

## SUPERPARAMAGNETIC NANO-PARTICLE PREPARATION FOR MEDICAL APPLICATION

[H.Hofmann](#), A.Petri, M.Chastellain, M.Hofmann

*Swiss Federal Institute of Technology Lausanne, [Laboratory for Powder Technology \(LTP\)](#),  
Lausanne, Switzerland*

**INTRODUCTION:** Today nanotechnology has developed to a stage, which makes it possible to produce, characterize and specially tailor the functional properties of nanoparticles for clinical applications and diagnostics. Such an approach would considerably improve the efficiency of drug delivery to the specific area of need in a human body, and most importantly minimize the negative side and after effects of dosage, localization and focus medical treatment. The use of magnetic nanoparticles can contribute to a precise delivery of drugs to the exact area (e.g. of inflammation, cancer etc.) by application of external magnetic fields.

On the other hand separations with magnetic polymer particles of nano- size are becoming increasingly important in all fields of science as well as in engineering and environmental technologies. The simple and fast separation method is mostly predetermined for automated separation processes (e.g. DNA separation, cell separation etc.) which can facilitate many operations. Highly functional magnetic particles are required for this technology to allow an application in as many fields

Therefore new more effective techniques to generate these nanosized magnetic particles are requested, which should be non-toxic and biocompatible. These particles with the consequent large active surface will be prepared in a specially designed segmented flow tubular reactor (SFTR) developed at LTP. Advanced techniques will applied to tailor the particles to have higher magnetic saturation, a semi-spherical to needle-like morphology, and to be superparamagnetic. The overall objectives of the research at LTP is to produce these nanoparticles (mostly g-Fe<sub>2</sub>O<sub>3</sub> or g-Fe<sub>3</sub>O<sub>4</sub> single domains of about 5-10 nm in diameter) as free particles or attached on a surface for targeted applications, e.g. cell engineering, cell biology and tissue repair. Among the special fields of applications are:

1. Free particles for potential clinical application like Drug delivery
2. Free particles for diagnostics
  - Quantitative histological imaging

- Cell separation
  - DNA sequencing
  - Blood purification
3. As a tool for cell-biology research
  4. To separate and purify cell populations

In all cases only superparamagnetic particles are of interest because they do not retain any magnetism after removing the magnetic field. The effectiveness of the particles depends upon

- high magnetic susceptibility for an effective magnetic enrichment
- size of particles, which should be monosized in the range of 9 – 15 nm to be superparamagnetic
- prevention of agglomeration of particles
- long range stability, i.e. high circulation time in the blood, if used in-vivo
- low sedimentation
- the polymer shell and the biological functionalization of this

The application of the particles in-vivo or ex-vivo needs special surface modification of magnetic particles, which has to be not only non-toxic and biocompatible but also stable to the reticuloendothelial system (RES). As phagocytosis depends strongly on the surface charge (hydrophobic/hydrophilic) the surface modification is an important factor in the processing of magnetic nanoparticles, otherwise they undergo phagocytosis by the Kupffer cells. Another approach is to develop magnetic nanoparticles with different surface charges and zeta potentials at their surfaces, but only limited results exist regarding the combination of the demand of very small particles for a long circulation time in the blood and high magnetic susceptibility.

Until now, especially in cell separation the potential of the magnetic separation technology remains limited due to the low binding capacity and insufficient surface area of the available materials. Together with appropriate functionality, enabling attachment of biological ligands

numerous new applications and emerging new technologies in biotechnology and medicine would be envisioned (e.g. purification of recombinant proteins in preparative quantities, which is not technological feasible at present)

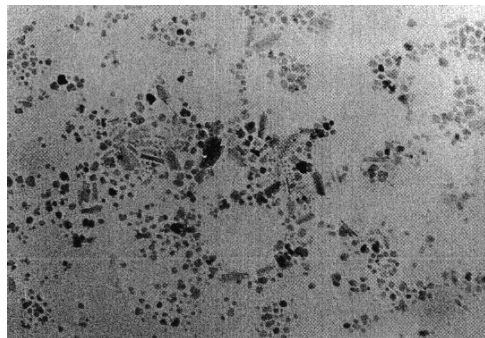
Although well-dispersed magnetic nanoparticles can be obtained by ball-milling,[7,8] a serious limitation on this techniques, beside the high-energy requirements, is the unavoidable contamination of the product, which necessitates the development of more economical and reliable technology to fabricate magnetic particles by well controlled chemical methods.

Iron oxide ( $\text{Fe}_3\text{O}_4$ ), the dominant magnetic material for the foreseen application, can be synthesized through the co-precipitation of  $\text{Fe(II)}$  and  $\text{Fe(III)}$  aqueous salts solution by addition of a base. The control of size, shape, and composition of  $\text{Fe}_3\text{O}_4$  or  $\text{g-Fe}_2\text{O}_3$  nanoparticles depends on the type of salt (chlorides, nitrates, perchlorates, etc.), the  $\text{Fe(II)}$  and  $\text{Fe(III)}$  ratio, and the pH and ionic strength of the media. Organized assemblies or complex structures have been used as reactors to obtain ultrafine magnetic iron oxide particles. Stable aqueous magnetic suspensions can be fabricated using various saturated and unsaturated fatty acids as primary and secondary surfactants. In practice, however, little control can actually be exercised over the size and size distribution of the micro-structures, and moreover, only small quantities of iron oxide can be obtained owing to the constraints of low reagent concentrations necessitated by this synthetic procedure.

*Aim of the Work:* The aim of this work is to synthesize and characterise improved ferrofluids for cell separation and drug delivery. The size-controlled precipitation of iron oxide particles and the coating step are the two main parts of the project. The nanoparticles are synthesized by co-precipitation of iron-based salts in different media. The use of various compounds such as dextran, starch, polyvinyl alcohol (PVA), sodium-dodecylsulphate (SDS) and silica allows to obtain stable colloids. The particles composition and morphology are characterized using TEM, XRD and FTIR. SQUID magnetometry is used to investigate the magnetic characteristics of the particles but this technique is discussed more in detail in the presentation D5.

**RESULTS:** TEM pictures show ellipsoidal particles. A first statistical analysis based on hundred particles per sample lead to an average size of less than 10nm with an ellipse aspect ratio of about 1.2. XRD patterns show a wide

amorphous background due to the presence of polymer, nevertheless typical peaks, which can be attributed to nanocrystalline magnetite ( $\text{Fe}_3\text{O}_4$ ) or maghemite ( $\text{g-Fe}_2\text{O}_3$ ) are also present. The size calculated from these data using the Scherrer formula confirms the TEM results. FTIR spectrometry led to the conclusion of a defect magnetite structure with a lattice parameter in between the one of bulk maghemite and magnetite.



*Fig. 1: Bright field TEM image of iron oxide particles stabilised with SDS. The sample consists of stable colloids at physiological pH, diluted and dried on a copper grid. The agglomerated structure is thought to be mainly due to the drying step*

**ACKNOWLEDGEMENTS:** This project is supported by EU - under the project MAGNANOMED - Magnetic Nanoparticles for Medical and Biological Diagnostics and Devices.