The EU FP7 NanoDefine Project

Development of an integrated approach based on validated and standardized methods to support the implementation of the EC recommendation for a definition of nanomaterial

SOPs, applicability range and method performance description for FFF coupled to counting techniques (spICPMS, ESI-CPS)

NanoDefine Technical Report D5.5

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The NanoDefine Consortium 2017

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under Grant Agreement n° 604347

NanoDefine in a nutshell

The EU FP7 NanoDefine project was launched in November 2013 and will run until October 2017. The project is dedicated to support the implementation of the EU Recommendation on the Definition of Nanomaterial by the provision of the required analytical tools and respective guidance. Main goal is to develop a novel tiered approach consisting of (i) rapid and cost-efficient screening methods and (ii) confirmatory measurement methods. The "NanoDefiner" eTool will guide potential end-users, such as concerned industries and regulatory bodies as well as enforcement and contract laboratories, to reliably classify if a material is nano or not. To achieve this objective, a comprehensive inter-laboratory evaluation of the performance of current characterisation techniques, instruments and software is performed. Instruments, software and methods are further developed. Their capacity to reliably measure the size of particulates in the size range 1-100 nm and above (according to the EU definition) is validated. Technical reports on project results are published to reach out to relevant stakeholders, such as policy makers, regulators, industries and the wider scientific community, to present and discuss our goals and results, to ensure a continuous exchange of views, needs and experiences obtained from different fields of expertise and application, and to finally integrate the resulting feedback into our ongoing work on the size-related classification of nanomaterials.

Bibliographic data

NanoDefine Technical Report D5.5

Report title: SOPs, applicability range and method performance description for FFF coupled to counting techniques (spICPMS, ESI-CPS)

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Publication date: 12/10/2017

Publisher: The NanoDefine Consortium

Place of publication: Wageningen, The Netherlands

Citation: Velimiroivc M., Laycock A.: SOPs, applicability range and method performance description for FFF coupled to counting techniques (spICPMS, ESI-CPS), NanoDefine Technical Report D5.5, NanoDefine Consortium, Wageningen, 2017

URL: http://www.nanodefine.eu/index.php/downloads/public-deliverables

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The NanoDefine project has received funding from the European Union's Seventh Programme for research, technological development and demonstration under grant agreement No 604347

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1 Glossary

Split ratio - the fraction of eluent flow from the FFF removed by the Cori-flow.

2 Abbreviations and acronyms

A4F	Asymmetric field flow field fractionation
BSA	Albumin standard
ESI-CPC	electrospray ionization-condensation particle counter
FFF	Field flow fractionation
NPs	nanoparticles
PSS	polystyrene size standards
RC.Net	Rapid Control (dot) Net
spICPMS	single particle inductively coupled plasma mass spectrometry

3 Summary

The performance of the interface prototype unit necessary for successful online FFF coupling to counting detectors is presented.

Special attention is given to the accuracy of the interface prototype split ratios and its implementation during online coupling of FFF with spICPMS for analysis of Au NPs.

This report also provides a new proposed technical setup to: (1) improve the range of dilution factors attain-able by the interface unit and (2) enable appropriate particle number concentrations in the sample suspensions to be obtained for particle counting by spICPMS after online coupling with FFF technique.

4 Introduction

The aim of NanoDefine task 5.4 was to develop a prototype interface unit which could be used to directly couple FFF separation methods to particle counting techniques such as spICPMS and ESI-CPS. The technical layout is reported in D5.4, while this technical report describes the performance of the interface prototype unit and its suitability for successful online coupling of FFF to particle counting detectors.

An extensive feasibility study on the coupling of FFF to the aerosol based counting technique (ESI-CPC) demonstrated that such an approach was incompatible. This is mainly due to the huge difference between the required sample flow rates for FFF (1 ml min^{-1}) and ES (<100 nl min^{-1}), as well as different eluents used in FFF that are not appropriate for ES analysis.

Therefore, this deliverable reports on the performance of the prototype interface unit to couple FFF to spICPMS.

5 FFF-spICPMS interface prototype

5.1 Software development for fully automated interface

The Eclipse FFF instrument can be controlled by typical Chromatography Data Systems, such as Agilent Openlab. Due to a change in the interfacing, implemented by Agilent, re-development of the Eclipse drivers according to the so called Rapid Control Driver Framework was required in order to be compatible with the prototype interface (make-up pump and Coriflow).

Figure 1 and Figure 2 show screenshots of the plugins developed for Openlab, which are embedded into the Dashboard established by Agilent. This was the first such RC.Net plugin developed by Superon and it took several months to reach this stage and the Plugins to be successfully tested.

