Size Control of hydrophilic polycentric Ferrofluids for Locoregional Tumor Therapy by Pulse Etching during Synthesis

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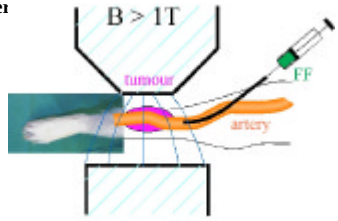
Biocompatible Ferrofluids are **magnetic nanoparticles**, that can be used as a delivery system for anticancer agents in locoregional **tumor therapy**, called "**magnetic drug targeting**". By this method of drug application, one attempts to concentrate a pharmacological agent in the tumor mainly in order to minimize unwanted side effects in the organism and to increase its locoregional effectiveness [1].

The study is done with biocompatible Ferrofluids of two origins: **commercial** "BioMAG / TargetMAG" products of Chemicell GmbH, Berlin and several biocompatible Ferrofluids from *ab initio* **synthesis at TUM physics-E17** [2].

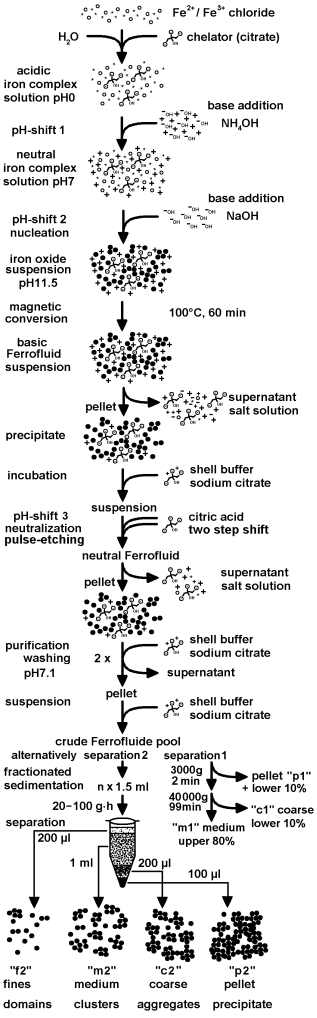
Commercial Ferrofluids have been successfully applied for the carcinoma treatment in rabbits [3-5]. However, in some cases aggregation of the nanoparticles occurred and the animals died because of embolic. As an attempt for the production of **secure therapeutic material** the structure was analyzed by various methods, which included first experminents on selective Ferrofluid synthesis and particle separation by size.



Cancer therapy by application of Ferrofluid FF

Strongly magnetic large Ferrofluid nanoparticle clusters (100 nm) by selective synthesis

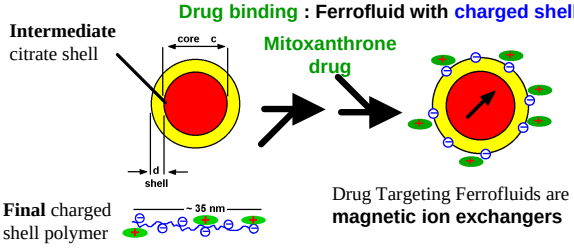
Synthesis of ferrofluid-clusters : size control by pulse etching



Synthesis flow chart of biocompatible Ferrofluid, size control by **pulse etching** and **separation by sedimentation** [2].

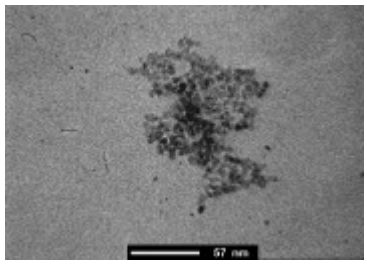
Shell exchange by drug binding charged polymer

Drug binding : Ferrofluid with charged shell



Drug Targeting Ferrofluids are **magnetic ion exchangers**

Ferrofluid shell exchange: Ferrofluid-clusters of medium size (50-100 nm diameter) are embeded by citrate and negatively charged **phosphodextrane** (10kD), after synthesis with an intermediate citrate shell



Structure of a polycentric Ferrofluid after **shell exchange** by **phosphodextrane** depicted by iron electron microscopy (no stain, O. Stroh, diploma thesis, TU München in prep.).

