MODIFICATION OF SURFACE OF FINELY DISPERSED MAGNETIC POWDERS WITH THE PURPOSE TO CREATE MEDICAL MATERIALS

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Processes of production of cross-linked polyacrylamide and dextran coating on the FDIP – (finely disperse iron powders) surface have been studied with the use of complex of physical and chemical methods of IR-, XPE-spectroscopy and X-ray phase analysis. While forming a polyacrylamide layer on the FDIP surface in photopolymerisation reaction, a process occurs concurrently which leads to ion-radical forms of oxygen adsorption on magnetic particles, that is manifested in IR spectrum by an intense doublet of bands is 1080 and 1120 cm^{-1}, as well as a transfer of proton of hydroxyl groups of the FDIP surface to a nitrogen atom of polyacrylamide, that is due to appearance of the component 401.0 eV in XPE spectrs of N1s-photoelectrons, corresponding to a NH^+ group. During production of the coating of cross-linked dextran on the FDIP surface it was found a formation of complex between ions of iron locating on an outer surface of the stabilizing coating having oxygen-containing groups of the dextran coating, that is supported by a shift of absorption bands of oxygen-containing groups into a long-wave number region, as well as emergence of two new components with bond energies of 709.2 and 712.2 eV in XPE spectruum of Fe2p-photoelectrons.

Directed delivery and distribution of anaesthetics (novocaine, lidocaine, trimecaine) immobilized on FDIP under the influence of an external magnetic field in body tissues of test animals have been studied. The data of emission spectral analysis relating to concentration of iron in soft and bone tissues of animals influenced by constant and alternating magnetic field on the front and rear sides over a period from 0 to 180 min are given.

A guided transport of drugs presents one of actual problems of modern magnetopharmacology since it allows to create the concentration of a medicinal preparation necessary for a curative effect in a certain body part, while its dose introduced is low, that makes it possible to improve a curative action sufficiently, to decrease a toxico-allergic reaction of the body; this expands possibilities of using efficient medicinal preparation with a high specific toxiacity [1-2].

Magneto-guided drugs that are designed to be introduced into blood, must represent a suspension of magnetic biocompatible particles with a size of 1-2 nm composed of a magnetic component, matrix, or a coating of a synthetic or natural polymer, and a drug involved in matrix pores or chemically immobilized on it [3].

A local accumulation of magnetic carriers in pre-selected area of the body is supposed to carry on by means of external sources of magnetic field of a respective strength and definite gradient.

FDIP (finely disperse iron powders) were produced by the Natanson method [3] through cathodic electro reduction of ferrous salts from aqueous solutions, with transfer of the resulting crystals into an organic layer containing a stabilizer, where oleic acid was used as such and a modifying additive - an unsaturated alcohol, isophitol. Previously, we have found , that a chemisorbed oleic acid on the FDIP – surface is preferably in ionized form developing by symmetric (ν_s = 1445 cm^{-1}) and asymmetric (ν_{as} = 1550 cm^{-1}) stretching vibrations of COO^- fragments in IR-spectra. The frequency difference $\Delta\nu = \nu_{as} - \nu_s \cong 100$ cm^{-1} is the evidence that a chelate bidentate structure of carboxylate complexes of $(R–COO^-)Fe$ is realized on the FDIP surface. Isophytol, having a lower surface tension (23,0 dynes/cm) compared to that of oleic acid (32,5 dynes/cm) mainly, in an outer layer of the stabilizing coating in process of a competitive adsorption.

FDIP are asymmetric dendrites with the specific surface area of 20 m^2/g, that is estimated by a thermal desorption of argon, and with particle size of about 200-400nm.

IR-spectra of initial and modifying FDIP were recorded by IR-Fourier- spectrometer "Perkin-Elmer", model 1720X, and M-80 Karl-Zeis-Jena in the 400–4000cm^{-1} region. Transmission in the region of 2000 cm^{-1} was ~ 5-10%. Content of the modifying coating in the FDIP surface was estimated by analyzer for C,H,N of "Perkin-Elmer". X-ray photoelectron spectra were obtained with spectrometer ES-2401 using K_α radiation of magnium anode. Calibration of the spectrometer was made by Au line of $4f_{7/2}$ electrons of bond energy E=84,0 eV.

The samples for registration were fixed by a sticky tape. UV_{0-0} spectra were recorded with instrument UV-VIS. A coercive force of magnetic powders was determined by a ballistic method.

1. Study of polyacrylamide formation process on FDIP surface

Polyacrylamide (PAA) coating on the FDIP surface was prepared using the reaction of photopolymerisation of acrylamide and N,N^1–methylene-bis-acrylamide in the glycerol solution [4-5] (Table 1), by means of initiator of riboflavin, thet was adsorbed preliminary onto the surface of magnetic particles.

Table 1
Composition and magnetic characteristics of FDIP-polyacrylamide particles

№	Weight content of components %		Coersife forse A/m	Elemental composition of polyacrylamide shell weight %			
	FDIP	Cross-linked PAA		C	H	N	O
1	97.03	2.97	1270,0	0,51	0,21	0,58	0,67
2	95,00	5,00	1197,0	2,54	0,35	0,98	1,13
3	93,58	6,48	1117,0	3,28	0,46	1,28	1,46
4	90,00	10,00	1120,6	5,08	0,70	1,97	2,25
5	85,80	14,20	780,0	7,20	1,00	2,80	3,20

Fig. 1 shows the IR-spectrum of riboflavin and the differential IR-Fourier spectrum which was obtained as a result of subtraction of the spectrum of the initial FDIP from the IR-Fourier spectrum of FDIP from the IR- Fourier spectrum of FDIP – riboflavin, respectively. The difference IR spectrum displays a number of absorption bands typical of riboflavin: 460, 1020, 1067, 1500, 1580, 1650, 1730 cm^{-1}, etc., there occurs a physical sorption of initiator in FDIP surfaces. Position of some bands are somewhat different than those in the IR spectrum

of the initial riboflavin whet can be explained by the fact that coming into adsorption force field of the FDIP surface, a riboflavin molecule forms new intermolecular bonds differing from associates in the starting state.

