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Deliverable 3.3	D3.3 (Linked to Task 3.1, 3.2, 3.3) Summary of OF2i applications for NPs monitoring
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CONTENTS

I. INTRODUCTION

Deliverable 3.3 "Summary of OF2i applications for NPs monitoring" (D3.3) summarizes the main achievements and work done as part of Work Package 3 (WP3), "OptoFluidic Force Induction (OF2i) Development" (see Fig. 1) which is led by Medical University of Graz (MUG). The producer of this document is Brave Analytics GmbH (BRAVE). The following work is performed within the European Union Horizon 2020 Research and Innovation Program, under the Grant Agreement number 862583.

WP3 is connected to Objective 3 aiming at developing an online monitoring tool for the characterization of Hydroxyapatite and ceramic nanoparticles. This includes the setup of small scale lab reactors (Task 3.1), lab tests at the research and technology organisation (RTO) for the relevant case studies (Task 3.2) and comparison of data with reference methods (Task 3.3).

Following results were obtained in close cooperation with our industrial partners Fluidinova (FLU) and Creative Nano (Cnano). They provided help with establishing small scale lab reactors as well as the synthesis processes. Most of the experimental work has been performed at the RTO MUG with reference measurements being performed on site and externally.

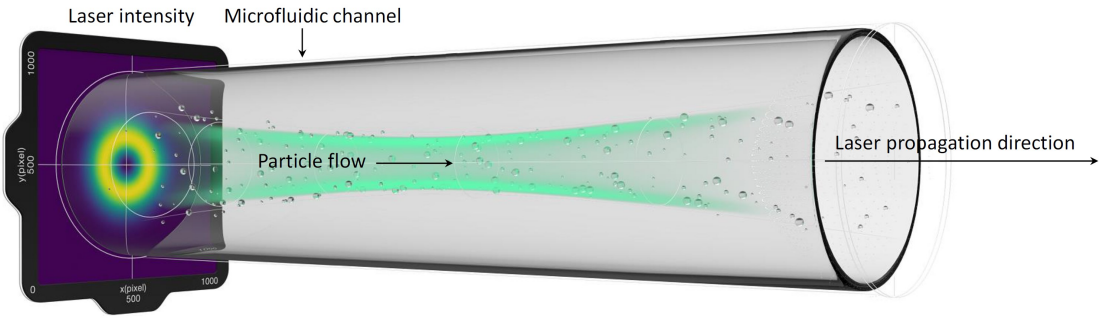

Figure 1. Schematics of the optofluidic force induction (OF2i) scheme.

II. OF2I SCHEME

The Optofluidic Force Induction (OF2i) technique is a Process Analytical Technology (PAT) based on the principle of two dimensional optical tweezers for high-throughput single particle analysis [1–3]. The particles under investigation are pumped through a microfluidic channel and become optically trapped. By monitoring the light scattered by the particles through a microscope objective, one obtains information of the scattering cross sections and via particle tracking the velocities and live visualization of individual particles .

These signals are used to calculate particle size and time-dependent number-based size distributions in real-time. First, the scattering signal can be evaluated via the well-known Rayleigh-Scattering theory [4] for particles of size well below the wavelength of the exciting laser. Second, we can use the information of particle position over time with our OF2i model which assumes spherical and dense particles. The particle size can then be obtained by solving Newton's equations of motion together with the measured particle velocity

$$\boldsymbol{v}(\boldsymbol{r}) = \boldsymbol{v}_{\text{fluid}} + \frac{\boldsymbol{F}_{opt}(\boldsymbol{r})}{6\pi\eta R}, \tag{1}$$

where $\boldsymbol{v}_{\text{fluid}}$ is the flow velocity, $\boldsymbol{F}_{opt}$ are the position dependent optical forces, η is the viscosity of the fluid and R the particle radius. For a more detailed introduction we refer you to paper describing the method [1].

To perform a valid measurement with OF2i certain requirements have to be met. First, since OF2i is a scattering based method, the optical contrast must be high enough. This means that the ratio of the refractive indices of the particle n_p to the surrounding medium n_b must be high enough in order to detect scattering signal. Secondly, being a single particle based method, OF2i requires low particle concentrations to avoid excessive scattering. For quantitative evaluation the refractive indices of the particles and medium, respectively, must be known. This enables further the measurement of extremely low concentrated samples or where samples might not be readily available. Thus, highly concentrated samples (often encountered in industrial processes) require dilution, which is done automatically by the sensor.

In some cases, sample kinetics can be observed since optical forces are inherently induced with the OF2i method. Depending on the sample this leads to more sophisticated insights into e.g. particle agglomeration behavior as seen in section III A.

