ABSTRACT&REFERENCES

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THE SYNTHESIS AND STUDY OF PROFILES OF THE ORNIDAZOLE IMPURITIES

p. 4-11

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Pharmacopoeial reference standards (PhRSs) provide the comparability of the test results of generic drugs. PhRSs of ornidazole impurities described in pharmacopoeias. Therefore, the establishment of PhRSs of the State Pharmacopeia of Ukraine (SPhU RSs) of ornidazole impurities is an essential task, the integral part of which is synthesis and characterisation of ornidazole impurities.

Aim: *To synthesize impurities of ornidazole as candidate materials for certification as SPhU RSs and study their profiles in the substance and infusion solution of ornidazole.*

Methods: *Traditional methods of organic synthesis, ^{1}H NMR spectroscopy, IR absorption spectrophotometry, the capillary method for the melting point determination, liquid chromatography with a spectrophotometric detector.*

Results: *Ornidazole-diol and ornidazole-epoxide were synthesized, and their structures were confirmed using ^{1}H NMR and IR spectra. Their chromatographic profiles in the substance and the infusion drug of ornidazole being under pharmaceutical development were studied. The problem with the ornidazole-diol determination by the manufacturer's procedure was found, and its correction was proposed. The purity of the compounds synthesized was approximately 99.5 %. In the substance, the content of ornidazole-epoxide exceeded 0.1 %, whereas the content of ornidazole-diol was negligible. In the drug, the content of ornidazole-epoxide reduced to zero with time, while the content of ornidazole-diol increased considerably (to approx. 3 %).*

Conclusions: *The efficient methods for the synthesis of ornidazole-epoxide and ornidazole-diol were developed, and the synthesis was conducted. The profiles of the synthesized impurities in the substance and the infusion drug of ornidazole being under pharmaceutical development were studied. It was found that ornidazole-epoxide and ornidazole-diol are present in the substance and the drug at the level which requires their identification and quantitative determination. TOrnidazole-diol and ornidazole-epoxide obtained by the proposed methods were shown to be of high purity, which enables to use them as the candidate materials for certification as SPhU RSs*

Keywords: *ornidazole impurities, synthesis, ornidazole-diol, ornidazole-epoxide, profile of impurities, ornidazole substance, infusion solution of ornidazole, pharmacopoeial reference standards, State Pharmacopeia of Ukraine*

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ACTUAL APPROACHES TO DEVELOPMENT OF NEW ANTIMICRIBIAL MEDICINES IN THE CONDITIONS OF EXTENSION OF ANTIBIOTIC RESISTANCE

p. 12-15

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Aim. *The grounding of expediency of studying the nature of interaction between metal nanoparticles and plasmid DNA of bacteria at the stage of pharmaceutical development of antimicrobial medicines based on metal nanoparticles as separate antimicrobial agents, as well as compositions of metal nanoparticles with known antimicrobial substances.*

Methods. *Methods of information retrieval and analysis of literature data have been used.*

Results. *Plasmid transmission of drug resistance is the most important mechanism of resistance in the bacterial population. A promising approach to solve the problem of overcoming the resistance of microorganisms is the use as an active pharmaceutical ingredient of antimicrobial medicines caused the destruction of R-plasmids or ensured their irreversible elimination. The study of the interaction of substances with plasmid DNA bacteria and the study of their effect on the transfer of resistance genes in bacterial populations should be used at the first stage of the creation of antimicrobial preparations, when a potential active pharmaceutical ingredient is select.*

Conclusion. *Creation and introduction into the production of medicines based on silver and gold nanoparticles is a promising direction, because nanoparticles of these metals, along with antimicrobial action, will provide irreversible elimination of plasmid from bacterial*

cells and can become a solution of the problem with antibiotic resistance

Keywords: *antimicrobial preparations, nanoparticles of metals, infectious diseases, microbial resistance, elimination of plasmids*

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VERIFICATION OF DISSOLUTION TEST FOR DOXYCYCLINE HYCLATE IN CAPSULES TO IMPLEMENT INTO THE PHARMACOPOEIAL MONOGRAPH

p. 16-20

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The study of dissolution profiles is important as a cheap and easy supplement to bioequivalence research, and as a variation to such studies. This method is not outlined in the State Pharmacopoeia of Ukraine for the doxycycline capsules. Therefore, according to the current requirements, it was necessary to verify the procedure recommended by the US Pharmacopeia to confirm that this laboratory test will be reproduced correctly, and to use it in our further studies. The ***aim*** *of our research was to verify the "Dissolution" test analytical procedure for doxycycline hyclate capsules, recommended by the US Pharmacopoeia.*

Methods. *Capsules of doxycycline hyclate 100 mg and set of mineral waters were taken as study objects. A standard sample of doxycycline was used for preparation the comparison solutions. All reagents and test specimens meet the requirements of the SPhU. The experimental data were obtained at the same time in a standardized*

procedure. For this purpose, 9 points were studied within the range 55–135 % with a step of 10 %. The obtained results were processed statistically in accordance with the requirements of the SPhU.

