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SCIENTIFIC PAPER

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THE INVESTIGATION OF PRIMARY PHYSICOCHEMICAL AND PHARMACO–BIOLOGICAL PROPERTIES OF POLYNUCLEAR IRON(III) COMPLEXES WITH DEXTRAN AND ITS DERIVATIVES

The results of the investigations of primary physicochemical and pharmaco–biological properties of polynuclear iron(III) complexes with low molecular dextran (LMD), hydrogenated low molecular dextran (H–LMD) and dextran carbonic acid (DCA) are presented. The investigations included the complex resistance to hydrolytic decomposition in highly acidic medium, the (TFH–A)–value, and neutral medium at 120°C, the (TFH–120)–value, the viscosity of the parenteral solutions, iron(III) resorption dynamics to serum after the i.m. and i.v. application of the preparation to rabbits, the acute toxicity (LD_{50}) in mice, and the residual iron(III) quantity at the i.m. application site. Iron(III) complexes with dextran carbonic acid (DCA) appeared to be the most suitable for use in veterinary and human medicine.

Key words: Polynuclear iron complexes, Low molecular dextran, Hydrogenated low molecular dextran, Dextran carbonic acid.

It is considered that about 20–30% of the world population suffers from hyposideremy (lack of iron and sideropenic anemia), so that the prevention and therapy of such conditions are a permanently existing problem in human medicine. This problem is also present in veterinary medicine, especially in the intensive production of swine.

To overcome this problem, a great number of pharmaceutical preparations on the basis of ferrous or ferric iron are used. For parenteral treatment (*i.m.* and *i.v.*), aqueous solutions of polynuclear iron(III) complexes with carbohydrates are used, such as dextran, hydrogenated dextran, carboxymethyl dextran, dextran carbonic acid, dextran heptanoic acid, dextrin, dextrin heptanoic acid, polygalactose, levan, inulin, xylitol hydro carbonic acid [1] and pululan [2]. Although up to date no exact correlation has been established between the physicochemical and pharmaco–biological properties of these complexes, first of all with respect to the type and characteristics of the ligand used to produce the complex, numerous works published on the topic indicate that, from the pharmaco–biological aspect, the best solutions for parenteral use are polynuclear iron(III) complex solutions with low molecular dextran (LMD), hydrogenated low molecular dextran (H–LMD), and dextran carbonic acid (DCA) [3–7].

The results of the investigation of the basic physicochemical and pharmaco–biological properties of these complexes and their standardized solutions for parenteral application in both human and veterinary medicine are presented in this study. The ligands and the corresponding iron(III) complexes were synthesized in the laboratory according to usual procedures and standardized as parenteral solutions with iron contents of 50, 75, or 100 mg Fe(III)/cm^3, respectively.

The parameters used for the assessment of the physicochemical and pharmaco–biological properties of the preparations were: resistance to the hydrolytic decomposition of the complex in very acidic medium, expressed as the total hydrolysis time (TFH–A) at ambient temperature, resistance to the hydrolytic decomposition of the complex in an extremely diluted solution at 120°C, in neutral medium, expressed as the total hydrolysis time (TFH–120), the parenteral solution viscosity, the dynamics of iron(III) resorption to serum after *i.m.* and *i.v.* application on rabbits, the acute toxicity (LD50) in mice, and the residual iron(III) quantity at the application site 10 days after the *i.m.* application.

EXPERIMENTAL

Complex synthesis

The investigated iron(III) complexes with LMD, H–LMD and DCA were obtained by a unique synthesis procedure at increased temperatures ranging from 80 to 130°C with iron(III)–oxy–hydroxide gel precipitated from 11.7% $FeCl_3$ solution (124.2 g) by adding 8.09% Na_2CO_3 solution (217.6 g) at room temperature. The complexes were synthesized from an initial Fe(III) to ligand mass reaction ratio from 1:1 to 1:4, in the presence of 10% NaOH (8.5 cm^3). With the reaction ratio given, the synthesis duration was determined by the moment when the total quantity of iron(III)–oxy–hydroxide gel was transformed into the solute form. After deionisation on ion exchange columns (very acid Lewatit S–100 and very alkaline Amberlite–IRA 410), all the complexes were standardized by evaporation as parenteral solutions with a Fe(III) content of 50, 75, and 100 mg/cm^3, respectively [8].

