ABSTRACT&REFERENCES

DOI: 10.15587/2519-4852.2018.128885

SCALING OF THE PROSPECTIVE ANTI-ULCER API SYNTHESIS

p. 4-8

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***Aim**: the scaling of the laboratory procedure for the synthesis of 5-(4-methylphenylaminomethyl-4-(2-methylphenyl)-1,2,4-triazole-4H-3-ylthioacetic acid 4-methoxyanilide (Triazoprazole) for reproduction in industrial conditions.*

***Methods.** In the development of industrial technology, the efficiency of synthesis (yields at each stage of synthesis, the possibility of carrying out synthesis without isolation of some intermediates), compliance with the principles of green chemistry, and economic feasibility were evaluated. In accordance with the concept of Quality by design, the principles of green chemistry and previously developed algorithms for optimizing industrial synthesis, the theoretical possibilities of synthesis in industrial conditions were analyzed. The optimal reaction conditions are determined experimentally.*

***Results.** As a result of the experimental studies, the possibility of the synthesis of the key intermediate, 5-methylphenylaminomethyl-4-(2-methylphenyl)-1,2,4-triazole-3-thione, without isolation of the intermediate product, has been shown to increase its yield in terms of starting materials. The time for carrying out individual stages of synthesis has been shortened, and the yield and purity of the products remain appropriate. For the alkylation of the key intermediate, the reaction temperature is chosen as the optimum conditions – 70 °C, the time is 1 hour, the use of the DMF-alkali system. Such conditions make it possible to ensure a high yield and purity of the final product.*

***Conclusions**: Scaling of the method of synthesis of a potential API with the antiulcer action of 5-(4-methylphenylaminomethyl-4-(2-methylphenyl)-1,2,4-triazole-4H-3-ylthioacetic acid 4-methoxyanilide for use in industrial production using Quality by design concept and "green chemistry" principles was carrying out, The number of stages of synthesis has been reduced and the conditions have been chosen in which the finished product is formed with the maximum yield and acceptable purity*

***Keywords:** active pharmaceutical ingredient, industrial synthesis, scaling, green chemistry, 1,2,4 triazole derivatives, antiulcer agents*

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DOI: 10.15587/2519-4852.2018.129642

THE SUBSTANTIATION OF THE SELECTION OF MEDICINAL PLANTS AND THEIR RATIONAL APPLICATION IN DISEASES OF THE HEPATOBILIARY SYSTEM

p. 9-16

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Aim of the work*. The aim of the work was to develop methodological approaches to justify the selection of medicinal plants and phytopreparations for diseases of the hepatobiliary system and to determine aspects of their rational use.*
Methods*. The studies were carried out by analyzing the scientific literature data and the results of our own experimental studies on determining the influence of groups of plant biologically active substances (BAS) on the links of the pathological process in diseases of the liver and bile ducts.*
Results*. Hepatoprotectors of plant origin are quite a large group of drugs and account for more than half of all hepatoprotectors available on the pharmaceutical market. Among the popular medicinal plants and preparations based on them (mono- and multicomponent), the silybum marianum, the artichoke, the fumarium officinalis, the main groups of active substances are flavonoids, hydroxycinnamic acids and alkaloids, respectively. However the spectrum of medicinal plants (and groups of biologically active substances) that is used to prevent and treat diseases of the hepatobiliary system is much broader. Therefore, the article substantiates the necessity of developing an algorithm for the selection of medicinal plants for the treatment of diseases of the hepatobiliary system, which is based on the definition of the main etiological and pathogenetic aspects of liver and biliary tract diseases, the peculiarities of the use of medicinal plants whose spectrum is determined by different groups of biologically active compounds.*
Conclusions*. Based on scientific data on the etiology, the main links of the pathological process and clinical and biochemical syndromes of diseases of the hepatobiliary system was presented the directions of treatment of these diseases with plant products. The necessity of development of methodological approaches to justify selection of medicinal plants and phytopreparations for diseases of the hepatobiliary system and to determine the aspects of their rational use is substantiated. The basic principles of the use of medicinal plants for diseases of the liver and bile ducts are formulated*
Keywords*: medicinal plants, selection methodology, rational use, hepatoprotective action, choleretic action*

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DOI: 10.15587/2519-4852.2018.127621

CURRENT STATE ASSESSMENT OF PHARMACEUTICAL CARE IMPLEMENTATION IN UKRAINE

p. 17-25

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At the modern stage of the pharmacy development, there were significant changes in the positioning of the pharmacist's role in the health care system. It has contributed to the development of pharmaceutical care (PC) and its implementation in Ukrainian pharmaceutical practice.

