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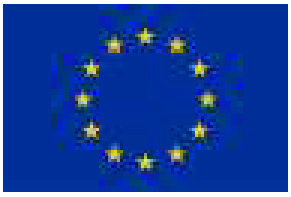

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Publishable Executive Summary

This deliverable discusses the state-of-the-art measurement techniques in the context of particle sizing and industrial application. Inline and offline techniques are shortly discussed, with a focus on the inline applicability of the considered techniques. In this discussion the terms inline, online and atline need to be discriminated. Inline monitoring will happen directly inside the process, at best faster than observable process changes. Online analyzers are connected to the process (e.g. in a bypass) and ideally have a similar time resolution like inline analyzers. Atline devices are separated but close to the process, while offline analysis happens spatially and timely separated. [1]

The technical state of the art in respect to selected processes are covered in more detail in deliverable 1.3.

Introduction

Nanoparticles have a huge field of applications nowadays. [2] The size of these particles strongly determines the properties of the products created and therefore there is a need to control particle size to ensure stable product quality. However, inline measurements of the particle size distribution are still challenging and not established in industrial processes. Currently particle size analysis is mostly done offline, which leads to a time gap between the results and the event and as a result the process cannot be influenced on the basis of these measurements. Since these offline techniques are often dilution based, product properties change and cannot be compared to the bulk material during the synthesis. Reasons why inline techniques cannot be applied are diverse. High concentration, multiple light scattering, harsh reaction conditions, and no capability to calibrate or model the reaction are omnipresent and hinder offline measurement techniques to be applied inline.

We want to give a short overview of available and/ or promising technologies for inline and offline particle characterization. It will be divided in two parts. The first will contain short descriptions of inline technologies and their applicability in industry. The second part will contain offline reference technologies, which are often applied instead of inline measurements. For some of these, ongoing research is being done to apply them inline, but none of those have an industrial inline application yet.

Inline Technologies

There are quite some inline technologies which are applied in industrial production processes. However, only a few of them primarily address particles sizes. The following list will focus on those which are reported to measure particle sizes to at least some degree. We want to emphasize that this list is not a complete list of techniques available, but contains those which are used in industry or have huge potential to be used in the future.

Photon-Density-Wave Spectroscopy (PDWS)

Photon-Density-Wave Spectroscopy is a calibration free, inline measurement technique that is based on multiple scattering and Mie-theory. Fibres emit intensity modulated laser light into the light scattering sample, which is detected at certain distances by another fibre. Analysis is done by a vector network analyser with respect to the change in intensity and phase shift at certain fibre distances. With both of these parameters it is possible to determine the absorption coefficient μ_a and reduced scattering coefficient μ_s' of the sample independently of each other. Based on Mie-Theory μ_s' can be translated into the particle size. [3] This approach is very well suited for highly scattering dispersions [4] as they occur often in industrial environments. [5] It can be applied inline, without sample taking and without dilution or sample preparation. Currently this technique is at TRL 4 and is aimed to be developed further within the NanoPAT project to TRL6. However, there are already a lot of different processes addressed in publications, among them being polymer synthesis, emulsion formation, crystallization and fermentation. [4,6-9] Current technology development aims at improving the analysis of polydisperse samples [10] and accessing the particle shape.

IR-/NIR-Spectroscopy (IR/NIRS)

IR-/NIR-Spectroscopy is based on the absorption and scattering in the IR-/NIR-Wavelength range. For inline approaches light is introduced by an ATR-probe and the measured spectrum is analysed. Since the light is usually absorbed to excite vibrations of chemical bonds, this technique is very well suited to see chemical changes during a process and therefore to determine concentrations of the product as well as intermediates. [11] However, a good understanding of the occurring chemicals and calibration with model building is needed to use it for process control. There are some publications on determining average particle sizes of polymers. [12-13] Due to the need for calibration, interpretation of this data is often complicated and not straight forward. A lot of effects occur and take place beside the growth of particles during a reaction, which has a rather small influence on the signal in comparison to chemical changes. IR-/NIR-Spectroscopy is state-of-the-art and applied in many processes to determine the chemical composition. Especially in the field of pharmaceutical and food quality assurance it is used as characterization tool (mostly offline). [11] To our knowledge, for nanoparticle systems it is not yet applied in industry to measure particle sizes.

