UDC 615.214:54.061/062:543.42:543.5
DOI: 10.15587/2519-4852.2021.228132

DEVELOPMENT OF DETERMINATION METHODS OF QUETIAPINE FUMARATE FOR FORENSIC-PHARMACEUTICAL PURPOSES

Olena Bevz, Igor Sych, Angelina Shaposhnyk, Irina Sych, Olga Kryvanych, Svitlana Taran, Lina Perekhoda

Quetiapine fumarate (an antipsychotic) is part of numerous generic drugs that are in fairly wide demand among the population, therefore, more and more data appear on the counterfeiting and smuggling of funds, as well as non-medical use, which are life-threatening for the population and explain the high prevalence of the active ingredient as object of forensic examination.

The aim. *To develop an algorithm for conducting a forensic pharmaceutical examination and propose a method for determining quetiapine fumarate for forensic pharmaceutical purposes.*

Materials and methods. *All studies were performed using reagents that meet the EP, USP and USPU requirements, Class A glassware and qualified devices.*

Identification by IR spectroscopy was performed in the range from 500 to 4000 cm^{-1} on the device "Nicolet 380 FT-IR Spectrometer by Thermo Fisher Scientific" using a prefix "Smart Perfomer" with a ZnSe crystal.

The UV absorption spectra of the solutions were recorded using a Specord 205 spectrophotometer from Analytik Jena AG (Germany).

TLC was performed on Merck chromatographic plates (silica gel 60G F254, Germany). The following systems were used as mobile phases: hexane – acetone – 25 % ammonia solution (60:40:2); methanol – 25 % ammonia solution (100:1.5), hexane – acetone – 25 % ammonia solution (50:45:5). Detection was performed under UV light (254 nm), followed by spraying with Dragendorff reagent.

Analysis by gas chromatography with mass detection was performed using a GC gas chromatograph with a mass spectrometric detector GCMS-QP2020. Data were analyzed using the program: GCMSsolution, LabSolutions Insight (Shimadzu Corporation, Tokyo, Japan).

Results. *An algorithm for conducting a forensic pharmaceutical examination in accordance with the current legislation of Ukraine has been developed, methods for determining quetiapine for forensic pharmaceutical purposes have been proposed.*

Conclusions. *The developed methods for determining quetiapine meet the requirements of the current legislation of Ukraine and the Ministry of Justice of Ukraine. The obtained data prove the high sensitivity and reproducibility of the methods and prove the possibility of their introduction into the practice of forensic examination*

Keywords: *quetiapine fumarate, forensic pharmaceutical expertise, spectral analysis, chromatography*

How to cite:
Bevz, O., Sych, I., Shaposhnyk, A., Sych, I., Kryvanych, O., Taran, S., Perekhoda, L. (2021). Development of determination methods of quetiapine fumarate for forensic-pharmaceutical purposes. ScienceRise: Pharmaceutical Science, 2 (30), 03–12. doi: http://doi.org/10.15587/2519-4852.2021.228132

1. Introduction

The issue of providing the state and the population with the necessary medicines of proper quality and safety is an important segment of both the national economy and a component of national security [1].

One of the offenses of drug trafficking is counterfeiting, which has an illegal and criminal origin, because the production of counterfeit medicines uses the brand names of well-known pharmaceutical companies, which in fact do not bear any responsibility for this product. These are well-organized illegal enterprises, sometimes even equipped no worse than legal manufacturers. In addition, counterfeiters sometimes use legal production lines.

According to the World Health Organization, counterfeit medicines make up about 10 % of the global drug market. In the CIS countries, this figure reaches 20 %, in Ukraine the share of counterfeit medicines, according to various data, is 15–25 % [2]. Counterfeits claim about 200,000 lives each year, and counterfeiters make about $ 50 billion. In most cases, counterfeit domestic drugs, usually known and tested. Also falsify popular imported drugs produced by reputable pharmaceutical companies. Counterfeit drugs, depending on the conditions of their production, are divided into four groups: placebo drugs; preparations that contain components not listed in the package, or components that may

be a threat to life and safety of human health; "modified drugs" that contain the active pharmaceutical ingredient, but its amount differs from that indicated on the package; copy preparations that contain the same substances and in the same quantities, but it is unknown where the manufacturer took the substance for production.

In addition to falsification, significant offenses in the circulation and rational administration of medicines include the illegal import of medicines into the state, the release of prescription drugs without a prescription, which sometimes leads to the use of medicines for non-medical purposes.

One such drug is the atypical neuroleptic quetiapine fumarate (2-[2-(4-dibenzo [b,f][1,4]thiazepin-11-ylpiperazin-1-yl)ethoxy]ethanolhemifumarate, formula $(C_{21}H_{25}N_3O_2S)_2 \cdot C_4H_4O_4$), molecular weight: 883.09) (Fig. 1).

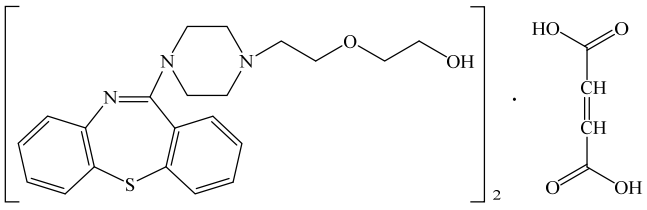


Fig. 1. The chemical formula of quetiapine fumarate

Quetiapine fumarate, a derivative of dibenzothiazepine, is a new antipsychotic drug that acts as an antagonist of adrenergic receptors and multiple neurotransmitters, including serotonin, norepinephrine, and histamine. It is used to treat schizophrenia, mental disorders, delusions (false beliefs), hallucinations, thinking disorders and loss of contact with reality [3–5].

Quetiapine fumarate is produced as a generic drug in many countries around the world in tablets as dosage form, containing the active substance 25 mg, 50 mg, 100 mg, 200 mg, 300 mg and 400 mg.

The following drugs containing quetiapine as an active substance have been registered on the territory of Ukraine: Quetiron (Acino Ukraine), Quetiapine (Pharma science Inc., Canada), Q pin (Alkem Laboratories Ltd., India), Ketilept (EGIS, Hungary), Quentiax (KRKA d.d. Novo Mesto, Slovenia), Quetixol (Farmlyga, Republic of Lithuania), Seroquel XR (AstraZeneca UK Limited, Great Britain) [6].

