

Iron oxide nanoparticles grafted with thermosensitive polymers and diblock elastin-like peptides studied by *in situ* dynamic light backscattering under magnetic hyperthermia

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Abstract

Magnetic hyperthermia is envisioned to become in a near future a well-recognized therapeutic method by oncologists to fight against certain incurable cancers such as glioblastoma [1]. On the other hand, local thermometry is emerging as intensive research area fostered by fundamental questions on how nanoparticles convert (electro)magnetic radiations into heat at the nano-scale and dissipate it into their surrounding medium, potentially in living tissues. Hyperthermia can involve plasmonic absorption (visible or near-infrared) by noble metal NPs, magnetic induction in the MHz or the GHz bandwidths, focused ultrasound (FUS) and other approaches. Recently several studies highlighted the possible high discrepancy between the local temperature in the direct vicinity of nanoparticles (within nm) and the macroscopic bulk solvent temperature. Thermal gradients of several tens of °C are authorized by the classical Fourier / Kelvin model of heat transfer as transient states at the timescale of picoseconds [2]. However, recent puzzling results also suggest that stationary gradients could be maintained between the surface of nanoparticles and the bulk. Chemical reactions occurring normally at high temperatures (homolytic bond cleavage [3], retro Diels-Alder reaction [4], Fischer-Tropsch reaction catalysis [5], gene expression *in vitro* [6, 7]...) were observed even in the absence of a macroscopic temperature increase. Cellular toxicity under radiofrequency magnetic field was thus more likely ascribed to reactive oxygen species production, a phenomenon sometimes referred to as “cold hyperthermia” [8].

The grafting of polymer chains at the surface of the NPs aids in the comprehension of this phenomenon, by measuring a macroscopic property of the NP suspension (e.g. fluorescence) and comparing it to a calibration curve built up by macroscopic heating. The nanometer dimensions of polymers with a thermo-cleavable bond and a fluorescent probe enables estimating temperature locally, i.e. in the near vicinity of the surface of the NPs [3]. Another approach consists in grafting onto iron oxide NPs polymer chains which are thermosensitive, i.e. which exhibit a transition between swollen and dehydrated states, as already shown with commercial synthetic polymers called Jeffamine™ [9].

In this presentation, I will present a novel dynamic backscattered light intensity setup combined with MH (Figure 1) enabling to follow the hydrodynamic diameter variation of thermosensitive magnetic nanoparticles *in situ* while applying a radiofrequency magnetic field [10]. A fiber-based backscattering setup enabled positioning of the DLS remote-head as close as possible to the coil of a magnetic heating inductor to afford probing of the backscattered light intensity, hydrodynamic diameter, and temperature. This approach provides a promising platform for estimating the response of magnetic NPs to application of a radiofrequency magnetic field or for understanding the behavior of other types of thermogenic NPs. Superparamagnetic iron oxide NPs were prepared by the coprecipitation of ferrous and ferric salts and functionalized with aminosilanes, then azides, using a sol-gel route followed by a dehydrative coupling reaction. Thermosensitive poly[2-(dimethylamino)ethyl methacrylate] (PDMAEMA) with an alkyne end-group was synthesized by controlled radical polymerization and was grafted using a copper assisted azide-alkyne cycloaddition reaction. Measurement of the colloidal properties by dynamic light scattering (DLS) indicated that the PDMAEMA-grafted iron oxide NPs exhibited changes in their Zeta potential and hydrodynamic diameter as a function of pH and temperature due to the grafted PDMAEMA chains. These changes were accompanied by changes in the proton spin relaxivities of the NPs, suggesting application as thermosensitive contrast agents for magnetic resonance imaging (MRI) [9].

