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Size analysis of biocompatible magnetic nanoparticles colloids

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The present study provides a dimensional analysis of the magnetic nanoparticles size within water based magnetic fluids, prepared in our laboratories, as obtained from transmission electron microscopy (TEM) and atomic force microscopy (AFM). The magnetic nanoparticles were prepared by chemical co-precipitation from ferric ($FeCl_3$) and ferrous salts ($FeCl_2$) in alkali medium (ammonia hydroxide) and functionalized with tartaric acid, β-cyclodextrin, perchloric acid and respectively, citric acid. The TEM images have been analyzed aiming to reveal diameter distribution histograms. The AFM was used to visualize and measure the magnetic nanoparticles diameter and height – the 3-D imaging representing one of the main advantages of this scanning technique. The suitability of the aqueous magnetic fluids for biomedical applications was discussed.

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1. Introduction

As a new branch of smart materials research, magnetic nanoparticles are more and more attractive due to their potential applications in many areas such as electronics, optics, magnetic fluids, magnetic data storage etc [1]. Their unique properties and remarkable performances are determined by the particle sizes, surface structure and inter-particles interactions. In recent years, nanotechnology has been developed to a stage that makes it possible to produce, characterize and specifically functionalize nanoparticles for biomedical applications. The magnetic fluids are stable colloidal systems consisting of single domain ferromagnetic particles coated with a surfactant and dispersed in a carrier liquid [2]. The coating of magnetic nanoparticles surface can effectively prevent the agglomeration of nanoparticles because of Brownian motion. Covering nanoparticles with adsorption layer usually results in increased resistance against the magnetic nanoparticles aggregation. In aqueous medium, electrostatic, steric or combined stabilization layers can develop [3]. The thickness of coating layer provides better stability, especially in the case of magnetic fluids, since the distance (typically 2-3 nm) between magnetic mono-domains is important when extern magnetic fields are applied [4]. To obtain the profile of the particle dimension curves the magnetic measurements and transmission electron microscopy have been traditionally used, recently the atomic force microscopy being introduced also.

The recent development of a large variety of magnetic fluids has led to a range of new biomedical and diagnostic applications. In biomedical applications, the magnetic particles in magnetic fluids are used either directly or as a component of polymeric supports for biologically active species. In vivo applications, like drug delivery [5-7], magnetic resonance imaging [8-9] or hyperthermia [10-11], additionally require particles being stable, biocompatible and biodegradable. These aspects are achieved by coating and embedding the particles in a suitable biocompatible material [12].

Water based magnetic fluids, like one presented by Tombàcz have hold great potential for biological applications, considering their influence in plant growth. Several such results were shown by Pavel *et al* [14] and Racuciu *et al* [15-16].

In this paper we present a comparative study on dimensional characteristics of four magnetic fluids samples prepared in our laboratories for bio-medical purposes (water dispersions).

2. Experimental

Aqueous suspensions of magnetic particles were obtained under identical reaction conditions by co-precipitation of Iron (III) and Iron (II) salts using aqueous ammonia, at 80ºC temperature, as described in [17]. The suspensions were finally washing with deionized water to obtain the pH value as closer as possible to 6.5. After washing, in the aqueous magnetic particles precipitate four coating molecules were added: at 90ºC temperature: perchloric acid (PA - sample), tartaric acid (TA – sample), citric acid (CA - sample) and respectively β-cyclodextrin (bCD – sample); the resulted dark suspensions were mechanically stirred for 1 h. The TEM images have been analyzed and the diameter distribution histograms have been drawn. As known, the chain and aggregates revealed among the isolated nanoparticles are particularly important for the magnetic fluid stability. TEM images were provided by a TESLA device using the diluted sample (10^4 in deionized water) deposition on collodion sheet. The AFM

technique was applied to visualize and to measure the nanoparticles diameter and height – the 3-D imaging representing one of the main advantages of this scanning technique. Both 3-D and phase recordings have been used. The AFM device assembled in our laboratory is working in the taping mode being provided with commercial standard silicon nitride cantilever (NSC21) characterized by a force constant of 17.5 N/m, 210 kHz resonance frequency, having tips with radius between 5 and 10 nm. The AFM images cover a range of areas, from 50 × 50 to 3 × 3 μm.

