Magnetic bioferrofluids with tailored properties for biomedical applications


Instituto de Ciencia de Materiales de Aragón. CSIC - Universidad de Zaragoza. Zaragoza

NanoBio-Europe2008
Barcelona, 9-13, June 2008
• Introduction: biomedical applications of magnetic nanoparticles

• Nano vs. Nano

• Superparamagnetic particles

• Hyperthermia

• Polymeric route to the production of iron oxide nanoparticles and ferrofluids
Interest of Magnetic Nanoparticles in Biomedical Applications

- Controllable sizes (≥ 100 nm - ≤ 10 nm) and shapes (spheres, needles, beads)
- Magnetic functionality => magnetic fields penetrate human tissues
- They obey Coulomb’s law => can be controlled at a distance
- They transfer energy from an ac magnetic field and convert it into heat
Biomedical Applications of Magnetic Nanoparticles

**Diagnosis**

- MRI
- Hyperthermia (MFH)
- Radiotherapy/Chimietherapy-combined MFH
- Thermal ablation

**Therapy**

- Sensors
- Cell separation
- Enzyme tests
- Immunoassays
- Drug delivery
- Arthritic treatments
- Chronic diseases
Magnetic (Nano)Particles

- Magnetic domains
- + Magnetic field $H$

Magnetisation
$M = m/V_m$

Magnetic force
$F_m = V_m (M/H) \nabla (B \cdot H/2)$
From the physics point of view, nano- is the interface separating the atomic from the macroscopic scales.

In the atomic world, there are properties whose critical lengths are at the nano-scale.

Atomic World ruled by the laws of Quantum Mechanics

Macroscopic World as we perceive it, ruled by Classical Mechanics and Electromagnetism laws.
Introduction to nano-size

At the scale below a critical length new properties arise that can give rise to new materials and new applications.

Critical lengths such as:

- one electron Fermi wavelength
- exciton Bohr radius
- single magnetic domain length

Lead to Quantum Dots and Superparamagnetic particles
Single-domain particles $\Rightarrow$ superparamagnets

When the size of a particle is smaller than the minimum allowing the formation of domains ($\approx 20 - 30$ nm), it becomes single-domain and superparamagnetic.
Biomedical Applications of Magnetic Nanoparticles

- Cell separation
- Enzyme immunoassay tests
- Sensitive detection of viral agents
- Drug delivery
- Contrast agents for magnetic imaging
- DMS as luminescent sensors
- Hyperthermia
- \( \cdots \) the limit is the imagination \( \cdots \)
Magnetic force-driven applications

Magnetic separation

Transfected cell separation in gen therapy

Drug delivery

Blood vessel

Tissue

Magnet
Magnetic nanoparticles as contrast agents for MRI

- Huge magnetic moments as compared to Gd chelates
- Proton relaxation is affected by the large magnetic field heterogeneity in the vicinity of the particles
- Can induce >10 fold increase in proton relaxivities
- Shortening of relaxation times, particularly $T_2$ (negative contrast)
- Very high resolution, close to molecular level
Magnetic systems can convert energy into heat under the effects of an alternating magnetic field

- inductive heating (eddy currents)
- hysteresis losses

No relevant at low ac magnetic fields

\[ P_{FM} = -\mu_0 f \oint H dM \]
Hypertermia

Superparamagnetic particles

- Neél relaxation
- Rotational Brownian motion

\[ \chi'' = \chi_0 \frac{\omega \tau}{1 + \omega^2 \tau^2} \]

\[ P_{SPM} = -\frac{1}{2} \mu_0 \chi'' \omega H_0^2 \]

\[ \omega \tau \sim 1 \Rightarrow E_{\text{máx}} \]

Biological range: 50 kHz \( \leq f \leq 1200 \) kHz, \( H < 15 \) kA/m and \( (H \cdot f)_{\text{max}} = 485 \) kHz\( \cdot \)kA/m

\[ E_{\text{máx}} (\gamma\text{-Fe}_2\text{O}_3, \ 10 \ \text{nm}) \]

\[ \omega \sim 1 \ \text{MHz} \]
The shortest relaxation time constant tends to dominate the effective relaxation time.

