Properties of Iron Oxide Particles Prepared in the Presence of Dextran

Kun Moo Lee, Sun-Geon Kim†, Woo-Sik Kim* and Sung Soo Kim*

Department of Chemical Engineering, Chung Ang University,
221, Huksuk-Dong, Dongjak-Ku, Seoul 156-756, Korea
*Department of Chemical Engineering, KyungHee University,
Seochun-Ri, Kiheung-Eup, Yongin-Gun, Kyunggi-Do 449-701, Korea

Abstract—Stable aqueous ferrofluids consisting of superparamagnetic iron oxide particles with nanometer size were prepared by adding aqueous dextran solutions of ferric and ferrous chlorides to ammonium hydroxide. The growth of the core particles was shown to be inhibited by the presence of dextran. Procedures to increase the rate of reaction by varying reaction parameters also inhibited the core growth as long as supply of core material was kept constant. The core particles actually existed in the fluid as chain aggregates, the size of which became smaller with the concentration of dextran by a dense coating of the core particles. The aggregate size was also affected by supplying oxygen in the reaction bath and varying the initial total iron concentration, but it was kept fairly constant with the variation in the other reaction parameters.

Key words: Ferrofluid, Iron Oxide, Dextran, Magnetic Liquid

INTRODUCTION

Ferrofluids, consisting of magnetic particles dispersed in a liquid medium, have found wide applications, mainly in the manufacture and processing of mechanical parts, such as media for shaft seals, speaker dampers, or liquid separation and abrasion processes [Popplewell, 1984]. Recently, ferrofluid use has been further extended to biomedical fields such as agents for MRI contrast, cell separation, anemia treatment and magnetic drug delivery [Groman et al., 1989; Palmacci and Josephson, 1993; Nowik et al., 1997; Kellar et al., 1999; Gunther et al., 2000]. In any of these applications, the surfaces of the ultrafine magnetic particles are modified by adsorbing surfactants or polymers to enhance their dispersibility in either aqueous or organic solvents. Aqueous ferrofluids are preferred for biomedical uses, due to their compatibility with body fluids. Among them dextran-ferrite ferrofluids have been widely studied due to their high stability and low toxicity in body fluids [Groman et al., 1989; Palmacci and Josephson, 1993; Nowik et al., 1997; Hasegawa et al., 1998; Jung and Jacobs, 1995; Jung, 1995; Coe et al., 1995; Kawaguchi and Hasegawa, 2000].

Recently, many researchers have filed a considerable amount of data about the nature of the primary(core) and aggregated particles, including their sizes [Kellar et al., 1999; Jung and Jacobs, 1995; Jung, 1995; Kawaguchi and Hasegawa, 2000; Lopez-Perez et al., 1997], chemical compositions [Groman et al., 1989; Jung, 1995; Babes et al., 1999; Mendenhall et al., 1996], crystalline structures [Nowik et al., 1997; Jung, 1995; Lopez-Perez et al., 1997] and magnetic properties [Groman et al., 1989]. In spite of these many publications, however, knowledge of the properties of aqueous ferrofluids has not been systematically accumulated so far, since the procedures and major parameters of reaction and after-treatment were

different from publication to publication. Furthermore, even a minor variation in them significantly affects the properties of the particles, sometimes leading to seemingly contradictory conclusions.

Hence we prepared a dextran ferrofluid by adding mixed iron salts in aqueous dextran solution to an ammoniacal solution in strictly predetermined procedures, and investigated systematically the effect of each reaction parameter on the properties of the core and aggregated particles.

EXPERIMENTAL

1. Preparation of Particles

To a solution of 50 ml of 7.5% NH_4OH was added 50 ml of 0.28 M $FeCl_3$ (Yakuri Pure Chemicals Co., Ltd.), 0.16 M $FeCl_2$ (Yakuri Pure Chemicals Co., Ltd.) and 12.5% w/v dextran, (Sigma Chemical Company, D1390, MW 71,000) over a 5 minute period with a syringe pump (Keun-A Mechatronics, KASP005/150MT). The order of reactant addition was reversed compared to other researchers [Groman et al., 1989; Nowik et al., 1997; Hasegawa et al., 1998] since we wanted to keep the concentration of dextran as low as possible to suppress its effect on particle formation. The reaction product containing black precipitate was stirred for 5 minutes and then aged for 30 minutes at 70 °C. The reaction and aging proceeded in nitrogen environment. The solution containing small particles was dialyzed against 1,000 ml of deionized water, with the water changed each day, to remove ions and excess dextran until the pH of the remaining solution decreased to 7. Large particles in the ferrofluid were then removed by centrifugation (Kontron CENTRIKON T-1180). The powder particles were recovered with a membrane filter (ADVANTEC MFS. Inc., 0.2 μm pore), and the black powder was freeze-dried for 3 days. The process variables were changed one by one to investigate their effect on the properties of the particles prepared: Among them, the initial molar ratio of Fe^{+3}/Fe^{+2} keeping a total iron concentration of 0.44 M, the total iron concentration with

