Ф А 2.2.1-32-367

MINISTRY OF HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY
faculty for foreign citizens' education
pharmaceutical chemistry department

QUALIFICATION WORK

on the topic: «**DEVELOPMENT OF POTENTIOMETRIC TITRATION METHOD FOR THE DETERMINATION OF FEXOFENADINE HYDROCHLORIDE IN DRUGS**»

Prepared by: higher education graduate of group Фм17(4,10д)англ-06
specialty 226 Pharmacy, industrial pharmacy
educational program Pharmacy
Taha ABBAD
Supervisor: associate professor of higher education institution of department pharmaceutical chemistry, PhD, associate professor Vasyl GRYNENKO
Reviewer: associate professor of higher education institution of department medicinal chemistry, DSc, associate professor Illya PODOLSKY

Kharkiv – 2022 year

ANNOTATION

The development of the method of alkalimetric quantitative determination of fexofenadine hydrochloride in tablets has been presented in the qualification work. The method is metrologically certified and its further application in pharmaceutical analysis is proved.

The work consists of an introduction, three chapters, general conclusions and literature. The content of the work is set out on 49 pages of typewritten text, containing 5 tables, 5 figures, 2 schemes.

Key words: fexofenadine hydrochloride, alkalimetry, potentiometry, tablets.

АНОТАЦІЯ

У кваліфікаційній роботі наведено розробку методики алкаліметричного кількісного визначення фексофенадину гідрохлориду в таблетках. Методика метрологічно атестована і доведено її подальше застосування у фармацевтичному аналізі.

Робота складається зі вступу, трьох розділів, загальних висновків та списку використаної літератури. Зміст роботи викладений на 49 сторінках машинописного тексту, що містить 5 таблиць, 5 рисунків, 2 схеми.

Ключові слова: фексофенадину гідрохлорид, алкаліметрія, потенціометрія, таблетки.

CONTENTS

INTRODUCTION

Actuality of problem. According to the World Health Organization (WHO), allergic diseases affect from 30 to 60% of the population. An increase in the number of allergic diseases is noted both among adults and among children. The most common type of allergic reaction is respiratory allergy in the form of allergic rhinitis, which occurs in 20-25% of the world's population, and over the past quarter century, the number of patients has tripled. Currently, antihistamines are among the best-selling in the world.

However, along with the anti-allergic effect, antihistamines also have a number of side effects, which are due to the fact that they act on all types of H-receptors. The greatest clinical significance is that first-generation antihistamines penetrate the blood-brain barrier, which is manifested by sedation, drowsiness, dizziness, impaired coordination of movements and other disorders of psychomotor function. Only with the advent of second-generation antihistamines has the quality of life of patients with allergic reactions significantly improved. The first antihistamines of the 2nd generation were developed in 1981. Their antiallergic activity is comparable to that of the 1st generation drugs, but they do not show sedative and some other side effects.

Fexofenadine is an antihistamine pharmaceutical drug used in the treatment of allergy symptoms, such as hay fever and urticaria. Therapeutically, fexofenadine is a selective peripheral H_1 blocker. Fexofenadine is practically not biotransformed, which ensures its safety. It is classified as a second-generation antihistamine because it is less able to pass the blood–brain barrier and cause sedation, compared to first-generation antihistamines.

In this regard, the quality control of this drug is of particular importance. Today, high-performance liquid chromatography (HPLC) is widely used both to establish the identity and purity of the drug, and to quantify it. The

spectrophotometric method in the analysis of the quantitative content of fexofenadine is not widely used today, despite the more affordable instrumentation for drug quality control laboratories. Therefore, we set ourselves the goal of developing a simple, fast, cost-effective method for determining fexofenadine in dosage forms.

Purpose of work - is to develop the potentiometric method for the determination of fexofenadine hydrochloride in drugs.

For this objective the following tasks were supplied:

1. to study the pharmacological properties and methods of analysis of fexofenadine hydrochloride;
2. to study methods for the determination of fexofenadine hydrochloride in tablets;
3. to develop method of quantitative determination for fexofenadine hydrochloride in substance;
4. to develop method of quantitative determination for fexofenadine hydrochloride in tablets;
5. to give statistic analyses for the obtained results.

Materials of this work are set out according to the task.

The object of the research is tablets "Allegra, 120 mg" (s. FT825).

The subject of the research is the development of the alkalimetric method with potentiometric titration for the determination of fexofenadine hydrochloride in tablets.

Methods of the research: titrimetric methods (alkalimetry with determining the end-point potentiometrically), quantitative determination, methods of mathematical statistics.

The practical value of the results. The presented scientific researches allow us to recommend data of the methods of assay for fexofenadine hydrochloride in tablets.

Scientific novelty. The developed method of alkalimetry with determining

the end-point potentiometrically of quantificative determination of fexofenadine hydrochloride can be used for its analysis in drugs.

The structure of the work. The work consists of an introduction, three chapters, general conclusions and list of references used, which is composed of 41 sources. Contents of work posted on 49 typewritten pages and contains 5 tables, 5 figures, 2 schemes.

CHAPTER I

FEXOFENADINE HYDROCHLORIDE

1.1 General information, characters of fexofenadine hydrochloride

Fexofenadine is a non-sedative antihistamine drug of the group of antagonists of specific H1 receptors; is a pharmacologically active metabolite of terfenadine. Indications for the use of fexofenadine are symptomatic treatment of seasonal allergic rhinitis and chronic idiopathic urticaria.

Fexofenadine contains one chiral center and can be resolved into two enantiomers. The pharmacological studies with (*R*) and (*S*)-enantiomer in humans showed a higher plasma concentration for (*R*)-fexofenadine than that of the corresponding isomer. The area under the plasma concentration–time curve (AUC_0–infinity), and the maximum plasma concentration (C_{max}) of R-(+)-fexofenadine were also significantly greater than those of the S-(-)-enantiomer [1,2].

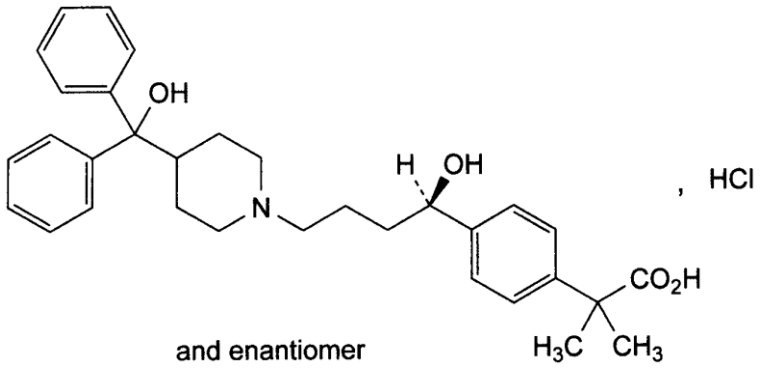
Fexofenadine's carbinol carbon is chiral. The racemic mixture is marketed as a single agent or in combination with the decongestant pseudoephedrine. Once or twice-daily administration is the norm.

The length of fexofenadine's acidic side chain is longer than cetirizine's which results in a less optimal H_1 receptor fit. Daily doses are 18 to 36 times higher than racemic cetirizine.

Fexofenadine is extensively protein bound and metabolism resistant. Approximately 5% of a dose is metabolized, and over 3% of that metabolism involves esterification of the terminal COOH group by gut flora. Fecal elimination predominates [3].

It was patented in 1979 and came into medical use in 1996. It is on the World Health Organization's List of Essential Medicines [4,5].

Chemical structure of fexofenadine hydrochloride:



$C_{32}H_{39}NO_4$,HCl M_r 538.1

Systematic chemical name:

2-[4-[(1*RS*)-1-hydroxy-4-[4-(hydroxydiphenylmethyl)piperidin-1-yl]butyl] phenyl]-2-methylpropanoic acid hydrochloride;

benzeneacetic acid, 4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]- α,α -dimethyl-, hydrochloride, (±)-;

(±)-2-[4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)piperidino]butyl]phenyl]-2-methylpropanoic acid, hydrochloride;

α,α-dimethyl-4-[4(hydroxydiphenylmethyl)-1-piperidinyl]butyl]benzene-acetic acid, hydrochloride;

(±)-*p*-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)piperidino]butyl]-a-methyl-hydratropic acid, hydrochloride.

Proprietary names: Allegra, Altiva, Fexofen-Sanovel, Fexophast, Tigofast.

Appearance. White or almost white powder.

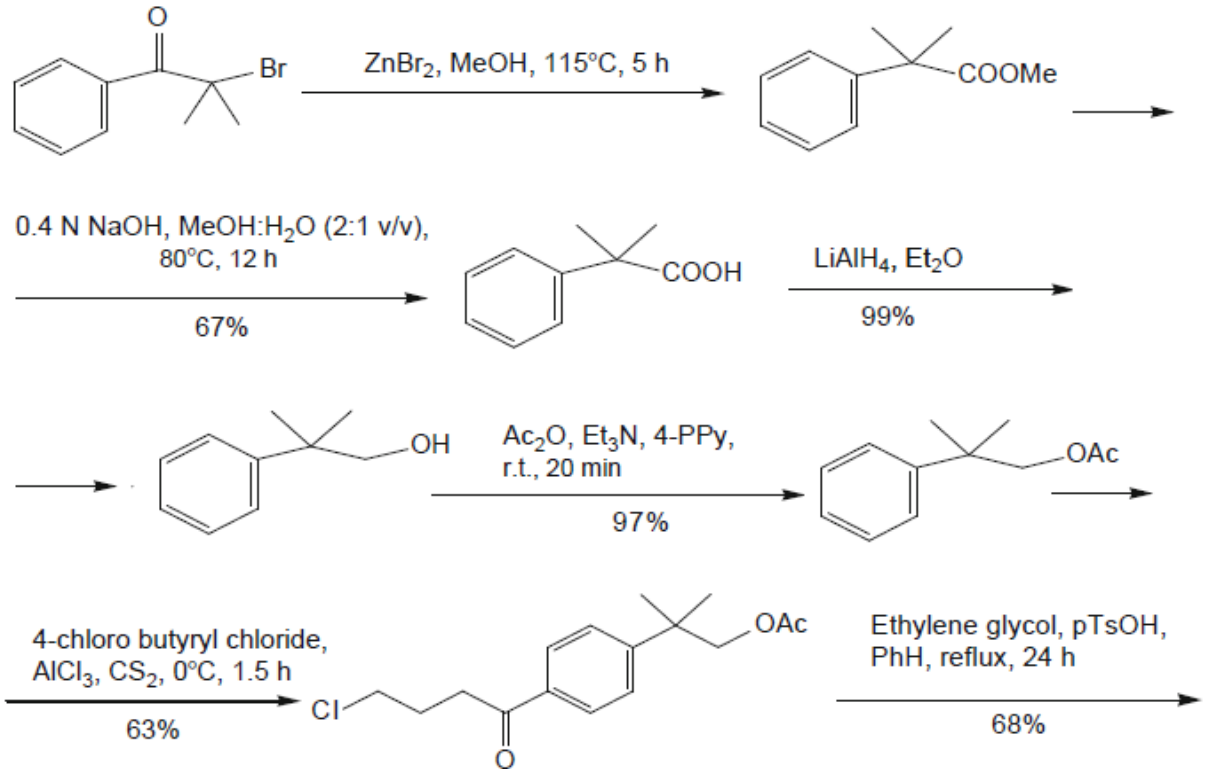
Solubility. Slightly soluble in water, freely soluble in methanol, very slightly soluble in acetone. It shows polymorphism.