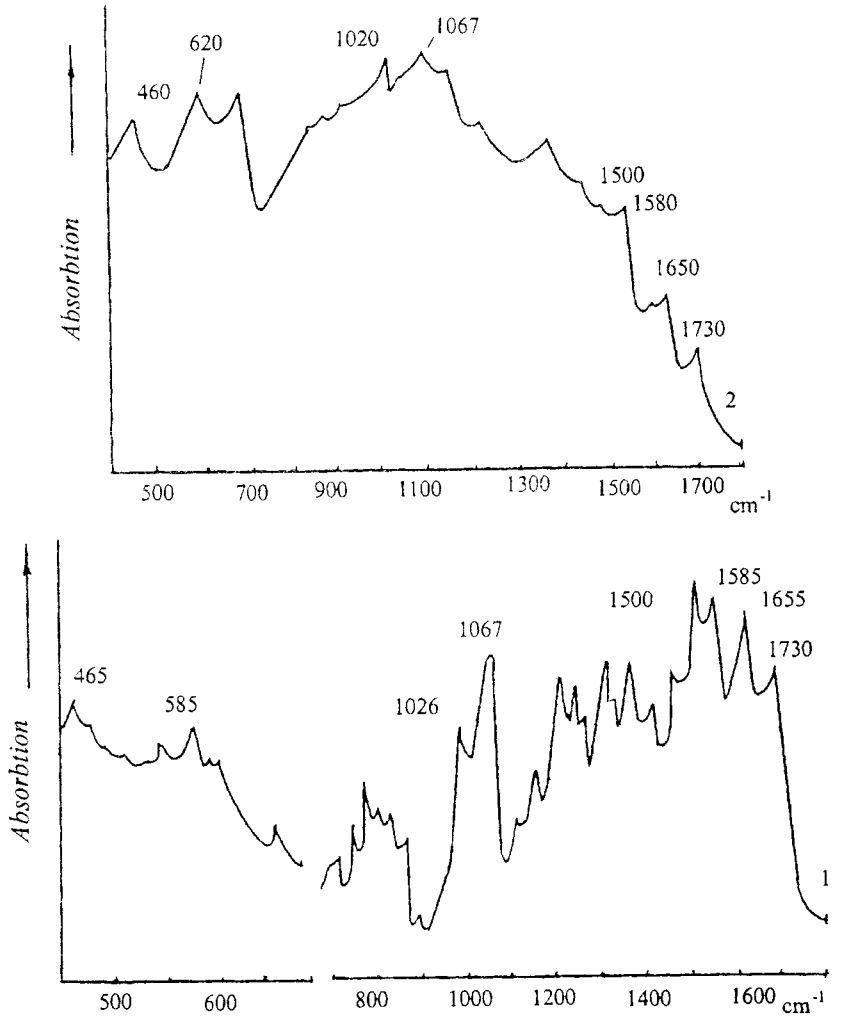


Fig.1. IR-Spectrum of riboflavin (1) and a differential IR-Fourier spectrum (2). Tablets with KBr.

Figure 2 gives vibrational spectra of the initial FDIP (spectrum 1) and FDIP-PAA-particles (spectrum 2). The band of 3428cm^{-1} in the IR spectrum of initial FDIP corresponds to stretching vibrations of the surface OH groups associated with H-bond and stretching vibration of molecules of water adsorbed by the FDIP surface. The absorption band of water adsorbed by KBr crystallites was compensated at the expense of positioning the same pellet in the reference channel. The 2851 and 2922 cm^{-1} bands characterize symmetric and antisymmetrical stretching vibrations of CH_2 groups of the stabilizing coating; the 1710 cm^{-1} band refers stretching vibrations of a carbonyl group of oleic acid, thet is free of H-bonds; absorption at 1620 cm^{-1} relates bending vibrations of water adsorbed by the FDIP-surface;

absorption bands of 1445 and 1550 cm^{-1} are assigned to symmetric and antisymmetric stretching vibrations of COO^- fragments [6]; a diffuse absorption band of 1050 cm^{-1} is assigned to stretching vibrations of Fe—OH [7].

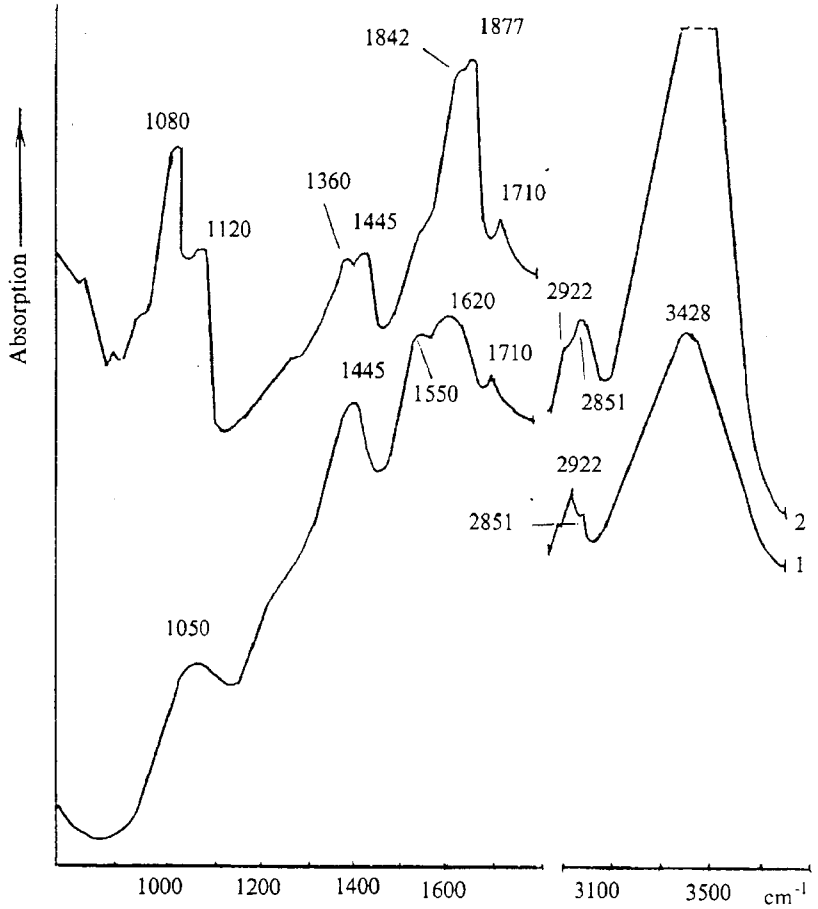


Fig.2. IR-Fourier spectrum initial of FDIP (1) and FDIP- polyacrylamide particles (2). Tablets with KBr.