RAMAN-Spectroscopy (RAMAN)

RAMAN-Spectroscopy is based on the RAMAN effect, i.e. on inelastic light scattering on molecules. This is a low photon yield scattering effect, which is often overshadowed by occurring fluorescence. Therefore, high intensity of the primary laser beam is needed, which may cause problems with e.g. explosive chemicals or molecules that are sensitive for radiation. If measured correctly it yields a high resolution spectra of the components during a reaction, similar to the IR-/NIR-Spectroscopy. [14] Due to the different transitions excited by the light, different molecules can be studied, e.g. Raman can work in watery environments in contrast to IR/NIR. Concentrations of the reactants can be determined if the system is modelled and calibrated correctly. In the recent year RAMAN-Spectroscopy became more popular and commercial devices are nowadays often applied in industry. It is used in medical fields as well as in chemistry. [15] However, even though RAMAN was occasionally used to track particle growth [13] it is hard to get reliable data, since the effects are overshadowed by the signals of chemical progression and calibration is needed to get the information.

Ultrasonic-Spectroscopy (US)

Ultrasonic spectroscopy is based on the emission of ultrasonic waves into the sample at different frequencies. Due to the interaction of the ultrasound with the particles in the medium a dampening of the wave can be observed. Analysing the signal with models for the dampening can give particle size distributions in a wide range of sizes and concentrations. Dilution is usually not necessary. [16] However, to get a correct particle size distribution a lot of assumptions have to be met, e.g. knowledge of the speed of sound in the medium and particles, the density of the sample, the heat capacity and the thermic expansion coefficient. [17] These can be challenging to obtain for the system of interest, especially in an industrial environment with unknown substances and unknown reaction intermediates. Additionally, influences like gas bubbles have a big impact on the results. [18] Additionally, sensitive products can be destroyed by the ultrasound treatment. [19] There are publications on inline particle sizing with a focus on large particles and aggregates. [20] However, for nanoparticle size analysis ultrasound spectroscopy has not yet become a factor in industrial application, even though there are commercial devices for example by Horiba.

Turbidity Spectrometry (TUS)

Turbidity Spectrometry is based on scattered light of particles or droplets in a dispersion. Depending on the particles concentration, different measurement configurations can be adopted. For relatively low concentrations the absorption is measured in transmission, for opaque systems the backscattering is collected in reflection. In contrast to PDW-Spectrometry absorption and scattering cannot be divided and will be measured as a sum. It can be very sensitive and have advantages at low particle concentrations, where only single light scattering occurs. As soon as multiple scattering occurs, saturation effects take place, which make it difficult to calibrate these kind of probes for higher particle concentrations. In the past turbidity probes where often used in bio applications, as well as to detect slight turbidity, e.g. when investigating water pollution. [21] Most of the time these measurements were carried out at a certain wavelength. New approaches use the whole visible spectra to gather more information. [22-23] One approach that uses the spectral information gathered by a turbidity probe is TUS [24], which is part of the NanoPAT project to detect particle size distributions and will be further developed to TRL6.

Inline Light-Microscopy

For larger objects inline optical microscopy is a nice tool to visualize the growth of particles or crystals. However, usually only structures above 1 µm can be resolved, which makes this technology hardly applicable for nanoparticles. Additionally, the analysis of the pictures taken during a reaction is often challenging since the amount of data is huge and image processing often lacks behind. Even though there are commercial solutions trying to cumulate the information into process trends. Since this kind of technology gives an easy access to size and morphology of the products, it is applied in recent bioprocesses and crystallizations, [8, 25-27] but mostly only in non-producing environments to understand process fundamentals.

