

MAGNETIC DRUG TARGETING: AN ANALYTICAL MODEL FOR THE INFLUENCE OF BLOOD PROPERTIES ON PARTICLE TRAJECTORIES

BERNHARD GLEICH^{1*}, THOMAS WEYH², BERNHARD WOLF^{1,2}

¹IMETUM Central Institute of Medical Engineering, Technische Universität München, Boltzmannstrasse 11, 85748 Garching, Germany

²Heinz Nixdorf-Lehrstuhl für Medizinische Elektronik, Technische Universität München, 80333 München, Germany

* Email: gleich@tum.de

Fax: x49.89.28910801

Received: 21.2.2008, Final version: 30.5.2008

ABSTRACT:

Investigations on the behaviour of superparamagnetic nanoparticles under the influence of a high gradient magnetic field in the vascular system is required for a better understanding of magnetic drug targeting. The influence on the particle transport of the non-Newtonian and Newtonian properties of blood as well as the influence of the heart rate was therefore studied. A analytical model was developed and the calculation of particle trajectories is presented and evaluated. The results show that the non-Newtonian properties of the blood have a positive influence on the number of retained nanoparticles. The calculations also showed that the number of retained nanoparticles was lower in oscillatory flow profile than in steady flow. The influence of the heart rate can be neglected for Womersley numbers smaller than 1.5.

ZUSAMMENFASSUNG:

Untersuchungen zum Verhalten von superparamagnetischen Nanopartikeln im vaskulären System unter Einwirkung eines starken Flussdichtegradienten sind notwendig um ein besseres Verständnis für das magnetische Drug Targeting zu erreichen. Aus diesem Grund wurde der Einfluss der Newtonschen und nicht-Newtonschen Strömungseigenschaften des Blutes sowie die Auswirkung des Herzschlages auf den Partikeltransport untersucht. Ein analytisches Model, welches die Berechnung der Partikeltrajektorien bei verschiedenen Strömungsbedingungen erlaubt wird dargestellt und ausgewertet. Die Berechnungen zeigen, dass sich die nicht-newtonschen Eigenschaften des Blutes positiv auf die Menge der, durch das Magnetfeld, angelagerten Partikel auswirken. Ebenfalls kann gezeigt werden, dass durch den Herzschlag weniger Partikel angereichert werden können. Der Einfluss des Herzschlages verschwindet für Gefäße mit einer Womersleyzahl kleiner als 1.5.

RÉSUMÉ:

Afin de mieux comprendre le ciblage des drogues magnétiques, des recherches sur le comportement des nanoparticules super paramagnétiques soumises à de grands gradients de champ magnétique dans le système vasculaire est requis. L'influence du rythme cardiaque ainsi que des propriétés Newtoniennes et non Newtoniennes du sang sur le transport des particules, ont donc été étudiées. Un modèle analytique a été développé et le calcul des trajectoires des particules est présenté et évalué. Les résultats montrent que les propriétés non Newtoniennes du sang ont une influence positive sur le nombre de nanoparticules en rétention. Les calculs montrent aussi que le nombre de nanoparticules retenues est inférieur dans le cas d'un profil d'écoulement oscillatoire que pour un écoulement établi. L'influence du rythme cardiaque peut être négligée pour des nombres de Womersley inférieurs à 1.5.

KEY WORDS: magnetic drug targeting, cancer, magnetic nanoparticle, magnetostatic, biomagnetics

© Appl. Rheol. 18 (2008) 52023-1–52023-7

This is an extract of the complete reprint-pdf, available at the Applied Rheology website

<http://www.appliedrheology.org>

52023-1

Applied Rheology
Volume 18 · Issue 5

This is an extract of the complete reprint-pdf, available at the Applied Rheology website

<http://www.appliedrheology.org>

satile flow profiles can be investigated. Experiments with animals have shown that magnetic drug-targeting is feasible [1, 27, 28]. Furthermore, the construction of targeting magnets is easy with the help of the calculated particle trajectories. Since the calculations are very fast to carry out, the optimal location of the magnet can be determined. However, for physical reasons it is not possible to generate local flux density maxima and thus local force maxima far away of the pole shoe. Therefore MDT is only feasible for the treatment of near surface tumors like breast cancer or tumors in the head area.