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Paper received: August 21, 2004
Paper accepted: January 27, 2005

Ligand preparation

Low molecular dextrans (LMD) with intrinsic viscosity values $[\mu]^{37}$ at 37°C ranging from 0.03 to 0.06 dl/g were obtained by the depolymerization of clinical dextran M_w = 70000 g/mol by aqueous solutions of hydrochloric acid of the concentration 0.058 mol/dm^3, according to the customary depolymerization procedure of by–fraction dextrans from clinical dextran production [9], choosing hydrolysis duration between 100 and 200 minutes.

The dynamic viscosity of the complex solutions was measured at 25°C by a Höppler viscosimeter. Determination of the intrinsic viscosity was based on the calculated values of the relative viscosities for solutions containing different ligand concentrations, by using an Ostwald viscosimeter.

Hydrogenated low molecular dextran (H–LMD) was obtained by hydrogenation of the corresponding LMD with $NaBH_4$ to a reductive group content less than 0.25% [10]. Dextran carbonic acid (DCA) was obtained by the electro–chemical oxidation of LMD in KJ or NaJ aqueous solutions till the reductive groups were reduced to less than 0.25% [8].

Standardization, physicochemical and pharmaco–biological investigations of the complex parenteral solutions

In the standardized complex solutions for parenteral application the iron(III), ligands and sodium chloride contents were determined using methods prescribed by the British Pharmacopoeia 1999 [11].

The parenteral solutions of all the complexes were sterilized at 120°C for 20 minutes and the samples were left for observation of possible organoleptic changes under the usual storage conditions.

To the complex parenteral solutions for veterinary use 0.5% of phenol was added before sterilization as a preservation additive, which enables multiple doses to be used from the same unit packing. Phenol was determined by titration with a bromide–bromate indicator [14] after qualitative isolation from the parenteral solution by steam distillation.

The TFH–A value indicates the time required for complete Fe(III) transformation from the complex to $FeCl_3$. The parenteral solution (1 cm^3) was diluted by distilled water (20 cm^3) and from the moment the conc. HCl (15 cm^3) was added by slowly stirring, the time was recorded until the solution colour changed completely from ruby (complex) to light yellow ($FeCl_3$). The TFH–120 value is the time required for complete decomposition of the complex to iron(III)–oxy–hydroxide at 120°C. The parenteral solution (3 cm^3) was diluted by distilled water (500 cm^3) and treated at 120°C until iron(III)–oxy–hydroxide gel particles appeared. The change of the iron level in serum in rabbits after *i.m.* and *i.v.* application was monitored stoichiometrically, using a method that enables the determination of the total iron in the serum including the unchanged form of the resorbed complex at the *i.m.* and *i.v.* application site [12]. Dynamics of the total iron(III) variations in the serum were observed until a level of approx. 1 mg/100 cm^3 Fe(III) was reached. The quantity of residual iron at the *i.m.* application site was also determined in rabbits [11]. The acute toxicity as the average lethal dose (LD_{50}) was determined on white mice [13].

RESULTS AND DISCUSSION

The results of the primary physicochemical and pharmaco–biological properties of polynyclear the iron(III) complexes synthesized with low molecular dextran (LMD), hydrogenated low molecular dextran (H–LMD), and dextran carbonic acid (DCA) under the determined conditions, are given in Tables 1 and 2. The results shown are average values from the values obtained from four parallel experiments. In Table 1 the basic parameters of the syntheses of some complexes are given, such as the initial reaction ratio of iron(III) as iron(III)–oxy hydroxide and ligand, the extreme viscosity number of the ligand used, the reaction temperature and synthesis time necessary for complete dissolution of the iron(III)–oxy hydroxide solid phase in the reaction mixture, denoting at the same time the end of the reaction.

