ABSTRACT&REFERENCES

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ELEMENTS OF STANDARDIZATION AND QUALITY CONTROL OF LABORATORY BATCHES OF PERITONEAL DIALYSIS SOLUTIONS CONTAINING DEXTROSE AND SODIUM LACTATE

p. 4–12

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Aim. *The aim of our work was to develop the analytical support for pharmaceutical development for laboratory batches of solutions for peritoneal dialysis containing dextrose and sodium lactate.*

Methods. *We used the following research methods: direct argentometric (determination of chloride ions), complexonometric (determination of the amount of calcium and magnesium ions), criometric (determination of osmolality and osmolarity), potentiometric methods, weighting, statistical methods and data processing of chemical experiments.*

Results. *Firstly in Ukraine the results of standardization and the analytical support for pharmaceutical development for laboratory batches of solutions for peritoneal dialysis are presented in the article.*

Conclusions. *Two procedures of quantitative determination of chloride-ions and complexonometric method of assay of the amount of calcium and magnesium ions are developed. These procedures are the basis for the quantitative determination of sodium chloride by calculation method and quantitative determination of magnesium ions by calculation method provided quantitative determination of calcium ions. The procedure of determination of the actual osmolality and osmolarity is established, acceptability criteria for osmolality and osmolarity for the solutions, which are investigated, are developed, the dependence between osmolality and osmolarity is established. The procedures of rapid quantitative determination of chlorides make it possible to assess the contribution of the stabilizer in total chloride content of solutions for peritoneal dialysis*

Keywords: *solutions for peritoneal dialysis, pharmaceutical development, standardization, argentometric method, potentiometric method, complexometric titration, osmolarity, osmolality, calcium ions, magnesium ions*

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INFLUENCE OF PEACH LEAF EXTRACT ON THE METABOLIC PROCESSES AND PROOXIDANT/ANTIOXIDANT BALANCE IN RATS IN CONDITIONS OF CHRONIC IMMOBILIZATION STRESS

p. 13–16

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The aim *– research of stressprotective action of thick extract of peach ordinary (Persica vulgaris) leaves (TEPL) on the impact on metabolism, antioxidant system and lipid peroxidation in conditions of chronic stress.*

Materials and methods. *Chronic stress was caused daily four hour immobilization of rats in tight boxes for 18 days. TEPL in a dose 100 mg/kg and reference drug syrup "Imunoton" in a dose of 15 ml/kg was administered before 5 days to the experiment and every day for 40 minutes before stress exposure. After 18 days lipid metabolism: level of triglycerides (TG) and total cholesterol in serum; carbohydrate metabolism: level of glucose in blood serum and liver glycogen were determined. State of the system lipid peroxidation / antioxidant protection (LPO / AOP) was assessed by the level of thiobarbituric acid reagents (TBA-Rs), reduced glutathione (SH) and catalase activity, cytolytic processes was assessed by the level of ALT in blood serum.*

Results. *TEPL and reference drug "Imunoton" in comparison with a group of untreated animals reduced levels of triglyceride respectively 1.7 and 2.1 times ($p<0.05$) and cholesterol 1.5 ($p<0.05$) and 1.2 times ($p> 0.05$) and levels of glucose in the blood serum respectively 1.5 and 1.4 times ($p<0.05$) and liver glycogen respectively 3.2 and 2.6 times ($p<0.05$), the marker of cytolysis ALT respectively 1.2 times ($p<0.05$) and increased the level of the antioxidant enzyme catalase respectively 2.3 and 1.6 times ($p<0.05$).*

Conclusions. *Stressprotective effect of TEPL was expressed in normalization of hyperlipidemia, preservation of constancy in carbohydrate metabolism, cytolytic processes inhibition, antioxidant protection enhancing. Unlike TEPL reference drug "Imunoton" containing extracts of Eleutherococcus, St. John's wort, Echinacea and has adaptogenic, immunostimulative action did not show significant effect on high level of cholesterol. Antioxidant action of TEPL exceeded the effect of the drug "Imunoton"*

Keywords: *thick extract, peach ordinary (Persica vulgaris), immobilization stress, metabolism, stressprotective effect*

