ABSTRACT&REFERENCES

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ANALYSIS OF PSYCHOTROPIC MEDICINES TRIAZOLAM, ESTAZOLAM AND ALPRAZOLAM MIXTURE USING HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY METHOD

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Poisoning of benzodiazepines, particularly triazolam, estazolam and alprazolam usually is caused by consumption of the drug in bigger doses than prescribed. So, for the fast determination of material caused poisoning, selective and effective methods of analysis are requested.

***Methods**. Benzodiazepines triazolam, estazolam and alprazolam, were chosen for investigation. Analysis was performed using chromatograph „Waters 2695" with a photodiode array detector (Waters 996, at wavelength 200–400 nm range), ACE C18 (2,1 mm × 5,0 cm, 5 µm) chromatographic column, gradient eluent flow (sulfuric acid buffer 0,1 % and ACN), eluent flow rate 0,1 ml/min and injection volume of 10 µl.*

***Results.** Methodics for identification and quantification of triazolam, estazolam, alprazolam and their mixture was developed using reference solutions. Validated methodic was adapted for identification and quantification of triazolam, estazolam, alprazolam in medicinal products.*

***Conclusions.** Selected methodic is suitable for qualification and quantification of the medicinal preparations: ACE C18 (2,1 mm × 5,0 cm, 5 µm) chromatographic column, gradient eluent flow (sulfuric acid buffer 0,1% and ACN), eluent flow rate 0,1 ml/min, injection volume of 10 µl and photodiode array detector. Mixture of components has been examined and retention times have been stated as follows: alprazolam (13,216 min), estazolam (13,407 min) and triazolam (14,340 min). Retention time upon repetition of analysis have not exceeded the relative error of $p < 0,05$ limitation.*

Limits of detection of alprazolam is 0,01 µg/ml, estazolam 0,012 µg/ml, triazolam 0,020 µg/ml. Limit of quantification of alprazolam is 0,022 µg/ml, estazolam 0,025 µg/ml, triazolam 0,045 µg/ml

***Keywords:** triazolam, estazolam, alprazolam, high-performance liquid chromatography, qualitative and quantitative determination*

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EVALUATION OF OPPORTUNITIES FOR THE USE OF MODERN METHODS FOR CORRECTION AND PREVENTION OF RISKS IN THE QUALITY CONTROL OF CLINICAL TRIALS

p. 10-16

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To organize and conduct a clinical trial (CT) at a high level, it is necessary to continuously monitor its quality, as the occurrence of non-conformances can threaten health and safety of the trial subjects, as well as lead to CT data loss or their unreliability. In general, for the effective CT quality control, it is expedient to continuously improve the quality management system of all parties who participate in the CT, including at the clinical site. Current regulatory requirements include an indication of the need for a continuous process of the quality management system improvement to ensure the proper level of the process performance, in particular, the system of non-conformances correction and prevention.

The aim *of this work was to evaluate the possibilities and problems of applying modern methods of risks correction and prevention in the CT quality management.*

Materials and methods. *To achieve the aim of the study, a meta-analysis of literature sources using PICO search technology was carried out and analysis of existing regulatory documents on the availability of methodologies, instructions and algorithms for selecting and applying the non-conformances correction and prevention tools during CT organizing and conducting.*

Results of the study. *The study showed that regulatory authorities see the need for standardized CT quality management systems to increase the number of qualified clinical sites, as well as more strict compliance with the ICH GCP principles. The analysis of regulatory documents showed the absence of unified harmonized requirements for carrying out the processes of correction and prevention of non-conformances within the framework of CT organizing and conducting.*

Conclusions. *Organizing and conducting of CT requires continuous monitoring of the quality of the processes carried out to ensure getting of complete and reliable data on the study drug. Given the lack of regulatory requirements governing the process of non-conformances correction and prevention, it seems expedient to develop an algorithm for work with CAPA-plan and its methodology, as well as SOP to standardize the conduct of this process*

Key words*: clinical trial quality management, CAPA plan, corrective actions, preventive actions, risk management*

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PHYSICO-CHEMICAL AND PHARMACO-TECHNOLOGICAL RESEARCH AT A SUBSTANTIATION OF RATIONAL COMPOSITION AND TECHNOLOGY OF SUPPOSITORIES «INDOXAM»

p. 17-23

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The development of new highly effective drugs in the form of rectal suppositories for the treatment of diseases of the prostate gland does not lose its relevance today, since the number of patients with these pathologies is increasing every year. These diseases adversely affect the physical, psychological health and quality of life of men in general.

