Nanoparticles for Drug Delivery

Nicomp® at-line

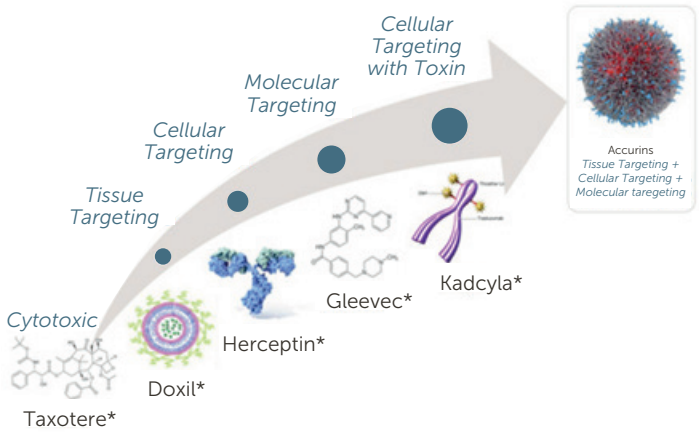

Figure 1. BIND Accurins technology

OVERVIEW

Nanomedicine research has grown quickly during the past few decades, with much of the focus placed on drug delivery. Nanoparticles provide benefits such as reducing toxicity and side effects. Controlling the size of these nanoparticles is critical. While the majority of the particle size measurements of this product is in the lab, it is now possible to make these measurements in line in the manufacturing environment. This application note explains the pioneering work performed at Bind Therapeutics (assets purchased by Pfizer in 2016) to incorporate in line dynamic light scattering measurements into the manufac-turing process of their Accurins® nanoparticle drug candidate.

INTRODUCTION

BIND Therapeutics, Inc. was a biopharmaceutical company developing targeted nanoparticle technologies called Accurins (see Figure 1) used to treat cancer and other serious diseases having large unmet medical needs. By combining controlled release polymer systems, targeting, and the ability to deliver large payloads of therapeutic agents, Bind was developing a nanotechnology enabled platform for a novel class of targeted therapeutics.

Accurins are typically 80 – 120 nm particles consisting of polylactide polyethylene glycol (PLA-PEG) co polymers with an active pharmaceutical ingredient (API) core. The PLA portion of the co polymers provides a relatively hydrophobic core for encapsu-lating hydrophobic APIs, and is biodegradable. The hydrophilic PEG portion of the polymer is expected to coat the surface of the particles and allow them to escape opsonization and removal from blood circulation by the phagocytic cells of the reticulo-endothelial system (RES). The 80 – 120 nm size is ideal to accumulate in the tumor site via the leaky vasculature (enhanced permeability and retention, or EPR effect) while avoiding filtering by the spleen.

It is also an ideal size for maintaining the desired physicochemical properties high drug loading, controlled release, and process ability, including the ability to terminally sterile filter and lyophilize.

Accurins are manufactured by a nanoemulsion process that uses high pressure homogenization to shear organic droplets dispersed within an immiscible aqueous phase. Control over the droplet sizes is critically important to determining the final size distribution of the drug product. Many factors influence the droplet size, including raw material attributes, particle formulation, homogenizer mechanical properties, aqueous phase composition, and process parameters. Homogenizer pressure is the process most easily manipulated to modulate size once the batch is being produced.

BIND 014 was an Accurin developed to deliver docetaxel to solid tumors, and cancer cells, expressing prostate-specific membrane antigen (PSMA). All of the experiments described here are for BIND-014 Accurins.

IN-LINE DYNAMIC LIGHT SCATTERING

Dynamic light scattering (DLS) is a preferred technique for measuring the size of submicron particles. DLS operates on the principle that small particles move randomly in fluids by undergoing Brownian motion. The translational diffusion due to brownian motion is detected by the system and then used to solve the Stokes-Einstein equation to determine the particle size (Equation 1).

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

Where:

D = Diffusion coefficient

k_B = Boltzman constant

η = Viscosity

R = Particle radius

DLS has been successfully used in the laboratory for decades with tens of thousands of installations, but few inline systems exist. Entegris now has several systems installed in customer manufacturing operations that track particle size during production runs. The online system removes a sample from the process, dilutes the sample to avoid multiple scattering effects, measures the sample, and then repeats the procedure (see Figure 2). The complete measurement cycle is approximately 2 minutes, providing continuous particle size information to the process engineers monitoring the manufacturing operation.

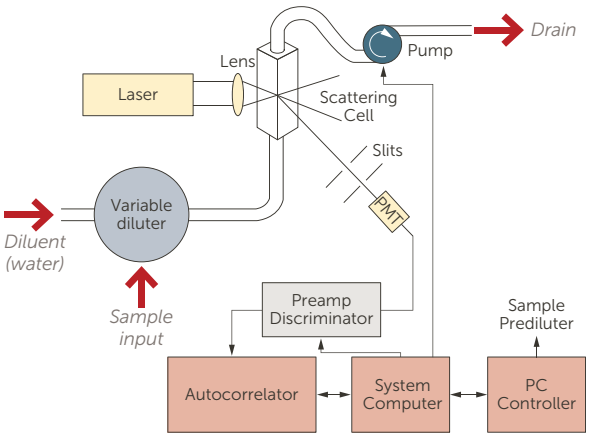

Figure 2. Simplified diagram of DLS system, with autodilution

EXPERIMENTAL DETAILS

The Entegris inline DLS system was installed downstream of a high pressure homogenizer and set up such that it can grab an emulsion sample from the process stream every ~2 minutes. The fluidics of the DLS are set up such that the emulsion sample is diluted in water in a similar manner to the downstream Accurin process, and autodiluted in a flow cell to a concentration that produces ideal light scattering intensity (~300 kCt/sec).

