

become relevant, but for their use, it's necessary to develop methods of quality control for study the release of the active substance and further quality control of the active pharmaceutical ingredient.

Aim. To develop a spectrophotometric method of quantitative determination based on the physico-chemical properties of argireline for further application for release studies of API and control of quality of patches under eyes.

Materials and methods. UV spectrophotometer Evolution 60S (USA), analytical balances Axis (Poland), a standard sample of argireline (series A456202), patches under eyes with argireline, dishes Class «A», reagents and solvents that meet the requirements of the State Pharmacopoeia of Ukraine (SPU).

Results and discussion. Argireline is a synthetic hexapeptide consisting of the amino acids arginine, glutamine, methionine and acetylated glutamic acid. Therefore, a general group reaction with ninhydrin was used for identification. The positive effect of the reaction led to the use of this reaction for the quantitative determination of API in patches by absorption spectrophotometry in the visible area. For develop a method for quantitative determination, 0.1% aqueous solution of Argireline was prepared, a reaction was carried out with a 0.2% alcohol solution of ninhydrin, and the nature of the absorption spectrum of the absorption of the colored solution was studied in the area from 400 nm to 700 nm.

It was found that the maximum of the colored solution of Argireline with ninhydrin is observed at a wavelength of 571 nm. To develop a spectrophotometric method, it was necessary to establish the reaction time, temperature, solution stability, the ratio of active substance and ninhydrin, and the subordination of the reaction product to the basic law of Bouguer-Lambert-Ber.

For transfer the method of quantitative determination of Argireline in patches, the features of sample preparation were studied and the following quantitative determination method was proposed: to the patches add of distilled water in a beaker, left for 30 min at room temperature and then the supernatant is transferred to a volumetric flask. Then to the solution (which contains 0.1 % of argireline) add 0.2% alcohol solution of ninhydrin in a molar proportion of active ingredient to ninhydrin (0.000011 mol: 0.00012 mol). Then the mixture is heated in a water bath for 10 minutes at a temperature of 100 °C; cool and after adjust the volume with purified water to the mark, absorbance is measured at a wavelength of 571 nm.

Conclusions. The results were showed that the release of the active ingredient over 30 minutes is more than 80%. The proposed spectrophotometric technique can be used for identification and quantity determination of Argireline in patches under eyes.

QUANTITATIVE DETERMINATION OF FLUPHENAZINE HYDROCHLORIDE IN TABLETS BY INDIRECT SPECTROPHOTOMETRIC METHOD USING OXONE

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Introduction. Fluphenazine hydrochloride (FLZ), 2-[4-[3-(2-(trifluoromethyl) phenothiazine 10-yl)propyl]piperazine-1-yl]ethanol dihydrochloride, is a typical antipsychotic drug used for the treatment of psychoses such as schizophrenia, manic phases of bipolar disorder, agitation, and dementia. It belongs to the piperazine class of phenothiazines (Fig. 1).

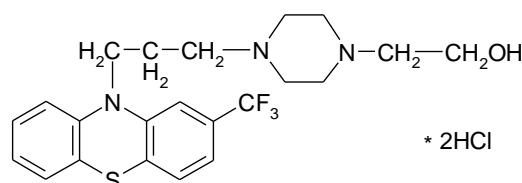


Fig. 1 The molecular structure of Fluphenazine hydrochloride

The British Pharmacopoeia (BP) recommended a non-aqueous potentiometric method for the determination of FLZ using perchloric acid as a titrant; the LOQ was 6.3 mg mL⁻¹.

The intense spectra of phenothiazines present wide possibilities for their quantitative determination in various formulations. The simple spectrophotometric methods usually involve the dilution (or extraction) of the preparation followed by a measurement of absorbance in the ultraviolet region. These procedures based on natural absorption lack specificity and are subject to interference from other ultraviolet absorbing drugs, coloring and flavouring agents or the oxidation products of the phenothiazine drugs. The official compendia BPh recommended for the determination of Fluphenazine hydrochloride in tablets, involve record second derivative UV absorption spectra of the solutions after preliminary stage of isolation analyte in the range 230 to 300 nm and measurements of the amplitude from the peak at about 266 nm to the trough at about 258 nm. The content of C₂₂H₂₆F₃N₃OS,2HCl in tablets calculate using the declared content of Fluphenazine hydrochloride BPCRS.