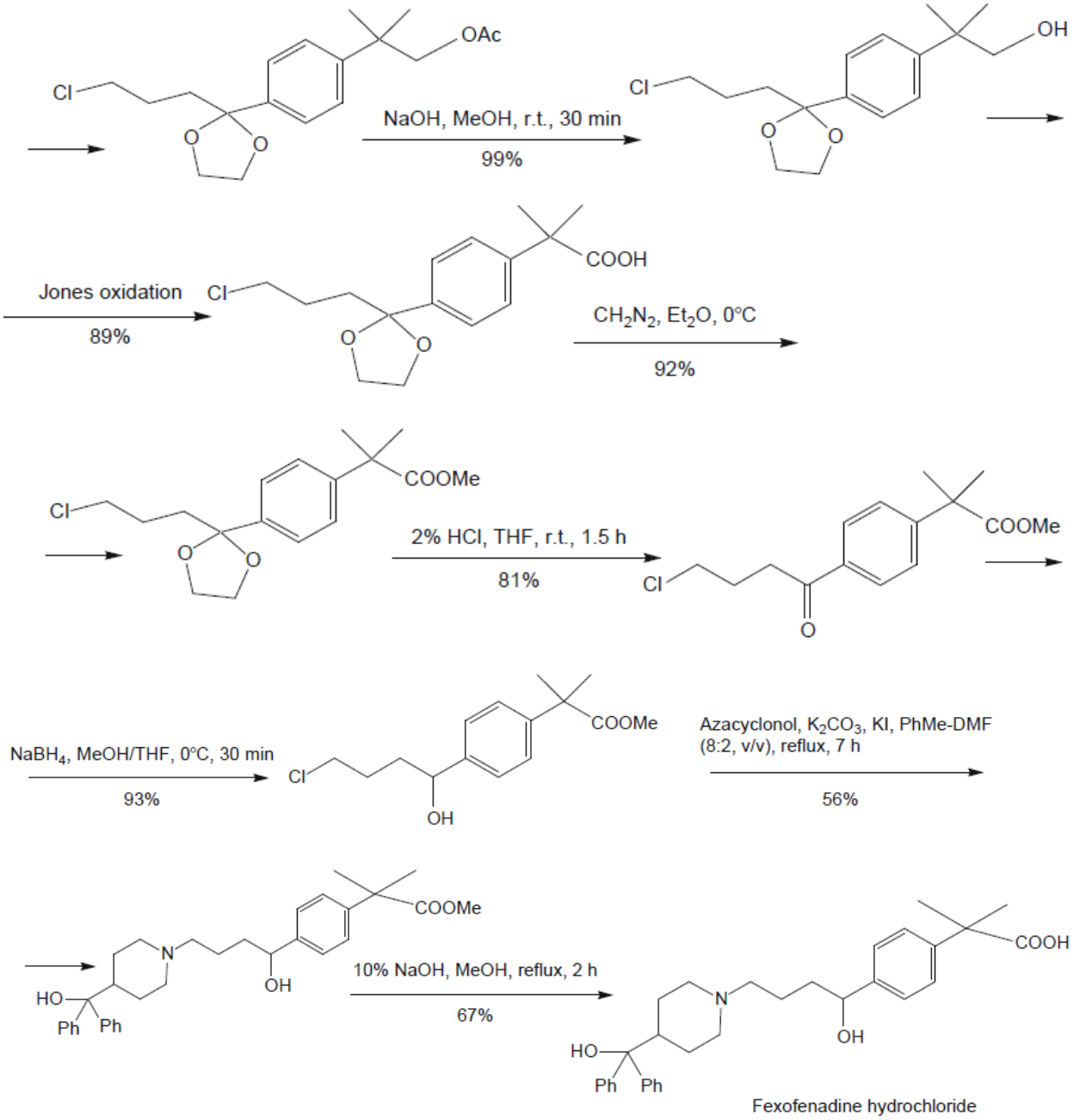
The solubilization behavior and thermodynamics of fexofenadine hydrochloride in the binary mixtures of ethanol and water at temperature range of T = (293.2–313.2) K are investigated and the generated solubility data are mathematically represented by using four cosolvency models (i.e. van't Hoff equation, modified Wilson, Jouyban-Acree and Jouyban-Acree-van't Hoff models). The models performance is illustrated by mean relative deviations (MRD%). Based

on the van't Hoff and Gibbs equations it is observed that the dissolution processes are endothermic and entropy-driven in every case [6].

1.2 Methods of synthesis

In general, the synthetic approach for preparation of Fexofenadine involves the reduction of a carboxylate derivative, 4-[4-[4-(hydroxybiphenylmethyl)-1-piperidinyl]-1-oxobutyl]-α,α-dimethyl benzene acetate; followed by hydrolysis with a base, for example alkali metal hydroxides, to get the carboxylic acid derivative Fexofenadine. The sequence of synthesis is depicted in Schema 1.1 [2,7,8]:





Schema 1.1 Synthesis of fexofenadine hydrochloride

1.3 Methods of identification

Identify the substance of fexofenadine hydrochloride by physicochemical properties, namely by IR- or UV-spectroscopy.

A. Infrared absorption spectrophotometry.

The infrared absorption spectrum of the substance should coincide with the infrared absorption spectrum of the chemical reference substance of fexofenadine hydrochloride *CRS*.

It the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues [9-11].

B. UV–vis spectroscopy

Fexofenadine is dissolved in water (5 mg/ml) to obtain the UV absorbance maxima. The λ_{max} of Fexofenadine is observed in water at a wavelength of approximately 190 and 220 nm (Fig.1.1) [2].

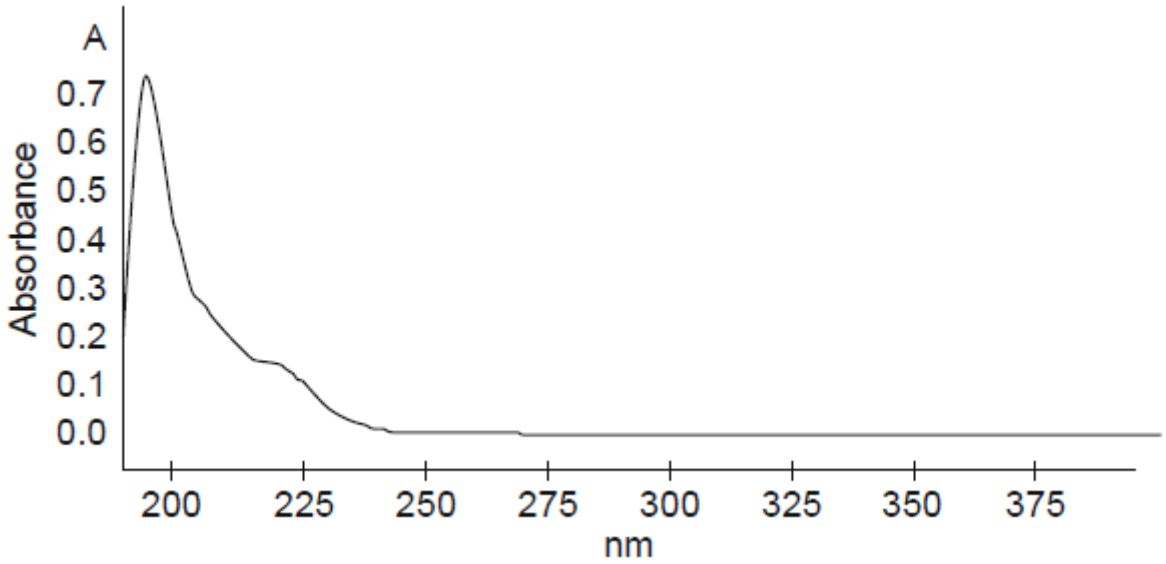
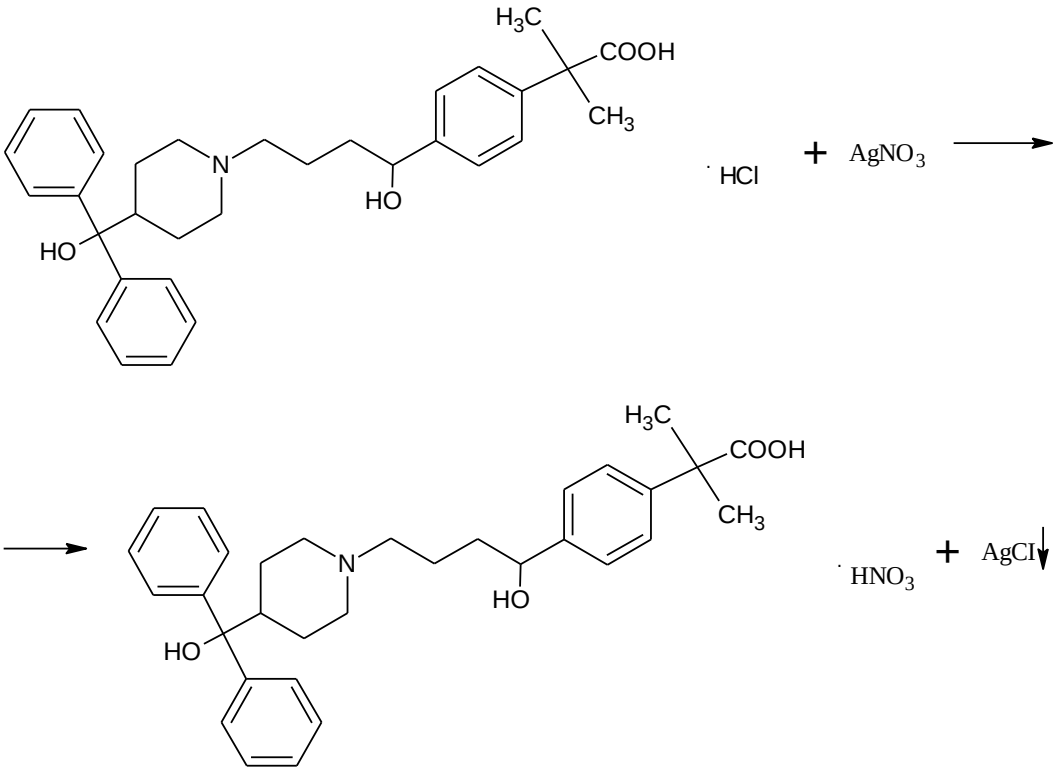
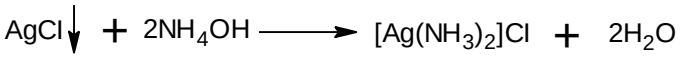


Fig. 1.1 UV absorption scan of aqueous solution of fexofenadine (5 mg/ml)

C. From chemical methods of identification use the reaction with silver nitrate for detection of the residue of hydrochloric acid. To do this, pre-dissolve the substance in methanol [9-11].



White precipitate of argentum chloride soluble in ammonia solution:



D. The retention time of the fexofenadine peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay* [9-11].

1.4 Methods of assay

The European, British and American Pharmacopoeia [9-11] recommends liquid chromatography to quantify fexofenadine hydrochloride.

Chromatography is performed on a liquid chromatograph with a UV detector under the following conditions:

Column:

— *size: l* = 0.25 m, ∅ = 4.6 mm;

— *stationary phase: phenylsilyl silica gel for chromatography R* (5 μm).

Mobile phase: Mix 350 volumes of *acetonitrile for chromatography R* and 650 volumes of the buffer solution; add 3 volumes of *triethylamine R* and mix.

Flow rate. 1.5 mL/min.

Detection. Spectrophotometer at 220 nm.

Injection. Test solution (b) and reference solution (a).

Run time. Twice the retention time of fexofenadine.

Calculate the percentage content of fexofenadine hydrochloride from the declared content of *fexofenadine hydrochloride CRS*.

The method for the quantitative determination of fexofenadine in the substance by the spectrophotometric method has been developed, the analytical wavelength was determined - 228 nm, the value of the specific absorption coefficient of fexofenadine hydrochloride in 5% sodium hydroxide solution was 173.9. The specificity of the method was established, the linearity was confirmed by the results of correlation analysis, it was shown that the technique is reproducible at the level of convergence and correct, based on the calculated open rate [12].

Conclusions

Fexofenadine is a non-sedative antihistamine drug of the H_1 receptor antagonist group and is used for the symptomatic treatment of seasonal allergic rhinitis and chronic idiopathic urticaria.

Fexofenadine may be identified as such on the basis of its characteristic infrared absorption and UV-spectrum, HPLC, thin layer chromatography and chemical reactions.

CHAPTER II

METHODS FOR THE DETERMINATION OF FEXOFENADINE HYDROCHLORIDE IN TABLETS

Fexofenadine is available under various trade names, such as Allegra, Altiva, Fexofen-Sanovel, Fexophast, Tigofast. These drugs are manufactured by the following companies: Sanofi Winthrop Industry - Tours (France), San Pharmaceutical Industries Limited, Micro Labs Limited, Flamingo Pharmaceuticals Ltd. (India), Sanovel Ilyach Sanai ve Tijaret A.Sh. (Turkey) [13].

As the object of study, we chose Allegra tablets from a European manufacturer – Sanofi.

Outer packaging of the object of study:

Active substance: fexofenadine hydrochloride.

1 tablet contains fexofenadine hydrochloride 120 mg (equivalent to 112 mg fexofenadine);

Excipients: microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, magnesium stearate, hypromellose, povidone, titanium dioxide (E 171), colloidal anhydrous silica, macrogol 400, a mixture of iron oxide yellow (E 172).