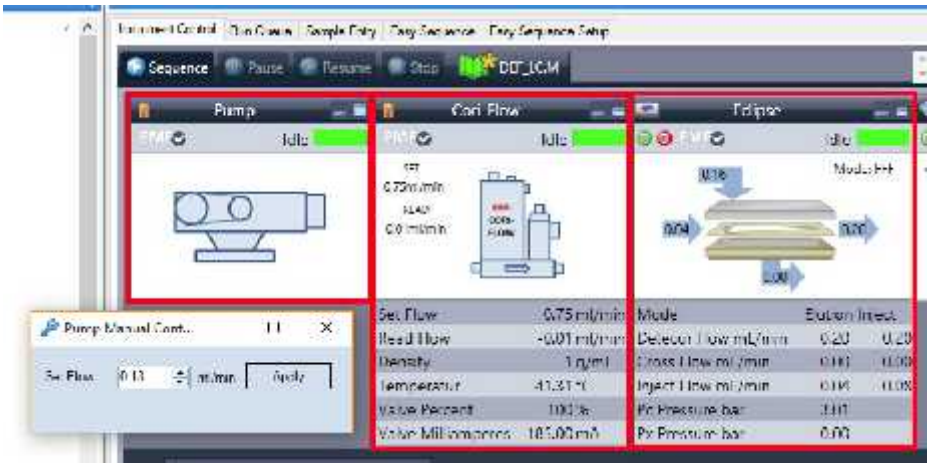

Figure 1: Screenshot of the 3 plugins in the Openlab dashboard.

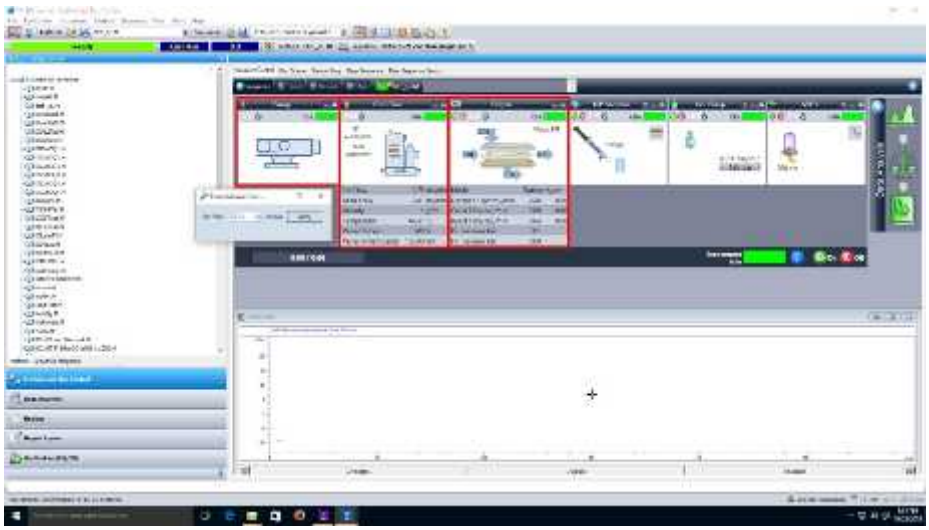

Figure 2: Full operators view for controlling the FFF and prototype interface.

The controller board developed by Superon is the limited to accessing and controlling only one CoriFlow unit. In addition Openlab has the limitation of being unable to access more than one Plugin at the same time. This avoids including all drivers in Openlab at once. To overcome this lag of control, Superon created additional stand-alone Software ("Control Center") to record the data and control one of the Coriflows and the pressure sensor. It can also be used for switching the diverter valve.

5.2 Training runs software

To enable the particle counting by spICPMS of eluent from A4F it is first necessary to reduce the particle number concentration. To achieve this with online coupling using the interface unit an estimate of appropriate dilution factors is required. Such estimates can be obtained from training runs performed prior to the online coupling. From observed particle size distributions and signal intensities, obtained from a training run, assumptions of the particle number concentration in the eluent, and therefore the required dilution factor to enable online coupling with spICPMS, can be made. Such software was developed by THERMO and interface prototype was assembled based on the estimated required dilution factors delivered from software.

6 The accuracy of the interface prototype split ratios (off-line tests)

In order to assess the accuracy of split ratios 1-50 of the interface prototype off-line tests were performed.

6.1 Materials and methods

The first experimental set up for testing the accuracy of split ratios of solutions (e.g. fluorescein, Sigma Aldrich) and particle suspensions of different sizes (e.g. polystyrene particle size standard of 46 ± 2nm, 102 ± 3 nm, 147 ± 3 nm, 199 ± 6 nm, and 269 ± 5 nm, Thermo Fisher Scientific). In order to assess the accuracy of the interface prototype split ratios the solutions or particle suspensions were delivered directly to the interface prototype using a peristaltic pump. In order to reach the required dilution factor the make-up flow and/or were adjusted, while the split ratio was kept fixed. A UV/VIS spectrophotometer (Perkin Elmer Lambda 35) was used to measure changes in the absorbance of samples processed through the interface prototype relative to the stock solution/suspension. These measurements allowed the achieved dilution factor to be compared to the theoretical dilution factor and evaluate the accuracy of the interface prototype split ratios. This approach was found to be inappropriate due to the low pressure supplied to the interface by the peristaltic pump and limitations in the sensitivity of the UV/VIS detector when analysing the diluted samples. For these reasons the experimental set up was modified whereby the peristaltic pump was replaced with an Agilent HPLC pump with autosmapler, which provided pressure to the system and increased the performance of the interface, and a more sensitive detector, an Agilent 1200 UV-DAD, was used.