†To whom correspondence should be addressed.
E-mail: sgkim@cau.ac.kr

the molar ratio of 0.28/0.16 was kept constant, the rate of addition of iron salts plus dextran solution, the concentration of dextran, and the temperature of aging. The order of mixing in the semibatch system was reversed, if necessary, to see its effect on the particle formation. The dextran was added after reaction and aging, to check the effect of decoupling the reaction and dispersion. The reaction and aging were often carried out in air environment. The effect of ultrasonification was also investigated.

2. Characterization of Particles

The shape and size of the core and aggregate particles were observed with a Transmission Electron Microscope (Carl Zeiss, EM 912 Omega). For this we dropped diluted sample fluids on carbon-coated TEM specimens. The diameters of typically fifty particles at least in each TEM picture were measured to obtain their number average diameter. A Laser Particle Size Analyzer (Otsuka, PAR-III) was used to measure the size of the aggregated particles presumably existing in the liquid. The surface charge of the particles was measured with Zeta-potentiometer (Otsuka, ELS-8000). FT-

IR (Nicolet Magna 750) spectra were measured to gain information on the chemical structure of the coated particles. The crystal structure of the dry powder was investigated by X-ray diffraction (XRD, Scintag SDS 2000). The core size was also determined from the line widths obtained from XRD. Saturation magnetization of the particles was measured as a function of temperature at 10,000 Gauss and their hysteresis curves were obtained at 5 K, with a SQUID Magnetometer (Quantum Design, MPMS).

RESULTS AND DISCUSSION

1. Characteristics of Iron Oxide Particles

1-1. Morphology of Iron Particles in the Liquid

Fig. 1 shows TEM pictures of four representative samples. Except the particles prepared without dextran, which existed in random aggregates, the core particles formed chain aggregates. The actual length of the chains in the fluid would be shorter since overlapping of the chains possibly occurred during the preparation of
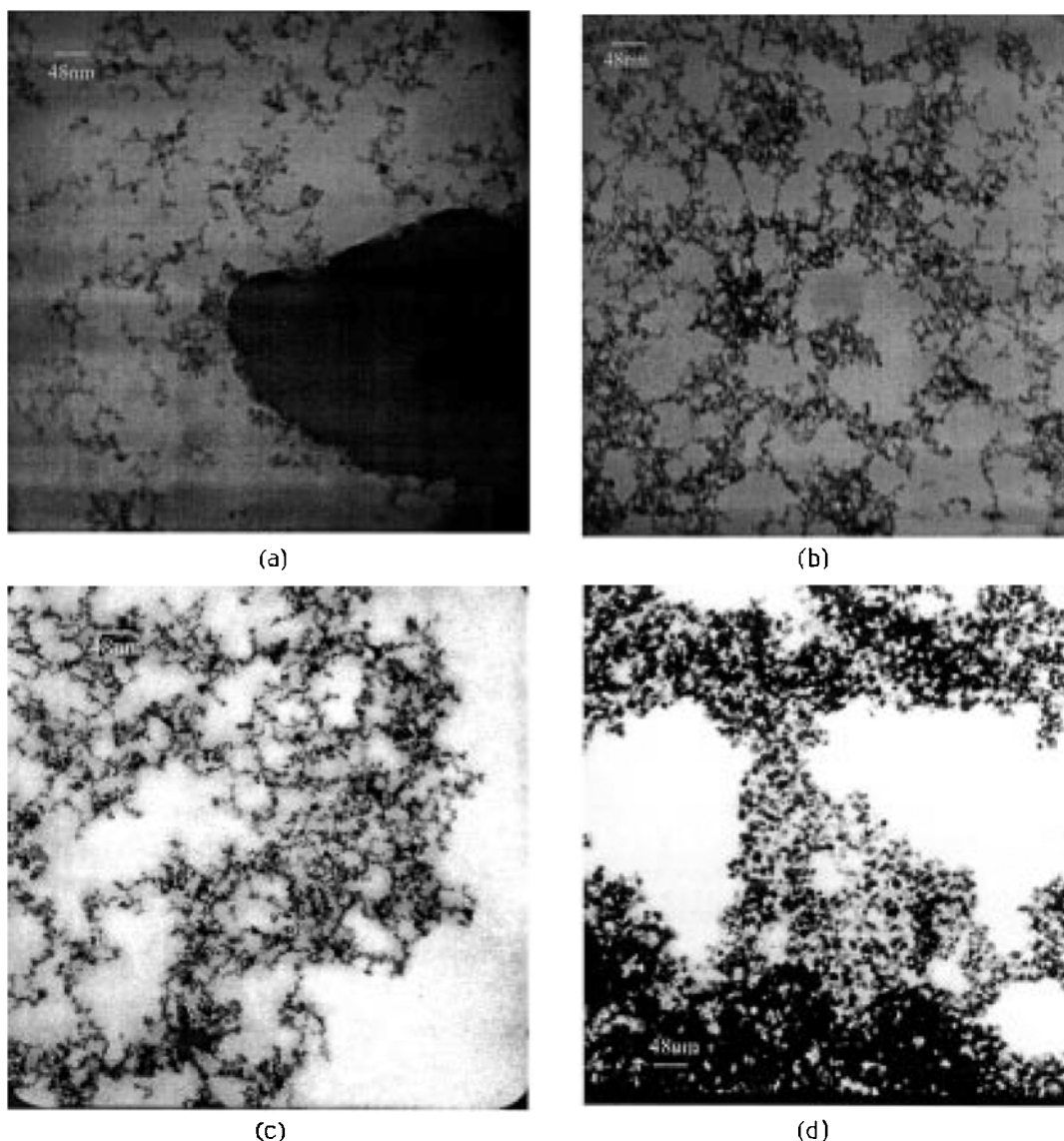

