УДК 615.22:615.453.4]-092.4
DOI 10.11603/mcch.2410-681X.2021.i1.12104

N. S. Shulyak[1,2], A. D. Abbeyquaye[1], D. B. Koval[1]
I. HORBACHEVSKY TERNOPIL NATIONAL MEDICAL UNIVERSITY[1]
VOLYN MEDICAL INSTITUTE OF THE VOLYN OBLAST COUNSIL[2], LUTSK

ROBUSTNESS EVALUATION OF HPLC DETERMINATION OF ATORVASTATIN AND LISINOPRIL ON COLUMN PUROSPHER C_8 STAR IN PHARMACEUTICALS

Introduction. *Innovative pharmaceutical development of various antihypertensive drugs with statins and the creation of domestic fixed-dose combinations of drugs with different effects is an urgent task of modern pharmacy, which will help attract more patients to the treatment and prevention of cardiovascular disease. Pharmaceutical development of atorvastatin and lisinopril by our scientific group proposes for using the ratio of (1/1) for lisinopril (10 mg) and atorvastatin (10 mg). HPLC (High-Performance Liquid Chromatography) technique is adopted as it is considered as the most common technique in realm of quality control analysis.*

The aim of the study *– to evaluate the robustness of HPLC (High-Performance Liquid Chromatography) method for the quantitation of lisinopril and atorvastatin and determine the analytical parameters that present greater influence in the final results of the analysis.*

Research Methods. *An efficient method to assess the robustness of analytical methods is by Youden's test, by means of an experiment design which involves seven analytical parameters combined in eight tests. In the recent studies, we assessed the robustness of a chromatographic method to quantify lisinopril and atorvastatin in tablets using Youden's test.*

Results and Discussion. *By using the criteria of Youden's test, HPLC method proved to be greatly robust regarding content of lisinopril and atorvastatin, when variations in seven analytical parameters were introduced. The most variation in effects of the analytical parameters in retention time (Rt) for lisinopril and atorvastatin HPLC quantitation was when used column supplier. Purospher C_8 STAR (55 mm×4 mm, 5 µm) is based on high purity silica and an almost complete surface coverage. Purospher C_8 STAR provides excellent peak symmetry for acidic, basic and even chelating compounds, highest column efficiency in terms of the number of theoretical plates, and exceptional stability from pH 1.5 to 10.5.*

Conclusion. *Youden's test can be applied successfully for the robustness evaluation in validation process of analytical methods and results ontained in our work should be interest to the scientific population dealing with pharmaceutical analytical chemistry.*

KEY WORDS: **atorvastatin; high-performance liquid chromatography; lisinopril; robustness; quantitative analysis; Youden's test.**

INTRODUCTION. Innovative pharmaceutical development of various antihypertensive drugs with statins and the creation of domestic fixed-dose combinations of drugs with different effects is an urgent task of modern pharmacy, which will help attract more patients to the treatment and prevention of cardiovascular diseases [1–4]. Analysis of modern scientific publications in Pubmed and ScienceDirect on the creation of pharmaceutical development based on lisinopril and atorvastatin has not yielded any results. Scientists are focused on the study of analysis methods of API in drugs, because SPhU or other pharmacopoeias have monographs on some substances of antihypertensive drugs, but usually for their analysis are used methods that can not be used for analysis of combination drugs [5, 6]. Pharmaceutical development of atorvastatin and lisinopril by our scientific group proposes for using the ratio of (1/1) for lisinopril (10 mg) and atorvastatin (10 mg). HPLC (High-Performance Liquid Chromatography) technique is adopted as it is considered as the most common technique in realm of quality control analysis.

The aim of the study was to evaluate the robustness of HPLC method for the quantitation of lisinopril and atorvastatin and determine the analytical parameters that present greater influence in the final results of the analysis.

RESEARCH METHODS. Atorvastatin calcium (purity 99.1 %, as determined by HPLC) and lisi-

nopril (purity 99.3 %, as determined by HPLC) were purchased from Sigma-Aldrich (Switzerland). 10 mg Atorvastatin calcium (standard sample) and 10 mg lisinopril (standard sample) were put in 100 mL measuring flask and dissolved in 50 mL diluent composed of 50 % v/v methanol and 50 % v/v perchloric acid (0.05 % v/v), ultrasound crushed and treated for 2 minutes and shaked 15 min with shaker. After that measuring flask was filled up to mark with diluent and filtered hrough 0.2 µm RC syringe filter before injection. Final concentrations of 0.1 mg/mL of both analytes. After filtration through the above filter, 10 µL were injected on the working column.

