ABSTRACT&REFERENCES

DOI: 10.15587/2519-4852.2019.165650

SELECTION OF FLAVORING AGENTS AND PRIMARY PACKAGING FOR THE COMBINED ORAL SOLUTION NAMED «MAGLYCIMET»

p. 4-9

Daria Snehyrova, Postgraduate Student, Junior Researcher, Department of Industrial Pharmacy, Scientific and Research Laboratory of Parenteral and Oral Liquid Medicines, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: dsnegireva2017@gmail.com
ORCID: *http://orcid.org/0000-0001-7084-7280*

Lyudmila Almakaeva, Doctor of Pharmaceutical Sciences, Professor Head of Laboratory, Scientific and Research Laboratory of Parenteral and Oral Liquid Medicines, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: almakaeva@ukr.net
ORCID: *http://orcid.org/0000-0001-8997-4634*

Aim. *The main aim of research is selection of flavoring agents and primary packaging for a combined oral solution named «Maglycimet» based on theoretical and experimental. The solution consists of magnesium aspartate, magnesium glutamate, glycine and methylcobalamin.*

Methods. *During the studying organoleptic, physicochemical and pharmaco-technological methods were used according to the requirements of the State Pharmacopoeia of Ukraine and the European Pharmacopoeia.*

Results. *We investigated a series of the obtained solution with various corrective agents and their concentrations in order to give the medicine pleasant organoleptic characteristics. In the course of research next sweeteners were used: sodium cyclamate with concentrations 0.05–0.15 %; saccharin sodium with concentrations 0.05–0.15 %; saccharin sodium and sorbitol in such ratios: 0.1 and 5 %, 0.1 and 8.5 %, 0.15 and 10 %; sucrose with concentrations 20–30 %. Studies were performed using methods of A. I. Tentsova and I.A. Egorov in three separate stages. At the first stage 12 series of solution with different sweeteners were obtained. Four of them were selected to the second stage. At the third stage the best one was chosen according to the evaluation of volunteers group. It turned out to be saccharin sodium with concentration 0.1 %. The following flavoring agents were also investigated: «cherry», «raspberry», and «peach» with concentrations from 0.1 to 1.0 %. As a result of the research it was determined that the sample with the «cherry» flavoring agent with concentration 0.6 % had the best taste. 100 ml vials of orange glass and polyethylene terephthalate (two types) allowed for utilization in Ukraine were investigated as primary packaging. After 3, 6, 9, 12 and 18 months of solution storage in bottles monitoring of the main quality indicators was made. It was established that all types of packaging did not cause changes in the main indicators of the solution quality, beyond the design of quality control methods. This allows us to recommend all types of test vials.*

Conclusions. *Sweetener saccharin sodium with concentration 0.1 % and a flavoring agent «cherry» with concentration of 0.6 % were chosen for the combined oral solution named «Maglycimet» based on the theoretical and experimental studies. Next types of bottles are recommended as a primary packaging: from orange glass and polyethylene terephthalate (two types)*

Key words: *oral solution, magnesium salts, correction of taste, primary packaging*

References

1. Spasov, A. A. (2000). Magniy v meditsinskoy praktike [Magnesium in medical practice]. Volgograd, 268.

2. Gromova, O. A., Torshin, I. Y., Grishina, T. R., Fedotova, L. E. (2012). Defitsit magniya kak problema stressa i dezadaptatsii u detey [Magnesium deficiency as a problem of stress and maladaptation in children]. Russkiy meditsinskiy zhurnal, 20 (16), 813–821.

3. DiNicolantonio, J. J., O'Keefe, J. H., Wilson, W. (2018). Subclinical magnesium deficiency: a principal driver of cardiovascular disease and a public health crisis. Open Heart, 5 (1), e000668. doi: http://doi.org/10.1136/openhrt-2017-000668

4. Al Alawi, A. M., Majoni, S. W., Falhammar, H. (2018). Magnesium and Human Health: Perspectives and Research Directions. International Journal of Endocrinology, 2018, 1–17. doi: http://doi.org/10.1155/2018/9041694

5. Kuznetsov, A. A., Kabakova, T. I., Kuznetsov, A. V. (2012). Udobstvo primeneniya kak ekonomicheskiy faktor optimizatsii ratsionalnogo ispolzovaniya lekarstvennyih sredstv [Ease of use as an economic factor in optimizing the rational use of medicines]. Fundamentalnyie issledovaniya, 10, 397–399.

6. Schiffman, S. S. (2018). Influence of medications on taste and smell. World Journal of Otorhinolaryngology – Head and Neck Surgery, 4 (1), 84–91. doi: http://doi.org/10.1016/j.wjorl.2018.02.005

7. Anurova, M. N., Bahrushina, E. O., Pyatigorskaya, N. V., Yambikova, O. M (2015). Printsipyi korrektsii vkusa peroralnyih geley s sinteticheskimi lekarstvennyimi veschestvami [Principles of taste correction oral gels with synthetic medicinal substances]. Farmatsiya i farmakologiya, 4 (11), 15–20.

8. Campbell, G. A., Vallejo, E. (2015). Primary Packaging Considerations in Developing Medicines for Children: Oral Liquid and Powder for Constitution. Journal of Pharmaceutical Sciences, 104 (1), 52–62. doi: http://doi.org/10.1002/jps.24223

9. Raina, H., Jindal, A. (2017). Packaging of Non-Injectable Liquid Pharmaceuticals. Journal of Applied Pharmaceutical Science, 2, 248–257.

10. Singh, K., Gupta, R. (2007). Stability studies on a cough syrup in plastic containers. Indian Journal of Pharmaceutical Sciences, 69 (3), 408–413. doi: http://doi.org/10.4103/0250-474x.34551

11. Almakaeva, L. G., Begunova, N. V., Almacaev, M. S. (2013). Issledovaniya po vyiboru pervichnoy upakovki dlya oralnogo rastvora arginina asparaginata. Tovaroznavchi aspekti spozhivchih tovariv. Kharkiv: Vid-vo NFaU, 9–10.

12. Derzhavna Farmakopeya Ukrayini (2014–2015). Vol. 1–3. Kharkiv: Derzhavne pidpriemstvo «Ukrayinskiy naukoviy farmakopeyniy tsentr yakosti likarskih zasobiv», 1128, 724, 732.

13. European Pharmacopoeia. 9th Edition. European Directorate for the Quality of Medicines (EDQM) (2016). Strasbourg: Council of Europe, 4016.

14. Japanese Pharmakopeia 16-th ed. (2011–2014). The Ministry of Health, Labour and Welfare.

15. Voda ochyshchena (2014). Derzhavna Farmakopeia Ukrainy. Dopovnennia 2. Kharkiv: Derzhavne pidpryiemstvo

«Ukrainskyi naukovyi farmakopeinyi tsentr yakosti likarskykh zasobiv», 129.

16. Lyuk, E., Yager, M. (2003). Konservantyi v pischevoy promyishlennosti. Svoystva i primenenie [Preservatives in the food industry. Properties and application]. Saint Petersburg: GIORD, 256.

17. Buldakov, A. S. (2003). Pischevyie dobavki [Nutritional Supplements]. Moscow: DeLi-print, 436.

18. Getalo, O. V., Tsihotska, O. O., Saliy, O. O. (2005). Rozrobka siropu z magniyu hloridom i vitaminom B6 [Development of syrup from magnesium chloride and vitamin B6]. Visnik farmatsiyi, 3, 59–61.

19. Sheryakova, Yu. A., Hishova, O. M. (2014). Podslastiteli v siropah i ih harakteristika [Sweeteners in syrups and their characteristics]. Vestnik farmatsii, 2, 106–111.

20. Chueshov, V. I., Hohlova, L. M., Lyapunova, O. O., Sayko, I. V., Gladuh, E. V., Egorov, I. A. et. al.; Chueshov, V. I. (Ed.) (2003). Tehnologiya likiv promislovogo virobnitstva [Technology of medicines for industrial production]. Kharkiv: Zoloti storinki, 720.

