Fraunhofer IMM

Fraunhofer Institute for Micro-engineering and Microsystems IMM

flowDLS

Nanoparticle sizing: inline dynamic light scattering

Introduction

Dynamic Light Scattering (DLS) is a very powerful and well-established method for the size characterization of particles in dispersion as well as for polymers in solution. Although the correct data analysis is not trivial in DLS, the measurement itself is simple, fast and non-invasive. In addition, the method does not rely on special properties of the analyte as, for instance, fluorescence – therefore it is applicable on a wide spectrum of analyte materials and solvents. For example, lipid nanoparticles containing mRNA-based pharmaceutical drugs, gathered large public interest recently as vaccines or for novel cancer treatment methods. These particles are routinely analyzed by DLS.

However, there is a lack of fast and cost effective inline/online particle sizing devices that take advantage of the benefits of Dynamic Light Scattering. Therefore, a new technique for measuring DLS continuously and in flow was developed, patented[1] and implemented in a fully integrable, easy-to-use instrument.

Basic principles

In DLS, the temporal evolution of the intensity of the light scattered by the sample after being irradiated by a laser light source is analyzed to measure the speed of the Brownian motion of the particles. This speed can be related to the hydrodynamic particle size using the Stokes-Einstein equation. The result is the mean value of a diameter equivalent to that of a spherical particle with the same hydrodynamic properties as the measured sample.

Active flow compensation

The system developed by Fraunhofer IMM is able to suppress the influence of the flow dependent movement before the calculation of the particle size is started. This substantial advantage is achieved by efficient digital image processing algorithms. After this treatment, the following data processing steps are basically the same as in conventional DLS measurements inside a cuvette.

High flow rate vs. small sample consumption

Analyzing nanoparticles in a production environment requires the instrument to be able to cope with high analyte flow rates. The current optical and fluidic setup allows the determination of particle sizes at flow rates up to 200 ml/min. The flow does not have to be steady – as long as it is laminar, measurements under pulsing or even alternating flow conditions are possible.

For process development however, it is vital to keep flow cell volume low to minimize costly sample consumption. The flowDLS principle was successfully miniaturized to accurately measure even in tiny microfluidic channels.

Cost-effective components

The novel imaging-based concept permits a smart combination of highly cost-effective optical and electronic components.

Therefore, the flowDLS system provides not only advanced features over current conventional setups, but is also an attractive economical alternative.

Instrumentation and control

For data processing, an integrated PC is connected to the electronics of the system. The flowDLS device auto-calibrates to different particle sizes and concentrations as well as to different flow velocities. Besides the initial setting of solvent parameters, no user input is required during operation. The instrument can be connected to an industrial process control system by a serial interface. The measurement results may also be tracked in real-time on the integrated touchscreen display.

Large and small-scale application examples

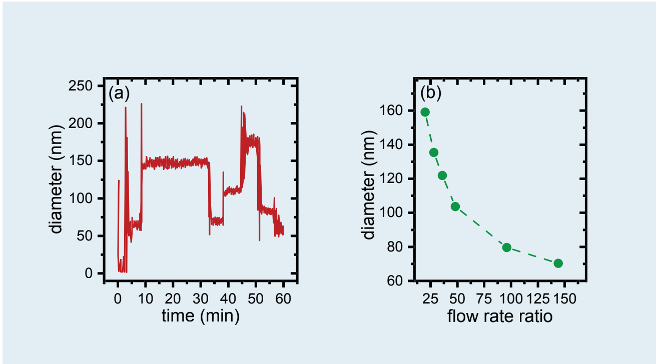
To demonstrate the potential of the flowDLS device, it was incorporated into a microreactor-based, continuous synthesis setup. Using this setup, vesicular structures from non-ionic surfactants ("niosomes") and functionalized silica particles were produced. In both cases, the flowDLS device served as a real-time monitoring system of the product stream and proved to be capable to detect quick changes in particle size upon a change of the process parameters (see panel (a) in the figure). By checking the particle size up- and downstream of a cross-flow filtration step, the flowDLS device revealed that the product passed the work-up routine unaltered[2]. When implemented into a process control system, a feedback loop can be established, for instance, to constantly control the product properties by automatically adjusting process parameters.

Another application example demonstrates the capability of the flowDLS to operate with minimal sample volumes: Inline DLS measurements were integrated directly into a microfluidic chip used for synthesizing lipid nanoparticles. The lipid and surfactant dissolved in ethanol are fed into water using a micronozzle within the microchannel where the nanoparticles start to precipitate. Changes in the flow rate ratio of water to ethanol leads to a change in the produced particle diameter, which can be readily observed using flowDLS within minutes (see panel (b) in the figure). In this way, a deep understanding of the underlying process dynamics can be gathered within minutes.

Further applications for inline/online DLS

The flowDLS device is particularly suitable for online monitoring directly at a production line of any process involving particle dispersions, polymer solutions or emulsions of components with differing refractive index. This allows a constant quality control of such product streams. Failed batches can be recognized and rejected quickly to minimize production costs.

For process development applications, using flowDLS allows the user to quickly gain a deep process understanding, while using minimal sample volumes.



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1 Höbel, P.; Maskos, M. (2018): Patent WO2018007328A1 | **2** Bomhard, S. et al. (2019): Chem. Eng. Technol. 42 (10), pp. 2085–2094