3. Results

The analysis of all TEM resulted in about 1,000 particles measured per each magnetic fluid sample. Magnetic particles display almost spherical geometry (Fig. 1). General asymmetric size distributions (Fig. 2) were evidenced, following statistic analysis.

In all magnetic fluids the coated magnetite nanoparticles have diameter values ranging between 1.06 nm and 30.17 nm.

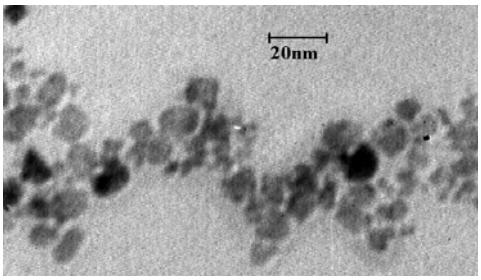

Fig.1. TEM picture for the TA sample

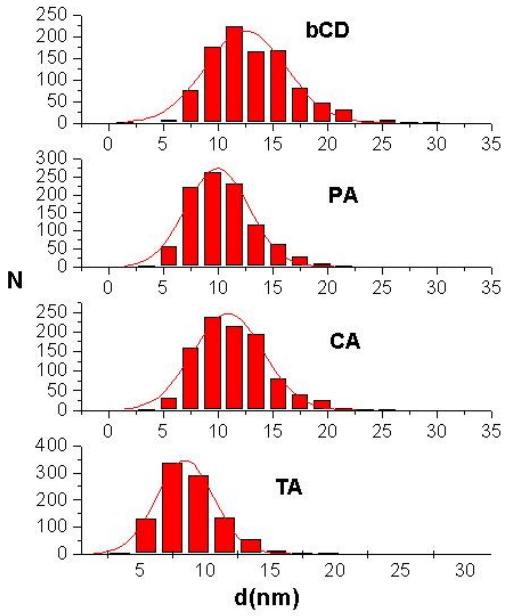

Fig. 2. Distribution histograms of magnetic nanoparticles coated with tartaric acid (TA-sample), coated with citric acid (CA – sample), coated with perchloric acid (PA – sample) or coated with β-cyclodextrin (bCD – sample).

The approach by means of normal distribution function *P(d)* of the diameter histogram was evidenced:

$$P(d) = \frac{1}{\sqrt{2\pi}\sigma\, d}\exp\left\{-\frac{[\ln(d/d_0)]^2}{2\sigma^2}\right\} \qquad (1)$$

where *d* is the particle diameter value, σ is the standard deviation, while lnd_0 corresponds to the mean value of *lnd*.

As shown in Fig. 3 the box-plot technique was applied as useful for comparative discussions of dimensional distributions aiming to identify the best magnetic fluids for biomedical applications – where the small particle size plays an important role in the passing through natural biological barriers. As known, the box-plot, technique proposed by Koopmans [18], is based on the representation of the next parameters: the 10%-90% interval (the box tails), the 25%-75% interval (the box length), the average value (point within box), the median value (line within the box) and exceptionally small or large values (points out of the box tails). The increase of the median particle diameter from TA to bCD magnetic fluid is evidenced in Fig. 3.

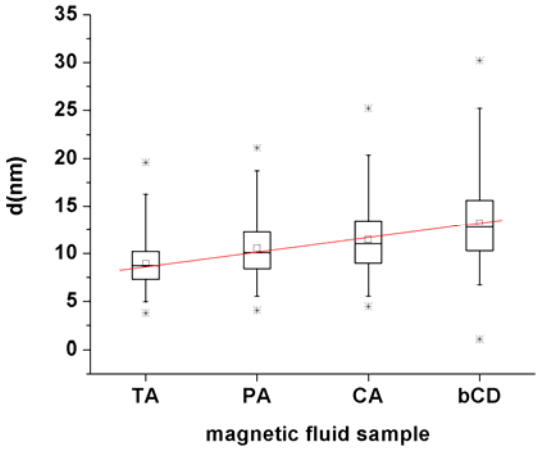

Fig. 3. Box-plot diagrams corresponding to the physical diameter of magnetic fluid samples analyzed in this study.