21. Tentsova, A. I. (1981). Aktualnyie voprosyi poiska i tehnologiya lekarstv [Actual questions of search and technology of medicines]. Kharkiv, 145.

DOI: 10.15587/2519-4852.2019.165655

CHROMATOGRAPHIC ANALYSIS OF *6-GINGEROL* AND *6-SHOGAOL* USING TLC AND HPLC METHODS

p. 10-15

Raimonda Jazokaite, Postgraduate Student, Department of Analytical and Toxicological Chemistry, Lithuanian University of Health Sciences, Sukilėlių str., 13, Kaunas, Lithuania, 50162
E-mail: raimonda0330@gmail.com

Mindaugas Marksa, Lecturer, Department of Analytical and Toxicological Chemistry, Lithuanian University of Health Sciences, Sukilėlių str., 13, Kaunas, Lithuania, 50162
E-mail: minzedas@gmail.com

Augusta Zevzikoviene, PhD, Associate Professor, Department of Analytical and Toxicological Chemistry, Lithuanian University of Health Sciences, Sukilėlių str., 13, Kaunas, Lithuania, 50162
E-mail: augustazev@gmail.com

Andrejus Zevzikovas, PhD, Professor, Department of Analytical and Toxicological Chemistry, Lithuanian University of Health Sciences, Sukilėlių str., 13, Kaunas, Lithuania, 50162
E-mail: andrejuszevzikovas@gmail.com

Nowadays spices are known not only for their taste and flavour, but also for their medicinal value. Zingiber officinale Rosc. (Zingiberaceae family) contains a number of bioactive phenolic constituents, which in pure form or it's derivates might be potential antioxidants, in the most cases scientists discover 6-gingerol and 6-shogaol as a major constituents of ginger rhizomes.

Methods. *For this investigation we have chosen four different food supplements, containing ginger and one traditional herbal medicine. The presence of two major ginger constituents in the investigation objects were analysed through TLC analysis, which was performed using CAMAG TLC Visualizer and other method was HPLC analysis, which required a high performance liquid chromatographic system Waters 2695 with fotodiode detector Waters 966 PDA.*

Results. *Our results suggest that ginger-containing food supplements and medicine contain two major constituents which leads to ginger biological active properties. Chromatographic analysis might be useful in providing information about quality of ginger rhizomes and commercial ginger products.*

Conclusions. *Selected chromatography methods are suitable for qualitative and quantitative evaluation of 6-gingerol and 6-shogaol in dietary supplements and other products*

Keywords: *ginger, Zingiber officinale Roscoe, TLC, thin-layer chromatography, HPLC, high power liquid chromatography, food supplements, qualitative analysis, quantitative analysis*

References

1. Kubra, I. R., Rao, L. J. M. (2012). An Impression on Current Developments in the Technology, Chemistry, and Biological Activities of Ginger (Zingiber officinaleRoscoe). Critical Reviews in Food Science and Nutrition, 52 (8), 651–688. doi: http://doi.org/10.1080/10408398.2010.505689

2. Jelled, A., Fernandes, A., Barros, L., Chahdoura, H., Achour, L., Ferreira, I. C. F. R., Cheikh, H. B. (2015). Chemical and antioxidant parameters of dried forms of ginger rhizomes. Industrial Crops and Products, 77, 30–35. doi: http://doi.org/10.1016/j.indcrop.2015.08.052

3. Alam, P. (2013). Densitometric HPTLC analysis of 8–gingerol in Zingiber officinale extract and ginger–containing dietary supplements, teas and commercial creams. Asian Pacific Journal of Tropical Biomedicine, 3 (8), 634–638. doi: http://doi.org/10.1016/s2221-1691(13)60128-8

4. Mukherjee, S., Mandal, N., Dey, A., Mondal, B. (2012). An approach towards optimization of the extraction of polyphenolic antioxidants from ginger (Zingiber officinale). Journal of Food Science and Technology, 51 (11), 3301–3308. doi: http://doi.org/10.1007/s13197-012-0848-z

5. Patel, D. K., Dhanabal, S. P. (2013). Development of bioanalytical parameters for the standardization of Zingiber officinale. Journal of Acute Disease, 2 (2), 134–136. doi: http://doi.org/10.1016/s2221-6189(13)60113-4

6. Salmon, C. N. A., Bailey-Shaw, Y. A., Hibbert, S., Green, C., Smith, A. M., Williams, L. A. D. (2012). Characterisation of cultivars of Jamaican ginger (Zingiber officinale Roscoe) by HPTLC and HPLC. Food Chemistry, 131 (4), 1517–1522. doi: http://doi.org/10.1016/j.foodchem.2011.09.115

7. Srinivasan, K. (2017). Ginger rhizomes (Zingiber officinale): A spice with multiple health beneficial potentials. PharmaNutrition, 5 (1), 18–28. doi: http://doi.org/10.1016/j.phanu.2017.01.001

8. European Pharmacopoeia (2016). 9th ed. Strasbourg: Council of Europe, 1367.

9. Tohma, H., Gülçin, İ., Bursal, E., Gören, A. C., Alwasel, S. H., Köksal, E. (2016). Antioxidant activity and phenolic compounds of ginger (Zingiber officinale Rosc.) determined by HPLC-MS/MS. Journal of Food Measurement and Characterization, 11 (2), 556–566. doi: http://doi.org/10.1007/s11694-016-9423-z

10. Nile, S. H., Park, S. W. (2015). Chromatographic analysis, antioxidant, anti-inflammatory, and xanthine oxidase inhibitory activities of ginger extracts and its reference compounds. Industrial Crops and Products, 70, 238–244. doi: http://doi.org/10.1016/j.indcrop.2015.03.033

11. Amir, M., Khan, A., Mujeeb, M., Ahmad, A., Usmani, S., Akhtar, M. (2011). Phytochemical Analysis and in vitro Antioxidant Activity of Zingiber officinale. Free Radicals and Antioxidants, 1 (4), 75–81. doi: http://doi.org/10.5530/ax.2011.4.12

DOI: 10.15587/2519-4852.2019.165682

B-LACTAM ANTIBIOTICS IN UKRAINE: MARKET AND CONSUMPTION ANALYSIS IN 2013–2018

p. 16-21

Larysa Yakovlieva, Doctor of Pharmaceutical Sciences, Professor, Merited worker of science and technology of Ukraine, Head of Department, Department of Pharmacoeconomics, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
ORCID: *http://orcid.org/0000-0002-9961-4664*

Tetiana Bahlai, Postgraduate student, Department of Pharmacoeconomics, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
ORCID: *http://orcid.org/0000-0003-1390-8571*

The strategy of combating the development of antibiotic resistance is a global challenge for the scientific community for the sake of life and health of the population. An analysis of the relationship between the levels of antimicrobial drug consumption and the development of antibiotic resistance is one of the tools to contain the resistance. An increase in the consumption of antimicrobial drugs may not significantly reduce the possibility of treating infectious diseases.

According to reports from the European Surveillance of Antimicrobial Consumption Network, β-lactam antimicrobial drugs are the most consumed antibiotic group in Europe among other. The consumption level of β-lactams in Ukraine is significantly lower than in the Europe. Such data require a detailed assessment of the level of consumption of β-lactam antimicrobial drugs, for individual INN and analysis of the balance of their use.

The aim *of the work is to analyze the market and consumption of antimicrobial drugs of the β-lactam group in Ukraine for 2013-2018 with the help of the ATC / DDD methodology, as well as comparison of the obtained consumption volumes with similar results in the European Union.*

Results*. The total amount of AMP of the β-lactam group presented in the Ukrainian market in 2018 is 343 trade names (TN), of which 92 are domestic and 251 are foreign manufactured, which indicates the high saturation of the Ukrainian pharmaceuticals by imported drugs*

In Ukraine, in 2017, penicillins consumed 4.48 times less than the EU average, while cephalosporins and carbapenems are almost the same.

