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Investigation of ferrofluid nanostructure by laser light scattering: medical applications

E K Nepomnyashchaya[1], E N Velichko[1], I V Pleshakov[1,2], E T Aksenov[1], E A Savchenko[1]

[1]Department of Quantum Electronics, Peter the Great Saint Petersburg Polytechnic University, Saint Petersburg 195251, Russia

[2]Laboratory of Quantum Electronics, Ioffe Institute, Saint-Petersburg, 194021, Russia

E-mail: elina.nep@gmail.com

Abstract. Investigation of ferrofluids nanostructure by the laser light scattering technique is presented. Experimental studies involved measurements of the intensity of the laser radiation scattered by ferrofluid particles in interaction with albumin and under the influence of magnetic field. The effects of the magnitude and duration of the applied magnetic field on the formation of aggregates of magnetic nanoparticles and also the influence of magnetic fluids of different concentrations on blood proteins are considered. The findings may be useful for medical applications.

1. Introduction

Magnetic fluids (also known as ferrofluids) represent a special category of smart nanomaterials in colloidal suspensions composed of single-domain magnetic nanoparticles [1]. Owing to their unique properties, magnetic fluids have found a widespread use in medicine. Their ability to be going to the point where the magnetic field intensity is the highest and to follow the field in their motion allow to direct magnetic nanoparticles with the blood flow to any point of the body [2]. Drug Coated magnetic particles can act as a drug delivery system. Their ability to effectively absorb electromagnetic radiation at specified frequencies and convert the energy into heat allows their use in magnetic fluid hyperthermia for the treatment of localized cancerous tumors [3]. By fixing antigens on a magnetic particle it is possible to effectively detect cancer cells, bacteria, and viruses via flow cytometry. Recent studies have shown that the introduction of magnetic nanoparticles with cancer antigens into the blood flow allows one to detect single tumor cells and even destroy them with the help of single pulses at the absorption frequency of a ferromagnetic nanoparticle. By using this technique referred to as theranostics not only the tumor but also all possible metastases can be destroyed and the patient can be completely cured [4, 5].

Despite the advantages offered by magnetic nanoparticles for cancer therapy, their use in clinical practice is still at the proof-of-concept stage. In order to reveal the consequences of the introduction of magnetic fluids into a body, experiments with the participation of animals and model objects are being carried out. In this paper, specific features of changes in the structure of magnetic nanoparticles in a liquid exposed to magnetic fields of different powers and durations are considered. In addition, the interaction of magnetic nanoparticles with human blood proteins is studied in order to reveal a possible influence of nanoparticles on the properties of proteins [6]. It is known that as soon as

extraneous particles are injected into the blood, they become a target of all safety systems of an organism. The basic mechanism is the spontaneous adsorption of plasma proteins (opsonization process). Thus, the introduction of a large number of nanoparticles into a body can lead to a malfunction of these proteins.

2. Materials and method

2.1 Laser correlation spectroscopy

To study the nanostructure of magnetic fluids and their conglomerates, we used the laser correlation spectroscopic technique. A typical scheme of the device is shown in Fig. 1. In this setup, a coherent linearly polarized light beam from a laser with a diameter of 1.2 mm was transmitted through a converging lens and focused on the sample. A He-Ne laser with wavelength λ = 632.8 nm, 5 mW power, high stability and narrow spectral line was chosen for laser correlation measurements. The scattered light at angle θ = 15° passed through an iris diaphragm and was detected by a photomultiplier. The signal from the photomultiplier arrived to a computer for the correlation analysis.

We modified the scheme by adding coils to generate a magnetic field in the sample. The applied field was varied in the range 0 – 300 Oe with accuracy ± 0.5 Oe. The field distribution between the magnet poles was measured by a Hall sensor. It was found that the field gradient at the sample location was less than 1 Oe/cm. More information about measurement of light scattering on magnetic nanoparticle could be found in [7].