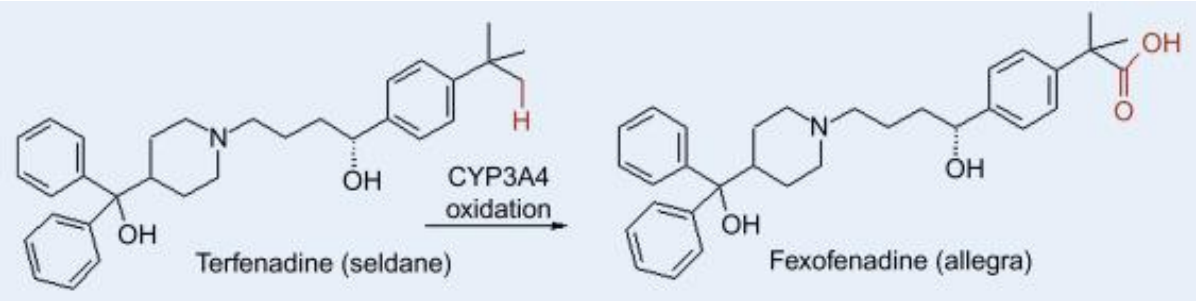
Main physical and chemical properties: capsule-shaped, peach-colored tablets, embossed with “012” on one side and embossed with the capital letter “e” on the other side.

Pharmacotherapeutic group: Antihistamines for systemic use. ATX code R06A X26.

2.1 Pharmacological properties of fexofenadine hydrochloride

2.1.1 Pharmacodynamics

Fexofenadine hydrochloride is a non-sedative antihistamine of the H_1 specific receptor antagonist group. Fexofenadine is a pharmacologically active metabolite of terfenadine.



It accounted for the antihistaminic properties of terfenadine, which is very rapidly metabolized via CYP3A4-catalyzed processes. Although the enantiomers of terfenadine are reported to have approximately equal antihistaminic activity, no data on the activity of the enantiomers of fexofenadine were found. Members of the organic anion transporter protein family and the drug efflux transporter P-glycoprotein are involved in the disposition of fexofenadine. A higher plasma concentration of the R-enantiomer is reported, showing some stereoselectivity in this process. Fexofenadine does not have the antiarrhythmic side effects of terfenadine [14].

In clinical studies of histamine-induced blistering and redness of the skin, the antihistamine effect of fexofenadine hydrochloride, administered 1 and 2 times daily, was observed within 1 hour, reaching a maximum after 6 hours and lasting for 24 hours. Signs of intolerance were not detected even after 28 days of reception. The clinical effect was observed after single oral doses of 10 to 130 mg. In this model of antihistamine efficacy, doses of at least 130 mg were required to provide a lasting effect for 24 hours. The maximum suppression of edema and redness exceeded 80%. Clinical studies of seasonal allergic rhinitis show that a dose of 120 mg is sufficient to be effective for 24 hours.

No statistically significant changes in the QT interval compared to placebo were observed in patients with seasonal allergic rhinitis who received a dose of up to 240 mg fexofenadine hydrochloride twice daily for 2 weeks. There were no similar changes compared to placebo in healthy volunteers who received up to 60 mg fexofenadine hydrochloride twice daily for 6 months, 400 mg fexofenadine hydrochloride twice daily for 6.5 days and 240 mg daily for one year. There were no statistically significant changes in the QT interval in children aged 6 to 11 years compared with placebo after fexofenadine hydrochloride 60 mg twice daily for 2 weeks. Even at plasma concentrations 32 times the therapeutic concentrations, fexofenadine in humans had no effect on delayed rectification potassium channels cloned from the human myocardium.

2.1.2 Mechanism of action

The mechanism of action of fexofenadine is to selectively antagonize H1 receptors on the surface of cells on multiple different organ systems. It is a second-generation H1 receptor blocker and is non-sedating. Fexofenadine also affects inflammatory mediators. Fexofenadine does not cross the blood-brain barrier and thus does not cause drowsiness like other H1 blockers. Second-generation antihistamines such as fexofenadine have less affinity for cholinergic and alpha-adrenergic receptors and therefore do not display the anticholinergic side effects that other antihistamines do. Fexofenadine can also inhibit other mechanisms such as mast cell, basophilic histamine, and inflammatory cell release [15].

2.1.3 Pharmacokinetics

Fexofenadine hydrochloride is rapidly absorbed after oral administration. The maximum concentration is reached in about 1-3 hours. The maximum concentration is approximately 289 ng/ml after a single dose of 120 mg once daily and approximately 494 ng/ml after a single dose of 180 mg once daily. 60-70% of fexofenadine is bound to plasma proteins. Fexofenadine is not metabolized in the

liver. It is metabolized very little, because the main substance of the drug is found in urine and feces. Elimination of fexofenadine from blood plasma occurs with a two-phase decrease and a terminal half-life of 11 to 15 hours after repeated use. The kinetics of single and multiple doses are linear at oral doses up to 120 mg 2 times a day. According to studies conducted so far, most of the dose is excreted in the bile, with urine in unchanged form excreted up to 10% [13,16].

2.1.4 Indication

Symptomatic treatment of seasonal allergic rhinitis in adults and children over 12 years of age.

Pharmacological options for the treatment of allergic rhinitis are well established, but additional research is needed on the efficacy of conventional pharmacotherapy in patients exposed to air pollution. A review of the studies investigating allergic rhinitis symptoms aggravated by air pollutants showed that fexofenadine HCl is the only allergic rhinitis medication with demonstrated efficacy and tolerability for the management of DEP-aggravated symptoms. Diesel exhaust particles (DEP) exposure has been shown to trigger numerous pro-inflammatory signalling pathways other than histamine-mediated ones [17,18].

DEP increases circulating neutrophils, eosinophils, and cytokines, and induces the expression of adhesion molecules as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) which are critical for T cell activation. Additionally, an exacerbation of the inflammatory response may result from the generation of reactive oxygen species and oxidant overload [19].

Noteworthy, it has been demonstrated that fexofenadine HCl has additional anti-inflammatory properties besides the anti-histaminergic activity. Fexofenadine HCl decreases cytokine levels, including ICAM-1 and VCAM-1 among others, inhibits eosinophil adherence and chemotaxis, inhibits cyclo-oxygenase 2, and reduces the production of leukotrienes and prostaglandins. These additional effects of fexofenadine could further contribute to the improvement of allergic rhinitis

symptoms aggravated by the inflammatory response induced by DEP; however, more research is needed to demonstrate this hypothesis [20,21].

2.2 Methods of analysis of Fexofenadine Hydrochloride Tablets

2.2.1 Identification

Due to the fact that the dosage form contains excipients, not always methods of analysis that are suitable for confirming the quality of the substance, can be used to analyze the dosage form. The USP contains a monograph on Fexofenadine Hydrochloride tablets. The following methods are offered for qualitative analysis [22]:

A. Infrared Absorption

The analysis is carried out in a mixture of acetonitrile and methanol (10:1).

The IR absorption spectrum of the potassium bromide dispersion of the residue from the sample exhibits maxima only at the same wavelengths as that of a potassium bromide dispersion from the Standard.

B. Chromatographic method

The retention time of the major peak in the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

2.2.2 Assay

The pharmacopoeial method is chromatographic method in Glacial acetic acid and water (17:983) [22].

A stability indicating HPLC method was developed and validated for the quantitative determination of fexofenadine hydrochloride. An isocratic separation was achieved using phenomenex (C18) column (250×4.6 mm, 5 μm) with flow rate of 1.0 ml/min and UV detection at 254 nm. The mobile phase consists of 5Mm acetate buffer: acetonitrile (50:50; v/v) with pH 9.4 adjusted with acetic acid. The drug was subjected to oxidative, acidic, basic, neutral, photolytic and thermal degradation. All degradation products were eluted in an overall analytical run time

of approximately 40 min with the parent compound fexofenadine hydrochloride at a flow rate of approximately 3.3±0.3 min. The method was linear over the concentration range of 31.5-500 μg/ml (r^2 = 0.999) with limit of detection and quantification of 3.5 μg/ml and 10.1 μg/ml, respectively. The method has the requisite accuracy, selective, precision and robustness to assay fexofenadine hydrochloride in tablets [23].

HPLC method for assaying fexofenadine hydrochloride in powder preparations prepared from Allegra 60 mg tablets has been developed. A chromatographic system comprising a YMC AM12S05-1506WT column, mobile phase of CH_3CN:H_2O:$HClO_4$:$NaClO_4$=500:500:1:5 (V/V/V/W), flow rate of 1 mL/min, and UV detector set at 220 nm was used. The retention time of fexofenadine was approximately 6.6 min. A regression analysis revealed that the method was linear over the standard curve range from 0.2 to 80 μg/mL [24].

A high performance thin layer chromatographic (HPTLC) method for estimation of fexofenadine hydrochloride as a bulk drug and in tablet dosage form has been developed. The stationary phase used was precoated silica gel aluminium plates 60 F254 with 250 μm thickness. The mobile phase used for separation was toluene: ethyl acetate: methanol: ammonia (30%) (0.5:7:3:0.6; v/v/v/v). The densitometric quantification was carried out at 220 nm. The calibration curve was found to be linear between 1-10 μg/spot [25].

A RP-HPLC method was developed and validated for determination of Fexofenadine in pharmaceutical dosage form by using Levocetirizine as an Internal standard (IS). The separation was achieved by Cap Cell Pack C18 column (250 × 4.5 mm, 5μ) column using acetonitrile: water (50:50 % v/v) as eluent at a flow rate of 1 mL/min, detection was carried out at 224 nm. The retention times for Fexofenadine and IS were found at 4.79 and 6.22 mins, respectively. Linearity was observed over the concentration ranging from 50-175 μg/mL and it was found to be linear with y = 0.011x + 0.168 (r^2 = 0.997) [26].

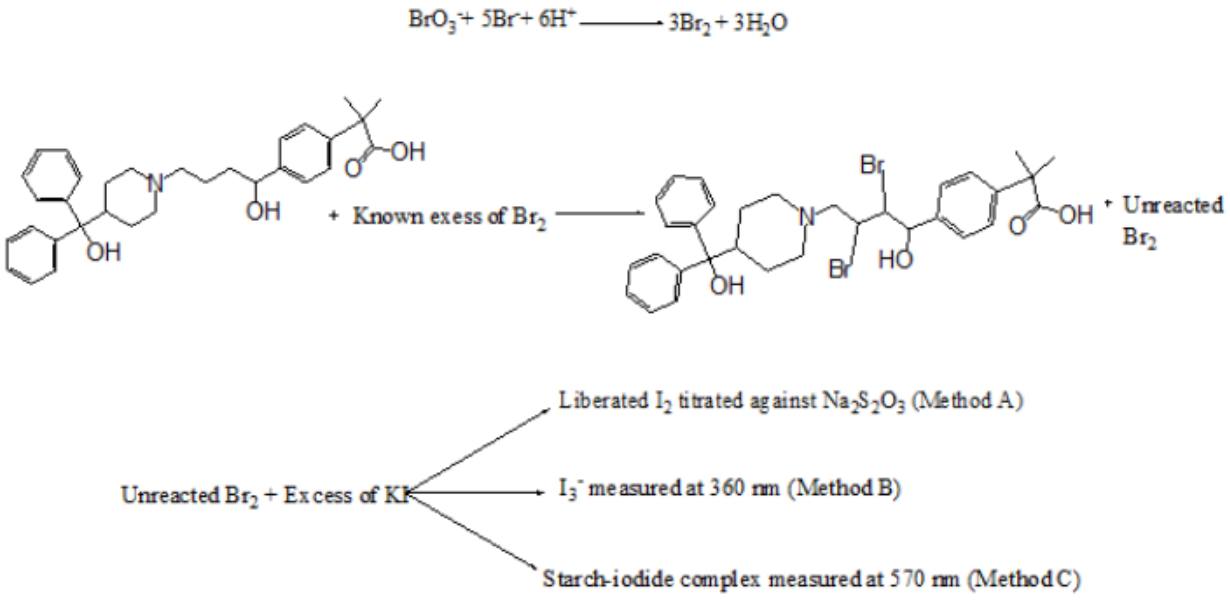
A liquid chromatographic (RP-HPLC) method for the quantitative determination of fexofenadine in pharmaceutical preparations was optimized and validated. Agilent Extend C18 column was used to perform the separation. The optimum chromatographic separation was achieved by the mobile phase consist of acetonitrile and 20 mM KH_2PO4 solution (pH 7.5) in 35:65 ratios respectively. The flow rate of 1.2 mL min^{-1} with a standard retention time of 3.5 min at a wavelength 220 nm was optimized [27].