6.2 Results

The accuracy of the interface prototype dilution factors for fluorescein and PSS (102 ± 3 nm) following first experimental set up is presented in Figure 3 and Figure 4, respectively. For both examples it can be clearly seen that a dilution factor of 5 was reached. After that

the accuracy of the dilution factor decreases. When the experimental parameters were set to achieve a theoretical dilution factor of 32x only 10x was observed, indicating that the theoretical split ratio was not achieved. Limitations in the sensitivity of the UV/VIS spectrophotometer mean that the higher dilution factors could not be accurately assessed and may have resulted in discrepancies between the measured and theoretical dilution factors. In addition the high concentrations of the stock solution were not representative of the sample concentration required for FFF system and may have influenced the split ratio achieved by the interface prototype. Therefore, the second test set up was established.
The accuracy of the interface prototype dilution factors (10-50x) for different PSS (46 ± 2nm, 102 ± 3 nm, 147 ± 3 nm, 199 ± 6 nm, and 269 ± 5 nm) following the second set up is shown in Figure 5. The presented data show that a dilution factor of 19x was achieved for all of the tested particle sizes, while at a theoretical dilution factor of 21.2x large discrepancies were observed. The possible reason for this observation is the influence of the injection-pump on the stabilization of CoriFlow after injection.

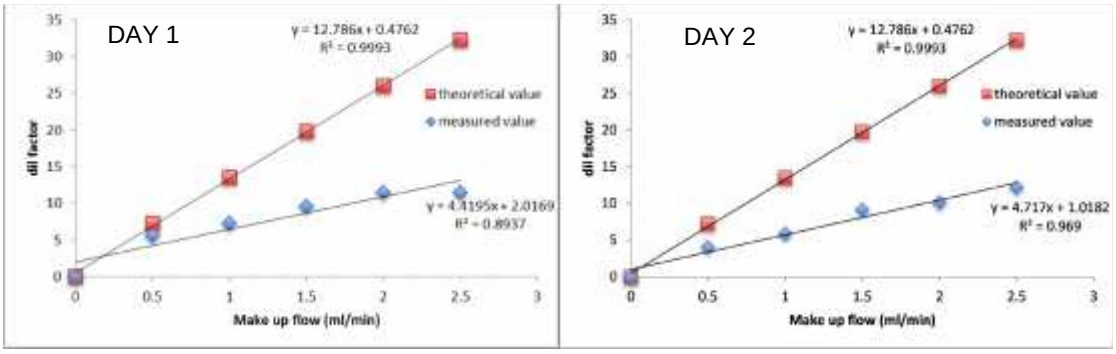

Figure 3: The accuracy of the interface prototype split ratios for fluorescein (first set up).

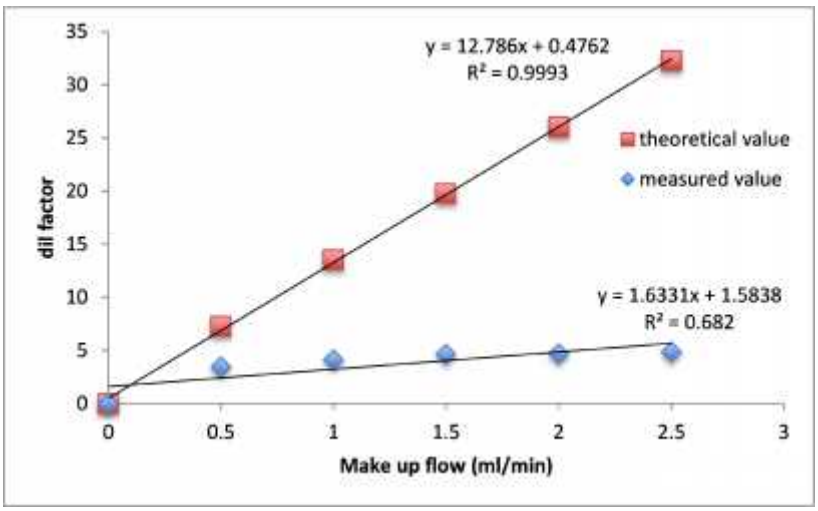

Figure 4: The accuracy of the interface prototype split ratios for PSS100 (first set up).

