An Analysis of Polymer Nanoparticle Size Distribution Using Cryo-EM and a Comparison to Other Techniques

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INTRODUCTION

This paper describes the study of the fluorescent polystyrene nanoparticles (G25) size distribution (PSD) using different techniques such as the Atomic Force Microscope (AFM), the Scanning Mobility Particle Sizer [1] (SMPS), Dynamic Light Scattering (DLS), and Cryo-Electron Microscopy (Cryo-EM).[2] Among these tools, Cryo-EM is confirmed as the most powerful structure determining technique that is well-suited to studying polymer nanoparticles in solution. Most importantly, the frozen-hydrated sample preparation allows the specimens to be kept and imaged in a state closest to how they naturally appear in water (native status). Furthermore, the high-resolution photos make it possible to detect the polymer particles down to 1 nm.

To evaluate the performance of advanced filters and mimic the behavior of natural polydisperse particles, we developed the G25 retention method.[3] This technique is now confirmed as a robust test method for sub-10 nm filters used to enable defect reduction techniques for advanced semiconductor manufacturing of today's complex electronic devices. Inline particle counters and wafer scanners are not currently capable of detecting these contaminants less than 10 nm. Therefore, to reveal the correct PSD of G25, especially to know the particle population in the range of 1–10 nm, becomes very important for filter evaluation.

EXPERIMENTAL

Instruments:

- Thermo Scientific Talos Arctica Cryo-TEM
- FastScan AFM (Bruker)
- TSI Model 3936 SMPS
- Dynamic Light Scattering (DLS)

Samples: Thermo Fisher Scientific Fluorescent polystyrene latex (G25) beads

RESULTS AND DISCUSSION

Size distribution study with different methods

1. DLS Results

In the DLS test, the scattering light intensity-weighted size distribution shows the PSD for G25 where the average size is 25 nm (see Figure 1). Although it can be converted into a number-weighted size distribution, the result is not accurate, sometimes misleading.

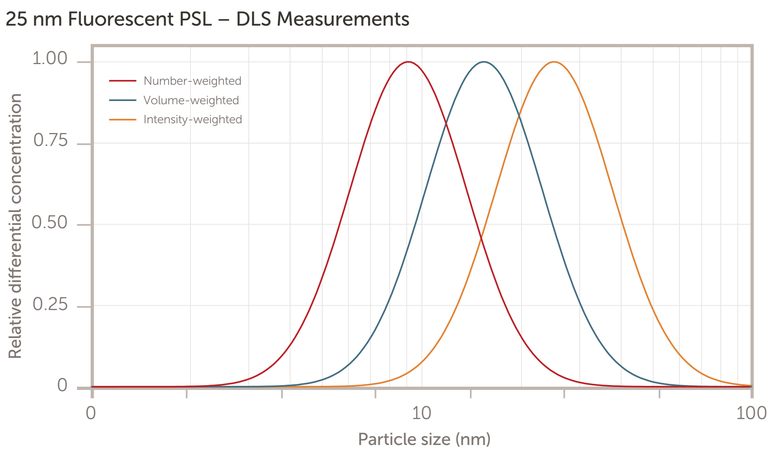

Figure 1. G25 particle size distribution collected with DLS. Orange is intensity-weighted size distribution which can be converted into volume- (blue) and number- (red) weighted sized distributions.

2. AFM Test

The spherical PSL beads are suitable to be measured by the AFM technique because the AFM measures height. In this study, the wafer surface is used for the sample preparation; 100 5×5 µm images were scanned and analyzed.

3. Scanning Mobility Particle Sizer (SMPS)[1]

An ultrafine nebulizer and a scanning mobility particle sizer (SMPS) are used for collecting G25 particle sizes and their PSD. The aerosol PSD is measured using an SMPS system capable of measuring particles as small as 5 nm in size.

4. Cryo-EM Test

A typical image of G25 is shown in Figure 2. Interestingly, more particles are found close to the edge due to the thickness of the ice film. For PSD analysis, a total of 40 images were analyzed (Figure 3).

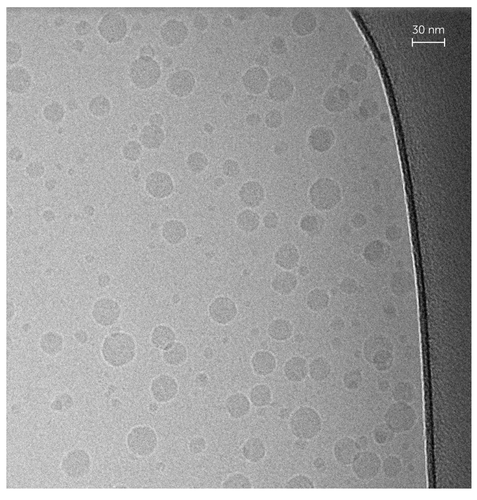

Figure 2. Cryo-EM image of G25 polymer particles.

