Continuous Manufacturing of Liposomes and Lipid Nanoparticles

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Abstract

BACKGROUND: Lipid-based formulations such as liposomes and lipid nanoparticles (LNP) are emerging product designs for safe and efficacious delivery of a variety of molecules for a wide range of applications, such as anti-cancer, anti-fungal, vaccine (e.g., mRNA encapsulated in LNP for COVID-19) and immune therapy. Continuous manufacturing is an advanced manufacturing approach that enhances manufacturing efficiency, robustness, capacity, and assurance of drug product quality. PURPOSE: A major challenge in nanoparticle manufacturing is to adequately control the process to ensure product quality, which directly impacts the safety and efficacy of the nanotechnology products. In this collaborative work between FDA and University of Connecticut over the last six years, a new approach for commercial scale manufacturing of lipid-based nanoparticle formulations was developed. METHODS/RESULTS: A novel GMP compliant continuous processing system was developed to produce nanoparticles using an ethanol injection method. Nanoparticles are formed using a customized injection port that forms a turbulent jet in co-flow. Multiple parameters are controlled and monitored during the processing, such as: (1) on-line particle size analysis (InProcess LSP); (2) online lipid concentration analysis using a turbidity probe (Optek) coupled with a predictive algorithm; and (3) online drug encapsulation using a UV-VIS spectrometer (Avantes) coupled with a predictive algorithm. Liposomal nanoparticles were successfully formed using this continuous processing system; along with, concentrating/buffer exchange and remote loading of the drug substances as a single unit step. This end-to-end adaptable continuous manufacturing system can produce liposomes with well controlled quality attributes (e.g., particle size, polydispersity and drug loading). CONCLUSION: The continuous processing system coupled with powerful online and inline process analytical technology enables faster development of a design space for future drug products. This novel continuous manufacturing system features real-time process control strategy, rapid assessment of process parameters and material attributes, and adequate control of the product quality and performance. The continuous manufacturing platform can also facilitate increases in production output by increasing the run time to better respond to changes in demand.

Introduction

Figure 1. The UConn continuous processing skid in a cleanroom at URI.

Materials and Methods

Figure 2. The UConn continuous processing skid undergoing a cleaning validation study.

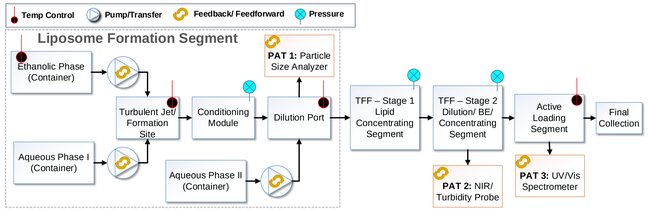


Figure 3. System block-diagram outlining key areas in the process from nanoparticle formation to drug loading (final product), ready for fill/ finish.

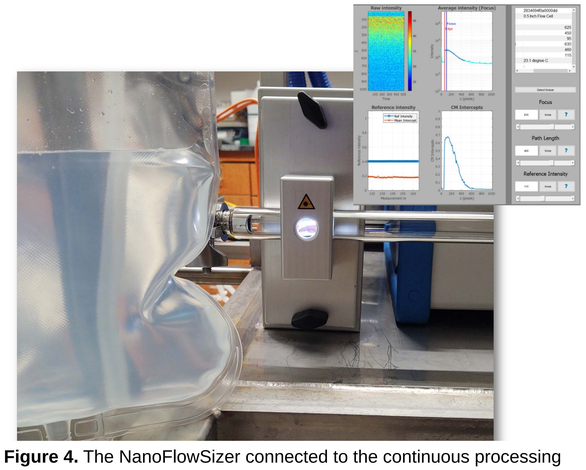


Figure 4. The NanoFlowSizer connected to the continuous processing system to monitor and control the nanoparticle formation process. Clean bag with liposomes on the left side of the image (clear/blue tint signals the presence of nanoparticles).

