Physical limits of pure superparamagnetic Fe_3O_4 nanoparticles for a local hyperthermia agent in nanomedicine

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Magnetic and AC magnetically induced heating characteristics of Fe_3O_4 nanoparticles (IONs) with different mean diameters, d, systematically controlled from 4.2 to 22.5 nm were investigated to explore the physical relationship between magnetic phase and specific loss power (SLP) for hyperthermia agent applications. It was experimentally confirmed that the IONs had three magnetic phases and correspondingly different SLP characteristics depending on the particle sizes. Furthermore, it was demonstrated that pure superparamagnetic phase IONs ($d < 9.8$ nm) showed insufficient SLPs critically limiting for hyperthermia applications due to smaller AC hysteresis loss power (Néel relaxation loss power) originated from lower out-of-phase magnetic susceptibility. © *2012 American Institute of Physics*. [http://dx.doi.org/10.1063/1.3689751]

In recent, superparamagnetic Fe_3O_4 nanoparticles (SPIONs) have been paid considerable attentions for a local hyperthermia agent in nanomedicine due to its officially approved high biocompatibility.[1] Accordingly, various technical and engineering approaches, i.e., developing various synthesis methods, controlling particle dipole-dipole interaction and particle dispersion status in ferrofluidics, and studying the effects of Fe^{2+}/Fe^{3+} ion distributions on heating ability etc., have been and are being made to improve the AC magnetically induced heating characteristics and the relevant magnetic properties of SPIONs for theragonosis agent applications.[2–4] For the applications to an *in-vivo* magnetic fluidic hyperthermia agent, magnetic nanoparticles should have pure superparamagnetic phase for easy transportation, good circulation, and no agglomeration in the blood vessel as well as have a smaller particle size, $d < 7 \sim 9$ nm, with a narrow size distribution (<10%) for both effective injection, i.e., intravenous injection, intraarterial injection, or intratumoral injection, into and excretion from human body.[5] In particular, they should produce a heat generation as high as possible at a small concentration (a higher specific loss power (SLP)) in the biological safe and physiologically tolerable range of the applied magnetic field ($H_{appl} < 190$ Oe) and frequency ($f_{appl} < 120$ kHz) to completely necrotize tumors with minimized systemic "side effects."[6–9] Considering these biotechnical requirements, the SPIONs reported so far have critical challenges for a hyperthermia agent, because the magnetic phase (intrinsic magnetic property) of the developed SPIONs is not well defined and has strong dependence on the particle sizes as well as correspondingly wide distribution of SLP values ($5 \sim 500$ W/g).[2–4,10] Therefore, systematic studies on the magnetic nature and the AC heating characteristics of IONs accurately controlled the particle sizes are essentially required to evaluate the biotechnical feasibility of IONs, particularly SPIONs, for a clinical hyperthermia agent in nanomedicine.

In this letter, we investigated the magnetic properties and the AC heating characteristics of IONs with different mean diameters, d, systematically controlled from 4.2 to 22.5 nm to explore what size of IONs show pure superparamagnetic phase and what the AC heating characteristics of the pure SPIONs are. In order to clearly study the physical relationship between magnetic phase of IONs and SLP characteristics, AC/DC hysteresis, out-of-phase (χ'') magnetic susceptibility, blocking temperature (T_B), and AC magnetically induced heating temperature ($T_{AC,mag}$) were employed to evaluate the magnetic and AC heating nature of IONs with different particle sizes.

IONs with various particle sizes were synthesized using both a high temperature thermal decomposition (HTTD) method and a seed-mediated growth method.[11,12] For the seed-mediated growth method, a 4.2 nm and a 5.8 nm IONs, which were synthesized using the HTTD method, were used as seed particles to make 7.9 nm and 9.8 nm IONs, respectively. In a similar way, the 7.9 nm and 9.8 nm IONs were used as seed particles for the larger IONs ($d \geq 11.8$ nm). By using the same procedure described above, all the IONs used in this study were synthesized. The synthesized IONs were coated with dimercaptosuccinic acid (DMSA) using

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