Laser diffraction versus Wetted Surface Area Comparison for a Milled API

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Application Note 110

Particle size measurements via laser diffraction have been the method of choice to characterize the changes in particle size as a function of milling time. However, recent advances in dispersion analysis offer a more rapid and sensitive measurement of changes in particle size than direct measurements of particle size.

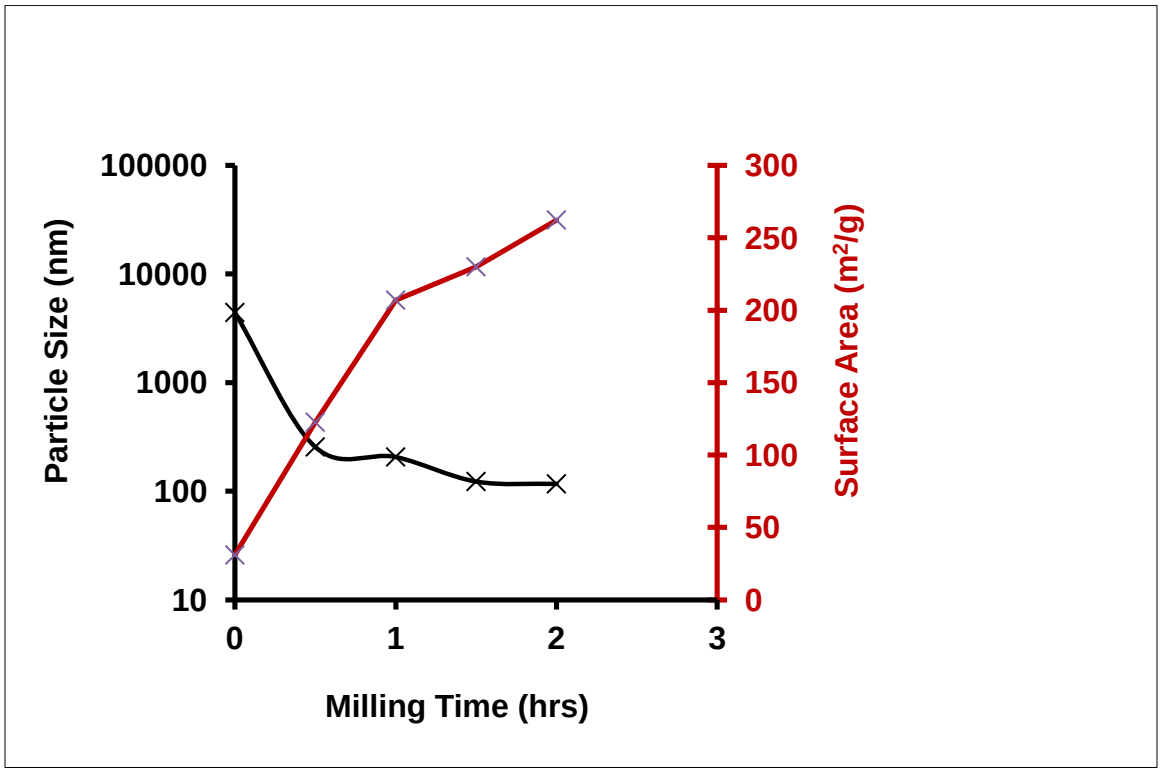
Laser diffraction relies on measuring the light scattered by particles to determine particle size distribution. Implicit in size analysis is the supposition that light diffracted by a single particle passes unobstructed to the light detecting sensors. The practical consequence of this constraint is that dispersions must be measured under very dilute conditions, i.e., <0.1%, Milling processes are performed at particle concentrations hundreds of times greater than can be used successfully in laser diffraction measurements, so samples must be diluted significantly in order to make accurate measurements. Even under dilute conditions, large particles can obscure the diffracted light from smaller particles. Consequently the ability to detect small particles amongst large particles is a challenge.

In addition, light scattered by small particles is diffracted to larger angles, and with substantially lower intensity in comparison with large particles. Accordingly, detecting the presence of fines in a milled material is challenging with laser diffraction.

Measurements of wetted surface area by NMR can overcome many of the inherent measurement limitations of laser diffraction. In comparison with large particles, small particles contribute a much higher percentage of the total surface area. Since large particles do not impact on the sensitivity of the surface area measurement, measurements via NMR are very sensitive to the presence of the smallest particle size fractions.

The data below compare wetted surface area via NMR with particle size measurements via laser diffraction as a function of milling time. Although the size measurements appear to plateau after 30 minutes milling time, surface area measurements confirm the continuous reduction in particle size as a function of milling time for this pharmaceutical API.

Note that the presence of API fines in a drug product can significantly alter the pharmacokinetics of drug absorption and in some cases, result in cytotoxicity. In addition, the presence of fines can cause issues with the physical stability of the drug product. The surfactant loading required to stabilize a colloidal dispersion is directly related to the wetted surface of the particle, hence direct measurements of the wetted surface area are critical to formulation development.


100000
10000
1000
100
10
Particle Size (nm)
300
250
200
150
100
50
0
Surface Area (m²/g)
0
1
2
3
Milling Time (hrs)