

Comparative studies on the binding, stabilization and delivery of macromolecular DNA and RNA attached to gold, manganese and zinc nanoparticles

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The attachment of nucleic acids to nanoparticles has many potential therapeutic or diagnostic applications. A majority of work has focused on the attachment of DNA oligonucleotides to gold nanoparticles via thiol linkage. Our patented approach utilizes cationic delivery peptides derived from protamine to mediate attachment of macromolecular DNA onto gold. This is an active bioprocess for DNA vaccine¹ where plasmid DNA is attached to gold via protamine stabilizing it from chemical and enzymatic degradation. This technique increases and prolongs gene expression in plants², which are traditionally difficult to transform. More recently we have extended this strategy to the nano-scale, attaching macromolecular DNA to gold nanoparticles circumventing the sulphur chemistry limitation. Further, and more importantly, our most recent data suggests the approach can be applied to therapeutic RNA molecules. Gold nanoparticles were fabricated by chemical synthesis or pulsed laser deposition exhibiting characteristic absorbance (530 nm), AFM and TEM. DNA or RNA was attached post-synthetically and compared by UV/Vis and dynamic laser light scatter spectroscopy (DLS). Peak shifts and intensity changes by UV/VIS confirmed interaction of the nucleic acids with nanoparticles mediated by protamine. DLS analysis demonstrated peaks at 182, 300 and 600 nm, for gold binding to protamine, RNA or DNA respectively. Gold is generally considered inert and reasonably well-tolerated in humans. However, we anticipate that zinc and manganese oxide nanoparticles may be better suited for the binding of therapeutic or diagnostic DNA or RNA molecules, respectively, and their potential biomedical applications. Therefore, in current work we have produced and characterized Zn and Mn oxide nanoparticles by chemical or physical methods. We are beginning to evaluate their binding and stabilization properties and their delivery as nanoconjugates with therapeutic DNA or RNA in human melanoma or tuberculosis cell-culture or animal models. Our recent results will be discussed in this presentation.

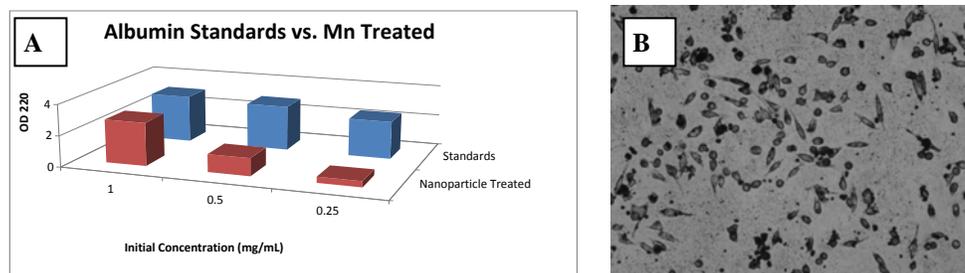


Figure 1. Association of serum albumin to MnO nanomaterial (A) and morphological effect of a standard 31.25 ug/ml dose on HeLa cells (B).

Reference:

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Determination of the surface area of suspensions of active pharmaceutical ingredients using NMR

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In formulations intended for oral administration, poorly water-soluble, highly permeable active pharmaceutical ingredients (API), classified according to the Biopharmaceutical Classification System as Class II, may suffer from an inadequate, or highly variable, rate and/or extent of drug adsorption (sometimes as a function of food in the stomach, i.e. fed fasted variability). There is currently much effort underway in producing nanoparticulate suspensions of such drug materials since reducing the API particle size is seen to result in increased bioavailability. Importantly, however, reducing the particle size of the API will significantly increase the specific surface area-to-volume ratio and dramatically increase the rate of dissolution of the drug in the gut milieu, thereby increasing the efficacy and reducing the potential toxicity (because less drug substance is needed). Thus, the dispersed (or wetted) surface area can be a critical measure of drug product performance.