An important issue in the substantiation of the composition and development of the technology for the production of suppositories is the study of their physico-chemical and pharmaco-technological properties that directly affect their consumer qualities and the mode of the technological process.

***Aim of the work** was the study of the physico-chemical and pharmaco-technological properties of the combined rectal suppositories "Indoxam" to select rational conditions of the technological process.*

***Materials and methods**. In order to substantiate the composition and technology of the combined rectal suppositories "Indoxam", modern physicochemical (thermal analysis, rotational viscometry method) and pharmaco-technological (disintegration suppositories, resistance to degradation) studies were used according to the requirements of SPHU.*

***Results.** To select the optimal ratio of polyethylene oxides in the suppository base, the resistance of suppositories to destruction and the disintegration time of samples made with different amounts of PEO-1500 and PEO-400 were studied. To determine the optimal technology for the preparation of the drug, a study was made of the decomposition temperature of the API, which makes it possible to determine the temperature regimes for the preparation of suppositories and the introduction of active substances into the base without the risk of destroying the structure of substances and changing their pharmacological actions. Since, under the influence of mechanical, thermal, and other actions, several types of destruction undergo suppositories, their rheological characteristics are also investigated.*

***Conclusions**. The results of pharmaco-technological research allowed to substantiate the optimal ratio of polyethylene oxides in suppository basis. The conducted thermogravimetric analysis of API and suppositories «Indoxam» established the thermal stability of substances and the absence of chemical interaction between the components in the composition of rectal drug. According to the rheological characteristics, the system identified the thixotropy and the optimal pouring temperature of the suppository mass*

***Keywords**: rectal suppositories "Indoxam", indole-3-carbinol, meloxicam, physico-chemical and pharmaco-technological research, composition, technology*

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SUBSTANTIATION FOR THE OPTIMAL STRATEGY OF RISK MANAGEMENT IN MARKETING COMMUNICATIVE ACTIVITIES OF PHARMACEUTICAL ENTERPRISES BASED ON MATHEMATICAL MODEL APPROACH

p. 24-31

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Aim. *To develop a mathematical model of risk analysis and evaluation in the marketing communication activity of pharmaceutical manufacturing enterprises in promoting a new medicine product under limiting and (or) saving investment funds for marketing communications. The obtained results allowed to make reasonable decisions as for choosing the optimal risk management strategy in marketing communication activities of pharmaceutical enterprises.*

Methods*. The implementation of the above tasks predetermined the choice of the following methods: content analysis, logical analysis, grouping and generalization, mathematical model methods, etc.*

Results*. The research resulted into introduction of the method of analysis and risk assessment in the marketing communication activity of pharmaceutical manufacturing enterprises in the promotion of a new medicine product using fuzzy modeling theory Fuzzy TECH.*

The developed mathematical model allows the subjects of the pharmaceutical market to reasonably and timely evaluate the impact of certain risk factors on the results of the marketing communications program's implementation when promoting a new medicine product under limiting and (or) saving investment funds for marketing communications. Taking into account the obtained results allows to make a managerial decision on choosing an optimal risk management strategy in marketing communication activities of enterprises: risk avoidance, risk transfer, risk reduction, risk taking.

Conclusions*. The given mathematical model is of practical value for the subjects of the pharmaceutical market, since it is not vulnerable to the number of input variables – higher or lower number of risk factors leads to higher or lower number of decision rules, with the model logic remaining unchanged*

Keywords: *risk factors, risk management strategies, marketing communicative activity, pharmaceutical enterprises, mathematical model*

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TECHNOLOGY OF OBTAINING AND INVESTIGATION OF CHEMICAL COMPOSITION OF DENSE EXTRACT OF HAWTHORN FRUITS

p. 31-39

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In the pharmaceutical market of Ukraine, liquid dosage forms of hawthorn are present and used in complex treatment of cardiovascular diseases. Ukrainian flora has more than 30 species of hawthorns, among which there are unofficial species of wild and cultural species with sufficient raw material base.