(a)

(b)

(c)

(d)

Fig. 1. TEM micrographs of iron oxide particles in environment of (a) air with 12.5% w/v dextran; (b) air with 2.5% w/v dextran; (c) nitrogen with 12.5% w/v dextran; (d) nitrogen with no dextran, otherwise under reference conditions.
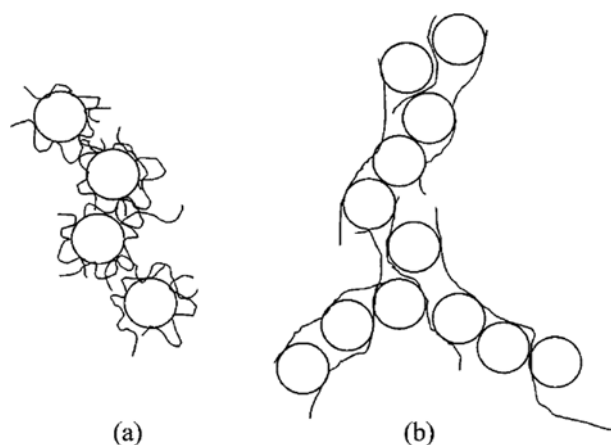
Fig. 2. Coagulation and dispersion of particles with polymers.
(a) at high concentration of dextran; (b) at low concentration of dextran

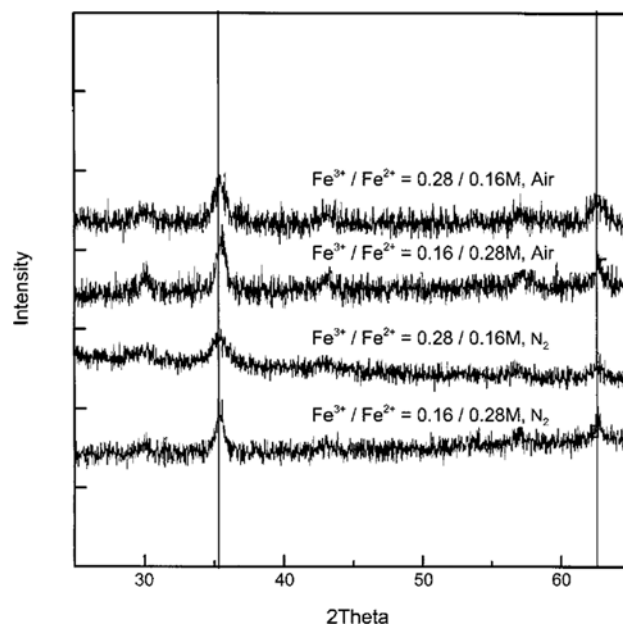Fig. 3. Variation in XRD patterns for various samples prepared in different Fe^{2+}/Fe^{3+} ratios, otherwise under reference conditions.