A series of bands attributed to vibrations of modificator groups appears in IR spectrum of FDIP with a PAA coating. The intense absorption band 1677 cm^{-1} characterizes stretching vibrations of the C=O amide groups; the low frequency shoulder of this band at 1642 cm^{-1} in assigned to bending vibrations of NH_2 groups of polyacrylamide [6]. The bands of 1360 and 1445 cm^{-1} are assigned to symmetric and asymmetric bending vibrations of CH_2 groups.

The absorption band of a low intensity that exists usually in the IR spectrum of polyacrylamide at 1130 cm^{-1} and corresponds to C—N deformation vibrations of amide group is overlapped in the given case by an intense doublet of bands of 1080 and 1120 cm^{-1}. In this region, vibrations of Fe—N must also be developed [7-8]. According to ref. [9], frequencies of a symmetric deformation vibration of ammonia adsorbed onto hematite with formation of coordination Fe—N bond are of low intensity and lie in the 1150-1280 cm^{-1} region. The strong doublet of bands which we observed in the IR spectrum has a somewhat an other position (1080 and 1120 cm^{-1}). These bands are assigned to vibrations of oxygen O—O in its ion-radical forms [10]. Taking into account, that the stabilizing coat on the FDIP represents

carboxylate complexes of Fe^{+2} and Fe^{+3} of oleic acid, photosorption of oxygen will occur on ions of iron of the stabilizing coat. In doing so, by analogy with data in ref. [10], the band of 1080 cm^{-1} is due to O—O bond in ion-radical of O_2^- stabilized in Fe^{+2}, and that of 1120 cm^{-1} characterizes vibrations of the O—O bond in ion-radical of O_2^- stabilized on Fe^{+3}.

Riboflavin adsorbed on the surface and that we used as photoinitiator, can initiate also photodextruction of water molecules [11] adsorbed on the surface of magnetic particles, that will make an additional contribution into photosorption processes, occurring on surface of magnetic particles.

A peak of C1s in X-ray photoelectron spectrum (XPS) of the initial FDIP is multicomponent (Fig.3): it contains maxima assigned to photoelectrons of the groups of stabilizing coating [12]. A maximum with E_{bond}=285 eV relates to CH groups 286.5 eV belong to the groups having C—O bond, 288.6 eV to C=O groups 289.6 eV characterizing COO^- groups. Two peaks are present in the O1s spectrum. The peak belonging to bond energy of 530.8 eV refers to oxygen atoms in a cordinational sphere of Fe atom, the maximum of 532.7 eV belongs to oxygen in organic fragments of the stabilizing coating.

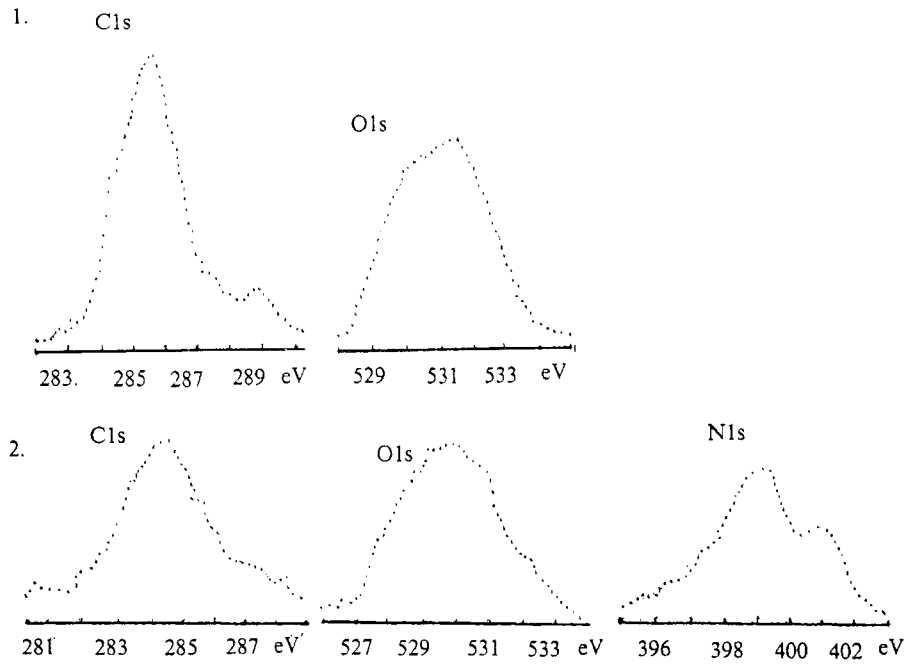
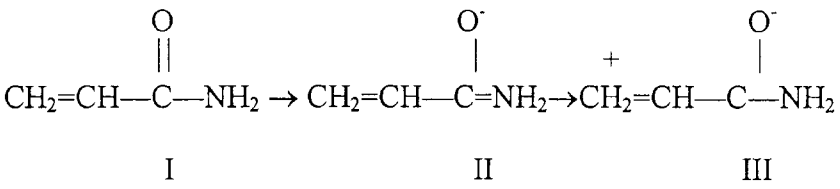


Fig.3. XPS-spectrum of the initial FDIP (1) and FDIP-polyacrylamide particles (2).

Fig.3 shows the XP-spectrum of FDIP-PAA particles, and Table 2 gives XPS data on the surface of initial FDIP and PAA-modified coating. The main peak is 284.0 eV in the spectrum of C1s photoelectrons that differs from the band of C1s photoelectrons for the initial powder of iron, i.e. the layer to be analyzed is, mainly, a coating of PAA on a FDIP surface. Signals of N1s photoelectrons are recorded in the XP- spectrum of FDIP modified by polyacrylamide, that is an evidence of nitrogen present in the examined coating. The spectrum of N1s photoelectrons is complicated: it consists of two components having bond energies of 399.0 and 401.3 eV. The main peak 399.0 eV belongs to N1s photoelectrons of nitrogen atoms in structure of polyacrylamide amino groups and the peak at 401.0 eV composing 0.3 of the total spectral area characterizes protonated amino groups of polyacrylamide (NH^+),

their appearance seems to be due to a proton transfer of the surface hydroxyl groups towards a nitrogen atom of PAA. During synthesis when molecules of acrylamide monomer penetrate into outer surface of the stabilizing coating, its coordination is made possible both by oxygen and nitrogen [13]. While complex is formed though an oxygen atom, a shape (II) is the most preferred,



I II III

whereas structures (I) and (III) have to take place for coordination of N.