Focused beam reflections measurements (FBRM)

Based on a measurement of the chord length of particles by a rotating laser focus, FBRM is only able to address particles larger than 1 µm. [28-29] However, one has to be aware that chord length distributions cannot be transferred into particle distributions based on the diameter and therefore it is not possible to directly compare these. Nevertheless FBRM is still one of the few calibration free, inline methods to get a hint on the particle size. The FBRM technology is available to the industry for quite a while, commercial solutions exist e.g. from Mettler Toledo. Still it is not commonly applied for nanomaterials, nor is it used in many industries. It still holds a lot of potential as recent publications in the field of material science show. [30-31]

Optofluidic Force Induction (OF2i)

OF2i is based on the tracking of the diffusion of particles through a channel. With the help of a laser a photonic force is applied to the particles in the channel, influencing the flow of these particles. [32-33] By tracking the induced movement the particle size distribution can be determined with the help of a model and special tracking algorithms. [34] This technique is at TRL4 and not yet applied in industrial cases, but shows great potential, since it can address a large range of particle sizes (20 nm – 10 µm). Development will be taken to a new stage of TRL6 in the NanoPAT project.

Offline Technologies

Nano particle characterization is currently done to the greatest part by offline measurement techniques. These are state of the art in industry and used since decades. However, these have limitations, especially concerning the concentration of particles. There are efforts to make some of them useable inline or in a bypass, but to our knowledge none is used in an industrial environment as inline techniques.

Electron Microscopy (EM)

The theoretical resolution of a typical electron microscope is roughly 200000 times better than the resolution of an optical microscope, since resolution is, according to Abbes law, related to the wavelength which is used to take an image. [35, S. 804] The way electron microscopes work is very similar to optical microscopes with the main difference of using electric and magnetic fields to diffract the electrons instead of optical lenses. [35, S. 805]

Due to the interactions between accelerated electrons and a sample low energy secondary electrons (SE), higher energy backscattered electrons (BSE), Auger-Meitner electrons and x-rays are produced. Different electron microscopy setups make use of different parts of these signals to investigate the morphology or the elemental composition of NP's. [36, p. 140-141] This flexibility in the selection of the signal and the related information is a strength of electron microscopy in comparison to other NP characterization technologies.

Scanning electron microscopes (SEM) scan a focused electron beam usually linearly across a sample. Typically, BSE and SE are detected. While BSE give a material contrast in the image the detection of SE leads to a topographical impression of the sample surface. [37, p. 1-6] For example Ayaz et al. [38] studied the surface of leaves and pollen of mint plants using SEM. The authors underlined the importance of SEM studies in the taxonomy of these plants.

In transmission electron microscopes (TEM) electrons are transmitted in a parallel beam through a sample. [35, p. 806] The scattered and unscattered primary electrons are used to create the image [36, p. 141] by a material and phase contrast. [39] Martínez Espinosa et al. [40] realized a green synthesis of silver nanoparticles using a plant extract as a reducing agent. High-resolution TEM images revealed particles with a diameter between 15 nm and 50 nm and hexagonal lattice structure, which was an unexpected result as similar synthesis procedures usually lead to cubic lattices.

Despite its versatile analytical approaches EM is limited by sample requirements. If the sample is not conductive enough charging artifacts might occur. These are usually suppressed by coating the sample with a conductive film. However small structural features might be hidden by the coating. [41] Recently the KLA-Tencor Corporation applied for a patent about a SEM apparatus for mitigating charging artifacts. [42]

Furthermore, samples investigated by EM need to be stable in a vacuum. Unprotected solvents will evaporate, hence structures and processes related to the solvent will be influenced. [40] Particle dispersions and biological samples can be addressed by special sample preparation methods, like freeze fracturing and etching. [42, p. 814-819]

Environmental scanning electron microscopy (ESEM) can account for both charging artifacts and instability of samples in high vacuum. [43] Rykaczewski et al. [44] demonstrated how ESEM can be used to study the formation of a film of Al_2O_3 NP's on condensing water droplets in situ. Nevertheless, the pressure in ESEM devices typically doesn't exceed a few millibars. [43]

For NP's that are stable in vacuum without a solvent more standard preparation methods might be used, such as depositing them on a carbon film supported by a copper grid. [36, p. 142] Still sample preparation remains the limiting factor for use of EM for monitoring NP production processes.