The authors had developed and described one titrimetric and two spectrophotometric methods for the determination of fexofenadine hydrochloride in bulk drug and in tablets based on bromination of fexofenadine hydrochloride by bromine generated in situ by the action of acid on bromate-bromide mixture. In titrimetry, fexofenadine is treated with a known excess amount of bromate-bromide mixture in acid medium followed by the determination of unreacted bromine iodometrically (method A). In spectrophotometry, the residual bromine is determined by its reaction with excess iodide and the liberated iodine (I_3^-) is either measured at 360 nm (method B) or iodine reacted with starch followed by the measurement of the blue colored starch-iodide complex at 570 nm (method C). Titrimetry allows the determination over the range of 4.5-30.0 mg fexofenadine whereas in spectrophotometry, Beer's law is obeyed in the concentration ranges of 2-20.0 and 0.6-6.0 μg mL^{-1} fexofenadine for method B and method C, respectively [28].

Comparative evaluation of sensitivity and selectivity of two fabricated coated wire membrane sensors enriched with zinc oxide and copper oxide nanoparticles with other conventional types for the quantification of antihistamine drug fexofenadine hydrochloride (Telfast 120 mg/tablet) has been described [29].

2.3 Methods of determination of fexofenadine hydrochloride in combined dosage forms

For the determination of fexofenadine hydrochloride and irbesartan in bulk and pharmaceutical preparations has been presented the method which based on the reaction of the above cited drugs with naphthol blue black dye in solutions containing Britton buffer to form ion-pair complexes extractable with chloroform and subsequently measured spectrophotometrically at 625 nm. All the reaction conditions for the proposed methods have been studied. The reactions were extremely rapid at room temperature and the absorbance values remained unchanged for at least 24 hrs. Beer's law was obeyed in the concentration ranges 2.7–53.8 and 10–244 μg mL^{-1} with detection limit of 0.013 and 0.75 μg mL^{-1} for fexofenadine hydrochloride and irbesartan, respectively. The possible reaction pathways are proposed and illustrated in Scheme 2.1 [30].



Scheme 2.1 Tentative reaction pathway for proposed methods

The development and validation of a simple simultaneous equation method by UV spectrophotometry for estimation of Fexofenadine hydrochloride and Montelukast sodium in bulk and tablets had been described. The maximum

absorbance was measured at 259 nm and 344.5 nm for Fexofenadine hydrochloride and Montelukast sodium respectively in 0.1N NaOH. The calibration curves showed a linear relationship between absorbance and concentration in the range of 50-180 µg/ml for Fexofenadine hydrochloride and 1-35 µg/mL for Montelukast sodium with correlation coefficient of 0.998 [31].

A spectrophotometric method has been developed for simultaneous estimation of Montelukast Sodium and Fexofenadine hydrochloride in pure and tablet dosage form. Proposed method involves formation of 'simultaneous equations' at 259.60 nm for fexofenadine hydrochloride and 283.00 nm for montelukast sodium using methanol as a solvent. The linearity was observed in the concentration range of 30–120 mg/ml for Fexofenadine and 6–20 mg/ml for Montelukast. The correlation coefficient was found to be 0.9927 for fexofenadine and 0.9985 for Montelukast [32].

A high performance thin layer chromatographic method has been developed for the simultaneous estimation of Fexofenadine hydrochloride and Montelukast sodium in pharmaceutical dosage form. The separation was carried out on Merck HPTLC aluminium plates of silica gel G60 F254, (20 × 10 cm) with 250 µm thickness using hexane: ethyl acetate: propanol (2:5:3, v/v/v) as mobile phase. Densitometric measurement was carried out in the absorbance mode at 230 nm. The drugs were resolved satisfactorily with R values of 0.31 ± 0.01 and 0.57 ± 0.01 for Fexofenadine hydrochloride and Montelukast sodium, respectively. The linear regression analysis data for the calibration plots showed good linear relationship with r^2=0.9996 and 0.9998 for Fexofenadine hydrochloride and Montelukast sodium, respectively in the concentration range of 1200–6000 ng $spot^{-1}$ for Fexofenadine and 100–500 ng $spot^{-1}$ for Montelukast [33].

A UV-spectrophotometric and RP-HPLC method was developed and validated for concurrent estimation of fexofenadine hydrochloride, montelukast sodium and ambroxol hydrochloride. In RP-HPLC chromatography, the retention time for fexofenadine hydrochloride, montelukast sodium and ambroxol

hydrochloride was 2.775 min, 9.529 min and 5.261 min, respectively and detection at λmax 210 nm for all three of drugs (overlain spectra). Linear regression analysis shows a good linear relationship; in the concentration range of 10-30, 10-50 and 5-25 μg/mL; for fexofenadine hydrochloride, montelukast sodium and ambroxol hydrochloride with $r^2 > 0.999$. The UV-spectrophotometric estimation was done by two methods; zero order and first derivative method. These methods were based on the measurement of absorbance at 220.20, 283.42 and 245.84 nm in zero order; 221, 287.52 and 262.25 nm in first order derivative method [34].

The scientists [35] had developed three pencil graphite electrodes for potentiometric determination of fexofenadine hydrochloride and montelukast sodium in their pure, synthetic mixtures, and combined dosage form. The first electrode was constructed using ammonium molybdate reagent as an ion pair with fexofenadine cation for the determination of Fexofenadine drug, the second electrode was constructed using cobalt nitrate as an ion pair with montelukast anion for the determination of Montelukast drug, the third electrode was prepared by incorporating the two previously mentioned ion pairs in the same graphite sensor, which makes this sensor sensitive to each Fexofenadine and Montelukast drug.

Also, it is possible potentiometric determination of fexofenadine hydrochloride drug by fabrication of liquid membrane electrodes. The first electrode was prepared from ion pair: molybdophosphoric acid reagent and fexofenadine cation with Di-n-butyl phthalate, the subsequent electrode was prepared with O-Nitro phenyl octyl ether and the third electrode was set up by Tri-n-butyl phthalate, respectively as a plasticizers for determination of Fexofenadine hydrochloride drug [36].

A simple, rapid and precise reverse phase liquid chromatographic (RP-HPLC) method was developed and subsequently validated for simultaneous estimation of Ambroxol hydrochloride and Fexofenadine hydrochloride in bulk drug and in a synthetic mixture. The method is based on High Performance Liquid Chromatography (HPLC) on a reversed – phase column, Hypersil ODS C18

(Hypersil ODS 250 x 4.6 mm, 5µ, Make: Thermo Scientific) prepacked column. The separation was carried out using a mobile phase containing a buffer and acetonitrile (56:44 v/v), was pumped at a flow rate of 0.8 mL/min, column temperature at 35º C using UV detection at 225 nm. Both the drugs were well resolved on the stationary phase and the retention times were around 2.424 minute for Ambroxol hydrochloride and 3.753 minute for Fexofenadine hydrochloride [37].

A RP-HPLC method has been developed for simultaneous estimation of fexofenadine and pseudoephedrine in their extended release tablet. The method was developed based on statistical design of experiments (DoE) and Response Surface Methodology. Separation was achieved on double end-capped C18 column (250 mm × 4 mm, 5 µm). In this experiment, two components of mobile phase, namely, acetonitrile (% v/v) and methanol (% v/v), were the factors whereas retention and resolution of the chromatographic peaks were the responses. The effects of different composition of factors on the corresponding responses were investigated. The optimum chromatographic condition for the current case was found as an isocratic mobile phase consisting of 20 mM phosphate buffer (pH 6.8) and acetonitrile and methanol in a ratio of 50:36:14 (% v/v) at a flow rate of 1 mL/min for 7 minutes. The retention of pseudoephedrine and fexofenadine was found to be 2.6 min and 4.7 min, respectively [38].

Conclusions

This chapter discusses methods for the determination of fexofenadine hydrochloride in tablets, as well as possible methods for qualitative and quantitative determination of fexofenadine hydrochloride in combination drugs.

CHAPTER III

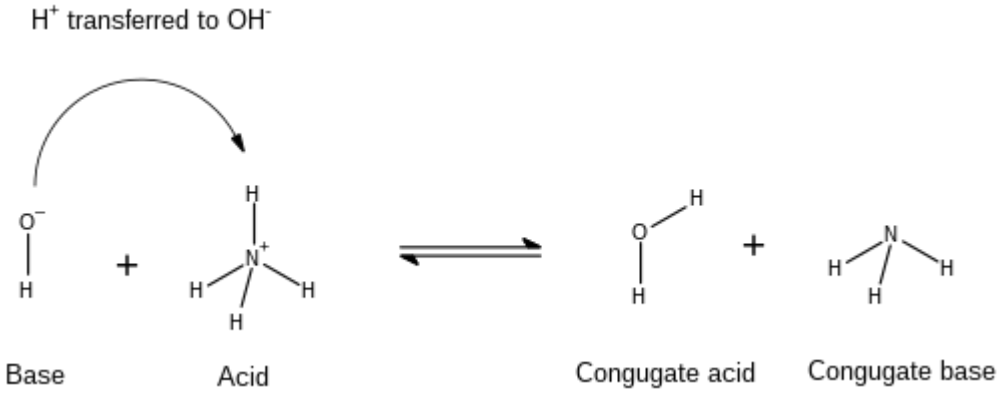
DEVELOPMENT OF METHODS FOR QUANTITATIVE DETERMINATION OF FEXOFENADINE HYDROCHLORIDE (Experimental part)

Methods of pharmaceutical analysis may not always be constant, because almost every day the requirements for the quality and purity of medicines and methods of quantification change. Therefore, it is necessary to improve existing and develop new methods of analysis.

3.1 Development of alkalimetric potentiometric method for quantitative determination of fexofenadine hydrochloride

According to the most accepted theory of acids and bases - the proteolytic theory of Bransted and Lowry - acid-base reactions are carried out by transferring a proton from acid to base. In other words, the acid is the donor and the base is the proton acceptor.

The method of acid-base titration is based on acid-base interaction reactions, which in General can be presented as follows:



Acids (neutral molecules, cations or anions) can donate a proton to a solvent or proton-coordinating base, with aqueous solutions forming the hydroxonium ion

H_3O^+ or in the general case the onium ion. The stronger the donor acid, the weaker the corresponding acceptor base.

The strength of the acid or base largely depends on the acid-base properties of the solvent. In any solvent, the strongest acid is the solvated proton, the liolium ion, and the strongest base is the liate ion (solvent anion). Thus, in aqueous solution, the strongest acid is the hydroxonium ion H_3O^+, and the strongest base is the hydroxyl ion OH^-; in liquid ammonia, the strongest acid is the ammonium ion NH_4^+, and the strongest base is the amide ion NH_2^-; in glacial acetic acid, the strongest base is the acetate ion CH_3COO^-, and the strongest acid is the acetone ion $CH_3COOH_2^+$.

Thus, the method of acid-base titration is based on the reactions:

$$SH^+ + S \rightleftharpoons 2SH$$

where SH is the solvent.

In addition to direct acid-base titration, inverse titration (residue) and substitution titration are used.

In direct determination, the result of the analysis is characterized by a smaller error than in the determination of the residue or substitute.

The standard reagents in the method of acid-base titration are always strong acids or strong bases, as reactions involving them are more complete than with their weak analogues.

The end point of titration can be determined by two methods: visually (indicator method) and instrumentally (potentiometrically). The indicator method is more often used for the analysis of medicinal substances.

Acid-base indicators are almost always organic compounds that exhibit the properties of weak acids or bases. They can be divided into several groups: phthalein (phenolphthalein, thymolphthalein), sulfophthalein (phenol red) and azoindicators (methyl orange and methyl red).

At visual observation with the acid-base indicator, the determination is about ±0.5 pH units [39].

Potentiometric titration is a volume-analytical method of analysis in which the equivalent volume of the titrant is determined by measuring, in the titration process, the electromotive force of a specially selected electrode pair.

The electrode pair consists of an indicator electrode and a reference electrode. The indicator electrode is chosen so that its potential depends on the concentration of ions involved in the titration or formed during the titration. The potential of the reference electrode during the titration process must remain constant. Mercury-calomel or silver chloride electrodes are used as an indicator.

In acid-base titration reactions, the change in the activity of hydrogen ions in solution is determined by the change in the potential of any electrode used to measure pH [39,40].

Quantitative determination of fexofenadine hydrochloride was performed by potentiometric titration.

In potentiometric titration, the volume of titrant at the equivalence point V_e can be determined by several methods:

1. on the graph of the titration curve in the coordinates [V; E], applying the tangent method;

2. on the graph [V; $\frac{\Delta \mathbf{E}}{\Delta \mathbf{V}}$],

where ΔE – change in electromotive force;

ΔV – the corresponding increase in the volume of the titrant.

The equivalence point corresponds to the maximum value $\frac{\Delta \mathbf{E}}{\Delta \mathbf{V}}$; calculated by the maximum value $\frac{\Delta \mathbf{E}}{\Delta \mathbf{V}}$ and accordingly, $\Delta(\frac{\Delta \mathbf{E}}{\Delta \mathbf{V}})$.

