Particle Size Measurement of Nanoparticles for Drug Delivery Applications

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Topics Covered

Introduction

Over the past few years, nanomedicine research has grown quickly with most of the focus being given on drug delivery.

Nanoparticles offer a number of benefits including reduced toxicity, minimum side effects and targeted efficacy. However, it is very important to control the size of these nanoparticles.

Although most of the particle size measurements are performed in the laboratory, the same can be performed at-line in the production setting. This article describes the ground-breaking work carried out at BIND Therapeutics in Cambridge, Massachusetts to implement online dynamic light scattering (DLS) measurements within the production process of nanoparticle drug candidate, Accurins.

Accurins

Biopharmaceutical company BIND Therapeutics specializes in developing targeted nanoparticle technologies known as Accurins (Figure 1). Accurins will be utilized for treating serious diseases such as cancer. The company is developing a nanotechnology-enabled platform by integrating controlled release polymer systems, targeting and delivering large payloads of therapeutic agents. This platform will lead to a new class of targeted therapeutics.

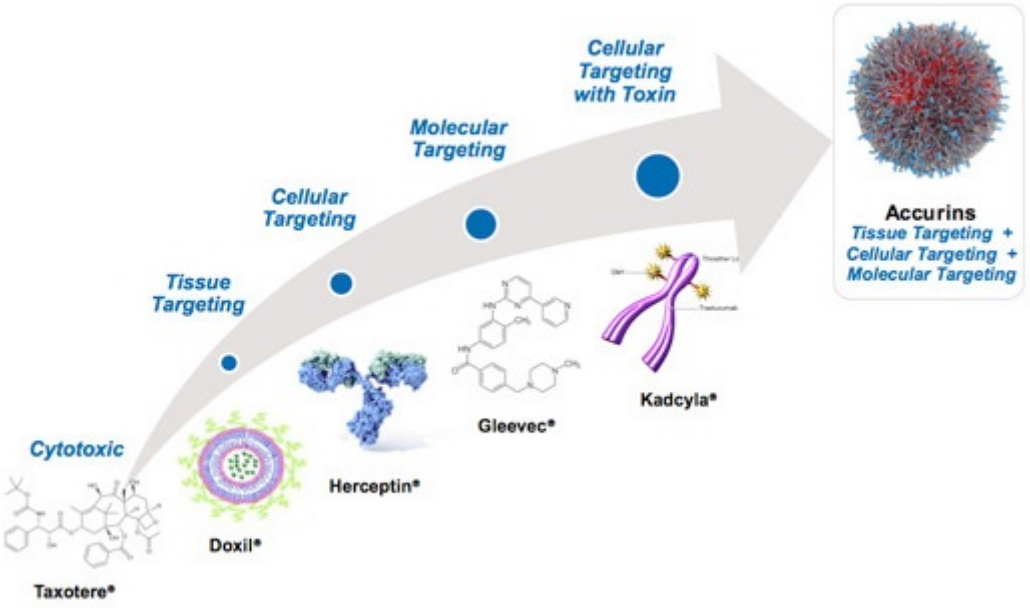

Figure 1. *BIND Accurins technology*

Accurins contain polylactide - poly ethylene glycol (PLA-PEG) co-polymers with an active pharmaceutical ingredient (API) core. The PLA part of the co-polymers is biodegradable and offers a moderately hydrophobic core for encapsulating hydrophobic APIs. The hydrophilic PEG part of the polymer is anticipated to coat the particles' surface and enable them to escape opsonization and ultimately prevent their removal from blood circulation by the phagocytic cells of the reticuloendothelial system (RES).

Accurins are produced using a nanoemulsion process, which utilizes high pressure homogenization to shear organic droplets spread within an immiscible aqueous phase. It is important to control the size of droplets so as to measure the final size distribution of the drug product. However, a number of factors affect the droplet size such as particle formulation, raw material attributes, aqueous phase composition, homogenizer mechanical properties and process parameters. Homogenizer pressure is a process parameter that can be easily manipulated to change size after the batch has been produced.

BIND is presently developing an Accurin called BIND-014 to deliver docetaxel to cancer and tumor cells expressing prostate- specific membrane antigen (PSMA). The experiments described in this article are for BIND-014 Accurins.

