ABSTRACT&REFERENCES

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RESEARCH OF THE CONCEPTUAL PRINCIPLES OF PHARMACEUTICAL INDUSTRY SUSTAINABLE DEVELOPMENT FORMATION

p. 4-9

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The analysis of the current state of the pharmaceutical industry of the country indicates its poor ability to meet the requirements in medicines for people by criteria defined by the National Drug (Pharmaceutical) Policy: accessibility, quality and rational use of medicines, and consequently – the inability to provide the nation's health potential and work ability. In this context, there is a necessity for more balanced and focused strategic development of the branch, in particular – based on the sustainable development paradigm.

Aim. *The aim of research was to define the concept of the sustainable development and its importance for pharmaceutical industry of Ukraine.*

Methods. *System approach, the historical method, comparison and synthesis were used in the study.*

Results. *Review of the main approaches to the interpretation of the concepts of "development", "movement", "sustainability", and their correlation was carried out. It was determined that the sustainable development provides balance, quality change, expansion and potential opportunities realization. The necessity of Ukrainian pharmaceutical industry development as part of sustainable development philosophy and concept was substantiated.*

Conclusion. *Determination of the sustainable development in pharmacy, in which, based on the general stability principles, the National Drug Policy strategic objectives and common mechanism to ensure such development were considered, was displayed*

Keywords: *pharmaceutical industry, development, sustainable development in pharmacy, the National Drug (Pharmaceutical) Policy*

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THE ANALYSIS OF SUCCINATE DEHYDROGENASE AND LACTATE DEHYDROGENASE ACTIVITY IN ACUTE AND CHRONIC HYPOXIA ON THE BACKGROUND OF 2-BENZAMIDO-2-(2-OXOINDOLIN-3-ILIDEN) ACETIC ACID DERIVATIVE ADMINISTRATION

p. 9-13

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Aim. *To study the influence of 2-benzamido-2-(2-oxoindolin-3-iliden) acetic acid derivative ZNM on succinate dehydrogenase and lactate dehydrogenase activity biochemical markers of energy metabolism and hypoxia in the rats' brain under acute hypobaric hypoxia (AHH) and normobaric hypercapnic hypoxia (NHH), as well as chronic hypobaric hypoxia (CHH).*

Materials and methods. *80 white nonlinear mature male rats 180–200 g in weight were used for research. AHH was modeled using flowing altitude chamber by stimulation the effect of 12000 m altitude "ascending" in rats. The rats were kept at the "high-altitude plateau" till the moment of the second agonal inspiration, then the "descent" to the previous zero height was performed.*

NHH was reproduced by placing the rats into a sealed chamber, 1000 ml capacity, and then duration of stay of the rats in a closed chamber from the moment of container closing till the second agonal inspiration was estimated.

CHH was modeled in the flowing altitude chamber by stimulation the effect of 4000 m altitude above sea "ascending" in rats. The animals were kept at this "height" during 2 hours every day within 4 weeks; hypoxia sessions were carried out before midday.

The studied substances were administered intraperitoneally 35 minutes before hypoxia modeling. The studied substance ZNM was administered in the dose of 15 mg/kg as water suspension, stabilized with Polysorbate 80. The reference drug Mexidol was administered in the dose of 100 mg/kg. The intact animals took an equivalent amount of water for injection with Polysorbate 80. The group of animals with stimulated CHH was treated by the remedies after 14th day of hypoxia modeling.

Results. *The activity of succinate dehydrogenase after ZNM administration, depending on the hypoxia type, significantly increased in the AHH group in 2.6 times, and in the NHH group – in 1.6 times comparing to the model pathology group. After Mexidol administration, the activity markers raised in the AHH group in 2.9 times, NHH – 1.7 times, CHH – in 1.3 times.*

At the same time, the activity of lactate dehydrogenase after ZNM and Mexidol administration decreased in the AHH group in 1.5 times, NHH – in 1.3 times (in 1.5 times after Mexidol administration). Under CHH conditions, the activity of lactate dehydrogenase after Mexidol administration stayed unchanged, and after ZNM administration it slightly but statistically significantly decreased by 7.5 % compared to the model pathology indexes.