We describe a method of directly measuring the surface area of API particles or droplets dispersed in a liquid. The (patented) technology is based on nuclear magnetic resonance (NMR) and it offers many important practical advantages in comparison with conventional surface area instrumentation. The technique is based on the fact that liquid in contact with or "bound" to the particle surface behaves differently than the bulk or "free" liquid. The NMR relaxation time of bound versus bulk liquid is markedly different: the relaxation time of the latter is much longer. There are no assumptions made about the particle size (distribution) or shape in the determination of the surface area. This instrument can also readily measure the volume fraction of solids in a dispersion. The theory underpinning this new approach to surface area measurements will be discussed, comparisons made with surface area measured using conventional BET gas adsorption and some examples given to illustrate the techniques applicability to a wide range of API's.

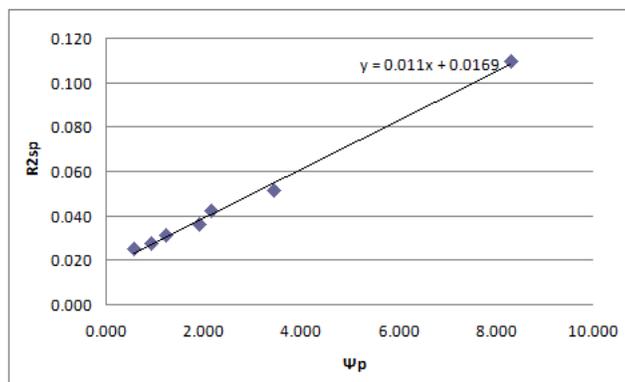


Figure 1. Typical Plot of Relaxation vs Volume Ratio for a nanosize API Suspension Mean Surface Area: $19 \text{ m}^2\text{g}^{-1}$ (Std Dev: 4.7; CV: 0.04)

Characterization of magnetic nanoparticles using quadrupole magnetic field-flow fractionation

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Quadrupole magnetic field-flow fractionation (QMgFFF) is an analytical and characterization technique for magnetic nanoparticles, such as those used for cell labeling and for targeted drug therapy. These nanoparticles are generally composite materials consisting of magnetic cores with biocompatible coatings carrying antibodies or therapeutic drugs. The coatings stabilize the particles in suspension and also reduce the magnetic dipole-dipole interactions between the particles in a magnetic field. QMgFFF is capable of determining not only the mean magnetite mass per particle but also the mass distribution of magnetite among the particles. The particles are separated as they elute through a thin helical channel that is mounted in an axisymmetric magnetic field gradient provided by a quadrupole electromagnet. The mechanism of FFF, which exploits the opposition of field-driven and diffusion-driven transport, causes the particles to elute from the channel in times related to the strength of their interaction with the magnetic field gradient.

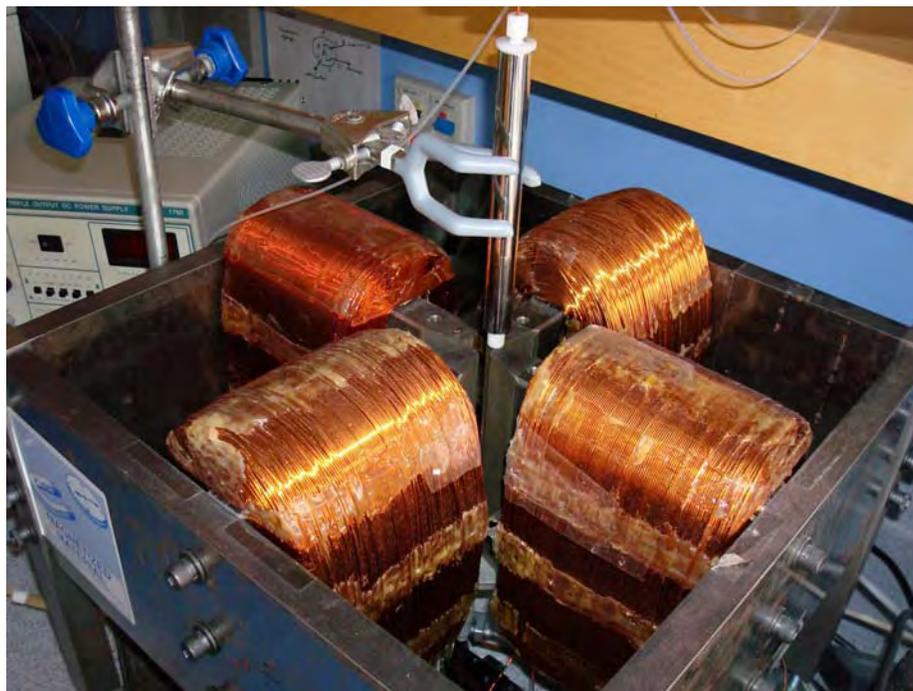


Figure 1. The quadrupole electromagnet with the helical channel held above. The channel is inserted into the aperture for sample analysis.

