THE USE OF HIGHLY DISPERSED IRON-BEARING COMPOSITES IN TREATMENT AND DIAGNOSIS: ADVANCES AND PROBLEMS

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There have been considered new effective medical technologies using highly dispersed iron-bearing magnetic particles. A considerable number of versatile options of obtaining such particles ahs been shown. Regardless the methods for their production, highly dispersed iron-bearing magnetic particles are composites consisting of metal nucleus and surrounding protective capsule of complex mixture. Their critical characteristic is the imaging possibility using magnetic resonance tomography, local heating by high-frequency magnetic field to initiate the mechanism of drug releasing.

There have been given the methods of having an impact on the obtained highly dispersed iron-bearing particles by changing their morphology: sizes, shorms, compositions, qualitative and quantitative ration “nucleus–membrane”. There have been specified yet unsolved problems: adequate estimation of such particles, the development of industrial regulations to obtain highly dispersed magnetic iron-bearing composites with tailor-made properties.

Key words: highly dispersed iron-bearing composites, magnetic particles.

The use of highly dispersed iron powder for medical purposes is well known. Medical drug for oral use — Ferrum reductum (See USSR State Pharmacopeia, X edition, SP-X) is produced by electrolysis of aqueous solution of ferrous (II) sulphate in the presence of ammonium chloride at 20–40°C and voltage 1.8–2.5 V [1]. Anode is pure iron, and cathode is a soft steel plate. The necessary condition for electrolysis of aqueous solution of ferrous (II) sulphate is the persistency of acid medium. pH value of the solution is to be kept in the range 3–4 pH units that is regulated by adding dilute solution of sulphuric acid solution into electrolyzer. The ferrum received on cathode (layer thickness is 4–6 mm) is flushed using distilled water up to the negative reaction on sulphate- and chloride ions, and dried at 50°C. Then it is reduced to subsieve powder and sieved [2]. According to SP-X, the preparation received in this way contains 99% of iron. SP-X concedes the occurrence in Ferrum reductum not more than 0.01% of high density metals. This drug preparation is taken as antianemic agent, in powder, pills, and tablets (0.2 g): 0.5–1.0 g, 3–4 times a day after meals, by drinking a weak solution of chloride hydride or gastric juice.

Ferrum reductum powder is described [3] to be used to produce hemosorbents for biomedical researches and clinical practice. Highly dispersed iron powder is fractionated in inert gas flow at the velocity of 0.02–1.0 m/s in magnetic field intensity interval of 10–1000 A/m to receive a certain particle-size fraction (0.5–2.5 mcm). The received iron particle fraction is baked at 1000–1500°C in inert gas flow or inert gas flow containing carbon or silicon oxide (IV) microparticles. Finally, three types of sorbents are received: uncoated iron-bearing composite, iron-bearing composite coated by carbon film, and iron-bearing composite coated by silica gel [3]. Then the surface of the sorbent is extra coated by gelatin or dextran to reduce traumatization of blood corpuscle. The modification of the surface is performed to eradicate pathogenic flora, retroviruses and remove antigens: the surfaces are coated by pharmaceuticals and antibodies by physisorption in saline solution at 40°C. The work [3] shows the received sorbents to exceed the known nonmagnetic types of sorbents in sorption efficacy in regard to low-, medium-, and high-molecular substances. To remove magnetic sorbents on the basis of Ferrum reductum from biological media it is sufficient to place magnetic fields up to mTesla that meets medical and sanitary standards [4].

There is another known variant of producing pure iron powders for oral use — carbonyl method [5]. Carbonyl iron is produced by means of thermal decomposition of iron pentacarbonyl by a equation: $Fe(CO)_5=Fe+5CO$. Carbonyl iron has the appearance of dark subsieve powder. It has no silicon, phosphorus, sulfur, but contains

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carbon [5]. At present, there has gained currency a dietary food supplement BoostIron (carbonyl bioavailable iron). The product of Santegra BoostIron™, developed for iron deficiency anemia prevention, contains 10 mg of iron in the form of carbonyl iron, as well as vitamin C, folic acid, and vitamin B_{12} necessary for its more complete uptake. Carbonyl iron has a number of advantages compared to other iron forms: it contains 98% of elemental iron, has no ferrous salts, nontoxic, and in contrast to iron salts has no side effects such as constipation and diarrhea; and digestible [6, 7]. The product is manufactured subject to all the standards of GMP (Good Manufacturing Practice); is taken by 1–2 tablets a day at mealtimes.