III. CASE STUDIES

For the SiC case study we cooperated closely with our industrial partner Cnano by installing a small scale lab reactor at the RTO. Reference measurements were performed using common offline methods such as Dynamic Light Scattering (DLS) and Laser Diffraction (LD). Furthermore, the complex sample behavior was observed and analyzed by generating a unique feedback parameter using the OF2i method which might lead to unforeseen IP within this project.

The Hydroxyapatite case study involved cooperation with our industrial partner FLU for the installation of a small scale lab reactor to perform synthesis and measurement of Hydroxyapatite nanoparticles. For consistencies sake reference measurements have been performed in the same fashion as for the SiC case study. Similarly to the SiC case study particle size and concentration has been measured.

For both case studies online and offline OF2i measurements have been performed successfully. In order to do so BRAVE accomplished the installation of PAT sensors at the RTO. Subsequently the samples have been synthesized in close cooperation with FLU and Cnano at the RTO in order to simultaneously perform online monitoring using the OF2i method. In both cases the influence of stirring as wells as of ultra sonication has been observed. Particle size distributions and concentrations were measured via the OF2i velocity model and depicted over time showing dynamic insights.

Comparison with reference methods has proven to be challenging due to the varying nature of each measurement technique and complex sample behavior. However, the results obtained via OF2i are in the same size range as the reference methods. More rigorous experiments are planned to get deeper understanding of the sample behavior.

Even in disregard of the known improvement possibilities we feel optimistic about the upscaling step within WP6. Two demonstrators have been built for the installation at the pilot plants within WP3. First meetings were held about the specification of upscaling and adaption requirements of the PAT sensors for a successful installation with the industrial partners.

A. SiC Case Study

In our first case study we have performed measurements with SiC nanoparticles. For this the synthesis has been performed according to the instructions given by Cnano at lab scale. SiC nanoparticles are spherical with a nominal diameter of 100 nm. However, electron microscopy images show aspherical particles with varying size since SiC tends to agglomerate in water.

Even with this in mind we see our results in good comparison to reference methods such as Dynamic Light Scattering (DLS). However, results obtained via Laser Diffraction (LD) differ significantly from the performed DLS measurements indicating higher polydispersity. We have observed particle sedimentation which can easily be overcome by stirring the sample, achieving the same effect as the circulating pumps at the pilot lines. Due to this no reasonable results could be obtained using nanoparticle tracking analysis (NTA) as a refernce method.

In the following we show example measurements of the SiC case study. Figure 2 shows the influence of continuous ultra sonication on the time dependent particle count in our system which is an indicator for particle agglomeration and sedimentation.

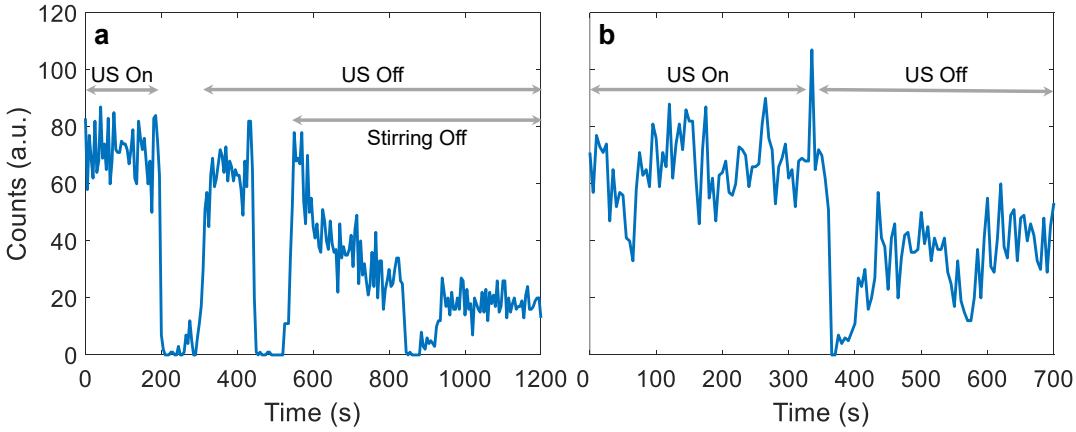

Figure 2. Particle count using the OF2i method for the SiC case study. The counts were averaged over five seconds each. Experiments performed include the use of ultra sonication (US) as well as magnetic stirring in the sample vessel. Notice the dependence on US by time evolution of the counts function in (a) along with deactivation of stirring. The influence of US without additional effects is shown in (b), where a significant change in particle count occurs over time.