Hybrid $\text{La}_{1-x}\text{Sr}_x\text{MnO}_3$ nanoparticles for magnetic fluid hyperthermia and MR imaging

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A promising approach in a development of new hybrid magnetic nanomaterials for medical applications is the use of complex magnetic oxides, among them $\text{La}_{1-x}\text{Sr}_x\text{MnO}_3$ manganese perovskites where magnetic properties of the cores can be suitably tailored. Further step is the conversion of the cores into non toxic suspension, stable at physiological pH and allowing their administration either by the direct intratumoral injection or by an intravenous one. The former case is achieved by coating with uniform silica shell, while the latter by the formation of a secondary layer, organic corona based on PEG chains on the silica shell. Stabilized suspensions exhibit outstanding properties for MFH application, namely high heating power up to $300 \text{ W/g}_{\text{Mn}}$ at the body temperature and the self-controlled heating mechanism rulling out the danger of local overheating of the health tissue.

The MRI relaxometric studies of LSMO@SiO_2 showed substantially higher r_2 giving an increase of the contrast, in comparison with those of commercial products based on iron oxides nanoparticles. It achieves at 37°C for suspensions of nanoparticles of sizes 20 nm as much as $500 \text{ s}^{-1}/\text{mM}_{\text{Mn}}$, see Figure. The viability above 90 % was evidenced by the tests on the culture of rat mesenchymal stem cells.

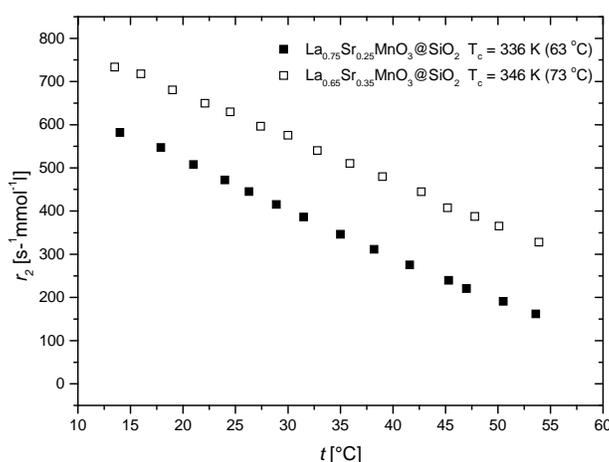


Figure 1. Temperature dependence of the relaxivity r_2 , measured at $B_0 = 0.5 \text{ T}$

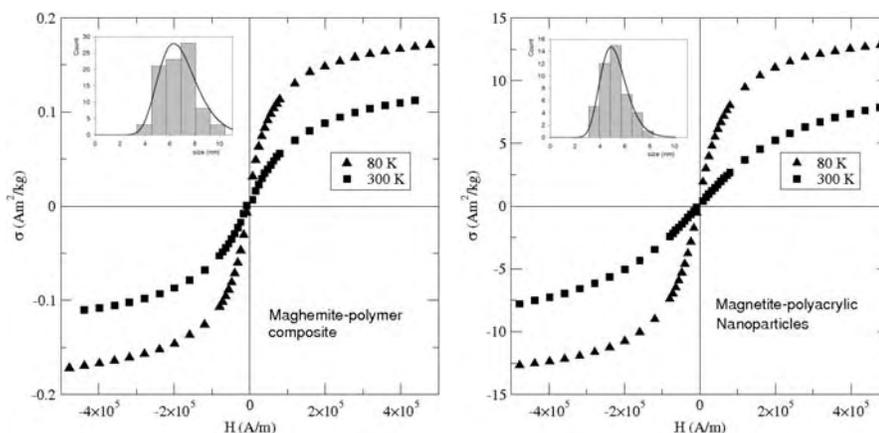
The support by the projects ASCR KAN20020061 and KAN201110651 is gratefully acknowledged.