In the last decade, thriving innovative technologies have resulted in arousing researchers' interest in nanopowders of magnetic materials — nanoparticles (from 1 to 100 nm in size) [8–22]. Scientific works in nanotechnologies are recognized worldwide as priority ones. The particles the size of which meets the above mentioned range differ from their larger analogues in the characteristics of physicochemical and biological properties that, on the one hand, results in the possibility of developing on their basis therapeutic and diagnostic agents with new working characteristics, and on the other hand, represents the necessity for thorough study of potential risks of human body when in contact with nanomaterials [23].

The literature describes several variants of production and application of nanosized iron-bearing particles for biomedical purposes. The work [24] represents the results on developing a magnetically operated system of delivery of chemicals based on nanosized iron particles. The powders of nanosized particles (from 5 to 100 nm) were received by electric spark dispersion of iron turnings into liquid media — distilled water, solution of orthophosphoric acid, ethyl hydroxide, and hexane. In all cases the product of electroerosion represented a suspension of highly dispersed iron-bearing composites in the listed liquid matrixes. The particles of magnetic phase were isolated from the suspension using centrifuge process, and then dried at 200°C. The powders isolated were studied by the methods of chemical analysis, electronic microscopy, electronography, X-ray phase analysis, infrared spectroscopy, and specific syrface of the powders and their magnetic susceptibility were estimated. The collected data is the evidence of a multiphase character of any powder produced by means of the method. All the samples are characterized by the presence of metallic iron phase ranging from16.9 до 42.2%. Moreover, the received samples appeared to have the phases of Fe_3O_4, FeOOH and iron carbides as well. The authors [24] mention that primary particles of composite are highly sintered. The size of aggregates amounts to 2 mcm. The powders produced are characterized by high specific magnetism and low coercive force. The examination of doxorubicine on nanoparticles and the study of antitumour activity of model prodrug "nanoparticle+ doxorubicine" in vitro, according to the authors, give evidence of the prospectivity of further development of magnetically operated systems of delivery of chemicals on the principle: drug — target organ in vivo.

The most important characteristic of magnetic nanoparticles is the possibility of their imaging using magnetic resonance imaging (MRI) technique, local heating by high-frequency magnetic field to initiate the mechanism of drug release [25, 26].

The presence of iron-bearing nanoparticles in an organ or tissue enables to increase significantly MR-signal. Currently, highly dispersed iron-bearing particles have been developed to examine gastrointestinal tract, lymph nodes, liver, brain, myocardium using MRI [13]. At present, highly dispersed iron-bearing particles for MR detection of tumours of various localization are commercial products [13, 27, 28].

The reports [29–31] published in online Proceedings of National Academy of Sciences introduce the data of most up-to-date innovation developments. The scientists of Harvard University and Duke University [29] have developed implantable "magnetic sponge" — a new material called macroporous ferrogel. Ferrogel contains iron nanoparticles. One can reversibly compress the "magnetic sponge" by magnetic field and control the release from the gel the therapeutic agents or cells and proteins embedded in the gel.

The report [30] represents the results of positive use of magnetic iron-bearing nanoparticles in ovarian cancer therapy. The main complicating factor in the treatment is known to be the entry of malignant cells in a female patient's abdominal cavity. And from there the cells disseminate other tissues, new masses growing, that makes cancer therapy inefficient. The authors [30] have developed highly dispersed magnetic iron-bearing particles with organic coating known as ephrin-A1-trap for ovarian cancer cells situated in ascitic fluid of the abdomen cavity. The efficiency of the suggested magnetic traps was tested on ascitic fluid taken from the mice with transferred human ovarian cancer, and on ascitic fluid taken from 4 women with ovarian cancer. The conclusion has been drawn that freely migrating tumour cells can be entrapped and removed using magnetic separation. The authors consider proven iron-bearing particles can be used in a system removing ascitic fluid from abdominal cavity, collect tumour cells by a magnet binding them with ephrim-A1, and combine such a cleaning procedure with standard ovarian cancer therapy.

The work [31] is devoted to a new medical technology called magnetic vascular intervention, a new system of drug delivery completing a medical technology already in existence — catheter stenting. The stents (thin metal frames) used in clinical practice are covered by medical coating preventing vascular occlusion due to the collection of smooth muscle cells inside the frame. However, the stents used in clinical practice are designed for single application only as they have a fixed drug dosage. According to the authors of the development, operated by magnetic field iron-bearing particles (~290 nm) with drug preparations can be delivered through a catheter and concentrated by a magnet inside a stent.

