CHIMIE FARMACEUTICĂ ȘI CONTROLUL MEDICAMENTULUI

DETERMINAREA CANTITATIVĂ A FE (III) ÎN FORME FARMACEUTICE LICHIDE CU COMPLECTUL «TITRION» PRIN METODA DE TITRARE AUTOMATĂ IODOMETRICĂ

AUTOMATIC IODOMETRIC TITRATION METHOD FOR QUANTITATIVE DETERMINATION OF FE (III) IN LIQUID PHARMACEUTICAL DOSAGE FORMS USING THE TITRATOR «TITRION»

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Rezumat. S-au cercetat și elaborat metode de analiză cantitativă a Fe (III) în două siropuri, care conțin una și aceeași substanță activă – compusul complex macromolecular a $Fe(OH)_3$ cu polimaltoza. Soluțiile s-au analizat, după descompunerea acestui compus complex în mediul H_2SO_4 prin metoda de titrare ampero-metrică cu doi electrozi indicatori de Pt în urma prelucrării soluției de analizat a Fe (III) cu exces de soluție de KI și titrarea ulterioară cu sau fără adăugarea soluției tampon acetat a ionilor cu soluție de $Na_2S_2O_3$. Dozarea s-a efectuat în mod automat cu titratorul «TITRION», folosind două regimuri de titrare în urma cărora s-a determinat volumul de echivalență al titrantului. S-a stabilit că soluția tampon acetat inhibă reacția de oxidare a Fe (III) cu un exces de soluție a iodurii de potasiu. Aceasta s-a folosit la studierea influ-enței timpului asupra reacției de oxidare în soluțiile de analizat a siropului Ferrum Lek și Ferimax. Soluțiile de analizat a siropului Ferrum Lek s-au analizat prin metoda cu adăugarea soluției tampon acetat cu titra-torul, folosind regimul de înregistrare a curbei de titrare și masa Fe (III) a constituit 49,57±0,34 mg/ 5 ml, iar în regimul de titrare pînă la intensitatea curentului de 0,1 μA – 49,92±0,92 mg/ 5 ml de sirop. În regimul de titrare automata cu înregistrarea curbei de titrare și de titrare pînă la intensitatea curentului de 0,1 μA, în care reacția de oxidare nu s-a inhibat cu soluție tampon acetat, masa Fe (III) în soluțiile de analizat a siropului Ferimax a alcătuit 49,71±0,42 mg/ 5 ml și 49,71±0,36 mg/ 5 ml respectiv de sirop. Ultimul regim de titrare pînă la intensitatea curentului 0,1 μA s-a folosit la inhibarea reacției de oxidare cu soluție tampon acetat, dar mai întâi soluțiile luate pentru analiză a acestui sirop s-au prelucrat cu picături de soluție de KMnO4. Masa Fe (III) calculată după rezultatele analizei acestui procedeu a constituit 50,09±0,45 mg/ 5 ml de sirop Ferimax. **Cuvinte cheie:** deficiență de fier, anemie feriprivă, metodă de titrare amperometrică automată cu doi electrozi indicatori, titrator, regim de titrare, procedeu de titrare, inhibarea reacției de oxidare, soluție tampon.

Summary. Methods of quantitative analysis of Fe (III) in two syrups containing one and the same active substance – the macromolecular complex compound of Fe(OH)3 with polymaltose, have been researched and developed. The solutions were analyzed after the decomposition of this complex compound in the H2SO4 medium by the amperometric titration method with two Pt indicator electrodes after the treatment of the Fe (III) analyte solution with excess of KI solution and subsequent titration of ions with Na2S2O3 solution, with or without the addition of acetate buffer solution. Assay was performed automatically with the titrator «TITRION», using two titration regimes following which the volume of equivalence of the titrant was determined. It was determined that the acetate buffer inhibited the oxidation reaction of Fe (III) with an excess of potassium iodide solution. This was used to study the influence of time on the oxidation reac-tion in the analysis solutions of Ferrum Lek and Ferimax syrup. Ferrum Lek syrup analysis solutions were analyzed with the titrator by the method of adding acetate buffer, using the titration curve recording regi-me and the mass of Fe (III) was 49,57±0,34 mg/ 5 ml and in the titration regime up to the current intensity of 0,1 μA – 49,92±0,92 mg/ 5 ml of syrup. In the automatic titration regime with the recording of the titra-

tion curve and titration up to the current of 0,1 µA, in which the oxidation reaction was not inhibited with acetate buffer, the mass Fe (III) in the solutions to be analyzed of Ferimax syrup was 49,71±0,42 mg/ 5 ml and 49,71±0,36 mg/ 5 ml of syrup, respectively. The last titration regime up to 0,1 µA current was used to inhibit the oxidation reaction with acetate buffer, but first the solutions taken for the analysis of this syrup were processed with drops of KMnO4 solution. The mass of Fe (III) calculated from the results of the analysis of this procedure was 50,09±0,45 mg/ 5 ml of Ferimax syrup.