The most commonly used INNs from the penicillin group – Amoxicillin and Amoxicillin with β-lactamase inhibitors, and the leaders in terms of consumption among cephalosporins are medicines for CITIs Ceftriaxone and Cefuroxime.

Conclusions*. Antimicrobials of the β-lactam group are well-studied and widely used in medical practice. They are widely represented in the Ukrainian market (343 TN), but only less than a third of them (92 TN) of domestic production, which indicates the high saturation of the Ukrainian pharmaceutical market with imported drugs. The volume of antimicrobial drugs used in the β-lactam group in Ukraine is almost 4.5 times lower than in the EU.*

The most commonly used drugs are Amoxicillin, from a group of penicillins with extended spectrum. Cefriaxone and Cefuroxime are most commonly used drugs among cephalosporins

Keywords*: pharmaceutical market; β-lactam antibiotics; consumption of medicines; ATC/DDD methodology*

References

1. Bennett, J. W., Chung, K.-T. (2001). Alexander Fleming and the discovery of penicillin. Advances in Applied Microbiology, 163–184. doi: https://doi.org/10.1016/s0065-2164(01)49013-7

2. Chellat, M. F., Raguž, L., Riedl, R. (2016). Targeting Antibiotic Resistance. Angewandte Chemie International Edition, 55 (23), 6600–6626. doi: https://doi.org/10.1002/anie.201506818

3. Van Loon, K., Voor in 't holt, A. F., Vos, M. C. (2017). A Systematic Review and Meta-analyses of the Clinical Epidemiology of Carbapenem-Resistant Enterobacteriaceae. Antimicrobial Agents and Chemotherapy, 62 (1). doi: https://doi.org/10.1128/aac.01730-17

4. Bell, B. G., Schellevis, F., Stobberingh, E., Goossens, H., Pringle, M. (2014). A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infectious Diseases, 14 (1). doi: https://doi.org/10.1186/1471-2334-14-13

5. Baditoiu, L., Axente, C., Lungeanu, D., Muntean, D., Horhat, F., Moldovan, R. et. al. (2017). Intensive care antibiotic consumption and resistance patterns: a cross-correlation analysis. Annals of Clinical Microbiology and Antimicrobials, 16 (1). doi: https://doi.org/10.1186/s12941-017-0251-8

6. Use of ATC/DDD. WHO. Available at: https://www.whocc.no/use_of_atc_ddd/

7. Georgopapadakou, N. H., Liu, F. Y. (1980). Penicillin-binding proteins in bacteria. Antimicrobial Agents and Chemotherapy, 18 (1), 148–157. doi: https://doi.org/10.1128/aac.18.1.148

8. Pottegård, A., Broe, A., Aabenhus, R., Bjerrum, L., Hallas, J., Damkier, P. (2015). Use of Antibiotics in Children. The Pediatric Infectious Disease Journal, 34 (2), e16–e22. doi: https://doi.org/10.1097/inf.0000000000000519

9. Saroglou, G., Cromer, M., Bisno, A. L. (1980). Methicillin-Resistant Staphylococcus Aureus: Interstate Spread of Nosocomial Infections with Emergence of Gentamicin-Methicillin Resistant Strains. Infection Control, 1 (02), 81–89. doi: https://doi.org/10.1017/s0195941700052590

10. Bush, K. (2013). Proliferation and significance of clinically relevant β-lactamases. Annals of the New York Academy of Sciences, 1277 (1), 84–90. doi: https://doi.org/10.1111/nyas.12023

11. Hilf, M., Yu, V. L., Sharp, J., Zuravleff, J. J., Korvick, J. A., Muder, R. R. (1989). Antibiotic therapy for Pseudomonas aeruginosa bacteremia: Outcome correlations in a prospective study of 200 patients. The American Journal of Medicine, 87 (5), 540–546. doi: https://doi.org/10.1016/s0002-9343(89)80611-4

12. Schaar, V., Uddback, I., Nordstrom, T., Riesbeck, K. (2013). Group A streptococci are protected from amoxicillin-mediated killing by vesicles containing -lactamase derived from Haemophilus influenzae. Journal of Antimicrobial Chemotherapy, 69 (1), 117–120. doi: https://doi.org/10.1093/jac/dkt307

13. Abraham, E. P. (1987). Cephalosporins 1945-1986. Drugs, 34, 1–14. doi: https://doi.org/10.2165/00003495-198700342-00003

14. Sudo, T., Murakami, Y., Uemura, K., Hashimoto, Y., Kondo, N., Nakagawa, N. et. al. (2014). Perioperative Antibiotics Covering Bile Contamination Prevent Abdominal Infectious Complications After Pancreatoduodenectomy in Patients With Preopera-

tive Biliary Drainage. World Journal of Surgery, 38 (11), 2952–2959. doi: https://doi.org/10.1007/s00268-014-2688-7

15. Abe, Y., Wakabayashi, H., Ogawa, Y., Machida, A., Endo, M., Tamai, T. et. al. (2016). Validation of Cefazolin as Initial Antibiotic for First Upper Urinary Tract Infection in Children. Global Pediatric Health, 3, 2333794X1562529. doi: https://doi.org/10.1177/2333794x15625297

16. Iakovlieva, L. V., Matyashova, N. A. (2013). The estimation out-patient consumption of penicillins in Ukraine. Farmatsevtychnyi zhurnal, 1, 26–31. Available at: http://nbuv.gov.ua/UJRN/pharmazh_2013_1_6

17. Yakovlieva, L. V., Matvieieva, O. V., Matiashova, N. O. (2010). Doslidzhennia spozhyvannia antybiotykiv hrupy tsefalosporyniv, predstavlenykh na farmatsevtychnomu rynku Ukrainy. Klinichna farmatsiya, 2, 22–26. Available at: http://dspace.nuph.edu.ua/handle/123456789/179

18. European Centre for Disease Prevention and Control. Antimicrobial consumption (2018). ECDC. Annual epidemiological report 2017. Stockholm: ECDC.

19. Bennett, J. E., Dolin, R., Blaser, M. J. (Eds.) (2015). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Elsevier, 3904.

DOI: 10.15587/2519-4852.2019.165681

ANALYSIS OF RESEARCH ON THE BENEFITS OF CLINICAL AND ECONOMIC EFFECTIVENESS, SAFETY OF INNOVATIVE DRUG CETUXIMAB IN THE TREATMENT OF COLORECTAL CANCER

p. 22-27

Elena Litvinova, Doctor of Pharmaceutical Sciences, Associate Professor, Department of Management and Economics of Enterprise, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

E-mail: hlitvinova@gmail.com

ORCID: *http://orcid.org/0000-0003-1578-7398*

The aim *of the work is to analyze and systematize literature data on the benefits of clinical and economic efficiency, safety of cetuximab in the treatment of colorectal cancer.*

Materials and methods. *Studies were conducted using databases on the Internet: PubMed; Food and Drug Administration, European Medicines Agency. It has used retrospective, logical, statistical and system-analytical research methods.*

Results. *The analysis of clinical data suggests additional utility, high efficacy of cetuximab in the treatment of patients with metastatic colorectal cancer RAS wild type and expression of epidermal growth factor receptors EGFR compared to other drugs. Cetuximab exhibits a synergistic effect with a number of cytostatic drugs, and also increases the effect of radiotherapy, with no increased toxic reactions when co-administered. The administration of cetuximab in the treatment regimen increases the resectability of primary nonresectable metastases in the liver, as well as survival without progression in both operated patients and in inoperable cases. The drug is considered relatively safe. Skin rashes caused by cetuximab are associated with a significant improvement in overall survival, progression-free survival and overall response rates. The use of cetuximab in patients with colorectal cancer is accompanied by a lower economic burden on the budget of drug provision for cancer patients than bevacizumab. It should be noted that the development of cetuximab biosimilars will reduce the cost of treatment and improve access to colorectal cancer therapy.*