A new medical technology was approved on rats. Stainless stents were implanted in carotid arteries of the animals. After the injection of magnetic composition through a catheter, the rats were placed in a magnetic field that was 10 times as weaker compared to a magnetic field of modern MR imagers. In this case there were magnetized both: the stents and the magnetic component of the composition administered. As a result, a magnetic composition with drug preparations was concentrated and kept by a magnetized stent. The drug delivery controlled by magnetic field enables to repeat the drug administration more than once, and use several therapeutic agents to treat stented blood vessels. The possibility of magnetic concentration of drug carriers in a certain place inside a stent enables to have a more pronounced curative effect using smaller drug dosages on the whole.

The authors [17] have developed two-stage chemicometallurgical way of preparing ultra-dispersed (nanocrystalline) iron powders. The technique specifies the production of colloidal iron hydroxide (III) by the reaction: $FeCl_3+3NH_3 \cdot H_2O \rightarrow Fe(OH)_3\downarrow+3NH_4Cl$. Colloidal size of iron hydroxide (III) particles (<100 nm) and the reduction of the received raw material in the wet and raw state in hydrogen flow at comparatively low temperature (below 570°C) makes it possible to produce metallic powder in ultra-dispersed state. According to the authors, the reduction process has five stages, and each of them differs in new iron forms. The reduction is completed by the formation of nanocrystalline powders α-Fe, the mean particle size being 18–20 nm. Nanodispersed α-Fe iron powders are pyrophoric that is explained by a high degree of dispersion of the metal. Specific surface area of the fresh powder is not below 95 m^2/g. After passivation the particles are enlarged, and specific surface area of powders is 25–45 m^2/g. The comparison of the nanopowders made in laboratory and those produced under pilot-plant conditions using the same technique has shown the significant change of the characteristics of the end product. Nanopowders made in laboratory conditions have the size of particles less than 68 nm, while the size of those made in similar pilot production is 68–100 nm, the size of particles of some part of the end product being even more than 100 nm. The findings of high-resolution electron microscopy of typical iron nanoparticles (the diameter about 15 nm) testify that the particles under study have a nucleus from α-Fe surrounded by oxide capsule, about 3 nm in thickness. The thickness of the capsule does not depend on the size of a nanoparticle. Larger particles, according to the data [17], are surrounded by a capsule of the same thickness. Iron nanoparticles have cutting, and they are undersized along Z axis. Except an oxide capsule, iron particles have been found to have nanosized growths in the form of oxide nanoparticles of significantly minor sizes compared to a base particle. According to high-resolution electron microscopy, an oxide capsule and oxide growths have ferrous oxide (III) — Fe_2O_3; magnetic iron — Fe_3O_4, and ferrous oxide (II) — FeO. The monograph [17] describes the application of nanopowders produced by chemicometallurgical way in the production of high-efficiency ecologically clean biological preparations of a new generation that are widely and successfully tested in plant industry, cattle production, poultry husbandry, fish-farming, and fodder production [32–37].

Highly dispersed iron powders produced by chemicometallurgical method and by high temperature condensation technique were used in the works [38, 39] to reveal the character of the effect the iron nanopartices have on animals depending on the dose of magnetic powder. Relying on the generalized curves “dose-effect” the authors have shown that there are the spheres of growth initiating and toxic effect of iron nanoparticles. Iron nanoparticles administered in animals’ bodies in doses less by 100 times than toxic threshold, show the characteristics of biotics, i.e., initiate the animals’ growth. These particles form qualitatively different response of the body compared to other chemical iron forms. It is the authors’ opinion that the observed effects are related to the ability of iron nanoparticles to have an effect on molecular and cellular levels, as well as on byosystem level. The stated regularities of the effect of iron nanoparticles on the organism have provided the basis for developing the drugs of a new generation initiating skin regeneration processes. The researchers [38, 39] mention that when working with such powders there are some problems related to their physicochemical properties. In water suspensions nanodispersed particles are aggregated and dissolved. The presence of bioligands in aqueous medium significantly accelerates the solution process that is surely related with the formation of complex stable compounds. The administration of nanoparticles in fat matrix initiates its oxidation. The obtained data have formed the basis of developing 1% two-phase ointment with iron nanoparticles. Iron nanoparticles are brought into hydrophobic phase — vaseline oil, thereby preventing their oxidation. Hydrophilic component of the ointment is methyl cellulose-based gel. The experiments on animals have shown iron nanoparticles being a part of a two-phase ointment to maintain their bioactivity [38, 39].