The United States Pharmacopoeia (USP), on the other hand, described an HPLC method for the determination of FLZ in pure form using UV detection at 254 nm, where the LOQ was 2.4 mg mL⁻¹. A similar approach was used for the determination of FLZ injection.

In this post peroxomonosulfate based Oxone (the triple salt 2KHSO₅·KHSO₄·K₂SO₄) reagent has been proposed an analytical reagent for the determination of Fluphenazine hydrochloride (FP) in tablets. This main principle of this method is based on the fact, that pharmaceutical drug contains a specific organic functional group, which on oxidation in the presence of selected oxidant (here Oxone is used as an oxidant) provides the new oxidized product. This type of oxidation reaction between the drug molecule and an oxidant establishes a stoichiometric relationship between the drug molecule and an oxidant. This relationship is the basis of quantitative estimation of drugs in pure form and their pharmaceutical preparations. In this research, oxidizing reagent Oxone oxidizes the sulfur atom of phenothiazine to the corresponding sulfoxides. Thus an oxidant Oxone establishes a 1:1 ratio with phenothiazine drug.

Aim. To develop a simple and rapid method for the quantitative determination of Fluphenazine hydrochloride in tablets using potassium hydrogen peroxomonosulfate as an analytical reagent.

Materials and methods. Fluphenazine Hydrochloride Tablets contain 5 mg fluphenazine hydrochloride per tablet. Inactive ingredients: hydroxypropyl methylcellulose, lactose monohydrate; polyethylene glycol; polysorbate 80, povidone, stearic acid, and titanium dioxide.

The triple salt 2KHSO₅·KHSO₄·K₂SO₄ (known by the tradename Oxone) is a form with higher stability. Kinetic studies were carried out in acid or buffer solutions under second-order conditions with KHSO₅ in the temperature 293 K. The reaction was followed by estimating the unreacted KHSO₅ as a function of time by using the iodometric method. 0.02 mol L⁻¹ phosphate pH buffer solutions were used. The liberated iodine was titrated against 0.02 mol L⁻¹ standard sodium thiosulphate solution.

Results and discussion. According to the results of the study of the reaction kinetics, it was found that at pH 1,2-4 the interaction between FLZ and KHSO₅ occurs quantitatively and stoichiometrically for 3-5 min: 1 mole of FLZ consumes 1 mole of KHSO₅ (Fig. 2).

