# CHIMIE FARMACEUTICĂ ȘI CONTROLUL MEDICAMENTULUI

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## ANALIZA CANTITATIVĂ A IODURII DE POTASIU ÎNTR-O FORMĂ FARMACEUTICĂ LICHIDĂ PRIN METODA AMPEROMETRICĂ DE DOZARE AUTOMATĂ CU DOI ELECTROZI INDICATORI DE PLATINĂ

## QUANTITATIVE ANALYSIS OF POTASSIUM IODIDE IN A LIQUID PHARMACEUTICAL DOSAGE FORM BY THE AUTOMATIC AMPEROMETRIC DOSING METHOD WITH TWO PLATINUM INDICATOR ELECTRODES

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**Abstract.** Medicines containing iodine have a variety of uses in medicine, while preparations based on potassium iodide are especially known in the prophylactic treatment following a nuclear accident, in order to block the assimilation of radioactive iodine in the thyroid gland. Thus, it was proposed to develop a new method for determining the mass of potassium iodide as an active substance in a liquid pharmaceutical form by the amperometric method with two Pt indicator electrodes. In the study, the titrator «TITRION» was used in the titration curve recording regime, in the titration curve recording mode. Electrodes were polarized with 25 mV and the solution was automatically dosed with standardized $Na_2S_2O_3$ solution. In the oxidation process of $I^-$ ions with $Br_2$ water, the reaction proceded according to the scheme $I^- \rightarrow IO_3^- \rightarrow 3I_2$. In order to eliminate the influence of the $I^-$ ion adsorption processes on the Pt indicator electrodes of the titrator, the electrodes were placed in the solution with c(NaOH)=1,0 mol/l.

**Keywords:** automatic amperometric titration, automatic amperometric method with two indicator electrodes, titrator, potassium iodide, iodine, buffer solution.

**Rezumat.** Medicamentele cu conținut de iod au o varietate de utilizare în medicină, totodată preparatele pe bază de iodură de potasiu fiind în special cunoscute în tratamentul profilactic în urma unui accident nuclear, în scopul blocării asimilării iodului radioactiv în glanda tiroidă. Astfel, s-a propus elaborarea unei noi metode de determinare a masei iodurii de potasiu ca substanță activă într-o formă farmaceutică lichidă prin metoda amperometrică cu doi electrozi indicatori de Pt. În studiu s-a folosit titratorului «TITRION», în regimul de lucru cu înregistrarea curbei de titrare. Electrozii au fost polarizați cu 25 mV și soluția s-a dozat automat cu soluție standardizată de $Na_2S_2O_3$. În procesul de oxidare a ionilor de $I^-$ cu apa de $Br_2$, reacțiile au decurs după schema $I^- \rightarrow IO_3^- \rightarrow 3I_2$ . Pentru a elimina influența proceselor de adsorbție a ionilor de $I^-$ pe electrozii indicatori de Pt a titratorului, electrozii s-au plasat în soluție cu c(NaOH)=1,0 mol/l.

**Cuvinte cheie:** titrare amperometrică automată, metodă amperometrică automată cu doi electrozi indicatori, titrator, iodură de potasiu, iod, soluție tampon.

## INTRODUCTION

In the case of a nuclear accident, radioactive iodine can constitute a significant part of the emitted radiation. Because of its volatile nature, iodine can be easily inhaled and absorbed by the lungs. Radioactive iodine accumulates in the thyroid gland exposed to extreme high radiation, with an increased risk of local damage caused by radiation. The absorption of radioactive iodine in the thyroid gland can be blocked by the immediate oral administration of a large dose of stable iodine [1]. Thus preparations containing potassium iodide are especially known in the prophylactic treatment of the effects of radioactive iodine on the thyroid gland in the event of the release of radioactive iodine into the air, following a nuclear accident.

Likewise, potassium iodide can be used as a preparation that inhibits the processes of iodination and release of thyroid hormones, preventing endemic goiter. When iodine enters the epithelial cells of the thyroid follicle under the influence of the enzyme iodide peroxidase, iodine is oxidized to form elemental iodine, which is incorporated into the tyrosine molecule. In this case, part of the tyrosine radicals in thyroglobulin is iodinated. Iodine tyrosine radicals condense into thyrotrons, the main of which is thyroxine (T4) and triiodothyronine (T3).

Currently, in the treatment of various pathologies, both for adults and children, liquid medicinal forms containing potassium iodide, prescribed by physicians, which are prepared in the production department of *Vasile Procopisin* University Pharmaceutical Center, are widely used.

