Preparation and Characterization of Ferrofluids for Locoregional Tumor Therapy

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Magnetic Drug Targeting is a promising approach for the locoregional treatment of tumors. An indispensable pre-requisite is the availability of appropriate ferrofluids as carrier for the chemotherapeutic drugs. Commercially available, biocompatible ferrofluids of Chemicell GmbH Berlin have been successfully applied for the treatment of VX-2 squamous cell carcinoma New Zealand White rabbits [1,2]. However, in some cases aggregation of the nanoparticles occurred and the animals died because of embolic.

The aims of the present project are the following: i) Characterization of commercially available ferrofluids in order to select charges for the medical application which contain no large particles. ii) develop methods to remove particles with the wrong size. iii) Investigation of the clustering and iv) The development of well defined biocompatible ferrofluids of a well defined size. The project has just started.

For the analysis of the size of the ferrofluids the dynamical light scattering has proved to be the appropriate method. With components of ALV we build up equipment which allows measurements of dynamical light scattering at different angles [*)]. Due to the small active volume of only 1x1x10 ? m^3 it is difficult to detect a small number of larger particles, especially in diluted solutions. Therefore, we used the back scattering geometry (170°) where we could work with the same concentration of

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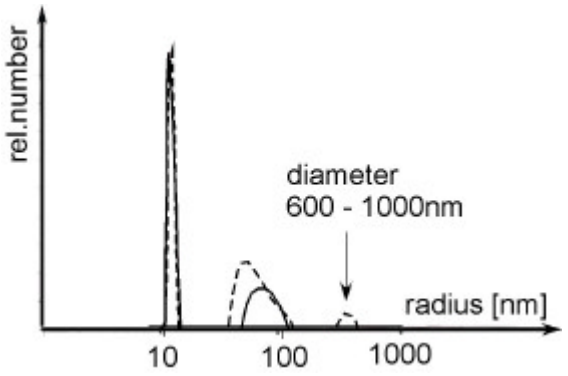

Fig.1: Dynamic light scattering on a ferrofluid sample, sampling time 3s (solid lines) and 1h (dashed lines).

ferrofluids as used in the medical application. A typical example is given in Fig. 1. There are 3 types of particles: with a radius of about 10nm, 70nm and larger 400nm. The latter are responsible for the embolic problem. We investigated 10 samples of Chemicell. The radii varied in the three types from 4 to 12 nm, from 30 to 200nm and from 200 to 2000 nm, respectively.

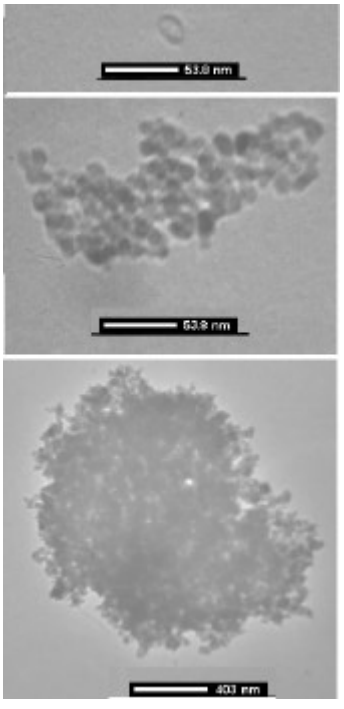

Fig. 2: EM pictures of different cluster measuring stick: 53.8 nm, 53.8 nm and 403 nm respectively

Fig. 2 shows the different types of ferrofluids as seen in the electron microscope. The particles are very inhomogeneous. A comparison of different samples shows that particles of similar size differ strongly in shape. ?

In a preliminary experiment we investigated the influence of a small magnetic field. In contrast to the harmful permanent aggregation a reversible magnetic structure generation was observed by dynamic light scattering in presence of a magnetic field of only 15mT (see Fig.3). Samples were prepared for the electron microscopy in the magnetic field. Micrometer sized chains were observed The chain length increased with the field strength. After removal of the field the chains disintegrated within the resolution (2 s) of the time resolved dynamic light scattering experiments.

The experiments have to be repeated with strong magnetic fields comparable to that used in magnetic drug targeting. The reversible magnetic chain structure formation may be of help for the desired particle concentration in the cancer tissue.

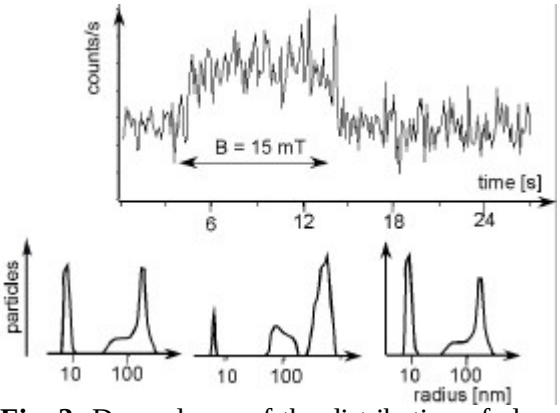

Fig. 3: Dependence of the distribution of cluster sizes on an applied magnetic field. Clusters which a diameter of about 1 ? m, formed in the magnetic field, decay in some seconds after turning-off the field.

[1] Alexiou, C., Arnold, W., Klein, R. J., Parak, F. G., Hulin, P., Bergemann, C., Erhardt, W., Wagenpfeil, S. and Lübbe, A. S., Locoregional cancer treatment with magnetic drug targeting. *Cancer Research* **60** (2000) pp. 6641-6648.

[2] Alexiou, C., Arnold, W., Hulin, P., Klein, R. J., Renz, H., Parak, F. G., Bergemann, C. and Lübbe, A. S., Magnetic mitoxantrone nanoparticle detection by histology, X-ray and MRI after magnetic tumor targeting. *J. of Magnetism and Magnetic Materials* **225** (2001) pp. 187-193.