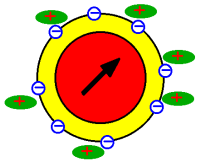
Preparation and Characterization of Ferrofluids for Locoregional Tumor Therapy

T. Nawroth[1], C. Alexiou[2], F.G. Parak[1]

1) Physik-Department E17, TUM, D-80748 Garching
2) Hals- Nasen- Ohrenklinik und Polyklinik, D-91054 Erlangen-Nürnberg

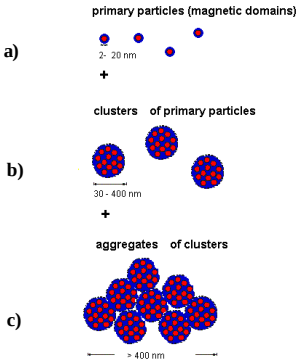
DFG-Schwerpunkt SPP1104 meeting 2003
27-29.9.2003 Benediktbeuern



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 [1-3]. However, in some cases aggregation of the nanoparticles occurred and the animals died because of embolic. As an attempt for the production of secure therapeutic material the structure was analyzed by various methods, which included first experminents on selective Ferrofluid synthesis and particle separation by size.

Structure investigation by Electron Microscopy EM, and Dynamic Light Scattering (DLS, PCS)

Hydrophilic shell Ferrofluids – three stage structure hierarchy



Due to EM and DLS investigations of several products, the hydrophilic shell Ferrofluids exhibit a three stage structure hierarchy:
a) primary particles (2-20 nm),
b) medium size clusters of primary particles (30 – 400 nm), and
c) permanent aggregates of clusters (> 400 nm).

The **medium sized clusters (b)** are the particles of interest **for medical application**: A strong macroscopic magnetic moment is accompanied with high load of bioactive material at outer and burried surfaces.

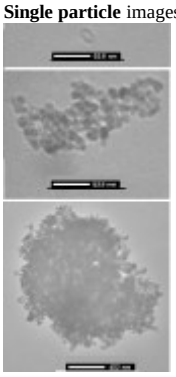
EM : direct Electron Microscopy (no stain, iron oxide imaging)

Particle radius: **Single particle** images

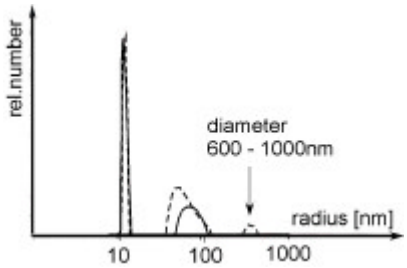
10 nm

70 nm

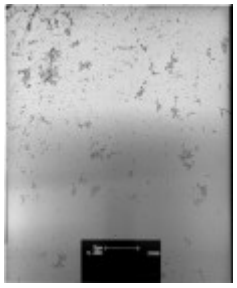
400 nm



DLS / PCS : Dynamic Light Scattering of concentrated solutions (original samples)

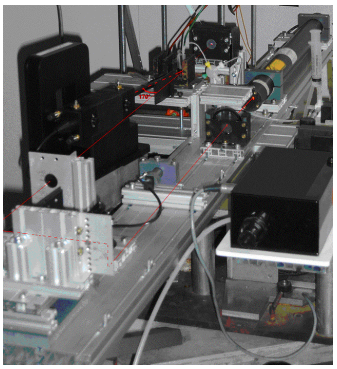


Dynamic light scattering of a Ferrofluid sample, sampling time are 3s (solid lines) and 1h (dashed lines). The large particles are difficult to detect (long time only), due to the small active volume.



Overview image of a commercial hydrophilic shell Ferrofluid with attached drug (Mitoxanthrone) obtained by direct Electron Microscopy. The sample consists of three types of nanoparticles: single domains, clusters and aggregates of clusters.

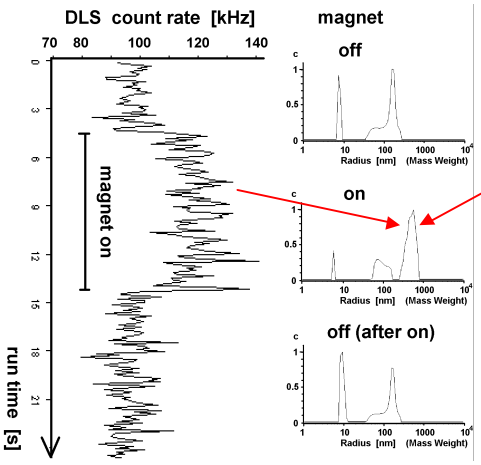
Magnetic dynamical light scattering (MPCS) and EM indicates reversible chain formation



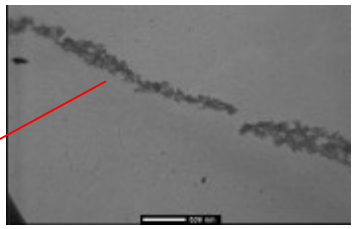
Dynamic **L**ight **S**cattering device (DLS) at TUM-E17. The modular setup can be equipped with a magnet or stopped-flow device for field and time-resolved experiments. The backscattering setup (170°) enables the investigation of concentrated original samples (5 % w/w).

Sample : CC_M450

In preliminary experiments 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.



Additional 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.



Magnetic electron microscopy (MEM) of Ferrofluid at 15 mT (preparation in MDLS setup)

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 deposition in the cancer tissue.

Conclusion : DLS, EM, selective synthesis and separation are required for application

The required **secure medical product** characterization and synthesis has to be as broad as the Ferrofluid properties:
Dynamic light scattering DLS / PCS of concentrated original samples, electron microscopy EM, magnetic structure analysis (DLS, EM), selective Ferrofluid synthesis and particle separation techniques (removal of permanent large aggregates, size > 0.5 µm).

References:

[1] Alexiou, Ch.; Schmid, R.; Jurgons, R.; Bergemann, Ch.; Arnold, W.; Parak, F.G. (2002) in Odenbach, S. (ed.) „Ferrofluids", pp. 233-251, Springer Verlag, Berlin
[2] 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.
[3] 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.