***The aim of the work** is to investigate and evaluate the current state of implementation of PC in common pharmacy of Ukraine, as well as identify the key issues in its practical implementation and possible ways to improve the national PC system.*

***Materials and methods:** for the estimation of PC quality a survey of pharmacists in 280 chemist shops in 10 regions of Ukraine was conducted. The evaluation of the survey results was carried out using statistical methods.*

***Research results.** It was established that most of the pharmacies serves 100–500 people per day, and 43 % of pharmacies keep track of regular visitors. The overall quality of PC in most cases (71 %) was unsatisfactory. The highest quality of PC was during the OTC-drugs selling (51 % – high, medium and low, 49 % – unsatisfactory), and the quality of the PC of prescription drugs and diagnostic services in most pharmacies was unsatisfactory. The assessment of the success of quality assurance factors implementation has shown that it is low or unsatisfactory. The continuous education assessment showed that in 71 % of pharmacies more than 50 % of pharmacists studied PC during graduation in the universities, but the proportion of cadres who studied PC in postgraduate education, is less than 50 %.*

***Conclusions.** The focus of the domestic PC system on the prevalence of care during the OTC-drugs selling and its practical absence in prescription drugs selling and the provision of diagnostic services is a significant obstacle to ensuring the overall PC quality. It has shown the need to develop new theoretical models and methodological approaches for the PC quality implementation*

***Keywords:** pharmaceutical care, medicines, over the counter medicines, continuous professional development, pharmaceutical service*

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DOI: 10.15587/2313-8416.2018.128867

ANALYSIS OF THE UKRAINIAN MARKET OF PARAPHARMACEUTICALS FOR PREVENTION OF KELOID SCARS

p. 25-31

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An analysis of the anti-keloid parapharmaceuticals (AKPF) market, for preventing the formation of keloid scar (KS) and providing the population with affordable drugs is an urgent issue at this time. Doctors have not yet identified the reasons for the formation of KS. The tendency to keloid formation was noted in such cases as: after surgical interventions, heredity, ethnic factors, immune pathologies, etc.

***Aim of the research** was to analyze the Ukrainian market of parapharmaceuticals (PF), which are used to prevent the formation of keloids.*

***Materials and methods.** Materials of the study were selected assortment of AKPF for the treatment of CS, which is present on the domestic market during 201–2017 by statistical, analytical and economic-mathematical methods of analysis.*

***Results of the research** show that PFs are used in prophylactic, physiotherapeutic, pharmacotherapeutic and pharmaceutical methods of treatment of KS and cosmetology procedures. The Ukrainian market of AKPF is represented exclusively by domestic producers ("Euro plus", PP "Ekobiz", TOV NVO "PhytoBiotechnology", a group of companies "Elfa", etc.). The suad of PF most often includes heparin, onion extract, D-panthenol. The presence of funds of the same composition is noted, but some are in market as drug and others – as PF. For consumers in the annotations on AKPF it is advisable to clearly recommend them to use PH only for the purpose of the first pre-care and prevention of the formation of keloids.*

***Conclusions** indicate that the highest proportion of AKPF (42.9 %) is presented in the form of a gel. In the analysis of AKPF price indexes for 2015–2017, it was established that the indicator of the liquidity ratio is within the range of 0.133–0.433. All domestic AKPFs have a high coefficient of solvency adequacy in 2015–2017. For 2015–2016, all calculated values of the availability of the analyzed goods are equal to or greater than one (D≥1). But in 2017 the value of the analyzed indicator is less than one, which is the result of an unstable situation in the pharmaceutical market of the country*

***Keywords:** keloids, parapharmaceuticals, analysis of the parapharmaceutical market, prevention of the formation of keloids, price affordability of parapharmaceuticals*

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DOI: 10.15587/2519-4852.2018.129599

METHODOLOGICAL APPROACHES TO THE SEARCH OF NEW HERBAL ANTICONVULSANTS

p. 32-36

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Aim. *Development of the most appropriate algorithm for the search and selection of herbs showing anticonvulsant properties, as well as to interpret the level of anticonvulsant activity of different groups of herbal substances using PASS tool.*