Since ultra sonic treatment decreases the amount of agglomerates (hence increasing the amount of single particles) and stirring reduces sedimentation we can easily observe differences in particle counts over time.

In another measurement we show the continuous measurement of particle size and concentration according to our velocity model. Figure 3 reports the particle size, again, comparing results obtained without (a) and with use (b) of ultra sonication. We further notice some larger particles in the size range of about 1300 nm (i). This is in good agreement with Cnano's DLS measurements in the absence versus during the application of ultra-sonication. More specifically, after a 5 hour experiment the particle size obtained with DLS is 1240 nm in the first case while under sonication conditions the size is 1000 nm.

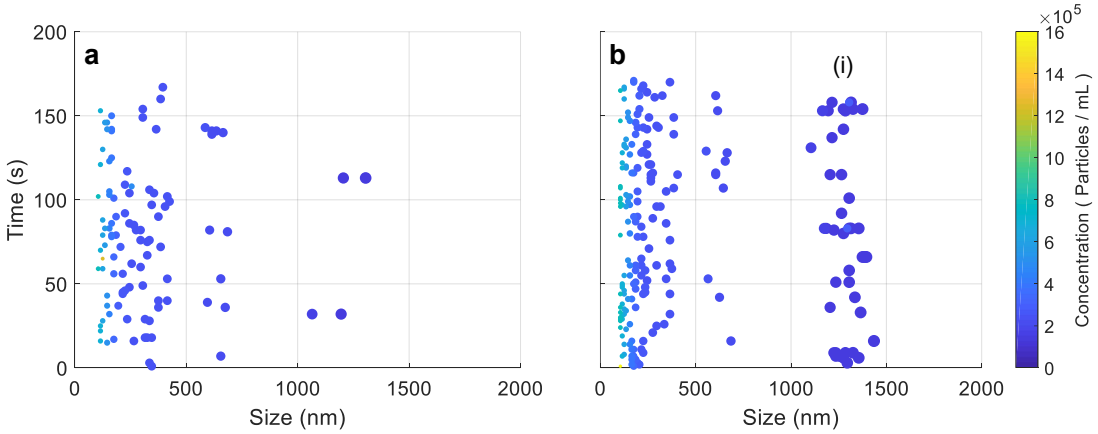

Figure 3. OF2i particle size distribution over time without (a) and with (b) US treatment. The color encoding indicates the particle concentration during experiment. Particle size is evaluated for the same measurement shown in figure 2 (b), each data point averaged over one second. The dot radius scales inversely proportional to the concentration.

In summary, the measurements of the SiC case study were successful. Particle agglomeration has been monitored in a continuous manner and matches our expectations in regard of ultra sonication and stirring.

B. Hydroxyapatite Case Study

In our second case study we have investigated the measurement of Hydroxyapatite nanoparticles. First, MUG has performed the synthesis using the lab scale reactor developed and provided by FLU. The maturation process of the synthesized product has been monitored by OF2i. Again a model for spherical and dense particles was assumed although imaging techniques showed rod shaped particles. This may also be included in a further model update. This however was not impeding us in observing relevant process parameters such as particle size and count. For the sake of consistency we performed the same reference measurements as for the SiC case study.

In figure 4 we report particle count over time for several hours. We observe an increase of particle count further indicated by linear interpolation. One challenge with this sample was the high solid content and viscosity which led to occasional clogging and required manual intervention (blanks in the figure e.g. 3-5 h). This has already been addressed by a new sample cell design as well as adapted tubings.