Prospective scientific tendency in benign and malignant neoplasm treatment is cryodestruction. International institute of cryodestruction has been established in Austria (Vienna). Cryosurgery is characterized by local application of ultralow temperatures (up to –196°C). According to the work [40], it is the first surgical intervention in oncology that blocks the malignancy blood supply. Experiments have proved the efficacy of radical cryodestruction to depend mainly on a cycle “quick freezing (40 K/min and more) with further slow self-defrosting”. Freezing rate of the lesion is directly connected with the efficiency of cold transmission from cryoapplicator to the tissue to be frozen. Polysurface chicken skin of the lesion results in no tight mechanical contact, and therefore, no heat contact between the cryoapplicator’s surface and the frozen tissue. The problem of bringing cryoapplicator’s surface and rough, chicken skin, often keratinizing lesions into contact has been solved by developing soft magnetic liners with high heat-conducting [41]. Ointment or gel compositions with highly dispersed magnetically soft filling material can act as heat-conductive liners. Due to their soft texture, such liners can repeat the relief of the most complex shape. The saturation of pathological tissue by highly dispersed particles of magnetically soft material by injecting soft magnetic compositions into the lesion cavities and canals open form the surface, and cryodestruction in magnetic field contribute to the formation of heat-conductive canals in the volume of the frozen lesion due to the chains of magnetic particles lining up along the lines of magnetic force. Thus, the frozen lesion appears to be penetrated in depth by a peculiar heat pipeline providing an effective and quick cold transmission from a cryoapplicator over the entire volume of the tissue to be frozen.

The works [41–46] represent the results of the comparative study of magnetically soft materials — magnetite and plasma chemical iron powders and iron-carbon composite as the components of heat-conductive media for magnet cryotherapy.

Plasma chemical production of nanodispersed powders is performed in arc plasma jets. There are evaporated the micron (10–20 micron) particles of the original substance, in particular, “P-10” iron powders (GOST 13610–79) and “09-A” active carbon (GOST 4453–74). Then the vapors of the original material the with gas flow (argon) enter a condensation chamber. Due to a counter gas flow, in the condensation chamber, there a great drop in temperature providing the formation of particles, 8–17 nm in size. The authors [41–44] show that after the passivation (to avoid spontaneous inflammation of iron powders) within 4 h in nitrogen flow with oxygen concentration 1–2%, plasma chemical iron particles represent a certain composite with a metal nucleus covered by a protective oxide layer of complex mixture. The formation of a protective coating on the surface of a metal nucleus prevents the composite powders from rapid dissolving in water. The findings of X-ray phase analysis, Moessbauer and X-ray fluorescent spectroscopy give the evidence of the presence of a significant part of amorphous phases and oxide forms in plasma chemical particles of metal iron. In plasma chemical powder of iron-carbon composite, a metal nucleus is coated by a protective carbon layer preventing the particles from dissolving in water. Iron-carbon composite has four iron phases, high percentage of iron-carbon structures, and iron oxides. Microscopic estimation of plasma chemical powders has stated stable aggregates within the range of 50–300 mcm. The results of the purity assessment of plasma chemical powders of the presence of water-soluble impurities indicate the absence of the ions of sodium, potassium, iron, and chloride-, sulfate-, and nitrate ions in aqueous recoveries. When in contact with water (of room temperature), plasma chemical powders are found to have trace amounts of iron ions (III) in aqueous recoveries on the third day only. The work [44] has stated that the heat conductivity of ointment compositions with iron exceeds that of magnetite compositions. The methods of ionometry and IR-spectroscopy have proved the absence of chemical interaction of nanostructural phases of metallic iron and iron-carbon composites with the components of some ointments of industrial production. Experiments in vivo have shown great affinity of heat conducting media with iron-carbon composite for biological tissues compared to similar composites with metallic iron. There have been developed criteria and standards of quality evaluation of plasma chemical powder of iron-carbon composite as the component of heat-conducting therapeutic agents for magnetic cryodestruction of lesions.