DISCUSSIONS

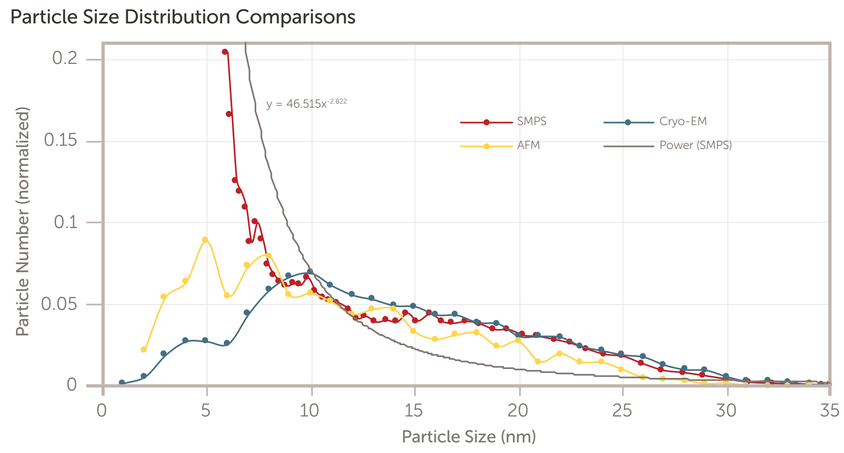

Figure 3. Overlapped graph of three PSD results of different techniques (Cryo-EM, SMPS, and AFM).

DLS results can be converted from intensity-weighted PSD into Number-weighted PSD, which provides an average size of 9 nm for G25 particles (Figure 1). However, it does not generate reliable PSD data due to the sample's polydisperse nature.

Figure 3 shows a comparison of the other three test methods. Interestingly, three curves intersect at 8 nm. When the particle size is bigger than 8 nm, three results show the same trend. However, when the size is less than 8 nm, the trends show quite a large difference. For Cryo-EM and AFM, both results have a decreasing trend when the particle size is smaller than 8 nm. The SMPS technique shows the number of particles increases similarly to a power-function (red dot in Figure 3) as the size decreases. The reason for this dramatic particle number increase is due to the large amount of dissolved NVR in the solution. The SMPS data could be misleading because the "power-function" theory is often incorrectly adopted when particles become smaller.

In the AFM test, the dissolved NVR affects the results as well. The PSD data shows this interference differently than the SMPS method. In the smaller size range (<8 nm), the AFM performs better than SMPS; it shows a similar trend as Cryo-EM does.

Based on these results, we conclude that the three methods agree when size >8 nm. However, only Cryo-EM can show the correct results for smaller particles (<8 nm). This is because this methodology has no dissolved NVR issues. Therefore, Cryo-EM is the best method to measure the size of polymer nanoparticles. Also, it can monitor if the particles are aggregated or not.

As a summary, Table 1 shows a comparison of the four methods.

Table 1. Four Technique Comparisons

Techniques	Cryo-EM	AFM	DLS	SMPS
Detectable size	Sub-1 nm	1 nm	1 nm	3–5 nm
NVR interference	No	Yes	No	Yes, strong
PSD study	Excellent	Possible	Not good for wide dispersed sample	>8 nm, okay
Test times	Long	Longest	Fast	Good
Particles in native	Yes	No	Yes	No
Cost	Expensive	Fair	Inexpensive, easy	Inexpensive
Sample concentration	>100 ppm	ppt–ppb	>1 ppm	ppb

CONCLUSIONS

Four critical techniques that can detect sub-10 nm nanoparticles are studied and compared using polydisperse polystyrene beads (G25). DLS shows the average size is 9 nm in N-weighted PSD but cannot provide the correct size distribution, while the other three tests can provide effective insight for particles above 8 nm. Cryo-EM has shown the most accurate results when the particles are smaller than 8 nm. Based on the analysis from dozens of Cryo-EM images, we concluded that G25 is a polydisperse particle ranging from 1 nm to 40 nm. Furthermore, the most significant particle size population is around 10 nm.

REFERENCES

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ACKNOWLEDGEMENT

The authors would like to thank Clint Haris and Haizheng Zhang for their continued support.

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