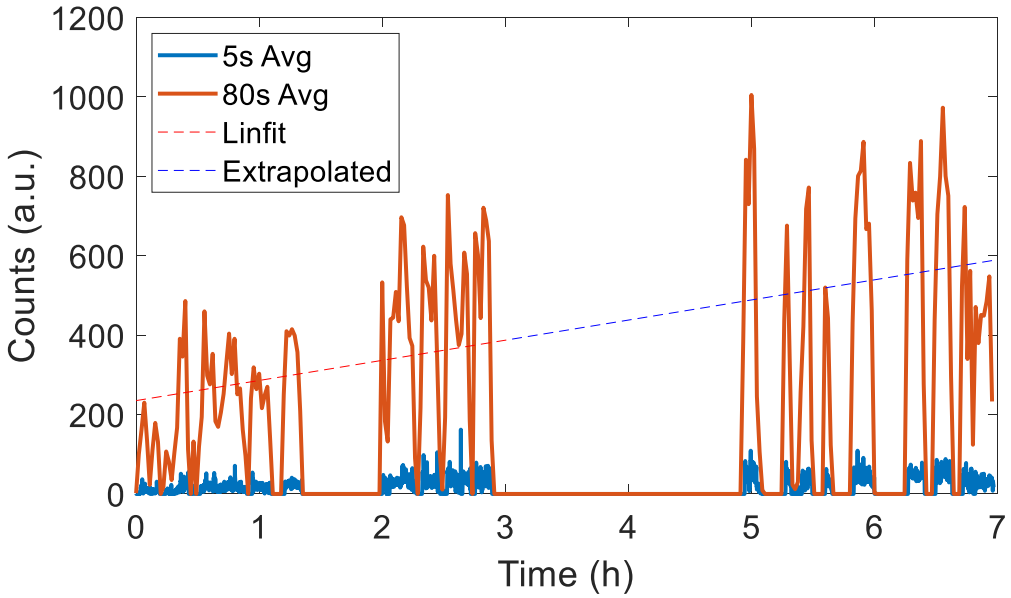

Figure 4. Particle count using the OF2i method for the Hydroxyapatite case study. The counts were averaged over five and 80 seconds over time. Experiments performed include the use of US as well as magnetic stirring in the sample vessel. The dashed lines describe the linear fit (red) and the extrapolation (blue) of the linear fit.

The concentration evaluation does not give full insight yet. If we combine concentration calculation with particle size, however, we can assign the concentration increase to a certain size range. These results are shown in figure 5 where we can see the concentration increase in the comparably small size range.

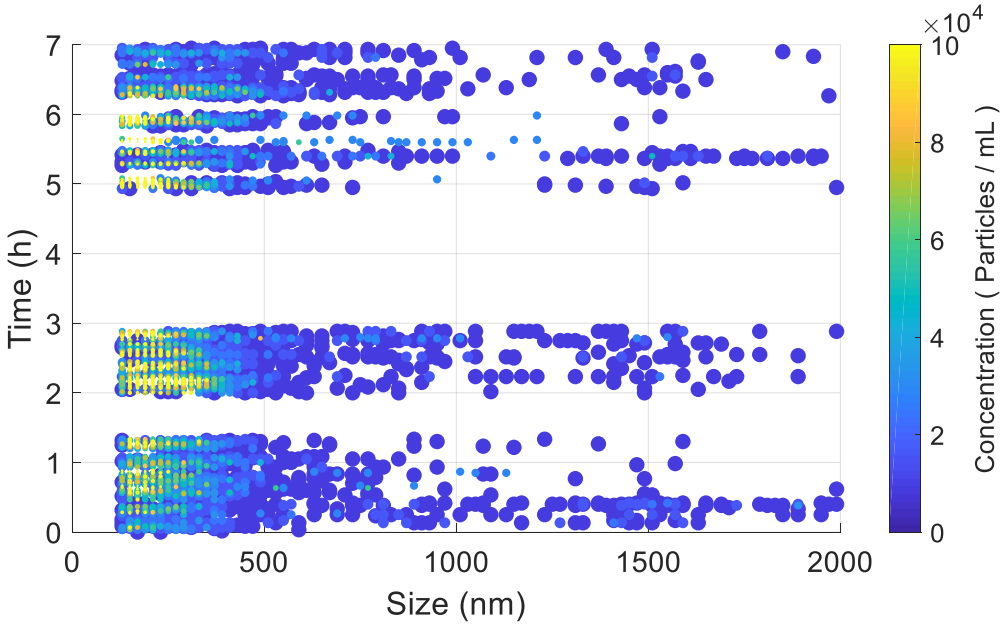

Figure 5. OF2i particle size distribution over time. The color encoding indicates the particle concentration during experiment. Particle size is evaluated for the same measurement shown in figure 4, each data point averaged over 60 seconds. The dot radius is inversely proportional to the concentration. The colorbar was scaled to a concentration of 10^5 for better visualization.

We have also performed offline DLS, NTA and LD measurements at a hourly rate as a reference. Again, in this case LD and NTA measurements were not feasible or gave reasonable results. The DLS measurements, however, did match the dynamics of the maturation process monitored by the OF2i method and showed decrease in average particle size with progressing time.

Further we have performed measurements for a finished product which reflects the expected performance. Thus, the monitoring of the Hydroxyapatite case study is concluded as a success.

IV. COOPERATION

Although highly anticipated by the Horizon 2020 program, in person meetings and visits were hardly possible due to COVID-19. Nevertheless, the cooperation via online meetings were always fruitful and enthusiastic and we are looking forward to visiting our partners within WP6. After many online meetings we finally managed to meet in person at the general meeting in Potsdam where the progress and results of all WPs has been presented. We are grateful to University of Potsdam for the organization of this assembly. The in person meeting is shown in the picture below.