***Results**. The conducted prediction showed that the total uncertainty of the results of the methodic is 1.04 %, which does not exceed the critical value (3.0 %). To determine the specificity, the effect of placebo was investigated. The calculation showed that the overall effect of placebo on the total absorption of the drug is non-significant (0.51 % ≤ 0.96 %). Also, the method is linear in the range of concentrations from 55 % to 135 %. The systematic error of the results meets the recommended criteria.*

***Conclusions.** The analysis of model mixtures of doxycycline hyclate showed the correctness of the investigated method*

***Keywords:** doxycycline hyclate capsules, verification, implementation, dissolution test, linearity, permissibility criteria, correctness of the procedure*

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RESEARCH OF THE TOXICOLOGICAL PROFILE OF THE NEW GEL, WHICH CONTAINS AN EXTRACT OF THE OAK BARK AND ALOE EXTRACT

p. 21-25

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On these days periodontal diseases are widely distributed and diagnosed in more than 75 % of the world population and occurs in all age groups. Drugs based on medicinal plants should be considered as promising products, which have therapeutic effect with minimum adverse reactions.

***The aim** of this work was to study the acute toxicity of new gel containing plant extract of oak bark and extract of aloe.*

***Methods.** Acute toxicity was studied in accordance with the guidelines on white nonlinear rats with 180–220 g in weight, by several steps: the study of acute toxicity of components of a new gel, the study of acute toxicity of a new gel under intragastric administration, intraperitoneal and skin administration.*

***Results.** It was established that it is not possible to determine LD_{50} by intragastric administration of extract of oak bark and extract of aloe, since administration of a maximum dose of 15100 mg/kg did not cause lethality of rats. In order to confirm this assertion, in further studies the acute toxicity of extracts was studied only at a dose of 15100 mg/kg. In terms of intraperitoneally administration, LD_{50} of extract of oak bark is 2580 (1930–3220) mg/kg, LD_{50} of extract of aloe – 2180 (1460–2900) mg/kg. At the subsequent stages of the study during the observation for 14 days, there were no visible signs*

of the toxic effect of the new gel on the functional state of the animals at the maximum recommended doses: intragastric – 15100 mg/kg and skin application – 22600 mg/kg.

Conclusions. *The complex of the conducted studies allowed establishing that the new gel does not have a toxic effect on organs and systems of experimental animals and does not have a lethal action. Extract of oak bark and extract of aloe under conditions of intragastric administration are classified as VI class of toxicity "Relatively harmless substances". In case of intraperitoneally administration, the studied extracts were classified as V class of toxicity "Practically nontoxic substances". According to the study of acute toxicity, the new gel, in conditions of intragastric administration and skin application, belongs to the VI class of toxicity "Relatively harmless substances"*

Keywords: *acute toxicity, extract of oak bark, aloe extract, gel, toxicity, extract*

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SELECTION AND VERIFICATION OF THE METHOD FOR PHYNELEFRINE HYDROCHLORIDE ASSAY IN SIMANOVSKY OINTMENT

p. 26-31

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Phenylephrine hydrochloride is a sympathomimetic with expressed local vasoconstrictor effect. Its ability to reduce swelling and hyperemia of the nasal mucosa is used in the Simanovsky ointment which is preparing for stock in the pharmacies of Ukraine. For the assay of phenylephrine hydrochloride in many single and multicomponent dosage forms, it is suggested to use a spectrophotometric method. However, in literary sources there are no examples of the use of spectrophotometric method for quantitative determination of phenylephrine hydrochloride in the studied ointment.

Aim. *The purpose of the research was to select and verify the optimal method for phenylephrine hydrochloride assay in the Simanovsky*

ointment with the possibility of its further use for the stability analysis of the dosage form during storage.

