Drug Delivery Using Nanoparticles

Study and control nanoparticles using the Nicomp® DLS system

Figure 1. Nicomp DLS instrument.

DRUG DELIVERY USING NANOPARTICLES

Considerable research and development is devoted to improving drug delivery through the use of nanoparticles. Although the definition of nanoparticle has become murky, typically they are defined being in the size range of 100 nm and below, Dynamic light scattering (DLS) is the preferred method in this size range and the Nicomp® is often used in this field of research. This application note summarizes how the Nicomp can be used to study and control nanoparticles used for drug delivery.

INTRODUCTION

Both ISO/TS 27687[1] and ASTM E2456[2] define nanoparticles as being in the size range of 100 nm and below, making this the most widely used classification. Less strict interpretations have extended the upper size range for both scientific, and other reasons. Now many nanomaterials greater than 100 nm in size are commonly called nanoparticles. The motivations for developing drug products in this size range include improved dissolution/bioavailablity, targeting, circulation time in the system, and area under the curve (AUC) pharmacokinetics.

Many of these drug products are developed to enhance targeting. A passive targeting approach increases the circulation time by reducing the size and cloaking the nanoparticle with a coating such as polyethylene glycol (PEG). An active targeting approach modifies the surface of the nanoparticle to seek and adhere to specific parts of the body, such as cancer tumors, while avoiding healthy tissue. Cell specific ligands on the surface of the nanoparticle can be added to bind specifically to complementary receptors.

The Nicomp DLS system (Figure 1) is an ideal instrument to measure both the size and zeta potential (surface charge) of nanoparticles used for drug delivery.

TYPES OF NANOPARTICLES

Nanocrystals

Active pharmaceutical ingredients (APIs) are often crystalline. Hydrophobic crystals can be difficult to formulate to be delivered in a hydrophilic carrier mechanism. By reducing the size to the nanocrystal range, a nanosupsension can improve the bioavailablity of drugs, where the dissolution velocity is the rate limiting step, such as poorly water soluble drugs.[3] These nanocrystal often need to be stabilized using surfactants or polymers including during processing. A decrease in particle size increases dissolution rate by both increasing the surface area A (Figure 2) and the saturation solubility C_s.

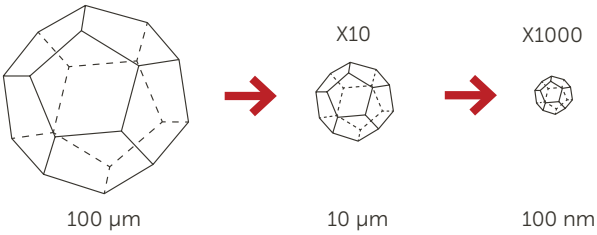

Figure 2. Surface enlargement with size reduction.

The Noyes-Whitney equation (Equation 1) shows how an increase in both A and C_s will affect the dissolution rate dC/dt.

$$\frac{dC}{dt} = \frac{DA}{Vh}(C_s - C_x) \quad \text{(Equation 1)}$$

Where

dC/dt = dissolution rate
D = diffusion coefficient
A = surface area
C_s = concentration at boundary layer
C_x = concentration API @ given time
V = volume dissolution medium
h = height of boundary layer

Lipid-based liquid crystalline nanoparticles (LCNPs) are another delivery system capable of increasing bioavailability of both hydrophobic and hydrophilic drugs. These are self-assembled structures prepared by high shear energy dispersing of a nonlamellar liquid crystalline matrix into the water phase. The particle size of the LCNPs is an important physiochemical property requiring proper analysis and control. The Nicomp DLS system has been successfully used to determine both the mean size, and presence of aggregates in LCNP dispersions.[4] Paclitaxel was loaded into a LCNP dispersion and analyzed by the Nicomp DLS system and TEM, see Figure 3.

