**Plasma-liquid Electrochemistry : a Fast Method for Synthesizing Magnetic Nanoparticles**

**Mathieu Létourneau**[1,2,3], Christian Sarra-Bournet[1], Myriam Laprise-Pelletier[1,2,3], Marc-André Fortin[1,2,3]

[1]Axe métabolisme, santé vasculaire et rénale, Centre de recherche du Centre hospitalier universitaire de Québec (AMSVR-CRCHUQ), Groupe de recherche en imagerie moléculaire (GRIM), 10 rue de l'Espinay, Québec, QC G1L 3L5, Canada

[2]Département de génie des mines, de la métallurgie et des matériaux, Université Laval, Québec, QC G1V 0A6, Canada

[3]Centre de recherche sur les matériaux avancés (CERMA), Université Laval, Québec, QC G1V 0A6, Canada

mathieu.letourneau.2@ulaval.ca

INTRODUCTION: Iron oxide nanoparticles (NPs) are a widely used contrast agent in magnetic resonance imaging (MRI). In general, these colloids are synthesized by thermal decomposition reactions, which require at least 24 hours as well as the work of a skilled chemist. As-synthesized particles covered with fatty acids are only dispersible in organic solvents.[1] A ligand exchange procedure is then needed to enable their aqueous dispersion. Such complex colloidal synthesis and ligand exchange steps can hardly be automated. New dual imaging scanners combining positron emission tomography and magnetic resonance imaging (PET/MRI) [2] are now available for clinical use. Dual MRI and PET acquisitions are expected to provide high anatomical resolution (in MRI) and high sensitivity (PET), an optimal combination for the development of new molecular and cellular tracking applications. In this context, new imaging probes are necessary, requiring the integration of PET-detectable radioisotopes to magnetic nanoparticles (e.g. $FeO_x$; modifying $^1H$ proton relaxation times). The synthesis procedure must fit within the decay time frame of common positron emitters (typically hours). Here we report a plasma-liquid electrochemistry technique allowing the fast synthesis of ultra-small metallic nanoparticles, within minutes.[3]

MATERIALS AND METHODS: In brief, plasma-liquid electrochemistry consists in the generation of atmospheric microplasma pointing at the surface of an aqueous solution containing metallic salts and ligands. In the plasma, electrons and ions are accelerated toward the surface, reducing metal ions in the solution and inducing the nucleation and growth of nanoparticles. The plasma acts as the cathode, and the anode is a graphite rod immersed in the liquid (Figure 1). The nanoparticles generated within 5 minutes at the plasma-liquid interface, are readily dispersed in water and covered with biocompatible ligands such as dextrane and dimercaptosuccinic acid (DMSA)). This is a significant advantage compared to the thermal decomposition method, and it would enable the doping of nanoparticles with fast decaying positron emitters used for PET, such as $^{64}Cu$ ($t_{½}$=12.7 hrs). To keep the time advantage offered by this technique, a rapid purification step is required. We have compared two purification techniques in this work: 1) dialysis, which removes the excess of ions and ligand molecules by osmotic exchange, and 2) size exclusion chromatography, in which nanoparticles pass through the column faster than ions and ligand molecules. The hydrodynamic diameter of the nanoparticles was assessed by dynamic light scattering (DLS) and size distributions of the nanoparticle cores were measured by transmission electron microscopy (TEM). Relaxometric properties of the purified contrast media were characterised by $^1H$ NMRD ($T_1$ and $T_2$ measurement) and 1-Tesla MRI.

RESULTS AND DISCUSSION: TEM micrographs revealed the presence of ultra-small particles of mean diameters in the range 2-3 nm (Figure 2.a,b). The colloids had hydrodynamic diameters of 4 - 5 nm (Figure 3). The purified iron oxide NP suspensions shorten the longitudinal ($T_1$) and transversal ($T_2$) relaxation time of water, as showed in Table 1. Relaxometric ratios ($r_2/r_1$) of 2.67 to 3.75, as well as MRI assessments (Figure 4), confirmed the “positive” contrast enhancement effect achieved with these colloidal suspensions. Finally, preliminary results showed that iron oxide NPs could be synthesized via plasma-liquid electrochemical method with other ligand molecules, such as DMSA.

CONCLUSION: Plasma-liquid electrochemistry allows the synthesis of ultra-fine and narrow nanoparticulate systems, with impact on the relaxation time of water allowing their use as contrast agents in MRI. The rapidity and simplicity of the technique could offer the possibility to synthesize magnetic and radioactive NPs for PET/MRI, upon demand. Finally, applications in internal radiotherapy are also being investigated.

