



Suitability of commercial colloids for magnetic hyperthermia

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ABSTRACT

Commercial nanoparticles supplied by Chemicell, Micromod and Bayer-Schering were characterised with regard to their nanocrystalline diameter, hydrodynamic diameter, total iron content and relative ferrous iron content. Additionally, calorimetric measurements were taken using a 900 kHz AC magnetic field of amplitude 5.66 kA/m. It was found that those samples containing relatively high (> 18%) ferrous content generated a substantially smaller (12% on average) intrinsic loss power (ILP) than those samples with a lower ferrous content. Two nominally identical Chemicell samples that differed only in their production date showed significantly different ILPs, attributed to a variation in batch-to-batch crystallite sizes. The highest ILP values in the cohort, ca. 3.1 nHm²/kg, were achieved for particles with hydrodynamic diameters of ca. 70 nm and nanocrystalline diameters of ca. 12 nm. These compare favourably with most samples prepared in academic laboratories, although they are not as high as the ca. 23.4 nHm²/kg reported for naturally occurring bacterial magnetosomes.

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Many research groups are exploring the potential of magnetic nanoparticles (MNPs) in biomedical applications [1]. Most such studies utilise bespoke MNPs that are synthesised in-house, which is desirable for ease of sample control and modification, but raises issues regarding formulation, reproducibility and quality assurance for any future efforts at technology transfer – particularly when the intention is to use the MNPs in human clinical trials. For the latter, commercially produced materials, particularly those certified and guaranteed to GMP standards, are much preferred by medical ethics committees. In addition, MNP manufacturing companies often possess the required resources and commercial drive that are needed to push through the medical approval processes, and deliver the new therapy as rapidly as possible to the patient.

One such case where the goal is the use of MNPs in human therapies is magnetic field hyperthermia – a cancer therapy involving the targeted administration of MNPs into the body, accumulation of those MNPs at sites of cancer, and the local heating of those MNPs with an externally applied AC magnetic field. To date, almost all reports in the literature deal with the

heating properties of bespoke MNPs. In this paper, we report on a survey of some commercially available MNPs as possible candidates for hyperthermia applications. We also compare the results obtained with previously published data on bespoke MNPs, using a new design rule parameter – the *intrinsic loss power* (ILP), – which in the case of superparamagnetic nanoparticles, and under certain assumed conditions, allows direct comparison of the particle-heating capabilities of materials recorded in response to different AC field strengths and frequencies.

The heat rise rate of a magnetic fluid in an AC magnetic field can be described by the phenomenological Box–Lucas equation:

$$T(t) = A(1 - e^{-Bt}) \quad (1)$$

where T is the temperature, t is time, A is the saturation temperature and B is a parameter related to the curvature of the heating curve. The product $A \times B$ at $t = 0$ is also known as the initial heat rise rate and is equivalent to the ratio $\Delta T/\Delta t$ used in the specific absorption rate (SAR) formula [2]:

$$\text{SAR} = \frac{\Delta T}{\Delta t} \frac{C}{m_{\text{Fe}}} \quad (2)$$

where C is the heat capacity of the fluid per unit mass of fluid, and m_{Fe} is the iron mass in the fluid per unit mass of fluid.

Although the SAR parameter – also known as specific loss power (SLP) – is quite often used in the literature to characterise the heating ability of MNPs, it has a significant limitation in that it

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is an extrinsic (equipment-specific) parameter. The SAR parameter for the same magnetic fluid will change when measured in AC magnetic field systems with different frequencies and strengths, as can be deduced from the formula for volumetric power dissipation [3]:

$$P = \mu_0 \pi \chi''(f) f H^2 \quad (3)$$

where μ_0 is the permeability of free space ($4\pi \times 10^{-7} \text{ NA}^{-2}$), χ'' is the out-of-phase (imaginary) component of susceptibility, and H is the applied field strength. Note that χ'' is intrinsically a function of f . The SAR parameter is proportional to P divided by the density of the magnetic material, hence SAR varies with both H , and f .

However, at low frequencies such as those currently used in most heating systems (ca. 10^5 – 10^6 Hz), and for the case of polydisperse MNPs in solution (with a crystallite polydispersity index (PDI) of more than 0.1), Rosensweig [3] has predicted that, to a good approximation, χ'' is frequency-independent. In such cases, the SAR parameter can be regarded as a function of f and the square of magnetic field strength only. Fig. 1 is an experimental validation of this principle, showing calorimetric values varying linearly with frequency in the range of 100–900 kHz for Micromod's 'nanomag 100 nm' MNPs.

We therefore introduce the 'intrinsic loss power' as a new design rule parameter, defining it as

$$ILP = \frac{P}{\rho H^2 f} = \frac{SAR}{H^2 f} \quad (4)$$

The ILP is a step towards an intrinsic, system-independent parameter, designed to allow more direct comparisons to be made between experiments performed in different laboratories and under different AC field strength and frequency conditions. It is valid under the conditions outlined above (frequencies of up to several MHz, samples with a crystallite PDI of more than 0.1) and also provided the applied field strength H is well below the saturation field of the MNPs, so that the hysteretic behaviour is essentially parabolic in nature. A further condition for using the ILP parameter to compare results between different systems is that similar environmental thermodynamic losses are involved. This is admittedly a difficult condition to guarantee between different laboratories, but to a first approximation it may be noted that most reports in the literature to date deal with calorimetric measurements undertaken with a thermally insulated system at

room temperature, as opposed to either a fully adiabatic system, or a thermally equilibrated system. In any case, despite the limitation inherent in the definition of the ILP parameter, we propose that it is at least a move towards a more intrinsic magnetic heating parameter than is the SAR parameter that currently has the most coinage.