The State Inspectorate for Quality Control of Medicines regularly detects low-quality samples of quetiapine drugs in Ukraine that do not meet the "packaging" - the size of the secondary packaging does not meet the requirements of regulatory documentation, there are also cases of criminal cases opened due to non-medical use of the drug [7].

In this aspect, pharmaceutical expertise is a very important component of detecting substandard drugs and warning the public against counterfeits and dangerous drugs, as the types, names of drugs and their manufacturers are increasing, and the quality of drugs and their therapeutic use raises many questions. When investigating crimes related to pharmaceutical smuggling, falsification and non-medical use, there is a need for forensic pharmaceutical examination, the task of which is to establish compliance of the composition of the drug, quality and other properties of organic and inorganic products with the requirements for pharmaceuticals established by current legislation and regulations of the State Pharmacopoeia of Ukraine, which defines the conditions and procedure for their manufacture and use [8, 9].

The aim of the research. To analyze the legal framework for the circulation of medicines, materials of criminal and judicial proceedings for the detection of counterfeits and non-medical use of quetiapine drugs, generalize and develop methods for detecting samples during forensic pharmaceutical analysis.

2. Research planning (methodology)

A wide range of quetiapine drugs, its inclusion in the protocols for the treatment of depression, bipolar disorder and schizophrenia leads to the need to develop methods for detecting the substance during forensic pharmaceutical examination.

According to the Unified State Register of Court Decisions, criminal proceedings were opened in 2018-2020 involving quetiapine drugs and cases of administrative offenses related to the illegal transportation of quetiapine drugs across the border.

According to the current legislation, each forensic examination or expert examination is conducted in accordance with the methodology included in the register of methods of forensic examination of the Ministry of Justice of Ukraine [10]. In the absence of a methodology, the expert has the right to conduct research in accordance with existing other sources (foreign methods, NSTU, TS, AND, QCM, Pharmacopoeia, etc.). In principle, an analytical approach designed to identify a controlled substance in a suspicious material should involve the determination of at least two unrelated parameters, one of which should provide information on the chemical structure of the analyte (e.g., IR spectroscopy, mass spectrometry; or combined methods such as GC-MS). The choice of these parameters in each case will depend on the type of research material and laboratory resources available to the expert. It is also generally accepted that different countries may have special requirements that will determine the actual working methods of a particular laboratory.

Expert research is carried out in the following stages (Fig. 2):

1. External inspection. Depending on the type and physical state of the object received for research (powder, tablet, liquid, plant raw material), the expert chooses a further analysis strategy. This describes the packaging of the sample, its labelling (if any), appearance, characteristics, etc.

2. Selection of a representative sample for analysis [11]. The main task of the sampling procedure is to create conditions for accurate and meaningful chemical analysis. Because most methods, both qualitative and quantitative, used in forensic drug research laboratories involve the use of very small aliquots of the material, it is critical that these small aliquots should be representative of the entire volume of material from which they are selected. Sampling should be carried out in accordance with the principles of analytical chemistry set out, in particular, in national pharmacopoeias or regulations of regional and internation-

al organizations. Using an approved sampling system also saves valuable resources and time by reducing the number of tasks required. Of course, in some cases, for legal reasons, the usual rules of sampling and homogenization cannot be applied. For herbal mixtures, other sampling strategies may be required, especially in cases where the same withdrawn batch contains multiple products with different trademarks. It should be noted that over time, the content of a product with a particular trademark may also change. In cases where large quantities of identical products or bulk materials are seized, conventional sampling strategies may be used.