\[ \tau_N = \tau_0 \exp \left( \frac{KV}{kT} \right) \]

\[ \tau_B = \frac{3\eta V_H}{kT} \]

\[ \frac{1}{\tau_{\text{eff}}} = \frac{1}{\tau_N} + \frac{1}{\tau_B} \]
Hypertermia

\[ \text{SAR} \left( \frac{W}{g} \right) = C \frac{\Delta T}{\Delta t} \cdot \frac{1}{m_{\text{SPM}}} \]

Non-adiabatic ----> heat losses ----> estimation of SAR
Adiabatic set-up for hyperthermia

**Sample, Thermometer**

**Coil (GEP Group, UZ)**

(no metallic components)

**Vacuum**

**LN$_2$**

**Electrical connections**

Operation range:

- $H = 0\text{ - }8\text{kA/m}$
- $f = 50\text{ – }300\text{ kHz}$

**Biological applications:**

- $H \cdot f < 4.85 \cdot 10^8\text{ A/m}\cdot\text{s}$

- $H < 15\text{ A/m}, f < 400\text{ kHz}$

Adiabatic set-up for hyperthermia

(see also poster from Ana Arizaga)
Superparamagnetic Particles for Biomedical Applications

- Functionalized magnetic nucleus (magnehite, other)
- Protecting core, anchoring element
- Functionalized tail for therapeutic uses: drugs, enzymes, etc.
- Biological vector: antigens, etc.
The magnetic nucleus should preferably be biocompatible, otherwise a strong protective coating (+ its validation!!) is required for *in vivo* applications.

- Maghemite
- Magnetite
- Co-ferrites and other (*in vitro*)
**Tailoring magnetic nanoparticles**

**Interest:**

- Important applications of magnetic nanoparticles are very exigent regarding size and shape dispersion.
- Polymers can provide a way to avoid agglomeration and easy surface functionalisation.

Production methods must focus on:

- narrow size dispersion
- variable size control
- variable shape control
- control of organization and particle-matrix interactions

**Size dependence of the Specific Absorption Rate (SAR)**

- Only particles within a narrow $\Delta D$ are efficient.
Tailoring magnetic nanoparticles

1. Synthesize the magnetic particles, normally magnetite or maghemite

2. Avoid agglomeration by keeping them dispersed in a surfactant

3. Eliminate surfactant to stabilise the particles either electrostatically or sterically

4. Functionalise the particles

**Thermal decomposition of Fe(CO)5.**
Tailoring magnetic nanoparticles

Fe(CO)$_5$ $\Delta$ Solvent: octyl ether

Maghemite, 10 nm

Maghemite, 14 nm

Maghemite, 20 nm

Size dispersion $\approx 5\%$

Size ranges: 4-20 nm
Tailoring magnetic nanoparticles

Fe(CO)$_5$ + Me$_3$NO $\xrightarrow{\Delta}$ Oleic acid + Octyl ether

$\gamma$-Fe$_2$O$_3$ + (RO)$_3$SiR' $\xrightarrow{\text{TEM}}$ R' - Si - OH

EFTEM
Tailoring magnetic nanoparticles with polymers

Hydrophilic PVP polymer + metal salt → homogeneous gel → nanocomposite

(eventually) → disgregation → PEG copolymerisation → ferrofluid

Either spheres and rods can be selectively prepared.

Polymers can provide a way to avoid agglomeration and easy surface functionalisation.

Simple and quick single-pot reaction
Spheric particle sizes 2 - 15 nm
Size dispersion ±10%
No aggregation. Uniform distribution.