TEM samples. Anyhow, their length seemed shorter the larger the concentration of dextran. For the sample with 12.5 wt% dextran, a translucent envelope was observed around core particles, probably related to the existence of dextran, since TEM only visualized the iron oxide cores, dextran in the colloid being transparent to TEM. This observation suggested us a model for conformal structure of the aggregates, as shown in Fig. 2. At higher concentration of dextran, the majority of dextran molecules primarily coated individual core particles, which were bridged to the rest of the molecules. The aggregates thus appeared in short chains. On the other hand, at lower concentration of dextran, most molecules of dextran took part in bridging the adjacent core particles, leading to long chain aggregates. The chain length also decreased as the reaction environment changed from nitrogen to air environment for the same concentration of dextran. This will be further discussed in the next section.

The average size of the core particles obtained from the TEM pictures ranged from 4.5 nm to 10 nm. The size decreased with the concentration of dextran, as shown in Table 1. According to Groman et al., 1989, synthesis of the oxide in the presence of dextran seemed to effect a tight association between the dextran and the oxide. It is believed that the initial drops added to the ammonia solution initiated the reaction and then nucleation. Addition of subsequent drops could participate either in the growth of the nuclei or in the formation of new nuclei, depending on the rate of the formation reaction of iron oxide. Crystal growth is probably inhibited by the presence of the adsorbing molecules [Jung et al., 1999]; this is supported by the fact that the size of the core particles was exceptionally larger for the sample prepared under nitrogen without dext-

Table 1. Variation of size of core particles (nm) with respect to the concentration of dextran

Reaction environment		Dextran concentration		
		12.5 wt%	2.5 wt%	No dextran
Air environment	TEM	4.7	5.0	5.8
	XRD	6.0	6.2	6.7
N_2 environment	TEM	6.2		9.8
	XRD	6.5		15.0

ran. An increase in the proportion of angular particles was also noticed for this sample. The particles prepared in air environment were always smaller than those in nitrogen. This will be briefly discussed in the next subsection.

The size of the core particles was also estimated by the Debye-Scherrer formula [Lopez-Perez et al., 1997] by using the half maximum width of peaks in X-ray diffraction patterns, such as Fig. 3. Some results of estimation are included in Table 1. The trend in the core size from XRD was the same as that from TEM, although the XRD size was always larger than the corresponding TEM size.

The core size decreased to be unmeasurable on the TEM image, as the addition rate of dextran-iron salt solution increased to 50 ml/min, 5 times that in the reference condition. The extreme smallness of the particles in the sample appeared in the XRD pattern as disappearance of all the crystalline peaks. The immediate addition of iron salts increased the reaction rate and thus the rate of nucleation of iron oxide at the expense of the size of the nuclei. Increase in NH_4OH concentration also reduces the size of the core particles down to 3 nm, from XRD results. Difference in the core particle size was not observed by changing the total concentration of iron salts from 0.44 M to 0.176 M, keeping the Fe^{3+}/Fe^{+2} ratio constant. This implies that the decrease in the reaction rate caused by lowering the concentration results in somewhat different effects on the size of the core particles: the reduction of nucleation rate certainly leads to a lower number of nuclei, but their size probably would not surpass that obtained under the reference conditions, due to the limited amount of core material this time. On the other hand, the particle size either from TEM or XRD was unmeasurably low for the sample prepared at 50 °C and 3.75 wt% NH_4OH. In these conditions, lowering both the temperature and NH_4OH concentration leads to a further decrease in the material available for making iron oxide as well as a further decrease in the rate of reaction. Thus, both the size and the number of core particles would be much smaller than those ob-

tained under reference conditions.