Methods. *Direct UV-spectrophotometry method for assay of phenylephrine hydrochloride in the studied ointment.*

Results. *For the quantitative determination of phenylephrine hydrochloride in the Simanovsky ointment, the method of direct spectrophotometry was selected after its extraction from the ointment base with 0.1 M hydrochloric acid. In order to prove the possibility of its use in the ointment analysis, the determination of the validation characteristics was made. The obtained results indicate that the requirements for the specificity of the method (δ_{noise}, %=0.47≤1.02), the parameters of linear dependence, the accuracy (δ, %=0.20≤1.02) and the precision (ΔZ=0.39≤3.20) are met. The study of the robustness of the technique shows the stability of solutions within an hour. The method was tested on the researched ointment. The metrological characteristics of methods for calculating the quantitative content of phenylephrine hydrochloride by the standard method and specific absorption index were determined. The obtained results indicate the possibility of using both methods.*

Conclusions. *For the assay of phenylephrine hydrochloride in the Simanovsky ointment, the method of direct spectrophotometry was chosen. Validation characteristics of the method indicate the possibility of its use for medicine analysis and study of its stability during storage. It was proved that the calculation of the quantitative content of phenylephrine hydrochloride in the ointment can be carried out using both the standard method and the method of specific absorption index*

Keywords: *compounding ointment, phenylephrine hydrochloride, spectrophotometry, verification*

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STUDY OF EXCIPIENTS QUANTITIES INFLUENCEIN THE COMPOSITION OF THE POWDER IN SACHET PACKAGES

p. 31-35

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For developing power in sachet packages with anti-inflammatory action a special task is optimal qualitative and quantitative composition of excipients. The purpose was to study the effect of excipient's quantities on the pharmaco-technological parameters of power.
Methods. *It was composed of various compositions of active components and excipients using the method of mathematical planning of the experiment. By random balance method was studied their effects on the physico-chemical, technological and organoleptic properties of powder.*
Results. *Analysis of the scattering diagrams for influence of quantitative factors on the mass appearance showed that the most significant on this indicator are quantities of calcium phosphate, sodium citrate, curcumin and lemon-lime flavor. Significant factors for bulk density and density after shrinkage are quantities of calcium phosphate, sodium citrate, lemon-lime flavor and titanium dioxide. The results of Carr's index are most influenced by the quantities of acid lemon-lime anhydrous, titanium dioxide and curcumin. Experimental values of fluidity are most depend on quantity of calcium phosphate. Quantities of calcium phosphate, sodium citrate and titanium dioxide are the most significant for the slope angle. The greatest influence on the mass loss rates during drying show the quantities of curcumin and malic acid. On the basis of the scattering diagram for appearance of the solution the decisive influence of quantities of calcium phosphate, sodium citrate, lemon-lime flavor and titanium dioxide was determined. Obviously, the significance of the quantity of lemon-lime flavor on smell of the solution. Analysis of the dispersion diagram for taste of the solution showed that the most important are quantities of calcium phosphate and acid citric anhydrous. The most significant factors for pH of the solution are the quantities of phosphate calcium and lemon-lime flavor.*
Conclusion. *The effects of excipient's quantities on pharmaco-technological and organoleptic properties of the powder in sachet packets is investigated*

Keywords: *power, sachet, quantities of excipients, pharmaco-technological indicators, random balance*

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MORPHOLOGICAL AND TAXONOMIC STUDY OF *OXYACANTHAE* ZBL. SECTION OF *CRATAEGUS* L. GENUS BY VEGETATIVE CHARACTERISTICS

p. 36-41

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On the territory of Ukraine in the wild the most widespread the representatives of the Oxyacanthae Zbl section of the Crataegus L. genus (hawthorn), which has 31 species in the world's flora, 13 species in the Ukrainian flora, 17 species of the flora of the CIS countries. Three species of this section (C. oxyacantha L., C. monogyna Jacq., C. curvisepala Lindm.) are included into the State Pharmacopoeia of Ukraine, and two species (C. oxyacantha L. and C. monogyna Jacq.) – to the European Pharmacopoeia.