Conclusion. *ZNM substance and the reference drug Mexidol normalize activity of succinate dehydrogenase and lactate dehydrogenase, which indicates the improvement of energy metabolism of cells in acute and chronic hypoxia*

Keywords: *antihypoxants, succinate dehydrogenase, lactate dehydrogenase, hypoxia, 2-benzamido-2-(2-oxoindolin-3-iliden) acetic acid derivatives, Mexidol*

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DETERMINATION OF AGOMELATINE IN URINE IN THE PRESENCE OF METABOLITES BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY (GC-MS)

p. 14-21

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Aim. *Development and validation of the method for quantitative determination of agomelatine in urine in the presence of its metabolites using GC-MS.*

Methods. *Chloroform was used to extract agomelatine from the urine samples, after sedimentation of uric acids by Calcium chloride. Identification and assay of the extracted agomelatine was carried out using Agilent 6890 N chromatograph with 5978 BMSD (Agilent technologies, USA) mass spectroscopy detector. Restek Rtx-5 (USA) column with 5 % phenyl methyl siloxane (30m×0.25mm;0.25μm) was used for separation of the components. Carrier gas was helium. Mass detection was performed during 70 eV electronic ionization and 400 V voltages. Scanning was carried out in Scan mode within 50–550 u.*

Results. *The developed method for agomelatine determination was validated in agomelatine linear concentration range 40–6000 ng/ml with the correlation coefficient 0.99975. The method is correct and reproducible by all parameters in the linear range of concentrations according to OECD/WHO GLP requirements, and FDA, EMA and Ministry of Health of Ukraine recommendations.*

Conclusion. *15 ng of agomelatine can be identified in 1 ml of urine, and 40 ng of it can be quantified by the displayed method. The total content of the detected metabolites on agomelatine concentration was approximately 35.0 %. The developed method is characterized by implementation simplicity, accuracy and reproducibility, and it can be used for chemical and toxicological analysis of agomelatine*

Keywords: *agomelatine, urine, antidepressant, identification, quantitative determination, extraction, metabolite, GC/MS, reference solution, validation*

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CHROMATOGRAPHY-MASS SPECTROMETRY STUDY OF LOW MOLECULAR ALIPHATIC, FATTY AND AROMATIC ACIDS OF *VERONICA TEUCRIUM* L. RHIZOMES

p. 22-25

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The aim *of our research was to identify and quantify of aliphatic, aromatic and fatty acids of Veronica teucrium L. rhizomes by the gas chromatography/mass spectrometric method.*

Methods. *The object of study was V. teucrium L. rhizomes, collected in 2015 in Kharkiv region. The analysis of acid's methyl esters was performed using chromatography-mass spectrometer 5973N/6890N MSD/DS Agilent Technologies.*

The injection of sample in chromatographic capillary column INNOWAX (0.25 mm × 30 m) was performed by a splitless mode. The identification of acid's methyl esters were performed by calculating of the equivalent length of the aliphatic chain (ECL); using data from the mass spectra libraries NIST 05 and Willey 2007 in conjunction with programs for identifying – AMDIS and NIST; also retention time of esters was compared with the retention time of standard compounds (Sigma). Internal standard method was used for quantitative calculations.