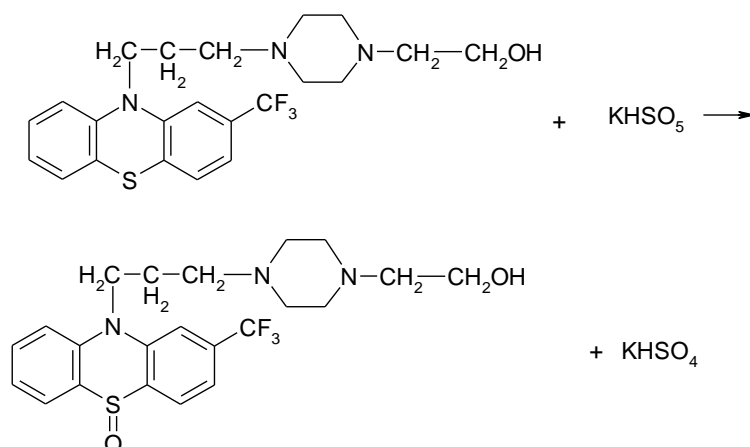


Fig. 2 Schema reaction of FLZ oxidation by Oxone in acidic medium

An original method for the rapid determination of Fluphenazine hydrochloride in tablets was developed. The drug are determined by a spectrophotometric technique based upon the absorbance of the sulphoxide derivative of the drug. The sulphoxide derivative are formed rapidly and quantitatively at the room temperature by the addition of a solution of potassium peroxomonosulphate (Oxone). The absorbance of the solutions on 348 nm is proportional to the concentration of the phenothiazine drug in the preparation and is specific for the intact drug in the presence of excipients and oxidative and photochemical decomposition products (It is taken into account by the behavior of the blank experiment (in the absence of oxidizer). It has been experimentally found that the molar absorption coefficient of fluphenazine sulfoxide ϵ is $5.9 \cdot 10^3 \text{ l mol}^{-1}$ (λ_{max} 348 nm).

To examine the precision and accuracy of results various statistical analysis such as relative standard deviation ($\text{RSD} \leq 2\%$) and $\delta = (\bar{x} - \mu) 100\% / \mu$ (μ is the true value) was also calculated for each sample. The proposed method was validated by recovery analysis, the standard additions method ($\delta < \text{RSD}$). The proposed methods was applied to the analysis of pharmaceutical preparations containing the drugs, and the results obtained compared favourably with those obtained by pharmacopoeial methods.

Conclusions. The obtained validation characteristics of the spectrophotometric method for determining the content of FLZ in the tablets "Fluphenazine hydrochloride" 5 mg meet the eligibility criteria for SPU, which indicates the possibility of its implementation in the practice of analysis of analytical laboratories.

DEVELOPMENT OF METHODS FOR THE QUANTITATIVE DETERMINATION OF 5-METHYLPYRIDINE-2-AMIDE 4-HYDROXY-1-R-2,2-DIOXO-1H-2 λ ⁶,1-BENZOTHAZINE-3-CARBOXYLIC ACID BY NITROGEN CONTENT

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Introduction. Nonsteroidal anti-inflammatory agents (NSAIDs) - one of the most used group of drugs that exhibit anti-inflammatory, analgesic and antipyretic effect. Most of the medicines of this group in the chemical structure relates to derivatives of acids, namely: salicylic (aspirin), anthranilic (mefenamic acid), arylacetic (diclofenac sodium), indolocic (indomethacin), propionic (ibuprofen) and enolic (oxicams and pyrasolones).

It is known that the anti-inflammatory effect of NSAIDs is realized by inhibiting the activity of the COX-2 enzyme, and the main side effects (erosive-ulcerative gastrointestinal lesions) appear when inhibiting COX-1. That is why, recently, in the treatment of inflammatory processes, preference is given to drugs with selective action on COX-2, such as oxicams.

Oxicams related to 4-hydroxy-1,2-benzothiazinecarboxamides of enolic acid showed high anti-inflammatory and analgesic effects, however, and they were not devoid of side effects. One of the major inconveniences of oxicamas is their complete incompatibility with many diseases. It is not recommended for use in people who have recently undergone surgery, pregnant, lactating, adolescents, and it has an adverse effect on the gastrointestinal tract and cardiovascular toxicity. That is why, in order to create more advanced painkillers with minimal side effects by modifying the structure of the oxicams at the Department of Pharmaceutical Chemistry of NPhU pyridylamides of 4-hydroxy-1-R-2,2-dioxo-1H-2 λ ⁶,1-benzothiazine-3carboxylic acid were synthesized.

One of these substances is 5-methylpyridine-2-amide 4-hydroxy-1-pentyl-2,2-dioxo-1H-2 λ ⁶,1-benzotiazine-3-carboxylic acid which is showed high level of analgesic activity and can be offered as a new drug.

Aim. The aim of our investigation is to develop a method of quantification of the substance of 5-methylpyridine-2-amide 4-hydroxy-1-pentyl-2,2-dioxo-1H-2 λ ⁶,1-benzotiazine-3-carboxylic acid. Since