The study carried out in the *Vasile Procopisin* University Pharmaceutical Center showed the proportion of liquid medicinal forms with potassium iodide content to be 3% according to medical prescriptions from all magistral preparations.

Potassium iodide is an expectorant remedy, from the group of secretostimulants, which has an important fluidizing effect, not only in case of peroral administration, but also local. This is mainly indicated in cases of chronic bronchitis, asthmatic bronchitis, bronchial asthma. [2]

Potassium iodide, in eye drops, is indicated in the treatment of retinal degenerative processes, cataracts in the initial stage and as an adjuvant remedy in the treatment of mycotic conjunctivitis and keratitis. The state nomenclature of medicines currently includes 4 commercial names of products containing potassium iodide as an active substance.

## MATERIAL AND METHODS

In study a liquid pharmaceutical form (LPF) prepared in the production department of *Vasile Procopisin* University Pharmaceutical Center of *Nicolae Testemitanu* State University of Medicine and Pharmacy of the Republic of Moldova have been used, which in the final volume of 100 ml of drug product contained: KI – 5,0 g; NaCl – 0,4 g; $NaHCO_3$ – 0,5 g.

*Laboratory glassware*: volumetric flasks of different capacities, two automatic pipettes from brand DACpette with the capacity of 100 – 1000 µl and 1000 – 5000 µl. The mass of $KIO_3$ sample was weighted using a glass vial, using the RADWAG AS 110.R1 balance.

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

The titration curve recording mode is divided into two areas. In the first zone, which is at the beginning of the titration and is still far from the equivalence volume, the titrator adds the titrant in larger and equal portions over certain time intervals. The second zone of this mode is near the equivalence point. In this area the titrator adds the titrant in smaller and equal portions also over certain time intervals. The entire automatic titration process is established, controlled and can be changed by the operator [4].

In this publication the electrodes were polarized by 25 mV and the current intensity measurement limit by the titrator was 50 µA when dosing the complex $I_3^-$ ions formed in the solution. In the working mode of the titrator, a solution with a theoretical concentration of $Na_2S_2O_3$ equal to 0,02 mol/l was used. This solution was automatically added to the solution which being dosed, at the beginning of the titration (first zone) in portions equal to 40 µl every 3 s and near equivalence point (second zone) – 4 µl every 5 s.

*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 with $c(1/6KIO_3)$ = 0,02 mol/l was prepared as follows. The calculated sample with a mass of 0,7133 g was weighted and dissolved in $H_2O$ in a 1 l volumetric flask, brought to the volume with $H_2O$ and homogenized. The solution with $\omega$(KI)=10 % was prepared from KI. These two solutions were kept in dark glass containers.

The primary standard solution of $KIO_3$ was used to standardize the secondary solution of $Na_2S_2O_3$ by the iodometric method of oxidant dosing, which uses substituent titration. The solution of $Na_2S_2O_3$ with $c(Na_2S_2O_3)$ = 0,1 mol/l was prepared from fixanal, $H_2O$ boiled and cooled to room temperature with the addition of $Na_2CO_3$ with a mass of 0,1 g per1 l of solution to stabilize it [5, 6]. 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.

Additionally, several solutions were used in the study. One of them was the acetate buffer solution, which was prepared from sodium acetate and concentrated acetic acid as follows. The mass of $CH_3COONa \cdot 3H_2O$ (5,44 g) was calculated and weighted to obtain a solution with a volume of 200 ml and $c(CH_3COONa)$ = 0,2 mol/l. The mass of this sample was transferred to a 200 ml volumetric flask and dissolved in $H_2O$. To the obtained solution 59-60 ml of concen-

trated $CH_3COOH$ acid was added and the obtained solution was diluted with $H_2O$ up to volume, obtaining a solution with pH=3,0-3,1. In the experiments, $Br_2$ water saturated solution without adding KBr to its preparation [7] and water-saturated solution of phenol [8] were also used.

The solution with c(NaOH)=1,0 mol/l was used for the desorption of $I^-$ ions from the Pt indicator electrodes of the titrator. This procedure was performed each time after recording several titration curves with the titrator, the Pt indicator electrodes being introduced into this solution for 25-30 minutes. At the end of the working day, the electrodes of the titrator were inserted and left until the next day in the c(NaOH)=1,0 mol/l solution for the desorption of $I^-$ ions [9].

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.