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REPARATIVE PROPERTIES OF NEW COMBINED CREAM ON THE MODEL OF THERMAL SKIN LESIONS IN RATS

p. 16–21

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*The **aim** of research was to study reparative properties of new combined cream on the model of thermal skin lesions in rats.*
***Methods.** Reparative properties of the new combined remedy in the form of cream with code name "Dermalipoin" for treatment of skin inflammations and microbial diseases were studied on the model of thermal skin lesions in rats. α-lipoic acid, urea, olive oil, tea tree oil, and PEG-400 were included in the ointment. Treatment efficiency was evaluated using planimetric indicators, which provided definition: burn area, epithelialisation period, and the number of animals with wounds that healed at different times, and healing factor compared to Methyluracil ointment and Titriol gel. Morphological studies were also carried out. Connective tissue condition and collagen formation in the healing process were estimated using Van Gieson's and Mallory's staining methods. Collagen fibers of connective tissue were painted in red by acid fuchsin using Van Gieson's method, collagen fibers were painted in dark blue by aniline blue using Mallory's method, and elastic fibers were painted in red by acid fuchsin.*
***Results.** On the model of thermal skin lesions in rats it was determined, that the use of the new cream Dermnalipoin decreased epitelization period by 9.6 days comparing to the control pathology ($p \leq 0,05$). The average degree of wound healing after the studied cream application was 37.7 %, Methyluracil ointment (reference drug) – 31 %, and Titriol gel (reference drug) – 18 % higher than the control without treatment. Results have shown that reparative properties of the studied cream (by healing factor and wound area coefficient) were higher than properties of the reference drugs.*
***Conclusion.** Dermnalipoin cream shows high reparative activity, which is manifested in burns healing process acceleration comparing to the control pathology and reduction of the severity of cyto-destructive processes. Therefore, the further study of the new cream as promising wound-healing and anti burn remedy is perspective*
***Keywords:** burns, α-lipoic acid, urea, olive oil, tea tree oil, reparation*

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DEVELOPMENT AND VALIDATION OF METHOD FOR QUANTITATIVE DETERMINATION OF SILDENAFIL AND N-DESMETHYL SILDENAFIL BY HPLC-MS/MS IN HUMAN BLOOD PLASMA

p. 22–32

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Aim. *To assess bioequivalence of sildenafil citrate tablet formulation produced by pharmaceutical company "Microkhim" (Rubezhnoe, Ukraine) it was developed and validated a prompt, specific and quite simple method for quantitative determination of sildenafil and its active metabolite – N-desmethyl sildenafil concentrations in the human blood using deuterium labeled internal standards. Direct liquid-liquid extraction procedure was utilized to extract the analytes from the blood plasma.*

Methods. *Contents of sildenafil and its metabolite in supernatant were determined by means of the high performance liquid chromatography / tandem mass spectrometric detection technique. Ionization of sildenafil, N-desmethyl sildenafil, sildenafil-d8 and N-desmethyl sildenafil-d8 was performed in the positive electrospray mode (ESI, Positive). Detection of the analytes was carried out in the multi reactions monitoring (MRM) regimen with the following m/z values for selected parent ions: 475,30; 483,20; 461,20 and 469,20, respectively. The daughter ion m/z value was selected to be 283,10 for all analytes.*

Results. *Analytical method proposed proved to demonstrate reliable accuracy and reproducibility for both analytes and has been validated within linear range 5,05–1009,92 ng/ml for sildenafil and 2,24–400,84 ng/mL for N-desmethyl sildenafil with correlation coefficient (r2) equaled to 0.9975 and 0.9973, respectively.*

Conclusions. *It was developed and validated a simple, specific and sensitive HPLC-MS/MS method for quantitative determination of sildenafil and its active metabolite N-desmethyl sildenafil concentrations in human blood plasma utilizing stable isotope labeled internal standards – deuterated sildenafil-d8 and N-desmethyl sildenafil- d8. Important feature of the method was a modified preanalytical procedures of biological samples preparation – direct liquid-liquid extraction that allowed to avoid laborious and time-consuming procedures such as evaporation to concentrate the samples with consequent recovery of dry residue, as well as to refuse from expensive solid-phase extraction. Application of the deuterium labeled internal standards allowed to suppress a biological matrix effect drastically, as well as to reach target LLOQ level. Experimental data obtained in the course of full validation of the method proposed that was performed in accordance with approved national and international technical and regulatory requirements, allowed to affirm high specificity, sensitivity, accuracy, reproducibility and efficiency of the method*

Keywords*: sildenafil, N-desmethyl sildenafil, pharmacokinetics, HPLC-MS/MS, matrix effect, deuterated standards, bioequivalence*