Table 2
X-ray-photoelectron characteristics of the FDIP and FDIP-polyacrylamide particles

Sample	C1s		O1s		Fe2p		N1s	
	E_{bond}, eV	%	E_{bond}, eV	%	E_{bond}, eV	%	E_{bond}, eV	%
FDIP initial	283.8	17	530.2	56	711.0			
	285.0	54	531.7	44				
	286.5	11						
	288.6	6						
	289.6	6						
FDIP with PAA coating	282.4	9	529.0	16	711.7		399.0	60
	284.2	55	530.0	75			401.0	40
	286.0	24	531.7	9				
	288.0	8						
	289.7	4						

The formation of a resonant structure (II) does not occur, since no significant changes in stretching frequencies of C=O, C—N, and NH linkages are observed. Perhaps, a proton transfer surface hydroxyl groups to nitrogen atom makes a general contribution to appearance of NH_2^+ groups in polymeric layer that is supported by the XP-spectrum.

Thus, it has been shown that as a result of photopolymeryzation reaction of acrylamide, using riboflavin as initiator, there is formed a biocompatible polyacrylamide coating on the FDIP surface that can act as a capacious and efficient container of drugs with a varied spectrum of action.

2. Spectroscopic study of production process of biocompatible coating from cross-linked dextran on surface of finely disperse powdered iron

Dextran belongs to polysaccharides [14], it is produced by technique of a microbiological synthesis; the major molecular chain of dextran consists of anhydo-D-glucopiranose cycles linked, preferably with α-1.6-glicoside bonds.

In addition to α-1.6-glicoside bonds in macromolecules of various preparations of dextran, these may contain a different quantity of α-1.2, α-1.3, or α-1.4-glicoside bonds, with aid of which there is accomplished usually addition of side chains to the major chain.

To prepare the biocompatible coating of a cross-linked dextran, it was used dextran from the firm "Polfa" (mol. weight 70000) and polyglukin (dry, technical, an average mol. weight 55000). Synthesis of iron-dextran particles was effected by means of emulsion polymerization [15]. As a cross-linking reagent there was used epichlorohydrine 2.4.6-trisdimetylaminometylphenol as an and initiator of polymerization, [16]. A hydrolytic stability of resulting micro particles was estimated by leaching dextran out of composition of iron-dextran particles into a solution after agitating of some amount of the sample with a phosphate buffer (pH 8.5) for an hour and centrifuging the suspension while measuring the concentration of dextran in a supernatant liquid by a formation of a stained complex with anthrone (keto-derivate of 9-hydroxy-anthracene) in a medium of a concentrated sulphuric acid for λ_{max}=625 nm.

Table 3 presents physical-chemical properties of the starting FDIP and FDIP-dextran particles, which differ from each other by duration of synthesis: 2-0.5 hr, 3.4-1 hr, 5.6-2 hr.

In the IR spectrum starting dextran [17] a strong absorbtion band in the range of 3100-3600 cm^{-1} is due to stretching vibration of OH group's dextrane, associated with H-bonds. A broad band with a main maximum at 2920 cm^{-1} characterizes stretching vibrations of CH groups. The 1650 and 1420 cm^{-1} bands shold be assigned to bending vibrations of molecules of the absorbed water and to internal bending vibration of methylene groups. The absorbtion in a region of about 1200-1400 cm^{-1} is due to external bending vibrations of methylene groups and CH groups as well as to planar vibration of hydroxyl groups of dextran [17-18].

Stretching vibrations of C—O and C=C pyranose rings, glycoside bond of C-O radical and spinning vibrations of CH_2 groups are developed in the 950-1200 cm^{-1} region. The most intense bands in this region are assigned to vibrations of a C-O bond of pyranose rings. Adsorption band in the range of 700-950 cm^{-1} characterizes equatorial (E) and axial (A) CH-groups, according to which a conformational analysis of dextran chain is performed usually. An amorphous dextran has a structural form EAAAA, that indicates conformation of C_1, that is developed in IR spectrum by the presence of bands at 758, 844, 912 cm^{-1}. A broad diffuse band in the low frequency region (400-600 cm^{-1}) is due to out of plane bending vibrations of hydroxyl groups and to obertone of hydrogen bonds. The absorption bands themselves, belonding to stretching and bending vibrations of H-bond, are displayed in the far IR spectral region (100-200 cm^{-1}).

Table 3
Composition in Physicochemical Properties of Parent FDIP and FDIP-Dextran Particles

№	Type of speciments	Elementary analysis		Specific surface area	Coercitiv energy
		C, % by weight	H, % by weight	S, m^2/g	H_c, kA/m
1	Initial FDIP	5.79	1.37	11.0	25.8
2	FDIP-dextran particles	6.75	1.20	7.3	62.5
3		7.90	1.36	2.7	77.6
4		8.33	1.42	5.9	57.2
5		17.40	2.51	6.2	64.1
6		26.90	4.70	7.3	9.44

Authors [18-20] have performed calculation of conformations and frequencies of normal vibrations and their intensity, developing in the IR spectrum, on model compounds contaming a hexapiranose cycle with different substituents.

During formation of the polymer coating of a cross-linked dextran, there takes place realization of intermolecular interactions between proton-donating groups of dextran and a stabilizing coat of FDIP. In addition, oxygen-containing groups of dextrane can take part in formation of complexes in the interface: a stabilizing FDIP coating – a cross-linked dextran. The authors [21] have shown that ferrous oxides as well as oxyhydroxides of iron (III) were able to form iron-polysaccharide complexes.

The absorption bands appear in the IR spectrum of FDIP-dextran particles, that characterize vibrations of groups of the modifying coating. Of special interest for studies was the IR-spectral region of FDIP-dextran particles, that recorded vibrations of oxygen-containing groups capable of forming complexes with oxides and ions of iron, existing in the FDIP surface, as well as with ferrous ions of the stabilizing coating [22]. For a more detailed study of the spectra obtained, it was applied the method of numerical differentiation (ND) of contours of absorption bands [23]. Figure 4 gives fragments of IR spectra of the cross-linked dextran (1) and FDIP-dextran particles (2), and their second derivatives (1' and 2'), respectively.

The 900-1200 cm^{-1} absorption bands are due to stretching vibrations, ν(C-O), of a piranose cycle, a glicoside oxygen as well as to C—C skeleton vibrations of a pyranose cycle and other vibrational modes [23]. Comparing the IR spectra of cross-linked dextran and FDIP-dextran particles and their second derivatives, one can observe a shift of absorption band in the IR spectrum from 998 to 1013 cm^{-1}, as well as appearance of a 1121 cm^{-1} component on a shoulder of the 1109 cm^{-1} band that may be due to formation of complexes between ferrous ions of the stabilizing coating and oxygen containing groups of the cross-linked dextran. The definite contribution into changes in IR spectra is made by a different character of intermolecular interactions, in particular, realization of hydrogen bonds in the cross-linked dextran and FDIP-dextran particles.