Recently Aliyah et al. [45] followed the growth of Ag@Au nanorods inline using liquid-cell transmission electron microscopy (LCTEM). However, their study was conducted on the sub-milliliter scale. Consequently, state-of-the-art EM methods are not capable of monitoring industrial batch syntheses of NP's in real time. Nevertheless, EM is an important offline reference tool and commercial solutions are available as benchtop device or highly accurate room filling devices.

Dynamic Light Scattering (DLS)

During a DLS measurement the investigated NP dispersion is irradiated with laser light. The NP's scatter the light and the secondary waves interfere with each other. Hence, constructive or destructive interference can be observed depending on the scattering angle. Since the NP's undergo Brownian motion their relative positions change with time. Hence in a certain scattering angle a fluctuating intensity can be measured. The speed of this fluctuation is correlated with the diffusion coefficient of the scattering NP's, which is related to their size. [36, p. 728]

DLS devices are commercially available by different companies (e.g. Anton Paar GmbH, Malvern Panalytical GmbH, Brookhaven Instruments) and the technology is established in research and industry. Nevertheless, the use of DLS measurements for monitoring NP production processes is limited. The size of the investigated NP's should fall between a few nanometers and approximately 2 microns. [36, p. 729] Also the Stokes-Einstein equation is often used to relate the diffusion coefficient of NP's to their size. This is only applicable to spherical NP's. [46, p. 428] However the number of scientific works dealing with anisotropic NP's is increasing year by year. [47]

Another limitation of DLS measurements is the sample concentration. If the NP concentration is too high multiple scattering occurs and the NP size cannot be calculated correctly. If the concentration is too low, too few scattered photons might be detected for a sufficient signal to noise ratio. [48] However industrial relevant dispersions can reach up to 70 mass-% of NP's. [5, p.287] These need to be diluted to be in a suitable concentration range, which is not applicable for inline measurements. Additionally, dilution might affect the sample properties such that they deviate from the NP's in the process environment. [49]

Recent works have tried to tackle the issues of DLS measurements with NP shape and concentration. F. E. Berger Bioucas et al. [50] have studied gold nanorods with polarized DLS. Using their setup, they were able to minimize multiple scattering effects and sample heating which is associated with concentrated samples of absorbing NP's. Their results indicate the possibility to determine the aspect ratio of the rods based on the comparison with suitable models.

At last industrial application of DLS for the inline monitoring of NP production processes is also limited to systems that are not stirred as this would introduce non-diffusive motion of the particles. Stirred systems might be addressed by an online solution using a bypass at the reaction vessel. [51]

Considering all the limitations of DLS measurements this technology isn't suitable for the inline monitoring of most NP production processes. Bypass solutions and specialized setups might be a workaround for some of the afore mentioned issues. Nevertheless, DLS is an established tool for offline reference analytics.

Laser Diffraction / Static Light Scattering (LD / SLS)

Laser diffraction, also known as static light scattering, is based on the angle dependent scattering of light at a particle. A laser illuminates the sample chamber and a Fourier lens bundles the light on a plane detector. Depending on the scattering pattern the particle size distribution can be calculated. For these calculations Mie-Theory can be used, or for larger particles the Fraunhofer diffraction theory is a good approximation to get the correct sizes. [52] There are some approaches that additionally use more backscattering angles, like multi-angle-light scattering (MALS) or more light sources and polarization, like Polarization Intensity Differential Scattering (PIDS), that work more or less on the same principle of detecting the scattering pattern of single scattering particles. These techniques are used as standard reference methods in industry and academia and commercial devices are available by different companies. However, it is an offline method that needs dilution of the samples down to 1:1000, which might change sample properties and sizes. [36, p. 728] The experiments could be done in a bypass system to address the offline character [54], but it's complicated to implement into an industrial environment, expensive, and most of the time not applicable because of high concentration of light scattering particles during the process. The size range that could be addressed by such systems, usually starts at around 100 nm and goes up to several mm, where sizes in the µm range works best. Even though, Laser diffraction is no inline technique and is not made primarily for nanoparticles it is one of the most used reference technologies all inline techniques have to compete with.