Results of the Research. *By means of gas chromatography/mass spectrometric method the reseach of carboxylic acids of V. teucrium L. rhizomes have been studied for first time, and in the result of the study 10 aliphatic, 16 fatty and 9 aromatic acids had been identified and quantified. The total content of identified carboxylic acids of V. teucrium L. rhizomes was 3068.06 mg/% (3.07 %). Among low molecular aliphatic acids malic, citric and levulinic; among fatty acids – saturated: myristic, palmitic and tetracosanoic, and unsaturated: oleic, linoleic and linolenic are dominant. The particular importance have identified aromatic acids – benzoic; phenolcarbonic: vanillic, veratrylic, p-hydroxybenzoic, gentisic, syringic and hydroxycinnamic: p-coumaric.*

Conclusions. *In the first time in V. teucrium L. rhizomes 10 low molecular aliphatic acids, 16 fatty acids and 9 aromatic acids had been identified and quantified by using gas chromatography/mass spectrometric method*

Keywords: *Veronica teucrium L., aliphatic acids, fatty acids, aromatic acids, gas chromatography/mass spectrometric method*

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DETERMINATION OF SERTINDOLE IN BIOLOGICAL MATERIAL BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY

p. 26-32

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The treatment by the new generation antipsychotic remedy Sertindole is often accompanied by QT interval prolongation accompanied and neuroleptic malignant syndrome, which often leads to fatal consequences, in case of its overdose or mixing with some other drugs. In most cases, the anatomical pathology analysis results do not give any sudden death explanation.

Aim. *Identification and quantitative determination of Sertindole using Gas Chromatography – Mass spectroscopy method in samples obtained after purification of the extracts from the biological material (liver) by solid-phase extraction.*

Methods. *Sertindole was isolated from the biological material by the mixture of Acetonitrile – Perchloric acid 70 % (1:1) with the following liquid extraction by 1,2-Dichloroethane (pH 11). The extracts after purification using the SPE Oasis HLB 30 mg (Waters, USA) cartridges were eluted by Ethanol 96 %, evaporated to dryness under Nitrogen flow, and then the residues were dissolved in 250 µl of Methanol.*

Identification and assay of Sertindole in the solutions and the model samples were carried out using Agilent 6890N chromatograph equipped by 5978B Mass detector (Agilent Technology, USA), RTX-5 column was used, 30 m×0,25 mm, 0,25 µm (Restek, USA). Temperature gradient: 50 °C (0,5 min), 25 °C/min till 150 °C, and then the temperature rise was 10 °C/min until 320 °C was reached. Isothermal mode was set at 320 °C (30 min). Injector temperature was 270 °C. Helium was used as a carrier gas (3 ml/min). Mass detection was performed at 70 eV electronic ionization and 400V voltage.

Results. *At the offered conditions of the analysis Sertindole retention time was 27.79±0.05 min (RSD 0,17 %). The method is characterized by linearity within 50–200 µg/ml. It was found that Sertindole detection limit without prior derivatization in SCAN mode is 25 µg/ml. In the model samples of liver tissues Sertindole was identified and quantitatively determined. The drug detection limit in the biological material is 2 µg/g.*

Conclusion. *Chromatographic conditions with Mass-selective detector (GC/MS) for Sertindole analysis were developed for the first time. The basic patterns of primary Sertindole fragmentation were shown. The scheme of chemical and toxicological analysis of the biological material to determine Sertindole by GC/MS method was offered. The developed method for Sertindole determination can be used in departments of forensic toxicology bureau*

Keywords: *Sertindole, schizophrenia, isolation, Acetonitrile, solid-phase extraction, liver, Gas Chromatography, Mass spectrometer*

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DEVELOPMENT OF TECHNOLOGY OF THE SOFT MEDICINAL FORM BASED ON THE EXTRACT OF COMMON HAZEL LEAVES