Sixteen different iron-oxide-based magnetic fluid samples from Chemicell GmbH, Micromod GmbH and Bayer-Schering Pharma were tested (Table 1), with different sizes and core-shell configurations. Note that two nominally identical particles from Chemicell (1 and 15) are included, which differed only by batch production date (9 months apart; sample 15 being the older). Furthermore, Micromod's BNF series (3, 10, 12, 16) are at the research stage and are not commercially available yet.

The hydrodynamic diameters of the samples were measured via dynamic light scattering (DLS) using a Malvern Zetasizer Nanoseries, and compared with the suppliers' specifications (see Table 1). The total iron content for each sample was evaluated using ICP-AES, and then used in the calorimetric measurements to prepare dilutions of samples with identical Fe concentrations. The relative ferric and ferrous iron concentrations in the samples were assessed using the chemical preparation process described by Iwasaki et al. [4], calibrated against a standard solution with known Fe content, and involving UV-vis spectroscopy (on a Jasco V-570 spectrometer). Under the assumption that the MNPs in the samples were magnetically non-interacting and log-normally distributed in size, their nanocrystalline grain sizes were determined by fitting their room temperature DC magnetisation curves (measured on a Quantum Design MPMS magnetometer) using the Langevin function [5].

Calorimetric measurements were made using a Thamway T162-5723B radio frequency amplifier with two matching boxes with a frequency range of 100–500 kHz and 500–900 kHz, respectively. The resonant circuit further consisted of a 20-turn water-cooled solenoid with 8 cm diameter. The maximum AC magnetic field amplitude that could be generated was 5.66 kA/m at 900 kHz. A round-bottom-shaped plastic sample holder was used and surrounded by layers of insulation to protect the sample against ambient heating from the coil. Temperature measurements were conducted with fibre-optic temperature probes (Astech TEM-4).

Comparison of the DLS measurement results of particle hydrodynamic diameter (given in Table 1) with the size information provided by the manufacturers indicates the value of independent size analysis. In general the supplied dimensions tend to be underestimated, – which may indicate some degree of aging-related agglomeration of the samples between manufacture and delivery, – which is more pronounced for larger particles. The polydispersity indices (PDI) for the hydrodynamic diameters of the MNPs ranged from 0.05–0.25, which indicate low- to mid-range polydispersity. After long-term observation (> 7 days) of the two samples with the largest measured hydrodynamic size, some sedimentation was observed.

ICP-AES measurements yielded data on the total Fe content for each sample – information that some but not all of the commercial suppliers had provided. Where comparison was possible, generally acceptable agreement (within $\pm 3\%$), was found.

The relative ferrous (Fe^{2+}) to ferric (Fe^{3+}) content of the samples were measured using UV-vis spectrometry after chemical analysis as follows. Two aliquots of each sample (with identical total Fe concentrations) were prepared, one of which had all its Fe^{3+} reduced to Fe^{2+} . This was achieved by dissolving a 500 μL aliquot of the magnetic fluid in an equal volume of a 1:1 mixture of 35% hydrochloric acid and water. The resulting solution (which was a yellow colour) was diluted to 25 mL with deionised (DI) water. Then two 5 mL parts of the solution were re-suspended

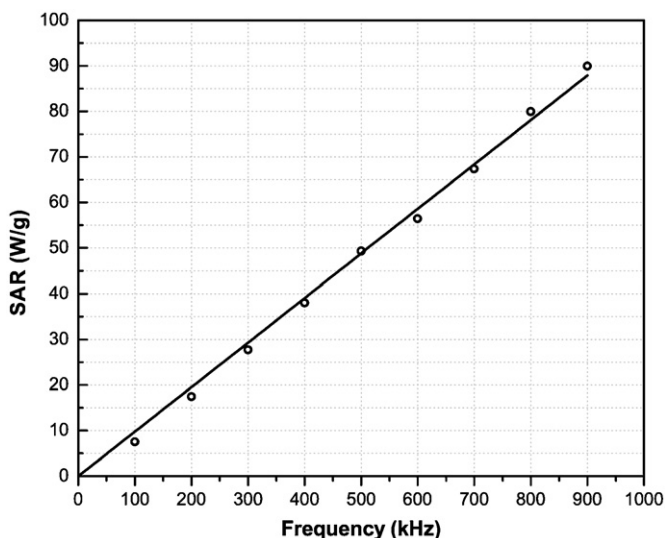


Fig. 1. SAR versus frequency for Micromod's nanomag-D 100 nm. All measurements were taken at $H = 5.66$ kA/m. The straight line is a linear fit of the data with intercept at the origin.

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