Three batches are described here:

1. A batch made with eleven in process samples, and variable pressure, throughout the homogenization in order to develop a pressure size correlation.
2. A batch made with slightly different process conditions that resulted in slightly smaller than target size for the first two in process samples. After adjusting the pressure the size was brought back to target for the final four samples.
3. A clinical scale development batch demonstrating stable size readings during the course of the eight samples taken at ~5 minute intervals confirming the pressure set point is appropriate.

RESULTS

Results from the first experiment (Figure 3 and Figure 4) show the pressure-to-size relationship we expected. As seen by the trend line curve fit, the response of size-to-pressure is ~9 nm per 1,000 psig.

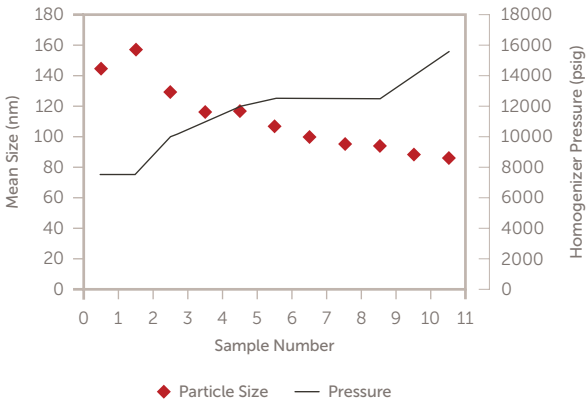

Figure 3. Homogenizer pressure vs. particle size

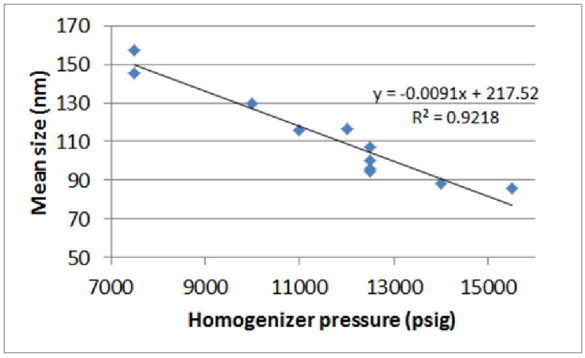

Figure 4. Correlation of pressure to mean size

The second experiment had initial size readings ~5 – 7 nm under the target size and hence a pressure adjustment was made (1,000 psig decrease). At later time points the mean particle size increased by ~5 – 10 nm as expected.

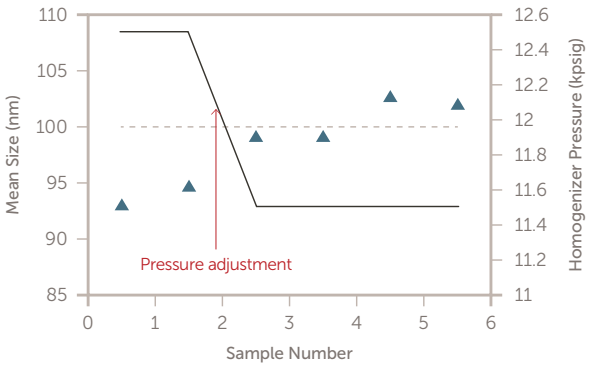

Figure 5. Homogenizer pressure vs. particle size

The last set of data is from the first experiment at clinical scale using the inline sizer. Although BIND had procedures in place to adjust pressure as necessary if the size fell outside of our target range, it was not necessary to do so. All eight measurements were very close to the 100 nm target.

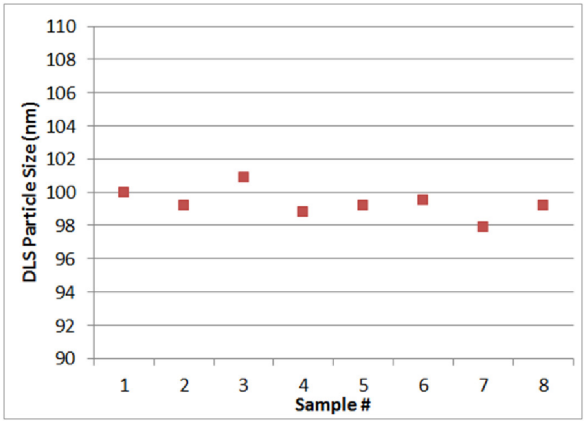

Figure 6. Mean size during a batch run

CONCLUSIONS

The inline DLS system was integrated into the Accurin manufacturing process and was used to determine optimum conditions and assure the particle size was within the desired specification during the complete batch. Taking the measurements inline reduces the lag time between making process changes and obtaining the particle size data required to asses if the change produced the desired effect. In addition, product quality is better monitored than by taking samples to the lab for offline batch analysis. Inline DLS is a valuable process analytical technology.

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