NANOPARTICLE SIZE CHARACTERIZATION :

" THE VALUE OF ADDING A NEW DIMENSION"

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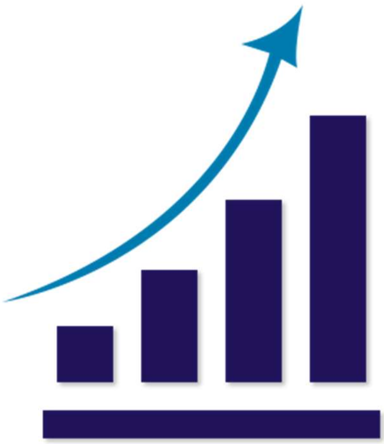
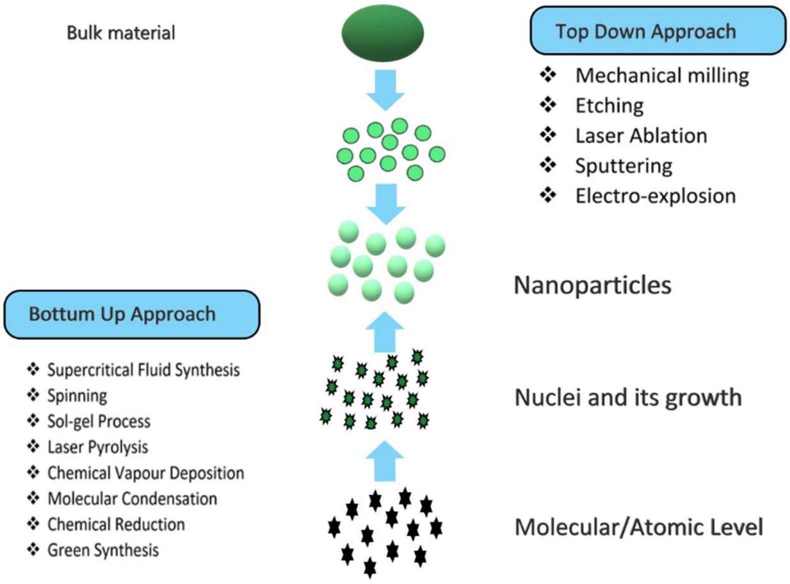
Introduction

Nanoparticle suspensions are increasingly used for a wide variety of applications such as pharmaceutics, catalysts, battery materials, inks, food ingredients, cosmetics, coatings, and paints. The overall nanotechnology market is difficult to define as it encompasses a wide range of materials, applications, and industry sectors. What is beyond question is that the nanotechnology market continues to experience extreme double digit growth rates in the near and long term future, and as the need for nanoparticles increases, so does the need for their measurement and analysis. Therefore reliable and efficient nanoparticle characterization will become even more important and requires instrumentation to handle these various applications.



Nanotechnology in healthcare has an exceptional potential to address a diversity of therapeutic issues by providing better diagnostics and therapy. A broad range of nanoparticles enabled products are available for medical applications (drug transportation), including liposomes, polymeric nanoparticles, lipid-based nanoparticles, micelles, nanocrystals, metal colloids, metal oxides, and many others.



Courtesy : Algae-based metallic nanoparticles: Synthesis, characterization and applications characterization and applications June 2019 Journal of Microbiological Methods 163:105656 Follow journal DOI: 10.1016/j.mimet.2019.105656