3. Qualitative chemical reactions (preliminary tests) to establish the nature of the object [12]

4. Research by GC-MS

5. Research by IR spectroscopy

6. Research by TLC (with standard sample)

7. Quantitative determination (drug, psychotropic substance, precursor)

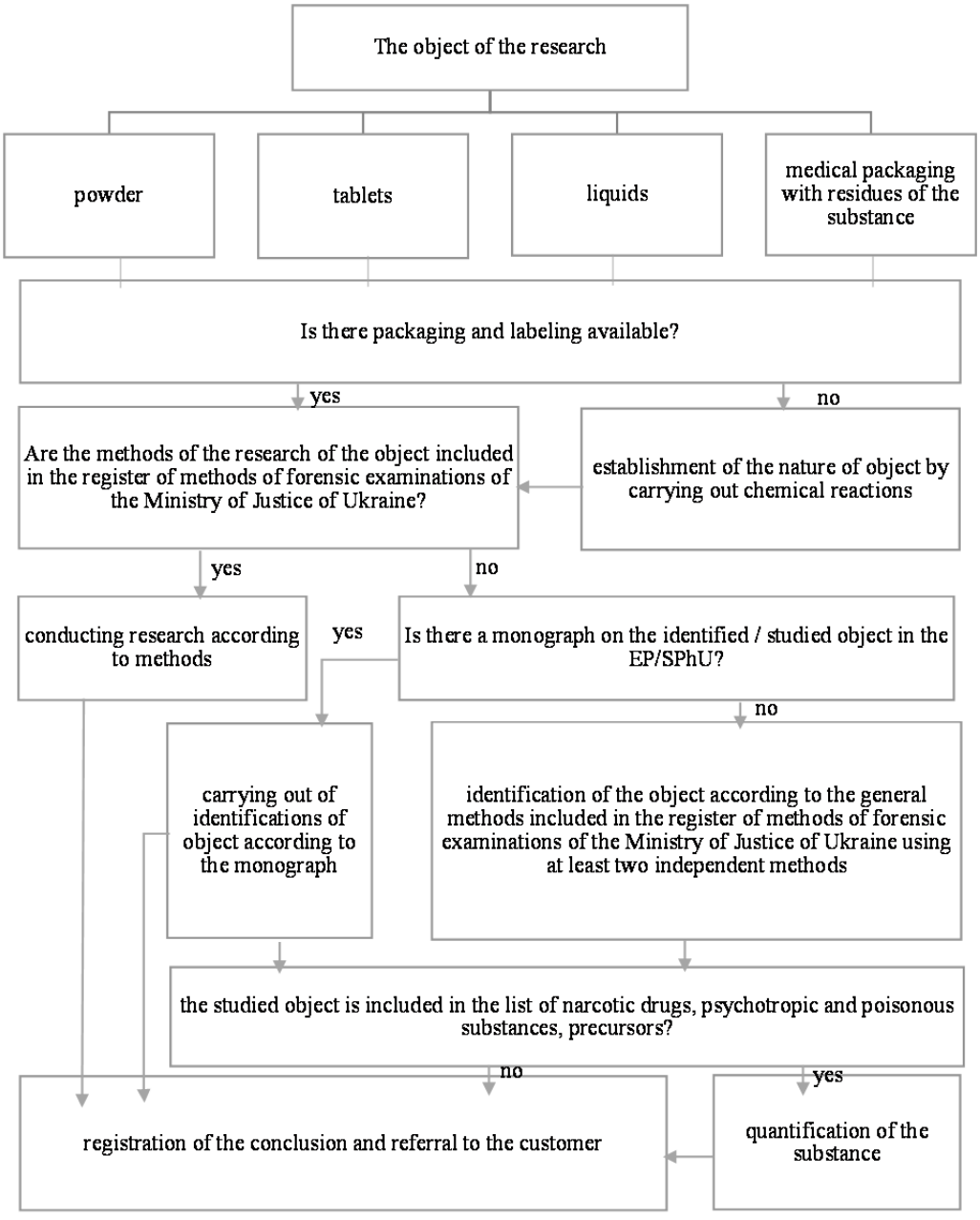


Fig. 2. Stages of forensic pharmaceutical examination

According to the register of methods of forensic examinations of the Ministry of Justice of Ukraine, the examination of quetiapine is not described, so the expert study can be based on general pharmacopoeial methods and methods of monograph on the drug. Given that quetiapine fumarate is not included in the list of narcotic drugs, psychotropic substances and precursors, as well as in the list of potent and toxic substances, quantification in forensic examination is not required. According to the European Pharmacopoeia and the Japanese Pharmacopoeia, quetiapine fumarate as the substance is identified by IR spectroscopy, there are no monographs on drugs.

The literature describes methods for the determination of quetiapine fumarate in pharmaceutical samples, including derivative and non-extraction absorption spectrophotometry in the ultraviolet region [13], fluorescent spectrophotometry [14], HPLC [15], electrophoretic capillary method, liquid chromatography in the ultraviolet region [16], etc.

Scientific publications for quetiapine fumarate do not contain information on available specific methods of determination in medicines. The available experimental data are ambiguous and insufficient to obtain a universal method for detecting this substance. Difficulties arise when trying to distinguish antipsychotics from each other and from other psychoactive substances. In addition, the clinical symptoms and pathomorphological picture of quetiapine poisoning are nonspecific [17].

The data described above contribute to the transfer of existing methods and their improvement to the tasks of forensic pharmaceutical examination, in accordance with the requirements of International Standards (ICH, ISO), current legislation and the requirements of regulatory authorities [18–20].

One of the available and express methods described for the analysis of active substances in the substance is spectrophotometry in the infrared region of the spectrum. The advantage of this method is the speed of identification of the active pharmaceutical ingredient without the need for additional reagents [21].

UV-spectrophotometric method and its variants are successfully used in pharmaceutical and chemical-toxicological analysis to determine non-volatile and juvenile organic substances, using their spectral characteristics.

The main advantage of GC-MS is that several samples can be analyzed simultaneously using a small amount of mobile phase, in contrast to the method of liquid chromatography. This reduces the time and cost of analysis and the possibility of environmental pollution. GC with MS detection contributes to the repeated detection of substances with the same or different parameters, as well as in the presence of other components of the drug or metabolites in biological fluids, followed by their identification.

Despite the introduction into the practice of forensic chemical analysis of modern instrumental methods of analysis, which are highly sensitive and selective, chromatography in a thin layer of sorbent has not lost its relevance due to availability, simple hardware and ease of execution. Given that the TLC method is included in the register of methods of forensic examinations, it can be considered as an informative research method [22].

It is important to use these methods as alternatives to determine quetiapine during forensic pharmaceutical examination.

3. Materials and methods

The study was conducted during 2020 using quetiapine generic drugs in a dosage of 25 mg "Quetixol" (p. F92246, Actavis Ltd., Malta), "Quetirone" (p. 02102019, Pharma Start, Ukraine), "Quetipine" (p. A8564, Pharma science Inc., Canada) and the Pharmacopoeial Standard Sample of SPhU – Quetiapine Fumarate (p. 4).

All studies were carried out in an accredited laboratory at the National Scientific Center «Hon. Prof. M. S. Bokarius Forensic Science Institute» using reagents that meet the EP, USP and USPU requirements [8, 23], Class A glassware and qualified devices.

In order to confirm the structure and the presence of appropriate functional groups, we used the method of molecular spectral analysis in the infrared region of the spectrum on the device "Nicolet 380 FT-IR Spectrometer by Thermo Fisher Scientific" using the attachment "Smart Perfomer" with ZnSe crystal (calibration certificate No. 84025 from 06.11.2020) by determining the position of the main functional groups in comparison with the spectrum from the electronic database. The IR spectrum of the compound was recorded in the range from 500 to 4000 cm^{-1}.

To prepare the stock solution, a portion of the powdered tablet equivalent to 50.0 mg of quetiapine fumarate was dissolved in 50 ml of ethyl alcohol with constant stirring with a magnetic stirrer for 60 min, then quantitatively transferred to a 100.0 ml volumetric flask and adjusted to the mark with solvent. Solution was filtered through a white tape filter, discarding the first 5 ml of filtrate. For further analysis, the filtrate was used to prepare ethanolic test solutions at concentrations from 1 μg/ml to 25 μg/ml.

The reference solution was prepared under the same conditions at a concentration of a standard sample of quetiapine fumarate of 0.50 mg/ml.

Control experiment – 96 % ethyl alcohol.