At-line Dynamic Light Scattering

Dynamic light scattering (DLS) technique is used for determining the size of submicron

particles. This method has been successfully utilized in labs for decades, but few in-process solutions exist. DLS is based on the principle that tiny particles move arbitrarily in fluids by undergoing Brownian motion. The system detects the translational diffusion caused by Brownian motion this diffusion is utilized to solve the Stokes-Einstein equation to measure the particle size (equation 1).

$D = k_B T/6\pi\eta R$ (1)

Where:

D = diffusion coefficient
k_B = Boltzman constant
π = viscosity
R = particle radius

Particle Sizing Systems (PSS) has installed a number of systems at the customer's production operations that are designed to monitor particle size during production runs. The advanced at-line system takes a sample from the process and dilutes it to prevent multiple scattering effects. It then measures the sample and repeats the entire process (Figure 2). The entire measurement cycle takes about 2 minutes and delivers continuous particle size data to process engineers who control the production operation.

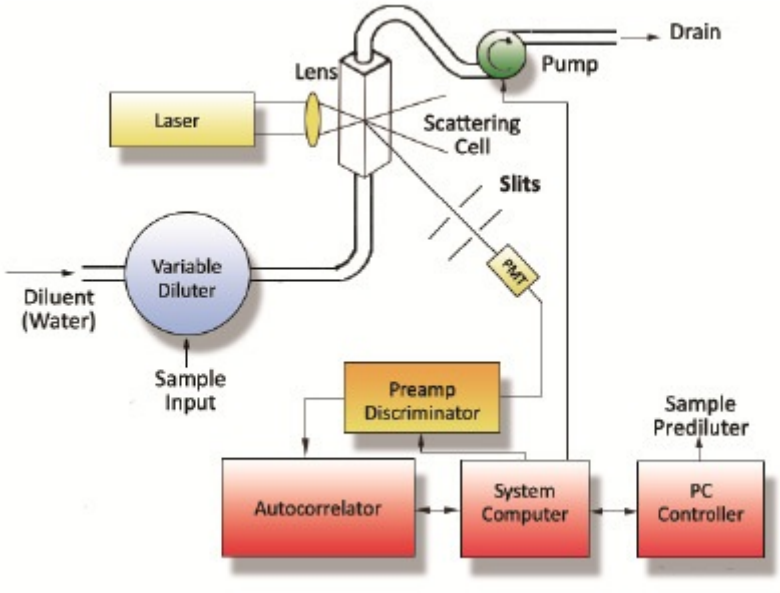

Figure 2. *Simplified diagram of the at-line DLS system, with autodilution*

Experimental Details

The at-line DLS system from PSS was installed downstream of a high pressure homogenizer and configured in such a way that it is able to capture an emulsion sample from the process stream every 2 minutes. The DLS' fluidics is set up in such a manner that the emulsion sample is diluted in water, similar to the downstream Accurin process, and then auto-diluted in a flow cell to a concentration to create an appropriate light scattering intensity (~300 kCt/s).

Three batches are illustrated here:

- A batch made with 11 in-process samples and inconsistent pressure all through the homogenization to develop a correlation between size and pressure.
- A batch produced with slightly different process conditions, leading to somewhat smaller than target size for the first two in-process specimens. Once the pressure is adjusted, the size was restored to target for the final four samples.
- A clinical-scale development batch shows steady size readings during the course of the eight samples obtained at approximately 5 minute intervals, and validates that the pressure set point is suitable.

Results and Discussion

Results obtained from the initial experiment (Figures 3 and 4) demonstrate the anticipated correlation between size and pressure. It can be observed from the trend line curve fit that the response of size to pressure is approximately 9nm/1,000psig.