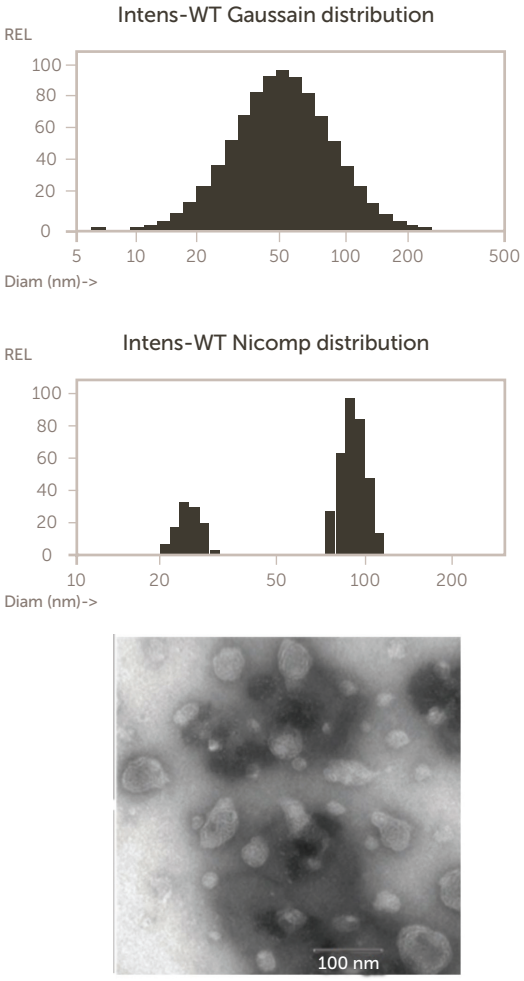

Figure 3. Nicomp and TEM results for an LCNP dispersion, copied with rights from.[4]

The TEM image indicates a bimodal particle size distribution of smaller near, 25 nm particles, plus larger particles on the scale of 100 nm. The upper Nicomp result is the Gaussian intensity distribution mean forcing the entire distribution into one peak. The lower Nicomp result utilizes the proprietary Nicomp non-negative least squares algorithm to report a higher resolution and more accurate description of the bimodal nature of the actual particle size distribution. This highlights a main advantage of the Nicomp DLS system – the ability to resolve multi-modal distributions even at concentrations as low as 0.2 mg/mL.[5]

Micelles

Another potential drug delivery system for increasing the solubilization of hydrophobic drugs is polymeric micelles.[6] Micelles are formed when the concentration of the polymer, in solution, exceeds a certain threshold concentration known as the critical micellar concentration (CMC). Polymeric micelles are core-shell nanostructures synthesized from amphiphilic block copolymers. Micelles have the advantages of being very small in size (10 – 100 nm), improving passive targeting to solid tumors. By modifying the surface with ligands polymeric micelles can become capable of site-specific drug delivery.

The Nicomp DLS system has been used for particle size measurements in many micelle based research projects.[7-11] In one study,[12] polymeric micelles were formed using copolymers polycaprolactone (PCL) and polyethylene glycol (PEG). Docetaxel (DTX) was used as the model drug and the surface was modified with a small molecular ligand of prostate specific membrane antigen (SMLP). Figure 4 shows the self-assembly of the micelles and the endocytosis process of the drug loaded final structure.

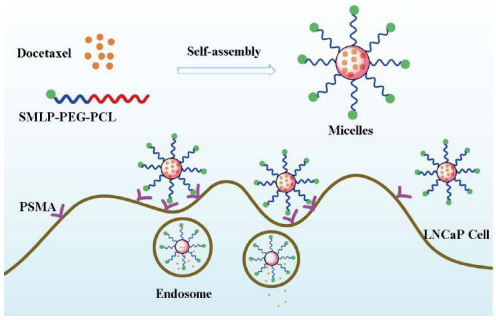

Figure 4. Preparation and endocytosis of DTX loaded polymeric micelles targeted to PSMA.[12]

The particle size by the Nicomp DLS system, and TEM of two samples used in this study, is shown in Figure 5. The data for non-targeted micelles are shown on the left, and the targeted on the right. The DLS data appears slightly larger than the TEM images, possibly due to shrinkage of the PEG shell induced by water evaporation before TEM analysis.