Size and surface effects in the magnetic properties of maghemite and magnetite nanoparticles

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Magnetic nanoparticles (NPs) of $\gamma\text{-Fe}_2\text{O}_3$ and Fe_3O_4 have been prepared by chemical methods to be used as magneto-optical sensors [1] and bioconjugated MRI contrast agents [2]. In the first case, the NPs have been embedded in a polymer matrix [3], while the magnetite NPs were covered with polyacrylic acid, that allows for bioconjugation. Size distributions and crystalline phase compositions were characterized by Transmission Electron Microscopy (TEM), Atomic Force Microscopy (AFM) and X-Ray Diffraction. The effect of size and surface effects have been studied from magnetization curves at different temperatures. In maghemite-polymer composites, the NPs are essentially superparamagnetic (SPM), with no signs of dipolar interactions and good H/T scaling of magnetization curves. However, the average size, deduced from Langevin equation fits, decreases at the low temperature range as a consequence of larger NPs blocking. This fact is in agreement with the size distribution histogram previously obtained. In the case of magnetite NPs, the behaviour is SPM but the effect of interparticle interactions can be noticed from the lack of scaling of the $M(H/T)$ curves. The size deduced from magnetic measurements (5 nm) agrees quite well with the average size obtained from TEM micrographs and, given the narrower size distribution, the effect of the blocking process is hardly seen in a short temperature range. Saturation magnetization follows the Bloch's law with an exponent of 2, as predicted in computer simulations [4]. The thickness of the polyacrylic shell, that determines the saturation magnetization values, is estimated from the sizes found in TEM, AFM and magnetic measurements.



Reference:

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- [2] "One-Step Synthesis of Highly Water-Soluble Magnetite Colloidal Nanocrystals", J. Ge et al., *Chem. Eur. J.*, 13, 2007, 7153-7161.
- [3] "Synthesis and magnetic properties of bulk transparent PMMA/Fe-oxide nanocomposites", S. Li et al., *Nanotechnology*, 20, 2009, 185607 (6 p).
- [4] "Finite-size effects in the magnetic properties of ferromagnetic clusters", P.V. Hendriksen et al., *J. Magn. Magn. Mater.* 104-107, 1992, 1577-1579.

High concentration zeta potential measurements using light scattering techniques

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The stability of colloidal dispersions depends upon the balance of the repulsive and attractive forces that exist between particles as they approach one another. The magnitude of the electrostatic repulsive force between particles can be determined by measuring the zeta potential of the dispersion and hence zeta potential measurements can be used to predict dispersion stability.

Laser Doppler electrophoresis is an accepted method for the measurement of particle electrophoretic mobility and hence zeta potential of dispersions of colloidal size materials. Traditionally, samples measured by this technique have to be optically transparent. Therefore, depending upon the size and optical properties of the particles, many samples will be too concentrated and will require dilution. The way in which this dilution is done is absolutely critical in determining the final zeta potential value measured.

The ability to measure samples at or close to their neat concentration would be desirable as it would minimize any changes in the zeta potential of the sample due to dilution. However, the ability to measure turbid samples using light scattering techniques presents a number of challenges. This presentation will discuss these and present a novel configuration capable of measuring the zeta potential of concentrated suspensions. Results obtained from a range of different samples will be presented and the effect of high concentration on the zeta potential values obtained will be discussed.