Structure investigation in parallel to synthesis required for secure product :

Electron Microscopy EM, and Dynamic Light Scattering DLS, Mössbauer spectroscopy, EPR

Analysis of structure, size and magnetism : feedback for selective synthesis and size control

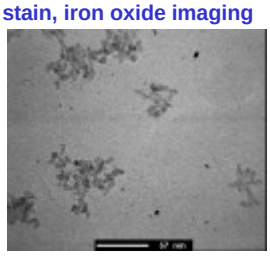
Size control by pulse etching

The **Ferrofluid cluster size** S(c,t) depends on reaction time t and acid concentration c during **pulse etching**.

The **average cluster size** can be **adjusted by** 2D-variation in **pulse etching** between large, medium, small clusters, and primary particles (single core nanoparticles).

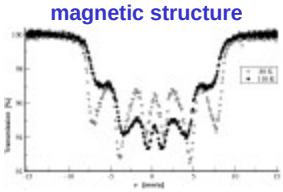
Acknowledgements : We thank the DFG, and the Margarete Ammon Stiftung for funding the DLS setup with compo-nents of ALV, Langen (ELV5000 correlator, single photon detector SP2, interference enhancer, 35 mW HeNe-laser with attenuator. We thank Dr. E.Hünges and Dr. K. Achterhold for help in the experiments.

EM - direct Electron Microscopy : no stain, iron oxide imaging



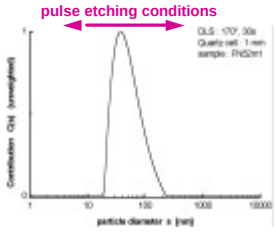
Structure of the **pulse etched** polycentric Ferrofluid after size separation depicted by **electron microscopy** (iron image) [2].

Mössbauer spectroscopy : magnetic structure



The **Mössbauer spectrum** of the polycentric Ferrofluid indicates a mixture of ?-Fe_2O_3 and Fe_3O_4 (O. Stroh d. thesis)

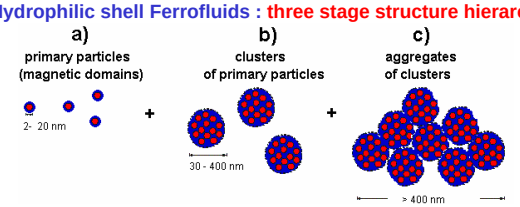
DLS : Dynamic Light Scattering of concentrated original samples



Particle size distribution of a **pulse etched** polycentric Ferrofluid obtained by **DLS** of the concentrated original sample "FN52m1" (back scattering, 170°, 50g/l) [2].

A special **D**ynamic **L**ight **S**cattering **DLS** device was constructed at TUM-E17 for investigation of optically dense **original samples** in thin layer cells.

Hydrophilic shell Ferrofluids : three stage structure hierarchy



Due to EM and DLS investigations of several products, the hydrophilic Ferrofluids exhibit a **three stage structure hierarchy** [2]:
a) Primary particles (2-20 nm, i.e. core particles, single domains),
b) Medium size clusters of primary particles (20 – 400 nm), and
c) Large 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, i.e. a **magnetic ion exchanger**.

References:

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Conclusion : synthesis, size control and analysis

- **Synthesis** with intermediate citrate shell and **size limitation** by two methods :
- **Size control** of medium Ferrofluid clusters by citric acid **pulse etching** of crude product
- **Size limitation** by **fractionated sedimentation** : exclusion of large aggregates (>400nm)
- **Shell** embedding and exchange by **drug-binging** negatively **charged** phosphodextrane
- **Structure and particle size** distribution analysis by EM and DLS demonstrate the main population of 20-200nm size, the biggest particles can pass the smallest blood vessels (500nm)
- The current investigations focus on magnetic properties by **EPR**, ferric oxide structure by **Mössbauer spectroscopy**, **drug loading** (Mitoxantron) and **blood interaction**.