Key words: iron deficiency, iron-deficiency anemia, automatic amperometric titration method with two indicator electrodes, titrator, titration regime, titration process, inhibition of oxidation reaction, buffer solution.

INTRODUCTION

Iron is an important element of the human body, essential for the proper functioning of many metabolic processes, such as oxygen and electron transport, deoxyribonucleic acid (DNA), steroid hormones and bile acids synthesis, being an integral part of tissue enzymes. Iron deficiency is one of the most widespread forms of malnutrition in the world. A lack of iron in the body lowers the level of hemoglobin in the blood, causing iron deficiency anemia. Although this deficiency is not the only cause of developing anemia, it is certainly the most important [1].To counter this phenomenon, doctors recommend among other medications, drugs containing the iron (III)-hydroxide polymaltose complex. The purpose of the further presented research is to develop a new method for the quantitative analysis of iron (III) liquid dosage forms applying the automatic amperometric titration method.

MATERIALS AND METHODS

To perform automatic amperometric assay with two Pt indicator electrodes [2], incorporated in a plastic tube, the „TITRION" kit, further titrator, of the company „EKONIS EKSPERT" was used The external appearance and the general characteristic of this titrator were presented in [3].

Two working regimes of this titrator were used in the study: 1 – titration up to the set point - automatic titration up to the given point by the operator of the end point of the current intensity (I, µA) with the automatic measurement of the volume of the titrant, consumed at the titration (volume of equivalence) and 2 - titration curve recording - automatic titration with the total recording of the titration curve, its display on the liquid analyzer screen and the determination of the volume of equivalence of the

titrant with the storage in the titrator's memory of the last recorded titration curve.

Both working regimes of the titrator are divided into two zones. In the first zone, which is at the beginning of the titration and is beyond the volume of equivalence, the titrator adds the titrant in larger and equal portions over certain time intervals. In the second zone, which is near the equivalence point, the titrator adds the titrant in smaller and equal portions also over certain time intervals [4]. The entire automatic titration process is set and controlled by the operator.

In this publication the electrodes were polarized by 20 mV and the current intensity measurement limit by the titrator was 50 µA for the titration of obtained I_2 In both working regimes of the titrator, a solution with a theoretical concentration of $Na_2S_2O_3$ equal to 0,01 mol/l was used. This solution was automatically added to the solution which was dosed at the beginning of the titration (first zone) in portions equal to 50 µl every 3 s and near equivalence point 4 µl every 4 s.

The Pt indicator electrodes were introduced and left until the next day in the solution with c(NaOH)=1,0 mol/l for iodine desorption [2].

In the study were used two syrups sold in pharmacies of Republic of Moldova, Ferrum Lek (manufacturer Sandoz Ilac Sanayi ve Ticaret A.S., Turkey) and Ferimax (manufacturer Bilim Ilac Sanayi Ve Ticaret A.Ș., Turkey). Both syrups contain as an active substance the macromolecular complex compound of iron (III) hydroxide with polymaltose, in an amount of 50 mg/ 5 ml of elemental iron.

Laboratory glassware and instruments: volumetric flasks of different capacities, graduated cylinders, beakers with the capacity of 25 and 50 ml, two automatic pipettes from brand DACpette with the capacity of 100 – 1000 µl and 1000 – 5000 µl. The masses of the studied syrups, as well as the mass of the KIO_3 sample, sed for the preparation of the analytical and standard solutions, were weighed into flasks with a capacity of 50 ml or glass vials, using the RADWAG AS 110.RI balance.

Preparation of solutions

All the solutions, which were used in the study, were prepared from reagents, with the qualification „chemical pure". They were prepared using double-distilled water. To remove volatile reducers from distilled H_2O at the second distillation, several $KMnO_4$ crystals were added thereto.

The primary standard solution of KIO_3, with c(1/6 KIO_3)=0,01 mol/l was thus prepared. The calculated KIO_3 sample with a mass of 0,35667 g was weighed and dissolved in double-distilled H_2O in a

1 l volumetric flask, brought to volume with H_2O and homogenized. The solution with $\omega(KI)=10$ % was prepared from KI and the 0,5 % starch solution with mass was prepared from starch according to the requirements described in [5]. The solution with the molar concentration of the equivalent equal to 2,0 mol/l was prepared from fixanals (c(1/2 H_2SO_4)=0,1 mol/dm³). The solution with c(1/2 H_2SO_4)=0,2 mol/l was prepared by dilution.

Additionally, KMnO4 and acetate buffer auxiliary solutions were used in the study. The first solution was prepared from the calculated and weighed sample of $KMnO_4$ for the preparation of 100 ml of solution with c(1/5 $KMnO_4$)=0,02 mol/l without standardizing it. The second solution was prepared from sodium acetate and concentrated acetic acid. The mass of $CH_3COONa \cdot 3H_2O$ (5,44 g) was calculated and weighed to obtain a solution with a volume of 200 ml and c(CH_3COONa)=0,2 mol/l. The mass of this sample was dissolved in H_2O, 59 ml of concentrated CH_3COOH acid solution was added to the solution obtained and the solution was diluted with H_2O to a volume of 200 ml, obtaining a solution with pH=3,0.