Table 2 shows the basic physicochemical and pharmaco–biological properties of the standardized parenteral solutions from Table 1 with an iron(III) content of 50, 75 or 100 mg of Fe(III)/cm^3, respectively, applicable parenterally (*i.m.* or *i.v.*) in human and veterinary medicine. The solutions for veterinary use must be preserved with 0.5% phenol, which enables multiple applications from the same unit packing. The viscosity of the solution, for easier parenteral application, predetermines the concentration of iron per unit of solution volume. The parenteral solution viscosity for a given iron(III) concentration depends on the type of

Table 1. Basic parameters of iron(III)complex synthesis with LMD, H–LMD, DCA

Property	Iron(III) complex with ligands						
	LMD	H–LMD			DCA		
Initial Fe(III)/ligand mass ratio in the reaction	1:3	1:2.5	1:3	1:4	1:1	1:2	1:3
Intrinsic viscosity of the ligand, $[\eta]^{37}$, dl/g	0.05	0.035	0.0505	0.0505	0.053	0.053	0.053
Reaction temperature, [°C]	85	130	130	130	120	120	100
Reaction time, [min]	60	120	120	120	100	100	100

Table 2. Physicochemical and pharmaco–biological properties of the parenteral solutions of iron(III)complex with LMD, H–LMD and DCA

Property	Iron(III) complex with ligands						
	LMD	H–LMD			DCA		
$C_{Fe(III)}$, mg/cm^3	74.50	99.85	74.20	49.30	98.30	98.70	75.60
C_{ligand} mg/cm^3	190.20	251.15	208.80	202.90	104.50	197.20	217.30
Mass ratio Fe(III)/ligand	1:2.56	1:2.51	1:2.81	1:4.11	1:1.06	1:1.99	1:2.87
NaCl, %	1.05	0.95	0.85	1.1	0.85	0.93	0.80
Phenol, %	0.48	0.49	0.45	0.5	0.46	0.46	0.50
TFH–A, min	0.8–1.8	5–8	9–11	9–11	4–5	9–10	9–10
TFH–120, min	<20	~30	>45	>45	~30	>45	>45
Dynamic viscosity of the final complex the solution, η^{25}, mP·s	31.2	21.2	13.2	24.4	9.7	13.2	17.1
Fe(III) at the *i.m.* application site, %	11	7.5	3.5	5.6	4	4	3
LD_{50} acute toxicity, mg Fe(III)/kg	495	~2500	>3000	>3000	>3000	>3000	>3000
	–	1430*	1890*	–	~1900*	~1900*	~1900*

*Parenteral solutions for veterinary use preserved by adding 0.5% of phenol

ligand used, its intrinsic viscosity number, $[\eta]^{37}$, and the initial iron(III) to ligand mass ratio. These values are especially indicative of the bonding capacity of the ligand, and its ability to dissolve and stabilize iron(III)–oxy hydroxide in the complex solution.

Therefore, LMD complexes with the intrinsic viscosity number $[\eta]^{37}$ = 0.05 dl/g, synthesized from the ratio 1:3, can be standardized by evaporation to a max. iron content of 75 mg Fe (III)/cm^3, preserving at the same time the viscosity of the solution suitable for parenteral application. For the same reason, H–LMD complexes which can be standardized as parenteral solutions with 100 mg Fe(III)/cm^3 concentration, were synthesized from an initial reaction mixture ratio 1:2.5 with a ligand with a lower intrinsic viscosity value, $[\eta]^{37}$ = 0.035 dl/g. Stable DCA complexes with the intrinsic viscosity value $[\eta]^{37}$ = 0.053 dl/g, can be obtained from very low reaction mixture ratios, 1:1 and 1:2, which can be standardized as low viscosity solutions with a high iron(III) content of 100 mg Fe(III)/cm^3.