The equivalent volume of titrant V_e is calculated by the formula:

$$V\,e = V_1 + (V_2 - V_1) \cdot \frac{A_{V1}}{A_{V_1} - A_{V_2}},$$

where V_1 – the volume of titrant corresponding to the last positive (negative) value A_V;

V_2 – the volume of titrant corresponding to the first positive (negative) value A_V;

$A_V=\Delta(\frac{\Delta E}{\Delta V})$ – increase in magnitude $\frac{\Delta E}{\Delta V}$.

When passing through the equivalence point A_V changes the sign to the opposite.

Potentiometric titration almost always gives more accurate results than indicator, especially in the analysis of turbid and colored solutions, allows you to automate the titration process [39,41].

Fexofenadine hydrochloride in its structure contains a carboxyl group and is a hydrochloride salt of an organic base. Therefore, we suggested that its quantitative content can be determined by alkalimetry. Ethyl alcohol was used as the solvent because fexofenadine hydrochloride is insoluble in water. To establish the ratio of the reaction of the interaction of fexofenadine hydrochloride with sodium hydroxide, the end point of the titration was determined potentiometrically. To prevent the titration error, a blank titration was carried out in parallel [41].

Method of determination. Transfer the 0.0600 g of the substance to a glass and dissolved in ethyl alcohol, and titrate with 0.1 M sodium hydroxide to a potentiometric endpoint.

A blank determination is performed parallel.

The content of fexofenadine hydrochloride in the substance should be from 98.0% to 102%, calculated on the dried basis [9].

Samples of fexofenadine hydrochloride of different weights of 0.2441 g and 0.3507 g were taken for alkalimetric potentiometric titration. Titration was performed at a rate of 0.1 ml in 2 minutes. As a result of the experiment, a volume of 0.1 M sodium hydroxide was determined potentiometrically and titrated. The volume of 0.1 M sodium hydroxide that went to potentiometric titration was determined from the titration curves and the formula. Due to this, it was determined

that the stoichiometric ratio between fexofenadine hydrochloride and sodium hydroxide is 1/2, as a sample weighing 0.2441 g was spent 2.55 ml of titrant.

The volume of sodium hydroxide used for titration was calculated according to the formula for which Table 3.1 was completed. The volume of 0.1 M sodium hydroxide used for titration was also found by integral (Fig. 3.1) or differential (Fig. 3.2) curves of potentiometric titration of fexofenadine hydrochloride.

Table 3.1

The results of alkalimetric potentiometric determination of fexofenadine

V_1, ml	ΔV, ml	E, μV	ΔE	$\frac{\Delta E}{\Delta V}$	$A_v=\Delta(\frac{\Delta E}{\Delta V})$
1	**2**	**3**	**4**	**5**	**6**
0.1		16			
	0.1		9	90	
0.2		25			0
	0.1		9	90	
0.3		34			+10
	0.1		10	100	
0.4		44			-30
	0.1		7	70	
0.5		51			+10
	0.1		8	80	
0.6		59			+30
	0.1		11	110	
0.7		70			-50
	0.1		6	60	
0.8		76			+40
	0.1		10	100	
0.9		86			+20
	0.1		12	120	
1.0		98			-70
	0.1		5	50	
1.1		103			0
	0.1		5	50	

Table 3.1 (Continued)

1	2	3	4	5	6
1.2		108			+60
	0.1		11	110	
1.3		119			-40
	0.1		7	70	
1.4		126			0
	0.1		7	70	
1.5		133			-10
	0.1		6	60	
1.6		139			0
	0.1		6	60	
1.7		145			+10
	0.1		7	70	
1.8		152			0
	0.1		7	70	
1.9		159			+40
	0.1		11	110	
2.0		170			-40
	0.1		7	70	
2.1		177			+50
	0.1		12	120	
2.2		189			+60
	0.1		18	180	
2.3		207			+100
	0.1		28	280	
2.4		235			+270
	0.1		55	550	
2.5		290			-210
	0.1		34	340	
2.6		324			-210
	0.1		13	130	
2.7		337			-70
	0.1		6	60	
2.8		343			-30
	0.1		3	30	

Table 3.1 (Continued)

1	2	3	4	5	6
2.9		346			+20
	0.1		5	50	
3.0		351			-20
	0.1		3	30	
3.1		354			0
	0.1		3	30	
3.2		357			-10
	0.1		2	20	
3.3		359			+10
	0.1		3	30	
3.4		362			

The equivalent volume of titrant was calculated by the formula:

$$V_e = 2{,}5 + (2{,}6 - 2{,}5) \cdot \frac{270}{270 - (-210)} = 2{,}55 \text{ ml}$$

The volume of the titrant at the point of equivalence V_e can be determined using the integrated potentiometric titration curve (Fig. 3.1) or the differential titration curve (Fig. 3.2).

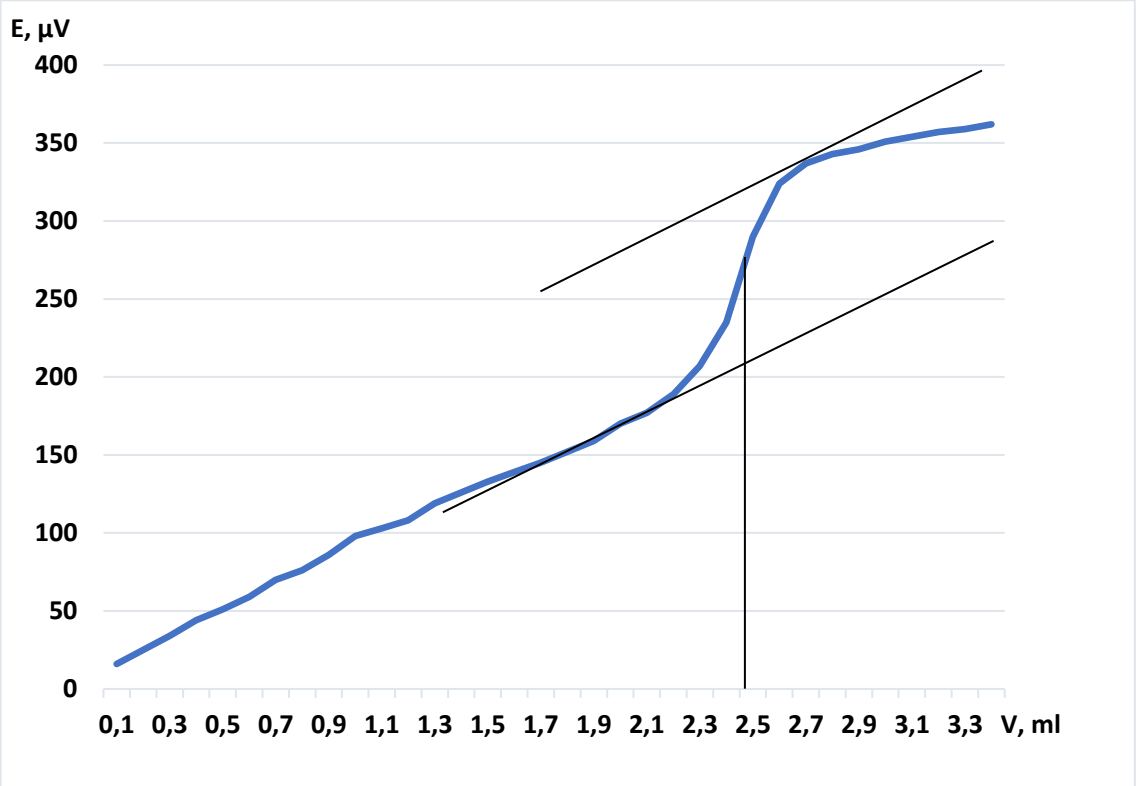


Fig. 3.1 Integral curve of potentiometric titration of fexofenadine hydrochloride (m=0.2441 g)

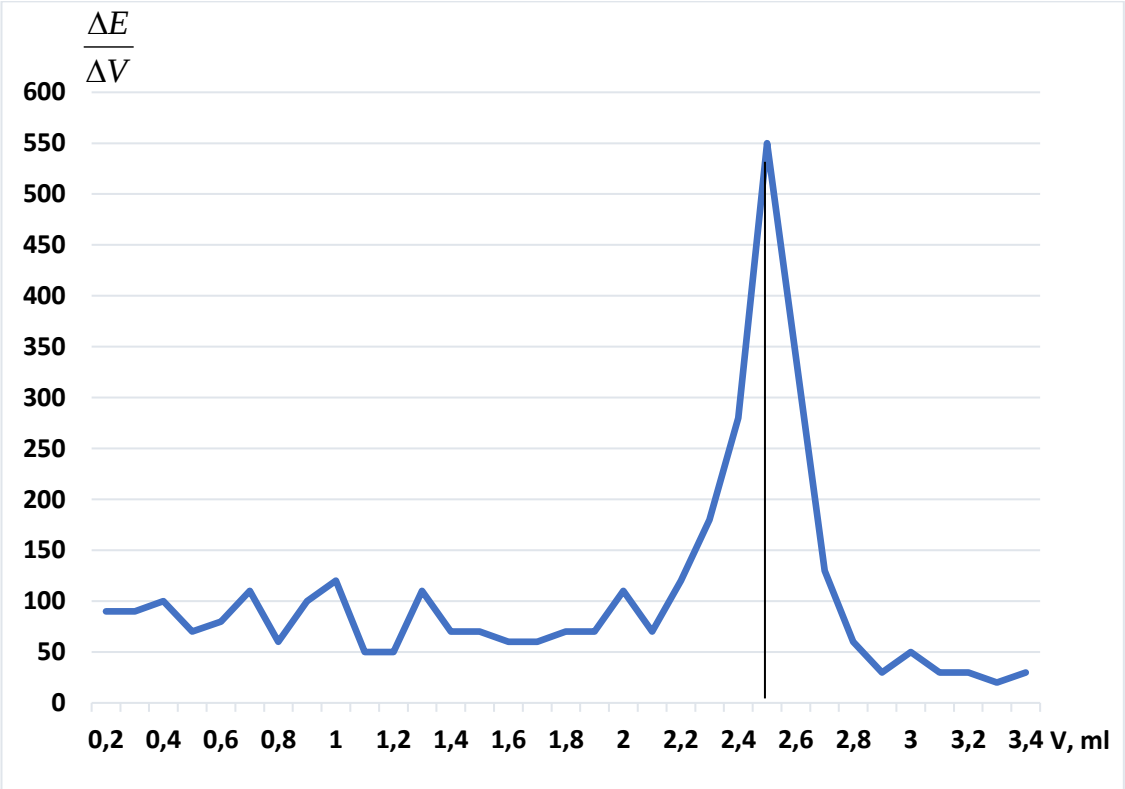


Fig. 3.2 Differential curve of potentiometric titration of fexofenadine hydrochloride (m=0.2441 g)

As can be seen from Fig. 3.3 and Fig. 3.4 the volume of sodium hydroxide spent on the titration of 0.3507 g is 3.5 ml. When calculating the quantitative content of fexofenadine hydrochloride, taking into account this volume, it was found that the stoichiometric ratio between fexofenadine hydrochloride and sodium hydroxide is 1/2.