Conclusions. *Thus, it has been shown that cetuximab is not only a clinically effective and relatively safe drug for the treatment of colorectal cancer, but also demonstrates its cost-effectiveness and additional benefits compared with other drugs, including bevacizumab*

Keywords*: cetuximab, colorectal cancer, clinical and economic efficiency, safety, epidermal growth factor receptor*

References

1. Cancer prevention and control through an integrated approach (2017). Geneva: World Health Organization, Available at: http://apps.who.int/gb/ebwha/pdf_files/WHA70-REC1/A70_2017_REC1-en.pdf

2. Celis, J. E., Pavalkis, D. (2017). A mission-oriented approach to cancer in Europe: a joint mission/vision 2030. Molecular Oncology, 11 (12), 1661–1672. doi: http://doi.org/10.1002/1878-0261.12143

3. Mach, J. P. (2017). Recombinant monoclonal antibodies, from tumor targetingto cancer immunotherapy, a critical overview. Molecular biology, 51 (6), 1024–1038. doi: http://doi.org/10.7868/s0026898417060131

4. Kelly, R. J., Smith, T. J. (2014). Delivering maximum clinical benefit at an affordable price: engaging stakeholders in cancer care. The Lancet Oncology, 15 (3), e112–e118. doi: http://doi.org/10.1016/s1470-2045(13)70578-3

5. Ferguson, J. S. J., Summerhayes, M., Masters, S., Schey, S., Smith, I. E. (2000). New treatments for advanced cancer: an approach to prioritization. British Journal of Cancer, 83 (10), 1268–1273. doi: http://doi.org/10.1054/bjoc.2000.1406

6. Collins, M., Latimer, N. (2013). NICE's end of life decision making scheme: impact on population health. BMJ, 346 (1), 1363–1363. doi: http://doi.org/10.1136/bmj.f1363

7. Dilts, D. M. (2014). Time Has Come to Raise the Bar in Oncology Clinical Trials. Journal of Clinical Oncology, 32 (12), 1186–1187. doi: http://doi.org/10.1200/jco.2013.54.5277

8. Polyakova, D. (2019). Half of the new drugs does not carry additional benefits. Weekly Pharmacy, 1174 (3). Available at: https://www.apteka.ua/article/487540

9. Sobrero, A. F., Maurel, J., Fehrenbacher, L., Scheithauer, W., Abubakr, Y. A., Lutz, M. P. et. al. (2008). EPIC: Phase III Trial of Cetuximab Plus Irinotecan After Fluoropyrimidine and Oxaliplatin Failure in Patients With Metastatic Colorectal Cancer. Journal of Clinical Oncology, 26 (14), 2311–2319. doi: http://doi.org/10.1200/jco.2007.13.1193

10. Cutsem, E. Van, Nowacki, M., Lang, I., Cascinu, S., Shchepotin, I. et. al. (2007). Randomized phase III study of irinotecan and 5FU/FA with or without cetuximab in the first-line treatment of patients with metastatic colorectal cancer. CRYSTAL trial. Journal of Clinical Oncology, 25 (18), 164.

11. Van Cutsem, E., Köhne, C.-H., Láng, I., Folprecht, G., Nowacki, M. P., Cascinu, S. et. al. (2011). Cetuximab Plus Irinotecan, Fluorouracil, and Leucovorin As First-Line Treatment for Metastatic Colorectal Cancer: Updated Analysis of Overall Survival According to Tumor KRAS and BRAF Mutation Status. Journal of Clinical Oncology, 29 (15), 2011–2019. doi: http://doi.org/10.1200/jco.2010.33.5091

12. Cunningham, D., Humblet, Y., Siena, S., Khayat, D., Bleiberg, H., Santoro, A. et. al. (2004). Cetuximab Monotherapy

and Cetuximab plus Irinotecan in Irinotecan-Refractory Metastatic Colorectal Cancer. New England Journal of Medicine, 351 (4), 337–345. doi: http://doi.org/10.1056/nejmoa033025

13. Heinemann, V., von Weikersthal, L. F., Vehling-Kaiser, U., Stauch, M., Oruzio, D., Schulze, M. et. al. (2008). Randomized trial comparing cetuximab plus XELIRI versus cetuximab plus XELOX as first line treatment of patients with metastatic colorectal cancer (mCRC): A study of the german AIO CRC study group. Journal of Clinical Oncology, 26 (15), 4033–4033. doi: http://doi.org/10.1200/jco.2008.26.15_suppl.4033

14. Wasan, H., Adams, R. A., Wilson, R. H., Pugh, C., Fisher, D., Madi, A. et. al. (2012). Intermittent chemotherapy (CT) plus continuous or intermittent cetuximab (C) in the first-line treatment of advanced colorectal cancer (aCRC): Results of the two-arm phase II randomized MRC COIN-B trial. Journal of Clinical Oncology, 30 (4), 536–536. doi: http://doi.org/10.1200/jco.2012.30.4_suppl.536

15. Ye, L.-C., Liu, T.-S., Ren, L., Wei, Y., Zhu, D.-X., Zai, S.-Y. et. al. (2013). Randomized Controlled Trial of Cetuximab Plus Chemotherapy for Patients WithKRASWild-Type Unresectable Colorectal Liver-Limited Metastases. Journal of Clinical Oncology, 31 (16), 1931–1938. doi: http://doi.org/10.1200/jco.2012.44.8308

16. Osumi, H., Shinozaki, E., Mashima, T., Wakatsuki, T., Suenaga, M., Ichimura, T. et. al. (2018). Phase II trial of biweekly cetuximab and irinotecan as third-line therapy for pretreated KRAS exon 2 wild-type colorectal cancer. Cancer Science, 109 (8), 2567–2575. doi: http://doi.org/10.1111/cas.13698

17. Cheng, A.-L., Cornelio, G., Shen, L., Price, T., Yang, T.-S., Chung, I. J. et. al. (2017). Efficacy, Tolerability, and Biomarker Analyses of Once-Every-2-Weeks Cetuximab Plus First-Line FOLFOX or FOLFIRI in Patients With KRAS or All RAS Wild-Type Metastatic Colorectal Cancer: The Phase 2 APEC Study. Clinical Colorectal Cancer, 16 (2), e73–e88. doi: http://doi.org/10.1016/j.clcc.2016.08.005

18. Pietrantonio, F., Di Bartolomeo, M., Cotsoglou, C., Mennitto, A., Berenato, R., Morano, F. et. al. (2017). Perioperative Triplet Chemotherapy and Cetuximab in Patients With RAS Wild Type High Recurrence Risk or Borderline Resectable Colorectal Cancer Liver Metastases. Clinical Colorectal Cancer, 16 (3), e191–e198. doi: http://doi.org/10.1016/j.clcc.2016.09.007

19. Stintzing, S., Miller-Phillips, L., Modest, D. P., Fischer von Weikersthal, L., Decker, T., Kiani, A. et. al. (2017). Impact of BRAF and RAS mutations on first-line efficacy of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab: analysis of the FIRE-3 (AIO KRK-0306) study. European Journal of Cancer, 79, 50–60. doi: http://doi.org/10.1016/j.ejca.2017.03.023

20. Lévi, F., Karaboué, A., Saffroy, R., Desterke, C., Boige, V., Smith, D. et. al. (2017). Pharmacogenetic determinants of outcomes on triplet hepatic artery infusion and intravenous cetuximab for liver metastases from colorectal cancer (European trial OPTILIV, NCT00852228). British Journal of Cancer, 117 (7), 965–973. doi: http://doi.org/10.1038/bjc.2017.278

21. Van Geel, R. M. J. M., Tabernero, J., Elez, E., Bendell, J. C., Spreafico, A., Schuler, M. et. al. (2017). A Phase Ib Dose-Escalation Study of Encorafenib and Cetuximab with or without Alpelisib in Metastatic BRAF-Mutant Colorectal Cancer. Cancer Discovery, 7 (6), 610–619. doi: http://doi.org/10.1158/2159-8290.cd-16-0795