Methods. *Literature analysis and PASS software were used for development of a clear algorithm for finding the most suitable herbs having anticonvulsant activity.*

Results. *The most rational decision in case of development of the algorithms for the targeted search of herbs for epilepsy treatment is to divide herbal objects according to their chemical composition and mechanism of action. It was found that certain groups of biologically active compounds (alkaloids, flavonoids, phenolic acids) and some members of the Betulaceae, Papaveraceae, Solanaceae, Fumariaceae, Lamiaceae, Polemoniaceae, Viscaceae, and Oleaceae families have anticonvulsant activity. PASS analysis resulted that antiepileptic activity is inherent, but not significant for most of the studied compounds. Particular expectations caused the analysis of the results of alkaloids protopine and sanguinarine due to their high indexes of activity – 0.813 and 0.820 %, respectively.*

Conclusion. *The algorithm for selection of the most promising herbs for the further detailed phytochemical and pharmacological studies concerning possibilities of their use for treatment of epilepsy was substantiated. PASS prediction analysis for different groups of herbal substances was carried out. As expected, according to the PASS prediction results, antiepileptic activity is inherent, but not significant for most of the studied compounds. The analyzed compounds have the likelihood of manifestation of antiepileptic activity: the indexes of activity of the analyzed substances are in range from 0.430 to 0.754 %. Several biologically active compounds may have neuroprotector activity; the highest indexes were obtained for histidine (0.680 %) and alanine (0.718 %). Amino acids asparagine and serine have shown probable presence of cognition activator activity (0.489 % and 0.554 %, respectively)*

Keywords: *antiepileptic activity, herbs, herbal substances, algorithm, PASS tool, index of activity*

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DOI: 10.15587/2519-4852.2018.128730

STUDYING THE INFLUENCE OF THE NATURAL ZEOLITE TABLETS MANUFACTURING TECHNOLOGY ON SORBTION KINETIC OF LONG-LIVING ^{90}Sr AND ^{137}Cs RADIONUCLIDES AND Pb^{2+} AND Hg^{2+} HEAVY METALS FROM WATER SOLUTION IN VITRO

p. 37-42

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Aim: *To study the influence of the technology on the adsorption activity of natural zeolite tablets (clinoptilolite) in relation to long-lived ^{90}Sr and ^{137}Cs radionuclides and Pb^{2+} and Hg^{2+} heavy metals from an aqueous solution in vitro.*

Methods: *Tablets were prepared by direct pressing and pressing with pre-wet granulation (a moisturizer – 7 % starch paste). Sorption capacity of enterosorbents was investigated by the method of static sorption at pH=2–8 at a temperature of 37 °C. The concentration of lead in solutions was determined by atomic absorption spectroscopy at the atomic absorption spectrophotometer C-115 PCS. The concentration of mercury was determined by the method of flameless atomization with the help of the mercury device PR-115. The content of radionuclides was determined by the radioactivity of the samples using a radiometer α-β-automaton NRR-610 "Tesla".*

Results: *Based on the results of the conducted studies, the adsorption activity of the model specimens of enterosorbents on the basis of natural zeolite in the form of tablets obtained by the technology of direct pressing and pressing with pre-wet granulation, was studied. It has been found that the sorption properties of samples relative to heavy metals and radionuclides depend to a greater extent on the acidity of the solution than on the technology of obtaining tablets. It was found that the process of ion exchange on experimental samples consists of two stages - fast and slow. This fact is explained by the adsorption of ions, primarily within the macro- and mesopor, on the material's surface, and the subsequent reduction of the velocity by diffusion of ions within the microporous space, and the last stage is limiting in the process of adsorption. Comparison of the obtained data on the sorption-selective properties of samples allowed to arrange the investigated ions in order of decreasing their interaction with sorbents $Pb^{2+}>Hg^{2+}>^{137}Cs>^{90}Sr$.*

Conclusions: *It is proved that the technology of obtaining tablets does not significantly affect the activity of the drug in vitro. The results of experimental studies will be used in the further development of the composition and technology of tablets containing natural zeolite (clinoptilolite) as the main active ingredient*

Keywords: *natural zeolite, tablets, direct compression, wet granulation, heavy metals, radionuclides, adsorption*

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DOI: 10.15587/2519-4852.2018.128046