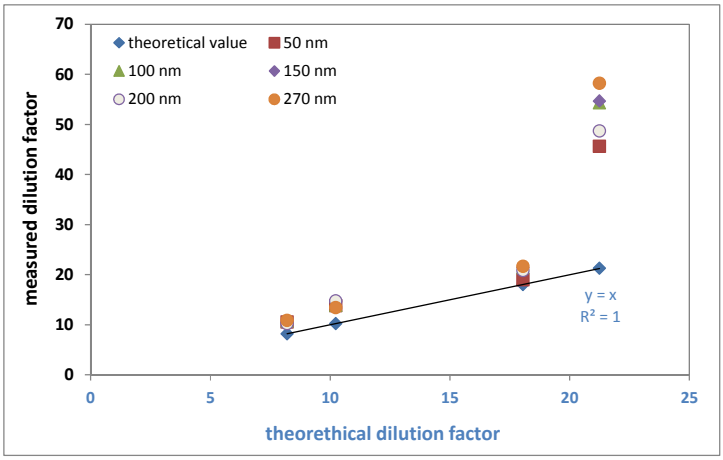

Figure 5: The accuracy of the interface prototype for PSS of different size (second set up).

7 The accuracy of the interface prototype split ratios (on-line tests)

In order to assess the accuracy of the interface prototype split ratios during on-line measurements a UV detector was installed after the dilution interface to check the recovery of the sample in the split flow. Two different samples were used; the albumin standard (BSA, Thermo Fisher Scientific) (2 g L^{-1}) and 102 ± 3 nm (5 mg L^{-1}) particle size standard (PSS100, Thermo Fisher Scientific).

7.1 Materials and methods

7.1.1 BSA

The BSA fractionation was carried out using an Agilent 1200 HPLC, Eclipse® DUALTEC with a SC channel, and external CoriFlow controller. A 50 mM sodium nitrate (Sigma Aldrich) solution was used as the background carrier. In order to check the recovery during the FFF experiments with BSA, a second detector was installed after the split setup to provide a recovery reference of undiluted sample. A flow rate meter was installed after the split to check the flow rate being removed by the CoriFow to the waste.

After the split, a second HPLC pump should deliver eluent at a flow rate that matched the rate at which the CoriFlow controller was removing the FFF eluent to the waste. However, due to the selectivity of the UV detector experiments were focused on how successfully the flow was split.

The actual detector flow rate during the estimated elution time of the sample was checked without applying any split ratio, e.g.:

$V(Detector)_{Measure}$ = 0.926 mL min^{-1} (set 1 mL min^{-1}).

When applying a dilution factor of 10x, 9 parts of the detector flow will be lead to the waste by the CoriFlow controller, e.g.:

$V(Cori)_{Set}$ = (0.926 * 0.9) mL min^{-1} = 0.83 mL min^{-1}.

The mass recoveries of BSA based on the area below the peak before and after the split were calculated using Wyatt ASTRA.

7.1.2 PSS100

The particle size fractionation was carried out using an Eclipse Dualtec with a LC channel (Wyatt Technology, Dernbach, Germany). 0.025% (v/v) FL-70^{TM} was used as background carrier. The sample (10 mg L^{-1}, 10 µL for recovery run) was injected with a large volume injection loop with a maximum injection volume of 900 µL (Agilent G2260A, Agilent, USA) to obtain the reference area of the PSS100 recovery peak. In order to estimate the accuracy of split ratio a range of dilution factors were targeted by varying the makeup flow rate provided by the second HPLC pump. The dilution factors targeted were 8-14 and 37, using injection volumes of the PSS100 of 10 and 20 µL (recovery run), respectively. The AF4 system was coupled online with a MALS detector with 17 + 1 observation angles operated (15 usable in aqueous medium with online DLS attached to angle 11) and a linear polarized laser at 658 nm (DAWN® EOS^{TM}, Wyatt Technology Europe GmbH, Dernbach, Germany) before the dilution interface, and Agilent 1200 UV-DAD detector (λ = 210 and 230 nm) after the dilution interface.

7.2 Results

7.2.1 BSA

The measured signal intensities recorded during the BSA elution by the UV detectors before and after the flow split are shown in Figure 6. The BSA mass recovery based on the area under the peak before and after the split is presented in Table 1.

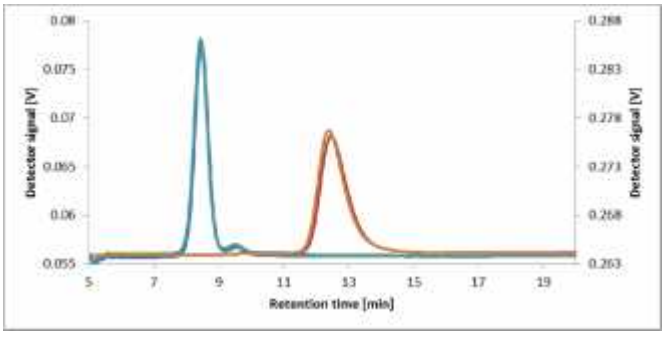

Figure 6: BSA signal intensity from both the UV before (earlier retention) and after (later retention) the split.