*Standardization of $Na_2S_2O_3$ solution*

To a certain volume of primary standard solution of $KIO_3$, with c(1/6 $KIO_3$) = 0,02 mol/l was added 5 ml of acetate buffer solution, a certain volume of $H_2O$ so that the volume was equal to 15 ml. Next, another 5 ml of solution with ω(KI)=10 % was added to this solution and the reaction mixture was left in the dark for 4 – 5 minutes. In the solution, an equivalent amount of $I_2$ was formed, which is insoluble in $H_2O$ [8], but in the presence of an excess of KI in the solution, complex $I_3^-$ ions were formed [5, 6], which were automatically dosed with $Na_2S_2O_3$ solution by the amperometric method with two Pt indicator electrodes with the titrator [3].

For the standardization of the solution with c($Na_2S_2O_3$) = 0,02 mol/l the titrator and the titration mode with the registration of the titration curve were used After the end of the automatic dosing, the operator displayed the titration curve on the screen, processed it according to the used manual of the titrator [4] and determined the equivalence volume of the titrant. The concentration of the $Na_2S_2O_3$ solution was calculated based on the law of equivalents. The automatic dosing was performed several times, the average concentration and then the correction factor of the $Na_2S_2O_3$ solution were calculated.

*Preparation of solution for analysis of LPF*

The solution for analysis of LPF was prepared as follows. Using an automatic pipette 0,40 ml of solution of this form was measured and this volume was transferred quantitatively into a 100 ml ground stoppered volumetric flask. To this solution was added 8-10 ml of $H_2O$, 3,0-3,2 ml of $Br_2$ water, the flask was stoppered and shaken. Over 1-2 minutes, to the obtained solution, 2,0 ml of solution with c(NaOH)=1 mol/l, 1,5-2,0 ml of saturated phenol solution were added, the solution was diluted to volume with $H_2O$ and homogenized.

The obtained solution was used to determine the mass of KI in LPF as follows. To different volumes (0,50-2,00 ml) of solution, measured using automatic pipettes, were added 5 ml of acetate buffer solution, different volumes of $H_2O$ so that the volume of each solution was equal to 15 ml, 5 ml of solution with ω(KI)=10 % and the obtained solution was left in the dark within 4-5 minutes. During this period of time, an equivalent amount of $I_2$ molecular was eliminated from the solution (more precisely, complex $I_3^-$ ions were formed [5, 6]).

After this, in each solution obtained as described above, the polarized electrodes of the titrator were inserted and the solution was automatically dosed with a standardized solution of $Na_2S_2O_3$ by the amperometric method with two Pt indicator electrodes.

## RESULTS AND DISCUSSION

For the quantitative determination of different amounts of $I^-$ ions, the oxidation reaction of these ions with $Br_2$ water, taken in excess, was most frequently used [10, 11]. Upon oxidation in solution the reaction takes place:

$$I^- + 3Br_2 + 3H_2O = IO_3^- + 6H^+ + 6\,Br^- \quad (1)$$

The oxidation reaction was carried out in a small volume of LPF solution (0,4 ml) and the excess of oxidant in this solution was removed in the basic medium by adding the saturated phenol solution. After that, the obtained solution was diluted with $H_2O$ up to 100 ml and used in the study, measuring different volumes for the quantitative determination of  ions in the acidic medium by the iodometric method of oxidant dosage [5, 6, 12].

$$IO_3^- + I^- + 6H^+ = 3I_2 + 3H_2O \quad (2)$$

and the eliminated $I_2$ was automatically dosed by the titrator with a standardized solution of $Na_2S_2O_3$ by the amperometric method with two Pt indicator electrodes.

In this method the analytical signal appears as follows. After the completion of reaction (2), both forms of the reversible redox half-reaction $I_2/I^-$ were present in the solution [13]. When introducing the two polarized Pt electrodes into this solution, the titrator recorded the current intensity (μA), because at the same time and in equivalent amounts the $I_2$ formed was reduced at the cathode, and the $I^-$ ions were oxidized at the anode [13].

When automatically dosing this solution by the

titrator with a standardized solution of $Na_2S_2O_3$ the concentration of the oxidized form of the reversible $I_2/I^-$ system always decreases after the addition of each titrant portion. Along with this, the intensity of the current in the dosing circuit also decreases and the titration curve, recorded by the titrator, represents a downward straight curve with a bend to the right at the end of the titration (Figure 1a). After each titration, the operator displays the titration curve on the liquid analyzer screen and determines the titrant equivalence volume (Figure 1).

In addition, reactions (1) and (2) proceed according to the scheme $I^- \rightarrow IO_3^- \rightarrow 3I_2$ and the amount of substance of $I^-$, taken for oxidation and quantitatively transformed into molecular $I_2$, increases by 6 times.