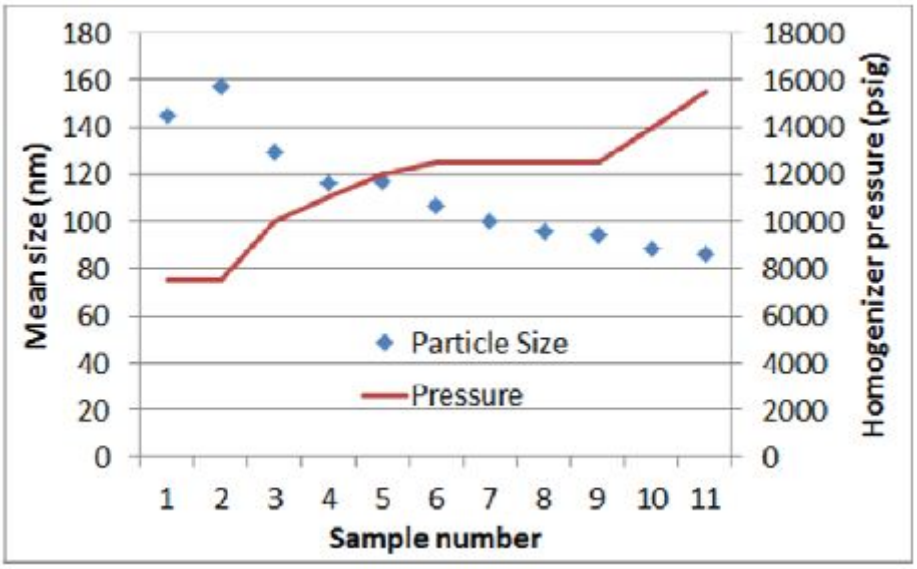

Figure 3. *Homogenizer pressure vs. particle size*

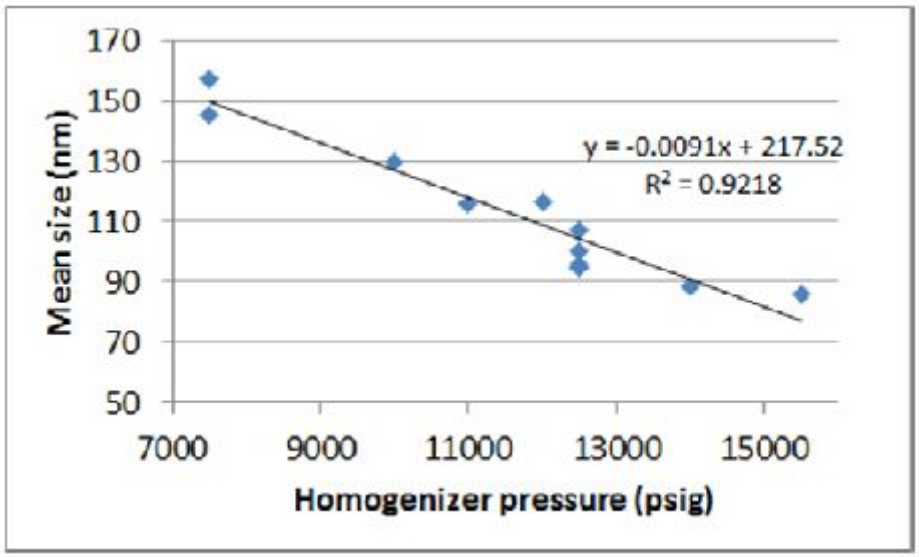

Figure 4. *Correlation of pressure to mean size*

In the second experiment, initial size readings of approximately 5 to 7nm were observed under the target size, and therefore the pressure was adjusted by decreasing 1,000psig. At later time-points, the size of the mean particle increased by roughly 5 to 10nm as predicted (Figure 5).