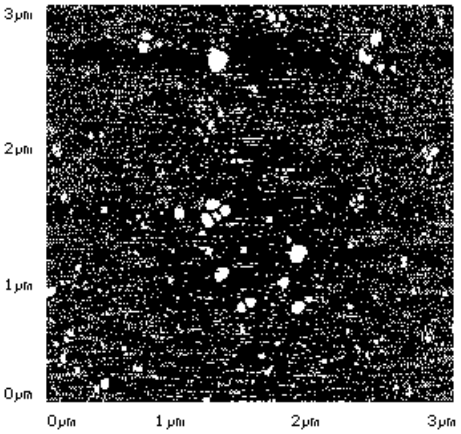

Fig. 4. Phase mode recording of ferrophase within magnetic fluid sample stabilized with perchloric acid (PA sample) (3×3μm).

The AFM investigation (with 5-10 times lower accuracy than TEM analysis method) revealed mainly topological details that could be captured using the AFM device having with tip radius between 5 and 10 nm. Repeated scanning was performed on numerous areas on the mica deposition slides so that the final number of the analyzed particles was about 1,000 like in the case of TEM analysis. In the Fig. 4 the phase mode recording for perchloric acid coated magnetic nanoparticles sample (PA) is presented for exemplification.

The 2-D recordings are shown in Fig. 5 for the magnetic nanoparticles coated with citric acid (CA). Aggregates having quasi-spherical shape or short particle chains were revealed.

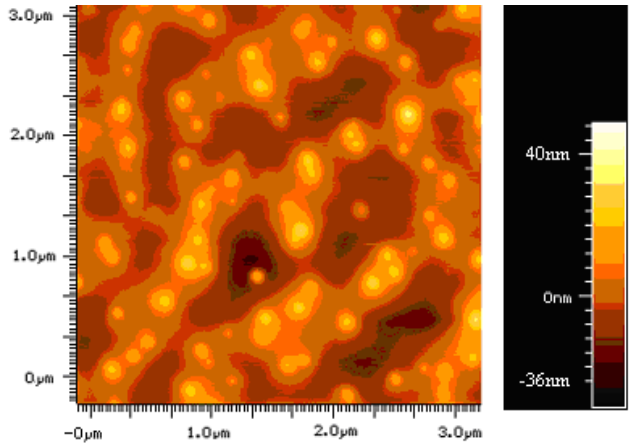

Fig. 5. 2-D image recorded using the AFM device for magnetic fluid sample stabilized with citric acid (CA sample).

In Fig. 6 an example of 3-D AFM images is presented for bCD magnetic fluid.

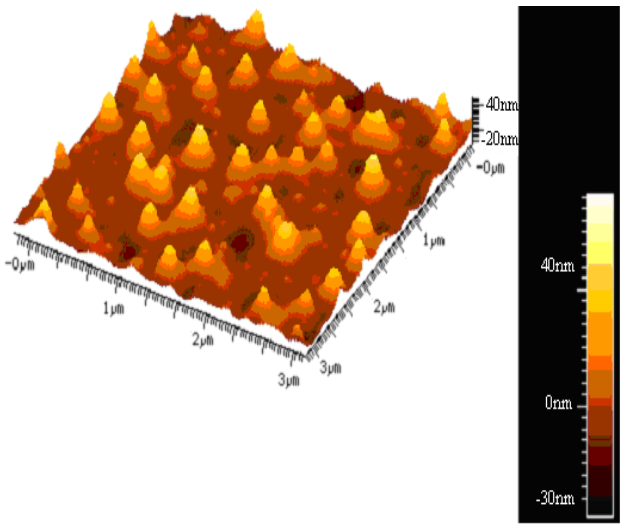

Fig. 6. AFM 3-D image recorded for magnetic fluid sample stabilized with β-cyclodextrin (bCD sample)

4. Discussion

The median values calculated for the physical diameter (TEM measurement) ranged between 8.945nm and 13.237nm accordingly to Table I. One can see that the smallest physical diameter value for magnetic nanoparticles coated with different biocompatible compounds was obtained in the case of the TA sample, i.e. tartaric acid coated magnetic nanoparticles.