Based on the data presented in Table 1 it is possible to split a sample by a certain ratio without any loss of recovery.

Table 1. The BSA mass recoveries before and after the split.

Mass Recovery (UV 1) [%]	Mass Recovery (UV 2) [%]
80.2	87.9

7.2.2 PSS100

Performing the on-line measurements where the interface prototype was connected to the

FFF system including the channel the highest dilution factor of 37.2x was obtained (Figure 7). The measured dilution factors were comparable to the theoretical values obtained from gravimetrical measurements. These results show that the obtained dilutions of 14.3x and 37.2x might be appropriate for coupling the FFF with spICPMS.

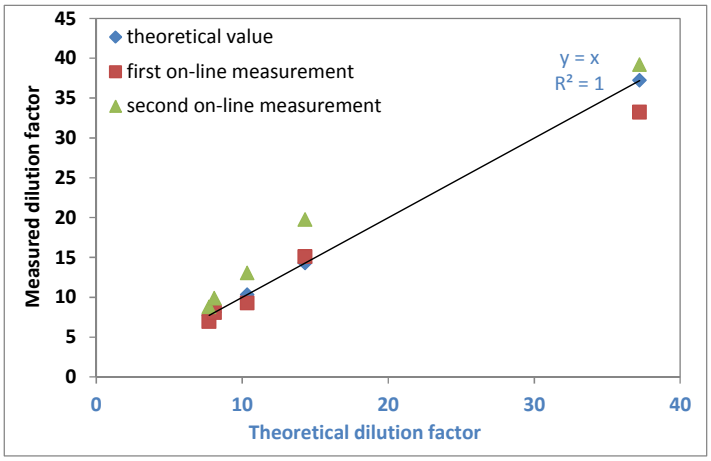

Figure 7: Calculated and measured interface prototype dilution factors.

8 FFF-spICPMS performance description (UNIVIE)

8.1 Materials and methods

The composition of PSS suspensions (conventionally used as standards for FFF) are not suitable for analysis by ICPMS. Therefore to assess the performance of the dilution interface for spICPMS gold NP suspension standards were selected. Gold NPs, which are the typical standard used for single particle analysis, were chosen due to their long-term stability, high density, being monoisotopic and their availability as highly mono-disperse suspensions with different primary particle sizes. To assess the performance of the interface with spICPMS two gold standard particle suspensions were selected with primary particle sizes of 30nm and 60nm (BBI Solutions, UK). These gold nanoparticle suspensions are suitable for FFF analysis with well-tested and established methods available (Meisterjahn et al., 2016).

To assess the performance of the dilution interface two experimental set-ups were established. The first used a fraction collector after FFF separation to collect 1 ml aliquots of the eluted fractionated sample suspension. These aliquots were then further diluted to an appropriate degree and the fractions analysed by spICPMS. The second set-up allowed on-line measurements of the fractionated particle suspensions; this was achieved by using a peristaltic pump to remove a split at a flow rate 0.12 ml min^{-1} from sample suspension flowing from the dilution interface at a flow rate of 1 ml min^{-1}. At the start of each measurement session freshly prepared pristine gold NP standard suspensions were analysed by spICPMS and used to calibrate the particles in the suspensions collected from the dilution interface.

8.2 Results

8.2.1 Off-line measurements

The tests with the fraction collector and off-line spICPMS analysis of the collected fractions were performed using a mono-disperse 60nm gold suspension and an admixed 30 nm and 60 nm (mass ratio 1:1) gold particle suspension. In order to achieve an appropriate particle number concentration each 1 ml aliquot was further diluted with Milli-Q prior to analysis by spICPMS. The results are summarized in Figure 8a-d.