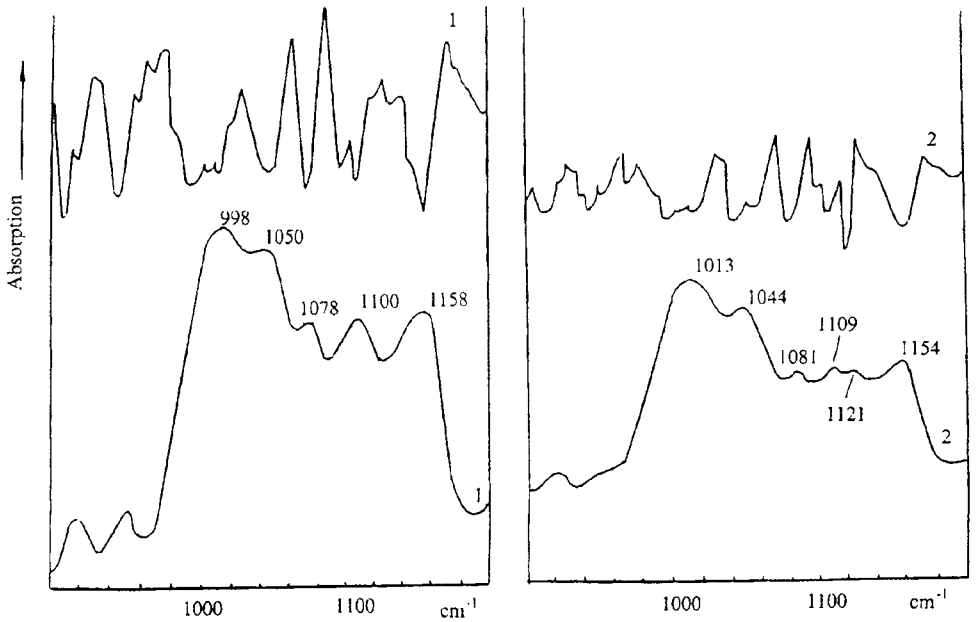


Fig.4. IR-spectrum of the cross-linked dextran (1) and FDIP-dextran particles (2), as well as their second Derivatives (1)1 and (2)1, respectively. Tablets with KBr.

The starting FDIP has a cubic face-centered α-structure of iron with interplanar distances of a=2.02Å. Also, an oxide film of Fe_3O_4 is formed on the FDIP surface having interplanar distances of 2.53Å. Difractogram of the cross-linked dextran (fig. 5, curve 1) has an amorphous halo at 22^0. A shoulder near 18^0 emerges in diffractogram of FDIP-dextran particles (fig 5, curve 2). The appearance of the additional component on the diffractogram is due to formation of complexes with ferrous ions present on the outer surface of the stabilizing coating, with oxygen containing groups of the cross-linked dextran.

The starting FDIP and FDIP-dextran pafticles were ivestigated by the XPS technique (Table 4 , fig. 6). C1s-spectrum of the original iron powder is multicomponent one. It contains peaks responsible for photoelectrons of groups of the stabilizing coating [12]: maximum with E_{bond}=283.2; 286.0; 288.6 and 289.8 eV refer to CH groups and groups including C—O, C=O and COO^- bonds, respectively. Two peaks are present in the O1s spectrum. The peak assigned to the binding energy 530.8 eV, may be attributed to oxygen atoms in a coordination sphere of iron, and the peak at 532.7 eV belongs to oxygen in organic fragments of the stabilizing coating. Photoelectron signals responsible for components of groups of the modyfing coating are registered in XPS spectra of modified samples of FDIP (Table 4, fig 6). In O1s spectrum, signals of photoelectrons responsible for components of groups of the stabilizing coating are absent in fact that is the evidence that the layer to be studied represents the cross-linked dextran.

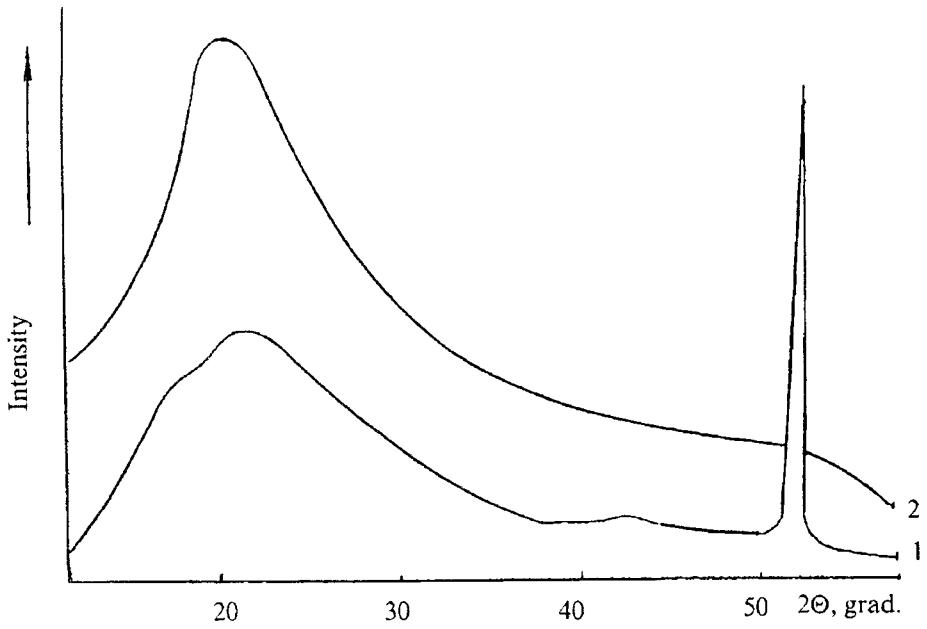


Fig.5. Diffractograms patterns of FDIP-dextran particles (1) and the cross-linked dextran (2).