p. 32-37

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Vascular diseases occupy an important place in the morbidity structure of the population of Azerbaijan. Varicose veins is the most spread pathology among them; it affects between 25 % and 50 % of the adult population of the country.
*The **aim** of the study was development of technology of the ointment containing Hazel thick extract.*
***Methods.** Physical and chemical methods were used for dispersion, density, emulsification rate, spreadability, and emulsion concentration determination.*
***Results.** The emulsifier concentration of 10% was selected in result of physical and chemical analysis. The oil phase dispersion degree depending on the № 1 emulsifier amount was shown using microscopy method. Thermal and colloidal stability of the ointment samples, as well as their spreadability was determined. It was found that the samples 3 and 4 are characterized by satisfactory spreadability indexes – 350 mm², that is significantly differs from the samples № 1 (1005 mm²) and № 2 (852 mm²). Decrease in the emulsifier concentration below 10 % leads to the emulsion instability. On the basis of the research results, rational emulsification conditions were selected. According to the microscopy analysis data and calculation of the emulsion concentration mixing time interval at 1500 rpm was investigated.*
***Conclusion.** The given research allowed developing of the composition and technology of the ointment containing common Hazel extract*
***Keywords:** Hazel extract, composition, technology, emulsion, ointment, emulsification, dispersion degree, stability, physical and chemical methods*

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THE STUDY OF STEROIDAL COMPOUNDS IN CANNA PLANT MATERIAL

p. 38-41

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Aim. *Identification and quantitative determination of steroidal compounds in Canna roots, rhizomes, leaves and flowers.*
Methods*. Identification and quantitative determination of steroidal compounds in Canna herbal material was carried out by Gas chromatography – Mass spectrometry method (GC/MS).*
Results. *In result of the study, 15 steroidal compounds were identified in Canna roots, 11 compounds – in rhizomes, 12 – in leaves, and 3 – in flowers. β-sitosterol, campesterol, and stigmasterol dominated quantitavely in all studied samples.*
The content of steroidal compounds in Canna was: 138.6 mg/kg in leaves, 130.5 mg/kg in roots, 126.7 mg/kg in rhizomes, and 37.01 mg/kg in flowers.
During the research work it was found that β-sitosterol was dominating compound by its quantitative content in all types of Canna plant material. Its content was 60.2 mg/kg in rhizomes, 57.0 mg/kg in roots, 47.0 mg/kg in leaves, and 31.52 mg/kg in flowers.
Conclusion*. The obtained results can be used for development of the methods for Canna quality control, as well as for obtaining biologically active substances from the herbal material*
Keywords: *Canna lily, roots, rhizomes, leaves, flowers, steroidal compounds, Gas chromatography – Mass spectrometry*

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DEVELOPMENT OF COMBINED COMPOSITION PESSARIES FOR GENITAL HERPES TREATMENT

p. 42-47

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Recently, the problem of therapy, as well as creation of effective remedies applied for genital herpes (GH) treatment is relevant for modern gynecology and pharmacy.
Aim*. Development of the combined composition pessaries containing Acyclovir and Tea tree and Thyme essential oils, together with confirmation of their pharmacological activity: antiviral and antibacterial.*
Methods*. The analysis of the assortment of drugs for GH treatment was carried out on the basis of the materials of the State Register of Medicinal Products of Ukraine and the Compendium. The pessaries disintegration and homogeneity was performed in accordance with the SPhU 2.0 requirements. Absorption spectroscopy method at wavelength (265±2) nm was used for determination of Acyclovir concentration in the solutions during release. Study of the antiviral activity of both Acyclovir, and Tea tree and Thyme essential oils, as well as the pessaries containing Acyclovir and the essential oils, was carried out on the base of the National Academy of Medical Sciences of Ukraine, in the State Institution «Institute of Epidemiology and Infectious Diseases named after L. V. Gromashevsky» (Kyiv), in the laboratory of viral infections experimental chemotherapy. The analysis of the antibacterial properties of the studied samples was carried out on the base of the State Institution «Mechnikov Institute of Microbiology and Immunology».*
Results*. In GH therapy, Acyclovir is the most prescribed and safe anti-viral drug. In result of research it was proved that the developed remedy in pessaries form containing Acyclovir, and Tea tree and Thyme essential oils inhibits type 2 herpevirus reproduction and is effective preventive drug on the experimental model of genital herpes infection in guinea pigs.*
Conclusion. *Combined remedies containing Acyclovir and herbal substances and showing anti-viral activity are absent on Ukrainian market. Considering the fact that pessaries have a number of advantages over the other dosage forms, development of the new remedies containing Acyclovir and Tea tree and Thyme essential oils is a promising direction for modern medicine and pharmacy*