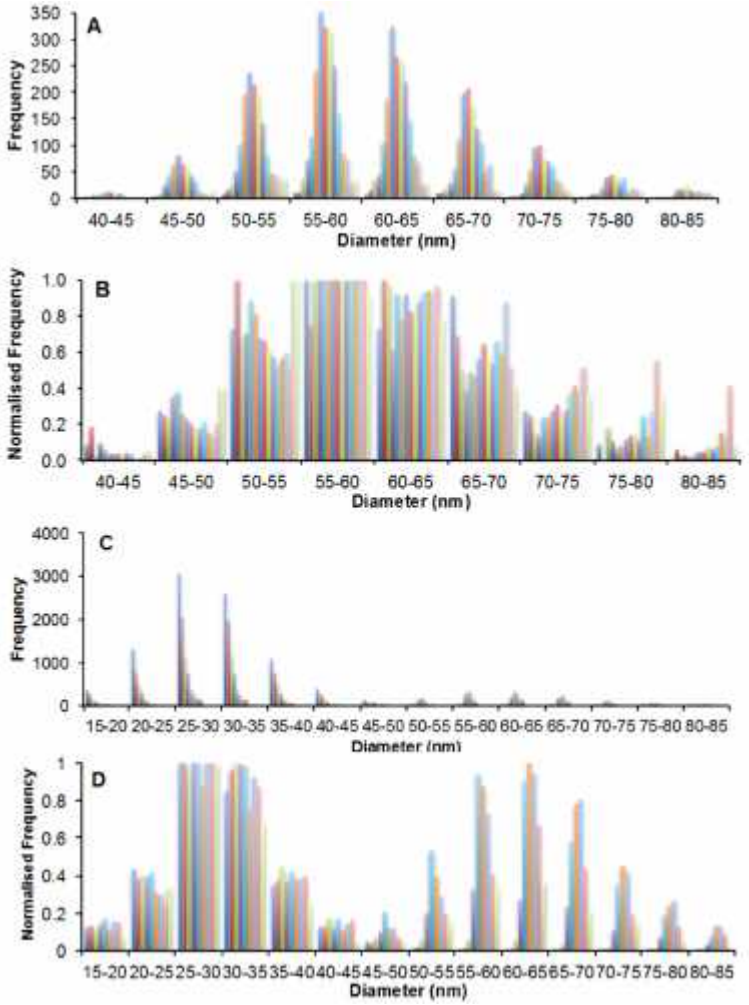

Figure 8: Particle distributions of aliquots collected by the fraction collector, at intervals of 1 ml, after separation by FFF and dilution by the FFF-spICPMS interface prototype. The columns in each interval represent the first to last aliquot measured when moving from left to right. A&B: 60nm gold nanoparticle suspension. C&D: Admixed 30nm and 60nm (mass ratio 1:1) gold nanoparticle suspension. A&C: Frequency distribution in each analysed 1ml fraction. B&D: Normalized frequency distribution whereby each analysed fraction was internally normalized.

The frequency distributions (Figures 8A&C) show that, as anticipated, the highest frequencies occur in the collected aliquots that correspond to the highest intensities observed with

the UV-vis and MALLS on-line detectors of the FFF and when the primary particle size is predominantly being eluted. The normalized frequency distributions (Figure 8b & Figure 8d) demonstrate that the earlier fractions contain a relatively higher proportion of smaller particles and vice versa for the later fractions.

Figure 8c-d highlight the limitations of the interface for measuring suspensions containing smaller particles where the particle number concentrations will be much higher for a given mass and therefore require much greater dilution factors. Therefore for particle suspensions containing smaller particles (primary particle size <60nm) much higher dilution factors than are currently achievable by the interface are required. Furthermore Figure 8c-d demonstrates that for poly-disperse samples a variable dilution factor is necessary in order to achieve a representative distribution of all particle sizes and achieve an appropriate particle number concentration to permit passive on-line analysis by particle counting methods such as spICPMS.

8.2.2 On-line measurements

Due to the limitations outlined in section 8.2.1 only 60 nm gold nanoparticle suspensions were used for the on-line measurement tests. The results are summarized in Figure 9.