The parenteral solutions of iron(III) complexes with LMD have an intensive brown colour, while H–LMD and DCA complexes have a ruby colour which they retain after sterilization. In LMD complex solutions precipitation of the solid phase is observed after 6 to 9 months storage under conventional conditions. The results given in Table 2 show that the iron(III) complexes with LMD have extremely low resistance to hydrolysis in acidic medium, TFH–A = 0.8–1.8 minutes, and low resistance to hydrolysis in neutral medium at 120°C, TFH–120 < 120 minutes, and the viscosity of their parenteral solutions is considerable, amounting to 31.2 mPa·s. These parameters are much better in iron(III) complexes with H–LMD and DCA. The increased viscosity, 24.4 mPa·s, of the iron(III) complex solution with H–LMD obtained from a 1:4 initial ratio, is the result of the increased ligand fraction in the complex. Both complexes are significantly resistant to hydrolytic decomposition in acidic medium, TFH–A = 5–11 minutes, and hydrolytic decomposition at 120°C with extreme dilution, TFH–120 > 30 minutes.

The dynamics of the total iron(III) level variations in rabbit serum after the *i.m.* and *i.v.* application of parenteral complex solutions are shown in Figure 1 (iron(III) complexes with LMD), Figure 2 (iron(III)

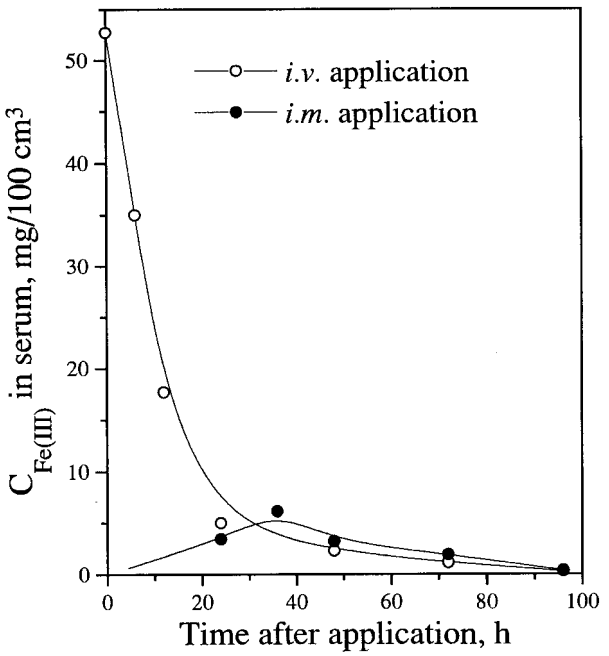

Figure 1. Dynamics of the total iron(III) level variations in the serum after the i.m. and i.v. application of the iron(III) and LMD complex solution ($[\mu]^{37}$=0.05 dl/g) with a Fe(III) to LMD ratio of 1:3.