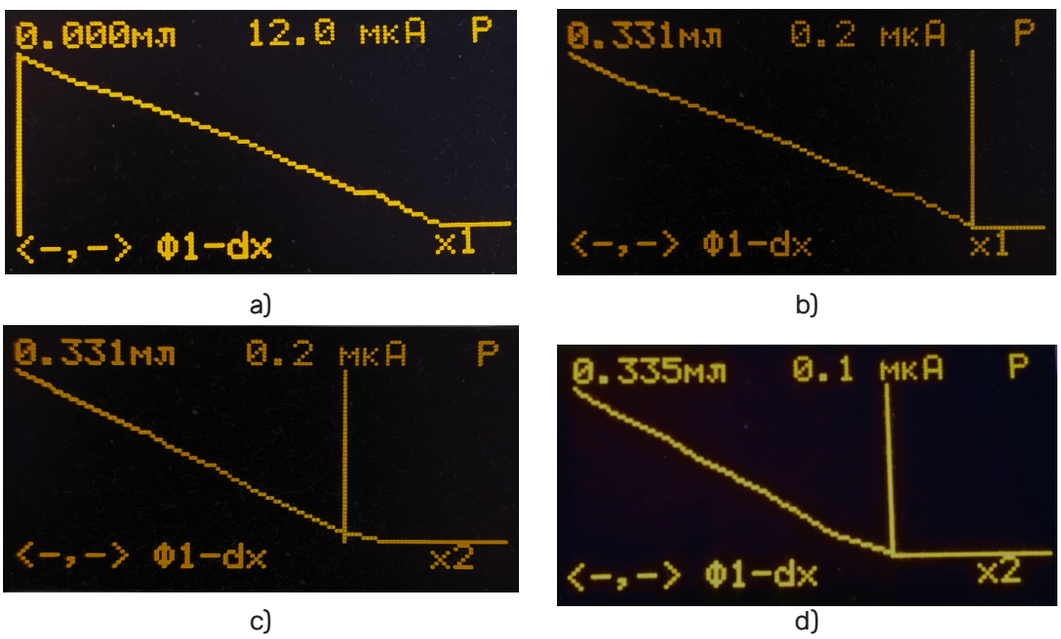
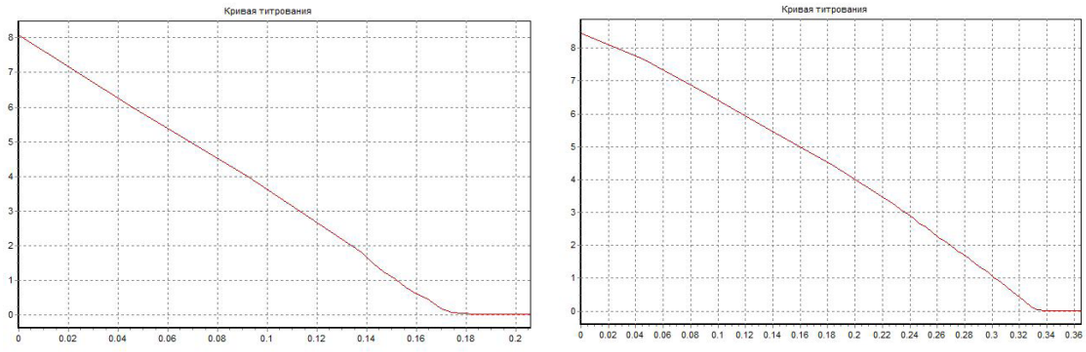



**Figure 1. General aspect of a titration curve of a solution of LPF (a), determination of the titrant volume near the equivalence point (b and c) and at the equivalence point (d).**

In the study, it was observed that the continuous use of the electrodes during the automatic recording of the titration curves with the titrator, influences the value of the current intensity (μA) at the beginning of the dosing for one and the same volume of LPF solution for analysis, taken for dosing (Figure 1a and Figure 2b). In addition the automatic titration curves recorded by the titrator, from descending linear curves become descending convex curves with a bend to the right at the end of the titration (Figure 2).




a) b)

**Figure 2. General appearance of two curves of automatic dosing of the LPF solution for the analysis with different volumes, recorded by the computer: a) 0,5 ml with the desorption of $I^-$ ions; b) 1,0 ml without desorption of $I^-$ ions.**

The authors of the monograph [9] experimentally demonstrated that the platinum indicator electrode inserted and held for different periods of time (in minutes) in a solution with c(KI)=0,1 mol/l absorbs $I^-$ ions and negatively influences on the appearance of the voltammograms of reduction of Fe (III) with this electrode.