INVESTIGATION OF THE EFFECTS OF EXCIPIENTS ON TECHNOLOGICAL PROPERTIES TABLETS OF PYROLA ROTUNDIFOLIA EXTRACT

p. 43-48

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Aim of the work. *To study the influence of excipients on the pharmacological and technological properties of round-leaved wintergreen extract tablets.*

Methods. *The subject of the study were 27 series of round-leaved wintergreen extract tablets. The study of the influence of excipients on the pharmacological and technological properties of tablets, namely: abrasion, strength, disintegration, homogeneity were carried out in accordance with the requirements of SPhU 2 edition. The appearance of tablets of round-leaved wintergreen extract was estimated on a five-point scale.*

Results. *The effect of 27 excipients on the pharmaco-technological indicators of the quality of tablets was studied during the creation of tablets by the method of direct compression. The experiments were done using the mathematical planning of the experiment – the Graeco-Latin square of the 2nd order.*

The results of the dispersion analysis of experimental data showed that the highest estimation of the appearance obtained tablets with neusilin US 2, vivapur 102, vivapur 112, pearlitol 100SD-mannitol. The best value for homogeneity of dosage of tablets with round-leaved wintergreen extract was obtained using potato starch, calcium anhydrous hydrogen phosphate, vivapur 302, pearlitol 300 DC-mannitol.

The fastest breakdown tablets were round-leaved wintergreen extract with neusilin US 2, magnesium stearate, sodium croscarmellose, flovelaks, vivapur 200, MCC burst, vivapur 302.

The greatest value of the strength of tablets with round-leaved wintergreen extract was obtained with sodium croscarmellose, tabletose 80, and procolv SMCC 90.

Lowest erosion of tablets with round-leaved wintergreen extract provide neusilin US 2, calcium stearate, sodium croscarmellose, procolv EASYtab SP, tabletose 80.

The generalized function of desirability allowed to select the optimal levels of factors (excipients) for each group of factors: neusilin US 2, magnesium stearate, sodium croscarmellose, procolv EASYtab SP, flovelaks.

Conclusions. *With the help of the Graeco-Latin square of the 2nd order, the influence of the 27th excipients on the pharmaco-technological properties of the tablets (appearance, homogeneity of dosage, disintegration, strength and erosion) and the generalized index – the function of desirability were studied. The experimental results allowed to select optimal excipients for further technological research*

Keywords: *round-leaved wintergreen, tablets, mathematical planning of the experiment, plant extracts, pharmacological and technological properties of the tablets*

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DOI: 10.15587/2519-4852.2018.129694

COMPARATIVE ANALYSIS OF THE NEPHROPROTECTIVE ACTION OF ADEMETIONINE AND GLUTATHIONE IN ISCHEMIA-REPERFUSION ACUTE KIDNEY INJURY

p. 49-55

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Despite significant advances in drug therapy and improvements in renal replacement therapy, mortality rate of acute kidney injury (AKI) continuously increases and is about 25–70 %. Ischemia-reperfusion AKI is not an exception with its multifactorial pathogenesis and rapid progressive development, usually resulting from trauma, sepsis, kidney transplantation, or an influence of toxic substances. For this reason, drugs with potent cytoprotective and antioxidant activity – ademetionine and glutathione have drawn our attention as remedies for the pathogenetic correction of ischemia-reperfusion AKI.

***Aim**. To compare the influence of ademetionine and glutathione on the functional state and antioxidant balance in kidneys of rats with ischemia-reperfusion AKI.*

***Methods**. Research was conducted on 28 mature non-linear white rats weighting 130–180 g, randomly divided into 4 groups (n=7): I group – control (pseudo-operated animals), II group – modeling of ischemia-reperfusion kidney injury (I/R), III group – administration of ademetionine (Heptral, "Abbott SpA", Italy) at a dose of 20 mg/kg prior to I/R modeling, animals of IV group were daily injected with glutathione (TAD 600, "Biomedica Foscama", Italy) at a dose of 30 mg/kg, V group –administration of mexidol (Mexidol,"Farmasoft", RF) at a dose of 100 mg/kg prior to I/R modeling. Functional state and histological changes in kidneys was estimated after 24 hours of reperfusion by the indices of diuresis, GFR, urine protein excretion, excretion of sodium and potassium ions with urine. Peroxidation processes in kidneys were evaluated by the malone dialdehyde and oxidative modification of proteins levels, antioxidant defense – by catalase and glutathione peroxidase activity. Histological examination was conducted by hematoxylin and eosin staining of kidney tissue sections.*

