International Journal on Magnetic Particle Imaging
Vol 10, No 1, Suppl 1, Article ID 2403019, 3 Pages

Infinite Science Publishing

Proceedings Article

Magnetic particle fractionation and in-line characterization for enhancing magnetic particle imaging tracers

Laura Kuger [a,*] · Elisa-Marie Lux [b] · Jochen Franke [c] · Philip Stoer [d] · Norbert Löwa [e] · Matthias Franzreb [a]

[a] Institute of Functional Interfaces, Karlsruhe Institute of Technology, Karlsruhe, Germany
[b] Institute of Mechanical Process Engineering and Mechanics, Karlsruhe Institute of Technology, Karlsruhe, Germany
[c] Bruker BioSpin MRI GmbH, Ettlingen, Germany
[d] micromod Partikeltechnologie GmbH, Rostock, Germany
[e] Physikalisch-Technische Bundesanstalt, Berlin, Germany
[*] Corresponding author, email: laura.kuger@kit.edu

© 2024 Kuger *et al.*; licensee Infinite Science Publishing GmbH

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Refining the size distribution of magnetic nanoparticles (MNPs) holds great potential for enhanced performance in magnetic particle imaging (MPI). This work demonstrates the coupling of a preparative-scale magnetic field-controlled size fractionation technique with in-line magnetic particle spectroscopy (MPS) for the real-time assessment of magnetic nanoparticle downstream processing performance. In-line magnetic particle spectroscopy monitoring allowed for the concurrent evaluation of the amplitude spectrum and derived parameters including the harmonic ratio A_5/A_3, enabling real-time selection of fractions with desired characteristics during the fractionation process. Furthermore, magnetic particle spectroscopy offered increased sensitivity and more comprehensive characterization capabilities than conventional in-line analysis techniques such as light absorption spectroscopy. These results potentially have significant implications for prospective applications in the realm of in-line magnetic particle spectroscopy analysis for real-time process control and quality assurance.

I. Introduction

For the advancement of Magnetic Particle Imaging (MPI) applications, enhancing the properties of magnetic nanoparticles (MNPs) plays a pivotal role. Achieving a MNP collective size distribution as narrow as possible is favored, as it substantially enhances their performance as MPI tracers [1, 2]. To address the size fractionation challenge, magnetic field-controlled chromatography emerges as a promising and scalable technique. It enables the selective manipulation of matrix/MNP interactions, leading to characteristic retention and retardation behaviors depending on the MNP's magnetic core sizes and hydrodynamic diameters. Compared with alternative separation techniques such as ultracentrifugation, magnetic field-controlled chromatography directly targets the properties of interest for subsequent MPI application [3, 4]. However, size fractionation of particle collectives in the 50-1000 nm range poses significant challenges due to the superposition of multiple effects, such as electrostatic interactions, convection, inertial forces, and brownian molecular movement. In-line MPS moni-

10.18416/ijmpi.2024.2403019

© 2024 Infinite Science Publishing

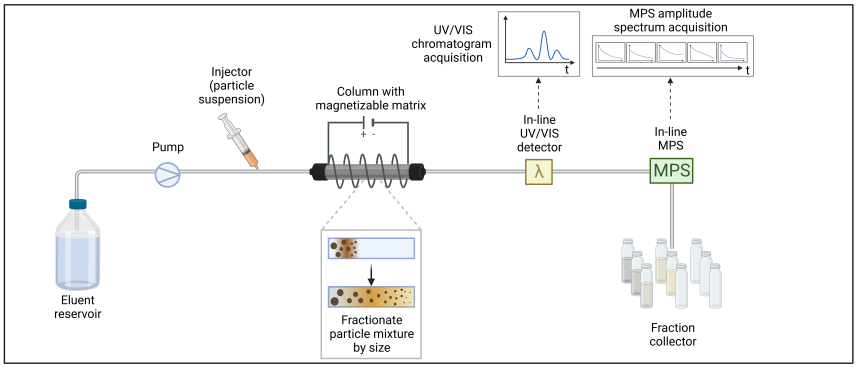

Figure 1: Schematic process flow diagram of a magnetic field-controlled chromatography process with in-line UV/VIS and in-line MPS analysis. Created with BioRender.com.