22. Sunakawa, Y., Ichikawa, W., Tsuji, A., Denda, T., Segawa, Y., Negoro, Y. Et. al. (2017). Prognostic Impact of Primary Tumor Location on Clinical Outcomes of Metastatic Colorectal Cancer Treated With Cetuximab Plus Oxaliplatin-Based Chemotherapy: A Subgroup Analysis of the JACCRO CC-05/06 Trials. Clinical Colorectal Cancer, 16 (3), e171–e180. doi: http://doi.org/10.1016/j.clcc.2016.09.010

23. Ciardiello, F., Normanno, N., Martinelli, E., Troiani, T., Pisconti, S., Cardone, C. et. al. (2016). Cetuximab continuation after first progression in metastatic colorectal cancer (CAPRI-GOIM): a randomized phase II trial of FOLFOX plus cetuximab versus FOLFOX. Annals of Oncology, 27 (6), 1055–1061. doi: http://doi.org/10.1093/annonc/mdw136

24. Nakamura, M., Aoyama, T., Ishibashi, K., Tsuji, A., Takinishi, Y., Shindo, Y. (2016). Randomized phase II study of cetuximab versus irinotecan and cetuximab in patients with chemo-refractory KRAS codon G13D metastatic colorectal cancer (G13D-study). Cancer Chemotherapy and Pharmacology, 79 (1), 29–36. doi: http://doi.org/10.1007/s00280-016-3203-7

25. Stintzing, S., Modest, D. P., Rossius, L., Lerch, M. M., von Weikersthal, L. F., Decker, T. et. al. (2016). FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial. The Lancet Oncology, 17 (10), 1426–1434. doi: http://doi.org/10.1016/s1470-2045(16)30269-8

26. Liu, G., Tu, D., Lewis, M., Cheng, D., Sullivan, L. A., Chen, Z. et. al. (2016). Fc- Receptor Polymorphisms, Cetuximab Therapy, and Survival in the NCIC CTG CO.17 Trial of Colorectal Cancer. Clinical Cancer Research, 22 (10), 2435–2444. doi: http://doi.org/10.1158/1078-0432.ccr-15-0414

27. Hazama, S., Maeda, H., Iwamoto, S., Kim, H. M., Takemoto, H., Kobayashi, K. et. al. (2016). A Phase II Study of XELOX and Cetuximab as First-Line Therapy in Patients With KRAS Wild Type Metastatic Colorectal Cancer (FLEET2 Study). Clinical Colorectal Cancer, 15 (4), 329–336. doi: http://doi.org/10.1016/j.clcc.2016.07.003

28. Takahashi, T., Emi, Y., Oki, E., Kobayashi, K., Tsuji, A. et. al. (2016). Multicenter phase II study of combination therapy with cetuximab and S-1 in patients with KRAS exon 2 wild-type unresectable colorectal cancer previously treated with irinotecan, oxaliplatin, and fluoropyrimidines (KSCC 0901 study). Cancer Chemotherapy and Pharmacology, 78 (3), 585–593. doi: http://doi.org/10.1007/s00280-016-3109-4

29. Terazawa, T., Nishitani, H., Kato, K., Hashimoto, H., Akiyoshi, K., Ito, Y. (2015). Phase II study of cetuximab with irinotecan for KRAS wild-type colorectal cancer in Japanese patients. Asia-Pacific Journal of Clinical Oncology, 13 (2), e132–e137. doi: http://doi.org/10.1111/ajco.12405

30. Folprecht, G., Gruenberger, T., Bechstein, W., Raab, H.-R., Weitz, J., Lordick, F. et. al. (2014). Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study)†. Annals of Oncology, 25 (5), 1018–1025. doi: http://doi.org/10.1093/annonc/mdu088

31. Abdel-Rahman, O., Fouad, M. (2015). Correlation of cetuximab-induced skin rash and outcomes of solid tumor patients treated with cetuximab: A systematic review and meta-analysis. Critical Reviews in Oncology/Hematology, 93 (2), 127–135. doi: http://doi.org/10.1016/j.critrevonc.2014.07.005

32. Petrelli, F., Ardito, R., Ghidini, A., Zaniboni, A., Ghidini, M., Barni, S., Tomasello, G. (2018). Different Toxicity of Cetuximab and Panitumumab in Metastatic Colorectal Cancer Treatment: A Systematic Review and Meta-Analysis. Oncology, 94 (4), 191–199. doi: http://doi.org/10.1159/000486338

33. Jiang, W., Yu, Q., Ning, R., Zhao, W., Wei, C. (2018). Efficacy of bevacizumab versus epidermal growth factor receptor inhibitors for wild-type RAS metastatic colorectal cancer: a meta-analysis. OncoTargets and Therapy, 11, 4271–4281. doi: http://doi.org/10.2147/ott.s168695

34. Cao, D.-D., Xu, H.-L., Xu, X.-M., Ge, W. (2017). The impact of primary tumor location on efficacy of cetuximab in metastatic colorectal cancer patients with different Kras status: a systematic review and meta-analysis. Oncotarget, 8 (32), 53631–53641. doi: http://doi.org/10.18632/oncotarget.19022

35. Yang, Y.-F., Wang, G.-Y., He, J.-L., Wu, F.-P., Zhang, Y.-N. (2017). Overall survival of patients with KRAS wild-type tumor treated with FOLFOX/FORFIRI±cetuximab as the first-line treatment for metastatic colorectal cancer. Medicine, 96 (12), e6335. doi: http://doi.org/10.1097/md.0000000000006335

36. Shankaran, V., Ortendahl, J. D., Purdum, A. G., Bolinder, B., Anene, A. M., Sun, G. H., Bentley, T. G. K. (2015). Cost-Effectiveness of Cetuximab as First-line Treatment for Metastatic Colorectal Cancer in the United States. American Journal of Clinical Oncology, 41 (1), 65–72. doi: http://doi.org/10.1097/coc.0000000000000231

DOI: 10.15587/2519-4852.2019.165640

STUDY OF FACTORS AFFECTING ON THE DEVELOPMENT OF THE PHARMACEUTICAL SECTOR ENTERPRISES

p. 28-33

Karina Golubtsova, Department Processes and Apparatuses of Chemical and Pharmaceutical Industries, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: paft@nuph.edu.ua

Rita Sahaidak-Nikitiuk, Doctor of Pharmaceutical Sciences, Head of Department, Department of Processes and Apparatuses of Chemical and Pharmaceutical Industries, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: sagaidak_rita@ukr.net
ORCID: *http://orcid.org/0000-0002-9337-7741*

Natalia Demchenko, PhD, Associate Professor, Department of Management and Administration, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: demchenata@ukr.net
ORCID: *http://orcid.org/0000-0001-5915-0087*

Aim. *The aim of the article is to study the factors influencing the development of enterprises in the pharmaceutical sector.*
Materials and methods. *Methods used in the study include methods for analysis and synthesis, mathematical statistics, and econometric and mathematical methods. The data used in the analysis were presented in the statistical yearbook of Ukraine.*
Results. *The present state and trends of development of enterprises of the pharmaceutical sector are investigated. The dynamics of changes in consumer price indices for pharmaceutical products and the volume of its sales in 2011–2018 testifies to excess of a rise in prices over growth in sales volumes. The analysis of the pharmaceutical market of Ukraine highlighted an increase of 11 % in the volume of pharmaceutical products in US dollars. The negative factors of the pharmaceutical sector development in Ukraine include the reduction of purchasing power of citizens. The comparison of the share of foreign and domestic producers in the domestic pharmaceutical market shows that the Ukrainian drugs are more accessible to the user. The analysis of world experience has highlighted that in Ukraine the lowest indicators of population spending on the purchase of medicines; while in Poland, Hungary, Bulgaria this figure is 4 times higher. By the number of pharmacies – in Ukraine, the highest figures in absolute terms. Applied methods of mathematical statistics, which allowed revealing the continuity of nonfunctional relationships between random variables, which allow establishing the connection between the net result (profit) and the size of the stocks of pharmaceutical enterprises in the Kharkiv region.*
Conclusions. *The study of the current state and trends of the pharmaceutical sector enterprises allowed to conclude that profitability depends on the organization of logistics management (inventory control), which will allow them to get rid of unnecessary costs and reach a new level of production of modern medicines*
Keywords: *pharmaceutical enterprise, pharmaceutical sector, management, development trends, stocks, medicines*

References

1. Hromovyk, B. P. (2004). Standarty farmatsevtychnoho upravlinnia. Farmatsevtychnyi zhurnal, 3, 18–28.

2. Hromovyk, B. P., Tereshchuk, S. I., Chukhrai, I. L.; Hromovyk, B. P., Tereshchuk, S. I. (Eds.) (2009). Orhanizatsiia ta ekonomika farmatsii. Vinnytsia: NOVA KNYHA, 816.