The absorption spectra of the test solutions and the optical density of the analytical solutions were recorded using a Specord 205 spectrophotometer from "Analytik Jena AG" (Germany). Measurements of optical density were performed using a quartz glass cuvette with a layer thickness of 10 mm in comparison with a solution of pharmacopoeial standard sample on the background of ethyl alcohol.

Chromatographic mobility of the test substances was determined on Merck chromatographic plates (silica gel 60G F254, Germany). Different eluents recommended by the International Association of Forensic Toxicologists were used as mobile phases: system 1 – hexane – acetone – 25 % ammonia solution (60: 40: 2); system 2 – methanol – 25 % ammonia solution (100: 1.5); and system 3 – hexane – acetone – 25 % ammonia solution (50: 45: 5).

Samples with concentrations of 20, 10, 8, 4, 2, 0.08, 0.04, 0.01 μg/ml were applied to the starting line. When the solvent front passed a distance of 10 cm from the starting line, the plate was removed from the chamber, dried in air at room temperature. Detection was performed under UV light at a wavelength of 254 nm, followed by spraying with Dragendorf reagent.

Analysis by GC-MS was performed using a GC gas chromatograph with a mass spectrometric detector GCMS-QP2020 (inv. No. 101450011, calibration certificate No. 08/6843K from 11.08.2020).

The GC parameters were as follows:

carrier gas – helium (1.10 ml/min in constant flow mode);

HP-5 capillary column, 100 % polymethylsiloxane (30 m×0.25 mm×0.25 μm;

J&W Scientific, Agilent Technologies Inc., California, USA);

injector temperature: 250 °C; sample injection volume: 1 µl; purge flow: 3.0 ml/min; the division factor is 1:50.

The temperature in the GC was programmed to increase from 0 to 60 °C (followed by exposure for 1 min), and then set to increase from 60 to 280 °C (speed 20 ºC/min) and finally to increase from 280 °C, and then exposure for 28 minutes.

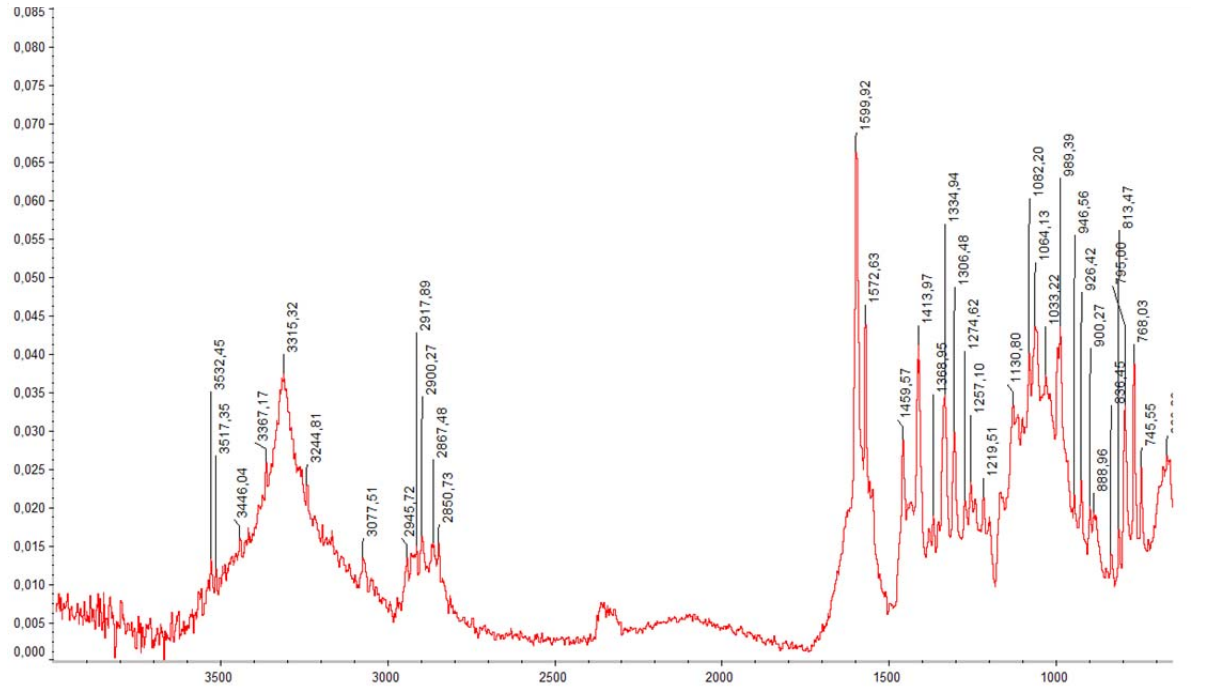
The MS parameters were as follows: detector gain: 0.95 kV + 0.00 kV; ion source temperature: 220.00 °C; interface temperature: 250.00 °C. Mass spectra were obtained in full scan modes in the range m/z 42-500.

Data were analyzed using the program: GCMSsolution, LabSolutions Insight (Shimadzu Corporation, Tokyo, Japan).