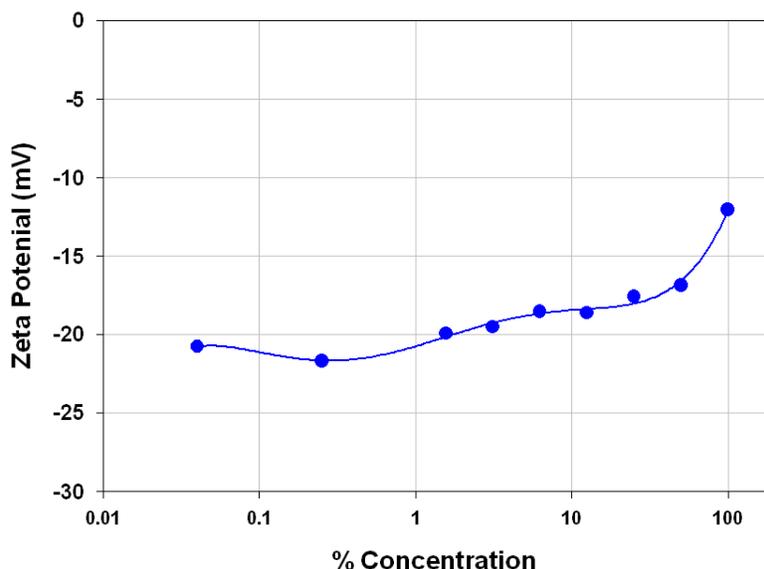


Figure 1. Zeta potential results for various concentrations of semi-skimmed milk

Structural modification and self-assembly of nanoscale magnetite synthesised in the presence of an anionic surfactant

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Many biological and industrial processes are crucially dependent upon the absorption of surfactants from an aqueous phase onto a solid surface. At the heart of this physical chemical process is the alteration of the interface properties caused by the adhesion and aggregation of the surfactant molecules at the solid surface.

Synthesis of magnetite (Fe_3O_4) in the presence of the surfactant sodium dodecyl sulphate (SDS) gives rise to a variety of nanoscale morphologies, some of which look remarkably similar to magnetite found in organisms, suggesting that similar processes may be involved. So, taking our inspiration from biology, where templates produce magnetite of defined shapes and sizes, we have been interested in investigating how surfactant molecules can similarly influence nanoscale magnetite formation e.g. Fig.1.

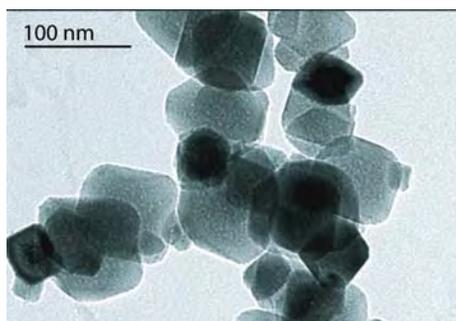


Figure 1.

Mesoporous nanocrystallites form with diameters of 40-100 nm and a morphology similar to the widely reported truncated dodecahedral shape seen in certain magnetotactic bacteria.¹ In addition to its "biogenic signature" this mesoporous nanomagnetite could be useful for targeted drug delivery.²

In this paper, we report structural modification and self-assembly of magnetite in the presence of the anionic surfactant SDS. SDS is commonly used to mimic hydrophobic binding environments such as cell membranes,³ and has recently been used to study the folding and thermal stability of cytochrome c (cyt c) a biologically important electron transfer system.⁴

Reference:

- [1] "The Iron Oxides", R. M. Cornell and U. Schwertmann, Wiley-VCH, Weinheim, 1996.
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Gas storage in silica nanoparticle-stabilised clathrate hydrates

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Gas clathrate hydrates are ice-like inclusion compounds capable of trapping and storing gases such as methane, CO₂ and hydrogen in hydrogen-bonded water cages. Their capacity is such that they are of interest for such applications as fuel storage and gas sequestration. Our research has focussed on addressing the practical challenge of reducing the time required for clathrate gas uptake (typically of the order of days) by reducing the size of water domains exposed to gas, and thereby increasing the surface area-to-volume ratio.

Silica nanoparticles (20-30 nm), when hydrophobically treated, are capable of forming a Pickering-type water-in-air emulsion when blended with water at high speed.^[1] This so-called "Dry Water" technology consists of silica-coated water droplets on a 50 µm scale, capable of flowing like a solid powder. We have demonstrated that methane clathrate hydrate can be formed within such droplets at 273 K and 8.6 MPa.^[2] The kinetics of clathration under these conditions were significantly enhanced, with the time to reach 90% of maximum capacity measuring 160 min (Figure 1). The micron-scale droplet size afforded by the silica coating allows for enhanced mass transfer from the droplet surface.