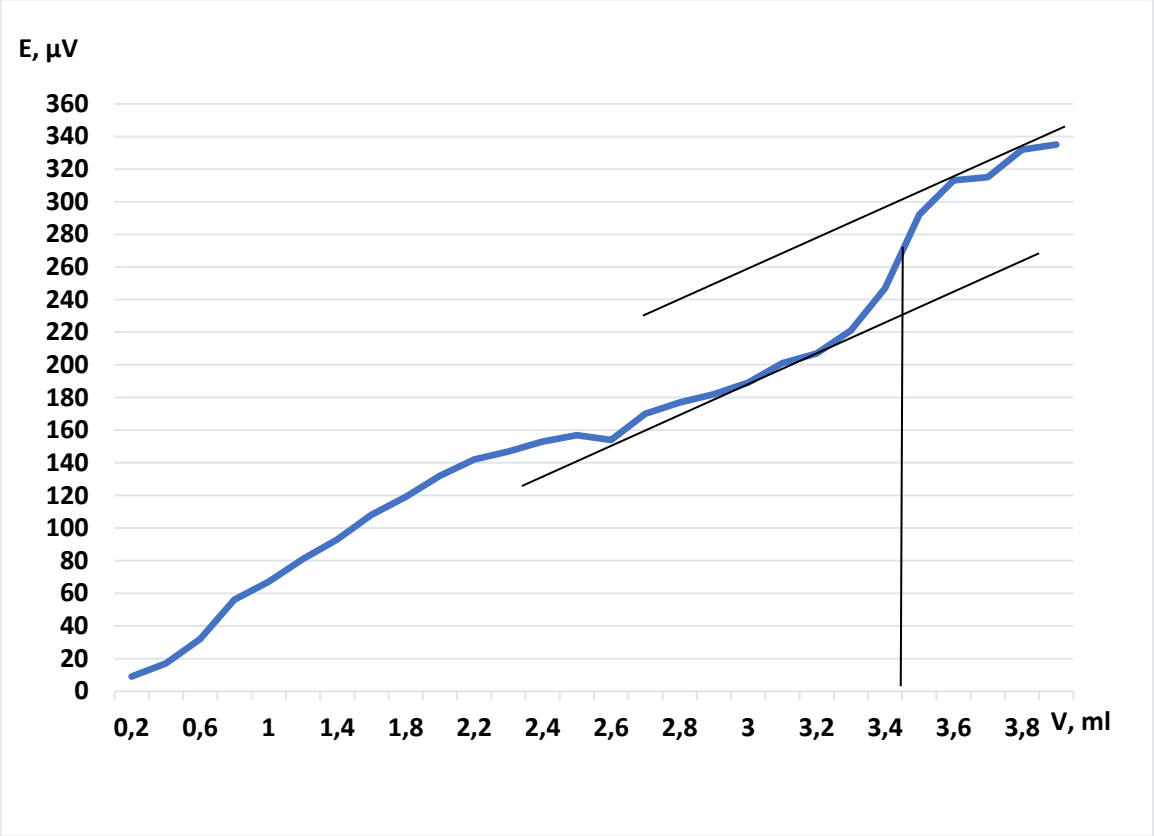


Fig. 3.3 Integral curve of potentiometric titration of fexofenadine hydrochloride (m=0.3507 g)

The volume of the titrant at the point of equivalence V_e can be determined using the differential curve of potentiometric titration (Fig. 3.4).

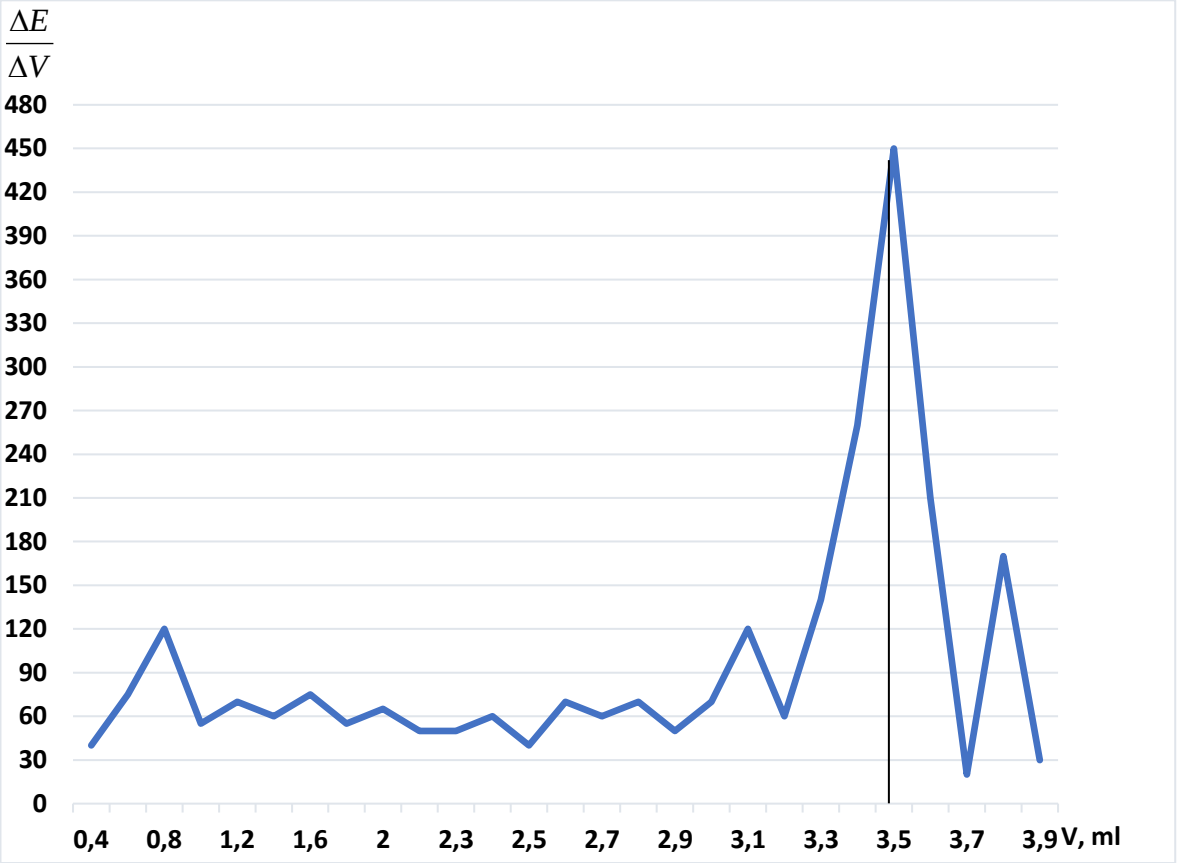
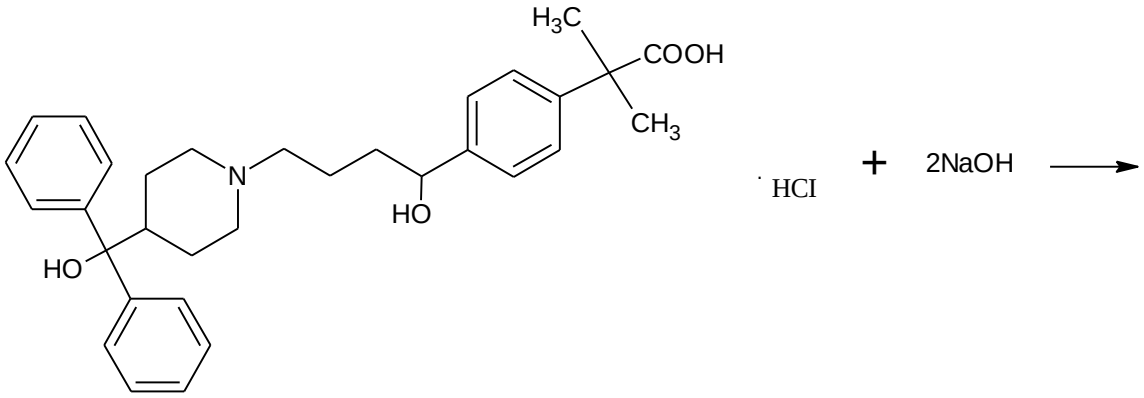
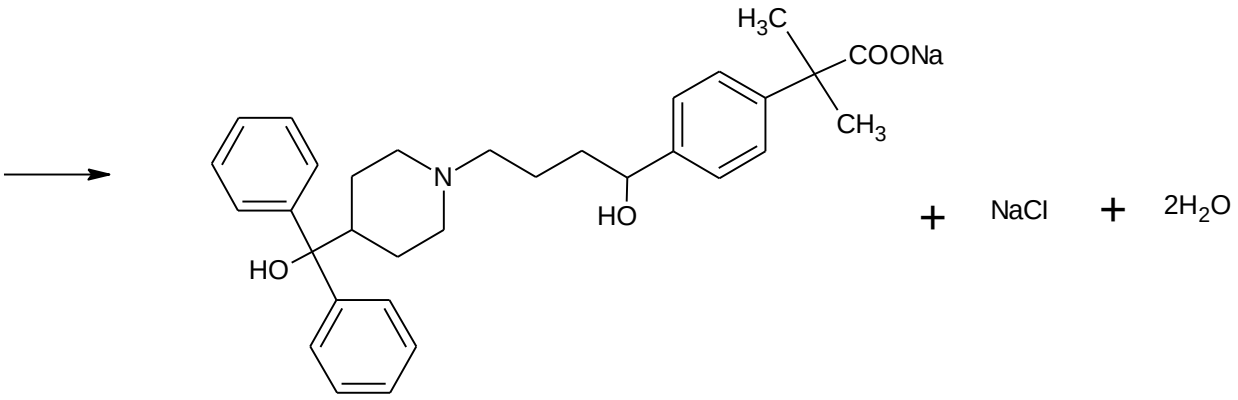


Fig. 3.4 Differential curve of potentiometric titration of fexofenadine hydrochloride (m=0.3507 g)

Thus, the reaction mechanism can be represented as follows:





$$T = \frac{c \cdot M \cdot s}{1000}\text{; s=1/2}$$

where C – molar concentration of the solution;

s – stoichiometric coefficient;

M – molar mass of fexofenadine hydrochloride g/mol.

Calculated the percentage content of fexofenadine hydrochloride in the substance using the following expression:

$$x, \% = \frac{(V - V_{bl.t.}) \cdot K \cdot T \cdot 100 \cdot 100}{m \cdot (100 - H)},$$

where

V – volume of 0.1 M sodium hydroxide used in the titration of fexofenadine hydrochloride, ml;

$V_{bl.t.}$ – volume of 0.1 M sodium hydroxide solution used in the blank titration, ml;

K – the coefficient of correction of the titrated solution;

T – titer of 0,1 M sodium hydroxide on fexofenadine hydrochloride, g/ml;

m – mass of the sample of fexofenadine hydrochloride, mg;

H – percentage content of water.

The quantitative content of fexofenadine hydrochloride is:

$$X, \% = \frac{(2.5 - 0.1) \cdot 0.02508 \cdot 0.9930 \cdot 100 \cdot 100}{0.0600 \cdot (100 - 0.5)} = 100.12\%$$

According to the European Pharmacopoeia, the quantitative content of fexofenadine hydrochloride should be from 98.0 per cent to 102.0 per cent (anhydrous substance) [9].

3.2 Testing of the developed method of quantitative determination on model mixtures

To use this method of analysis of the dosage form, it was necessary to establish the effect of excipients on the quantification of fexofenadine hydrochloride in tablets. To do this, the method was tested on model mixtures.

Method of determination. 0.1200 g of fexofenadine hydrochloride and excipients (microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, magnesium stearate, hypromellose, povidone, titanium dioxide (E 171), colloidal anhydrous silica, macrogol 400, a mixture of iron oxide yellow (E 172)) to obtain a mass of 0.2740 g is placed in a glass, shaken with 30 ml of ethyl alcohol and titrated with 0.1 M sodium hydroxide, determining the end-point potentiometrically.

Carry out a blank titration.

Calculate the amount of fexofenadine hydrochloride in the model mixtures, in milligrams, using the following expression:

$$X, mg = \frac{(V - V_{bl.t}) \cdot K \cdot T \cdot m \cdot 1000}{m},$$

where

V – volume of 0.1 M sodium hydroxide used in the titration of fexofenadine hydrochloride, ml;

$V_{bl.t.}$ – volume of 0.1 M sodium hydroxide solution used in the blank titration, ml;

K – the coefficient of correction of the titrated solution;

T – titer of 0,1 M sodium hydroxide on fexofenadine hydrochloride, g/ml;

m – mass of the sample of fexofenadine hydrochloride in the model mixtures, g.

The content of fexofenadine hydrochloride in the model mixture should be from 114.0 mg to 126.0 mg.

The results of alkalimetric potentiometric quantitative determination of fexofenadine hydrochloride in the model mixture are shown in Table 3.2.

Table 3.2

Results of quantitative determination of fexofenadine hydrochloride in model mixtures

№	Mass of fexofenadine hydrochloride in the model mixture, mg	V_{NaOH}, ml	$V_{NaOH\ (bl.t.)}$, ml	T, g/ml	Found the amount of fexofenadine hydrochloride, mg
1	120.00	4.90	0.10	0.02508	119.18
2		4.95			120.42
3		4.83			117.44
4		4.80			116.70
5		4.92			119.67
6		5.05			122.90

The obtained results of quantitative determination were subjected to statistical processing.

The results of statistical processing of the sample can be reliable only if this sample is homogeneous [41].

The magnitude scale of the variation of R (for the results obtained in ascending order):

$$R = |116.70 - 122.90| = 6.20$$

Test criteria for identifying of gross errors:

$$Q_1 = \frac{|116.70-117.44|}{6.20} = 0.11 \qquad Q_2 = \frac{|117.44-119.18|}{6.20} = 0.28$$

$$Q_3 = \frac{|119.18-119.67|}{6.20} = 0.08 \qquad Q_4 = \frac{|119.67-120.42|}{6.20} = 0.12$$

$$Q_{5} = \frac{|120.42 - 122.90|}{6.20} = 0.40$$

The numerical value of the control criterion Q (P, ν) for the confidence probability P=95

Q(P,n)=Q(95%,6)=0.56 [41]

All Q <Q (P, ν), i.e. the sample can be considered homogeneous.