Solvents used in experiments were HPLC gradient grade purchased from Merck Darmstdat, Germany. Analytical Balance Mettler Toledo MPC227, pH-metter Metrohm 827, deionized water from TKA Micro system, with final conductivity less than 0.05µS/cm. IKA orbital shaker KS4000i was used for sample agitation. The nylon and regenerated cellulose RC 0.45 µm syringe filters were purchased from Agilent Technologies.

Dionex Ultimate 3000 UHPLC system controlled by Chromeleon version 6.80, composed of quaternary LPG pump ultimate 3000, autosampler ultimate 3000, ultimate 3000 column compartment, four channel UV-Vis detector ultimate 3000 RS. Shimadzu Nexera XR UPLC system with LPG Quaternary Pump LC-20AD with degasser DGU-20A5R, Autosempler SIL-20AC, PDA detector M20-A, Column Oven and Controller CBM-20A controlled by Lab Solutions version 5.97. The used column Purospher C_8 STAR (55 mm×4 mm, 5 µm), purchased from Sigma-Aldrich Supelco. Elution profiles obtained for test samples prepared of atorvastatin (10 mg) and lisinopril (10 mg) using mobile phase composed of potassium dihydrogen phosphate (25 mM, pH 7.25) and methanol (40:60, v/v). Separation was achieved at flow rate 1.0 mL/min with column temperature at 48 °C and UV detection at 215 nm.

Sample preparation

Twelve tablets of each preparation were studied to obtain statistically significant results. The tablets with declared contents of 10 mg atorvastatin and 10 mg of lisinopril were purchased from local drug store, pharmacy. The tablets were put in 100 mL measuring flask and dissolved in 50 mL diluent composed of 50 % v/v methanol and 50 % v/v perchloric acid (0.05 % v/v), ultrasound crushed and treated for 2 minutes and shaked 15min with shaker. After that measuring flask was filled up to mark with diluent and filtered hrough 0.2 µm RC syringe filter before injection. Final concentrations of 0.1 mg/mL of both analytes. After filtration through the above filter, 10 µL were injected on the working column.

RESULTS AND DISCUSSION. The robustness evaluation of HPLC method for lisinopril and atorvastatin quantitation was performed using the method proposed by Youdene Steiner. Seven analytical parameters were selected and small variations were induced in the nominal values of the method. Then, eight runs were performed with an aim to determine the effect of each parameter in the final result. The seven analytical parameters employed, as well as the introduced variations are demonstrated at Table 1. The analytical conditions at the nominal values are represented by capital letters and the conditions with the small variation are represented by lowercase letters [7–13].

The seven parameters and its respective variations were combined in eight assays or chromatographic runs, performed in a random order. Table 2 demonstrates the factorial combination of the parameters for the Youden's test. The analyses results are shown by letters from *s* to *z*. Hence, when combination 1 was assayed, the obtained result was *s*. When combination 2 was assayed, the obtained result was *t*, and so successively.

In each combination, three injections of each sample and standard solutions were carried out, at

Table 1 – **Analytical parameters and variations for the robustness evaluation of HPLC method for lisinopril and atorvastatin quantitation**

Parameter	Nominal condition				Variation		
A/a	Methanol in mobile phase	60	–	A	50	–	a
B/b	25 mM potassium dihydrogen phosphate pH 7.25 in mobile phase	40	–	B	60	–	b
C/c	pH of solution potassium dihydrogen phosphate in mobile phase	7.25	–	C	7.3	–	c
D/d	Column temperature, °C	48	–	D	42	–	d
E/e	Mobile phase flow rate, ml/min	1.0	–	E	1.2	–	e
F/f	Column supplier	Purospher C_8 STAR	–	F	Grace Platinump C_8 EPS	–	f
G/g	Chromatograph model	Shimadzu Nexera XR UPLC system	–	G	Agilent 1260 Infinity II system	–	g

Table 2 – **Factorial combination of the analytical parameters for robustness evaluation**