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RESEARCH OF THE INFLUENCE OF GERMANIUM COORDINATION COMPOUNDS WITH NIACIN AND OXYETHYLIDENDIPHOSPHONIC ACID ON FATTY ACID COMPOSITION OF BLOOD SERUM LIPIDS

p. 32–35

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*The **aim** of research was to study the influence of Germanium coordination compounds with Niacin (МІГУ-1) and Germanium with nicotinic and oxyethylidendiphosphonic acids (OE-5) on fatty acid composition of blood serum lipids in rats.*
***Methods.** Gas chromatography method was used by the authors.*
***Results.** The influence of Germanium coordination compounds with Niacin (МІГУ-1) in the doses of 70 mg/kg, 30 mg/kg, and 10 mg/kg; Germanium with nicotinic and oxyethylidendiphosphonic acids (OE-5) in the doses of 20 mg/kg, 10 mg/kg, and 5 mg/kg; as well as nicotinic acid in the doses of 100mg/kg, 70 mg/kg, 30 mg/kg, and 10 mg/kg on fatty acid composition of blood serum lipids in rats was studied.*
***Conclusion.** Germanium coordination compounds with Niacin kept more pronounced effect, comparing to nicotinic acid, on the fatty acids ratio in blood serum in animals by increasing the unsaturated fatty acids content and decreasing the saturated fatty acids content. Therefore, the further study of displayed compounds as potential drugs for prevention of the cardiovascular system diseases is promising*
***Keywords:** Germanium, nicotinic acid, fatty acids, lipids, bisphosphonates, blood serum, dosage*

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THE STUDY OF INFLUENCE OF THE BINDERS CONCENTRATION AND THE METHOD OF GRANULATION ON TECHNOLOGICAL PROPERTIES OF NATURAL ZEOLITE GRANULES

p. 36–39

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***Aim**. To study influence of the method of granulation, type and concentration of the excipients on technological properties of natural zeolite granules.*
***Methods**. The granules were obtained using laboratory extruder, granulating mixer and dragee boiler. According to the SPhU methods, bulk density before and after shrinkage, fluidity, abrasion resistance of granules, and disintegration time were determined.*

***Results**. In accordance to the given research results, influence of the method of granulation on technological properties of the granules was studied; the optimal concentrations of potato starch glue and polyvinylpyrrolidone solution on the levels of 7–10 % and 5–10 % as binders for obtaining natural zeolite granules using extruder, granulating mixer and dragee boiler were substantiated.*
***Conclusion**. Influence of the type and concentration of binder, as well as the method of granulation on technological properties of natural zeolite granules was proved. The results of research will be used for development of the composition and technology of tablets, containing natural zeolite as an active pharmaceutical ingredient*
***Keywords**: natural zeolite, granules, excipients, fluidity, bulk density, disintegration time, abrasion resistance*

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THE SYNTHESIS OF 4-AMINO-5-(PYRIDIN-2(3)-YL)-1,2,4-TRIAZOLE (4*H*)-3-YLTHIO ACETAMIDE DERIVATIVES AS POTENTIAL ANTI-INFLAMMATORY SUBSTANCES

p. 40–44

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***Aim.** A targeted synthesis of the potential anti-inflammatory agents – 4-amino-5-(pyridin-2-yl)- and 4-amino-5-(pyridin-3-yl)-1,2,4-triazole (4H)-3-ylthio acetamides.*
***Materials and methods.** The standard methods of organic synthesis, microwave synthesis, physico-chemical methods to proof the structure of the synthesized compounds were used for this work.*
***Results.** Initial 4-amino-3-mercapto-5-(pyridine-2 (3)-yl)-4H-1,2,4-triazoles obtained from carboxylic acids hydrazides through the stage of obtaining of appropriate potassium dithiocarbazinate followed by condensation of hydrazine in the traditional boiling ethanole and microwave irradiation without solvent. The appropriate thioacetamides derivatives were obtained by alkylation of 4-amino-3-mercapto-5-(pyridin-2 (3)-yl)-4H-1,2,4-triazole by N-aryl substituted б-chloroacetamides in conditions of alkaline catalysis.*
***Conclusion.** The synthesis of potential anti-inflammatory substances – 4-amino-5-(pyridin-2 (3)-yl)-1,2,4-triazole(4H)-3-ylthio acetamides was planned and carried out. It was established, that the initial intermediates synthesis – 4-amino-3-mercapto-5-(pyridine-2 (3)-yl)-4H-1,2,4-triazoles – can be carried out without solvent and without the use of lead acetate. For the compounds synthesized, pharmacological screening for anti-inflammatory activity was planned*
***Keywords:** microwave synthesis, 4-amino-3-mercapto-1,2,4-triazole, pyridine, acetamides, alkylation, computer prediction, anti-inflammatory activity*