1-2. Crystallinity and Magnetic Properties of Magnetic Particles

XRD patterns for the samples prepared in different Fe^{3+}/Fe^{2+} ratios both in nitrogen and air environments are shown in Fig. 3. Although the precision of the diffraction data was relatively low due to line broadening, there are certainly minor differences in the XRD patterns for the samples prepared under nitrogen and air environments. The main peak, around $35.4°$, was thus slightly shifted to a larger angle, as indicated by the auxiliary vertical line, for the sample obtained under air environment. The XRD patterns of the particles prepared in nitrogen and air environments showed characteristics of spinel phases such as magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), respectively. The crystalline structure was not affected by changing Fe^{3+}/Fe^{+2} from $0.28/0.16(=1.75)$ to $0.16/0.28(=0.57)$. This supports the indication of Babes et al. [1999] that the difference in susceptibility of the particles (thus their crystalline structure) was not so significant except for ranges of the ratio between 2 to 2.5. Thus it is suggested that the formation of maghemite, a more oxidized form, leads to smaller particles than that of magnetite, a less oxidized form. On the other hand, from Fig. 3, the XRD crystallite size varied from 6.5 nm for $Fe^{3+}/Fe^{+2}=0.28/0.16$ to 10.1 nm for $0.16/0.28$ under nitrogen environment. They were 6.0 nm and 7.5 nm, respectively, for the same ratios in air environment. Therefore, this also leads us to conclude that the more oxidative atmosphere either by working in an air atmosphere or by using higher Fe^{3+}/Fe^{+2} ratios favored smaller particles. Babes et al., 1999 showed that the preparation yield decreased and the core size increased by limiting the oxidation by air. They also showed that with decreasing the Fe^{+3}/Fe^{+2} ratio, the mean particle size increased, as well as the proportion of large particles, while the preparation yield decreased. Their definition of the yield (the conversion during a given period) is related to the rate of reaction. Therefore, in our experimental conditions, it is again deduced that smaller particles originated from higher rate of formation for ferric oxide than for ferrous oxide.

The hysteresis curves of the particles at 5 K are shown in Fig. 4. The Figure shows that the squareness of each curve is close to 0, which is typical of superparamagnetism. Saturation magnetization was about 100 emu/g of iron oxide. The saturation magnetization of the particles prepared in a nitrogen atmosphere was slightly larger
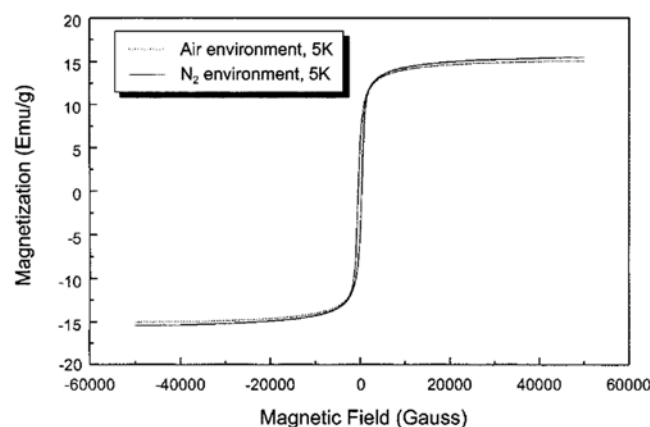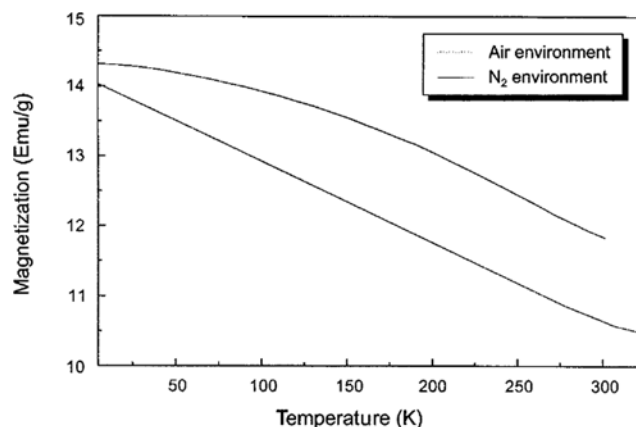

Fig. 5. Temperature effect on the saturation magnetization of the particles prepared in air and N_2 environment, respectively, under otherwise reference condition.

than that in air environment, reflecting the difference of magnetite and maghemite as expected from the discussion of the previous subsection. As shown in Fig. 5, the difference in magnetization increased with temperature.

2. Characteristics of Dextran-Iron Oxide Colloids

2-1. Stability of the Ferrofluid

All the reaction mixtures, after reaction and subsequent aging, were dialyzed for 3 days until their pH's were down to 7. We call these ferrofluids. All the iron particles with dextran, if any, were well dispersed in our ferrofluids within the ranges of our experimental conditions. Fig. 6 is an indication of the stability of the ferrofluids. The average diameters of particles measured each day with the Laser Particle Size Analyzer for 6 days after the ferrofluids were prepared remained almost at the corresponding initial value. This state of dispersion continued for more than three months at room temperature. The fluid was also stable with almost the same LPA