The pH of some of the solutions to be analyzed and of those in which the acetate buffer was used, was measured and controlled using an I160M ionometer, connected to a glass indicator electrode and a silver-silver chloride reference electrode.

For the quantitative determination of Fe (III) in the solutions to be analyzed in the studied liquid pharmaceutical forms, the iodometric method of oxidant dosing (substituent titration method) was used. In this method as a titrant the solution of $Na_2S_2O_3$ is used as a secondary standard solution [6, 7, 8]. This solution was prepared from fixanal (c($Na_2S_2O_3$)=0,1 mol/l), using double-distilled H_2O to which was added Na_2CO_3 with a mass of 0,1 g per1 l of solution to stabilize it [6, 7]. Solutions with concentrations of the order of 0,01 mol/l were prepared based on the solution with c($Na_2S_2O_3$)=0,1 mol/l by its dilution. A solution containing the same mass of Na_2CO_3 in one liter of solution was also used for dilution. The standardization of these solutions was carried out in this way.

To different volumes of standard KIO_3 with c(1/6 KIO_3)=0,01 mol/l was added 5 ml solution of KIO_3 with (KI)=10 %, 2 ml of solution with c(1/2 H_2SO_4)=0,2 mol/l. he mixture was allowed to stand for 5 minutes in the dark. The solution was treated by removing an equivalent amount of I_2, which was then titrated with dilute $Na_2S_2O_3$ solution in the presence of starch as an indicator, added towards the end of the titration, until the blue color disappeared. A microburette with a capacity of 2 ml was used for dosing, and the titrant concentration was calculated based on the law of equivalents.

Preparation of solutions for the analysis of liquid pharmaceutical forms

The solutions for the analysis of the studied liquid pharmaceutical forms were prepared under equal conditions of volume of syrup, taken for analysis, equal or different volume of solution with c(1/2 H_2SO_4)=2,0 mol/l and decomposition temperature of iron (III)-hydroxide polymaltose complex. For this, with the help of an analytical balance, a volumetric flask with a capacity of 50 ml was weighed. With the help of an automatic pipette, 0.7 ml of syrup was added to it, respectively the balloon was closed with the ground stopper and weighed again. The mass of the syrup taken for analysis was determined by the difference, and then its density.

Subsequently, different volumes of solution with c(1/2 H_2SO_4)=2,0 mol/l were added to the flask and the flask was introduced into the water bath at a certain temperature and over certain intervals the red-brown color of iron (III)-hydroxide polymaltose complex disappeared, obtaining a color of the yellowish solution, characteristic of Fe (III) sulphate in the case of Ferrum Lek syrup and slightly yellowish with a violet hue in the case of Ferimax syrup. After that, the flask was immediately removed from the bath with hot water, cooled to room temperature under the tap, diluted to the level with distilled H_2O and homogenized.

RESULTS AND DISCUSSION

In previous publications [9-11], the quantitative determination of Fe (III) in various pharmaceutical forms was studied, which contained as active substance the macromolecular complex compound of $Fe(OH)_3$ with polymaltose, spectrophotometric method in basic medium. The sample for analysis of the pharmaceutical form was decomposed in the presence of H_2SO_4 and the flask with sample and sulfuric acid solution were introduced into the bath with hot water (100°C), after which Fe (III) was determined quantitatively by spectrophotometric method. Thus in [11] Fe (III) was quantitatively determined with sulfosalicylic acid by the spectrophotometric and iodometric method in the acidic and basic medium for Ferimax syrup and in the basic medium for Ferrum Lek syrup.

The results obtained for Ferimax syrup showed that in the acid medium the mass of Fe (III) in 5 ml of syrup was lower than that declared by the manufacturer, while in the basic medium the results obtained were satisfactory [11]. According to the data in the literature, confirmed by our research, in the basic me-

dium by spectrophotometric method with sulfosa-licylic acid can be determined quantitatively Fe (II), Fe (III) or the sum of Fe (II) and Fe (III) in the same sample solution to be analyzed [12-14]. For the acidic medium the question remained open for this syrup. This prompted us to further study the quantitative determination of Fe (III) by automatic amperometric titration method with two Pt indicator electrodes with the titrator in Ferrum Lek and Ferimax syrups, which contain one and the same active substance – iron (III)-hydroxide polymaltose complex .