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PHARMACEUTICAL DEVELOPMENT OF THE ANTI-EPILEPTIC TABLETS ON THE BASIS OF LEVETIRACETAM SUBSTANCE. THE SPECIFICITY OF PHARMACO-TECHNOLOGICAL STUDIES AT STANDARDIZATION OF THE REMEDY

p. 45–48

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Remedies containing Levetiracetam are widely used in medical practice for treatment of different forms of epilepsy. In result of pharmaceutical development, manufacturing formulation for the tablets on the basis of Levetiracetam substance was obtained, and the new technology for its production was developed.

*The **aim** of research within the pharmaceutical development of the remedy was to determine the necessity of the complex of operations related to the standardization of the remedies Levetiracetam 250, film coated tablets 250 mg and Levetiracetam 500, film coated tablets 500 mg. Experimental studies should be devoted to determination of quality target product profile (QTPP), according to ICH Q8 recommendations. Concerning the specificity of the mentioned drugs production, the amount of work was determined to develop pharmaco-technological indexes for their implementation to the relevant specifications for the finished drug product, as well as for the intermediate products obtained at different stages of the technological process.*

***Methods.** By results of tests, which were carried out in accordance to pharmacopoeia requirements, the eligibility criteria of pharmaco-technological parameters for the corresponding control objects were determined.*

***Results.** Results of quality target product profile (QTPP) studies were used for development of specifications for the remedies Levetiracetam 250, film coated tablets 250 mg and Levetiracetam 500, film coated tablets 500 mg, which were completed in the form of quality control methods and specifications for the finished drug product series.*

Experimental research of the samples of products, which were obtained at appropriate stages of the technological process, were carried out; pharmaco-technological indexes, which were implemented into the specifications for the finished drug product, as well as the specifications for the intermediate products, were developed. According to the given data estimation, it was displayed, that pharmaco-technological indexes are rather important both for the quality of drug assesment, and for evidence base formation to confirm the reproducibility of the technological process.

***Conclusion.** The results of research within standardization of the remedies Levetiracetam 250, film coated tablets 250 mg and Levetiracetam 500, film coated tablets 500 mg show processability of obtaining drugs, which LLC "Pharma Start" carries out, as well as guarantee of the drugs quality from batch to batch*

***Keywords:** quality target product profile, standardization, specification, eligibility criteria, pharmaco-technological indexes, anti-epileptic tablets, development, technology*

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SELECTION OF THE EXCIPIENTS TO CREATE TABLETS OF ADAMANTANE-1-AMMONIUM 2-((5-(ADAMANTANE-1-YL)-4-PHENYL-4H-1,2,4-TRIAZOLE-3-YL)THIO)ACETATE BY THE METHOD OF WET GRANULATION. PART 1

p. 49–53

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Recently, mental health is one of the most serious problems faced by all countries due to at least every fourth person have such problems at any given period of life. In European region, prevalence of mental disorders is rather high. According to the WHO data, among 870 million of people living in European region, about 100 million feel themselves anxiously and depressed; more than 21 million suffer from disorders associated with alcohol; more than 7 million – with Alzheimer's disease and other dementia types; about 4 million suffer from schizophrenia; 4 million – bipolar affective disorders, and 4 million – panic disorders.

Numerous studies in area of the dosage form influence on therapeutic effect have shown, that the optimal activity of drug substance is achieved only under condition of a rational dosage form appointment. Besides, in this way many side effects of remedies can be avoided.

It is known that most of neuroleptics are used in tablet form. Accordingly, development of technology of adamantane-1-ammonium 2-((5-(adamantane-1-yl)-4-phenyl-4h-1,2,4-triazole-3-yl) thio)acetate tablets is important.

*The **aim** of the present study is selection of the optimal excipients to create tablets of adamantane-1-ammonium 2-((5-(adamantane-1-yl)-4-phenyl-4h-1,2,4-triazole-3-yl)thio)acetate by the method of wet granulation with the content of active substance 70 mg.*

Methods. *Four groups of the excipients with different physical and technological properties were studied. Experimental work was carried out using modern equipment for determination of tablets' weight uniformity, abrasion, time for disintegration and receiving.*

16 excipients were studied; most of them recently appeared in the market, so there is no information about their use in pharmaceutical technology for creation of tablets.

During study of four qualitative factors one of the variance analysis plans was used – four factorial experiment based on the Hyper-Graeco-Latin square.