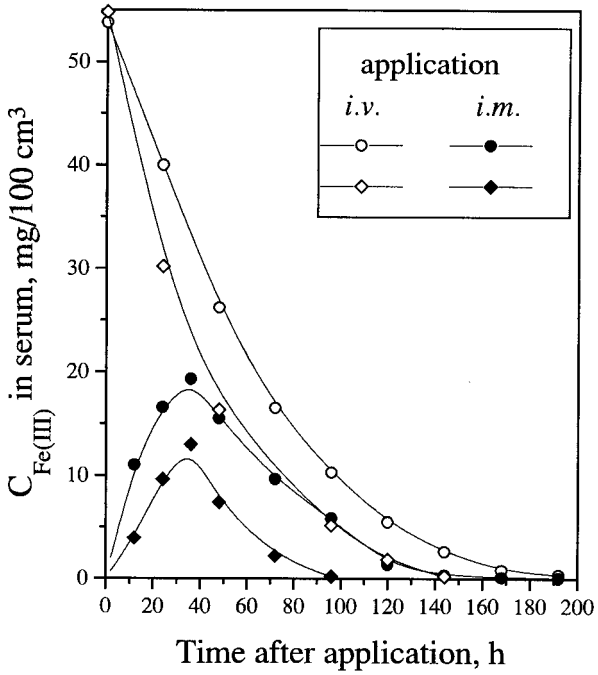

Figure 2. Dynamics of the total iron(III) level variations in the serum after the i.m. and i.v. application of the iron(III) with H–LMD complex solution ($[\mu]^{37}$ = 0.035 dl/g) with a Fe(III) to H–LMD ratio of 1:2.5 (◊♦), and the iron(III) with H–LMD complex solution ($[\mu]^{37}$ = 0.05 dl/g) with Fe(III) to H–LMD ratios of 1:3 and 1:4 (o●).

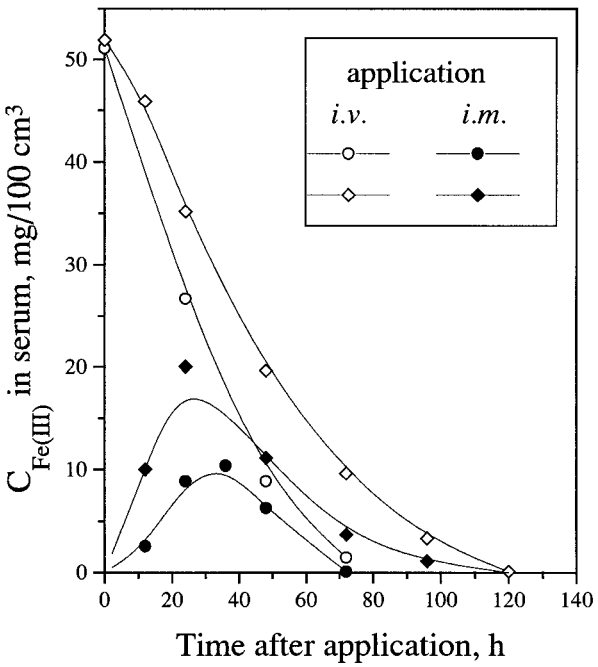

Figure 3. Dynamics of the total iron(III) level variations in the serum after the i.m. and i.v. application of the iron(III) with DCA complex solutions ($[\mu]^{37}$ = 0.053 dl/g) obtained from the reaction ratios 1:1 (o●), 1:2, and 1:3 (◊♦).

complexes with H–LMD) and Figure 3 (iron(III) complexes with DCA). The changes of the total iron(III) level values in the serum after the *i.m.* and *i.v.* application of parenteral complex solutions with LMD are shown in Figure 1.

The results given in Figure 1 show that the total iron(III) retention in the serum and after the *i.m.* and *i.v.* application was about 100 h and that the maximum concentration (7.5 mg Fe(III)/100 cm^3) was reached 36 hours after the *i.m.* application. High acute toxicity, LD_{50} = 495 mg Fe(III)/kg, is evident from Table 2, as well as a significant quantity, 11%, of non–resorbed iron at the *i.m.* application site.

The dynamics of the total iron(III) level variations for three complex types, complexes with H–LMD, complexes synthesized from a 1:2.5 ratio ($[\eta]^{37}$ = 0.035 dl/g), and 1:3 and 1:4 ratios ($[\eta]^{37}$ = 0.05 dl/g), respectively, are shown in Figure 2.

The dynamics of the total iron(III) level variations in serum after the *i.m.* and *i.v.* application of complex solutions obtained from the initial reaction ratios of 1:3 and 1:4 are practically identical and are presented by a single curve (Figure 2), characterized by the total iron(III) retention of about 200 h and a high maximum iron(III) level value in the serum of about 18 mg/100 cm^3 reached 36 hours after application. It can be seen in Table 2 that these complexes have very low toxicity LD_{50}>3000 mg Fe(III)/kg and a small amount of residual iron(III) at the *i.m.* application site, 3.5–5% mg Fe(III), after 10 days. Complexes synthesized from 1:2.5 ratio with H–LMD with a lower intrinsic viscosity value are inferior in respect to the observed parameters, with a total iron(III) retention time about 100 h, a maximum iron(III) level in the serum about 12 mg/100 cm^3 reached after 36 hours, residual iron(III) at the *i.m.* application site 7.5% and an acute toxicity LD_{50} of about 2500 mg Fe(III)/kg.