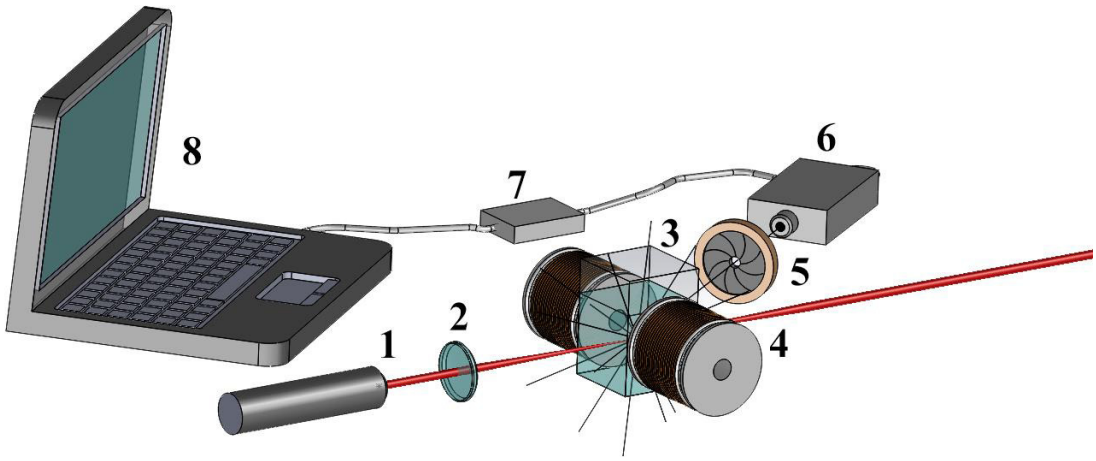

Figure 1. Scheme of a laser correlation spectrometer. 1 – laser radiation source; 2 – converging lens; 3 – sample; 4 – coils; 5 – iris diaphragm; 6 – photomultiplier; 7 – AD converter; 8 – computer

Laser correlation spectroscopy allows one to estimate sizes of nanoparticles in a fluid from measurements of scattered radiation parameters. The experiments involve recording of the time dependence of the scattered light intensity and the calculation of its autocorrelation function. According to the dynamic scattering theory, the autocorrelation function of the light scattered by particles in a solution will carry information on the diffusion coefficient (D) of these particles. By using the Stokes-Einstein relation

$$D = k_b T/6\pi\eta R, \quad (1)$$

we can calculated the radii of nanoparticles or of their agglomerates. Here, η is the viscosity of the medium, k_b is the Boltzmann constant, T is the temperature, and R is the particle radius. Conclusions on the agglomeration and de-agglomeration of the particles and their degree of coupling can be drawn by measuring the sizes of scatters.

To derive information about sizes of nanoparticles the distribution of scattered light intensity on D coefficient I(D) is counted. Special algorithm based on Tikhonov regularization method [8] is used for calculation of intensity distribution I(D) from autocorrelation function. Then R is recounted from D by relation (1) and final dependence I(R) is calculated.

To evaluate the accuracy of experimental studies the test objects — water solutions of latex microspheres with specified sizes of 30 nm, 45 nm, and 75 nm were investigated. A series of 20 measurements were conducted for polydisperse solutions of microspheres of three sizes. The results of statistical analysis proved high accuracy of our method of analysis of particle sizes in polydisperse solutions — the percentage error was 6 % (at a confidence level of 95 %).

2.2 *Object of study*

The objects used in our studies were nanoparticles of magnetite Fe_3O_4 in water. The samples of ferrofluids were produced in our laboratory by the method described in [9]. It was shown in it that FF nanoparticles follow a log-normal distribution with a scaling parameter of 0.17. Aqueous dispersions are typically stable for long periods. However, at physiological pH nanoparticles form aggregates in the form of flocculates. Therefore, the oleic acid was used as a surfactant that prevented particle aggregation while storage. The average radius of the particles was about 4 nm ÷ 6 nm and typical concentrations were between 0.02 vol. % to 0.2 vol. %.

