Editorial

Are Magnetic Multicore Nanoparticles Promising Candidates for Biomedical Applications?

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THE application of magnetic nanoparticles (MNPs) in a biomedical context is a rapidly developing field. The MNP suspended in aqueous liquids can be introduced into the blood stream or the tissue of a patient, allowing for the utilization of magnetic effects, such as magnetic losses, magnetic forces, and localized sources of magnetic fields.

Magnetic hyperthermia uses the magnetization reversal losses of such particles in an alternating magnetic field to achieve local heating of the tissue to treat tumors. Magnetic drug targeting uses the magnetic force acting on drug-loaded MNP in an external static field gradient to accumulate them in the tissue areas to be treated by the drugs. Magnetic bioseparation removes or concentrates certain components from blood or other biological fluids by specifically binding magnetic particles to the target and collecting the magnetically labeled targets by means of a magnetic gradient. For medical imaging, MNPs are used as a contrast enhancer in magnetic resonance imaging (MRI) or as tracer materials in magnetic particle imaging (MPI).

Very small iron oxide nanoparticles show a superparamagnetic behavior with zero remanent magnetization due to thermal relaxation processes within the crystal lattice. With increasing particle volume, the particles turn to ferrimagnetism (the magnetic energy of the crystal lattice dominates the thermal relaxations) and the particles show a hysteresis during magnetization reversal. For some medical applications, it is advantageous to use larger particles that have a ferrimagnetic behavior, since these ferrimagnetic particles show higher specific heating losses and higher magnetization than small superparamagnetic cores. Unfortunately, one of ferrimagnetism's properties is a remanent particle magnetization, which leads to an agglomeration of MNP, even in the absence of an external magnetic field and even when using coated particles. If particle agglomerates reach a critical size of close to the size of a red blood cell, around 6 μm, they are at risk of occluding blood vessels of a patient and cause dangerous side effects.

To prevent such agglomeration, a novel particle type is proposed for applications—superferrimagnetic multicore nanoparticles (MCNPs) [1]. Superferrimagnetism describes the magnetic behavior of certain clusters of small superparamagnetic particles (grains). Due to exchange interactions between the single grains, these clusters show a ferrimagnetic behavior with a hysteresis when exposed to a magnetic field (a magnetic structure like that of larger ferrimagnetic single core particle is formed) but show a very weak remanence in a zero field (comparable to that of superparamagnetic particles) due to statistical orientation of easy axes of the grains. Typically, such MCNPs consist of superparamagnetic grains about 10 nm size, which form moderate ferrimagnetic clusters (MCNPs) in the size range of 20–80 nm. This means that these relatively large MCNPs show a very weak remanent magnetization (much smaller than that of single core particles of the size of the clusters) and, thus, only a very low tendency to form agglomerates, which is an excellent basis for medical applications.

MCNPs are prepared by different routes. Mostly, for the preparation of biocompatible iron oxide MCNP, alkaline co-precipitation is used. For this, an alkaline medium is added to an acidic solution of iron salts and after reaching pH 7, MNPs precipitate from the solution. By using defined parameters for Fe^{2+}/Fe^{3+} ratio, temperature, pH, and type of base, a multicore structure of particles can be obtained.

Beside this modified standard procedure, MCNPs can be prepared by inverse microemulsion, sol–gel synthesis, flow injection, electrospray synthesis, sonochemical method, and thermal decomposition. Although only iron oxide is currently approved for medical *in-vivo* applications, other MNPs consisting of FePt, Mn–Zn–ferrite, Mn–ferrite, or FeAg also show a pronounced multicore structure with a corresponding magnetic behavior.

In the literature, very often, each structure of agglomerated particles (mostly caused by dipole–dipole interactions of single cores with a remanent magnetization) is termed as multicore. But real multicore particles in the sense of the here discussed particle structures (which show a superferrimagnetic behavior) show a very close packing of the single grains with very small gaps, leading to exchange interactions between the single grains. See Fig. 1 for typical examples of such particles.

As mentioned before, some of the medical applications of MNP might show higher performance when using superferrimagnetic MCNPs instead of superparamagnetic MNP. This is being true especially for applications basing on magnetic attraction forces (bioseparation and targeting) or magnetic losses in an alternating field (hyperthermia).

Up to now, for magnetic bioseparation, mostly small superparamagnetic particles or magnetic particles of several micrometers (magnetic microspheres or beads) are used.

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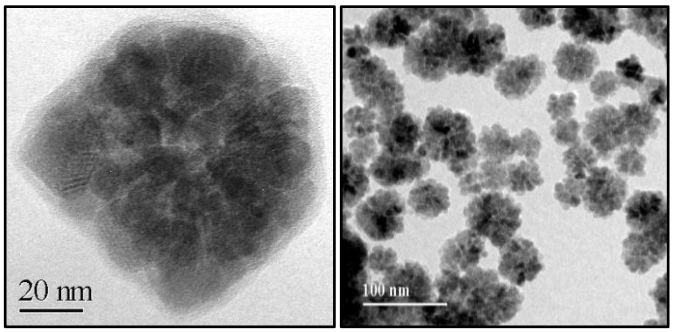

Fig. 1. TEM images of (left figure) a typical iron oxide superferrimagnetic multicore particle, from [2] with permission from the publisher and (right figure) an ensemble of iron oxide MCNP as described in [3].