Our subsequent investigations have shown that the formation rates of CO₂ and krypton clathrate hydrates can also be enhanced using dry water.^[3] The effects of nanoparticle-to-water ratio on clathrate formation have been examined, alongside the temperature and pressure dependence of dry water gas clathrates. While surfactant-based clathration methods may offer greater kinetic enhancement, the associated retardation of methane capacity, and inability to store CO₂, suggest that dry water presents a more practical route to clathrate hydrate gas storage.

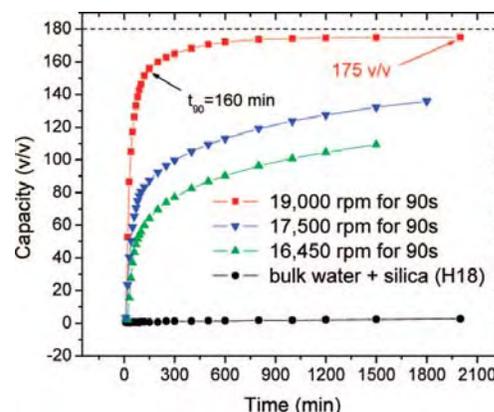


Figure 1: Kinetic plot of methane uptake over time, for dry waters prepared at different blending speeds.^[2]

Reference:

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Synthesis, characterisation of magnetic nanoparticles for bioapplications

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Recently, there has been a great of interest in the nanostructure materials, particularly those fabricated from transition metals because of their potential applications in sensing, catalysts and biotechnology.¹

Much progress has been made on the synthesis of magnetic nanoparticles with a number of methods developed including those involved reverse micelles, co-precipitates in aqueous solutions, thermal decomposition of carbonyl complexes in organic media at high temperatures. A remaining challenge, however, is how to synthesise the nanostructures suitable for biomedical applications, i.e. they have to be size and shape controllable, soluble and stable in the aqueous solutions and biofunctionalised.

In this work, we present our recently studies on the synthesis of series magnetic NPs including cobalt,² cobalt platinum alloy,³ cobalt ferrites,⁴ nanoparticles and platinum coated cobalt iron alloys nanostructures.⁵ Colloidal stable and water soluble Co and CoPt were directly fabricated in water utilising reduction methods. Their morphology, solid spherical and rod for Co and solid spherical, hollow or nanowires/nanochains for CoPt alloys, was tuned by varying synthesis conditions such as concentrations and structures of the ligands. Monodisperse cobalt ferrites with controllable shape (spherical, cubes or star) and platinum coated cobalt iron NPs were synthesised in organic solvents. These NPs, then can be transferred into water using ligand exchange processes.

Transmission electron microscope (TEM), high resolution transmission electron microscope (HRTEM), X-ray diffraction (XRD), dynamic light scattering (DLS) and SQUID magnetometry were used for characterisation.