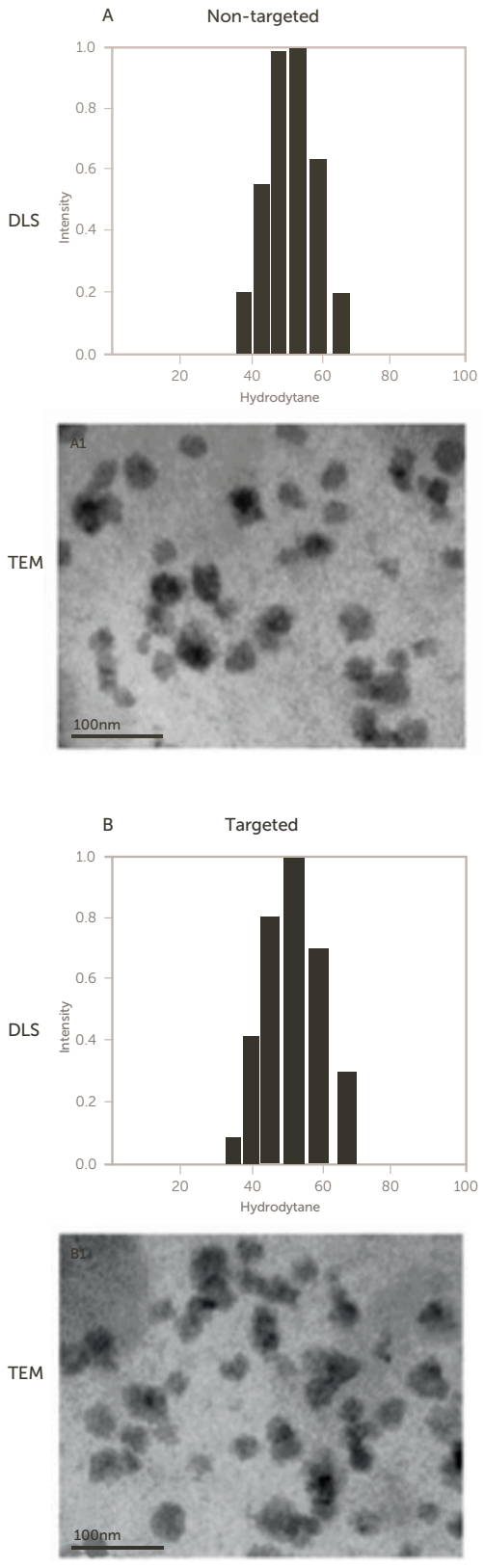

Figure 5. Size of non-targeted (upper) and targeted (lower) polymeric micelles by DLS and TEM.[12]

Liposomes

Liposomes are bilayer vesicles routinely used in the pharmaceutical industry as a drug delivery system for transport of chemotherapeutic drugs to the tumor area. They are composed of phospholipids that have a polar end attached to a nonpolar chain that self-assemble into bilayer vesicles with the polar ends facing the aqueous medium and nonpolar ends forming a bilayer. In pharmaceutical applications, the active pharmaceutical ingredient (API) is usually incorporated into the liposome either into the hydrophilic pocket or sandwiched between the bilayers depending on the hydrophilicity of the API, see Figure 6. Surface modification is common for targeted delivery.

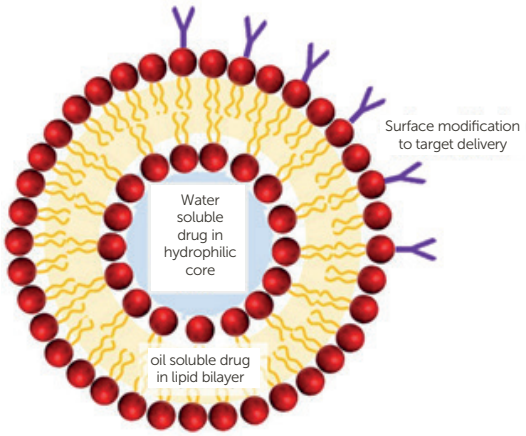

Figure 6. Complex liposome structure.

Monitoring the particle size while processing liposomes is critical and the Nicomp DLS system is frequently used for this application.[13-20] In one internal Entegris study, liposomes were created using a formulation of 3:1:1 HSPC, cholesterol and mPEG-DSPE. The sample was first mixed by rotor stator at 7200 rpm for 10 minutes, then passed through a Microfluidizer[21] at 25,000 psi using a Y chamber to create the liposomes. The samples were processed 1, 3, 5, and 10 passes through the microfluidizer. An image of the premix and processed samples (left to right) is shown in Figure 7.

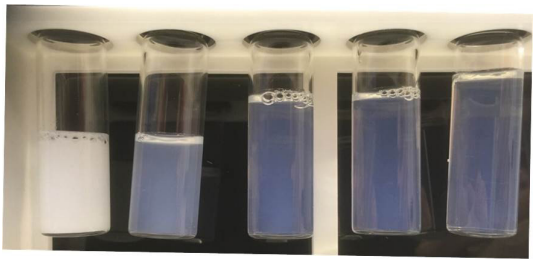

Figure 7. Pre-mix, 1, 3, 5, and 10 passes.

The liposome samples were analyzed on both the Nicomp DLS system and the AccuSizer® single particle optical sizing (SPOS) system. DLS was used to determine the reduction of the intensity mean size during processing, while the AccuSizer (LE sensor range 0.5 – 400 µm) was used to quantify the presence of larger particle tails of the distribution. The Nicomp DLS results are shown in Figure 8, and the AccuSizer SPOS results are shown in Figure 9.