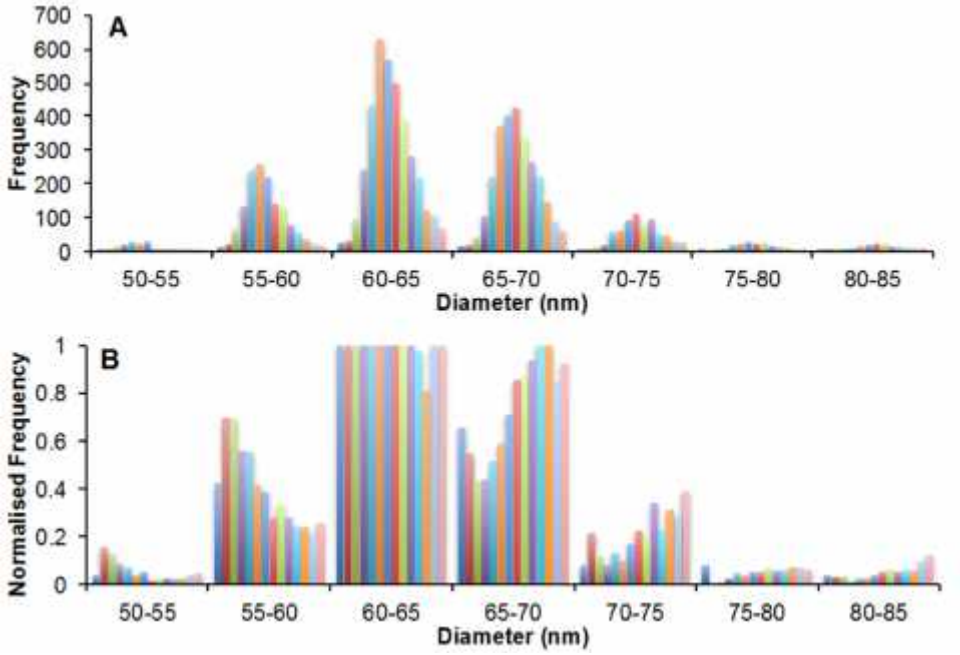

Figure 9: Particle distributions measured from the online analysis of 60nm gold nanoparticle suspensions by spICPMS after fractionation by FFF and dilution with FFF-spICPMS interface prototype. Each series of columns is representative of particles eluted in 1 minute periods with the columns in each interval represent the first to last aliquot measured when moving from left to right. A: Frequency distribution observed in 1 minute intervals of online analysis. B: Normalized frequency distribution whereby each analysed interval was internally normalized.

The results from online measurements show the same trends as those found for the offline experimental set up discussed in section 7.2. By using the peristaltic pump to only supply a flow of 0.12 ml min^{-1} from the total flow of 1 ml min^{-1} from the dilution interface the parti-

cle number concentration entering the ICPMS was appropriate for single particle analysis.

9 Summary of FFF-spICPMS performance description reported in WP7 template

Technical characteristics sheet for characterization of FFF-spICPMS in comparison to the state of the art is presented below:

Criteria (generally)	**Criteria (more specific)**	**FFF characterisation State of art from D3.2** (Yes/No)	**FFF characterisation State of art after D5.5** (Yes/No)	**Notes**
Nanoparticles in powder or liquid suspensions or embedded in a matrix	Dispersed in liquids	Yes	Yes	
	Solid particulate form	No	No	
	Dispersed or embedded in different kinds of matrices	No	No	
Dispersbility by dispersion protocols	Dispersible in aqueous media	Yes	Yes	
	Dispersible in non-polar liquids	Yes	Yes	Channels for organic liquids available. Not routinely used
	Dispersible in polar liquids	Yes	Yes	
	Dispersible in material-specific media	Yes	Yes	Case by case decision
	Can be aerosolized	No	No	
Substance Nature	Inorganic	Yes	Yes	
	Size-dependent absorption / fluorescence	Yes	Yes	
	Carbon based	Yes	Yes	
	Organic, particulate	Yes	Yes	
	Organic, non-particulate	Yes	Yes	Macromolecules and similar are possible
	Biological	Yes	Yes	
	Composite	Yes	Yes	
	Other			
Composite	Core/shell	Yes	Yes	
	Multiple coatings	Yes	Yes	
	A mix of two or more different materials	Yes	Yes	
Number of nanoscaled di-	1	No	No	
	2	No	No	Yes for small aspect ra-

mensions				tios
	3	Yes	Yes	
Shape of nano-particles	Sphere or similar	Yes	Yes	
	Equiaxial	Yes	Yes	
	Tubes, fibres, rods	No	No	Yes in certain cases. Separation can be achieved; sizing would require sample-similar standards or external sizing methods.
	Flakes and discs	No	No	Yes in certain cases. Separation can be achieved; sizing would require sample-similar standards or external sizing methods.
	Other			
Thermal degra-dation sensitivity	Above 0°C	No	No	
	Sensitivity above 25°C	Yes	Yes	
	Sensitivity above 37°C	Yes	Yes	
	Sensitivity above 50°C	Yes	Yes	
	Sensitivity above 100°C	Yes	Yes	
	Sensitivity above 150°C	Yes	Yes	
	Sensitivity above 500°C	Yes	Yes	
	Sensitivity above 1000°C	Yes	Yes	
Cooling degra-dation sensitivity	Sensitive below 25 °C	Yes	Yes	
	Sensitive below 0 °C	Yes	Yes	
	Sensitive below -18 °C	Yes	Yes	
	Sensitive below -35 °C	Yes	Yes	
	Sensitive below -78 °C	Yes	Yes	
	Sensitive below -195 °C	Yes	Yes	
E- beam sensi-tivity	e- beam sensitive	Yes	Yes	
	Not e-beam sensitive	Yes	Yes	
Sample disper-sity and modali-ty	Monodisperse sample	Yes	Yes	
	Polydisperse sample	Yes	Yes	
	Monomodal sample	Yes	Yes	
	Multimodal sample	Yes	Yes	
Conductivity properties	Conductive	Yes	Yes	
	Semiconductive	Yes	Yes	
	Insulator	Yes	Yes	
Magnetic prop-erties	Magnetic	Yes	Yes	
	Non magnetic	Yes	Yes	
Functionaliza-	Functionalised	Yes	Yes	

