QUANTITATION OF ETHYLMORPHINE CONTENT IN EYE DROPS USING REACTION WITH DIPEROXY ACID

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Introduction. Previously, we established that diperoxyadipic acid stoichiometrically and quantitatively reacts with Ethylmorphine according to the scheme (Fig.) [1]:

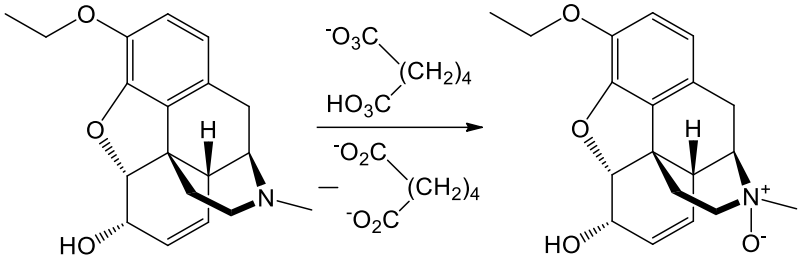

Fig. Scheme of the process of oxidation of ethylmorphine by diperoxyadipic acid using the example of the monoanion of diperoxyacid

For one mole of alkaloid (R_3N), 0.5 mole of diperoxyadipic acid is consumed, and at pH 8-8.4, the interaction is completed in 5-10 min. By determining the amount of diperoxyacid consumed in the reaction by iodometric titration, it is possible to quantitatively determine the alkaloid in aqueous solutions.

Aim: To develop a new method for quantitative determination of the alkaloid content of ethylmorphine in eye drops produced *ex tempore*.

Methods: The purity of the diperoxy acid (content of the main substance, *w*, *wt* %), as well as the concentration of the diperoxy acid in the stock solution and post-reaction mixtures ($c(CH_2)_4(CO_3H)_2$, mol/L) were determined by iodometric titration. A stock solution of diperoxy acid is prepared by weighing out an appropriate portion of a pure solid or by measuring out an appropriate volume of a pure liquid, placing it in a suitable flask, and diluting to a known volume.

A sample (about 0.0100 – 0.0200 g) was dissolved in 20 mL of distilled water in a 100 ml Erlenmeyer flask and 5 ml of a 0.01 mol/L solution of sulfuric acid was added or to 5 mL of 0.01 mol/L sulfuric acid solution was added to 0.5 – 1.0 mL of the tested solution (0.02 mol/L) of diperoxy acid in an Erlenmeyer flask. The flask was purged with argon for 25 s and a pinch or 1 – 2 mL of 5% potassium iodide solution was added. After closing, the flask is placed in the dark for 1 min. Then 20 mL of distilled water was added and the mixture was titrated with 0.02 M aqueous sodium thiosulfate solution. The content of the main substance in the preparation (*w*, %) or the molar concentration ($c(CH_2)_4(CO_3H)_2$) were calculated according to the equations, respectively:

$$w = \frac{0.02 \cdot K \cdot V_T \cdot M \cdot 100\%}{m \cdot 4 \cdot 1000}$$

$$c(CH_2)_4(CO_3H)_2 = c(Na_2S_2O_3) \times V_T(Na_2S_2O_3) \times K/(4V(CH_2)_4(CO_3H)_2)$$

where: $c(Na_2S_2O_3)$ is molar concentration of the titrant [mol/L], $V_T(Na_2S_2O_3)$ is volume of the titrant [mL]; 4 is coefficient calculated based on the stoichiometry of the reactions:

$$(CH_2)_4(CO_3H)_2 + 4KI + H_2SO_4 = (CH_2)_4(CO_2H)_2 + 2I_2 + 2H_2O$$

$$I_2 + 2Na_2S_2O_3 = Na_2S_4O_6 + 2NaI$$

Results: Ethylmorphine hydrochloride eye drops were analyzed. Composition of eye drops: Ethylmorphine hydrochloride 0.1g; Sodium chloride 0.075 g; distilled water 10.0 g.

Procedure for quantitative determination of Ethylmorphine in eye drops. Transfer 0.50 ml of eye drops to a 100 ml Erlenmeyer flask, add 3.00 mL of diperoxyadipic acid solution (0.02 mol/L), 15 mL of 0.2 mol/L phosphate buffer mixture with pH 8.4, mix and leave for 10 minutes. After that, the solution is acidified with 2 mL of a 0.1 mol/L sulfuric acid solution, 2 mL of a 5% potassium iodide solution is added with stirring, and the released iodine is immediately titrated with a 0.02 mol/L sodium thiosulfate solution until the yellow color disappears (*V*, mL). In parallel, a control experiment is conducted. To 15.5 mL of distilled water in a 100 mL Erlenmeyer flask, add 3.00 mL of diperoxyadipic acid solution, acidify 0.5 mL of sulfuric acid solution, add 2 mL of 5% potassium iodide solution and titrate the released iodine with 0.02 mol/L sodium thiosulfate solution until the yellow color of the solution disappears (V_0, mL). The content of Ethylmorphine hydrochloride X, in g, is calculated by the formula:

$$\mathrm{X} = \frac{(V_0 - V) \cdot K \cdot T \cdot 10.0}{a}$$

where, *V* is the volume of 0.02 mol/L sodium thiosulfate solution used in the work experiment, ml; V_0 – volume of 0.02 mol/L sodium thiosulfate solution used in the control experiment, ml; *K* is the coefficient of correction of the molar concentration of sodium thiosulfate solution to 0.0200 mol/L; *a* is the volume of the studied eye drop solution taken for analysis, mL; *T* is the titer of sodium thiosulfate solution. 1.00 mL of 0.0200 sodium thiosulfate solution corresponds to 0.003859 g of Ethylmorphine hydrochloride, which should be 0.085 – 0.116 g (±15%) in 10.0 mL.

The results of the analysis of eye drops according to the developed procedure.

$$\mathrm{X}_1 = \frac{(4.00 - 2.60) \cdot 0.9600 \cdot 0.003859 \cdot 10.0}{0.50} = 0.104 \text{ g}$$

$$\mathrm{X}_2 = \frac{(4.00 - 2.66) \cdot 0.9600 \cdot 0.003859 \cdot 100}{0.50} = 0.100 \text{ g}$$

$$\mathrm{X}_3 = \frac{(4.00 - 2.63) \cdot 0.9600 \cdot 0.003859 \cdot 100}{0.50} = 0.102 \text{ g}$$

$\overline{\mathrm{X}}$ = 0.102 g; S = 0.002; $\Delta\overline{x}$ = 0.005; RSD = 1.96% (*n* = 3; *P* = 0.95%).

Conclusion. A new method was developed and the possibility of quantitative determination of Ethylmorphine content in the medicinal product using diperoxyadipic acid as an analytical reagent was demonstrated. The obvious advantages of the developed method are the speed and simplicity of the analysis, as well as the absence of the use of toxic solvents or expensive reagents.

References:

1. Blazheyevskiy M.Ye., Mozgova O.O., Moroz V.P., Kryskiv O.S. Diperoxyadipic acid N-oxidation of ethylmorphine in aqueous medium: a kinetic and mechanistic study. New and traditional in the research of modern representatives of medical science: a collection of theses of scientific works of the participants of the international scientific and practical conference (Lviv, February 25–26, 2022). – Lviv: PO "Lviv Medical Association", 2022. – 100 p. (P. 60–64).