Table 4
X-ray Photoelectron Characteristics of the Surface of Initial FDIP and FDIP-Dextran particles

Specimen	C1s		O1s		Fe2p	
	E_b, eV	Rel.%	E_b, eV	Rel.%	E_b, eV	Rel.%
Initial FDIP	283.2	17	530.8	56	711.0	
	285.0	54	532.7	44		
	286.5	11				
	288.6	6				
	289.6	6				
FDIP-dextran particles	284.0		531.2	20	709.2	
	285.0	59	533.0	64	711.4	
	286.5	18	534.5	16	712.2	
	288.0	8				
	289.2	4				

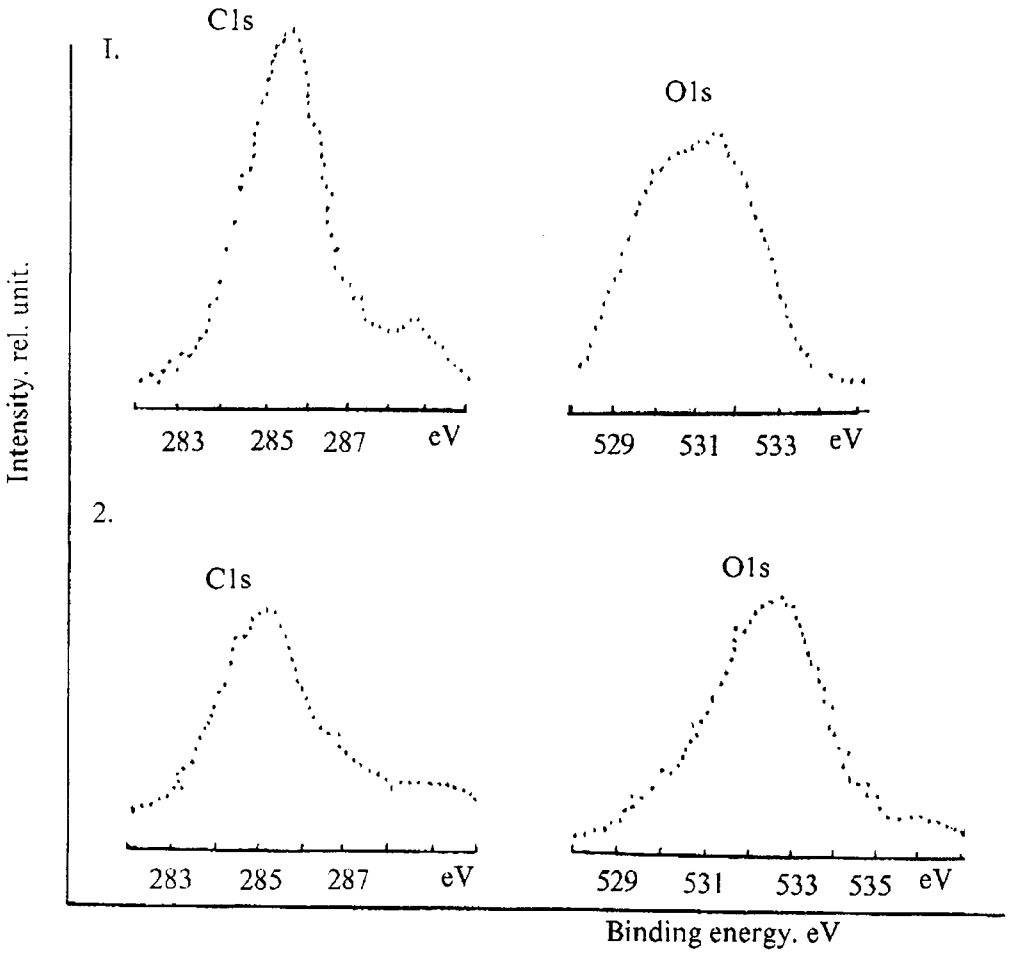


Fig.6. XPS-spectrum of the initial FDIP (1) and FDIP-dextran particles (2).

Essential differences are observed in XPS spectra of Fe2p-photoelectrons of the original FDIP and FDIP-dextran particles (Table 4). In the original FDIP it is registed one peak of binding energy 711.0 eV responsible for carboxyl complexes of iron, while for FDIP-dextran particles we observe additional two components with binding energies of 709.2 and 712.0 eV, that confirms a formation of iron complexes on the outer surface of the stabilizing coating with oxygen containing groups of dextran.

Thus, the use of complex of physicochemical methods has shown, that a polymer coating of a cross-linked dextran was forming on the FDIP surface. It was found that oxygen-containing groups of the cross-linked dextran formed complex with ferrous ions locating on the outer surface of the stabilizing coating of FDIP that was manifested by a shift of absorption bands of oxygen containing groups into the long-wave region, by appearance of two components with bond energies of 709.2 and 712.2 eV in XPS spectra of Fe2p photoelectrons, and by distortion of structure of amorphous dextran.

3. The Distribution of Anaesthetics Immobilised in Finely Disperse Iron Powders, in the Body of Experimental Animals

The problem of the directed transport of drugs in the body to target organs has remained highly topical in the last 10-15 years [1,2,24,25]. One way of solving this problem is to use magnetically controllable carriers with the aid of external sources of magnetic field. As a rule, the magnetic component used a highly dispersed metallic iron or its oxides and, as biocompatible matrix, proteins or polysaccharides [26-28]. In [29] magnetic albumin microspheres of diameter 1-2 μm containing 80% magnetic microcarrier and 20% form-shaping components were devised, which included the drug substance (adriamicin, mitomycin, 5-fluorouracil [27], etc.). In [30] investigations concerned with developing methods and forms of the magneto-controlled behaviour of antitumour preparations in experiments on laboratory animals and in [31] antibiotics,etc. are reviewed.

Ferromagnetic particles and suspensions themselves, without the drug,display high biological activity when introduced into the animal body [32]. With regard to the results of exposure of the living body to a magnetic field, it is well known [31] that it lengthens the lifespan of the test animals and inhibits the growth of various experimental tumours. The introduction of finely disperse metal powders, including iron, into the animal body for therapeutic purposes was examined in [33]. An important problem is the distribution of the ferromagnetic material in the organs and tissues and also the pathways for its conversion and the dynamics of its elimination from the body. In [34] the atom-adsorption method was used to study the change in the iron content of the animal organs after intraperitoneal administration of ultradisperse magnetic particles based on magnetite and FDIP over a period of 14 days. The greatest tropicity for magnetic colloids was displayed by the liver and spleen.

The aim of the present paper is to report the results of a study of the ability of a medicinal substance, immobilized on FDIP, to enter in directed form and deposit itself at the focus of pathology under the influence of a magnetic field. We studied the distribution of iron introduced intraperitoneally into the body of the experimental animals in the form of an aqueous suspension of FDIP and a drug – anaesthetic in the soft and bone tissues of the animal as a function on the time of exposure to contact (CMF) or alternating (AMF) magnetic filds on the front or rear side of exposure.