Analytical parameter	Factorial combination							
Methanol in mobile phase	A	A	A	A	a	a	a	a
25 mM solution potassium dihydrogen phosphate pH 7.25 in mobile phase	B	B	b	b	B	B	b	b
pH of solution potassium dihydrogen phosphate in mobile phase	C	c	C	c	C	c	C	c
Column temperature	D	D	d	d	d	d	D	D
Mobile phase flow rate	E	e	E	e	e	E	e	E
Column supplier	F	f	f	F	F	f	f	F
Chromatograph model	G	g	g	G	g	G	G	g
Result	s	t	u	v	w	x	y	z

the work concentration. After the alteration of chromatographic column or mobile phase composition, there was a waiting of 30 min for system stabilization. The evaluated results in each combination were peak area, retention time (Rt), tailing factor (T), theoretical plates number (N) and lisinopril and atorvastatin content.

For evaluating the effect the following equation was used:

Effect C/c=(s+u+w+y)/4–(t+v+x+z)/4Eq. (1).

Through the use of robustness elavulation, it is possible to establish certainly the parameters which present higher influence in the final result of the analyses and perform a more rigorous control in the eventual variations of these parameters that may occur during a routine analysis of quality control fixed combination of lisinopril and atorvastatin.

In our study, main challenges were directed to find optimal chromatographic conditions for HPLC determination of lisinopril and atorvastatin in pharmaceuticals. Our objective of the chromatographic method development was to achieve a peak tailing factor <1.5, retention time up to 3 min, along with very good resolution. In both equipments (Shimadzu Nexera XR UPLC system and Agilent 1260 Infinity II system), were carried out simultaneously the assays for the robustness evaluation of the chromatographic method. The results obtained in the eight runs to enalapril sample and standard solutions. In Table 3 are presented effects of the parameter variations in the analysis.

By using the criteria of Youden's test, HPLC method proved to be greatly robust regarding content of lisinopril and atorvastatin, when variations in seven analytical parameters were introduced. The most variation in effects of the analytical parameters in retention time (Rt) for lisinopril and atorvastatin HPLC quantitation was when used column supplier. Purospher C_8 STAR (55 mm x 4 mm, 5 µm) is based on high purity silica and an almost complete surface coverage. Purospher C_8 STAR provides excellent peak symmetry for acidic, basic and even chelating compounds, highest column efficiency in terms of the number of theoretical plates, and exceptional stability from pH 1.5 to 10.5.

Table 3 – **Effects of the analytical parameters in retention time (Rt) for lisinopril and atorvastatin HPLC quantitation**

Effect	Rt lisinopril (min)	Rt atorvastatin (min)
Methanol in mobile phase	-0.21	-0.47
25 mM solution potassium dihydrogen phosphate pH 7.25 in mobile phase	-0.11	-0.17
pH of solution potassium dihydrogen phosphate in mobile phase	0.02	0.5
Column temperature	-0.04	-0.02
Mobile phase flow rate	-0.09	0.02
Column supplier	-3.97	-3.02
Chromatograph model	0.01	0.02

CONCLUSION. The main target of the work was to evaluate the robustness of HPLC method for the quantitation of lisinopril and atorvastatin and determine the analytical parameters that present greater influence in the final results of the analysis. Youden's test can be applied successfully for the robustness evaluation in validation process of analytical methods and results ontained in our work should be interest to the scientific population dealing with pharmaceutical analytical chemistry.

Funding. Authors are grateful to the Ministry of Health of Ukraine Fund for providing scholarship for studies related to solutions for development of original combinations of antihypertensive agents, their analysis and standardization (0120U104201 (No. 509 of February 24, 2020).

LIST OF LITERATURE

1. Law M. R. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis / M. R. Law, N. J. Wald, A. R. Rudnicka // Bri. Med. J. – 2003. – **326** (7404). – P. 1423–1429.

2. Lipid-lowering therapy with statins, a new approach to antiarrhythmic therapy / J. Tamargo, R. Caballero, R. Gomez [et al.] // Pharmacol. Ther. – 2007. – **114** (1). – P. 107–126.

3. Effects of statin treatment on cardiac function in patients with chronic heart failure: a meta-analysis of randomized controlled trials / L. Zhang, S. Zhang, H. Jiang [et al.] // Clin. Cardiol. – 2011. – **34** (2). – P. 117–123.