3. Gholamhossein, M., Hosein, S. (2014). The Importance of Competitiveness in New Internationalized and Competitive Environment of Pharmaceutical Industry. Iranian journal of pharmaceutical research, 13 (2), 351–352.

4. Frolova, H. I., Frolova, V. Yu. (2012). Konkurentospromozhnist pidpryiemstv farmatsevtychnoi haluzi Ukrainy. Visnik Berdianskoho universytetu menedzhmentu i biznesu, 1 (17), 146–152.

5. Kotvitska, A. A., Kostiuk, V. H. (2016). Doslidzhennia suchasnykh pidkhodiv do formuvannia asortymentnoi polityky vitchyznianykh farmatsevtychnykh pidpryiemstv. Sotsialna farmatsiia v okhoroni zdorovia, 2 (2), 37–43.

6. Kotvitska, A. A. (2008). Metodolohiia sotsialnoi spravedlyvosti farmatsevtychnoho zabezpechennia naselennia. Farmatsevtychnyi zhurnal, 2, 8–12.

7. Kutsenko, V. (2009). Zdorovia natsii yak stratehichnyi resurs derzhavy. Visnyk Natsionalnoi Akademii Nauk Ukrainy, 6, 44–51.

8. Lebedynets, V. O., Kovalenko, S. M. (2011). Otsiniuvannia, analizuvannia ta upravlinnia ryzykamy dlia yakosti na farmatsevtychnomu pidpryiemstvi. Upravlinnia, ekonomika ta zabezpechennia yakosti v farmatsii, 6 (20), 10–15.

9. Nemchenko, A. S., Khomenko, V. M., Yarmola, I. K. (2008). Ekspertna otsinka problem derzhavnoho ta rehionalnoho upravlinnia farmatsevtychnoiu haluzziu. Farmatsevtychnyi zhurnal, 1, 3–9.

10. Pestun, I. V., Mnushko, Z. M. (2008). Stan ta perspektyvy makrootochennia na diialnist farmatsevtychnykh orhanizatsii v Ukraini. Upravlinnia, ekonomika ta zabezpechennia yakosti v farmatsii, 1 (1), 8–14.

11. Posylkina, O. V., Sahaidak-Nikitiuk, R. V., Zahorii, H. V., Horbunova, O. Yu., Yurchenko, A. P. (2011). Lohistychnyi menedzhment farmatsevtychnoho pidpryiemstva. Kharkiv: NFaU, 772.

12. Bilynska, M. M., Radysh, Ya. F. (Eds.) (2013). Derzhavne upravlinnia okhoronoiu zdorovia v Ukraini: henezys i perspektyvy rozvytku. Kyiv: NADU, 424.

13. The Pharmaceutical Industry in Figures.The European Federation of Pharmaceutical Industries and Associations. Available at: https://efpia.eu/publications/downloads/efpia/2018-the-pharmaceutical-industry-in-figures/

14. Singh, A., Henske, P. (2003). Has the Pharmaceutical Blockbuster Model Gone Bust? A New Bain & Company Reveals New Drug Commercialization Costs Have Now Reached $1.7 Billion While ROI Has Plummeted to Just 5 %. Available at: https://www.businesswire.com/news/home/20031208005181/en/Pharmaceutical-Blockbuster-Model-Bust-New-Bain-Company

15. Statystychnyi shchorichnyk Ukrainy. Available at: http://www.ukrstat.gov.ua/druk/publicat/kat_u/publ1_u.htm

16. Problemy i perspektyvy diialnosti farmatsevtychnykh kompanii v Ukrainu. Available at: https://pro-capital.ua/press_center/procapprog/view/12/

17. Butnyk, O. M. (2004). Ekonomiko-matematychne modeliuvannia perekhidnykh protsesiv u sotsialno-ekonomichnykh systemakh. Kharkiv: Vyd.Dim «Inzhek»; SPD Liburkina L. M., 304.

18. Nakonechnyi, S. I., Savina, S. S. (2004). Matematychne prohramuvannia. Kyiv: KNEU, 432.

19. Klebanova, T. S., Kyzym, M. O., Cherniak, O. I. et. al. (2009). Matematychni metody i modeli rynkovoi ekonomiky. Kharkiv: VD «INZhEK», 456.

20. Prokopenko, I. F., Hanin, V. I., Petriaieva, Z. F.; Prokopenko, I. F. (Ed.) (2004). Kurs ekonomichnoho analizu. Kharkiv: Lehas, 384.

DOI: 10.15587/2519-4852.2019.165763

DEVELOPMENT OF METHOD OF QUANTITATIVE DETERMINATION OF CARDIAZOL SUBSTANCE WITH USING HIGHLY EFFICIENT LIQUID CHROMATOGRAPHY

p. 33-38

Iryna Drapak, PhD, Associate Professor, Department of General, Bioinorganic, Physical and Colloidal Chemistry, Danylo Halytsky Lviv National Medical University, Pekarska str., 69, Lviv, Ukraine, 79010
E-mail: iradrapak@ukr.net
ORCID: *http://orcid.org/0000-0002-6830-2908*

Borys Zimenkovsky, Doctor of Pharmaceutical Sciences, Professor, Department of Pharmaceutical, Organic and Bioorganic Chemistry, Danylo Halytsky Lviv National Medical University, Pekarska str., 69, Lviv, Ukraine, 79010
E-mail: d35.600.02@meduniv.lviv.ua
ORCID: *http://orcid.org/0000-0002-8872-6847*

Ivan Bezruk, Postgtaduate student, Department of Pharmaceutical Chemistry, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraina, 61002
E-mail: vania.bezruk@gmail.com
ORCID: *http://orcid.org//0000-0002-1212-1649*

Liudas Ivanauskas, PhD, Professor, Department of Analytical and Toxicological Chemistry, Lithuanian University of Health Sciences, A. Mickevičiaus g. 9, Kaunas, Lithuania, LT 44307
E-mail: liudas.ivanauskas@lsmuni.lt
ORCID: *http://orcid.org/0000-0001-5390-2161*

Lina Perekhoda, Doctor of Pharmaceutical Sciences, Professor, Department of Medicinal Chemistry, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: linaperekhoda@ukr.net
ORCID: *http://orcid.org/0000-0002-8498-33IX*

Svitlana Harna, Doctor of Pharmaceutical Sciences, Professor, Department of Quality, Standartization and Sertification of Drugs, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: garnaya57@gmail.com
ORCID: *http://orcid.org/0000-0001-8849-4495*

The aim. *Development of methods of quantitative determination of Cardiazol substance using high-performance liquid chromatography.*

Materials and methods. *The method of high-performance liquid chromato-graphy (HPLC) was to determine of quantitative determination of Cardiazol substance ([3-Allil-4-(4^1-methoxyphenyl)-3H-thiazole-2-ylidene]-(3^2-trifluoro-methylphenyl)amine hydrobromide) using Shimadzu Nexera X2 LC-30AD (Shimad-zu, Japan). The acetonitrile of the HPLC grade (Sigma-Aldrich GmbH, Switzerland) was used in the work and other chemicals and solvents were of analytical grade. The test substance was diluted in acetonitrile at a final concentration of 400 μg/ml.*