Results and Discussion

Particle size, lipid concentration and drug encapsulation were controlled and monitored using this continuous processing system. The particle size data from on-line particle size analyzer was used as feedback loop to control the critical process parameters (such as flow rate) to maintain the particle size at a user-specified target. For example, a controlled particle size state (set to 110 d.nm) was reached in 6 minutes. The mean particle size was 111.5 d.nm with a standard deviation of 5.35 d.nm over the entire run (Figure 6). Quality attributes such as particle size (Z-average), lipid concentration and drug encapsulation were measured by inline process analyzers, in good agreement with offline measurement (Figure 6).

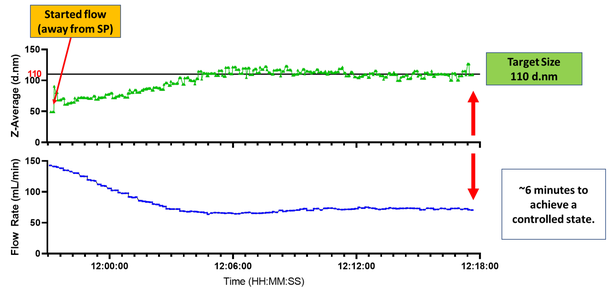


Figure 5. Automatic particle size control was successfully demonstrated on the UConn continuous processing system. The user set a desired particle size and the system automatically adjusted process parameters to meet the desired particle size.

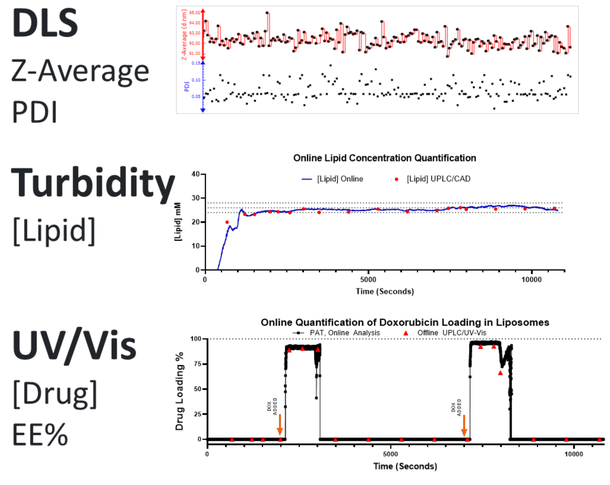


Figure 6. Three examples of data from process analytical technology that is integrated in this processing system. Particle size, lipid concentration, drug concentration and drug encapsulation are measurable on this system.

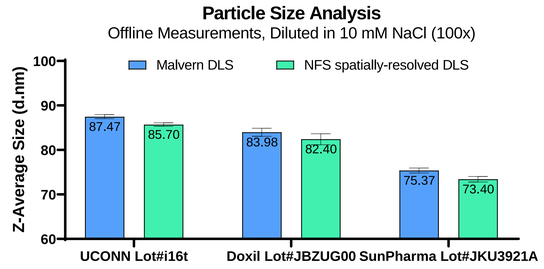
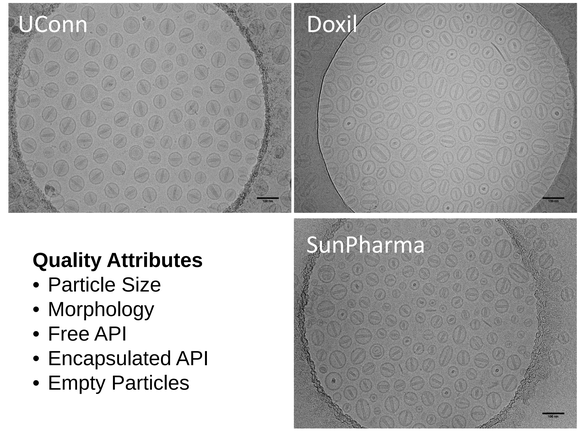


Figure 7. A comparison between commercially available particle size instruments and tested products.



Quality Attributes
- Particle Size
- Morphology
- Free API
- Encapsulated API
- Empty Particles

Figure 8. Cryo-TEM images of the particles from Figure 7.

Conclusion

The continuous processing system coupled with powerful online and inline process analytical technology enables faster development of a design space for future drug products. This novel continuous manufacturing system features real-time process control strategy, rapid assessment of process parameters and material attributes, and adequate control of the product quality and performance. The continuous manufacturing platform can also facilitate increases in production output by increasing the run time to better respond to changes in demand.

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