***Results**. It was established the use of studied drugs in I/R AKI ameliorated excretory kidney function of rats, which was realized in an increase in GFR and diuresis with simultaneous decrease in azotemia and proteinuria. It was accompanied by a restoration of ion-regulatory kidney function, confirmed by an increase in sodium reabsorption with recovery of proximal and distal tubular transport. Analysis of antioxidant system shows an inhibition of lipid peroxidation processes on the background of antioxidant system activation with significantly better effect of glutathione, which was confirmed by the histological study.*

***Conclusion.** As it is shown, both ademetionine and glutathione exhibit nephroprotective effect in rats with ischemia-reperfusion acute kidney injury. At the same time, effect of glutathione administration significantly exceeds that of ademetionine by the restoration of the functional state of nephrons as well as the effect on the prooxidant – antioxidant balance in renal tissue, which is confirmed by the histological study. Obtained results give a background for the further research of nephroprotective potential of the ademetionine and glutathione in conditions of AKI of different etiology.*

***Keywords:** nephroprotective effect, ademetionine, glutathione, ischemia-reperfusion, acute kidney injury*

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DOI: 10.15587/2519-4852.2018.129813

THE ANALYSIS OF THE SALE OF ANTIHYPERTENSIVE DRUGS IN THE PHARMACIES OF KYIV

p. 56-58

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Aim. *Antihypertensive drugs (AHD) belong to the category of the most commonly used drugs in the pharmaceutical market of Ukraine. This is due to the significant prevalence of arterial hypertension (AH) in many countries of the world, including Ukraine. The purpose of this research is to develop a new approach to optimizing the pharmacotherapy of cardiovascular diseases in the framework of pharmaceutical care based on comprehensive clinical and economic assessments of the use of antihypertensive drugs of various clinical and pharmacological groups, conducted from the positions of pharmacy institutions and outpatient hospitals, taking into account the economic interests of patients.*

Materials and methods. *The research was taken retrospectively in 100 commercial pharmacies in the city of Kyiv (daily visitors – 400–500). Analysis of the AHD assortment, which was presented in it in 2017, was carried out with the help of appropriate documentation of pharmacies. To assess the range of AHD on the domestic pharmaceutical market, the data of the "Medicines" information system of Morion Company were used (as of October 2017).*

Results. *During the year, antihypertensive drugs were presented in pharmacies in a fairly wide assortment, mainly foreign products – 175 trade names (TN), 43 international non-proprietary names (INNs). In general, almost half of INNs (56.58 %) and 1/4 part of TN (28.78 %) were presented in pharmacies of the total amount of AHD in the pharmaceutical market of Ukraine. According to the results of the frequency analysis, the same AHD was in high demand by the population in pharmacies during the year but these drugs were differed in rating. These preparations make 21.41 % of all sold packages of AHD in pharmacies – 19.67 %. Only two drugs among the drug-leaders were foreign-made, others were domestic drugs. They had a relatively low packing cost – up to 10.00 UAH. Consequently, the price factor was often decisive in choosing AHD visitors to pharmacies. Preparations of the first and second line of therapy, as well as combined AHD, are the drugs which were often bought by patients in pharmacies. Interestingly, all preparations of the first line of hypertension are representatives of ACE inhibitors (3 TN Enalapril and 1 TN of Captopril). In addition, the combined AHD Captopress-D also contains an ACE inhibitor Captopril. Preparations of this group have proved well in clinical practice, they can be used at any stage of hypertension, they improve the quality of life of patients and the prognosis of the disease, and the combination «ACE inhibitor + Thiazide diuretic» (among the leading drugs – the drug Captopress-D) is recognized as one of the most effective and appropriate for the appointment of combined antihypertensive therapy. Therefore, doctors often prescribe this pharmacological group to patients with AH. However, the high demand for them among drugstore visitors is likely related to their low cost.*

Conclusion. *Acquiring most AHDs by patients in pharmacies was appropriate and necessary for the treatment of hypertension, because 94 % of TN AHDs from the range of the pharmacy were available in the State form of Ukraine (they had an index "V" based on the results of the VEN-analysis) in 2017*

Keywords: *antihypertensive drugs, ABC- and VEN-analysis, arterial hypertension, cardiovascular diseases, combination*

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