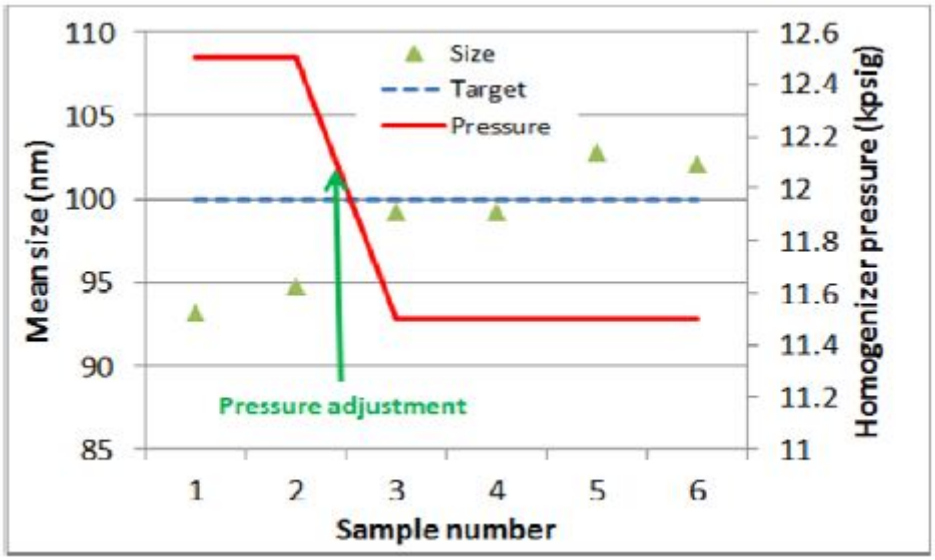

Figure 5. *Homogenizer pressure vs. particle size*

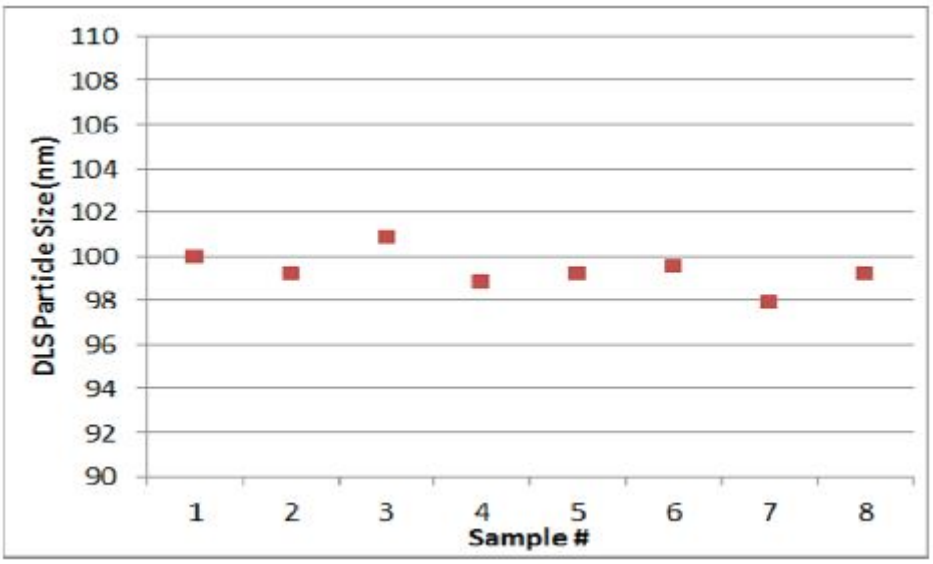

Figure 6. *Mean size during a batch run*

In Figure 6, the final set of data was obtained from the initial experiment at clinical-scale by means of the at-line sizer. BIND had the required processes to change pressure in case the size fell beyond the target range; however, this was not required. All eight measurements were found to be close to the 100nm target.

Conclusion

Particle Sizing Systems' at-line DLS system was incorporated into the Accurin production process and was utilized to ascertain optimum conditions and also to ensure that particle size was within the preferred specification during the entire batch run.

Measurements taken at-line not only reduces the lag time between process changes, but also gives particle size information needed to assess whether the change had yielded the desired effect. Moreover, the quality of a product is suitably monitored when compared to taking samples to laboratories for off-line batch testing.

About Particle Sizing Systems

Since our inception in 1978 we have been providing leading edge instrumentation for the field of particle size analysis. We are an applications driven company that provides solutions to our customer's most complex particle sizing and zeta potential monitoring problems. From wet to dry, online to research laboratory we have engineered a compete family of modular designed instruments that can be configured to meet the specific demands of an application.

This information has been sourced, reviewed and adapted from materials provided by Particle Sizing Systems.

For more information on this source, please visit Particle Sizing Systems.

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Single Particle Optical Sizing (SPOS)

The PSS AccuSizer operates using the principle of single particle optical sizing (SPOS). This technique generates high accuracy, high resolution particle size distribution results as well as concentration data in particles/mL. The AccuSizer platform includes multiple configurations designed to meet a wide array of applications including laboratory and online systems. Multiple sensor options cover a wide range of particle size and

concentration limits. Advanced fluidics modules can handle low concentration samples requiring no dilution to highly concentrated inks and CMP slurries using our patented two stage exponential dilution system.

Dynamic Light Scattering

The Nicomp dynamic light scattering (DLS) system measures particle size below 1 nm and zeta potential to study particle charge. The unique Nicomp algorithm provides the highest resolution results for samples containing more than one peak. Other unique capabilities include auto-dilution and auto-samplers to facilitate high sample throughput.

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Primary Activity

Particle Size Analysis Equipment