The total iron(III) level variations after the *i.m.* and *i.v.* application of parenteral solutions of three types of complexes of iron(III) with DCA with a high viscosity value, ($[\eta]^{37}$ = 0.053 dl/g), synthesized from Fe(III) to a DCA initial reaction ratio of 1:1, 1:2, and 1:3 are shown in Figure 3.

Based on the results shown in Table 2 and Figure 3 it can be concluded that iron(III) complexes with DCA synthesized from Fe(III) to DCA ratios of 1:2 and 1:3 have almost identical pharmaco–biological values: a total iron(III) retention time in the serum after *i.m.* and *i.v.* application of about 120 h, a maximum total iron(III) level in the serum of about 19 mg/100 cm^3 reached about 30 hours after the *i.m.* application, low toxicity LD_{50}>3000 mg Fe(III)/kg, and a minimal quantity of residual iron(III) at the *i.m.* application site, 4%. Complexes of this type, obtained from a 1:1 ratio, have similar properties but a slightly lower stability.

Based on the results shown in Tables 1 and 2 and Figure 1, 2 and 3, it is evident that the investigated complexes and their parenteral solutions for *i.m.* and *i.v.* application (except to some extent iron(III) complexes with LMD) fulfil the requirements for iron preparations for parenteral application [1], such as: sufficient stability ensuring lack of precipitation, a high iron(III) content per volume unit of parenteral solution, a low viscosity value, low toxicity, quantitative iron(III) resorption at the *i.m.* application site, high effectiveness, sterility and storage stability. The advantages of complexes obtained with H–LMD and DCA over the complexes with LMD with respect to the parameters investigated, can be connected to the reductive activity of LMD originating from the terminal glucose and complex synthesis procedure applied, i.e. alkaline medium. Namely, LMD with intrinsic viscosity values of 0.04–0.06 dl/g, obtained by the depolymerization of clinical dextran M_w = 70000 g/mol in aqueous hydrochloric acid solutions, can have 12 to 20% reduction activity (defined as the terminal glucose content) [9]. The sodium hydroxide present in the reaction mixture has multiple functions in the process of complex synthesis. Partially, it transforms terminal glucose units into acid gluco–metha–saccharase residues [15] and such chains have no reductive activity, which is the main cause of alkaline LMD degradation during complex synthesis. This phenomenon is confirmed by the fact that if the LMD solution is treated with sodium hydroxide, without the presence of iron(III)oxy hydroxide gel, under the same conditions as the complex synthesis, in spite of evident caramelization, there is a significant decrease of the initial reduction activity of the LMD treated. Also, the reduction activity of the LMD used for the synthesis was found to be much higher than that of the LMD separated from the synthesized complex by hydrolytic decomposition in neutral medium, heavily diluted and at elevated temperature [10]. Sodium hydroxide also contributes to breaking of the hydrogen bonds between LMD molecules and water partially replacing the hydrogen atoms from the hydroxyl groups by the more electropositive sodium atom, as well as to breaking of hydrogen bonds in the iron(III)–oxy hydroxide gel, thus improving their interaction with LMD molecules [16]. However, the presence of sodium hydroxide in the reaction mixture during the synthesis at the reaction temperature at the same time causes alkaline–thermal and oxidative decomposition of the LMD molecules up to 5% [10] and the partial reduction of iron(III), which might be the cause of the increased toxicity of these complexes and the intensive brown colour of their parenteral solutions. In iron(III) complexes with H–LMD and DCA there are no such occurrences, since their reductive activity was eliminated by hydrogenation [10] and electro–oxidation [8] of the aldehyde group in the terminal glucose unit of the LMD molecule, respectively. As a result, the parenteral solutions of the iron(III) complex with LMD have high viscosity (~30 mPa·s), low TFH–A (0.8–1.8 min) and TFH–120 values (< 20 min), noticeable acute toxicity (LD_{50} = 495 mg Fe(III)/kg), a relatively low maximum Fe(III) level in the serum of 7.5 mg/cm^3, and a significant quantity of residual Fe(III) at the *i.m.* application site of 11%. In H–LMD and DCA, the reduction activity is eliminated by hydrogenation or electro–oxidation, there are no significant differences between them, and their complexes are very suitable for parenteral application. DCA ($[\mu]^{37}$ = 0.053 dl/g) has an advantage as a ligand in the preparatory sense because it gives stable complexes even from the initial iron(III) to ligand mass reaction ratios of 1:1 and 1:2, that can be standardized as parenteral solutions with a Fe(III) content of 100 mg/cm^3 without increasing the viscosity of the solution, which is very important from the aspect of parenteral application techniques. To obtain such a complex with H–LMD, the lower intrinsic viscosity of the initial reaction ratio is 1:2.5, lowering at the same time the intrinsic ligand viscosity value to $[\mu]^{37}$ = 0.035 dl/g, and that degrades the values of important complex characteristics.