4. Effect of statins and ACE inhibitors alone and in combination on clinical outcome in patients with coronary heart disease / V. G. Athyros, D. P. Mikhailidis, A. A. Papageorgiou [et al.] // J. Hum. Hypertens. – 2004. – **18** (11). – P. 781–788.

5. The State Pharmacopeia of Ukraine in 3 vol. State Enterprise “Ukrainian Scientific Expert Pharmacopoeial Center of the Quality of Medicines” 2nd iss. – Kharkiv: State Enterprise “Ukrainian Scientific and Experimental Pharmacopoeial Center for the Quality of Medicinal Products”, 2015. – 1128 p.

6. European Pharmacopoeia. European Pharmacopoeia. – 10 edn. – 2020. – Access mode : https://www.edqm. eu/en/european_pharmacopoeia_10th_edition.

7. ICH Q2 (R1). Validation of analytical procedures. Text and methodology : Int. Conf. Harmoniz. – Geneva, 2005. – P. 1–17.

8. Epshtein N. A. Investigation of robustness at validation of HPLC and UPLC methods: a modern approach including risk analysis / N. A. Epshtein, V. L. Sevastianova, A. I. Koroleva // Drug Develop. Registr. – 2018. – **1** (22). – P. 96–109.

9. Steiner Y. E. H. Statistical manual of the association of official analytical chemists / Y. E. H. Steiner. – The Association of Official Analytical Chemists ed. Arlington, 1975. – P. 33–36; 70–71; 82–83.

10. da Costa Cesar I. Robustness evaluation of the chromatographic method for the quantitation of lumefantrine using Youden’s test / I. da Costa Cesar, G. A. Pianetti // Braz. J. Pharm. Sci. – 2009. – **45** (2). – P. 235–240.

11. Karageorgou E. Youden test application in robustness assays during method validation / E. Karageorgou, V. Samanidou // J. Chromatogr. A. – 2014. – **1353**. – P. 131–139.

12. Peleshok K. Robustness evaluation of the chromatographic determination of valsartan in pharmaceuticals / K. Peleshok, O. Dutchak, F. Abdelmalek Mohamed // Здобутки клініч. і эксперим. медицини. – 2020. – № 3. – С. 26–31.

13. Peleshok K. Y. Youden’s test of the chromatographic determination of atenolol in pharmaceuticals / K. Y. Peleshok, D. B. Koval // Мед. та клініч. хімія. – 2020. – **22**, № 2 (84). – С. 61–65.

REFERENCES

1. Law, M.R., Wald, N.J., & Rudnicka A.R. (2003). Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *Bri. Med. J.,* 326 (7404), 1423-1429. DOI: 10.1136/bmj.326.7404.1423.

2. Tamargo, J., Caballero, R., Gomez, R., Nunez, L., Vaquero, M., & Delpon, E. (2007). Lipid-lowering therapy with statins, a new approach to antiarrhythmic therapy. *Pharmacol. Ther.,* 114 (1), 107-126. DOI: 10.1016/j.pharmthera.2006.12.002.

3. Zhang, L., Zhang, S., Jiang, H., Sun, A., Zou, Y., & Ge, J. (2011). Effects of statin treatment on cardiac function in patients with chronic heart failure: a meta-analysis of randomized controlled trials. *Clin. Cardiol.,* 34 (2), 117-123. DOI: 10.1002/clc.20821.

4. Athyros, V.G., Mikhailidis, D.P., Papageorgiou, A.A., Bouloukos, V.I., Pehlivanidis, A.N., Symeonidis, A.N., & Elisaf, M. (2004). Effect of statins and ACE inhibitors alone and in combination on clinical outcome in patients with coronary heart disease. *J. Hum. Hypertens.,* 18 (11), 781-788. DOI: 10.1038/sj.jhh.1001748.

5. (2015). *The State Pharmacopeia of Ukraine in 3 vol. State Enterprise “Ukrainian Scientific Expert Pharmacopoeial Center of the Quality of Medicines” 2nd iss.* Kharkiv: State Enterprise “Ukrainian Scientific and Experimental Pharmacopoeial Center for the Quality of Medicinal Products”.

