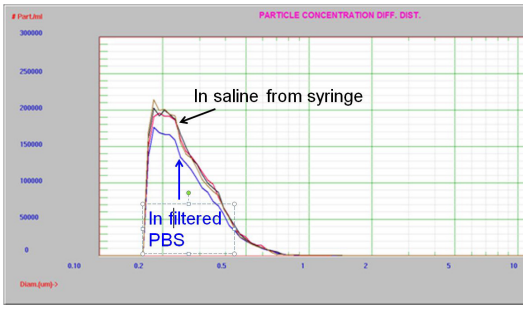

Figure 7. IgG diluted with PBS and saline from syringes

DISCUSSION

The differences in the particle count, assuming a large portion results from the silicone oil emulsion droplets, from syringe-to-syringe was best observed at the smaller particle sizes, as seen in Figure 5. The AccuSizer FX Nano SIS system was able to detect the smaller particles at 0.2 – 0.5 µm since it has the sensitivity to measure down to 0.15 µm. This same small particle sensitivity is sought after in many applications. It is most highly desirable when analyzing proteins, both protein in filtered PBS, as shown in Figure 6 and the protein/saline mixture seen in Figure 7.

CONCLUSIONS

The AccuSizer FX Nano SIS system meets all requirements defined in USP tests <787> and <788>. It is the ideal system for analyzing subvisible particles because it has the sensitivity to detect particles down to .15 µm, using sample volumes down to 100 µL. The sensitivity in this lower range provides much more interesting results that can aid researchers performing therapeutic protein aggregation studies[3] in injectables and parenteral drugs. The unique technology designed into the AccuSizer FX Nano SIS provides capabilities not available in any other liquid particle analyzer. This is true partly because this is not just a liquid particle counter, it is a sophisticated particle size analyzer as well.

References

[1] USP <787>, Subvisible particulate matter in therapeutic protein injections

[2] USP <788>, Particulate matter in injections

[3] Entegris Application Note Protein Aggregation

FOR MORE INFORMATION

Please call your Regional Customer Service Center today to learn what Entegris can do for you. Visit entegris.com and select the Contact Us link to find the customer service center nearest you.

TERMS AND CONDITIONS OF SALE

All purchases are subject to Entegris' Terms and Conditions of Sale. To view and print this information, visit entegris.com and select the Terms & Conditions link in the footer.

Entegris

Corporate Headquarters
129 Concord Road
Billerica, MA 01821
USA

Customer Service
Tel +1 952 556 4181
Fax +1 952 556 8022
Toll Free 800 394 4083