Keywords: *composition, pessaries, Acyclovir, essential oils, herpeviral infection, Genital form*

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PREDICTION OF THE COMPETITIVENESS DYNAMICS OF PHARMACY CHAINS

p. 47-52

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In market economy, one of the main tasks of any enterprise (organization) is to defeat rival competitors. It should not be single or random victory, but it should be natural result of effective management of this process.

Aim *of the present study was development of the methodical approaches for the pharmacy networks competitiveness dynamics modelling under volatile market situation conditions.*

Methods. *Multivariate correspondence analysis method was used for research.*

Results. *53 indexes influencing on the resulting indicator level were analyzed initially for prediction of the pharmacy networks competitiveness dynamic. Using a multiple correspondence analysis, a mathematical model was developed; the model allows predicting the pharmacy networks competitiveness dynamics on the basis of the "competitiveness index" calculation – a numeric index taking positive values in case of increasing competitiveness and negative ones – in case of the absence of its positive dynamics.*

Conclusion. *Methodical approaches to the pharmacy networks competitiveness prediction that allow making management decisions aimed at negative external influences resisting and leadership achieving according to the organization's strategic goals were offered*

Keywords: *prediction, competitiveness dynamics, pharmacy networks*

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EXPERIMENTAL STUDY OF STATE OF GASTRIC MUCOSA IN RATS UNDER INTRODUCTION OF NEW DERIVATE OF 4-[4-OXO-4H-QUINAZOLINE-3-YL] BENZOIC ACID (PC-66)

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Screening studies have revealed that the new derivate of 4-[4-oxo-4H-quinazoline-3-yl] benzoic acid (compound PC-66) possess significant antinociceptive and weakly expressed anti-inflammatory and antipyretic activity on different models of pain and inflammation. The condition of gastric defense under influence of PC-66 is unknown.

The aim *of this study was to explore the ability of PC-66 in comparison with diclophenac sodium produce gastric lesions on intact and rats with adjuvant arthritis, and to determine the role of influence on prostaglandin-H-synthase and stable metabolits of nitric oxide in the pathogenesis of these damages.*

Materials and methods: *The impact of PC-66 compound and a diclofenac sodium was explored on macroscopic changes in gastric mucosa under conditions of long-term administration and of experimental inflammation.*

The spectrophotometric method revealed active prostaglandin-endoperoxide synthase in the rats` GM homogenates against accumulation of oxidized form of adrenaline electron donor. The total content of nitrites and nitrates was determined by reaction with Griess reagent after preliminary restoration of nitrates with a suspension of zinc dust in ammonia solution.

Results and Discussion. *PC-66 compound, unlike the reference medicine, did not cause significant gastric lesions under conditions of its long-term administration to intact rats. We found that during diclofenac administration, the activity of PGH-synthetase in GM significantly decreased compared to the control, whilst under the influence of PC-66, the activity of this enzyme remained practically unchanged. Administration of PC-66 compound to rats, unlike diclofenac, was associated with a significant increase of stable NO metabolites in GM, whilst this index decreased compared to control under the influence of investigational NSAID.*

Conclusions: *4- [4-oxo-4H-quinazoline-3-yl] benzoic acid has no damaging effect on the gastric mucosa both in intact animals and in rats with experimental inflammation. The basis of its GM safety rests on lacking inhibitory effect on production of vasodilator molecules in GM of PC-66 compound, unlike diclofenac sodium*

Keywords: *4- [4-oxo-4H-quinazoline-3-yl] benzoic acid, gastrotoxicity, PGH – synthetase, NO metabolites*

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