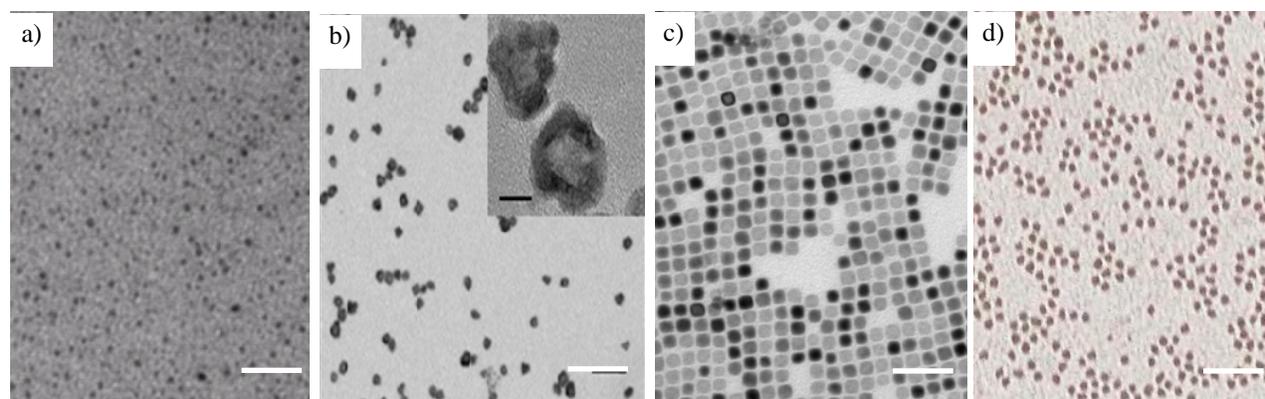


Figure 1. TEM images of a) Co, b) CoPt hollow, c) CoFe_2O_4 cubes and d) CoFe@Pt nanoparticles. Inset is HRTEM of CoPt hollow NPs. Scale bar: 50 nm

Reference:

- [1] Pankhurst, Q. A.; Connolly, J.; Jones, S. K.; Dobson, Applications of magnetic nanoparticles in biomedicine, *J. Phys. D-Appl. Phys.* (2003), 36, (13), R167-R181. [2] Lu, L. T.; Tung, L. D.; Robinson, I.; Ung, D.; Tan, B.; Long, J.; Cooper, A. I.; Fernig, D. G.; Thanh, N. T. K. Size and shape control for water-soluble magnetic cobalt nanoparticles using polymer ligands, *J. Mater. Chem.* (2008), 18, (21), 2453-2458. [3] Lu, L.T.; Tung, L.D.; Long, J.; Fernig, D.G.; Thanh, N.T.K, Facile synthesis of stable, water-soluble magnetic CoPt hollow nanostructures assisted by multi-thiol ligands, *J. Mater. Chem.* (2009), 19, 6023-6028. [4] Lu, L. T.; Tung, L. D.; Fernig, D. G.; Thanh, N. T. K., Synthesis and characterisation of cobalt ferrite nanoparticles with controllable size and shape, *J. Phys. Chem.* (2009), in preparation. [5] Lu, L. T.; Tung, L. D.; Maenosono, S.; Maclaren, M.; Fernig, D. G.; Thanh, N. T. K., Synthesis and characterisation of CoFe and CoFe@Pt core/shell nanoparticles for biomedical applications, *Chem. Mater.* (2009), In preparation.

Continuous Hydrothermal Flow Synthesis of materials for UV attenuation and photocatalysis

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As sustainability climbs the political agenda, our group has focused on developing the Continuous Hydrothermal Flow System (CHFS), an innovative and novel process for the clean synthesis of a broad variety of industrially useful nano ceramic oxides. Successful development of this system will have a wide ranging impact on the production of bio-ceramics, catalysts, photo-catalysts, fuel cell materials, oxygen storage materials and dielectric materials.

The basic concept of a continuous hydrothermal flow synthesis (CHFS) system is that one (or more) feeds containing a substance to be reacted is brought into contact with a superheated water feed which is typically above the critical pressure and temperature (378°C, 22.1 Mpa),¹ whereupon a rapid reaction occurs at the point where the fluids meet. The unique properties of supercritical water (scH₂O) meant that it is an ideal clean solvent for the synthesis inorganic nanoparticles CHFS utilises the unique properties of scH₂O to continuously produce crystalline nanoparticles in a single rapid step.²

A range of materials for UV-attenuation and photocatalysis have been investigated using CHFS including titania and zinc oxide. Libraries of doped zinc oxide (shown below), doped titania and zinc-titania co-precipitates were synthesised. To investigate the properties of doped zinc oxide, 56 unique crystalline doped titania nanopowders were made using a (CHFS) system which uses a supercritical water and aqueous metal salt solutions as reagents. The samples were investigated using a number of analytical and related methods including UV-Vis spectroscopy, powder X-ray diffraction, photoluminescence and in selected cases, by X-ray photoelectron spectroscopy. The nanopowders were evaluated as photocatalysts for the decolourisation of a model pollutant methylene blue dye.

	Ce	Fe	Sr	La	Y	Ag	Mn	Ga	Nd	(ZnO)
0.5 mol%										
1.0 mol%										
1.5 mol%										
	V	Ni	Cr	Co	Ti	S	Er	Gd	Pr	Al
0.5 mol%										
1.0 mol%										
1.5 mol%										

Figure 1: Library of 56 crystalline doped zinc oxide nanopowders made with 19 unique dopants each at 3 nominal doping concentrations.