Disc Centrifuge

A large variety of particle sizing technologies have been developed that rely on analysis of the sedimentation behavior. These methods differ by the used force field, the type of the determined size distribution or the initial spatial distribution of particles during the measurement. They commonly use a relation between the sedimentation speed and the particle size given by Stokes law, [55, p. 300-302] or a modification of it for the use of centrifugal fields. [56, p. 271] This short review shall be limited to the use of centrifugal fields, because small particles won't sediment by gravity or their signal will be broadened due to their Brownian motion. [56, p. 270]
In general sedimentation methods can also be divided into integral and differential methods. Since it's challenging to account for the initial conditions in integral centrifugation approaches and convection currents can hamper accurate results [56, p. 272] this short review shall be limited to differential methods.
Differential sedimentation centrifugation (DSC) can be realized by disc centrifuges. [56, p. 274-275] There are commercially available devices by Brookhaven Instruments or CPS Instruments.
Due to the need of a centrifugal field DSC methods can't be used for the inline monitoring of NP production processes. But also atline solutions will be limited due to several factors.
Usually particle sizes between 10 nm and 50 µm can be analyzed. For certain particle materials this range might be extended. [56, p. 270; 3]
The investigated size range is closely related to the run time. Depending on the exact conditions and the used device measurement time can be as short as 4 min, but can easily exceed several hours. The latter should be avoided because of peak broadening due to Brownian motion of the particles. Acceptable measurement times will vary around 20 min and can be achieved for broad size distributions by gradually increasing the speed of the centrifuge during the measurement. [56, p. 283-285]
Furthermore, stable particle sedimentation will require a density gradient in the centrifuge. There are many possible ways to build up a density gradient in aqueous and nonaqueous media.

[56, p. 273-274] EVONIK for instance analyzes their synthesized silica particles in a disc centrifuge following the norm ISO 20927:2019. Here an aqueous sucrose gradient is suggested.
Another limitation of DSC measurement is given by Stokes law, which is used to calculate the particle sizes, but holds only true for spherical particles. [56, p. 289] Nadler et al. [57] have investigated different carbon nanotubes treated with different dispersing methods using a disc centrifuge. Their resulting particle size distributions were responsive to the tube diameter, but not to their length.
Also, it should be mentioned that special setups are needed, if the particle density is lower than density of the dispersion medium. [56, p. 285-287]
Considering the relatively long measurement times and the difficult data interpretation for non-spherical particles, DSC measurements are not well suited for the monitoring of nanoparticle production processes. Nevertheless, they remain a valuable offline reference tool owing to their high resolution. [56, p. 277-282]

Various

X-Ray Scattering (SAXS / WAXS)

By the use of X-Rays as radiation source, the scattering patterns of mostly solid samples can be analysed according to the size or particles. [58-59] However, this technique is seldomly used for industrial processes outside of research applications, because it is difficult to set up and not well suited for online or atline measurements. Even very fast processes can be investigated in a very small scale. [51]

Conclusions

Looking at the field of technologies that are able measure particle size and especially particle size distributions only few are inline techniques. Of the inline techniques, IR/NIR and RAMAN stood out as most used inline spectroscopic technique. However, both are not used in industry for particle size analysis. There are some particle sizing inline technologies which have a huge potential to be used in industrial environments, and these will be developed to a TRL within NanoPAT.

Table 1: Pending activities

Description of pending work that was not achieved at the time of submitting the deliverable	N/A
Time at which the result is expected	N/A
Place where it will be reported	N/A

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