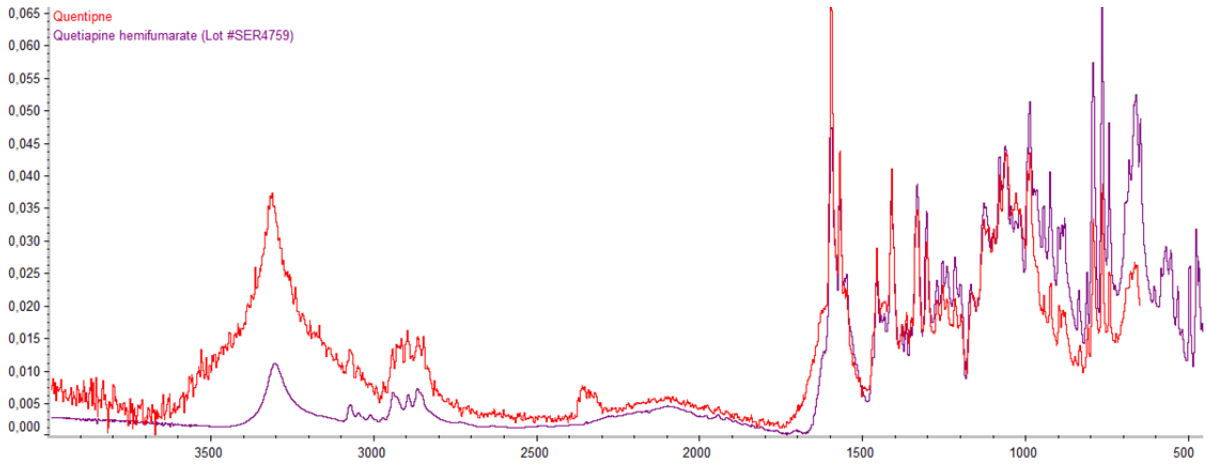
4. Research results

When quetiapine was determined by TLC, the following R_f values were established: in system 1 – 0.63, in system 2 – 0.50 and in system 3 – 0.66. Chromatographic zones have clear contours and high density, the mobile phases used are common solvent systems for basic substances. When viewing the plates in UV light at a wavelength of 254 nm, the appearance of fluorescence of the zones of all applied samples was observed. After treatment of the plates with Dragendorff reagent, the chromatographic zones of all samples were stained orange.

The method of quetiapine absorption bands of valence oscillations characteristic of quetiapine, which were detected in the areas: 1599, 1572, 1413, 768 cm^{-1} (Fig. 3), were determined by the method of spectrophotometry in the infrared region.



a



b

Fig. 3. IR spectra: *a* – a sample of quetiapine fumarate in tablets; *b* – spectrum of quetiapine fumarate from the electronic base

The use of this method does not require additional sample preparation of the quetiapine sample, the method is express and accurate.

Ultraviolet absorption spectrophotometry and GC-MS were used to identify and quantify quetiapine fumarate in the samples.

In the absorption spectrum of ethanolic solutions of all objects of study and the standard sample of quetiapine, it was found that despite the different composition of excipients of drugs, in the spectra of all samples there is a plateau at 290 nm (Fig. 4).

The subordination of solutions to the basic law of light absorption was investigated on the spectrum of ethanolic solution of a standard sample of quetiapine fumarate (Fig. 5). It was found that the dependence of the optical density on the concentration of ethanolic solutions of quetiapine fumarate is observed in the concentration of the substance from 0.005 mg/ml to 0.03 mg/ml.

For the GC-MS method, selectivity was previously established by comparing the chromatograms of tablet samples and model samples with the library of mass spectra. Each sample was analyzed three times. The retention times and peak areas were stably reproduced (Fig. 6).

The total chromatogram of the samples showed a single peak after 25.5 min, which is specific for quetiapine fumarate.

The signals of a number of fragments with characteristic masses with m/z 45, 95, 144, 209, 210, 211, 239, 321 which are the most intense in the mass spectrum of the compound were chosen as characteristic ions for quetiapine (Fig. 7).

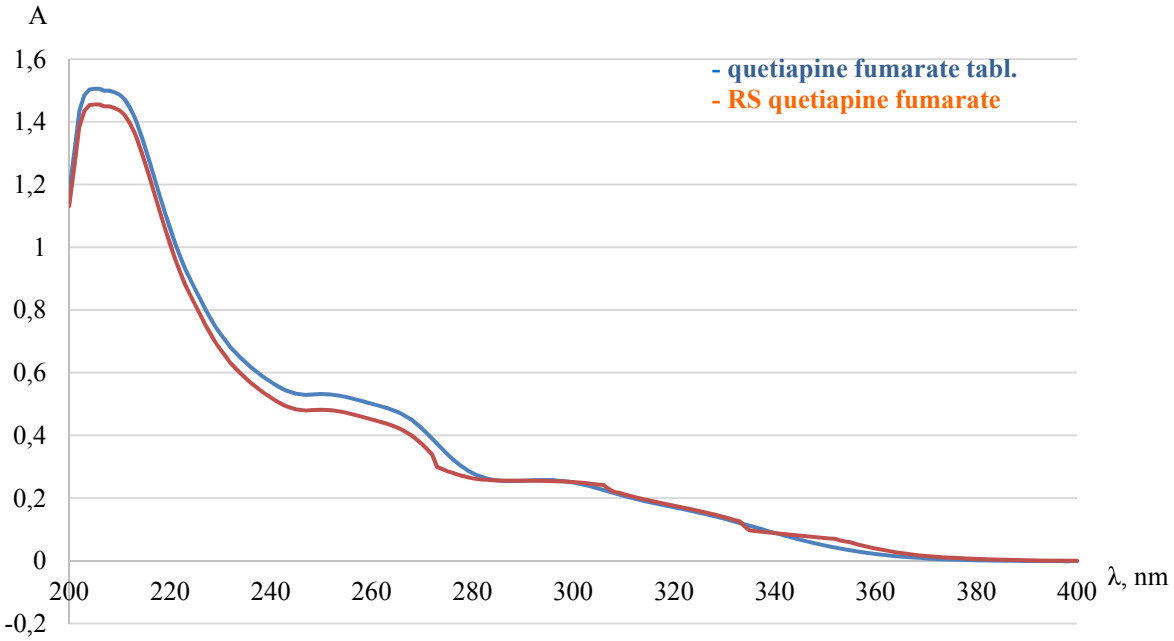


Fig. 4. UV spectra of ethanolic solutions of quetiapine tablets (blue) and standard sample solution of quetiapine fumarate (red)