Aim. *Carry out a morphological and taxonomic study of the Oxyacanthae Zbl section by vegetative characteristics.*

Methods. *The mathematical approach (graph analysis method) was used. The system was subjected to 140 morphological vegetative features of the hawthorn sections of the Oxyacanthae Zbl., which grow on the territory of Ukraine and adjacent countries. 2380 positive and negative states of taxonomic signs were analyzed.*

Results. *On the basis of the calculated coefficients of pair affinity were established taxonomic relationships between species of the Oxyacanthae Zbl section. The main group of hawthorns was found which generalizes the morphological characteristics of the section Oxyacanthae Zbl. by vegetative characteristics.*

Conclusions. *For the first time, the morphological and taxonomic study of the Oxyacanthae Zbl section was conducted by vegetative characteristics. It was established that the section was divided into 5 branches, which, in general, correlate with the range of species growth. The basic morphological vegetative features of the section were established*

Keywords: *hawthorn, section, vegetative characteristics, morphology, taxonomy, graph analysis, hierarchical series*

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STUDY OF INFLUENCE OF PRIMARY PACKAGING ON THE STABILITY OF THE ORIGINAL VETERINARY PREPARATION

p. 42-47

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A great importance during the design of veterinary drugs is given to the choice of primary package, the material which is directly contact with the dosage form. Stability of samples of veterinary medicines should be investigated in packages that will be used during serial production of drugs. It is also necessary to investigate the processes that can occur with active pharmaceutical ingredients under the influence of substances contained in the packaging material. On the basis of these data, determine the shelf life of the veterinary drugs in the appropriate package.

Aim. *The influence of primary packaging on quality characteristics of solution based on silver citrate codenamed "Argocid", namely ampoules of 10 ml capacity and vials with a capacity of 50 ml made of light-protection glass; plastic containers (ampoules) in a capacity of 10 ml and 50 ml vials.*

Methods. *Methods of research were conducted in accordance with the requirements of the State Pharmacopoeia of Ukraine.*

Results of the research. *It was investigated that 10 ml plastic containers of Pharmalene®, 50 ml bottles of Riblene® FL 20 PH of low density polyethylene, do not cause changes in the quality of the veterinary solution regulated in the specification and allow the product to remain stable for a shelf life of 2 years. In the process of storing a silver-citrate solution of in a polymeric package of 10 ml Pharmalene® grade polyethylene occurred a volume reduction of up to 1.5 % over a period of 2 years. However, the evaporation rate of the solvent is too small for the concentration of active substances to exceed the acceptable values.*

Conclusions. *It was established that all investigated types of containers are suitable for use as an initial packaging for the veterinary drug "Argocid", a solution for intramammary administration on the basis of silver citrate, since they allow the drug to be stable for 2 years*

Keywords*: veterinary drug, primary packaging, stability, silver citrate*

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IN VITRO SUSCEPTIBILITY STUDY OF *CANDIDA SPP.* ISOLATES TO NEW COMBINED POTENTIAL MEDICINAL PRODUCT FOR THE TREATMENT OF VAGINAL CANDIDIASIS

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Research of the antimicrobial action of model specimens of a potential drug in various fixed combinations and the advent of specific antimycotic activity of model samples of a new, combined, potential drug and medicine product, selected as a reference "Neo-Penotran®" (Exeltis Healthcare S.L., Spain).

Aim of the research *was to determine the susceptibility of in vitro Candida spp. isolates to a new combined drug containing a substance with an antimycotic activity for the treatment of vaginal candidiasis.*

Materials and methods. *Candida albicans (ATCC 10231) and Candida albicans (clinical isolate) from the material, urogenital pathways from women with a diagnosis of candidiasis were used to prove the activity and determine the sensitivity.*

The study of antimicrobial activity was carried out using the serial dilutions method in trypticase-soybean broth, which allowed to ensure a uniform distribution of the drug in the nutrient medium in contact with pathogenic strains, and the subsequent transfer to Petri dishes on Sabouraud agar - the most accurate evaluation of the results.

Results *of the study of the antimycotic activity of 7 model specimens showed antimycotic activity in only 3 model specimens in relation to both the reference strain Candida albicans ATCC 10231 and the clinical strain of Candida albicans.*

Conclusions. *The results of the studies indicate that there is a strong in vitro antimycotic effect of the new potential combined drug against pathogenic test strains: Candida albicans ATCC 10231, Candida albicans (clinical isolate), which is not inferior to the selected reference medicine. Minimum inhibitory concentration of the test drug in vitro was established for pathogenic test strains: Candida albicans ATCC 10231, Candida albicans (clinical isolate). The study of various combinations and concentrations of the combined drug made it possible to exclude the presence of negative interaction between components of the experimental specimen and to select the most promising and effective sample for further experimental studies of combinations of antimycotics for intravaginal use*

Keywords: *suppositories, vaginal candidiasis, antimycotic activity*

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