Table I. The dimensional analysis results.

Sample	d_0 (nm)	σ (nm)	Exceptional small values (nm)	Exceptional large values (nm)
TA	8.9	2.38	3.77	19.58
PA	9.9	2.84	4.08	21.12
CA	10.9	3.31	4.48	25.18
bCD	13.2	3.97	1.06	30.17

From Fig. 3 we can see that the box corresponding to TA-magnetic fluid sample is situated toward the smaller diameter values, the box length lying between 7.45nm and 10.3 nm – the median value of 8.945nm being symmetrically situated within the box. This is the narrowest of the four distributions (2.93 nm box length), presenting also the exceptionally large diameter of 19.58 nm. This is not surprisingly since the other physical data presented above (Table 1) have already suggested that the best magnetic fluid (among the four discussed inhere) is that stabilized with tartaric acid. Other authors that tested tartaric acid as coating molecule for the $CoFe_2O_4$ magnetic nanoparticles, within their magnetic fluids succeeded in obtaining about 6nm average size [19].

On the other hand the box-plot corresponding to bCD - magnetic fluid sample is characterized by highest values of the box parameters, i.e. larger box length (5.34 nm), median value (13.23 nm) and exceptionally large diameter (30.175 nm). One can see that in all cases the median and average values practically coincide and that the box tails are asymmetrical.

The AFM 3-D images (Fig. 6) showed that the larger topological details are not single large particles but mostly agglomerates of small magnetic nanoparticles.

In the case of bCD magnetic fluid sample the 3-D AFM recording revealed the aggregates having quasi-spherical shape and short particle chains, the aggregate height being up to 30 nm (Fig. 6). The smallest colloidal particles were best evidenced in the phase recording mode.

So, the possibility to evidence the shape and height of particles and particle aggregates seems to be the main benefit of AFM application in the dimensional investigation of magnetic nanoparticles suspensions, i.e. magnetic fluids. In the TA magnetic fluid sample analyzed in this study, the magnetic nanoparticles aggregates as well as rare short chains of linearly associated particles (2-D images as well as 3-D images) appeared as formed by small number of particles, getting height values of 10-20 nm. The CA and PA magnetic fluids represent intermediate cases. In

the TA and PA magnetic fluid samples the particle height was lower than its diameter in most of the cases. However, when we are dealing with magnetic particles agglomeration then the superposition of several magnetic nanoparticles may result in particle aggregates with relatively big height. One of this situation can be observed in the bCD magnetic fluid sample (Fig. 6).

The interpretation of the frequency of the particles aggregates within the magnetic fluid on the base of the fluid deposition and drying upon the specific supports - either for TEM or for AFM investigations - is not quite adequate since the observed aggregates may be formed quite during the deposition process so that their frequency within the initial fluid might be much lower. The existence of such particles agglomerations and particles chains impose the improvement of the preparation protocol since they suggest that the attractive electric and magnetic forces are not totally balanced by the electrostatic or steric repulsion conferred by the compound coating molecules, so that the phenomenon of magnetic nanoparticles precipitation in weak magnetic field gradient can threaten the magnetic colloid stability.

5. Conclusions

In this study, the microstructural investigations of four batches of aqueous magnetic fluids stabilized with different biocompatible molecules were carried out. As shown by TEM and AFM techniques, the finest ferrophase diameter for the tartaric acid coated magnetic nanoparticles was evidenced.

Similar histograms of physical diameters have been obtained for all analyzed samples from TEM investigation. The topological characterization of some large particles aggregates and short chains of ferrophase particles in the investigated magnetic fluids by means of 3-D AFM data was carried out. The dominance of small size nanoparticles well dispersed within the carrier fluid is able to ensure the magnetic fluid stability and property for biological applications.

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