Implementation of an at-line nanoparticle size analyzer in a continuous nano-manufacturing line considering critical measurement and process conditions

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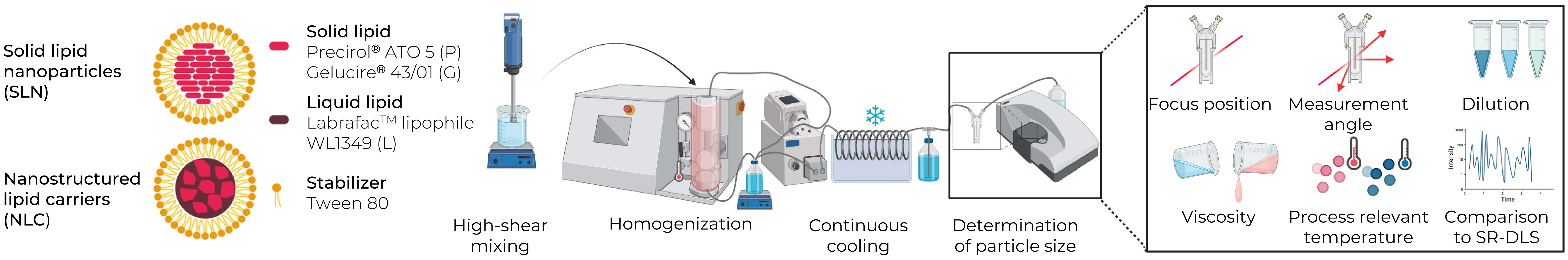
Introduction

A Process Analytical Technology (PAT) strategy for process and product monitoring is important to ensure adequate product quality. This is especially true for nanopharmaceuticals, as minor changes during the manufacturing process can lead to significant product quality changes, which in turn can drastically alter biopharmaceutical performance. In this context, size is a critical quality attribute. Currently, particle size characterization is done offline via dynamic light scattering (DLS), which is associated with interruption of the manufacturing process, delayed quality feedback, and batch-to-batch quality variation. Alternatively, at-line and inline measurements can be performed using DLS or spatially-resolved (SR-) DLS. However, the implementation of at-line and inline particle size analyzers in a continuous nano-manufacturing line requires a sound understanding of the most influential measurement and process conditions.

Methods

Selection of matrix composition → Preparation of nanoparticles → Testing of measurement conditions



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Results

It was found that for standard DLS the use of measurement angles of 175° provided the broadest concentration range and the most reliable results. As in these studies highly concentrated nano-dispersions were used (i.e., 10% (w/w) solid content), a sufficiently high dilution factor was of utmost importance to facilitate reliable measurements (see Fig. 1). This not only allows for unhindered particle movement and avoids multiple scattering of the dispersed particles, but also reduces the effect of the dynamic viscosities. The preliminary studies for measurements at different process steps and thus different product temperatures revealed a direct correlation of the particle sizes (see Fig. 2). Finally, particle sizes determined via the implemented at-line measurement system were in agreement with the offline DLS (see Fig. 3). The discrepancy between standard DLS and SR-DLS can be explained by the different wavelengths used, with this effect being more pronounced at higher polydispersity index [1].

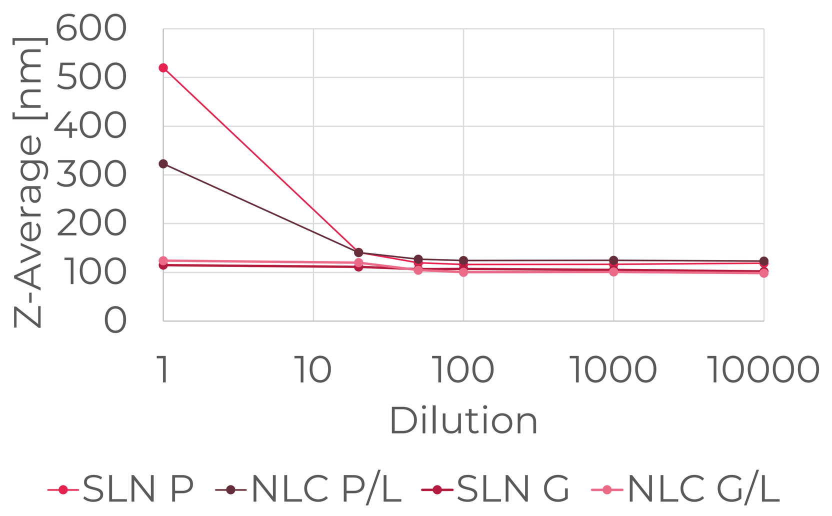

Fig. 1. Particle size of SLN and NLC using different dilution factors (undiluted – 1:10000)