Conclusion. The presented data is indicative of increasing interest in highly dispersed iron-bearing magnetic particles. By now, a great success is achieved in their usage for biomedical purposes, in therapy and diagnosis in vitro and in vivo. There have been developed a great variety of variants of highly dispersed iron-bearing particles production. By convention, they can be divided into two large groups: production from compact materials (vaporization–condensation, electric spark dispersion, mechanical dispersion) and chemical methods (thermal decomposition, electrolysis, low-temperature reduction of colloid particles of hydroxides). The data collection makes it possible to consider highly dispersed iron particles regardless the way of their production, as certain composites consisting of a metallic nucleus and a protective capsule of complex mixture surrounding it.

Nanochemistry of magnetic materials is one of the most revolutionary branches of modern science. The detection of extraordinary physicochemical and biological properties of nanoparticles compared to a substance macrostate has provoked keen interest in nano-objects. On the other hand, still there is no clear classification of highly dispersed particles in literature. And the terms used in literature — highly dispersed, ultra-dispersed, nanodispersed, nanocrystalline, nanostructural — are relative enough. The term “nanostructural” particles is frequently referred to an interval from 1 to 100 nm, though there are diverse judgments. For example, in the work [14] the range of nanosized particles is one order higher and ranges from 1 to 1000 nm. But at the same time, some researchers show the properties of nanoparticles, 10–30 nm in size, to differ significantly from the particles, 100 nm in size. Nanoparticles with high surface energy are prone to aggregation. In this case, we can speak about nanostructural phases that show collective properties of their components — nanoparticles.

The data collection of numerous reports in literature carries inference that there have been found leverages over the characteristics of the produced magnetic iron-bearing particles by changing their morphology: size, shape, composition, qualitative and quantitative “nucleus–membrane” relationship. At the same time, when passing from the production of laboratory variants of highly dispersed magnetic particles to their pilot production, it is not always possible to succeed in controlling the set of factors having an effect on chemical and magnetic particles of the target product, and therefore, on medical and biological importance of the produced particles. The problem of an adequate quality evaluation of highly dispersed magnetic particles remains still open.

The further manufacturing formulae development of the production of highly dispersed magnetic iron-bearing composites with tailor-made properties and the solution of their quality control problem will make it possible to introduce widely the results of current researches into clinical practice.

References

1. *Gosudarstvennaya farmakopeya SSSR*. X izdanie, stat’ya 267 [State pharmacopeia of USSR. X edition, article 267]. Moscow: Meditsina; 1968.

2. http://lekmed.ru/lekarstva/antianemicheskie/zhelezo-vosstanovlennoe

3. Kutushov M.V., Glukhoedov N.P. *Sposob polucheniya magnitoupravlyaemogo kompozita dlya biomeditsinskikh tseley* [Method of making magnetically operated composite for biomedical purposes]. Patent Rossiyskoy Federatsii №2109522 [Patent of Russian Federation No.2109522]. 1998.

4. Kuregyan A.G., Belikov V.G. *Khimiko-farmatsevticheskiy zhurnal — Chemical and Pharmaceutical Journal* 2001; 35(2): 27–34.

5. Volkov B.L., Syrkin V.G., Tolmasskiy I.S. *Karbonil'noe zhelezo* [Carbonyl iron]. Moscow: Metallurgiya; 1969; 158 p.

6. CDC Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 1998; 47: 1–29.

7. Stoltzfus R.J. Defining iron-deficiency anemia in public health terms: reexamining the nature and magnitude of the public health problem. *J Nutr* 2001; 131: 565–567.

8. Vidal-Vidal J., Rivas J., Lopez-Quintela M.A. Synthesis of monodisperse maghemite nanoparticles by the microemulsion method. *Colloids and Surfaces A: Physicochem Eng Aspects* 2006; 288: 44–51.

9. Qiu J., Yang R., Li M., Jiang N. Preparation and characterization of porous ultrafine Fe_20_3 particles, Materials Research Bulletin. *J of Materials Research Bulletin* 2005; 40: 1968–1975.

10. Petrova O.S., Gudilin E.A., Chekanova A.E., Knot'ko A.V., Murav'eva G.P., Maksimov Yu.B., Imshechnik V.K., Suzdalev I.P., Tret'yakov Yu.D. *DAN — Reports of Academy of Sciences* 2006; 410(5): 1–5.

11. Suzdalev I.P., Maksimov Yu.B., Imshechnik V.K., Novochikhin S.V., Matveev V.V., Gudilin E.A., Chekanova A.E., Petrova O.S., Tret'yakov Yu.D. *Rossiyskie nanotekhnologii — Russian Nanotechnologies* 2007; 2(5–6): 73–84.