Table 1: Magnetic nanoparticle collectives investigated with selected properties. The volumetric hydrodynamic diameters were analyzed via DLS, the saturation magnetizations were determined using alternating gradient magnetometry (AGM), and the iron content was measured via Inductive-Coupled Plasma - Optical Emission Spectrometry (ICP-OES). DLS and AGM values are given as mean values (fivefold measurement for DLS, threefold measurement for AGM) ± standard deviation.

	d_{50}/nm	M_S/Am^{2}kg^{-1}	x_{Fe}/mg$_{\mathrm{Fe}}$/mg$_{\mathrm{MNP}}$
synomag®-D, 70 nm	73.8 ± 1.7	56.6 ± 0.4	0.516
synomag®-S, 90 nm	109.7 ± 1.5	44.0 ± 0.3	0.380
perimag®, 130 nm	132.0 ± 2.7	26.6 ± 0.1	0.343
nanomag®-D, 250 nm	272.3 ± 13.2	38.2 ± 0.3	0.406

toring has proven to provide valuable insights into the real-time performance of this delicate process and offers major advantages for quality control [5]. Also, it potentially enables real-time process control through feedback loops in continuous fractionation processes, such as in Simulated Moving Bed (SMB)-chromatography [6]. Four commercial, unfunctionalized magnetic nanoparticle collectives with polysaccharide shells are investigated in this study. In the first step, the central aim was to assess the responses of the size fractionation results to variations in process parameters via analyzing the hydrodynamic diameters (DLS), as well as the off-line amplitude spectra (MPS) of the product fractions. Subsequently, we demonstrate the implementation of an in-line MPS unit for real-time monitoring and evaluation of the magnetic field-controlled single-column chromatography process.

II. Experiments, Methods and Materials

Four magnetic nanoparticle systems (micromod Partikeltechnologie GmbH, Rostock, Germany) were characterized prior to fractionation, see Table 1. The employed chromatographic system was an ÄKTA purifier (Cytiva, Marlborough, USA), which featured eluent pumps, injection valves, and a fraction collector, refer to Figure 1 for an illustration of the system configuration. The modular design of the system facilitated the connection of the column's outlet tube to an in-line UV/VIS cell and a flow cell [7] inserted into the MPS unit (MPS3, Bruker BioSpin MRI GmbH, Ettlingen, Germany). The UV/VIS cell directly transmitted data to the UNICORN 5.2 chromatography software. The induced magnetization of the column's effluent was measured within the MPS unit at an excitation field strength of 25 mT and excitation frequency of 25.25 kHz in regular time intervals of 8 s for 1 s each. Both the UV/VIS signal and the MPS signal were synchronized in time based on the flow rate and the tubing volume between the UV/VIS cell and the MPS unit. The chromatography column had a volume of 4.3 ml and was packed with ferritic steel particles ($M_S = 152.6\mathrm{Am^2kg^{-1}}$, $d_{50} = 31\,\mu\mathrm{m}$) using a specific column packing procedure. The magnetic background field was generated by a Helmholtz configuration featuring four coils, and the magnetic flux intensity was altered at will by adjusting the current. Refer to our previous works for a comprehensive description of the magnetic field-controlled chromatography system setup [6, 8].

III. Results

Within this abstract, we are only describing the results for one of the collectives investigated, namely synomag®-D 70 nm (injection volume $V_{inj} = 0.5$ ml, injected particle concentration $c_{inj} = 6.82$ g/L). Figure 2 displays the chromatograms and in-line monitored MPS data of two

 © 2024 Infinite Science Publishing

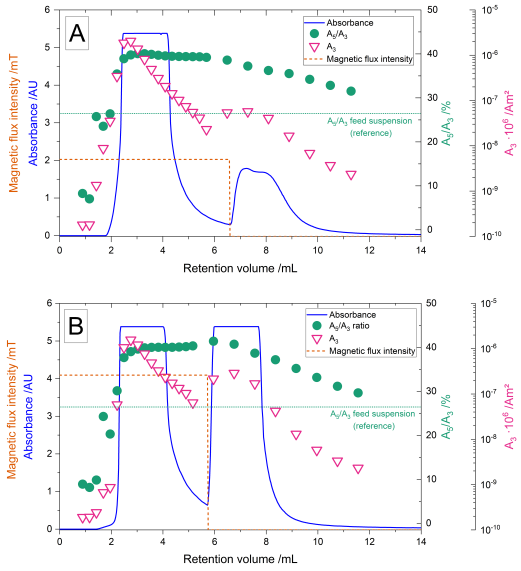

Figure 2: Inline MPS and UV/VIS monitoring of the size fractionation process of synomag®-D 70 nm nanoparticles. The absorbance (blue line) was plotted on a linear scale, while the harmonic ratio A_5/A_3 (green symbols) as well as the third harmonic A_3 (pink symbols) were plotted on a logarithmic scale. The elution of the second peak was induced by switching off the magnetic field and simultaneously increasing the flow rate. The background magnetic flux intensities were set to (A) $B = 2.04\,\mathrm{mT}$, and (B) $B = 4.08\,\mathrm{mT}$.