With the aim of improving this approach and applying it in cellular environments, we develop another biocompatible and biomimicking coating based on recombinant proteins of the VPGXG pentapeptide sequence of elastin, a natural protein of the extracellular matrix that exhibits thermosensitivity (X being any amino acid but proline). More precisely we designed diblock ELP proteins with a thermosensitive block (sketched in dark blue on Figure 2) that undergoes a swelling-deswelling transition at a critical temperature, and a hydrophilic block (light blue) proving steric repulsion. In a precedent work, we showed that diblock ELPs form well defined nanoparticles above their transition temperature, with a compaction of their core when temperature increases [11]. Here we report their grafting onto iron oxide nanoparticles synthesized by a polyol route, resulting into magnetic thermosensitive nanoparticles with high magnetic heating efficiency, significant temperature-size response and improved colloidal stability in biological buffers (e.g. phosphate buffer saline).

Although the size variation still correlates with the variation of macroscopic temperature (Figure 2) rather than at the nanoscale, this experimental approach improve the understanding of magnetic heating by iron oxide NPs in more complex environments like in intra-cellular compartments.

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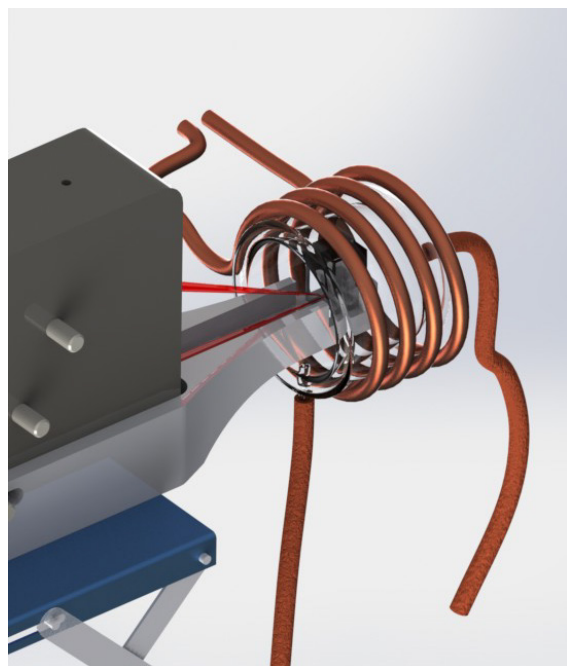


Figure 1: Setup for simultaneous application of magnetic hyperthermia (MH) and dynamic light scattering (DLS) measurement.

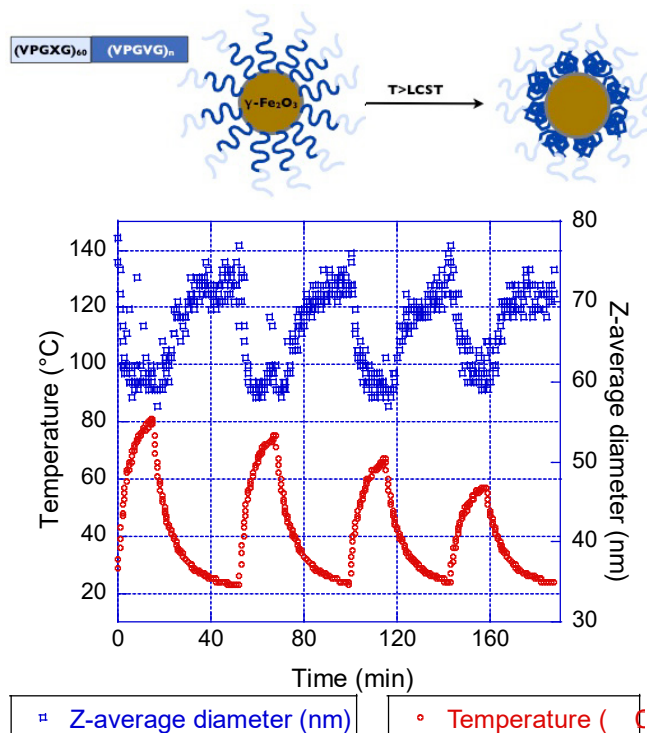


Figure 2: Sketch of iron oxide nanoparticles coated with thermosensitive diblock elastin-like peptides (ELP) and corresponding DLS curve under MFH.