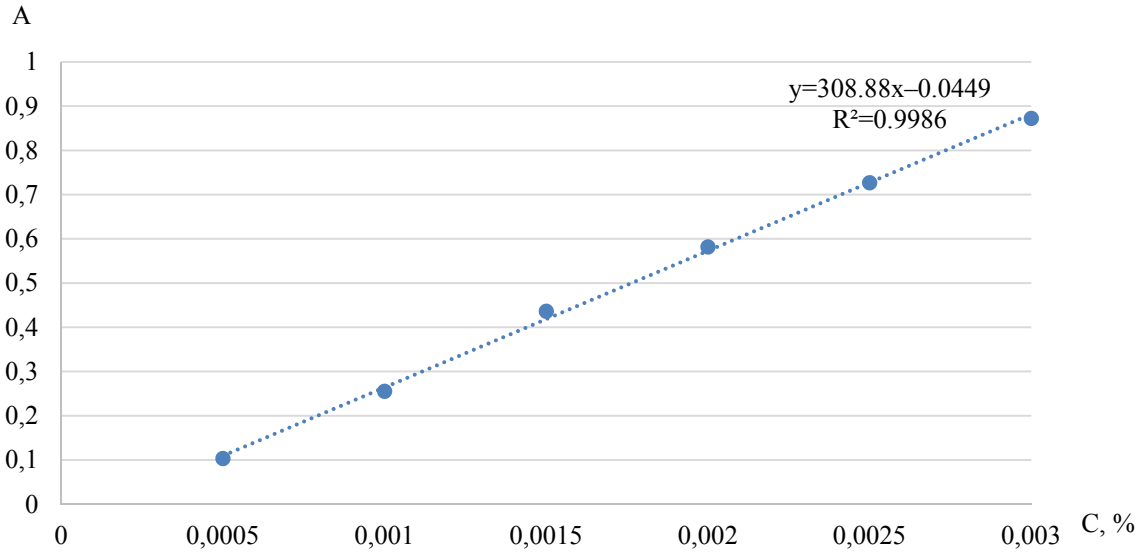


Fig. 5. Calibration graph of the dependence of the optical density on the concentration of ethanolic solutions of quetiapine fumarate at a wavelength of 290 nm

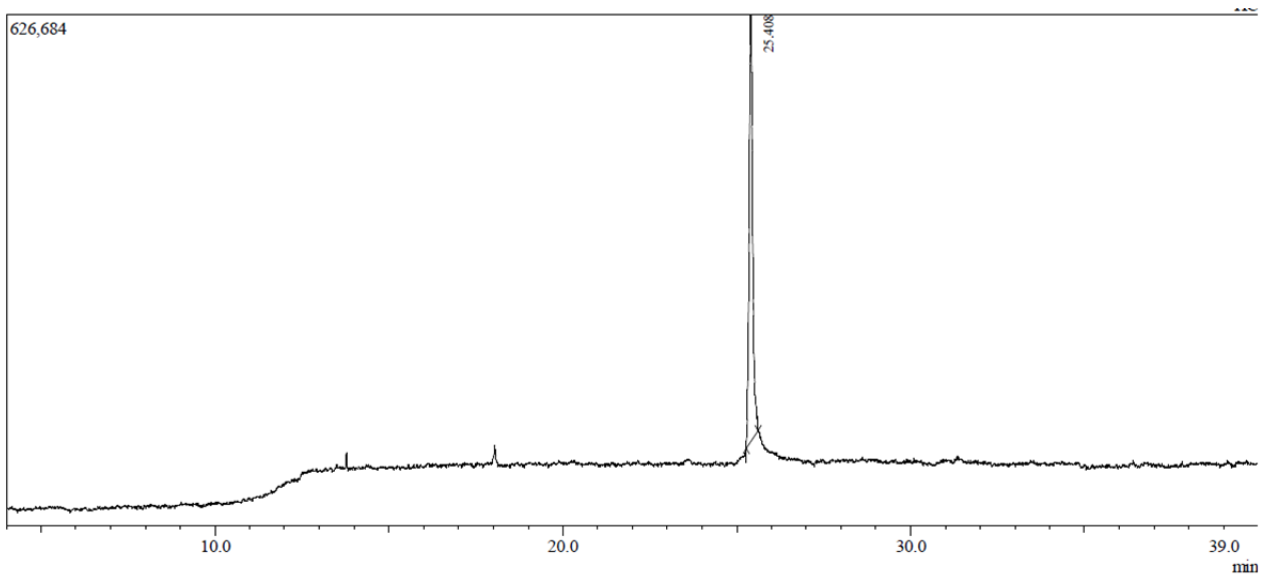
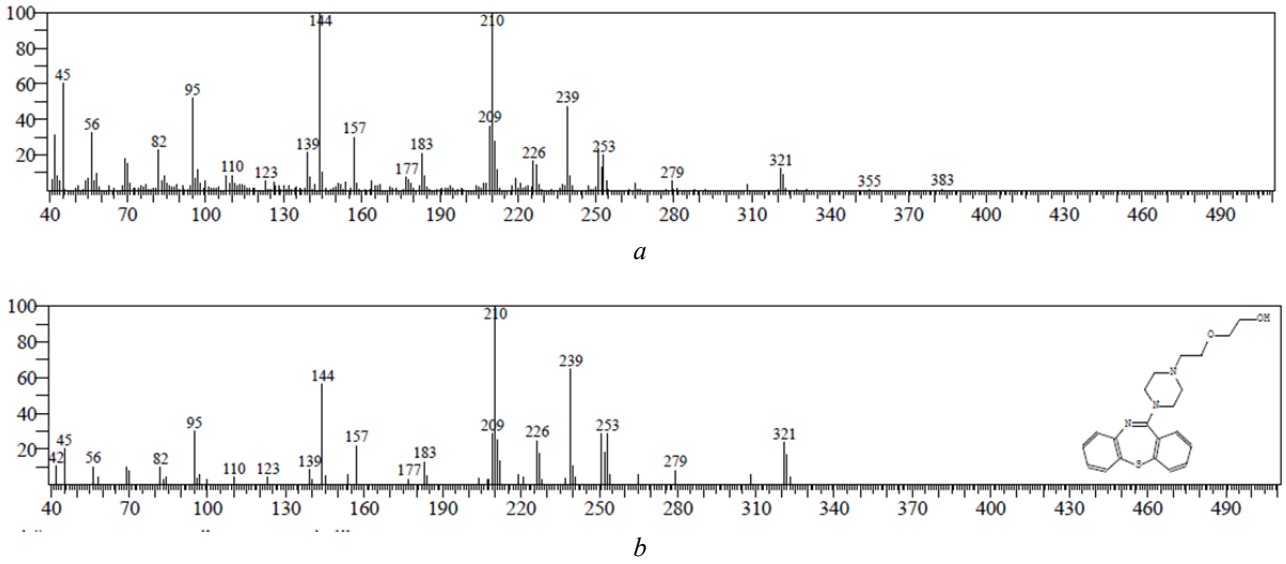


Fig. 6. Typical GC of quetiapine fumarate samples



a

b

Fig. 7. Mass spectra: *a* – test sample; *b* – sample from the electronic database of spectra

5. Discussion of research results

To identify the sample for forensic pharmaceutical purposes, the method of absorption spectrophotometry in the infrared region is proposed, which is express, accurate and sensitive, does not require the use of additional reagents and special sample preparation. Previous studies [21] indicate that it is possible to determine the active substance even in matrix tablets, no excipients and polymeric compounds interfere with the determination, which confirms the specificity of this technique for the determination of quetiapine in samples.