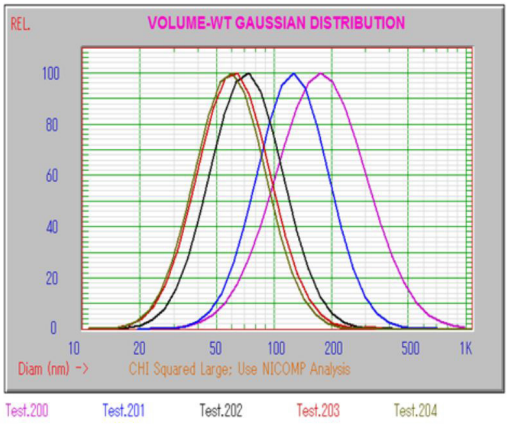

Figure 8. Nicomp DLS results from right to left; premix, 1, 3, 5, and 10.

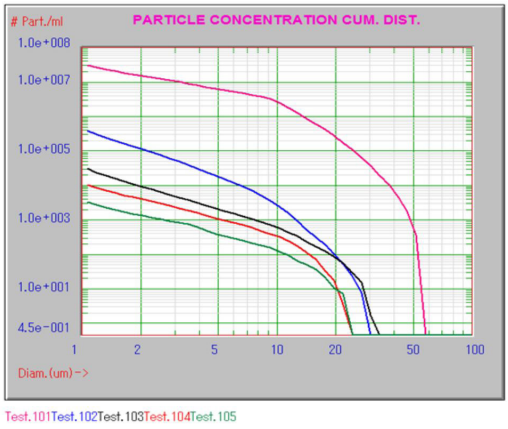

Figure 9. AccuSizer SPOS results right to left; premix, 1, 3, 5, and 10 passes.

Using both DLS to determine mean size and SPOS to quantify the presence and concentration of tails is common in many industries and is an integral part of USP <729> Globule-size distribution in lipid injectable emulsions.[22]

Online DLS for process monitoring

While the vast majority of DLS measurements are made in the laboratory, Entegris has installed several systems in customer manufacturing operations that track particle size during production runs.[23] These systems have been used to monitor high-pressure homogenization processes used during the manufacture of nanoparticles for drug delivery The at-line 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 10). The complete measurement cycle is approximately two minutes, providing continuous particle size information to the process engineers monitoring the manufacturing operation.

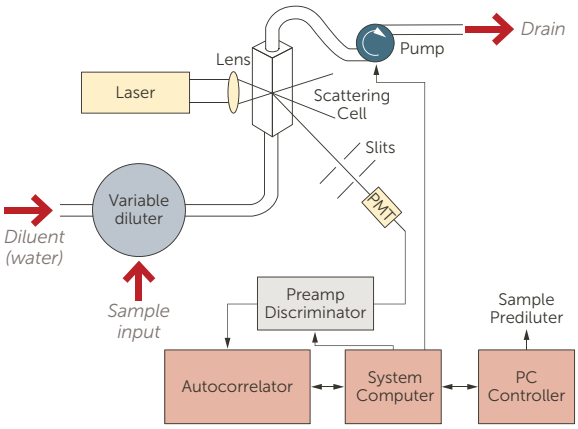

Figure 10. Online DLS system schematic.

Figure 11 shows online DLS results as a function of pressure downstream of a high pressure homogenizer. The goal was to determine and the optimum pressure to keep the particle size very close to 100 nm in size. After the optimum pressure (~10 k psi) was determined the online DLS system was used to assure the complete batch was manufactured within specification.

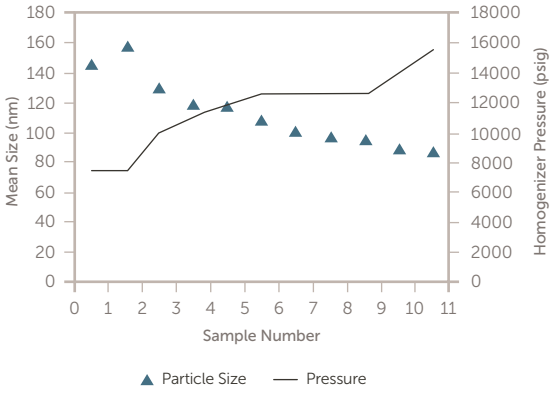

Figure 11. Pressure vs. particle size in process DLS results.

CONCLUSIONS

The Nicomp DLS system is widely used for particle size and zeta potential analysis of drug delivery systems in the nano scale in research,[24-39] quality release testing and in process monitoring. The AccuSizer SPOS provides a complementary technique for determining the concentration of larger particles that could indicate instability or non-optimized formulation or process conditions.

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