12. Chekanova A.A., Dubov A.Z., Petrova O.S., Goodilin E.A., Eremina E.A., Maksimov Yu.V., Tretyakov Yu.D. Synsthesis and investigation of water soluble microspheres with incapsulated iron oxide nanoparticles. In: *Book of abstracts of 8-th SSC*. Bratislava; 2008; p. 216.

13. Pershina A.G., Sazonov A.E., Mil'to I.V. *Byulleten' sibirskoy meditsiny — Bulletin of Siberian medicine* 2008; 2: 70–78.

14. Dobretsov K.G., Afon'kin V.Yu., Stolyar S.V., Ladygina V.P., Sipkin A.V., Lopatin A.S. *Vestnik otorinolaringologii — Otorhinolaryngology Reporter* 2009; 2: 69–71.

15. Baranov D.A., Gubin S.P. *Radioelektronika. Nanosistemy. Informatsionnye tekhnologii — Radioelectronics. Nanosystems. Information technology* 2009; 1(1–2): 129–147.

16. Gubin S.P., Koksharov Yu.A., Khomutov G.B., Yurkov G.Yu. *Uspekhi khimii — Advances of Chemistry* 2005; 74(6): 539–574.

17. Kovalenko L.V., Folmanis G.E. *Biologicheski aktivnye nanoporoshki zheleza* [Biologically active iron nanopowders]. Moscow: Nauka; 2006; 124 p.

18. Minukhin V.V., Goncharova L.V., Levitin E.Ya., Vedernikova I.O. *Zaporozhskiy meditsinskiy zhurnal — Zaporozhian Medical Journal* 2008; 6: 89–91.

19. Arruebo M., Fernandez-Pacheco R., Irusta S. et al. Sustained release of doxorubicin from zeolite-magnetite nanocomposites prepared by mechanical activation. *Nanotechnology* 2006; 17: 4057–4064.

20. Arruebo M., Galan M., Navascues N. et al. Development of magnetic nanostructured silica-based materials as potential vectors for drug-delivery application. *Chemical Materials* 2006; 18: 1911–1919.

21. Harikrishna D., Raghavendra S.N., Venkateshwarlu Y. et al. Devarakonda β-Galactoside prodrugs of doxorubicin for application in antibody directed enzyme prodrug therapy. Prodrug monotherapy. *Arch Pharm Res* 2007; 30(6): 723–732.

22. Jie Lu., Monty Liong, Jeffrey I. Zink et al. Nanoparticles as a delivery system for hydrophobic anticancer drugs. *Small* 2007; 3(8): 1341–1346.

23. Bunatyan N.D., Uteshev D.B., Sayadyan X.C., Yavorskiy A.N. *Farmatsiya — Pharmacy* 2008; 8: 3–5.

24. Galanov A.I., Yurmazova T.A., Savel'ev G.G., Buldakov M.A., Rudyk Yu.V., Litvyakov N.V., Nechaev K.A., Tuzikov S.A., Cherdyntseva N.V., Yavorskiy N.A. *Sibirskiy onkologicheskiy zhurnal — Siberian Journal of Oncology* 2008; 3(27): 50–57.

25. Leary S.P., Liu C.Y., Apuzzo M.L. Toward the emergence of nanoneurosurgery. Part II. Nanomedicine: diagnostics and imaging at the nanoscale level. *Neurosurgery* 2006; 58: 805–823.

26. Hofmann A., Wenzel D. et al. Combined targeting of lentiviral vectors and positioning of transduced cells by magnetic nanoparticles. *Proc Natl Acad Sci (USA)* 2009; 106: 44–49.

27. Berry C., Curtis A. Functionalisation of magnetic nanoparticles for application in bio-medicine. *J Phys D Appl Phys* 2003; 1: 36.

28. Bonnemain B. Superparamagnetic agents in magnetic resonance imaging: physiochemical characteristics and clinical applications — a review. *J Drug Target* 1998; 6: 167–174.

29. http://www.nanonewsnet.ru/news/2010/

30. http://www.lifescieneestoday.ru/index.php/nanotechnologii-v-medicine

31. http:// www.medlinks.ru/article.php?sid=40776

32. Gorshkov M., Musatova V., Kovalenko L.V. et al. *Ptitsevodstvo — Poultry industry* 2000; 2: 36–40.

33. Kovalenko L.V., Pavlov G.V., Folmanis G.E., Vavilov N.S. *Doklady RAN — Reports of RAS* 1998; 360: 571–573.

34. Kovalenko L.V., Folmanis G.E. *Dostizheniya nauki i tekhniki APK — Achievements of science and technological advances of agro-industry* 2001; 9: 7–8.