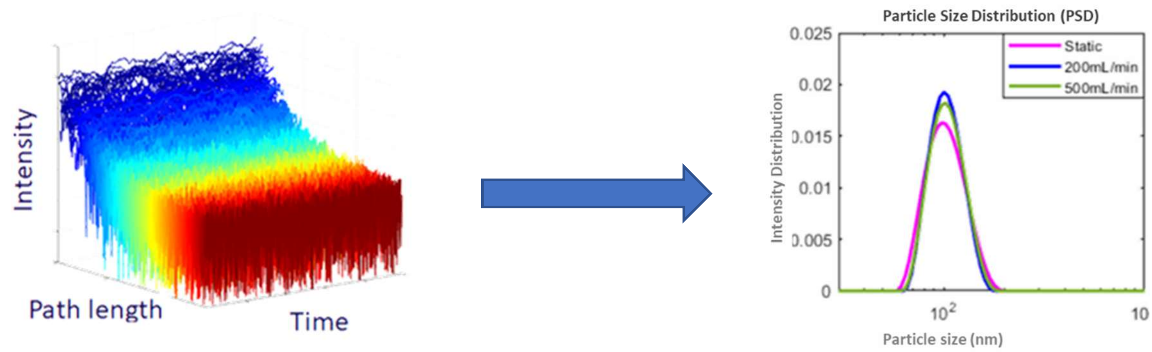
Nanoparticles can be obtained through bottom-up, e.g. solution-based particle formation processes (crystallization, precipitation, etc.) or top-down methods by applying size reduction technologies (nano milling, microfluidization, homogenisation, etc.). Therefore, the ability to control the process and fine tune material properties depends on ability to precisely measure the particle size. Current methods of controlling nanosuspension fabrication in both lab and production-based environments rely on traditional offline analytical methodologies. These offline analyses are time-consuming and do not provide a suitable process control measure. As a result, in most cases, one does not properly understand and control nanoparticle formation processes and quality.

Various challenges for real-time nanoparticle size characterization during processing exist preventing proper implementation of Process Analytic Technology (PAT). These include concentration of the nanoparticle suspensions, rheology properties, turbidity levels and state of the fluid movement (flow versus static). In order to reliably measure particle size, these challenges need to be addressed.

“A NEW DIMENSION “

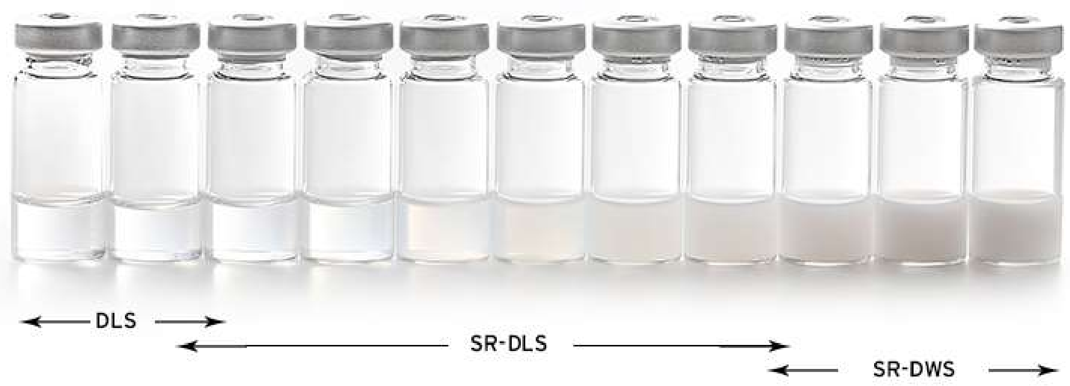
--- Spatially-Resolved Dynamic Light Scattering (SR-DLS) & Diffusion Wave Spectroscopy (SR-DWS)

SR-DLS/DWS is based on Low Coherence Interferometry (LCI) and can measure nanoparticle size inline, online, at line or offline under static and flowing conditions without sample preparation (like dilution). Particle size data can be obtained in <10s, enabling real-time process monitoring. LCI enables one to measure light scattering data as a **function of depth** in a sample (spatially resolved) which enables measurements at very small path lengths and direct measurement of flow profiles and velocity of the suspension. For SR-DLS, particle size information is obtained by interpretation of time correlation functions as a result of Brownian motion of nanoparticles, similar to conventional dynamic light scattering. Significantly higher turbidity ranges are accessible by SR-DLS since the spatially (or depth) resolved data allows isolation of single scattered data at short pathlength in the sample. For flowing suspensions, both flow and Brownian motion contribute to the correlation functions. Separation of the Brownian component, in which the nanoparticle size information is embedded, is therefore required. For laminary flow conditions the Brownian motion part can be obtained and further processed into particle size information.