Next, calculate the metrological characteristics of the average result.

Number of experiments: n = 6; *ν = n-1;* *ν = 5*

The average result: $\bar{x} = \frac{\sum_{i}^{n} x_i}{n}$ $\bar{x} = 119.39$

Dispersion:

$$S^2 = \frac{\sum_{i}^{n} x_i^2 - n\bar{x}^2}{n}$$ $S^2=4.9084$

Standard deviation:

$$\mathbf{S} = \sqrt{\mathbf{S}^2}$$ S=2.2155

Relative (relative to the mean result) standard deviation:

$$S_{\bar{x}} = \frac{S}{\sqrt{n}}$$ $S_x = 0.9045$

Confidence interval the result of a separate determination (*P=95%):*

$$x_i \pm \Delta x = x_i \pm t(P,\nu) \cdot S$$ Δx=5.6951

Confidence interval of the average result with a probability of 95%:

$$\bar{x} \pm \Delta\bar{x} = \bar{x} \pm \frac{S \cdot t(P,\nu)}{\sqrt{n}}$$ $\Delta\bar{\mathbf{x}}$=2.3250

t(P,ν)=2.5706 – tabular value of the Student's criterion [41].

The relative error of a single determination:

$$\varepsilon = \frac{\Delta x}{\bar{x}} \cdot 100\%$$ ε = 4.77%

The relative error of the average results:

$$\bar{\varepsilon} = \frac{\Delta\bar{x}}{\bar{x}} \cdot 100\% \qquad \bar{\varepsilon} = 1.95\%$$

Metrological characteristics of the alkalimetric potentiometric method for the quantitative determination of fexofenadine hydrochloride are given in Table 3.3.

Table 3.3

Metrological characteristics of alkalimetric potentiometric method for determination of fexofenadine hydrochloride

μ	ν	$\bar{\mathbf{x}}$	S^2	S	P	t(P,ν)	$\Delta\bar{\mathbf{x}}$	ε,%
120.00	5	119.39	4.9084	2.2155	95	2.5706	2.3250	4.77

The relative error of a single determination is 4.77%, so the method can be used to quantify fexofenadine in tablets.

3.3 Quantitative determination of fexofenadine hydrochloride in Allegra tablets

The method of alkalimetric potentiometric quantification of fexofenadine hydrochloride, tested on model mixtures, was used to quantify fexofenadine hydrochloride in Allegra tablets.

Method of determination. Weigh and powder 20 tablets. a quantity of the powder containing 120 mg of fexofenadine hydrochloride, is placed in a glass, shaken with 30 ml of alcohol and titrated with 0.1 M sodium hydroxide, determining the end-point potentiometrically.

Carry out a blank titration.

Each ml of 0.1 M sodium hydroxide is equivalent to $C_{32}H_{39}NO_4$, which should be from 114.0 mg to 126.0 mg, based on the average mass of the tablet.

The content of fexofenadine hydrochloride should be from 95.0 per cent to 105.0 per cent, based on the nominal content.

Calculate the amount of fexofenadine hydrochloride in milligrams, using the following expression:

$$X, mg = \frac{(V - V_{bl.t}) \cdot K \cdot \text{T} \cdot m_{av.} \cdot 1000}{m},$$

where

V – volume of 0.1 M sodium hydroxide used in the titration of fexofenadine hydrochloride, ml;

$V_{bl.t.}$ – volume of 0.1 M sodium hydroxide solution used in the blank titration, ml;

K – the coefficient of correction of the titrated solution;

T – titer of 0,1 M sodium hydroxide on fexofenadine hydrochloride, g/ml;

$m_{av.}$ - mass of the average tablet of fexofenadine hydrochloride, mg;

m – mass of the sample of fexofenadine hydrochloride, mg.

The results of quantitative alkalimetric potentiometric titration of fexofenadine hydrochloride in tablets are shown in Table 3.4.

Table 3.4

The results of alkalimetric potentiometric titration of fexofenadine hydrochloride in Allegra tablets

№	Mass of the sample powder tablets, g	T, g/ml	K	$V_{NaOH,}$ ml	$V_{NaOH\ (bl.t.)}$, ml	Found fexofenadine hydrochloride in tablets, mg
1	0.2709	0.02508	0.9900	4.90	0.10	120.54
2	0.2741			4.85		117.90
3	0.2685			4.80		119.09
4	0.2692			4.75		117.51
5	0.2700			4.91		121.20
6	0.2670			4.87		121.54

Metrological characteristics of the average value of the alkalimetric potentiometric method for the quantitative determination of fexofenadine hydrochloride in tablets are shown in Table 3.5.

Table 3.5

Metrological characteristics of the average result of alkalimetric potentiometric method for determination of fexofenadine hydrochloride in Allegra tablets

ν	$\bar{x}$	S^2	S	S_x	P	t(P,ν)	Δx	$\Delta\bar{x}$	$\bar{\varepsilon}$,%
5	119.63	2.9440	1.7158	0.7005	95	2.5706	4.4107	1.8006	1.51

Thus, we can conclude that the content of active substance in the tablets is 119.63 ± 1.8006 mg, and the relative error of the average result ±1.51% does not exceed the norm of tolerances ± 5%. Therefore, it is proved that the method is reproducible and can be used to quantify fexofenadine hydrochloride in the drug.

Conclusions

1. A method of alkalimetric potentiometric quantitative determination of fexofenadide hydrochloride has been developed.

2. It is experimentally established that the ratio between fexofenadine hydrochloride and 0.1 M sodium hydroxide solution is 1/2.

3. The method of alkalimetric potentiometric titration is metrologically certified on model mixtures.

4. It is proved that the alkalimetric potentiometric method of quantitative determination of fexofenadine hydrochloride is reproducible, express, accurate, as the content of active substance in tablets is 119.63 ± 1.8006 mg, and the relative error of the average result ±1.51% does not exceed the allowable deviations ± 5%.

5. The method of alkalimetric potentiometric titration can be used for further analysis of fexofenadine hydrochloride both in substance and in dosage forms.

GENERAL CONCLUSIONS

1. Generalized literature data on methods of synthesis, analysis and pharmacological activity of fexofenadine hydrochloride.

2. A method of alkalimetric potentiometric quantitative determination of fexofenadine hydrochloride has been developed.

3. It is experimentally established that the ratio between fexofenadine hydrochloride and 0.1 M sodium hydroxide is 1/2.

4. The method of alkalimetric potentiometric titration is metrologically certified on model mixtures.

5. It is proved that the alkalimetric potentiometric method of quantitative determination of fexofenadine hydrochloride is reproducible, express, accurate.

6. The method of alkalimetric potentiometric titration can be used for further analysis of fexofenadine hydrochloride both in substance and in dosage forms.

REFERENCES

1. Miura M., Uno T., Tateishi T., Suzuki T. Pharmacokinetics of fexofenadine enantiomers in healthy subjects // Chirality. 2007. Vol. 19. P. 223–227.
2. Kumar L., Alam M. S., Meena C. L., Jain R., Bansal A. K. Fexofenadine hydrochloride. In *Profiles of drug substances, excipients and related methodology*. 2009. Vol. 34. P. 153-192.
3. Lemke T.L., Zito S.W., Roche V.F., Williams D.A. Essentials of Foye's Principles of Medicinal Chemistry. 2017. 1481 p.
4. Fischer, Jnos; Ganellin, C. Robin (2006). Analogue-based Drug Discovery. John Wiley & Sons. p. 548.
5. World Health Organization (2021). *World Health Organization model list of essential medicines: 22nd list (2021)*. Geneva: World Health Organization.
6. Mirzaei S., Taghe S., Pirhayati F. H. et al. Measurement and correlation of fexofenadine hydrochloride solubility in ethanol+ water mixtures at T=(293.2 to 313.2) K // *Journal of Molecular Liquids.* 2021. Vol. *329. P.* 115554.
7. Giacomo B.D., Coletta D., Natalini B.N., Ni M.H., Pellicciari R. A new synthesis of carboxyterfenadine (fexofenadine) and its bioisosteric tetrazole analogs // Il Farmaco. 1999. Vol. 54. P. 600–610.
8. Kleemann A., Engel J. Pharmaceutical Substances: syntheses, patents, applications / Thieme Medical Publishers; 4th edition. 2001. 2488 p.
9. European Pharmacopoeia. 6th ed. Strasbourg: European Directorate for the Quality of Medicines, 2008. Vol. 2. P. 1888–1890.
10. British Pharmacopoeia / The British Pharmacopoeia Secretariat. London, 2013. Vol. 1. P. 10952. http://www.vek-com.ru/78022.html
11. The United States Pharmacopeia 36. Rockville, 2013. NF31. Vol. 2. P. 3573-3579.
12. Khadzhieva Z.D., Chumakova V.A., Gubanova L.B. Development of technique for the quantitative determination of fexofenadinein substance

spectrophotometric method // Научные Ведомости. Серия Медицина. Фармация. 2015. № 22 (219). Вып. 32. С. 158-163.

13. Аллегра® (Allegra®) таблетки, вкриті оболонкою 120 мг. Компендіум. Лікарські препарати. Джерело: https://compendium.com.ua/dec/275404/317373/
14. Lemke T.L., Williams D.A., Roche V.F., Zito S.W. Foye's Principles of Medicinal Chemistry. 7th ed. 2013. P. 1058-1059.
15. Craun K.L., Schury M.P. (2020). Fexofenadine. *StatPearls [Internet]*. https://www.ncbi.nlm.nih.gov/books/NBK556104/
16. Аллегра 120 мг. Інструкція для медичного застосування лікарського засобу. https://mozdocs.kiev.ua/likiview.php?id=44882
17. Naclerio R., Ansotegui I.J., Bousquet J. et al. International expert consensus on the management of allergic rhinitis (AR) aggravated by air pollutants: Impact of air pollution on patients with AR: Current knowledge and future strategies // World Allergy Organ J. 2020. Vol. 13. P. 100106.
18. Li C.H., Sayeau K., Ellis A.K. Air pollution and allergic rhinitis: role in symptom exacerbation and strategies for management // J Asthma Allergy. 2020. Vol. 13. P. 285–292.
19. Carlsten C., Blomberg A., Pui M. et al. Diesel exhaust augments allergen-induced lower airway inflammation in allergic individuals: a controlled human exposure study // Thorax. 2016. Vol. 71. P. 35–44.
20. Axelrod D., Bielory L. Fexofenadine hydrochloride in the treatment of allergic disease: a review // J Asthma Allergy. 2008. Vol. 1. P. 19–29.
21. Ellis A. K., Murrieta-Aguttes M., Furey S., Picard P., Carlsten C. Effect of fexofenadine hydrochloride on allergic rhinitis aggravated by air pollutants // *ERJ open research*. 2021. Vol. *7* (2). P. 1-10.
22. The United States Pharmacopeia 36. Rockville, 2013. NF31. Vol. 2. P. 3573-3579.

23. Sanam S., Nahar S., Saqueeb N., Rahman S.A. A Validated RP-HPLC Method and Force Degradation Studies of Fexofenadine Hydrochloride in Pharmaceutical Dosage Form // *Dhaka University Journal of Pharmaceutical Sciences.* 2018. Vol. *17* (1). P. 43-50.
24. Tokumura T., Kawakami M., Kitada R., Kurita T. Validated Assay Method for Fexofenadine Hydrochloride in Powder Preparations of Allegra® 60 mg Tablets to Develop a New Method for Grinding Tablets on Dispensing in Japan // *J. Pharm.* 2016. Vol. *5. P.* 359-362.
25. Sutar P.M., Bansode D.A., Dhaneshwar S.S. Development and validation of hptlc method for analysis of fexofenadine hydrochloride as a bulk drug and in tablet dosage form // World Journal of Pharmaceutical Research. 2015. Vol. 4, Issue 5. P. 1757-1769.
26. Malothu N., Paladugu T., Katamaneni P. Development and Validation of RP-HPLC Method for Determination of Fexofenadine in Pharmaceutical Dosage Form by Using Levocetirizine as an Internal Standard // *Int. J. Pharm. Biol. Sci*. 2018. Vol. *8. P.* 619-625.
27. Akbel E., Bulduk İ. RP-HPLC Method Development and Validation for Quantification of Fexofenadine in Pharmaceutical Products // *Avrupa Bilim ve Teknoloji Dergisi.* 2021. Vol. 32. P. 1048-1053.
28. Raghu M.S., Shantharam C.S., Yogesh Kumar K. Application of Bromate-Bromide Mixture as a Green Brominating Agent for the Determination of Fexofenadine Hydrochloride Pharmaceutical Dosage Form // *J. Anal. Pharm. Res.* 2018. Vol. *7. P.* 13-21.
29. Al-Mohaimeed A. M., Alarfaj N. A., El-Tohamy M. F., Al-Harbi H. Prospective of ultrasenstive nanometal oxides electrochemical sensors for pharmaceutical analysis of antihistamine drug fexofenadine hydrochloride // *Int. J. Electrochem. Sci*. 2020. Vol. *15. P.* 4774-4788.
30. Ashour S., Bayram R. Sensitive extractional colorimetric analysis of fexofenadine hydrochloride and irbesartan bases through acid-dye

complexation using naphthol blue black in pure form and pharmaceuticals // *Modern Chemistry.* 2017. Vol. *5* (6). P. 14-21.