Figure 6. General Meeting in Potsdam - June 2022

Figure 7. Official handover of BRAVE PAT sensor stations to the RTO Medical University of Graz. Middle: Two sensor stations specifically developed for the two case studies, respectively.

The picture above shows the official handover of the BRAVE PAT sensor stations to the RTO Medical University of Graz. These are OF2i based devices for the monitoring of the ceramic nanoparticles as well as Hydroxyapatite nanoparticles at RTO scale pilots (Milestone 4).

We were happy to meet our industrial partners from Cnano at the NanoWeek 2022 conference in Cyprus where BRAVE has presented their OF2i technology. The conference was accompanied by fruitful discussions with our industrial partner at the poster session as seen in the picture below.

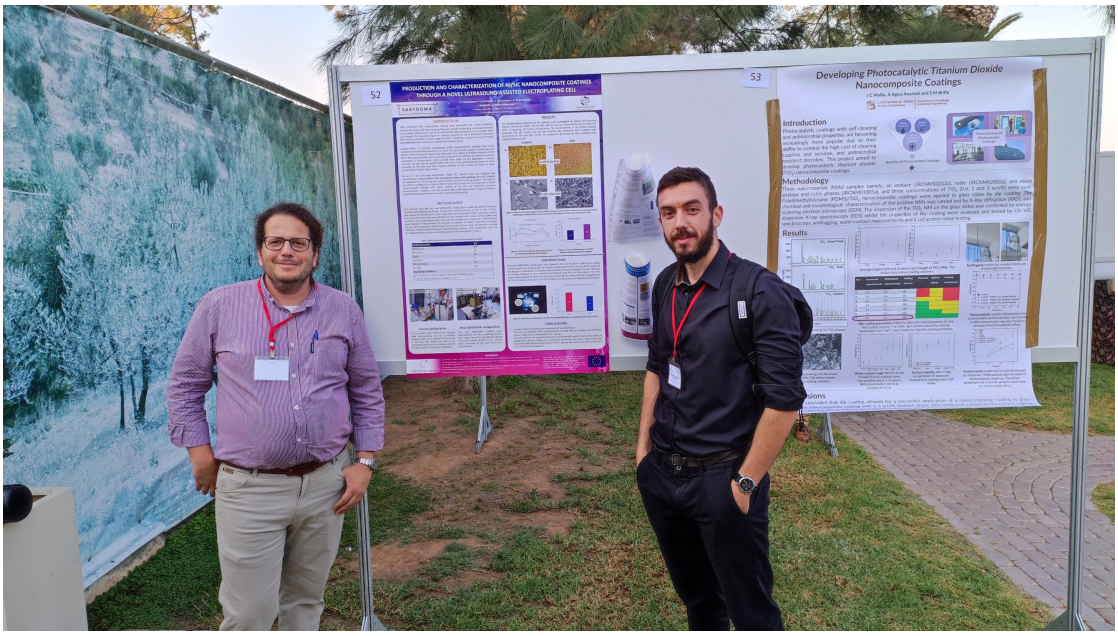

Figure 8. Industrial partners from Cnano presenting their latest work on ceramic nanoparticles.

Even with all the restrictions imposed by COVID-19 pandemic, a successful installation of the lab scale reactor provided by FLU was achieved at the RTO. Our partners from FLU assisted via online meeting to perform a first successful synthesis reaction. Partners from BRAVE, MUG and FLU are depicted in the image below.

Figure 9. Image captured during the online meeting with the industrial partners from FLU during synthesis reactor installation at the RTO MUG.

V. SUMMARY

The goals of WP3 have been reached successfully and in time. Cooperation with the industrial partners Creative Nano and Fluidinova have given a lot of insight in the capabilities of our approach to real-time particle characterization both in regard of methodology and sample dependencies. This was possible thanks to our highly responsive and cooperative industrial partners but also the consortium itself.

Although the results are very promising and agree with reference measurements, we are working on updating the OF2i velocity model to account for non-spherical particles and gain even more detailed results. Performed experiments and evaluations led to a new and promising process feedback parameter. Furthermore, we aim to tailor the sensor station to the specific needs of our partners regarding software and hardware specifications.

The upcoming task "Definition of upscaling specifications" within WP3 is ongoing and first meetings have already been held. The OF2i PAT sensor stations are prepared for the transfer to the industrial partners within WP6 after a few adaptions. Considering cooperation so far, we are looking forward to visits at the industrial plants for better preparation of future installments.

VI. BIBLIOGRAPHY

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