Upon decomposition of the active substance in the presence of the H_2SO_4 solution from these syrups, Fe (III), sulphate is formed in the final solution, which slightly oxidizes the excess of potassium iodide, forming molecular iodine [10]. Iodine is hardly soluble in water, but in the presence of excess I$^-$ ions in the solution, the complex ion I_3^- [6, 7] is formed and the reversible oxide-reduction system I_3^-/3I$^-$ appears. When two Pt electrodes polarized with only 10–20 mV are introduced into this solution, current appears [15], the intensity of which depends on the I_3^-/3I$^-$, ratio, because at the titration the following reaction takes place [7]:

$$+ 2\bar{e} = , = 0,54 V$$
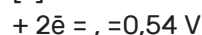
For the case when the titrator records the titration curve, the operator at the end of the titration receives information about the general appearance of the curve and determines the volume of equivalence of the titrant [4] (Figure 1).
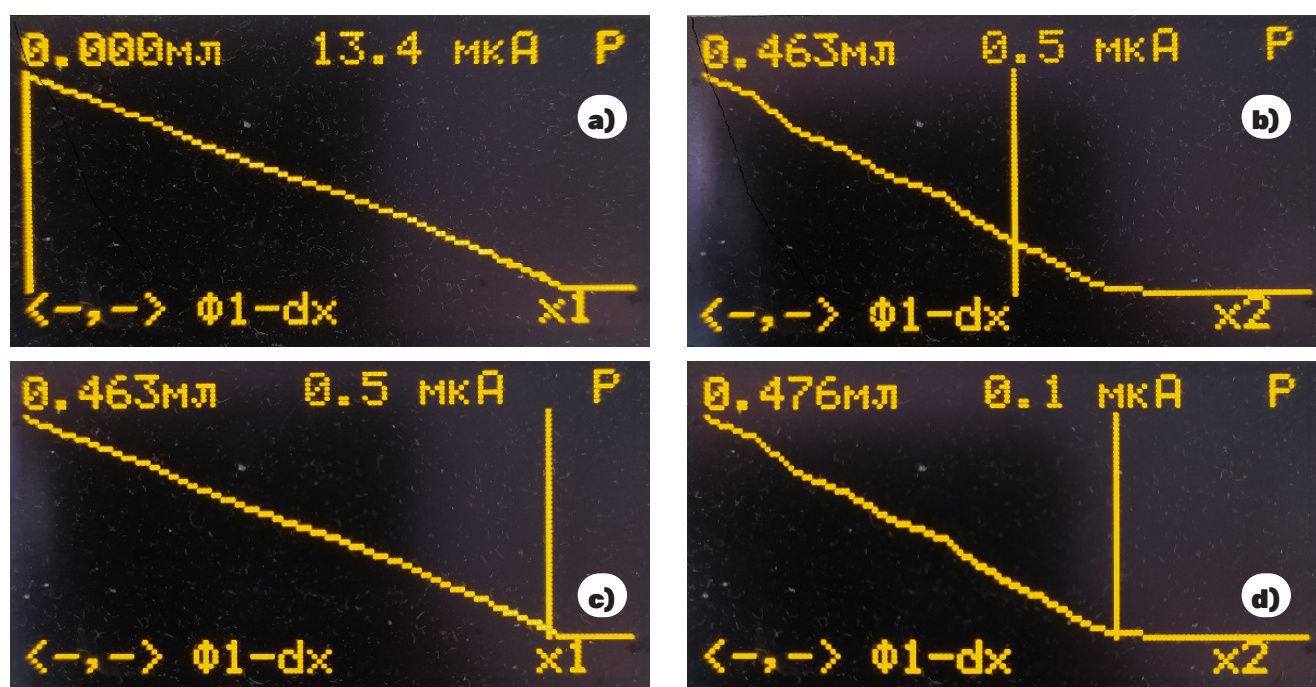

Figure 1. General appearance of a titration curve of a Ferrum Lek syrup test solution (a), determination of the volume of equivalence of Na2S2O3 near the equivalence point (b and c) and at the equivalence point (d).

The titration regime with the titrator up to the set point is used in case of knowing the current intensity at the equivalence point. As we can see from Figure 1 the equivalence volume of $Na_2S_2O_3$ was determined at the current intensity of 0,1 µA. This value of current intensity was used in the titration regime up to the set point with the titrator [4] (Figure 2)

Figure 2. Data obtained at assay *of* **a solution to be analyzed of Ferimax syrup by automatic amperometric method with two Pt indicator electrodes polarized up to 0,1 µA current intensity with $Na_2S_2O_3$ standardized solution without the addition of acetate buffer: a) at the beginning of titration; b) in the zone farthest from the equivalence point; c) in the zone near the equivalence point; d) the titrant volume at the equivalence point. (V_0=50,0 ml; V_1=2,50 ml; m=0,8681 g; ρ=1,2404 g/ml; F=1,073)**

In the preventive experiments it was established that the acetate buffer solution with pH 3.0 inhibits the oxidation reaction of KI by Fe (III) from the solutions to be analyzed but does not influence the volume of equivalence of $Na_2S_2O_3$. It was used to inhibit the KI oxidation process after a certain time interval, the influence of time on the KI oxidation process with Fe (III) from the syrup solutions to be analyzed and to decrease the possible slow reactions. For example, the oxidation in acid medium of and with oxygen [7, 16]. For this, to different volumes of solutions for analysis of Fe (III) and H_2O, but a constant volume equal to 5,0 ml of KI solution, over a certain period of time, 5,0 ml of acetate buffer was added, so that the final volume was equal 20,0 ml and the solution obtained was automatically titrated with the titrator using $Na_2S_2O_3$ solution as titrant.