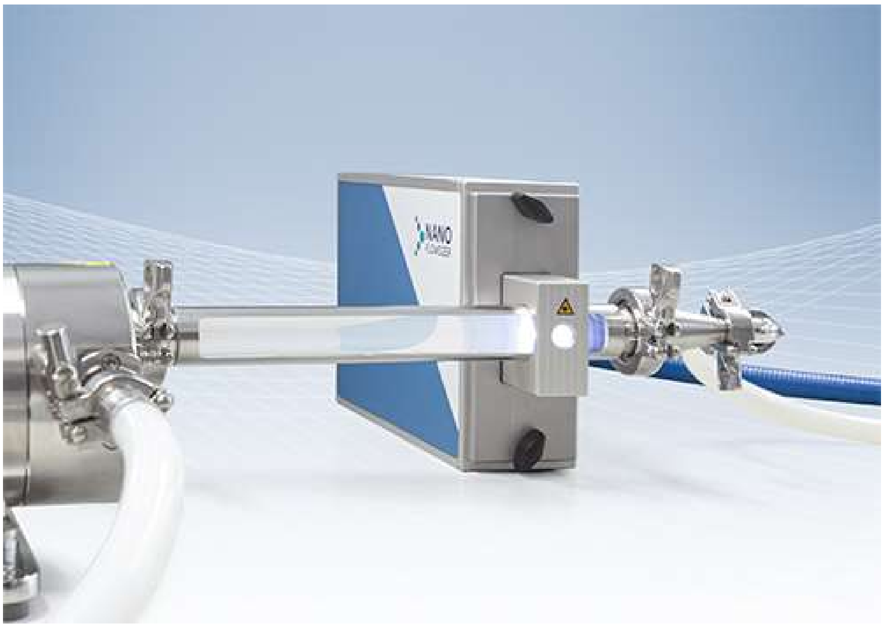


This makes SR-DLS suitable for measurements under flow conditions in industrial processes. Measurements are through a glass interface to about 3 mm into the sample, without disturbing the process. The SR-DLS technology solution is particularly suited for direct and realtime analysis of particle size information in early development up to commercial manufacturing under GMP regime. There is no interaction between the device and the flowing fluid hence offering a non-invasive particle size measurement solution which eliminates the risk of contamination or poor representability when samples have to be taken for offline analysis.

Up to significant turbidity ranges SR-DLS can be applied, as long as sufficient single scattered light can be detected at shorter path lengths. In case of extremely highly concentrated (turbid) suspensions only multiple scattered data may be present which eliminates the possibility to derive accurate particle size data by DLS. In case only multiple scattered data is available particle size information can still be obtained by Diffusion Wave Spectroscopy which is also applied as spatially resolved measurement with the same technology. The light scattering data generated is processed differently for SR-DWS compared to SR-DLS and results in mean particle size data only. Especially in top down applications such as nano-milling, turbidities and concentrations would become difficult for characterization in real-time with conventional methods but possible with SR-DWS. Development work in this area is also part of the PAT4Nano project.