For the investigation we employed emission spectral analysis [35] and used drugs (novocaine, lidocaine and trimecaine) applied through adsorption from aqueous solutions to the surface of the highly iron powders. The FDIP were obtained by an electrolitic method which we modified, the natural polysaccharide dextran serving as biocompatible cover [14].

The experiments were conducted on guinea pigs weighing up to 250g and white mice weighing up to 40g. All the animals were divided into four groups: one group was the control

and the following three FDIP-dextran-novocaine (FDIP-D-N), FDIP-dextran-lidocaine (FDIP-D-L) and FDIP – dextran-trimecaine(FDIP-D-Tri). Each sample containing one drug and intended for a series of experiments contained up to 85% FDIP, 12% medicinal substance and 3% dextran or 10 mg of anaestetic per ml of suspension.

The animals of each group were divided into two subgroups, depending on the type of magnetic fields – CMF (induction 33-5 mT) and AMF (induction 30-7,5 mT). The time of exposure to the magnetic fields was 0-180 min. The ferromagnetic suspension was administered to the animals intraperitoneally in an amount of 0,1 ml for mice and 0,5 ml for guinea pigs, i.e. 25 mg/kg weight, respectively. The animals were placed at a distance of 15 cm from the magnetic field source, for which we used a Polyus–1 apparatus for magnetotherapy with a continuous mode of operation. At the end of a defined exposure time to the magnetic fields, the animals were decapitated under ether anaestesia.

To investigate the amount of ferromagnetic material accumulated in the tissues, we isolated the following sections: 1) the soft tissue of the front limb; 2) the soft tissue hind limb; 3) the soft tissue of the lateral surface of the abdomen; 4) the bone tissue of the front limb; 5) the bone tissue of the hind limb; and 6, the bone tissue of the mandible. In each case we investigated the tissues on the side of exposure to the magnetic field (the front) and on the rear side (the rear). Portions of the tissues were reduced to ash in a muffle furnace at a temperature of 500°C for 1h. The ash residue in a mixture with spectrally pure graphite powder was combusted in an alternating current arc. Then, using an SP-3 spectrograph (Carl Zeiss Jena, Germany), we photographed the spectra of the samples and alongside them the scale and spectrum of iron. In each spectrum we photometered the iron line (α=3020,5 Å) and the calcium line (λ =3159Å). The quantitative iron content in the portions of tissues exposed to the magnetic field was determined from the formula:

$$Fe = \frac{PFeBPCaA - PFeAPCaB}{PCaBPCaA}$$

where PFeB and PCaB are the optical density of the iron line or the calcium line, respectively, in the spectra portions of tissues exposed to the magnetic field, and PFeA and PCaA are the same for tissues not exposed to it. The results are shown in Figs 7 and 8 and Tables 5 and 6. As follows from the figures, the maximum accumulation of iron in the tissues occured within 30-60 min. of the start and then the amount of accumulated iron either stabilized throughout the observation period or fell. Table 5 presents the results referring specifically to the times of 30-min and 60-min exposure to the magnetic field.

A comparative analysis on the front side of exposure (fr) to the CMF and AMF (30 min and 60 min from the start, Table 5) shows that for tissues Nos 1, 2, 5, 6 a far greater effect was observed on exposure to the CMF and for tissues Nos 3 and 4 on exposure to the AMF. The results of the CMF and AMF exposures on the rear side (rear) differed: on exposure to the CMF for the particles with novocaine and trimecaine larger values were observed for nearly all the tissues, while in the case of lidocaine larger values were obtained on exposure to the AMF (Table 5).

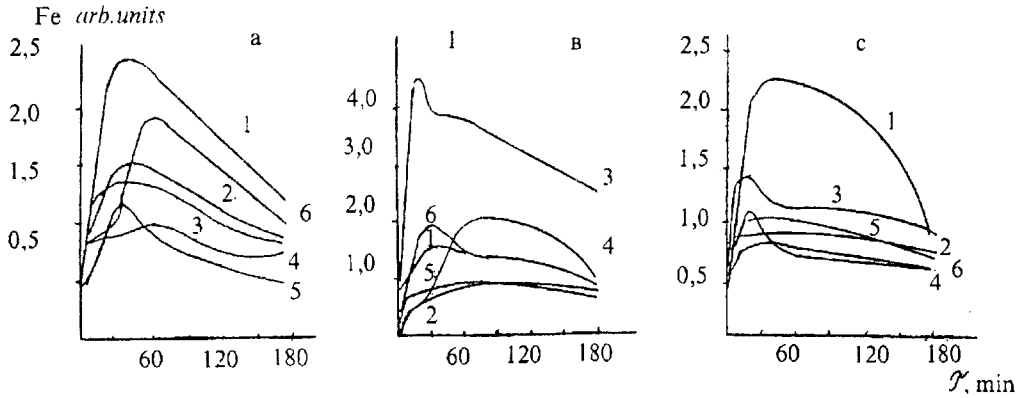


Fig.7. Change in the iron content of the tissues of the living body after administration of FDIP-D-N (a), FDIP-D-L (b), FDIP-D-Tri (c) and the action of the CMF on the side of exposure (fr.) . In Figs 8 and 9 the numbers on the curves correspond to the tissue numbers.

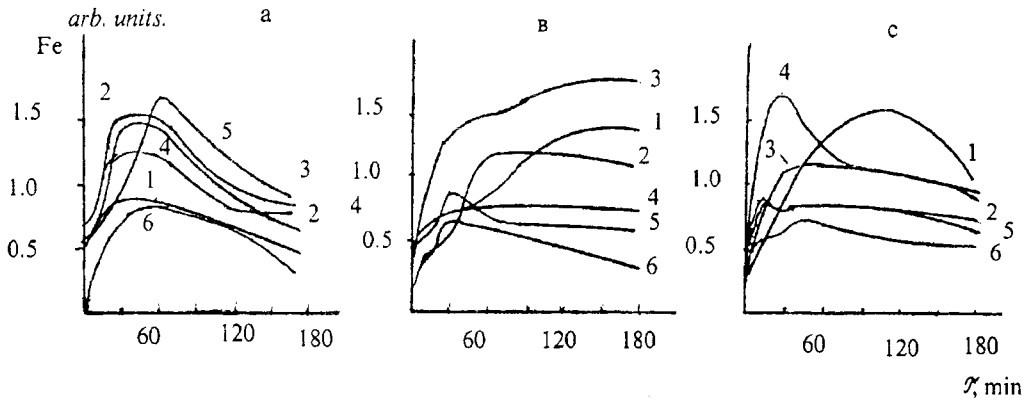


Fig.8. Change in the iron content of the tissues of the living body after the administration of FDIP-D-N (a), FDIP-D-L (b), FDIP-D-Tri (c) and on the rear side of the exposure to the CMF.