Several methods are used for the desorption of $I^-$ ions from Pt electrodes [9]. In this study, it was used to wash the electrodes several times with NaOH solution with c(NaOH)=1 mol/l before recording the curve or to put them in this solution for 25-30 minutes after recording 2-3 automatic titration curves with the titrator.

The mass of the active substance of potassium iodide (m(KI), g), in LPF was calculated according to the formula:

$$m(KI) = K \cdot T(Na_2S_2O_3/KI) \cdot V(Na_2S_2O_3) \cdot \frac{V_0 \cdot V_t}{6V_1 \cdot V_f}, \quad (3)$$

where,

$K$ – correction coefficient of the titrant compared to the theoretical concentration of 0,02 mol/l of $Na_2S_2O_3$ solution;

$T(Na_2S_2O_3/KI)$ – the theoretical titer of the $Na_2S_2O_3$ solution with c($Na_2S_2O_3$) = 0,02 mol/l relative to the molar mass of the equivalent of KI, g/ml;

$V(Na_2S_2O_3)$– equivalence volume of the titrant, ml;

$V_0$ – the capacity of the volumetric flask with the solution to be analyzed of LPF after the oxidation of $I^-$ ions to the ions and the removal of the excess of oxidant taken for analysis, ml;

$V_1$ – the volume of the LPF solution to be analyzed after oxidation and removal of excess of oxicant taken for analysis, ml;

$V_t$– the total volume of LPF solution, ml;

$V_f$– – the fraction of LPF solution taken for oxidation and analysis, ml.

The experimental data obtained and the results of calculating the mass of potassium iodide (m(KI), g), in LPF according to equation (3) are presented in Table 1.

**Table 1 Data for calculation of the KI mass in LPF after performing the reactions according to the scheme $I^- \rightarrow IO_3^- \rightarrow 3I_2$ and the automatic dosing of $I_2$ with $Na_2S_2O_3$ solution by the amperometric method with two Pt indicator electrodes.**

| № | V1, ml | V ($Na_2S_2O_3$), ml | m(KI), g |
|---|---|---|---|
| 1 | 0,50 | 0,165 | 4,98 |
| 2 | 0,70 | 0,233 | 5,03 |
| 3 | 0,80 | 0,265 | 5,00 |
| 4 | 0,90 | 0,297 | 4,98 |
| 5 | 1,00 | 0,335 | 5,06 |
| 6 | 1,20 | 0,394 | 4,96 |
| 7 | 1,50 | 0,499 | 5,02 |
| 8 | 1,70 | 0,567 | 5,04 |
| 9 | 2,00 | 0,666 | 5,03 |
| | (K=1,092; T(Na2S2O3/KI)=0,0032 g/ml; V0=100 ml; Vt=100 ml; Vf=0,4 ml) | | |

The results of determining the mass of potassium iodide in LPF according to realation (3) were processed statistically [14] and are presented in Table 2. The mass of KI in LPF was 5,01±0,03 g, having a confidence interval of 95%.

**Table 2 Primary statistical processing of experimental data, obtained when determining the mass of potassium iodide in LPF by the method of automatic iodometric dosing of oxidants**

| № | Measure | Value, unit of measurement |
|---|---|---|
| 1 | Average $\bar{X} = \frac{\sum_{i=1}^{N} x_i}{N}$ | 5,01 |
| 2 | Range $R = x_{max} - x_{min}$ | 0,10 |
| 3 | Relative percent range $R_{\%} = \frac{R}{x} \cdot 100$ | 1,996 |
| 4 | Median deviation $\bar{d} = \frac{\sum_{i=1}^{N} \lvert x_i - \bar{x} \rvert}{N}$ | 0,028 |
| 5 | Relative mean deviation $\overline{d_r}, \% = \frac{\bar{d}}{x} \cdot 100$ | 0,56 |
| 6 | Standard deviation $S = \sqrt{\frac{\sum_{i=1}^{N} (x_i - \bar{x})^2}{N-1}}$ | 0,033 |
| 7 | Relative standard deviation $s_r, \% = cv, \% = \frac{S}{\bar{x}} \cdot 100$ | 0,66 |

## CONCLUSIONS

A new method was developed to determine the mass of potassium iodide as an active substance in a liquid pharmaceutical form by performing the reactions according to the scheme nd the automatic dosing of $I_2$ with standardized $Na_2S_2O_3$ solution by amperometric method with two Pt indicator electrodes.

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