different fractionations. Figure 2A illustrates the fractionation under a background magnetic field of $B = 2.04\,\mathrm{mT}$, while Figure 2B depicts the process at $B = 4.08\,\mathrm{mT}$. Notably, the UV/VIS signal saturates due to high particle concentrations resulting in absorbances exceeding the detector limit of 5.4 AU, whereas the parameters derived from the MPS signal (e.g. the third harmonic A_3, pink symbols), remain unsaturated. Furthermore, when compared to the UV/VIS signal and to the concentrations analyzed off-line, the third harmonic A_3 demonstrates a clear dependence on particle concentration, as previously observed with other MPI tracers. Additionally, monitoring the harmonic ratio A_5/A_3 throughout the fractionation process provides valuable insights into the concentration-independent characteristics of the respective fractions. For instance, the initial peak representing the fine fraction contains particles with significantly higher harmonic ratios A_5/A_3 of up to 40.1 %, compared to the second peak where this parameter decays gradually with increasing retention volume. This indicates that, through the manipulation of the MNP's trajectories within the column using a combination of hydrodynamic and magnetic forces, larger particles and agglomerates that do not have a favorable impact on the dynamics and the MPS performance of the collective were retained in the column. This theory was confirmed through off-line DLS analyses, which revealed a significantly larger median diameter in the coarse fraction when the magnetic field was switched off (for $B = 4.08\,\mathrm{mT}$: $d_{50,fine} = 45.5\,\mathrm{nm}$, $d_{50,coarse} = 61.6\,\mathrm{nm}$, separation efficiency of $\kappa = d_{25}/d_{75} = 0.64$). In summary, this study showcases the potential of integrating preparative-scale magnetic field-controlled chromatography with real-time MPS for the downstream enhancement of MNP collectives for MPI applications. As opposed to UV/VIS process monitoring alone, in-line MPS provides increased sensitivity, a large dynamic range, and the capability to precisely target and select specific MNP fractions with desired properties during the process.

Acknowledgments

The authors acknowledge the financial support of the German Research Foundation (DFG) and the Priority Programm 2045 for the funding (grant number FR 2131/6-2).

Author's statement

Conflict of interest: Authors state no conflict of interest.
Informed consent: Informed consent has been obtained from all individuals included in this study.

References

[1] D. Eberbeck, F. Wiekhorst, S. Wagner, and L. Trahms. How the size distribution of magnetic nanoparticles determines their magnetic particle imaging performance. *Applied Physics Letters*, 98(18), 2011, doi:10.1063/1.3586776.

[2] R. M. Ferguson, A. P. Khandhar, and K. M. Krishnan. Tracer design for magnetic particle imaging (invited). *Journal of applied physics*, 111(7):7B318–7B3185, 2012, doi:10.1063/1.3676053.

[3] J. Lohrke, Herstellung und charakterisierung neuer nanopartikulärer spio-kontrastmittel für die magnetresonanztomographie, PhD thesis, Halle (Saale), Martin-Luther-Universität Halle-Wittenberg, Diss., 2010, 2010,

[4] N. Löwa, P. Knappe, F. Wiekhorst, D. Eberbeck, A. F. Thünemann, and L. Trahms. Hydrodynamic and magnetic fractionation of superparamagnetic nanoparticles for magnetic particle imaging. *Journal of Magnetism and Magnetic Materials*, 380:266–270, 2015, doi:10.1016/j.jmmm.2014.08.057.

[5] N. Löwa, F. Meier, R. Welz, H. Kratz, H. Paysen, J. Schnorr, M. Taupitz, T. Klein, and F. Wiekhorst. Novel platform for the multidimensional analysis of magnetic nanoparticles. *Journal of Magnetism and Magnetic Materials*, 518:167443, 2021.

[6] L. Kuger, C.-R. Arlt, and M. Franzreb. Magnetic/flow controlled continuous size fractionation of magnetic nanoparticles using simulated moving bed chromatography. *Talanta*, 240:123160, 2022, doi:10.1016/j.talanta.2021.123160.

[7] N. Löwa, P. Radon, D. Gutkelch, R. August, and F. Wiekhorst. Hyphenation of field-flow fractionation and magnetic particle spectroscopy. *Chromatography*, 2(4):655–668, 2015, doi:10.3390/chromatography2040655.

[8] C.-R. Arlt, A. Tschöpe, and M. Franzreb. Size fractionation of magnetic nanoparticles by magnetic chromatography. *Journal of Magnetism and Magnetic Materials*, 497:165967, 2020, doi:10.1016/j.jmmm.2019.165967.

 © 2024 Infinite Science Publishing