Results and discussion. *The method of quantitative determination of Cardiazol substance with the help of highly effective liquid chromatography is developed. The developed conditions of testing are selected experimentally. The following optimal conditions for the chromatographic distribution were found: column C8 (250×4.6 mm; speed of the mobile phase 1 ml/min; thermostat temperature of the column 35 °C; detecting wavelength 300 nm; holding time of the test compound is 13.9 min. Suitability of determination methods.*

The following optimal conditions for chromatographic separation were revealed: a C8 column (250×4.6 mm, a mobile phase speed of 1 ml/min, a column thermostat temperature of 35 °C, a detection wavelength of 300 nm. Under the proposed conditions, the retention time of the tested component is 13.9 minutes. The performance of the column was determined for its main indicators, such as the theoretical number of plates (over 65000) and the coefficient of symmetry (about 1.00). The method of quantitative determination was tested in accordance with the recommendations of the Ukrainian and European Pharmacopoeia. The proposed method meets all requirements. The method has been tested for the effects of various factors such as flow rate, the composition of the mobile phase and the temperature of the column thermostat. It is established that the influence of these factors is insignificant and does not affect the results obtained by this method.

Conclusions. *An analytical method for quantitative determination of Cardiazole substance with cardioprotective action has been developed on the basis of the high-performance liquid chromatography method. The conditions for chromatographic analysis (HPLC) were standardized. Requirements for the test "Checking the suitability of the chromatographic system" were established. The statistical processing of the results of the experiment shows that the relative uncertainty of the average result was within the permissible limits. The developed method for the determination of Cardiazole will be used for further study of substance as a component of various dosage forms*

Keywords: *Cardiazole, cardioprotective activity, analysis, method of quantitative determination, high performance liquid chromatography*

References

1. Kovalenko, V. M., Dolzhenko, M. M., Nesukai, Ye. H., Diachenko, Ya. S. (2016). Comparative characteristics of the cardiovascular disease prevention in Ukraine and Europe according to EUROASPIRE IV data: a hospital line. Arterial'naya gipertenziya, 1, 41–80.

2. The top 10 causes of death. WHO. Available at: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

3. Yeromina, H. O., Drapak, I. V., Perekhoda, L. O., Yaremenko, V. D., Demchenko, A. M. (2016). Synthesis of 2-(4-aryl(adamantyl)-2-phenyliminothiazol-3-yl)-ethanol derivatives and prediction of their biological activity. Der Pharma Chemica, 8 (3), 64–70.

4. Perekhoda, L., Yeromina, H., Drapak, I., Kobzar, N., Smolskiy, O., Demchenko, N. (2017). The antioxidant properties of 1-[2-(R-phenylimino)-4-methyl-3-(3-[morpholine-4yl]propyl)-2,3-dihydro-1,3-thiazol-5-yl]ethane-1-one derivatives under conditions of artificial oxidative stress in vitro. Saudi Journal of Medical and Pharmaceutical Sciences, 3 (1), 55–59.

5. Drapak, I., Perekhoda, L., Vynogradova, O., Protopopov, M., Suleiman, M., Sych, I., Kobzar, N., Kiz, O. (2018). The use of the docking studies with the purpose of searching potential cardioprotectors. Pharmacia, 2, 40–46.

6. Perekhoda, L. O., Drapak, I. V., Suleiman, M. M., Sych, I. A., Yaremenko, V. D. (2017). Synthesis and in silico research of derivatives of 3-allyl-4-(R-phenyl)-N-(R1-phenyl)thiazole-2-imine. Der Pharma Chemica, 9 (13), 95–98.

7. Herashchenko, I. V., Drapak, I. V., Demchenko, A. M., Perekhoda, L. O., Niektiehaiev, I. O. (2017). Pat. No. 122197 UA. Hidrobromid [3-alil-4-(41-metoksyfenil)-3N-tiazol-2-iliden]-(32-tryfluorometylfenil)aminu, shcho maie kardioprotektorni vlastyvosti. No. u201707267; declareted: 10.07.2017; published: 26.12.2017, Bul. No. 24.

8. O' Sullivan, J., Blake, K., Berntgen, M., Salmonson, T., Welink, J. (2018). Overview of the European Medicines Agency's Development of Product-Specific Bioequivalence Guidelines. Clinical Pharmacology & Therapeutics, 104 (3), 539–545. doi: https://doi.org/10.1002/cpt.957

9. Andrade, E. L., Bento, A. F., Cavalli, J., Oliveira, S. K., Schwanke, R. C., Siqueira, J. M. et. al. (2016). Non-clinical studies in the process of new drug development – Part II: Good laboratory practice, metabolism, pharmacokinetics, safety and dose translation to clinical studies. Brazilian Journal of Medical and Biological Research, 49 (12). doi: https://doi.org/10.1590/1414-431x20165646

10. Haleem, R. M., Salem, M. Y., Fatahallah, F. A., Abdelfattah, L. E. (2015). Quality in the pharmaceutical industry – A literature review. Saudi Pharmaceutical Journal, 23 (5), 463–469. doi: https://doi.org/10.1016/j.jsps.2013.11.004

11. Baumann, M., Baxendale, I. R. (2015). The synthesis of active pharmaceutical ingredients (APIs) using continuous flow chemistry. Beilstein Journal of Organic Chemistry, 11, 1194–1219. doi: https://doi.org/10.3762/bjoc.11.134

13. Yeromina, H. O., Yeromina, Z. H., Sych, I. A., Perekhoda, L. O. (2017). Rozrobka metodyky kilkisnoho vyznachennia substantsiyi hidrobromidu (3-etyl-4-fenil-3N-tiazol-2-iliden)- [4-(6,7,8,9-tetrahidro-5N-[1,2,4]tryazolo[4,3-a]azepin-3-yil)fenil]aminu. Upravlinnia yakistiu v farmatsiyi: mat. XI nauk.-prakt. konf. Kharkiv, 64.

14. Shim, J.-S. K., Tolan, J. W., Fink, D. W. (1980). Fluorometric Determination of Thiazole-Containing Compounds. Journal of Pharmaceutical Sciences, 69 (3), 275–279. doi: https://doi.org/10.1002/jps.2600690308

15. El-Walily, A. F. M., Gazy, A. A., Belal, S. F., Khamis, E. F. (2000). Quantitative determination of some thiazole cephalosporins through complexation with palladium (II) chloride. Journal of Pharmaceutical and Biomedical Analysis, 22 (2), 385–392. doi: https://doi.org/10.1016/s0731-7085(99)00281-2

16. Nikolin, B., Imamović, B., Medanhodžić-Vuk, S., Sober, M. (2004). High performance liquid chromatography in pharmaceutical analyses. Bosnian Journal of Basic Medical Sciences, 4 (2), 5–9. doi: https://doi.org/10.17305/bjbms.2004.3405

17. Pakhomov, V. P. (2003). Khromatohrafiya u khimiko-farmatsevtychnykh doslidzhenniakh. Khymyko-farmatsevtycheskyi zhurnal, 37 (8), 55–56.