In order to study the interaction of magnetic nanoparticles with proteins of the blood plasma, albumin was used. Typical albumin size is 3.6 nm and the concentration is 100 mg/ml. This protein was chosen because of its high importance for the human organism. It performs a variety of functions, including the transport of substances in the body. Distortions in the structure of this protein can result in irreversible changes and cause a serious harm to the human health. Our task was to reveal changes in the protein structure which can occur at its mixing with a solution of magnetic fluid.

3. Results and discussion

It is known that it is preferable to use nanoparticles with radii of 5 – 50 nm for medical purposes because nanoparticles of these sizes are slowly removed by the reticuloendothelial system, which gives them sufficient time to accumulate in the tumor or other target region of the body [2]. In addition, large particles can damage small capillaries of both the extremities and the brain. Therefore, the nanoparticles should have a high colloidal stability in biological media because agglomeration processes are highly undesirable. We carried out measurements of the dependence of sizes of magnetic particle agglomerates on the applied magnetic field. Experimental results are shown in Fig. 2. R is the radii of particles in nanometers, H is the magnetic field value in Oe (given value), I(R) is the relative intensity of light scattered on each size of particles (counted from autocorrelation function).

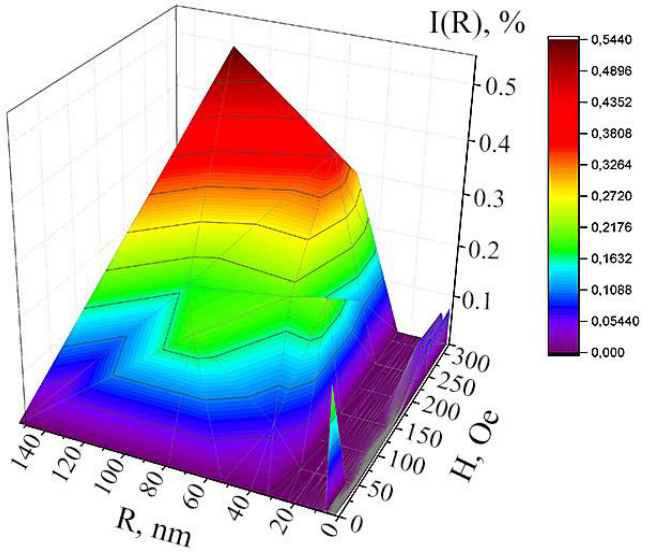

Figure 2. Dependence of sizes of magnetic nanoparticle agglomerates on applied magnetic field

It can be seen that under the fields lower than150 Oe the sizes of the majority of agglomerates do not exceed 40 nm. A further increase in the field gives rise to the formation of agglomerates with a radius of 60 – 140 nm, which exceeds the limit allowable in medical applications. Thus, it can be concluded that the maximum field should not exceed 150 Oe.

Then dynamic characteristics of the agglomerate formation were measured. A magnetic field of 150 Oe was applied to the sample for a long time (up to 40 minutes). The result is shown in Fig. 3, t stands for the field implementation time in minutes.

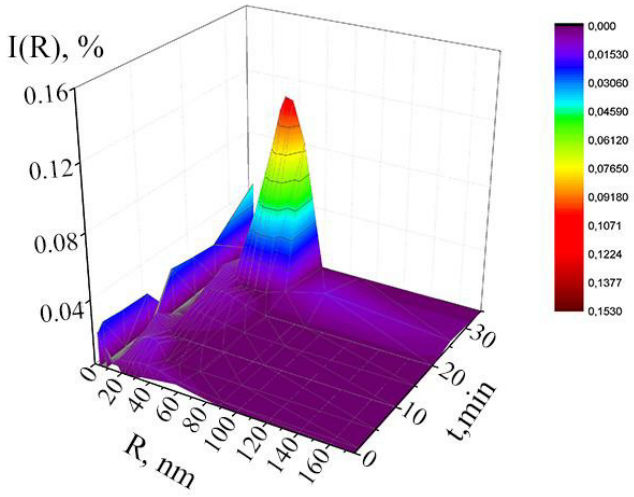

Figure 3. Dependence of sizes of magnetic nanoparticle agglomerates on magnetic field application period