ACKNOWLEDGEMENTS

This work was supported by the German Ministry for Science and Education (BMBF) within the framework of nanotechnology for medical applications under grant number 13N8536. The authors would like to thank Angela Otto from the Technische Universität München as well as Christoph Alexiou, Roland Jurgons and Christian Seliger from the University of Nürnberg-Erlangen.

REFERENCES

[1] Alexiou C, Arnold W, Klein RJ, Parak FG, Hulin P, Bergemann C, Erhardt W, Wagenpfeil S, Lubbe AS: Locoregional cancer treatment with magnetic drug targeting, *Cancer Res* 60 (2000) 6641-6648.

[2] Dames P, Gleich B, Flemmer A, Hajek K, Seidl N, Wiekhorst F, Eberbeck D, Bittmann I, Bergemann C, Weyh T, Rosenecker J, Rudolph C: Targeted delivery of magnetic aerosol droplets to the lung, *Nature Nanotech* 2 (2007), 495-499.

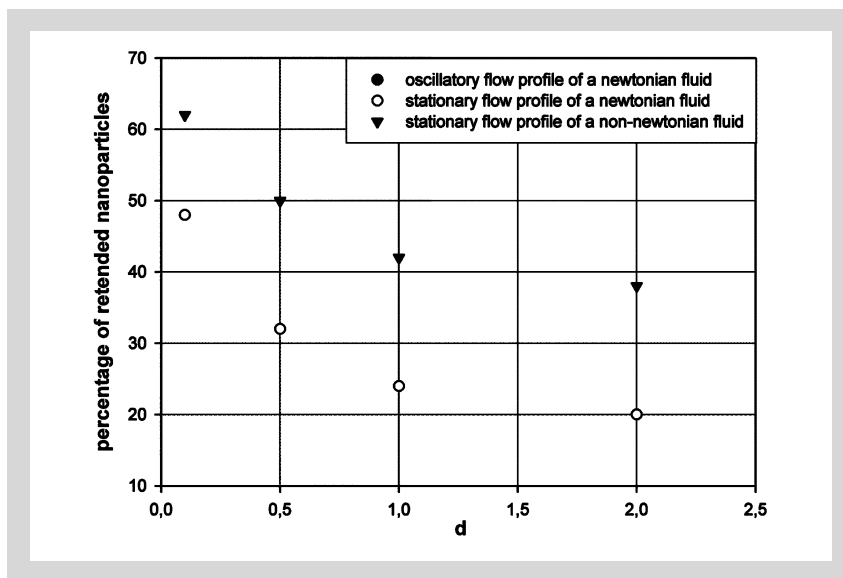
[3] Krotz F, Sohn HY, Gloe T, Plank C, Pohl U: Magnetofection potentiates gene delivery to cultured endothelial cells, *J. Vasc. Res.* 40 (2003) 425-434.

[4] Mykhaylyk O, Antequera YS, Vlaskou D, Plank C: Generation of magnetic nonviral gene transfer agents and magnetofection in vitro, *Nat. Protoc.* 2 (2007) 2391-2411.

[5] Plank C, Schillinger U, Scherer F, Bergemann C, Remy JS, Krotz F, Anton M, Lausier J, Rosenecker J: The magnetofection method: using magnetic force to enhance gene delivery, *Biol. Chem.* 384 (2003) 737-747.

[6] Gupta PK, Hung CT: Targeted delivery of low dose doxorubicin hydrochloride administered via magnetic albumin microspheres in rats, *J. Microencapsulation* 7 (1990) 85-94.

[7] Gupta PK, Hung CT: Comparative disposition of adriamycin delivered via magnetic albumin



microspheres in presence and absence of magnetic field in rats, *Life Sci* 46 (1990) 471-479.

[8] Gupta PK, Hung CT, Lam FC: Application of regression analysis in the evaluation of tumor response following the administration of adriamycin either as a solution or via albumin microspheres to the rat, *J. Pharm. Sci.* 79 (1990) 634-637.

[9] Torchilin VP: Drug targeting, *Eur. J. Pharm. Sci.* 11 Suppl 2 (2000), S81-91.

[10] Lubbe AS, Alexiou C, Bergemann C: Clinical applications of magnetic drug targeting, *J. Surgical Res.* 95 (2001) 200-206.

[11] Lubbe AS, Bergemann C, Huhnt W, Fricke T, Riess H, Brock JW, Huhn D: Preclinical experiences with magnetic drug targeting: tolerance and efficacy, *Cancer Res* 56 (1996) 4694-4701.