In both titration regimes, the titrator gave the possibility to obtain the value of the equivalent volume of titrant, which was used to calculate the unknown mass of Fe (III) (m_x) in both syrups, according to the formula:

in which:

F- correction coefficient of the titrant compared to the theoretical concentration of 0,01 mol/l of $Na_2S_2O_3$ solution;

– the titrant's volume of equivalence, ml;

0,5585 – Fe content in mg equivalent to 1 ml of solution with a theoretical $Na_2S_2O_3$ concentration of 0,01 mol/l;

– the capacity of the volumetric flask with Fe (III) solution to be analyzed, obtained after the decomposition of Fe(OH)$_3$ polymaltose complex in the sample taken for the analysis of corresponding syrup, ml;

– the fraction of Fe (III) solution taken for the automatic titration with the titrator of the respective syrup, ml;

m – the mass of the syrup taken to decompose the Fe(OH)$_3$ polymaltose complex, g;

ρ – the density of the syrup, g/ml.

As a result of many additional experiments with solutions to be analyzed of Ferimax syrup, the influence of some factors on the results of the analysis according to formula (1) was established These factors are the decomposition temperature of the sample, the acidity of the solution at the decomposition of the sample, the presence in the analyte solution of the reducing agents, the pH of the solution. The influence of these factors on Fe (III) analysis in Ferrum Lek syrup solution was not observed.

In order to elucidate the influence of some factors exposed above, two solutions for the analysis of these two syrups were prepared. In two flasks of the same capacity, 0,7 ml of each syrup was added with an automatic pipette. In the volumetric flask containing Ferrum Lek syrup was added 2,0 ml of solution with c(1/2 H_2SO_4)=2 mol/l, and in the flask with Ferimax syrup – 3,0 ml of the same acid with the same concentration. Then the volumetric flasks were introduced one by one into water bath and the Fe(OH)$_3$ polymaltose complex decomposed at a temperature of ~ 75 - 80°C and the solutions to be analyzed were obtained according to the indications already described.

These solutions were used to study the oxidation reaction of Fe (III) with ions, taken in excess depending on the time of the oxidation reaction, as a result of which the final product is complex ions. In these experiments, 3,00 ml of solution for the analysis of each syrup was taken, 5,0 ml of KI solu-

tion and 7,0 ml of H_2O were added. Over a period of time from the start of the reaction, 5,0 ml of acetate buffer solution with pH=3,0 was added to the reaction mixture to inhibit the oxidation reaction, and ions were automatically dosed with the titrator and $Na_2S_2O_3$ solution. The obtained results were used to calculate the amount of substance of $Na_2S_2O_3$, which was consumed when dosing the solutions after inhibiting the reaction and building the dependence $n(Na_2S_2O_3)=f(t)$ (Figure 3).
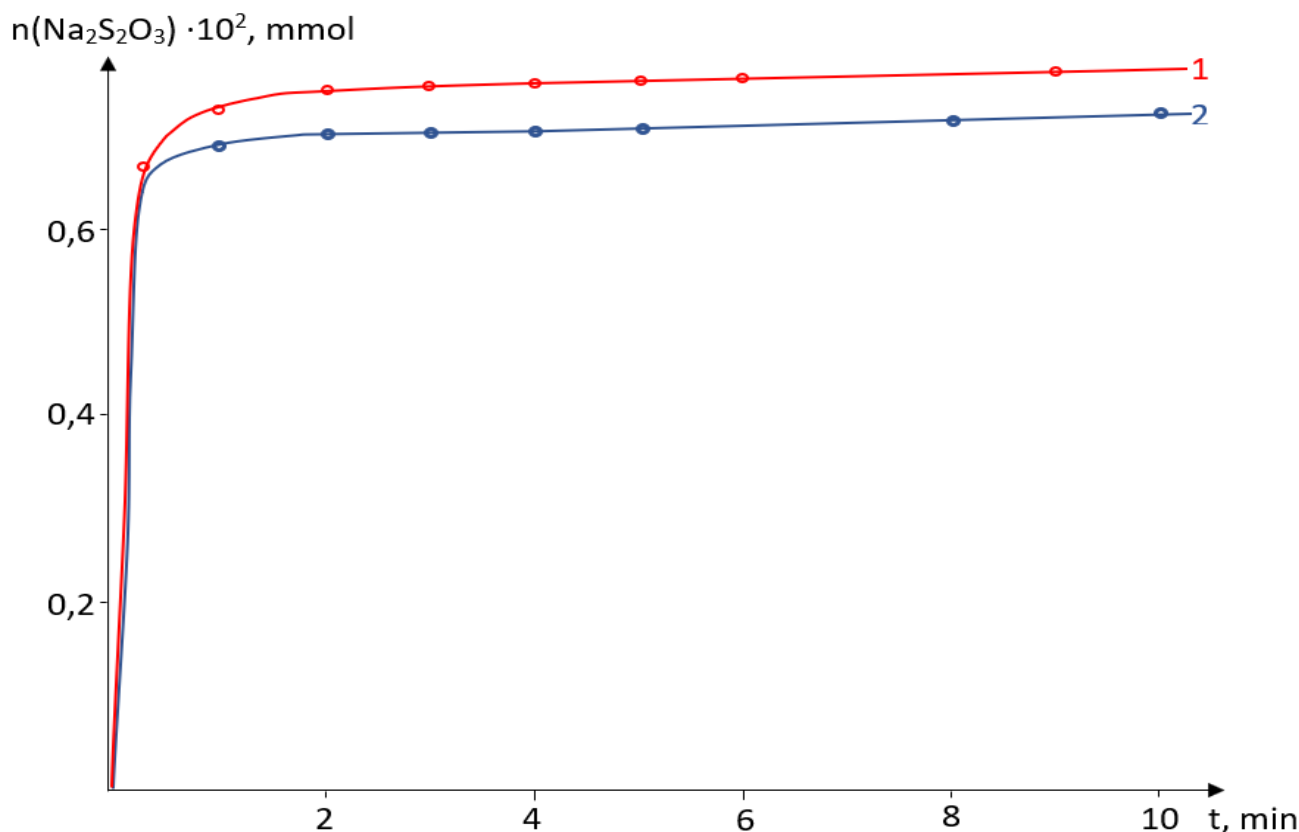

