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MINISTRY OF HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY
DEPARTMENT OF INDUSTRIAL TECHNOLOGY OF MEDICINES AND COSMETICS
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ФУНДАМЕНТАЛЬНІ ТА ПРИКЛАДНІ ДОСЛІДЖЕННЯ У ГАЛУЗІ ФАРМАЦЕВТИЧНОЇ ТЕХНОЛОГІЇ

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TITRIMETRIC MICRO-DETERMINATION OF ETHACIZINE IN TABLETS USING OXONE

Kryskiw L.S. [1]***, Kucher T.V.*** [1]***, Kryskiv O.S.*** [2]***, Moroz V.P.*** [2]***, Blazheyevskiy M.Ye.*** [2]
[1]**I. Horbachevsky Ternopil National Medical University**
[2]**National university of pharmacy, Harkiv, Ukraine**

Introduction. Ethacizine (*Syn.* ethacyzine) is a class Ic antiarrhythmic agent. It is used in Ukraine and some other countries for the treatment of severe and/or refractory ventricular and supraventricular arrhythmias, especially those accompanied by organic heart disease. It is also indicated as a treatment of refractory tachycardia associated with Wolff–Parkinson–White syndrome. Ethacizine Hydrochloride (ETC) is chemically an ω-aminoacyl derivative of phenothiazine, a diethylamine analogue of Moracizine (syn. Etmozine). Both Ethacizine and Moricizine are N_{10}-acylderivatives and also contain a urea (as part of the urethane) group. IUPAC Name Ethyl (10-(3-(diethylamino)propanoyl)-10H-phenothiazin-2-yl)carbamate hydrochloride (Fig. 1).

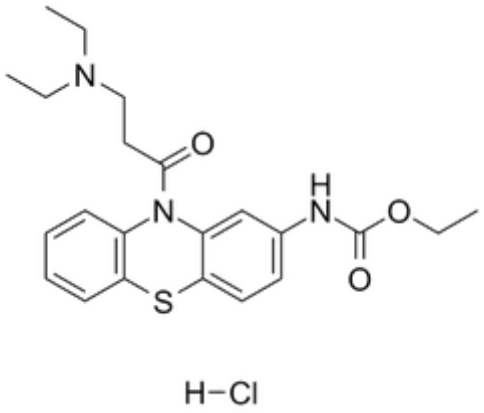


Fig. 1 Structural formula of Ethacizine Hydrochloride

The official method depends on non-aqueous titration (perchloric acid method) or High-Performance Liquid Chromatography (HPLC) of the dosage forms. Quantitative determination of drugs in dosage forms (tablets, injection solutions) is carried out using various physico-chemical methods also. An extraction-photometric method has been proposed for the quantitative determination of ethacysine as well as the method of direct UV spectrophotometry in a medium of 0.01 M sulfuric acid at 268 nm. A method for the quantitative determination of ethacizine in tablets in the form of a sulfone derivative using the fluorimetric method has been developed. In the perchloric acid method, the medium has to be scrupulously anhydrous. This is inconvenient in practice and even trace amount of water will affect the results.

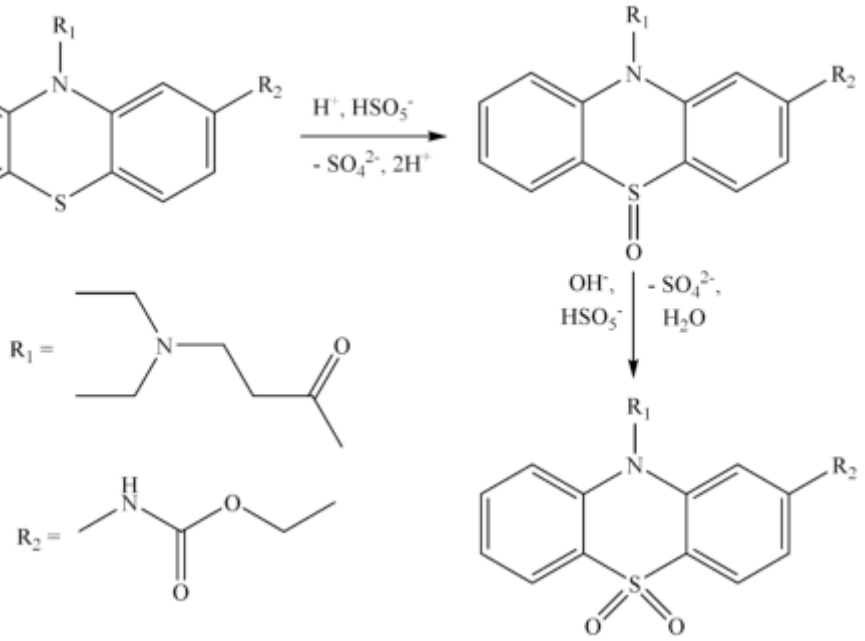
The aim of the study. To develop a new ox-red method for micro-determination of ETC in the pure form and in pharmaceutical preparations using $KHSO_5$ as an oxidizing agent by iodometric titration.

Methods of research. "Ethacizine" tablets, 0.05 g each (JSC Olpha (Lithuania).

In the experiments, Oxone® was used for the oxidation of *Ethacizine* to its sulfone. The active ingredient of Oxone® is potassium peroxomonosulfate ($KHSO_5$), which is a component of a highly stable triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$. The

kinetics of the S-oxidation reaction of ET in an alkaline medium (phosphate buffer with pH 8.4) was studied by the method of sampling by consuming $KHSO_5$ (iodometric titration of the oxidant residue). The released iodine was titrated with a thiosulfate solution with a concentration of 0.02 mol/l, measuring the volume with an accuracy of ± 0.01 ml (using a 10 ml microburette).

Main results. It was found that in a phosphate buffer solution (pH = 8.4) under conditions of excess oxidant, the reaction proceeds quantitatively and stoichiometrically in 20 min (2 mol of $KHSO_5$ is consumed per 1 mol of ETC) with the formation of the corresponding sulfone derivative ethacizine. The nature of the product formed during the interaction of ethacizine with the oxidizing reagent under the conditions of the analysis was confirmed by comparing the R_f values in four solvent systems, as well as by comparing the UV absorption spectra with those of solutions of samples of authentic Ethacizine sulfone obtained by counter synthesis. In all cases, the spots of the chromatograms of the test and standard solutions of the ethacizine sulfone witnesses were identical in color and R_f value. Sulfone of ethacizine: UV-spectrum: ε (λ_{max} =279 nm) = 13.699 L mol^{-1} cm^{-1}; ε (λ_{max} =306 nm) = 5.99×10^3 L mol^{-1} cm^{-1}; ε (λ_{max}=328 nm)=4.553×10^3 $L\cdot mol^{-1}\cdot cm^{-1}$.The scheme of the oxidation process of ethacizine to the corresponding sulfone is shown in Fig. 2.



Based on the results obtained, a new indirect titrimetric method for quantitative micro-determination of ethacisine in the bulk drug and tablets of 0.05 g was developed, which involves the use of $KHSO_5$ as a reagent. A known excess of reagent is added to the drug solution, followed by a buffer solution with pH 8.4, and after 20 min the residual reagent is determined by iodometric titration.

Conclusions. A new method was developed and the possibility of quantitative determination of ethacisine in the bulk drug and 0.05 g tablets by iodometric titration using $KHSO_5$ in the form of Oxone as an oxidizing reagent was demonstrated. RSD <1.75% (n=5; P=0.95). A statistical comparison of the results obtained for tablets with those of an official method shows excellent agreement and indicates no significant difference in precision.