HIGH MAGNETIC FIELD GRADIENT PARTICLE SEPARATION FOR BIOMEDICAL APPLICATIONS

Lennart Göpfert, Arian Mustafa, Benedikt Mues, Ioana Slabu

RWTH Aachen University and University Hospital Aachen, Institute of Applied Medical Engineering
Pauwelsstraße 20, D-52074 Aachen, Germany, email: lennart.goepfert@rwth-aachen.de

Abstract – **In this study, the feasibility of magnetic nanoparticles (MNP) separation by size using high magnetic field gradients is presented. This method is used to isolate specific fractions of MNP after the synthesis to increase the MNP quality for biomedical applications. For the generation of high magnetic field gradients, steel wool is magnetized in an electromagnetic field. Depending on the gradient, MNP with specific sizes are attracted towards the steel wool. In this way, differently sized MNP fractions can be obtained from a polydispersed MNP sample. Here, the separation feasibility of MNP into two fractions from a continuous flow is demonstrated.**

I. INTRODUCTION

Magnetic nanoparticles (MNP) are high potential drug carriers as they can be targeted in a quantitatively precise manner using magnetic fields [1]. One important field of application is local cancer therapy for customized treatment. Anti-cancer drugs can be thermosensitively bonded to the MNP and thus released on site by heating the MNP in an alternating magnetic field [2]. Further, by local overheating to approximately 43 °C, so-called hyperthermia, cancer tissue is damaged while healthy tissue remains unharmed [3]. Hence, two-fold cancer treatment with minimal side effects for the patient is provided. However, the size and size distribution of MNP influence their drug-loading efficiency, pharmacokinetics, biodistribution, cancer-targeting properties, kinetics of cellular internalization, and toxicity [4]. Consequently, for hyperthermia and targeted cancer therapy, MNP with specific sizes are necessary. Often, the synthesis of monodispersed MNP is challenging and an alternative approach to reduce polydispersity isolating specific fractions of MNP from a mixture is required [5].

In this work, the feasibility of MNP separation by size via high magnetic field gradients is presented. For this, a magnetic MNP separation setup was developed allowing the separation of MNP in a continuous flow. The feasibility of MNP separation by size into two fractions is demonstrated using polydisperse MNP.

II. MATERIALS AND METHODS

Figure 1 displays the magnetic separation setup. It consists of an electromagnet (coil with 1200 turns and iron core, ALLIEDPUREIRON®, PURON Metals) and a fluidic system. In this work, the current was set to 1 A resulting in a magnetic field strength of 0.14 T. In the air gap of the electromagnet a glass pipe filled with steel wool (Carl Roth, Germany, $\rho = 7.87$ g/cm³) is placed to generate high magnetic field gradients (see Figure 1). The MNP are continuously flowing through a tubing next to the steel wool inside the glass pipe. A pressure controller (OB1 MK3+, Elveflow, France) with a gauge pressure of 28 mbar maintains the flow. After crossing the air gap of the electromagnet, the tubing splits into three branches, each having its own outlet. From these outlets, the MNP are collected in three different containers. The system is fully closed and can therefore be operated in sterile conditions, which is important for future medical applications.

For the size analysis of the MNP, Dynamic Light Scattering method (DLS) was applied (Zetasizer Nano ZS, Malvern Panalytical, Germany). For the experiments, a MNP mixture [6,7] with an average diameter $d_h = (77.5 \pm 23.2)$ nm was used.

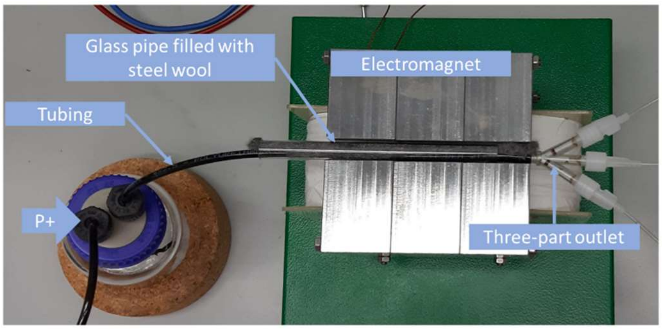

Figure 1: Experimental setup of continuous magnetic separation of MNP using local magnetic field gradients. Gauge pressure (P+) is introduced via the second inlet of the container.

III. RESULTS AND DISCUSSION

The results of the DLS measurements used to analyze the MNP size from each of the three outputs of the setup as well as from the inlet sample are shown in Figure 2 a. The smallest diameters were measured at output A, showing MNP fractions with an $d_h = (40.6 \pm 15.8)$ nm. Between the MNP of the inlet sample, $d_h = (77.5 \pm 23.2)$ nm, and the MNP fractions at the outputs B, $d_h = (85.7 \pm 24.7)$ nm, and C, $d_h = (80.1 \pm 24.6)$ nm, no significant difference in size could be measured.