6. (2020). European Pharmacopoeia. European Pharmacopoeia. 10 edn. Retrieved from: https://www.edqm. eu/en/european_pharmacopoeia_10th_edition.

7. ICH Q2 (R1). (2005). *Validation of analytical procedures. Text and methodology*: Int. Conf. Harmoniz. Geneva.

8. Epshtein, N.A., Sevastianova, V.L., & Koroleva A.I. (2018). Investigation of robustness at validation of HPLC and UPLC methods: a modern approach including risk analysis. *Drug Develop. Registr.,* 1 (22), 96-109.

9. Steiner, Y.E.H. (1975). Statistical manual of the association of official analytical chemists. The Association of Official Analytical Chemists ed. Arlington.

10. da Costa Cesar I., & Pianetti G.A. (2009). Robustness evaluation of the chromatographic method for

the quantitation of lumefantrine using Youden's test. *Braz. J. Pharm. Sci.,* 45 (2), 235-240. DOI: 10.1590/S1984-82502009000200007.

11. Karageorgou, E., & Samanidou, V. (2014). Youden test application in robustness assays during method validation. *J. Chromatogr. A.,* 1353, 131-139. DOI: 10.1016/j.chroma.2014.01.050.

12. Peleshok, K., Dutchak, O., & Abdelmalek Mohamed, F. (2020). Robustness evaluation of the chromatographic determination of valsartan in pharmaceuticals. *Zdobutky klinichnoi i eksperymentalnoi medytsyny – Achievements of Clinical and Experimental Medicine,* 3, 26-31. DOI: https://doi.org/10.11603/1811-2471.2020.v.i3.11579.

13. Peleshok, K.Y., & Koval, D.B. (2020). Youden's test of the chromatographic determination of atenolol in pharmaceuticals. *Medychna ta klinichna khimiia – Medical and Clinical Chemistry,* 2, 61-65. DOI: https://doi.org/10.11603/mcch.2410-681X.2020.v.i2.11361.

Н. С. Шуляк[1,2], А. Д. Аббейкує[1], Д. Б. Коваль[1]
ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ[1]
ВОЛИНСЬКИЙ МЕДИЧНИЙ ІНСТИТУТ[2], ЛУЦЬК

ВИВЧЕННЯ РОБАСНОСТІ ВЕРХ-МЕТОДИКИ ВИЗНАЧЕННЯ АТОРВАСТАТИНУ ТА ЛІЗИНОПРИЛУ НА КОЛОНЦІ PUROSPHER C_8 STAR У ЛІКАРСЬКИХ ЗАСОБАХ

Резюме

Вступ. *Інноваційна фармацевтична розробка різних антигіпертензивних лікарських засобів зі статинами та створення вітчизняних комбінованих препаратів із фіксованою дозою з різними ефектами є актуальним завданням сучасної фармації, що допоможе залучити більше пацієнтів до лікування і профілактики серцево-судинних захворювань. Фармацевтична розробка аторвастатину і лізиноприлу, якою займається наша наукова група, пропонує використовувати співвідношення 1/1 для лізиноприлу (10 мг) та аторвастатину (10 мг). Високоефективну рідинну хроматографію (ВЕРХ) вважають найпоширенішим методом аналізу для контролю якості лікарських засобів.*

Мета дослідження *– вивчити робасність методу ВЕРХ для кількісного визначення лізиноприлу та аторвастатину і визначити аналітичні параметри, що мають більший вплив на кінцеві результати аналізу.*

Методи дослідження. *Ефективний метод оцінки робасності аналітичних методів за допомогою Юден тесту шляхом розробки експерименту, який включає сім аналітичних параметрів, об'єднаних у восьми тестах. У дослідженнях ми оцінювали робасність хроматографічного методу для кількісного визначення лізиноприлу та аторвастатину в таблетках з використанням Юден тесту.*

Результати й обговорення. *При використанні критеріїв Юден тесту метод ВЕРХ підтвердив робасність щодо визначення вмісту лізиноприлу та аторвастатину, коли було введено зміни семи аналітичних параметрів. Найбільшу різницю у впливах аналітичних параметрів на час утримування (Rt) для кількісного визначення лізиноприлу та аторвастатину методом ВЕРХ відмічено при застосуванні різних колонок. Колонку Purospher C_8 STAR (55 мм×4 мм, 5 мкм) створено на основі високочистого діоксиду кремнію, яким майже повністю покрита поверхня. Вона забезпечує хорошу пікову симетрію для кислотних, основних і навіть хелатуючих сполук, найвищу ефективність колонки з точки зору кількості теоретичних тарілок та винятковку стабільність pH від 1,5 до 10,5.*