During the forensic chemical analysis, the TLC method using various eluents was proposed, which was approved by the International Association of Forensic Toxicologists and Detection in UV Light (254 nm) and Dragendorf reagent. The interchangeability of eluents and detection pathways has been confirmed. The advantage of this method is the ability to identify the substance and determine impurities without the use of expensive equipment, ease of execution and speed of analysis [24].

It is experimentally proven that the detection limit of quetiapine is 0.01 μg/ml. The obtained limit was consistently repeated during repeated measurements, including when performed by different specialists on different days using an additional placebo solution, which confirms the accuracy, reliability and reproducibility of the proposed TLC method.

The method of absorption spectrophotometry in the ultraviolet region was used to determine quetiapine in the substance and drugs, using a mixture of ethyl alcohol with 0.1 M sodium hydroxide solution, or acidified ethanol with 0.1 M hydrochloric acid solution, resulting in a wavelength of 23 optical density [25]. The quetiapine detection limit under these conditions was 6 mg/ml. Also, when used as a solvent for ethanol at the selected analytical wavelength of 207 nm, the optimal concentration of quetiapine for determination is 5 mg/ml [26]. When measuring the optical density of aqueous solutions of the active substance, the analytical wavelength was 290 nm, for which the substance was determined at a concentration above 6 mg/ml [27].

As a result of the obtained of the method of absorption spectrophotometry in the ultraviolet region, it was found that the standard sample of quetiapine and quetiapine tablets of all manufacturers have a well-marked maximum at a wavelength of 290 nm. It was determined that the limit of detection of quetiapine by the proposed method is 2.5 μg/ml.

Typically, the GC-MS method provided high sensitivity and accuracy, but according to the literature, all previous studies used time-consuming sample preparation, such as derivatization of the sample before determination, without determining the minimum concentration of quetiapine that can be determined under these conditions [28]. The proposed and used GC-MS method is characterized by relatively simple sample preparation, relatively short analysis time, the ability to detect the substance without the use of standard samples, due to the presence of large electronic libraries of mass spectra. The detection limit is 30 ng of the substance.

The combination of signals of characteristic fragments in the mass spectrum and retention time in the column provides a fairly high selectivity of identification of this compound by GC-MS and proves that the method can be used to detect and quantify quetiapine fumarate in detecting adulteration and traces of quetiapine in samples during forensic pharmaceutical examination.

The advantage of our study, in comparison with the previously described methods for determining quetiapine fumarate, is the selection and testing of a set of spectral and chromatographic methods for detecting quetiapine fumarate and its traces in samples, as well as determining the limit of detection of quetiapine fumarate and confirmation of the interchangeability of the proposed methods for forensic pharmaceutical purposes.

Study limitations. The proposed methods for determination of quetiapine fumarate can be used taking into account the modern equipment of forensic laboratories.

Prospects for further research. The proposed methods for determining quetiapine fumarate will be submitted for consideration for further use in forensic examination.

6. Conclusions

Physicochemical techniques for the detection of quetiapine fumarate and its traces in samples in a laboratory have been developed and tested in National Scientific Center "Hon. Prof. M. S. Bokarius Forensic Science Institute". The proposed methods meet the requirements of current legislation of Ukraine. The obtained results demonstrate that the proposed strategy of examination can be used for the study of quetiapine fumarate for forensic pharmaceutical analysis.

Conflict of interests

The authors declare that they have no conflicts of interest.

References

1. Falsyfikatsiia ta obih falsyfikovanykh likarskykh zasobiv: kryminalno-pravove doslidzhennia (2013). Odesa: Vydavnychyi dim «Helvetyka», 232.

2. Kalyniak, M., Blavatska, O. Problema yakosti ta bezpeky likarskykh zasobiv. Falsyfikatsiia ta kontrol yakosti.

3. Iqbal, Y., Connell, C., Worthington, M., Elrafei, H., Mulvaney, C., Kaewchaluay, C. (2019). Quetiapine dose for people with schizophrenia. Cochrane Database Of Systematic Reviews, 7, 15. doi: http://doi.org/10.1002/14651858.cd013372

4. Vieta, E. (2013). Quetiapine in Bipolar DepressionContents. Quetiapine in Bipolar Depression, 5–86. doi: http://doi.org/10.2217/quetiapine.final.13_08_10

5. Brett, J. (2015). Concerns about quetiapine. Australian Prescriber, 38 (3), 95–97. doi: http://doi.org/10.18773/austprescr.2015.032

6. Derzhavnyi reiestr likarskykh zasobiv Ukrainy. Available at: http://www.drlz.com.ua/ibp/ddsite.nsf/all/shlist?opendocument&sklad= %EA %E2 %E5 %F2 %B3 %E0 %EF %B3 %ED

7. Reiestr dokumentiv shchodo yakosti LZ. Available at: http://pub-mex.dls.gov.ua/QLA/DocList.aspx

8. Derzhavna Farmakopeia Ukrainy. Vol. 1 (2015). Kharkiv: Derzhavne pidpryiemstvo «Ukrainskyi naukovyi farmakopeinyi tsentr yakosti likarskykh zasobiv», 1128.

9. Pro sudovu ekspertyzu (1994). Zakon Ukrainy No. 4038-XII. 25.02.1994. Available at: https://zakon.rada.gov.ua/laws/show/4038-12#Text

10. Ministerstvo yustytsii Ukrainy. Reiestr metodyk provedennia sudovykh ekspertyz. Available at: https://rmpse.minjust.gov.ua/

11. Guidelines on Representative Drug Sampling (2009). New York: United Nations, 44.

12. Rapid testing methods of drugs of abuse (1994). United nations international drug control programme. New York: United Nations, 105.