Fig. 4. Hysteresis loop for the particles prepared in air and N_2 environment, respectively otherwise under reference condition.
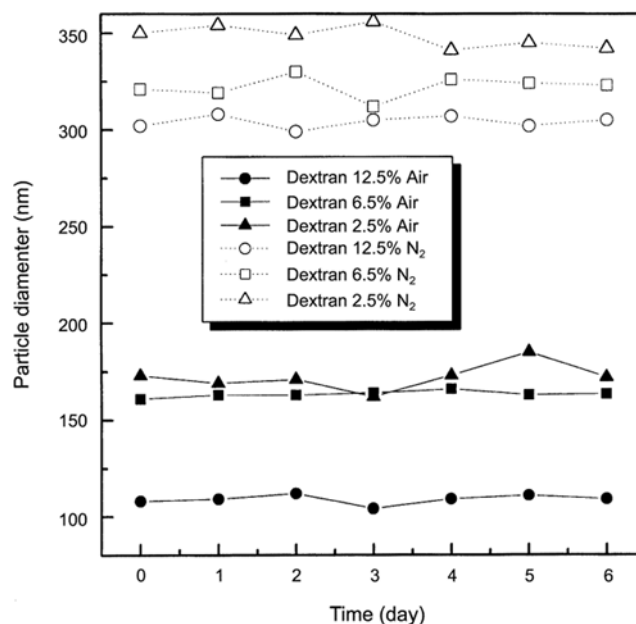

Fig. 6. Particle diameter of the ferrofluids prepared as a function of time elapsed after preparation.

diameter for at least 3 days at temperatures of 4 °C and 50 °C, but at 70 °C precipitation occurred only after 2-3 hours.

2-2. Effect of Dextran

The LPA diameters shown in Fig. 6 correspond to intensity average diameters, also known as PCS (photon correlation spectroscopy) diameter, effective diameter, or the Stokes diameter. This is a function of the sixth power of the physical diameter and is very sensitive to the larger particles that are present in the distribution [Jung, 1995]. Thus, typical LPA diameters of the ferrofluid prepared under reference conditions were 300 nm, as compared to a number average diameter of 52 nm. The LPA diameters were much larger than the TEM diameters shown in the previous section. The differences in number average particle sizes from TEM and PCS measurements were attributable to the formation of chain aggregates by adsorption of hydrated dextran layers, as described in the previous subsection. The fact that the LPA diameters decreased with the concentration of dextran as shown in Fig. 6 supports the model proposed in Fig. 2. When the order of reactant addition was reversed, the LPA diameter of the resultant ferrofluid was reduced to 210 nm, similar to the 227 nm measured by Jung et al., 1995. This reduction of the diameter probably came from the improved dispersion effect by higher concentration of dextran in the latter conditions.

Plots of zeta-potential vs. pH for the samples prepared with various dextran concentrations are shown in Fig. 7. In the figure, two samples were measured for each concentration of dextran for reproducibility of the data. The particles with no dextran had negative charge at most of the pH range except very low value. In contrast, the particles with dextran had very low zeta-potentials, irrespective of pH though their values ranged from positive to negative. This means the particles were well coated with dextran even at low concentration of the latter.

The FT-IR spectra of the particles with different amounts of dextran are shown in Fig. 8. Even the intense absorption at ~600 cm^{-1} of
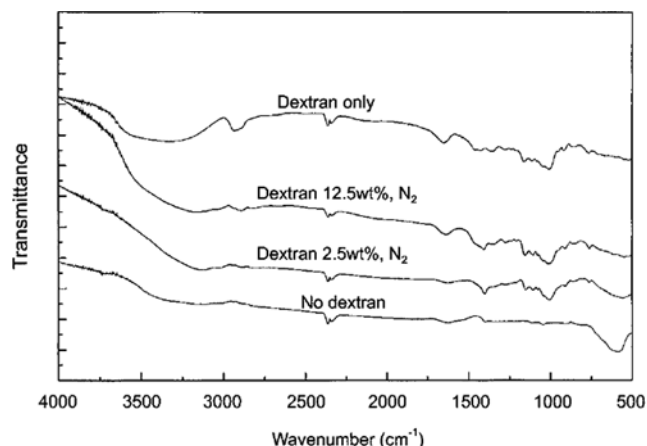
Fig. 8. IR spectra of the samples prepared with various amounts of dextran, under otherwise reference conditions.

the iron oxide surface vibrational modes was obscured by the dextran bands [Jung, 1995]. Characteristic bands of dextran appear at ~3,400 cm^{-1}, ~1,600 cm^{-1}, ~2,900 cm^{-1}, 1,250-1,460 cm^{-1}, 1,040-1,150 cm^{-1}, which become more clear with the dextran concentration.