Small MNPs show a high surface-to-volume ratio, which is unfavorable for separation efficiency. Due to their larger particle volume (which determines the magnetic attraction force), the MCNPs show a higher separation efficiency than small MNP. On the other hand, due to their smaller hydrodynamic diameter, MCNPs show a higher diffusion coefficient than the beads, which leads to a higher binding kinetics to the target cells. In experiments with breast cancer cells, it was found that MCNPs show cellular uptake comparable to that of usually used smaller superparamagnetic MNP [2]. This behavior makes MCNP attractive for use in bioseparation and for biosensors [4]. Ko and Lim [5] doped MCNPs with Cs and fluorescein isothiocyanate, which allows a radiometric or fluorescence monitoring of the labeling and separation process.

As discussed earlier, the MCNPs show a high magnetic separation efficiency. This behavior also makes these particles very promising for application in magnetic drug targeting. The MCNPs combine a low agglomeration behavior and a sufficient surface area for coupling pharmaceutical agents (such as small superparamagnetic MNP) with a good magnetic targeting efficiency due to the relatively large volume of the particles (such as magnetic beads) [6].

MCNPs might exhibit their highest potential in hyperthermia application. In several studies, it was confirmed by means of heating performance measurements that heat generation from MCNPs is very suitable for magnetic particle hyperthermia [7]–[9], where Lartique *et al.* [9] report a specific heating power of up to 1500 W/g. In animal investigations [10] with mice, bearing experimentally grown tumors on their shoulders, a particle concentration of MCNPs of 0.9% by mass in tumor tissue was sufficient to reach thermal ablative temperatures within a 5-mm-diameter tumor. The tumor temperature increase reached 20 K in the first 60 s of magnetic heating for an alternating magnetic field of 24 kA/m and 400 kHz.

MCNPs also show a very high potential for applications in medical imaging. MCNPs as contrast agents for MRI enhance T1 or T2 relaxation times depending on their size and particle structure [9], [11], [12]. Furthermore, a gold layer around the MCNPs enables these particles to serve as contrast agent for MRI and optical tracking at the same time [13]. Another dual sensing application is MRI combined with fluorescence mediated tomography obtained by bonding a fluorescent dye to the MCNPs [14]. Even more, MCNPs are promising tracers in MPI [15]. MPI performance depends on the cluster size of MCNPs as well as the grain size as was demonstrated by careful cluster separation experiments [16]. Loewa *et al.* [17] performed experiments in which MCNPs (present within the commercial iron oxide MRI contrast agent Resovist) were isolated by a magnetic separation process, leading to a significant improvement in MPI performance of the sample.

MCNPs are model systems for, in the literature, often mentioned possibility of combining diagnostic and therapeutic functions, which would turn them into theranostic nanomedicines. However, the optimal particle size for imaging and the optimal particles size for treatment are often different, since they are based on different physical effects, which require different magnetic properties. For MCNPs, Cervadoro *et al.* [18] presented nanoflakes, which show promising performance as an MRI contrast agent and for hyperthermia all in one. Attaluri *et al.* [19] presented the MCNPs, which are suitable for hyperthermia and enable imaging by means of X-ray, MRI, and fluorescence at the same time. Chuang *et al.* [20] describe clusters of mixed MNP and gold nanoparticle, which can be used for MRI and photothermal therapy simultaneously. In animal experiments, they demonstrated an enhanced MRI contrast in a tissue by the impact of the magnetic particles component and therapeutic antitumor effects of laser-induced photothermal therapy mainly from the gold component of the particles. For gold coated MCNPs, Lai *et al.* [21] report on multifunctional particles, enabling magnetic/photothermal hyperthermia in combination with surface-enhanced Raman spectroscopy suitability.

In summary, superferrimagnetic MCNPs show excellent potential for application in medical diagnostics and therapy. For future establishment of MCNPs in diagnostics and therapy, these particles need further optimization regarding the size of grains and clusters. The main promising application fields of MCNPs are in bioseparation as well as magnetic hyperthermia and drug targeting. Furthermore, they might find use as magnetic tracers for MPI. Mostly applications in bioseparation and biosensors are established already. While the magnetic properties of MCNPs are interesting, future applications in medicine are even more so. Now, the promising magnetic behavior of MCNPs has to be transferred to the stage of *in-vivo* animal tests to demonstrate experimentally their excellent performance for different medical applications. Up to now, there are only a few animal studies confirming the very promising heating performance of MCNPs in magnetic hyperthermia and suitability as contrast agents for the MRI.

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