**References**

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[3] Richmonds, C.; Sankaran, R. M., Applied Physics Letters, **13** (2008).

## Figures and Tables

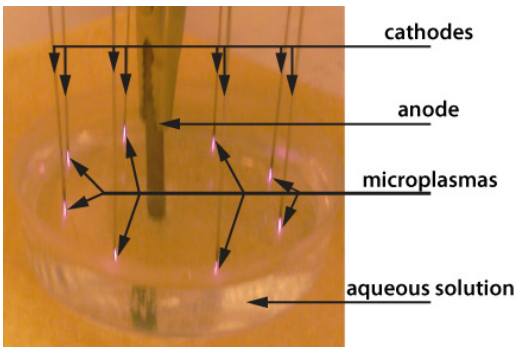


**Figure 1.** Plasma-liquid electrochemistry apparatus for nanoparticle synthesis.

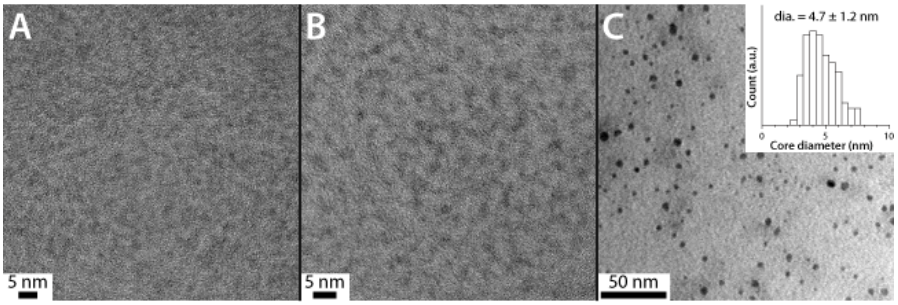


**Figure 2.** TEM micrograph (200 keV) of **a)** $FeO_x$-dextran nanoparticles purified by dialysis, **b)** by chromatography, and **c)** TEM of $FeO_x$-DMSA nanoparticles (120 keV) purified by dialysis (inset : size distribution, measured with ImageJ).

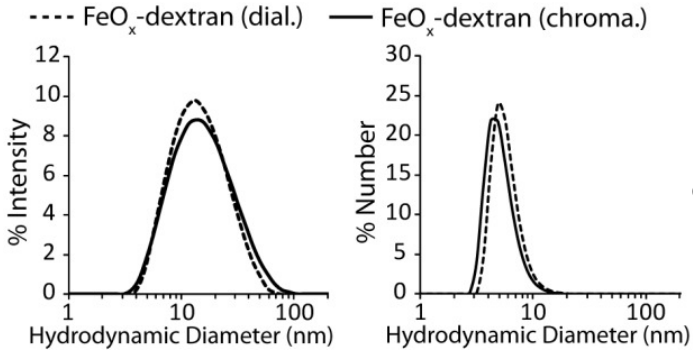


**Figure 3.** DLS measurement after dialysis and chromatography.

**Table 1.** Longitudinal and transversal relaxation times ($T_1$, $T_2$) of aqueous NP suspensions.

| Product | $T_1$ (ms) | $T_2$ (ms) | $r_2/r_1$ |
|---|---|---|---|
| $FeO_x$-dextran (dialysis) | 1663 ± 5 | 766.6 ± 0.5 | 3.22 |
| $FeO_x$-dextran (chromatography) | 2014 ± 9 | 1214 ± 1 | 2.67 |
| $FeO_x$-DMSA (dialysis) | 1511 ± 5 | 477.3 ± 0.3 | 3.75 |

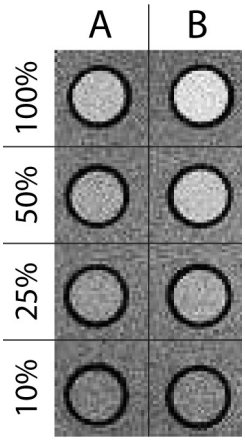


**Figure 4.** $T_1$-weighted MRI measurements of dextran-covered nanoparticle suspensions purified by a) dialysis and b) chromatography. The sequence is SE 2D with 1.9 mm slice thickness (0.1 mm gap), FOV = 70mm (200x200), 1 NEX with TR/TE: 1000/10.8 ms; total acquisition time: 200 seconds.