These results can be explained as follows: The MNP flowing through the tubing show a magnetic response when a magnetic field is applied. This is due to the magnetic force, which proportionally depends on the magnetic field gradient and the magnetic moment of the MNP. Consequently, the separation of MNP is particularly effective for MNP with high magnetization values in areas with the highest magnetic field gradients. In many cases, magnetization values increase with MNP size. As the highest magnetic field gradient is close to the steel wool, the MNP with bigger diameters are more strongly attracted to the sites of outputs B and C (see Figure 2 b). The remaining MNP with smaller diameters leave the tubing through output A.

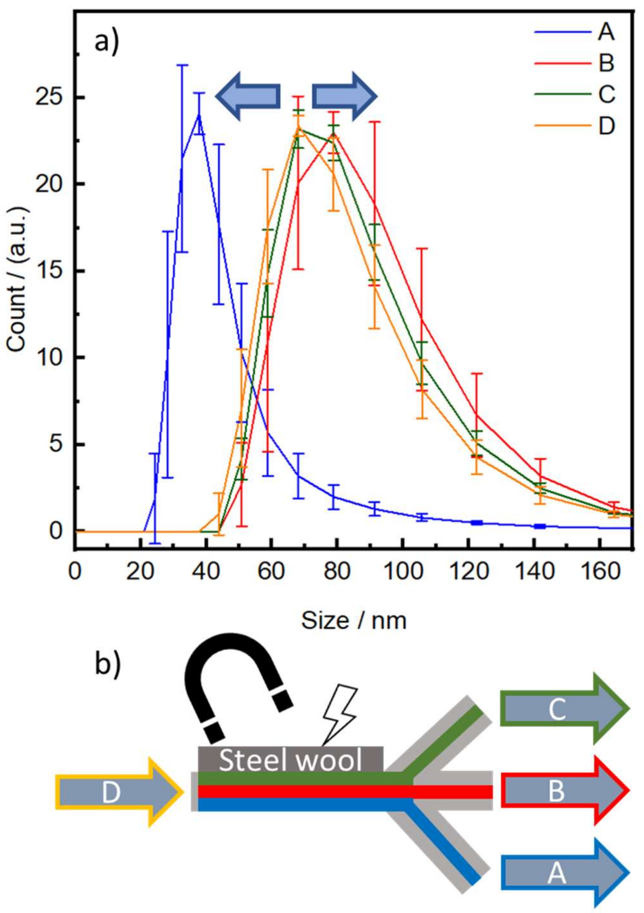

Figure 2: a) Number weighted size distribution of the diameter of the MNP inlet sample (D), and samples from the outputs A, B and C. b) Sketch of the fluidic system.

IV. CONCLUSION

In this work, a concept for the continuous separation of MNP by means of high local magnetic field gradients was proposed. The first MNP separations by size were successfully performed.

REFERENCES

[1] Slabu, I., Röth, A., Güntherodt, G., Schmitz-Rode, T., & Baumann, M. (2013). Simulation of magnetic nanoparticles in blood flow for magnetic drug targeting applications. *Biomedical Engineering/Biomedizinische Technik*, *1*(aop).

[2] Ferreira, R. V., da Mata Martins, T. M., Goes, A. M., Fabris, J. D., Cavalcante, L. C. D., Outon, L. E. F., & Domingues, R. Z. (2016). Thermosensitive gemcitabine-magnetoliposomes for combined hyperthermia and chemotherapy. Nanotechnology, 27(8), 085105.

[3] Christophi, C., Winkworth, A., Muralihdaran, V., & Evans, P. (1998). The treatment of malignancy by hyperthermia. Surgical oncology, 7(1-2), 83-90.

[4] Arami, H.; Khandhar, A.; Liggitt, D.; Krishnan, K.M. In vivo delivery, pharmacokinetics, biodistribution and toxicity of iron oxide nanoparticles. Chem. Soc. Rev. 2016, 44, 8576–8607

[5] Laurent, S., Forge, D., Port, M., Roch, A., Robic, C., Vander Elst, L., & Muller, R. N. (2008). Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. *Chemical reviews*, *108*(6), 2064-2110.

[6] Engelmann, Ulrich M., et al. "Heating efficiency of magnetic nanoparticles decreases with gradual immobilization in hydrogels." Journal of Magnetism and Magnetic Materials 471 (2019): 486-494.

[7] Mues, Benedikt, et al. "Assessing hyperthermia performance of hybrid textile filaments: The impact of different heating agents." Journal of Magnetism and Magnetic Materials 519: 167486.