13. Basavaiah, K., Rajendra Prasad, N., Ramesh, P. J., Vinay, K. B. (2010). Sensitive and selective extraction-free spectrophotometric determination of quetiapine fumarate in pharmaceuticals using two sulphonthalein dyes. Journal of Pre-Clinical and Chemical Research, 4 (1), 24–31.

14. Islam, M. M., Mahmoud, A. O., Dalia, M. N., Sayed, M. D. (2018). Analysis of quetiapine in human plasma using fluorescence spectroscopy. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 196, 196–201. doi: http://doi.org/10.1016/j.saa.2018.02.019

15. Sathiya, R., Krishnaraj, K., Muralidharan, S., Muruganantham, N. (2010). A Simple and Validated HPTLC Method of Evaluation for Quetiapine fumarate in Oral Solid Dosage Form. Eurasian Journal Of Analytical Chemistry, 5, 246–253.

16. Bavirisetti, K., Battula, S., Shankar Dubey, S. (2013). Validation of Quetiapine Fumarate in Pharmaceutical Dosage by Reverse-Phase HPLC with Internal Standard Method. Journal of Chemistry, 2013, 1–8. doi: http://doi.org/10.1155/2013/578537

17. Belova, M. V., Klyuyev, E. A., Melnikov, E. S., Poryadina, M. N. (2020). Chemical and Toxicological Diagnosis of Acute Poisoning with Clozapine, Olanzapine, Quetiapine and Risperidone. Russian Sklifosovsky Journal of Emergency Medical Care, 9 (2), 188–194. doi: http://doi.org/10.23934/2223-9022-2020-9-2-188-194

18. ICH Harmonized Tripartite Guideline: Q8 (R2) on pharmaceutical development (2017). The international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH), 24

19. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty- first report (2007). WHO Technical Report Series, No. 943. Geneva: World Health Organization.

20. Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2. Second updated edition. Good manufacturing practices and inspection (2007). Geneva: World Health Organization, 46.

21. Deepak, S., Rana, A. C. (2010). Formulation development of Quetiapine Fumarate SR matrix tablets. Der Pharmacia Sinica, 1 (1), 48–57.

22. Merzlikin, S. I., Kucher, T. V., Stepanenko, V. I., Pogosyan, O. H., Golik, M. Yu. (2020). Application of thin layer chromatography for the analytical diagnostics of combined prochlorperazine poisonings. Journal of Organic and Pharmaceutical Chemistry, 18 (2 (70)), 54–58. doi: http://doi.org/10.24959/ophcj.20.195619

23. The European Pharmacopoeia (2018). European Directorate for the Quality of Medicines & HealthCare of the Council of Europe. Strasbourg, 6. Available at: http://online6.edqm.eu/ep900/

24. Ciura, K., Rutecka, A., Szewczyk, A., Nowakowska J., Kawczak, P., Bączek, T. (2019). Study of the chromatographic behavior of selected antipsychotic drugs on RP-TLC based on quantitative structure–retention relationships. Journal of the Iranian Chemical Society, 16 (5), 1019–1027, doi: http://doi.org/10.1007/s13738-018-01576-0

25. Anand, B. K., Ch. Saila, P., Kotapadu, A., Chitra, K. (2014). A facile UV spectrophotometric estimation of quetiapine fumarate in pharmaceutical dosage form. Journal of Pharmacy Research, 8 (10), 1341–1343.

26. Eapen, S. C., Velekkat, P., Kutty, S. V., Jyothi, T. S. (2011). Development and validation of UV-spectrophotometric method for determination of quetiapine fumarate in pure and pharmaceutical formulation. International Journal of Pharmacy and Technology, 3, 3535–3542.

27. Vinay, K., Revanasiddappa, H., Ramesh, P., Rajendraprasad, N. (2011). Titrimetric and sensitive spectrophotometric methods for the assay of Quetiapine fumarate in pharmaceutical formulations. Chemical Industry and Chemical Engineering Quarterly, 17 (1), 99–106. doi: http://doi.org/10.2298/ciceq100407059v

28. Xiujuan, C., Chen, L., Lijun, C., Jian, L., Zheyuan, Q., Runsheng, Z. et. al. (2019). A rapid LC-MS/MS method for simultaneous determination of quetiapine and duloxetine in rat plasma and its application to pharmacokinetic interaction study. Journal of Food and Drug Analysis, 27 (1), 323–331. doi: http://doi.org/10.1016/j.jfda.2018.07.003

Received date 07.02.2021
Accepted date 22.04.2021
Published date 30.04.2021

Olena Bevz, PhD, Assistant, Department of Medicinal Chemistry, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: bevz.helen@gmail.com

Igor Sych, PhD, Head of the physical and chemical Research Sector Forensic Research Laboratory, National Scientific Center «Hon. Prof. M. S. Bokarius Forensic Science Institute», Zolochevskaya str., 8A, Kharkiv, Ukraine, 61177
E-mail: sychigor@hotmail.com

Angelina Shaposhnyk, PhD, Associate Professor, Department of Natural Disciplines International, Institute of International Education for Study and Research, V. N. Karazin Kharkiv National University, Svobody sq., 4, Kharkiv, Ukraine, 61022
E-mail: angelinakudelko@gmail.com

Irina Sych, PhD, Associate Professor, Department of Medicinal Chemistry, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: irina777sych@gmail.com

Olga Kryvanych, PhD, Associate Professor, Department of Pharmaceutical Disciplines, Uzhgorod National University, Narodna sq., 3, Uzhgorod, Ukraine, 88000
E-mail: olgabevz87@gmail.com

Svitlana Taran, Doctor of Pharmaceutical Science, Professor, Department of Medicinal Chemistry, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: svitlanagrig@gmail.com

Lina Perekhoda, Doctor of Pharmaceutical Science, Professor, Head of department, Department of Medicinal Chemistry, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: perekhodalina@ukr.net