31. Sowjania G., Sastri T. UV Spectrophotometric method development and validation for simultanious determination of fexofenadine hydrochloride and Montelukast sodium in tablets // *World J Pharm Pharm Sci.* 2018. Vol. *6* (10). P. 780-789.
32. Patle D., Nagar S. UV-visible spectrophotometric estimation of montelukast and fexofenadine by simultaneous equation method in bulk & combined tablet dosage form // *Current Trends in Biotechnology and Pharmacy*. 2017. Vol. *11* (4). P. 382-388.
33. Tamilselvi N., Sruthi K., Arivukkarasu R., Vanathi P., Visakh D. Development of validated HPTLC method for simultaneous estimation of fexofenadine hydrochloride and montelukast sodium in tablet dosage form // *Research Journal of Pharmacy and Technology.* 2016. Vol. *9* (4). P. 469-473.
34. Sharma K., Bhatia R., Anghore D. et al. Development and validation of UV-spectrophotometric and RP-HPLC methods for simultaneous estimation of fexofenadine hydrochloride, montelukast sodium and ambroxol hydrochloride in tablet dosage form // *Analytical Chemistry Letters.* 2018. Vol. *8* (6). P. 829-843.
35. Nashed D., Noureldin I., Sakur A. A. New pencil graphite electrodes for potentiometric determination of fexofenadine hydrochloride and montelukast sodium in their pure, synthetic mixtures, and combined dosage form // *BMC chemistry.* 2020. Vol. *14* (1). P. 1-9.
36. Abass A.M., Hassan O.S., Rikabi A.L., Salim, H.T., Ahmed A. Potentiometric determination of fexofenadinehydrochloride drug by fabrication of liquid membrane electrodes // *Egyptian Journal of Chemistry.* 2021. Vol. *64* (11). P. 5-6.
37. Buchupalli P., Medidi S. RP-HPLC method for the simultaneous estimation of ambroxol hydrochloride and fexofenadine hydrochloride in bulk and in a

tablet mixture // *Journal of Applied Pharmaceutical Science.* 2015. Vol. *5* (02). P. 074-080.

38. Kayesh R., Sarker A.S.M., Sultan M., Jahan M. A simple and improved HPLC-PDA method for simultaneous estimation of fexofenadine and pseudoephedrine in extended release tablets by response surface methodology // *Journal of Chemistry. 2017*. Vol. 2017, Article ID 9395023, 10 pages
39. Фармацевтичний аналіз : навч. посіб. для студ. вищ. фармац. навч. закл. / П. О. Безуглий, В. А. Георгіянц, І. С. Гриценко та ін.; за заг. ред. В. А. Георгіянц. Харків, 2013. 552 с.
40. Аналітична хімія: навч. посіб. для студ. фар мац. вузів і ф-тів III-IV рівнів акредитації / В.В. Болотов, О.М. Гайдукевич, О.М. Свєчникова та ін.; за заг. ред. В.В. Болотова. Харків, 2001. 456 с.
41. Державна Фармакопея України : в 3 т. / Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів». 2-е вид. Харків : Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів», 2015. Т. 1. 1128 с.

Ф А 2.2.1–32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department of pharmaceutical chemistry

Level of higher education master

Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of Department
of pharmaceutical chemistry

_____
Victoriya GEORGIYANTS
"_29__" __June____ 2021

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Taha ABBAD

1. Topic of qualification work: «Development of potentiometric titration method for the determination of fexofenadine hydrochloride in drugs», supervisor of qualification work: Vasyl GRYNENKO, PhD, assoc. prof.,
approved by order of NUPh from "17th" of February 2022 № 76

2. Deadline for submission of qualification work by the applicant for higher education: april 2022.

3. Outgoing data for qualification work: Fexofenadine is synthetic antihistamine pharmaceutical drug which is nowadays widely used in various medicinal formulations in the treatment of allergy symptoms, such as hay fever and urticaria. That is why it deserves special attention. Despite the fact that the drug is not completely new, the methods of quantitative determination for it have not been developed enough, which indicates the need to continue work to improve existing and develop new methods for determining the study drug, suitable for pharmaceutical analysis, in particular, for determining the substance in medicinal products.

4. Contents of the settlement and explanatory note (list of questions that need to be developed): to study the pharmacological properties and methods of analysis of fexofenadine hydrochloride; to study methods for the determination of fexofenadine hydrochloride in tablets; to develop method of quantitative determination for fexofenadine hydrochloride in substance; to develop method of quantitative determination for fexofenadine hydrochloride in tablets; to give statistic analyses for the obtained results.

5. List of graphic material (with exact indication of the required drawings):
5 tables, 5 figures, 2 schemes.

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Vasyl GRYNENKO, associate professor of higher education institution of pharmaceutical chemistry department	29.06.21	29.06.21
2	Vasyl GRYNENKO, associate professor of higher education institution of pharmaceutical chemistry department	17.01.22	17.01.22
3	Vasyl GRYNENKO, associate professor of higher education institution of pharmaceutical chemistry department	14.02.22	14.02.22

7. Date of issue of the assignment: «_29_» June 2021.

CALENDAR PLAN

№	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1	Study and analysis of reference data on the use of expectorants. Writing 1 chapter.	Jun-Nov 2021	**done**
2	Study, processing and analysis of literature data on the use of Fexofenadine, methods of its synthesis, analysis and metabolism and physic-chemical properties. Writing 2 chapter.	Dec 2021 - Jan 2022	**done**
3	Development of the procedure for the determination of Fexofenadine	Jan-Feb 2022	**done**
4	Statistical processing of experimental data. Writing 3 chapter.	March 2022	**done**
5	Summing up, preparation for defense	April 2022	**done**

An applicant of higher education _____ Taha ABBAD

Supervisor of qualification work _____ Vasyl GRYNENKO

ВИТЯГ З НАКАЗУ № 76

По Національному фармацевтичному університету
від 17 лютого 2022 року

1. Нижченаведеним студентам 5-го курсу 2021-2022 навчального року, навчання за освітньо-кваліфікаційним рівнем «магістр», галузь знань 22 охорона здоров'я, спеціальності 226 – фармація, промислова фармація освітня програма – фармація, денна форма навчання (термін навчання 4 роки 10 місяців), які навчаються за контрактом, затвердити теми магістерських робіт:

№ з/п	Прізвище студента	Тема магістерської роботи	Посада, прізвище та ініціали керівника	Рецензент магістерської роботи
по кафедрі фармацевтичної хімії				
1.	Аббад Таха	Розробка методу потенціометричного титрування фексофенадину гідрохлориду в лікарських препаратах Development of potentiometric titration method for the determination of fexofenadine hydrochloride in drugs	доц. Гриненко В.В.	доц. Подольський І.М.

Підстава: подання декана, згода ректора.

Ректор
Вірно. Секретар

Національний фармацевтичний університет
Факультет з підготовки іноземних громадян
№02010936
місто Харків

Ф А 2.2.1-32-353

REVIEW

of scientific supervisor for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy

Taha ABBAD

on the topic: «Development of potentiometric titration method for the determination of fexofenadine hydrochloride in drugs»

Relevance of the topic. The qualification work is devoted to the development of a potentiometric method for the determination of fexofenadine hydrochloride for the quantitative determination of a modern antihistamine drug with fexofenadine hydrochloride, which is nowadays widely used in various medicinal formulations. That is why it deserves special attention.

Practical value of conclusions, recommendations and their validity. The quality of drugs directly depends on the methods of their analysis, and therefore the development of new and improvement of existing methods for the analysis of drugs is an urgent task today. The results of the study can be applied in practice to develop regulatory and technical documentation for fexofenadine hydrochloride formulations.

Assessment of work. The qualification work consists of an introduction, three chapters, conclusions and a list of references. The work was done at a high scientific level; the applicant of high education independently reviewed the scientific literature in the field of pharmacological studies of antihistamine drugs. Under the guidance of the supervisor, the experimental part of the work and a review of the literature were completed.

General conclusion and recommendations on admission to defend. The qualification work meets the requirements for theses and can be recommended for defense to the Examination Commission of the NUPh.

Scientific supervisor _____ Vasyl GRYNENKO

« 15th» of April 2022

Ф А 2.2.1-32-356

REVIEW

for qualification work of the master's level of higher education, specialty 226 Pharmacy, industrial pharmacy

Taha ABBAD

on the topic: «Development of potentiometric titration method for the determination of fexofenadine hydrochloride in drugs»

Relevance of the topic. The quality of drugs directly depends on the methods of their analysis, and therefore the development of new and improvement of existing methods for the analysis of drugs is an urgent task today. The qualification work is devoted to potentiometric titration method for the quantitative determination of fexofenadine hydrochloride, which is simple, fast and cost-effective and can use for determining fexofenadine hydrochloride in the substance and dosage forms.

Theoretical level of work. For the study, a drug was chosen that is currently very widely used in medicine. When studying the literature, issues related to the use of modern antihistamine drugs, as well as methods for their analysis, were investigated.

Author's suggestions on the research topic. An important stage of research is their metrological processing, in connection with which it was necessary to assign more attention to the validation characteristics of the method of quantitative determination.

Practical value of conclusions, recommendations and their validity. The developed procedure of potentiometric titration can be used to quantify fexofenadine hydrochloride in the composition of medicinal formulations, and can be included in the regulatory and technical documentation as well as pharmacopoeial monographs.

Disadvantages of work. The work submitted for review does not have any significant shortcomings or disadvantages that affect compliance with the requirements of qualifying works.

General conclusion and assessment of the work. The work meets the requirements for qualification works of the master's level and can be recommended for defense in the Exam Commission of the NUPh.

Reviewer _____ assoc. prof. Illya PODOLSKY

« 22nd» of April 2022

Ф А2.2.1-38-287

ВИТЯГ З ПРОТОКОЛУ № 12

засідання кафедри фармацевтичної хімії

Національного фармацевтичного університету

від _26 квітня_ 2022 р.

ПРИСУТНІ:

проф. Георгіянц В.А., Власов С.В., Євтіфєєва О. А. Сидоренко Л.В.; доц.: Абу Шарк А.І., Бевз Н. Ю., Бур'ян Г.О., Гарна Н.В., Головченко О.С., Горохова О.В., Гриненко В.В., Грудько В.О., Колісник О.В., Петрушова Л.О., Северіна Г.І., ас. Григорів Г.В., Смєлова Н.М.

ПОРЯДОК ДЕННИЙ: заслухати звіт про стан виконання кваліфікаційних робіт.

СЛУХАЛИ: доповідь здобувача вищої освіти Таха АББАД студента факультету з підготовки іноземних громадян на тему «Розробка методу потенціометричного титрування фексофенадину гідрохлориду в лікарських препаратах / Development of potentiometric titration method for the determination of fexofenadine hydrochloride in drugs», керівник доцент закладу вищої освіти кафедри фармацевтичної хімії, к.ф.н. Василь ГРИНЕНКО.

УХВАЛИЛИ: рекомендувати кваліфікаційну роботу Таха АББАД до офіційного захисту в ЕК.

Зав. кафедри фармацевтичної хімії,

професор **Вікторія ГЕОРГІЯНЦ**

Секретар кафедри фармацевтичної хімії,

доцент **Лідія ПЕТРУШОВА**

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Таха АББАД до захисту кваліфікаційної роботи за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Розробка методу потенціометричного титрування фексофенадину гідрохлориду в лікарських препаратах».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Таха АББАД при проведенні досліджень і написанні роботи виявив себе досить відповідально. До написання роботи і підготовки до захисту ставився дуже серйозно. Робота цілком відповідає вимогам, що висуваються до кваліфікаційних робіт магістерського рівня і може бути рекомендована до захисту в Екзаменаційній комісії НФаУ.

Керівник кваліфікаційної роботи

_____ Василь ГРИНЕНКО

«15» квітня 2022 р.

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Таха АББАД допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувачка кафедри
фармацевтичної хімії

_____ Вікторія ГЕОРГІЯНЦ

«26» квітня 2022 року

Qualification work was defended

of Examination commission on

« ___ » _____ 2022

With the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Oleh SHPYCHAK /