2-3. Effect of Reaction Environment and Reaction Variables

As already shown in Fig. 6, the air environment led to the formation of smaller particles than did the nitrogen environment. This result coincided with the TEM observation in the previous subsection. It is believed that the reduction of the core size also affected the LPA diameter. Gunther et al., 2000 discussed that the oxidation of dextran broke down dextran's molecular structure, leading to smaller particle aggregate. Thus, in the presence of air, the oxidation of dextran might occur as well as that of ferrous ion. A similar conclusion was reached from the effect of sonication of the ferrofluids prepared. Oxidation through 20-min sonication reduced the LPA diameter of the ferrofluid prepared under nitrogen environment from 300 nm to 220 nm, while the diameter of the ferrofluid obtained under air environment was not affected at all.

The influence of parameters such as NH$_4$OH concentration, total Fe concentration, Fe^{3+}/Fe^{2+} ratio, injection flux and aging temperature on LPA size of the particles was also studied. No significant
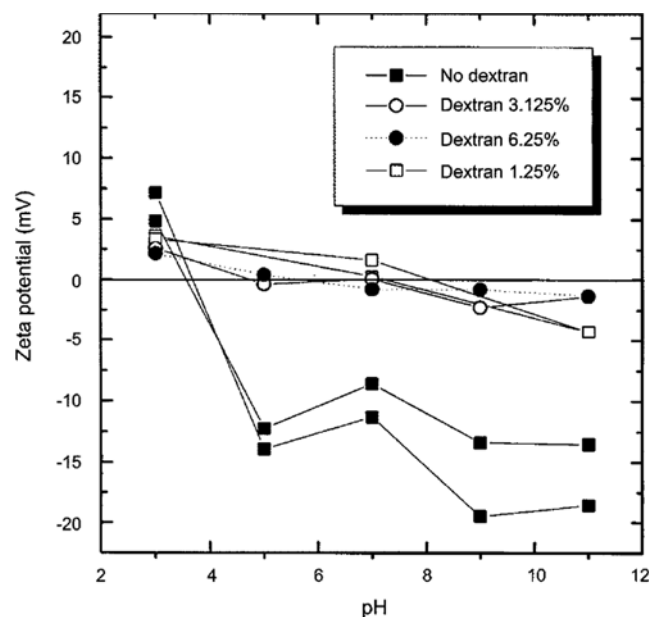
Fig. 7. Effect of pH on zeta potential of the ferrofluid in air environment under reference conditions, identified symbols correspond to different runs on identified particles.
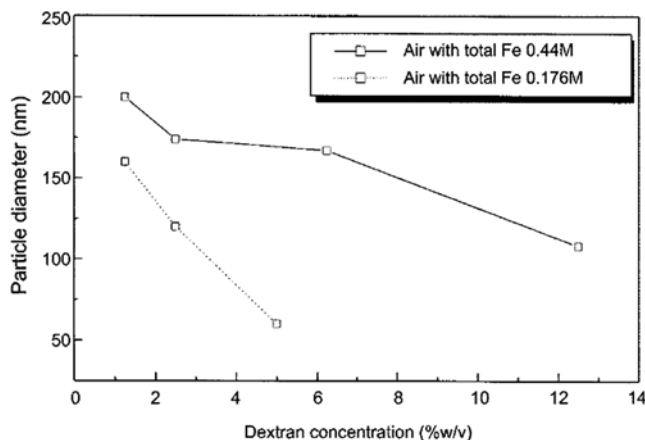
Fig. 9. Variation in particle diameter (LPA) with dextran concentration.

effects of NH_4OH concentration, Fe^{3+}/Fe^{2+} ratio and injection flux were observed. The aging temperature has a slight effect on the LPA size, which varied only from 95 nm at 50 °C to 110 nm at 80 °C. In contrast, the total concentration of iron salts had an appreciable effect on the LPA diameter. Fig. 9 shows the variation in the LPA diameter of the particles with respect to the dextran concentration for different total concentrations of iron salts in air environment. The size at 0.44 M Fe is larger than at 0.176 M Fe, though the difference between the two sizes decreasing. As described earlier, lower iron concentration reduced the number concentration of the core particles, keeping their size similar to that in the reference conditions. In this case, since the concentration of dextran remained at the same value as in the reference conditions, dextran would adsorb more densely on the surface of the core and form aggregates similar to type (a) in Fig. 2.