Reference:

[1] Darr, J. A. & Poliakoff, M. 1999, "New directions in inorganic and metal-organic coordination chemistry in supercritical fluids", *Chemical Reviews*, vol. 99, no. 2, pp. 495-541.

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Synthesis and characterisation of TiO₂ (anatase) nanoparticles grafted with dopamine-PEG derivatives

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There is a growing interest in the use of nanocrystalline titanium dioxide as a biomaterial. Originally used as photocatalytic disinfectants under ultraviolet radiation, TiO₂ nanoparticles have recently been investigated as potential photosensitizing agents for photodynamic therapy, with the aim of targeting malignant cells *in vivo*¹. In fact, these nanoparticles can trigger the formation of reactive oxygen species which may locally induce cell toxicity and death. Moreover, the TiO₂ radio-opacity may provide additional advantages in diagnostics, since titania nanoparticles can potentially be used as new labels for X-ray bioimaging applications².

We aim at using crystalline TiO₂ nanoparticles for targeting and imaging, by taking advantage of their oxidising properties and/or radiopacity. In an earlier work, we developed a non-aqueous synthesis of size-controlled anatase nanoparticles, which maintain good stability profiles in aqueous conditions³. For *in vivo* administration, however, it is well established that surface decoration of nanoparticles with densely grafted, protein repellent polymeric chains such as polyethylene glycol (PEG), is necessary to avoid recognition and clearance by phagocytic cells. We proposed a bio-inspired approach to adsorb PEG-based polymers on the TiO₂ nanoparticles utilising terminal dopamine groups as chelating enediol ligands. The reaction results in a significant change of the nanoparticle optical properties, easy to monitor under UV-vis spectroscopy. By adopting a Langmuir model we identified at least two different adsorption mechanisms which influence the final grafting density of the polymeric ligand on the surface. After purification, these coated nanoparticles showed satisfactory stability at physiological pH conditions. These findings open the path to the tailoring of highly crystalline nanoparticles with a polymeric shell of specific desirable characteristics, while maintaining colloidal stability. The safe cytotoxic profile (in dark) of these nanoparticles was demonstrated by *in vitro* studies on different murine cell lines.

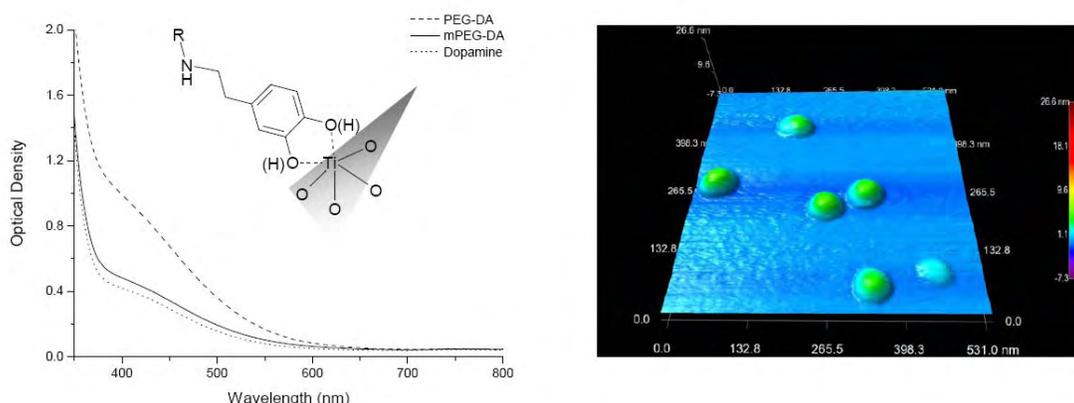


Figure 1. *Left.* UV-Vis curves obtained following addition of dopamine-grafted ligands to titania nanoparticles. *Right.* AFM picture of PEGylated TiO₂ nanoparticles adsorbed on mica.

Reference:

- [1] Thevenot, P. et Al., *Nanomedicine-Nanotechnology Biology and Medicine* 2008, 4, 226
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