The NanoFlowSizer



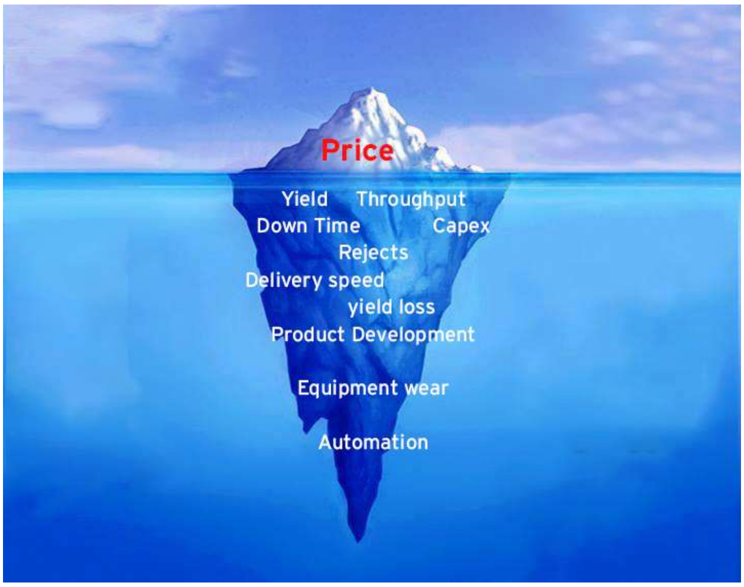
The NanoFlowSizer is a new and unique innovative system for continuous, real-time nanoparticle size characterization of colloidal systems, nanosuspensions, nanoemulsions and other dispersed nanoproducts directly in manufacturing processes (inline) or in a laboratory setting (offline). As inline instrument, the NanoFlowSizer is a powerful non-invasive Process Analytical Tool (PAT) allowing close monitoring of particle size characteristics in your process in either development laboratories, pilot plants or commercial operations, without the need of sampling. NanoFlowSizers can be integrated easily in any production process by using flow-through cells allowing high speed measurements of even highly turbid nanomaterial using new SR-DLS/DWS technology and smart XsperGo software.

“THE VALUE”

PAT enables inline nanoparticle size measurement, independent of market or application. Either used in batch manufacturing or continuous operations, both applications could potentially result in significant cost savings. Enhanced product quality through real-time process control will include major benefits for nanoparticle development and manufacturing:

- → Reducing batch-scrapping; Out of specification products, as the risk for batch-scrapping (e.g. from over-milling) is reduced with real-time process monitoring. The end point for a process such as milling is unknown, and the danger of under- or over-processing and thereby leading to product failure is prevalent.
- → Production time savings; unnecessary processing by allowing automated process endpoint determination. Furthermore reduction in processing time/energy will also be beneficial to sustainability ambitions as well as reducing wear and tear of expensive capital processing equipment such as nano-mills.
- → Higher product throughput: inline analysis is monitoring the process in real time. This will reduce processing time, improve product quality and reproducibility, and thereby lead to fewer product rejections resulting in improved product throughput. The movement from batch to continuous processing can also be realized as an option and this can provide a significant step-up in throughput.

- → Speed up development cycles: Inline analysis will time compared to off-line particle size monitoring in the R&D environment evaluating lab scale research quantities to development pilot scale. It will moreover critically allow accurate process end-point evaluation.
- → Supporting right first-time pilot and commercial scale manufacture.
- → Reducing contamination risks to sterile nanosuspensions induced by invasive sampling e.g. all injectables are produced under sterile conditions with a very rigorous and specific pass/fail criteria for bioburden.
- → Real-time process evaluation and implementation of feedback loops to correct for any deviations in measured quality attributes.



Although for various applications some of the aforementioned benefits might differ, it has been reported that annual savings, could be in excess of millions of dollars. A business case outlining details on each of these saving potentials should be individually developed, depending on the application.

InProcess-LSP is an active member of the PAT4Nano consortium.

The PAT4Nano project is funded under the Horizon 2020 program: project 862413. PAT4Nano aims to develop Process Analytical technologies (PAT) tools to enable the continuous, rapid, and reliable online/inline measurement of nanoparticles. In PAT4Nano the consortium end user partners are involved in diverse applications in pharmaceuticals, inks/pigments, and materials for catalysis, batteries, and glass manufacture. They are working in very close collaboration with various technology providers and research centers. More information can be found on [*www.pat4nano.com*](http://www.pat4nano.com)

PAT4nano
Real-time Nanoparticle Characterization