Figure 3. Dependence $n(Na_2S_2O_3)=f(t)$ on the oxidation reactions of Fe (III) in the solutions for analysis of Ferrum Lek syrup (1) and Ferimax (2) syrup with KI solution, taken in excess. 1 – $c(Na_2S_2O_3)=0,0106$ mol/l; 2 – $c(Na_2S_2O_3)=0,01106$ mol/l;

These results were also used to calculate the unknown mass of Fe (III) (m_x) in the solutions to be analyzed for these syrups according to formula (1) depending on the time of the oxidation reaction (Table 1).

Table 1. Results of the automatic titration dosage of complex ions with $Na_2S_2O_3$ solution as a function of the time of the oxidation reaction of Fe (III) with an excess of ions in the solutions to be analyzed of these two syrups

№	t, min	a) Ferrum Lek		b) Ferimax	
		$V(Na_2S_2O_3)$, ml	m_x, mg/ 5 ml	$V(Na_2S_2O_3)$, ml	m_x, mg/ 5 ml
1	0,3	–	–	0,609	44,78
2	1,0	0,684	48,28	0,619	45,52
3	2,0	0,700	49,34	0,631	46,40
4	3,0	0,709	49,97	0,632	46,47
5	4,0	0,710	50,04	0,640	47,06

6	5,0	0,711	50,11	0,637	46,84
7	6,0	0,713	50,25	–	–
8	8,0	–	–	0,647	47,58
9	9,0	0,722	51,10	–	–
10	10,0	–	–	0,656	48,24

a) **(V_0=50 ml; V_1=3,00 ml; m=0,84655 g; ρ=1,2094 g/ml; F($Na_2S_2O_3$)=1,06)**
b) **(V_0=50 ml; V_1=3,00 ml; m=0,8591 g; ρ=1,2273 g/ml; F($Na_2S_2O_3$)=1,106)**

Figure 3 shows that the components of the oxidation reaction of Fe (III) n the solution of each syrup, taken for analysis, and the ions, taken in excess, react quite quickly. The amount of $Na_2S_2O_3$ substance consumed in the titration within 3–5 minutes reaches a maximum value and further increases monotonically as the oxidation reaction time increases.

The same result was obtained when calculating the unknown mass of Fe (III) (m_x) in the solutions taken for the analysis of these syrups (Table 1). The monotonous increase in the amount of substance of $Na_2S_2O_3$ consumed by titration and the unknown mass of Fe (III) (m_x) depending on the time of the oxidation reaction can be explained by the slow oxidation of the and ions with dissolved oxygen [7, 16].

Based on the results obtained in Figure 3 and Table 1 for Ferrum Lek syrup, the oxidation and titration process of the analyte solutions of this syrup was further used with addition of acetate buffer solution to inhibit the oxidation reaction. After this process, described above, to the reaction mixture at more than 5.0 minutes after the start of the oxidation reaction was added 5,0 ml of acetate buffer solution with pH=3,0 and the ions were automatically dosed with titrator and standardized $Na_2S_2O_3$ solution.