CONCLUSION

The quality of iron(III) polynuclear complexes with carbohydrates depends, in the first place, on the ligands used.

Among the investigated complexes, the best results were obtained with the complex with dextran carbonic acid (DCA) with the intrinsic viscosity value $[\mu]^{37}$ = 0.053 dl/g, synthesized from the initial iron(III) to DCA mass reaction ratio 1:2, standardized as a parenteral solution with a Fe(III) content of 100 mg/cm^3, with the following properties: Fe(III) = 98.7 mg Fe(III)/cm^3; DCA = 197.2 DCA/cm^3; NaCl = 0.93%; dynamic viscosity at 25°C = 13.2 mPa·s; pH = 6.8; TFH–A = 9.7 min; TFH–120 > 45 min; max. Fe(III) level in serum = 19 mg/100 cm^3 36 hours after the *i.m.* application, maintaining the Fe(III) level >1 mg/100 cm^3 for a total of 120 h; residual Fe(III) at the *i.m.* application site = 4%, and acute toxicity LD_{50} = 3000 mg Fe(III)/kg.

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IZVOD

ISPITIVANJE PRIMARNIH FIZIČKO–HEMIJSKIH I FARMAKO–BIOLOŠKIH KARAKTERISTIKA POLINUKLEARNIH KOMPLEKSA GVOŽĐA(III) SA DEKSTRANOM I NJEGOVIM DERIVATIMA

(Naučni rad)

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Prikazani su rezultati ispitivanja osnovnih fizičko–hemijskih i farmako–bioloških svojstava polinuklearnih kompleksa gvožđa(III) sa niskomolekulskim dekstranom (LMD), hidrogenovanim niskomolekulskim dekstranom (H–LMD) i dekstrankarbonskom kiselinom (DCA). Ispitivanja obuhvataju otpornost na hidrolitičko razlaganje kompleksa u jako kiseloj sredini (TFH–A)–vrednost i neutralnoj sredini na 120°C (TFH–120)–vrednost, viskozitet parenteralnih rastvora, dinamiku resorpcije gvožđa(III) do seruma posle *i.m.* i *i.v.* aplikacije preparata kunićima, akutnu toksičnost (LD_{50}) na miševima i količina zaostalog gvožđa(III), na mestu *i.m.* aplikacije.

Najbolje rezultate prema ispitivanim parametrima pokazali su kompleksi gvožđa(III) sa dekstrankarbonskom kiselinom (DCA).

Ključne reči: Polinuklearni gvožđe kompleks, Nisko molekularni dekstran, Hidrogenovani nisko molekularni dekstran, Dekstran karbonska kiselina.