Results. *Based on pharmaco-technological properties and morphometric experiments, wet granulation method was offered for adamantane-1-ammonium 2-((5-(adamantane-1-yl)-4-phenyl-4h-1,2,4-triazole-3-yl)thio)acetate tablets obtaining. Considering the literature data [3,6,10], relying on the research of the modern outstanding scientists: prof. Groshovui T. A., Kazarinov M. O., Borzunov Ye. E., Shteyngart M. V. and the experience of previous technological research, we offered theoretical composition of the tablets, namely set of factors that are often used in tablets production by wet granulation method*

Keywords: *adamantane-1-ammonium 2-((5-(adamantane-1-yl)-4-phenyl-4h-1,2,4-triazole-3-yl)thio)acetate, tablets, excipients, wet granulation, neuroleptic action*

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ANALYSIS OF ASSORTIMENT OF MEDICINES FOR THE TREATMENT OF BENIGN PROSTATE DISEASES FOR THE EVALUATION OF PARTICULAR MARKETING OPPORTUNITIES FOR DOMESTIC MANUFACTURERS

p. 53–61

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Distribution of urological diseases such as prostatitis and prostatic hyperplasia leads to deterioration of physical and psychological health of the working population of our country, which ultimately affects (in a macroeconomic sense) the ability to produce gross national product, increases the amount of payments for medical sick-leave certificate. In connection with the above mentioned the search for new treatment regimens of these diseases are urgent issues of modern medicine and the development of new drugs remains a burning issue for the national pharmacy. Therefore, it is appropriate to determine the state of the market, trends in the consumption of drugs to treat these diseases. Our studies are the basis for the rationale for finding, developing and bringing to market innovative drugs.

The aim *was to study the structure and trends of the Ukrainian market of medicines for the prevention and treatment of benign prostate diseases to identify marketing opportunities for domestic pharmacy.*

Materials and methods. *The study was conducted with using structural analysis, logical and graphical methods as well as methods of marketing analysis.*

Results. *Were detected the dynamics of changes and trends of Ukrainian pharmaceutical market of that group. Market structure revealed by the number of names, brands, the forms of production, producing countries and its composition. The results show that over the past 15 years the number of regis-*

tered drugs of this group decreased, but increased the number of offers from domestic producers. Still, the structure of the market is depended from import – drugs from foreign origins occupy about 70 % of the domestic market and the range of more than 78 % in terms of implementation. Market drugs for the treatment of benign prostate disease has a positive trend in both sales volume dynamics and the structure of the range. For the overall results in 2016 it is indicated an increase in sales of goods "Pharmaceutical basket" in monetary terms.

***Conclusions**. Based on the detected changes were developed some proposals for the domestic pharmaceutical industry - the market is relatively limited supply of domestic complex drugs that are composed of plant material, because the development and output of innovative drugs is a promising area of development*

***Keywords:** pharmaceutical market, medicines, diseases of the prostate, marketing research*

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SCIENTIFIC AND EXPERIMENTAL SUBSTANTIATION OF THE TECHNOLOGY FOR ANTIGENS OF *CANDIDA* FUNGI PURIFICATION

p. 62–65

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*Every year, the number of patients with candidiasis increases. Many researchers believe that the creation of vaccines against candidiasis is a promising direction in the fight against this disease. The authors substantiated the technology of C. albicans and C. tropicalis fungi cells disintegration to produce antigens. The **aim** of this work was to substantiate the technology C. albicans and C. tropicalis fungi antigens purification from ballast substances.*

***Materials and methods**. First and foremost, it was necessary to separate unbroken cells from destroyed cells remnants. Then, purification from shallow mechanical residues in solution containing fungi antigens was necessary. To prevent possible contamination of equipment and personnel, sterilization of the antigens solution became important. The use of ultrafiltration and gel chromatography was analyzed for separation of substances by molecular weight analysis. Determination of activity of the obtained fungi antigens fractions in prevention and treatment of candidiasis was carried out experimentally in mice.*

***Results.** According to the research results, the technology of purification of fungi antigens, consisting of sequential processes: centrifugation, previous, sterilizing and ultrafiltration, was developed.*

***Conclusion.** Our studies in mice suggest that the developed technology of antigens C. albicans and C. tropicalis purification provides the necessary result in candidiasis prevention and treatment*

***Keywords**: antigen, vaccine, candidiasis, technology, filtration, ultrafiltration, centrifugation, therapy, prevention, immunity*

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