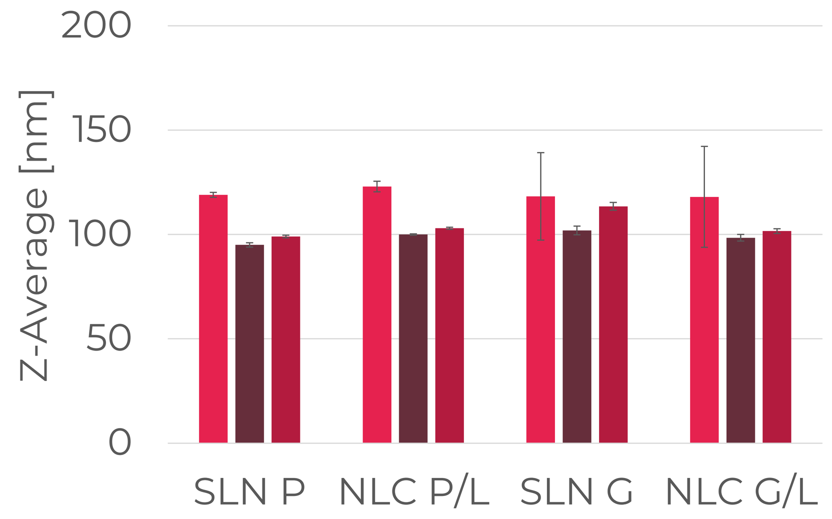

Fig. 2. Correlation of particle sizes at final cooling, crystallization and process temperature

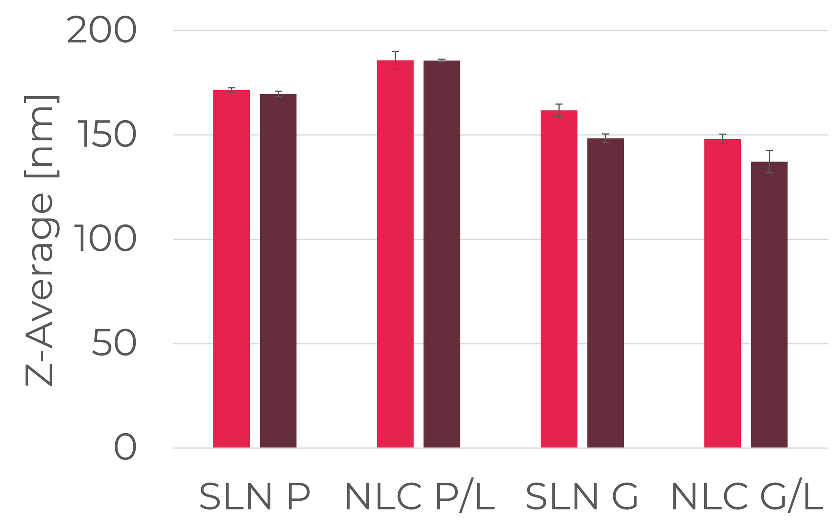

Fig. 3. Comparison of at-line and offline DLS measured particle sizes

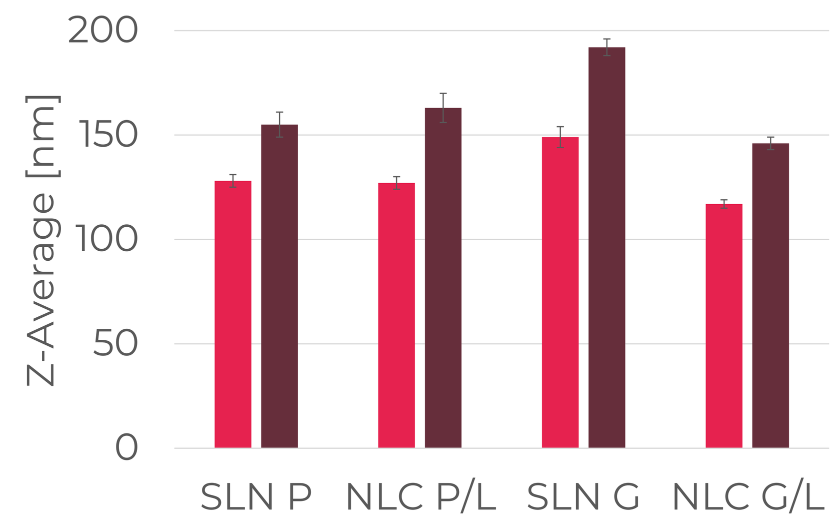

Fig. 4. Comparison of offline standard DLS and SR-DLS measured particle sizes

Conclusion and Outlook

The present work presents a promising strategy for at-line particle size measurements during the production of nano-systems in continuous production lines. In future studies, at-line data will be compared to inline data obtained by implementing the NanoFlowSizer into the manufacturing process.

References

[1] InProcess-LSP. 2023. How do results from different dynamic light scattering instruments compare?. AZoNano, viewed 05 September 2023, https://www.azonano.com/article.aspx?ArticleID=5571.

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