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

19. European Pharmacopoeia (2017). European Directorate for the Quality of Medicines & Health Care. Strasbourg.

DOI: 10.15587/2519-4852.2019.169511

DEVELOPMENT OF THE METHOD OF SIMULTANEOUS QUANTITATIVE DETERMINATION OF LORATADINE AND AUXUILARY SUBSTANCES IN THE COMBINED SYRUP "LORATADIN+"

p. 39-47

Alla Glushchenko, PhD, Associate Professor, Department of Quality, Standardization and Certification of Medicines, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: allaglushchenko05@gmail.com
ORCID: *http://orcid.org/0000-0001-6315-3117*

Ivan Bezruk, Postgraduate student, Department of Pharmaceutical Chemistry, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: vania.bezruk@gmail.com
ORCID: *http://orcid.org/0000-0002-1212-1649*

Liudas Ivanauskas, PhD, Associate Professor, Head of Department, Department of Analytical and Toxicological Chemistry, Medical Academy of Lithuanian University of Health Sciences, Eivenių g., 4, Kaunas, Lithuania, LT-50161
E-mail: liudas.ivanauskas@lsmuni.lt

Victoriya Georgiyants, Doctor of Pharmacy, Professor, Head of Department, Department of Pharmaceutical Chemistry, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: vgeor@ukr.net
ORCID: *http://orcid.org/0000-0001-8794-8010*

Aim*. The aim of the present study was to develop a method for the simultaneous determination of loratadine and auxiliary substances – methyl parahydroxybenzoate and propyl parahydroxybenzoate in the combined "Loratadine+" syrup in the presence of a bupleurum aurus grass extract.*

Materials and methods*. Liquid chromatography separation was performed using a Shimadzu Nexera X2 LC-30AD HPLC system (Shimadzu, Japan) composed of a quaternary pump, an on-line degasser, a column temperature controller, the SIL-30AC autosampler*

(Shimadzu, Japan); the CTO-20AC thermostat (Shimadzu, Japan) as well as the SPD-M20A diode array detector (DAD).

Results and discussion. *Identification of the main component and impurities in the combined syrup was performed by determining the retention times of peaks of loratadine, methyl parahydroxybenzoate and propyl parahydroxybenzoate on the chromatogram of the test solution, obtained by quantifying them, which coincided with the retention times of the corresponding peaks on the chromatogram of the reference solution.*

When developing a quantitative determination method, it was found that using the gradient mode, the best separation between the compounds was observed, the separation coefficient between the peaks of methyl parahydroxybenzoate and the peaks closest to it became more than 2.5, in the case of propyl parahydroxybenzoate this index was more than 3.

To confirm the correctness of the proposed method, validation studies were carried out in accordance with the requirements of SPHU. It was established that the uncertainty of sample preparation is 1.5 % for loratadine, 1.47 % for methyl parahydroxybenzoate, and 1.53 % for propyl parahydroxybenzoate, which does not exceed the acceptance criteria. The specificity of the technique was confirmed by comparing the chromatograms of the reference solution, the test solution and the chromatogram of the blank solution. Requirements for the linearity of the method were performed over the entire range of concentrations for loratadine and both excipients. The correlation coefficients were 0.9999, 0.9999 and 0.9995, respectively. The correctness of the technique was carried out according to two criteria - practical and statistical insignificance, which were determined in the course of experimental studies. The results of the assessment of intralaboratory precision showed that the obtained values of the confidence interval of the average result to the criteria of acceptability. Based on the results of the determination of robustness, it was found that for optimal chromatographic conditions, a freshly prepared reference solution can be used within 24 hours.

Conclusions. *A method was developed for the simultaneous quantitative determination of loratadine and auxiliary substances - methyl parahydroxybenzoate and propyl parahydroxybenzoate in the syrup of "Loratadine+". The conditions that allow to correctly determining all the components in the presence of a bupleurum aurus grass extract were determined. The correctness of the methodology is confirmed by validation studies*

Keywords: *loratadine, methyl parahydroxybenzoate, propyl parahydroxybenzoate, quantitative determination, combined drugs, hepatoprotective action*

References

1. Arshad, H., Khan, A., Assad, U., Kittaneh, M., Berkelhammer, C. (2016). Antihistamine-Induced Hepatitis: 2 Cases Involving Loratidine. Case Reports in Hepatology, 2016, 1–2. doi: http://doi.org/10.1155/2016/6890313

2. Breidak, O. O., Kuzminov, O. B. (2015). Otsinka kumuliatyvnoi aktyvnosti diazolinu, loratydynu ta dezloratydynu u pidhostromu ekspyrementi na bilykh myshakh. Biolohiia tvaryn, 17 (4), 178.

3. Gubergic, N. B., Fomenko, P. G., Lukashevich, G. M., Golubova, O. A. (2012). Farmakoterapevticheskie effekty i klinicheskie vozmozhnosti etalonnogo preparata silimarina. FARMATEKA, 2, 24–31.

4. Pegova, R. A., Vorobeva, O. A., Kolchik, O. V., Bolshakova, A. E., Zhilcova, O. E., Melnikova, N. B. (2014). Rastitelnye masla. Sostav i perspektivy ispolzovaniia masla semian tykvy Cucurbita Pepo v terapii (obzor). Medicinskii almanakh, 2 (32), 127–135.

5. Asadi-Samani, M., Kafash-Farkhad, N., Azimi, N., Fasihi, A., Alinia-Ahandani, E., Rafieian-Kopaei, M. (2015). Medicinal plants with hepatoprotective activity in Iranian folk medicine. Asian Pacific Journal of Tropical Biomedicine, 5 (2), 146–157. doi: http://doi.org/10.1016/s2221-1691(15)30159-3

6. Zhuravlova, L. V., Kryvonosova, O. M. (2013). Porivnialna kharakterystyka hepatoprotektornykh zasobiv: kliuch do ratsionalnoho zastosuvannia. Suchasna hastroenterolohiia, 4 (72), 35–41.

7. Thompson, M., Jaiswal, Y., Wang, I., Williams, L. (2017). Hepatotoxicity: Treatment, causes and applications of medicinal plants as therapeutic agents. The Journal of Phytopharmacology, 6 (3), 186–193.

8. Majee, C., Mazumder, R., Choudhary, A. N. (2019). Medicinal plants with anti-ulcer and hepatoprotective activity. International Journal of pharmaceutical sciences and research, 10 (1), 1–11. doi: http://doi.org/10.13040/ijpsr.0975-8232.10(1).1-11

9. Deshwal, N., Sharma, A. K., Sharma, P. (2011). Review on hepatoprotective plants. International Journal of Pharmaceutical Sciences Review and Research, 7 (1), 15–26.

10. Jehangir, A., Nagi, A. H., Shahzad, M. S., Azam, Z. (2010). The hepatoprotective effect of Cassia fistula leaves in Isoniazid and rifampicin induced hepatotoxicity in rodents. Biomedica, 26, 25–29.

11. Björnsson, E. (2016). Hepatotoxicity by Drugs: The Most Common Implicated Agents. International Journal of Molecular Sciences, 17 (2), 224. doi: http://doi.org/10.3390/ijms17020224

12. Naboka, O. I., Khouari, S., Glushchenko, A. V., Georgiyants, V. A. (2014). Antioxidation properties of extracts of aerial part of Bupleurum aureum, Hill-growing soltword herb, Fumaria Schleicheri and Cynara scolymus in vitro and in vivo Journal of Chemical and Pharmaceutical Research, 6 (7), 172–177.

13. Glushchenko, A., Vladymyrova, I., Georgiyants, V. (2018). The substantiation of the selection of medicinal plants and their rational application in diseases of the hepatobiliary system. ScienceRise: Pharmaceutical Science, 2 (12), 9–16. doi: http://doi.org/10.15587/2519-4852.2018.129642

14. Glushchenko, A. V., Puliaev, D. S., Georgiianc, V. A., Naboka, O. I. (2016). Sposob vvedeniia sukhogo ekstrakta volodushki zolotistoi v sirop «Loratadin». Vestnik farmacii, 4 (74), 6–9.

15. Korobko, D. B., Poliak, O. B., Lohoida, L. S., Zarivna, N. O., Semianiv, O. V. (2014). Rozrobka i validatsiia metodyk identyfikatsii loratadynu v tabletkakh. Aktualni pytannia farmatsevtychnoi i medychnoi nauky ta praktyky, 1 (14), 55–58.

16. Florin, A., Grigoriv, I. C., Ciobanu, C. (2016). Validation and Application of a RP-HPLC Method with UV Detection for Loratadine Determination. Revista de Chimie-Bucharest-Original Edition, 67 (6), 1227–1231.