Висновок. *Юден тест можна успішно застосовувати для вивчення робасності в процесі валідації аналітичних методик, а результати, отримані в нашій роботі, повинні зацікавити наукову спільноту, яка займається фармацевтичною аналітичною хімією.*

КЛЮЧОВІ СЛОВА: **аторвастатин; лізиноприл; високоефективна рідинна хроматографія; робасність; кількісний аналіз; Юден тест.**

Н. С. Шуляк[1,2], А. Д. Аббейкуе[1], Д. Б. Коваль[1]
ТЕРНОПОЛЬСКИЙ НАЦИОНАЛЬНЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ ИМЕНИ И. Я. ГОРБАЧЕВСКОГО МОЗ УКРАИНЫ[1]
ВОЛЫНСКИЙ МЕДИЦИНСКИЙ ИНСТИТУТ[2], ЛУЦК

ИЗУЧЕНИЕ РОБАСНОСТИ ВЭЖХ-МЕТОДИКИ ОПРЕДЕЛЕНИЯ АТОРВАСТАТИНА И ЛИЗИНОПРИЛА НА КОЛОНКЕ PUROSPHER C_8 STAR В ЛЕКАРСТВЕННЫХ СРЕДСТВАХ

Резюме

Вступление. *Инновационная фармацевтическая разработка различных антигипертензивных лекарственных средств со статинами и создание отечественных комбинированных препаратов с фиксированной дозой с различными эффектами является актуальной задачей современной фармации, что поможет привлечь больше пациентов к лечению и профилактике сердечно-сосудистых заболеваний. Фармацевтическая разработка аторвастатина и лизиноприла, которой занимается наша научная группа, предлагает использовать соотношение 1/1 для лизиноприла (10 мг) и аторвастатина (10 мг). Высокоэффективная жидкостная хроматография (ВЭЖХ) считается самым распространенным методом анализа для контроля качества лекарственных средств.*

Цель исследования *– изучить робастность метода ВЭЖХ для количественного определения лизиноприла и аторвастатина и определить аналитические параметры, что оказывают большее влияние на конечные результаты анализа.*

Методы исследования. *Эффективный метод оценки робастности аналитических методов с помощью Юден теста путем разработки опыта, который включает семь аналитических параметров, объединенных в восьми тестах. В исследованиях мы оценивали робастность хроматографического метода для количественного определения лизиноприла и аторвастатина в таблетках с использованием Юден теста.*

Результаты и обсуждение. *При использовании критериев Юден теста метод ВЭЖХ подтвердил робастность относительно определения содержания лизиноприла и аторвастатина, когда были введены изменения семи аналитических параметров. Наибольшую разницу во влияниях аналитических параметров на время удерживания (Rt) для количественного определения лизиноприла и аторвастатина методом ВЭЖХ отмечено при применении различных колонок. Колонку Purospher C_8 STAR (55 мм×4 мм, 5 мкм) создано на основе чистого диоксида кремния, которым почти полностью покрыта поверхность. Она обеспечивает хорошую пиковую симметрию для кислотных, основных и даже хелатирующих соединений, самую высокую эффективность колонки с точки зрения количества теоретических тарелок и исключительную стабильность pH от 1,5 до 10,5.*

Вывод. *Юден тест можно успешно применять для изучения робастности в процессе валидации аналитических методик, а результаты, полученные в нашей работе, должны заинтересовать научное сообщество, которое занимается фармацевтической аналитической химией.*

КЛЮЧЕВЫЕ СЛОВА: **аторвастатин; лизиноприл; высокоэффективная жидкостная хроматография; робастность; количественный анализ; Юден тест.**

Received 22.01.21

Address for correspondence: *N. S. Shulyak, I. Horbachevsky Ternopil National Medical University, Maidan Voli, 1, Ternopil, 46001, Ukraine, e-mail: shulaknatali11@gmail.com.*