The results obtained in the dosing of the solutions for the analysis of this syrup, with standardized solution of $Na_2S_2O_3$ and the titrator, using the two titration regimes are presented in Table 2 and 3.

The data in Tables 2 and 3 have been statistically processed and are shown in Table 4. The average mass of Fe (III) in Ferrum Lek syrup was 49,92±0,34 (for the automatic titration regime with the recording of titration curve) and 49,92±0,29 (for the automatic titration regime up to the point of 0,1 µA), with a 95% confidence interval.

Table 2. Data for the calculation of the unknown mass of Fe (III) in the solution for analysis of Ferrum Lek syrup at automatic dosing with the titrator and $Na_2S_2O_3$ solution by amperometric method with two Pt indicator electrodes with titration curve recording.

№	V_1, ml, solution to be analyzed	V($Na_2S_2O_3$), ml	m_x, mg/ 5 ml
1	1,00	0,233	48,15
2	1,50	0,354	49,38
3	2,00	0,476	49,80
4	2,50	0,593	49,63
5	3,00	0,705	49,17
6	3,50	0,837	50,05
7	4,00	0,945	49,43
8	4,50	1,072	49,85
9	5,00	1,197	50,09

(V_0=50 ml; m=0,8418 g; ρ=1,2026 g/ml; F=1,049)

Table 3. Results of the quantitative analysis of Fe (III) Fe (III) in the solution for analysis of Ferrum Lek

syrup at automatic dosing with the titrator and $Na_2S_2O_3$ solution by amperometric method with two Pt indicator electrodes up to the 0,1 μA current intensity.

№	V_1, ml	$V(Na_2S_2O_3)$,ml	m_x, mg/ 5 ml
1	1,00	0,230	49,73
2	1,50	0,343	49,44
3	2,00	0,456	49,30
4	2,50	0,578	49,99
5	3,00	0,696	50,16
6	3,50	0,812	50,16
7	4,00	0,924	49,95
8	4,50	1,043	50,12
9	5,00	1,167	50,47

(V_0=50,0 ml; m=0,8371 g; ρ=1,1959 g/ml; F=1,084)

Table 4. Primary statistical processing of experimental data obtained at automatic amperometric dosing with two Pt indicator electrodes of Fe (III) with titrator in Ferrum Lek syrup analysis solutions.

№	Measure	Value, unit of measurement	
		with titration curve recording	up to the 0,1 μA current intensity
1	Average	49,57	49,92
2	Range R=	1,34	1,17
3	Relative percent range R,%=	2,70	2,34
4	Median deviation	0,346	0,291
5	Relative mean deviation	0,698	0,583
6	Standard deviation	0,435	0,373
7	Relative standard deviation	0,878	0,747

Additional experiments showed that in Ferimax syrup analysis solutions with higher acidity than in Ferrum Lek syrup, Fe (III) ions can be determined quantitatively with $Na_2S_2O_3$ solution by iodometric method both, with and without the addition of acetate buffer solution to inhibit the oxidation reaction.

This was confirmed in the experiments performed after the following procedure. To different volumes of Ferimax syrup analysis solution 5,0 ml of KI solution with ω(KI)=10 % was added and the mixture was left to stand for 5 minutes, after which different volumes of H_2O was added so the final volume was equal to 20 ml and the obtained iodine was automatically titrated with solution and titrator, using the two titration regimes. The data obtained by titration and calculation of the unknown mass of Fe (III) (m_x) according to formula (1) are presented in Table 5 and 6.

Comparing the results in Tables 5 and 6 with those in Table 1, where the titration procedure was used with the addition of acetate buffer solution, we concluded that obtaining lower results of the unknown mass of Fe (III) (m_x) in the Table 1 was conditioned by the change in the pH of the solution. Upon inhibition of the oxidation reaction with acetate buffer solution, the pH in the experiments in Table 1 changed from 1.97 to 3.0. Under these conditions, the product of the oxidation reaction could react with some ingredients in the solution to be analyzed in this syrup, because the acetate buffer does not interfere with the titration reaction with $Na_2S_2O_3$ solution. These ingredients in the Ferimax syrup analysis solution are methylparaben and propylparaben, which have been used as preservatives [17, 18] and can react with oxidants.

Table 5. The results of the quantitative analysis of Fe (III) in the solution to be analyzed of Ferimax syrup by automatic amperometric titration method with two Pt indicator electrodes with automatic recording of the titration curve, without the addition of acetate buffer.

№	V_1, ml	$V(Na_2S_2O_3)$,ml	m_x, mg/ 5 ml
1	1,00	0,231	50,96
2	1,50	0,337	49,75
3	1,70	0,381	49,44
4	2,00	0,453	49,97
5	2,50	0,564	49,14
6	3,00	0,674	49,56
7	3,50	0,788	49,67
8	3,70	0,834	49,73
9	4,00	0,891	49,14

(V_0=50,0 ml; m=0,8624 g; ρ=1,232 g/ml; F=1,106)

Table 6. Quantitative analysis of Fe (III) in the solution to be analyzed of Ferimax syrup by automatic amperometric titration method with two Pt indicator electrodes up to 0,1 µA current intensity, without the addition of acetate buffer.