Tailoring magnetic nanoparticles with polymers
Adequate polymer design leads to nanocomposites which disperse in a phosphate buffer saline solution as nanoparticles coated with PEG.
Maghemite ferrofluids

Ferrofluids are persistent for more than one month

**MAGNETIC STABILITY**

- Freshly prepared
- After one month

**M(emu) a.u.**

**T(K)**

**ZFC//FC(250e)**

**Maghemite rods**

\( \chi''(\text{emu/OegFe}_2\text{O}_3) - 24\text{h} \)

\( \chi''(\text{emu/OegFe}_2\text{O}_3) - 1\text{month} \)

- 852 Hz
- 117 Hz
- 1 Hz

24 hours
1 month
NMR relaxometry

Relaxivities $R_1$ and $R_2$ quantifies the increased nuclear relaxation rates $1/T_1$ and $1/T_2$ of nuclei (typically protons) due to the presence of magnetic centers.

- $R_1$ and $R_2$ relaxivities compared with commercial ENDOREM®
- PEI-25 $R_1$ relaxivity compares to ENDOREM®
- PEI-25 $R_2$ relaxivity higher over the whole field range.
<table>
<thead>
<tr>
<th>Material</th>
<th>Size (nm)</th>
<th>$H$ (kA/m)</th>
<th>$f$ (kHz)</th>
<th>$Hf/(Hf)_{ma}$</th>
<th>SAR (W/g)</th>
<th>SAR * (W/g)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>magnetite</td>
<td>8</td>
<td>1.4 - 6.3</td>
<td>410</td>
<td>1.2 - 5.3</td>
<td>78</td>
<td>11.3</td>
<td>Hiergeist et al, J. Magn. Magn. Mat., 201 (1999) 420-422</td>
</tr>
<tr>
<td>magnetite</td>
<td>7.5 - 46</td>
<td>32.5</td>
<td>80</td>
<td>5.4</td>
<td>75.6</td>
<td>2.1</td>
<td>Ma et al, J. Magn. Magn. Mat., 268 (2004) 33-39</td>
</tr>
<tr>
<td>maghemite</td>
<td>7 - 18</td>
<td>15</td>
<td>410</td>
<td>12.7</td>
<td>900</td>
<td>22.9</td>
<td>ibid., 280 (2004) 358-368</td>
</tr>
<tr>
<td>magnetite</td>
<td>6 - 10</td>
<td>7</td>
<td>63</td>
<td>0.9</td>
<td>85</td>
<td>93.7</td>
<td>Wang et al, J. Magn. Magn. Mat., 293 (2005) 334-340</td>
</tr>
<tr>
<td>maghemite</td>
<td>d ≈12 needles</td>
<td>5</td>
<td>150</td>
<td>1.1</td>
<td>158</td>
<td>144</td>
<td>A. Millán et al (in preparation)</td>
</tr>
</tbody>
</table>

(*) Referred to standard $H = 4.85 \text{ kA/m}$, $f = 100 \text{ kHz}$ values
Nanomagnets for theragnostic

MRI

PAVIA

Florence

Zaragoza

Hyperthermia

Adiabatic and non adiabatic magnetothermia set ups (50 - 500 kHz, 0 - 8 kA/m, down to 80K

Low NMR frequencies (few kHz - 10 MHz) down to 4.2 K, multinuclear operational mode,

\( \chi_{ac} \) susceptibility set up
50 - 500 kHz
1.5 - 350 K

Interested may contact: amillan@unizar.es or palacio@unizar.es
Group TERMOMAG

Ana ARIZAGA
Ramon BURRIEL
Javier CAMPO
Miguel CASTRO
Clara GONZALEZ
Miguel A. GONZALEZ
Gemma IBARZ
Ricardo LOPEZ
Emma LYTHGOE
Eva NATIVIDAD
Angel MILLAN
M Carmen MORON
Lucas OLO
Elias PALACIOS
Rafael PIÑOL
Ines PUENTE
Alberto RODRIGUEZ
Clara RODRIGUEZ
Cristina SAENZ de PIPAON
Jorge SANCHEZ
Nuno J. O. SILVA
Leticia TOCADO
Ainhoa URTIZBEREA
ACKNOWLEDGEMENTS

MEC, MAT2004-03395-C02-01

CONSOLIDER - MAT2007-61621

Programa CENIT - Ingenio 2010
Industrial Consortium

European Network of Excelence, 6FP

Proyecto de colaboración industrial
Escalado de producción

Molecular Nanoscience

Programa Consolider
Ingenio 2010