tion / no functionalisation	Not functionalised	Yes	Yes	
Agglomeration/ aggregation state	Nanoparticles are aggregated	No	No	
	Nanoparticles are not aggregated	Yes	Yes	
	Nanoparticles are agglomerated	No	No	
	Nanoparticles are not agglomerated	Yes	Yes	
counting, separative or ensemble techniques	Single particle counting	N/A	Yes	Particle number weighted distribution can be achieved by collecting fractions and further dilution before spICPMS analysis if required dilution is not sufficient. Reaching higher dilution ratios by cascading with secondary flow controller is also a possibility.
	Calculate number or concentration from ensemble methods	Yes	Yes	
	Method combination (hyphenated methods)	Yes	Yes	
Working range	Size range	1 - 1000 nm	1 - 1000 nm	
	Concentration range	20 µg/L – 500 mg/L	20 µg/L – 500 mg/L	Detector dependent
	Minimum sample volume	10 µL	10 µL	
	Linearity/proportionality	Yes	Yes	Detector dependent
	Limits of detection/quantification	> 1 nm	> 1 nm	Detector dependent
	Sensitivity (Counting efficiency) as a function of size	good	good	Detector dependent
Limits of detection/quantification	What is the lower limit to detect	1 nm to 10 nm	1 nm to 10 nm	Membrane and detector dependent
Trueness	Indicate the trueness of this CM	good	good	If reference materials available
Trueness in weighting the size fractions	Specify the trueness in weighting the size fractions of this CM	good	good	Mass quantification if performed by mass specific detector
Robustness	Specify the robustness of this CM	average	average	Important parameter is the membrane quality
Precision	Specify the precision of the CM	1 nm to 10 nm	1 nm to 10 nm	Can be tuned to needs
Resolution	Specify the resolution of	1 nm to 10 nm	1 nm to 10 nm	determined by size

	this CM			standards
Size distribution	Is it possible to measure size distribution?	Yes	Yes	
Selectivity	discrimination from non-nanoparticles of the same composition	No	No	Pre-treatment of the sample is necessary.
	discrimination from non-nanoparticles of another composition (matrix particles)	No	No	Pre-treatment of the sample is necessary. Depends on detection technique.
	discrimination from nanoparticles of another composition	Yes	Yes	Depends on detection technique.
	Impurities	N/A	N/A	
Measures aggregation	Is it possible to measure aggregation or agglomeration of particles?	No	No	
Measures individual particles	Does this CM measure individual particles?	No	No	
Counting constituent particles in aggregations	Is the method able to count constituent particles in aggregates?	No	No	
Composition	Does this CM analyse composition?	Yes	Yes	Depending on constituents and applied detection technique.
Specification of the type of size (diameter)	Specify: for example hydrodynamic…	"Hydrodynamic diameter"	"Hydrodynamic diameter"	Diffusion coefficient (FlowFFF) hydrodynamic diameter can be derived, volumetric diameter (SedFFF or CFFF). In few cases when MALS is applicable also rms and geometrical diameter, respectively.
Destructive method or not	Is it a destructive method?	No	No	Fractions can be collected; sample will be diluted.
Other Specificity				
Vacuum	Does the method operate under vacuum?	No	No	
Sample support	Does this CM need preparation on suited supports?	No	No	

10 Conclusions

The original aim of this deliverable was to develop an interface capable of diluting eluent from FFF by a factor of up to 1000x, which could also be adjusted dynamically (dilutions varied during the analysis), in order to enable the online measurement with the particle counting technique of spICPMS. The current interface prototype was operated manually and "certified" for a dilution factor of up to 10x. Under ideal conditions (static, with no change of dilution factor during analysis) a dilution factor of approximately 35x was achieved.

The evaluation of the current state of the FFF-spICPMS is that the method requires further optimization before it can be applied to real samples. It is proposed that the current interface prototype could be improved in order to achieve a higher dynamic range of dilution factors that are desired, but not with the resources within NanoDefine project.

In order to achieve particle number concentrations suitable for single particle counting methods from diluted FFF eluents higher dilution factors that can be reliably varied during the analysis are required. This is especially the case for real samples that contain smaller particle sizes and/or are poly-disperse. The current prototype interface cannot achieve this and for this reason the technique is not yet at a stage whereby an SOP for FFF-spICPMS can be prepared. Therefore, under the current developments, collecting fractions and subsequent dilution after FFF and further spICPMS analysis manually is recommended.

11 References

Meisterjahn, B., Wagner, S., von der Kammer, F., Hennecke, D., Hofmann, T. 2016. Silver and gold nanoparticle separation using asymmetrical flow-field flow fractionation: Influence of run conditions and of particle and membrane charges. Journal of Chromatography A 1440, 150-159.