№	V_1, ml	$V(Na_2S_2O_3)$,ml	m_x, mg/ 5 ml
1	1,00	0,232	50,11
2	1,50	0,347	49,97
3	2,00	0,464	50,11
4	2,20	0,503	49,39
5	2,50	0,578	49,94
6	3,00	0,685	49,32
7	3,50	0,808	49,87
8	4,00	0,915	49,41
9	4,50	1,026	49,25

(V_0=50,0 ml; m=0,8681 g; ρ=1,2401 g/ml; F=1,083)

To confirm this statement, the procedure of preventive addition, to the solution to be analyzed of Ferimax syrup, of $KMnO_4$ solution added dropwise as in [8]. In this case, the purple color of the $KMnO_4$ solution quickly disappeared and this solution was not added, when the purple color was stable for ~ 5 seconds. This solution was further analyzed after the analysis procedure with inhibition of the oxidation reaction of Fe (III) with excess of ions with acetate buffer solution and automatic dosing with titrator of

ions with standardized $Na_2S_2O_3$ solution as described above. The results obtained are shown in Table 7, and the calculation of the unknown mass of Fe (III) (m_x) was performed according to formula (1).

The data for the calculation of the unknown mass of Fe (III) (m_x) in the solutions to be analyzed of Ferimax syrup in Tables 5, 6 and 7 have been statistically processed [19] and are shown in Table 8. For the automatic titration regime with the titrator and the recording of the curve the average mass of Fe (III)

was (49,71±0,42) mg/5 ml of syrup. The same average mass of Fe (III) of (49,71±0,28) mg/5 ml of syrup was obtained by automatic titration with the titrator and $Na_2S_2O_3$ solution, when the titration regime was used up to the current intensity of 0,1 µA. This titration regime was also used after preventive treatment of solutions to be analyzed of Ferimax syrup, taken for analysis, with a few drops of $KMnO_4$ solu-

tion and their automatic titration with $Na_2S_2O_3$ solution after the addition of acetate buffer solution to inhibit the oxidation reaction. In the latter case, the mean mass of Fe (III) was (50,09±0,45) mg/5 ml of syrup. In all three cases (Table 8) the confidence interval was 95%.

Table 7. Data obtained after the preventive treatment of the solutions to be analyzed of Ferimax syrup with $KMnO_4$ solution and their subsequent analysis by automatic amperometric titration method with two Pt indicator electrodes up to the current intensity of 0,1 µA.

№	V_1, ml	$V(Na_2S_2O_3)$, ml	m_x, mg/ 5 ml
1	1,50	0,358	51,03
2	2,00	0,472	50,46
3	2,50	0,584	49,95
4	2,75	0,649	50,46
5	3,00	0,697	49,68
6	3,20	0,756	50,52
7	3,50	0,806	49,24
8	4,00	0,937	50,09
9	4,50	1,039	49,37

(V_0=50,0 ml; m=0,847 g; ρ=1,210 g/ml; F=1,072)

Table 8. Primary statistical processing of experimental data obtained by automatic iodometric dosage of Fe (III) with $Na_2S_2O_3$ solution and titrator, in the solutions to be analyzed of Ferimax syrup

№	Measure	Value, unit of measurement		
		1	2	3
1	Average	49,71	49,71	50,09
2	Range R=	1,82	0,86	1,79
3	Relative percent range R,%=	3,661	1,730	3,574
4	Median deviation	0,352	0,324	0,467
5	Relative mean deviation	0,708	0,652	0,932
6	Standard deviation	0,545	0,357	0,589
7	Relative standard deviation	1,096	0,718	1,176

1 – titration with titration curve recording; 2 – titration up to the current intensity of 0,1 µA; 3 – preventive treatment of the solutions to be analyzed with KMnO4 solution and titration up to 0,1 µA current intensity, in the presence of acetate buffer solution.

CONCLUSIONS

A new method for quantitative determination of Fe (III) by automatic amperometric titration method with two Pt indicator electrodes in Ferrum Lek and Ferimax syrups was elaborated. For analysis of Ferimax syrup the influence of some factors on the results of the analysis was established, such as the decomposition temperature of the sample, the acidity of the solution at the decomposition of the sample, the presence in the analyte solution of the reducing agents and the pH of the solution. As a result of experiments is was shown that change in the

pH of the solution lead to the inhibition of the oxidation reaction with acetate buffer solution of methylparaben and propylparaben, which have been used as preservatives. The influence of these factors on Fe (III) analysis in Ferrum Lek syrup solution was not observed. The elaborated method can be recommended for the determination of iron in liquid pharmaceutical forms.

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