A comparison of the distribution of the iron over the soft and bone tissues of the animal body (Figs.7 and 8) showed that a characteristic feature of all the tissues was a rapid accumulation of iron in the first 10-20 min and a relatively slow decrease in its content in the next 160-170 min. The highest iron content was observed for tissue No.3 of systems (6) and (8), i.e. for the FDIP-D-particles on the side exposure (fr) both for the CMF and AMF (Table 5). In tissues Nos 1 and 2 the particles with different drugs showed up differently: more iron accumulated in the case of novocaine and trimecaine on exposure to the CMF, on the front side, but longer retention was observed on the rear side on exposure to the AMF. In nearly all systems the bone tissues Nos 4-6 in the time interval studied, accumulated iron in much smaller quantities than did the soft tissues, which is quite understandable, but lost it much more slowly.

Table 5
Iron content of the animal body (arb. units) 30 min and 60 min after intraperitoneal administration of immobilized an aesthetics and application of a constant magnetic field (CMF) or an alternating magnetic field (AMF)

№	Time, min	CMF, side (rear) FDIP-dextran-			AMF, side (rear) FDIP-dextran-		
		N	L	Tri	N	L	Tri
1	30	0.87	0.77	0.93	0.88	0.89	0.79
	60	0.88	0.86	1.38	0.87	0.91	0.80
2	30	1.25	0.61	0.86	1.42	1.80	0.81
	60	1.26	1.27	0.81	1.64	1.79	0.93
3	30	1.53	1.43	1.15	1.39	1.84	1.50
	60	1.51	1.53	1.16	1.30	1.81	1.51
4	30	1.48	0.76	1.71	0.64	1.25	0.69
	60	1.50	0.81	1.24	0.91	1.30	0.67
5	30	0.87	0.91	0.87	0.75	0.94	0.73
	60	1.69	0.74	0.82	0.80	1.02	0.74
6	30	0.61	0.72	0.74	0.57	0.63	0.59
	60	0.84	0.62	0.68	0.60	0.81	0.49
		CMF, side (fr)			AMF, side (fr)		
1	30	2.38	1.58	2.25	1.46	1.18	1.09
	60	2.33	1.42	2.23	1.50	1.10	1.10
2	30	1.48	0.73	0.87	1.31	1.78	0.70
	60	1.48	0.93	0.88	1.42	1.71	0.69
3	30	1.36	3.90	1.15	1.42	4.84	1.63
	60	1.37	3.84	1.13	1.62	4.53	1.70
4	30	0.89	2.09	0.87	1.40	0.96	0.84
	60	1.02	1.99	0.71	1.67	0.96	0.83
5	30	1.21	0.92	0.95	0.71	0.87	0.91
	60	0.90	0.95	0.99	0.74	0.91	0.90
6	30	1.07	1.97	0.80	1.20	0.83	0.69
	60	1.96	1.42	0.76	1.24	0.91	0.68

From Figs 7 and 8 and Table 5 it can be seen that for all particles (with novocaine, lidocaine and trimecaine) a higher level of iron accumulation in all tissues on exposure to the CMF was observed on the front side of exposure (fr.) The same dependence, but less pronounced, was obserwed for tissues exposed to the action of AMF (Table 5).

We will compare the curves of iron accumulation for the particles with novocaine, lidocaune and trimecaine, other things being equal (Figs 7 and 8). In the main, the differences are slight: for particles with novocaine and trimecaine the values of accumulated iron are wery close, somewhat higher for trimecaine, but far larger for lidocaine, especially for tissues Nos 3 and 2. These differences are obviously due to the different size of the molecules of the drugs and, accordingly, to the different absorption properties. Thus, the shortest is the lidocaine molecule (2,6 –dimethyl-N,N'-diethylamino-acetanilide hydrochloride), the trimecaine molecules is longer than it by one methyl group (2,4,6-trimethyl-N,N'-diethylamino-acetanilide hydrochloride) and the longest of them is the novocaine molecule (β-diethylamino-ethyl ester of n-aminobenzoic acid hydrochloride). A comparison of the results in the more/less terms is given in Table 6.

Table 6

Comparative characterization of the distribution of iron in the tissues of the animal body after administration of immobilized an aesthetics and exposure to a constant magnetic field (CMF) or an alternating magnetic field (AMF) measured on the side of exposure (fro) or the rear (rear) (according to the maximum of the curve for each tissue)

System number	Magnetic field	Side of exposure	Iron distribution in tissues
		FDIP-dextran-novocain	
1	CMF	(rear)	5>>3>4>2>>1>6
2	CMF	(fr)	1>>6>>2>3>5>4
3	AMF	(rear)	2>3>>4~1>5>6
4	AMF	(fr)	4>3>1>2>6>5
		FDIP-dextran-lidocaine	
5	CMF	(rear)	3>>2>1>4>5>6
6	CMF	(fr)	3>>4>6>1>5~2
7	AMF	(rear)	3>2>4>5>1>6
8	AMF	(fr)	3>>2>>1>4~5~6
		FDIP-dextran-trimecaine	
9	CMF	(rear)	4>1>3>5>2>6
10	CMF	(fr)	1>>3>4~5~2~6
11	AMF	(rear)	3>>2>1~5>4>6
12	AMF	(fr)	3>>2>5~4>2~6

Thus, on administering the immobilized anaesthetics, novocaine, lidocaine and trimecaine to the animals in the magnetic FDIP-dextran carrier and applying a magnetic field, the maximum accumulation of iron in the tissues occurs in a time from 20-180min. Accumulation of iron is somewhat greater in a constant magnetic field than in an alternating, being greater on the side of exposure to the field than on the rear in the case of the CMF and about the same in the case of the AMF. Heavier accumulation is observed in soft tissues than in bone tissues and among the soft tissues that of the lateral surface of the abdomen sharply stands out. In terms of the amount of iron accumulated in the tissues the anaesthetics used are in the order: novocaine < trimecaine < lidocaine.

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