35. Zorin E.V., Folmanis G.E. *Sakharnaya svekla — Sugar beet* 2001; 5: 16–17.

36. Kovalenko L.B., Folmanis G.E. *Sakharnaya svekla — Sugar beet* 2000; 4/5: 20.

37. Vinogradova D.L., Malyshev R.A., Folmanis G.E. *Ekonomicheskie aspekty primeneniya nanotekhnologiy v zemledelii* [Economic aspects of nanotechnology utilization in agriculture]. Moscow: Issled. tsentr problem kachestva podgotovki spetsialistov; 2005.

38. Glushchenko N.N., Baytukalov T.A., Bogoslovskaya O.A., Ol'khovskaya I.P., Arsent'eva I.P., Folmanis G.E. Dispersnye nanosistemy — osnova ranozazhivlyayushchikh sredstv. V kn.: *Vseros. nauch.konf. «Fiziko-khimicheskie i prikladnye problemy magnitnykh dispersnykh nanosistem»* [Disperse systems is the base of wound healing substances. In: All-Russian Scientific Conference "Physical and Chemical and Applied Problems of Magnetic Disperse Nanosystems"]. Stavropol; 2007; p. 237–241.

39. Baytukalov T.A. *Fiziko-khimicheskie osobennosti ranozazhivlyayushchikh svoystv nanochastits zheleza i magniya v sostave razlichnykh polimerov.* Avtoref. dis. … kand. khim. nauk [Physical and chemical characteristics of wound healing properties of iron and magnesium nanoparticles as part of different polymers. Abstract of Dissertation for the degree of Candidate of Chemical Science]. Moscow; 2006.

40. http://www.medicine-service de/clinics/crio.html

41. Shabalkina E.Yu. *Nanodispersnye magnitomyagkie materialy kak komponenty teploprovodyashchikh sred dlya magnitokriovozdeystviy*. Avtoref. dis. … kand. farm. nauk [Nanodisperse magnetically soft materials as components of heat conducting media for magnetic cryotherapy. Abstract of Dissertation for the degree of Candidate of Pharmaceutical Science]. Moscow; 2010.

42. Kochenov V.I., Tsybusov S.N., Cherkasova O.G., Shabalkina E.Yu. Magnitnye lekarstvennye sredstva v kriokhirurgii opukholey. V kn.: *12-ya Mezhdunarodnaya Plesskaya konferentsiya po magnitnym zhidkostyam. Sb. nauch. trudov.* Ples, Rossiya [Magnetic pharmaceuticals in tumour cryosurgery. In: 12th International Plyos conference on magnetic liquids. Collection of scientific papers. Plyos, Russia]. 2006; p. 431–433.

43. Shabalkina E.Yu., Cherkasova O.G., Matyushina G.P., Gribanova S.V., Kharitonov Yu.Ya., Krasnyuk I.I., Mochikina O.A., Kochenov V.I., Tsybusov S.N. Prigotovlenie i issledovanie magnitnykh kompozitsiy s nanodispersnym zhelezo-uglerodnym poroshkom na gidrofil'nykh osnovakh dlya magnitokriotonzillektomii. V kn.: *Vseros. nauch. konf. «Fiziko-khimicheskie i prikladnye problemy magnitnykh dispersnykh nanosistem»* [Preparation and research of magnetic compositions with nanodisperse iron-carbon powder on hydrophilic bases for magnetic cryotonsillectomy. In: All-Russian Scientific Conference "Physical and Chemical and Applied Problems of Magnetic Disperse Nanosystems"]. Stavropol; 2007; p. 59–62.

44. Shabalkina E.Yu. *Farmatsiya — Pharmacy* 2009; 4: 9–11.

45. Shabalkina E.Yu. *Farmatsiya — Pharmacy* 2008; 5: 57–60.

46. Shabalkina E.Yu., Cherkasova O.G., Kochenov V.I., Tsybusov S.N., Kharitonov Yu.Ya., Arzamastsev A.P. *Nizegor Med Z — Nizhny Novgorod Medical Journal* 2008; 4: 55–60.