CONCLUSIONS

Dextran ferrofluids were prepared by the reaction of ammonium hydroxide with mixed iron salts added slowly in the presence of dextran. The core oxide particles of nanometer size were superparamagnetic and characterized as magnetite with saturation magnetization of about 100 emu/g of iron oxide. They were seemingly connected along a multiplicity of dextran chains forming apparently branched chainlike aggregates. The presence of dextran during the reaction kept the oxide particles effectively dispersed in water but suppressed their growth. Their size decreased with the rate of reaction by increasing the addition rate of iron salt-dextran mixture, the concentration of ammonium hydroxide and conversion of ferrous to ferric oxide in the core. The size of the dextran-oxide aggregates decreased by either increasing the concentration of dextran or decreasing the total iron concentration, due to the increased amount of adsorption per core particle. The aggregate size also decreased by oxidation, probably due to chain breakup.

ACKNOWLEDGEMENT

REFERENCES

Babes, L., Denizot B., Tanguy, G., Le Jeune, J. J. and Jallet, P., "Synthesis of Iron Oxide Nanoparticles Used as MRI Contrast Agents: A Parametric Study," *J. Colloid and Interf. Sci.*, **212**, 474 (1999).

Coe, E. M., Bereman, R. D. and Monte, W. T., "An Investigation into the Size of an Iron Dextran Complex," *J. Inorg. Biochem.*, **60**, 149 (1995).

Groman, E. V., Josephson, L. and Lewis, J. M., "Biodegradable Superparamagnetic Materials for Use in Clinical Applications," USP 4827945 (1989).

Gunther, W. H. H., Fujii, D. K., Kellar, K. E., Black, C. D. V., Desai, V. C., Beeber, M., Wellons, J., Fahlvik, A. K. and Naevestad, A., "Superparamagnetic Contrast Media with Starch and Polyalkylene Oxides," USP 6123920 (2000).

Hasegawa, M., Ito, Y., Yamada, H., Nagae, H., Tozawa, N., Hino, Y., Kito, K., Hokukoku, S., Lawaczeck, R., Ebert, W., Pfefferer, D., Wagner, S. and Kresse, M., "Water Soluble Carboxypolysaccharide-Magnetic Iron Oxide Complex Having a Small Particle Diameter," USP 5766572 (1998).

Jung, C. W. and Jacobs, P., "Physical and Chemical Properties of Superparamagnetic Iron Oxide MR Contrast Agents: Ferumoxides, Ferumoxtran, Ferumoxsil," *Magn. Reson. Imaging*, **13**(5), 661 (1995).

Jung, C. W., "Surface Properties of Superparamagnetic Iron Oxide MR Contrast Agents: Ferumxides, Ferumoxtran, Ferumoxsil," *Magn. Reson. Imaging*, **13**(5), 675 (1995).

Kawaguchi, T. and Hasegawa, M., "Structure of Dextran Magnetite Complex: Relation between Conformation of Dextran Chains Covering Core and Its Molecular Weight," *J. Mater. Sci.: Materials in Medicine*, **11**, 31 (2000).

Kellar, K. E., Fujii, D. K., Gunther, W. H. H., Briley-Saebo, K., Spiller, M. and Koenig, S. H., "NC100150, A Preparation of Iron Oxide Nanoparticles Ideal for Positive-Contrast MR Aniography," *Magn. Resonn. Mater. In Phys., Biol. And Med.*, **8**, 207 (1999).

Lopez-Perez, J. A., Lopez-Quintela, M. A., Mira, J. and Rivas, J., "Preparation of Magnetic Fluids with Particles Obatined in Microemulsions," *IEEE Trans. on Magn.*, **33**(5), 4359 (1997).

Mendenhall, G. D., Geng, Y. and Hwang, J., "Optimization of Long-Term Stability of Magnetic Fluids from Magnetite and Synthetic Polyelectrolyte," *J. Colloid and Interf. Sci.*, **184**, 519 (1996).

Nowik, I., Semmler, W. and Molodtsov, S., "Size Distribution of Magnetic Cores in Contrast Materials for MRI Diagnostics," *Hyperfine Interactions*, **112**(1-4), 77 (1997).

Palmacci, S. and Josephson, L., "Synthesis of Polysaccharide Covered Superparamagnetic Oxide Colloids," USP 5262176 (1993).

Popplewell, J., "Technological Applications of Ferrofluids," *Phys. Technol.*, **15**, 150 (1984).