After 20 minutes of exposure to the magnetic field, agglomerates of size larger than 40 nm began to appear in solution. After this, the number of small agglomerates also substantially increased. This may indicate that it is necessary to limit the exposure of a body to a magnetic field by a time period of twenty minutes. According to some studies [3], in order to destroy cancer cells by the method of Magnetic Fluid Hyperthermia, the field application during 30-40 minutes is sufficient for the local tumor heating to 41-54°C and cell destruction. The duration of exposure can be decreased by using a repeated procedure within 48 hours. This reduces the danger of colloidal stability disturbance and increases the safety of the procedure.

To investigate the effect of magnetic nanoparticles on albumin, we measured agglomerate sizes in a solution as functions of the magnetic fluid concentration. In the experiments, magnetic nanoparticles in water at a concentration of 0.02 vol. % were used. The solution of magnetic nanoparticles (from 0 to 1 μl) was added to 1 ml of albumin. The result is shown in Fig. 4. C is the volume of added magnetic fluid.

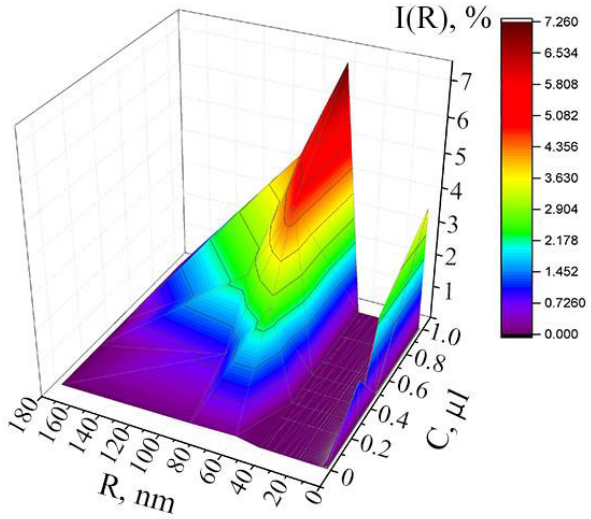

Figure 4. Dependence of sizes of magnetic nanoparticle agglomerates with albumin on concentration of magnetic particles

The size of albumin at a zero concentration of magnetic nanoparticles was about 4 nm. Addition of 0.1 μl of the ferrofluid gave rise to the formation of agglomerates with a radius of about 70 nm, which indicates that a part of magnetic nanoparticles was deposited on the surfaces of albumin molecules. The concentration of such agglomerates increased with increasing concentration of the ferrofluid and reached a dangerous limit after 0.4 μl of ferrofluid was added. Thus, it can be seen that magnetic nanoparticles exert a considerable influence on blood proteins even if they are coated with oleic acid. However, at low concentrations this effect is not so appreciable. When a specially designed protein layer is used as a surfactant instead of oleic acid, the influence of magnetic particles on proteins can be further reduced. In this case their use becomes relatively safe.

4. Conclusion

Our studies have revealed that the formation of aggregates of magnetic particles of size 40 nm occurs in a magnetic fluid under an applied magnetic field higher than 150 Oe and with an exposure time of 20 minutes or longer. These values can serve as thresholds for the magnetic field and the duration of exposure in biomedical research, in which the sizes of conglomerates of magnetic particles should not exceed 40 nm. It has also been found that magnetic nanoparticles coated with oleic acid exert a

considerable influence on blood proteins (albumin). Extensive studies are needed to find the parameters of ferrofluids and the conditions of their use appropriate for their safe and efficient application in human therapy.

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