[12] Lubbe AS, Bergemann C, Riess H, Schriever F, Reichardt P, Possinger K, Matthias M, Dorken B, Herrmann F, Gurtler R, Hohenberger P, Haas N, Sohr R, Sander B, Lemke AJ, Ohlendorf D, Huhnt W, Huhn D: Clinical experiences with magnetic drug targeting: a phase I study with 4'-epidoxorubicin in 14 patients with advanced solid tumors, *Cancer Res* 56 (1996) 4686-4693.

[13] Laissy JP, Idee JM, Fernandez P, Floquet M, Vrtovsnik F, Schouman-Claeys E: Magnetic resonance imaging in acute and chronic kidney diseases: present status, *Nephron* 103 (2006) c50-57.

[14] Wang YX, Hussain SM, Krestin GP: Superparamagnetic iron oxide contrast agents: physicochemical characteristics and applications in MR imaging, *Eur Radiology* 11 (2001), 2319-2331.

[15] Zhang Z, van den Bos EJ, Wielopolski PA, de Jong-Popijus M, Bernsen MR, Duncker DJ, Krestin GP: In vitro imaging of single living human umbilical vein endothelial cells with a clinical 3.0-T MRI scanner, *Magma* 18 (2005) 175-185.

[16] Gleich B, Hellwig N, Bridell H, Jurgons R, Seliger C, Wolf B, Alexiou C, Weyh T: Design and evaluation of magnetic fields for magnetic drug targeting in cancer, *IEEE Trans. Nanotech.* 6 (2006) 164-170.

[17] Ilg P, Kröger M: Magnetization dynamics, rheology, and an effective description of ferromagnetic units in dilute suspension, *Phys. Rev. E* 66 (2002) 021501.

Figure 6: Fraction of retained nanoparticles in relation to the distance, d, between field sources and vessel for different flow profiles.

- [18] Ilg P, Kröger M, Hess S, Zubarev AY: Dynamics of colloidal suspensions of ferromagnetic particles in plane Couette flow: Comparison of approximate solutions with Brownian dynamics simulations, *Phys. Rev. E* 67 (2003) 061401.
- [19] Shibeshi SS, Collins WE: The Rheology of Blood Flow in a Branched Arterial System, *Appl. Rheol.* 15 (2005) 398-405.
- [20] Womersley JR: Mathematical theory of oscillating flow in an elastic tube, *The Journal of physiology*, 127 (1955), 37-38P.
- [21] Womersley JR: Oscillatory flow in arteries: the constrained elastic tube as a model of arterial flow and pulse transmission, *Phys. Medicine Biol.* 2 (1957) 178-187.
- [22] Visser J: On Hamaker Constants: A Comparison between Hamaker Constants and Lifshitz - Van der Waals Constants, *Adv. Colloid Interf. Sci.* 3 (1972) 331-363.
- [23] O'Neill ME: A sphere in contact with a plane wall in a slow linear shear flow, *Chem. Eng. Sci.* 23 (1968) 1293-1298.
- [24] Sharma MM, Chamoun H, Rama Sarma DSHS, Schechter RS: Factors Controlling the Hydrodynamics Detachment of Particles from Surfaces, *J. Colloid Interf. Sci.* 149 (1991) 121-134.
- [25] Schneck DJ: An Outline of Cardiovascular Structure and Function, *The Bio-medical Engineering Handbook*, Bronzino JD (Ed.) CRC Press LLC (2000) Boca Raton.
- [26] Truskey GA, Yuan F, Katz DF: *Transport Phenomena in Biological Systems*, Pearson Prentice Hall Upper Saddle River (2004) 793.
- [27] Alexiou C, Jurgons R, Schmid R, Erhardt W, Parak F, Bergemann C, Iro H: Magnetic Drug Targeting--a new approach in locoregional tumor therapy with chemotherapeutic agents. *Exp. Animal Stud.* 53 (2005) 618-622.
- [28] Alexiou C, Jurgons R, Schmid R, Bergemann C, Henke J, Erhardt W, Huenges E, Parak F: Magnetic drug targeting--biodistribution of the magnetic carrier and the chemotherapeutic agent mitoxantrone after locoregional cancer treatment, *J. Drug Targeting* 11 (2003) 139-149.