Aim. *To develop a technology for obtaining of dense fruit extracts of unofficial hawthorn species and to determine the chemical composition of the obtained extracts.*

Methods. *For determination of BAS dense of hawthorn fruit extracts was used spectrophotometric method and the method of high performance liquid chromatography (HPLC).*

Results. *The technological scheme of obtaining dense extracts of hawthorn fruit was developed. The content of amino acids, flavonoids and hydroxycinnamic acids was established in extracts of fruits C. prunifolia Sarg., C. pseudokyrtostilla Klok. and C. leiomonogyna Klok.. The content of flavonoids ranged from 4.27 % ± 0.01 to 10.94 % ± 0.10; hydroxycinnamic acids – from 1.45 % ± 0.02 to 2.56 % ± 0.10. By used the HPLC method in all extracts was detected rutin, chlorogenic and ferulic acids. In dense extract of C. prunifolia Sarg. fruits apigenin-7-O-rhamnoside was identified; C. pseudokyrtostilla Klok. and C. leiomonogyna Klok. – apigenin-7-O-glycoside, apigenin, luteolin; C. leiomonogyna Klok. – luteolin-7-O-diglycoside and quercetin.*

Conclusions. *Dense fruit extracts of C. prunifolia Sarg., C. pseudokyrtostilla Klok. and C. leiomonogyna Klok. were obtained. For the first time, the HPLC method in extracts has determined the content of flavonoids and hydroxycinnamic acids. A comparative study of the amino acid composition of the extracts was carried out*

Keywords: *hawthorn, fruits, dense extracts, chemical composition, technology, flavonoids, hydroxycinnamic acids, amino acids*

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REDOX-DEPENDENT MECHANISMS OF BRAIN NEUROPROTECTION OF RATS WITH EXPERIMENTAL DIABETES MELLITUS

p. 39-46

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The aim*. To investigate the efficacy regulation of redox-dependent mechanisms neuroprotection in case of various pharmacological schemes including N-acetylcysteine (NAC) and melatonin (Mel) in the brain of rats with experimental type 1 diabetes mellitus (DM 1).*
Methods. *NAC (1.5g/kg), Mel (10 mg/kg) or their combination (NAC+Mel) where administrated to rats with induced DM 1 for 5 weeks. State of the mitochondria electron transport chain (ETC),velocity of generation superoxide radicals (SR), activity of nNOS, concentration of lactoferrin, "free iron", methemoglobin, 8-oxoG in the cells of rats` brain were determined by electron paramagnetic resonance (EPR) method using a computerized spectrometer PE-1307 at the temperature of liquid nitrogen (T=77K).*
Results. *During 7-week after induced DM 1, the rate of superoxide radicals (SR) generation by brains` mitochondria of rats with DM 1 was significantly higher and the activity of neuronal nitric oxide synthase (nNOS) was decreased compare to control group. The reduction in the activity of mitochondrial ETC Complex I and the growth of level 8-oxoG, concentration of "free iron" complexes, NO-FeS proteins, lactoferrin and MetHb concentration in the brain tissue of animals with DM1 were determined. Administration of all investigated pharmacological groups caused decreasing the rate of SR generation and recovering activity of nNOS by brains` mitochondria. After pharmacological intervention with NAC/Mel or NAC+Mel the levels of 8-oxoG and NO-FeS proteins were significantly decreased, activity of «free iron» complexes were normalizedinthe tissue of rats`*

brain with DM 1. Therapy of NAC also caused reduction level of MetHb and a combination therapy of NAC + Mel caused reduction level of lactoferrin of the rats` brain with DM 1.

Conclusion. *At induction of type 1 diabetes, mitochondrial ETC was damaged by products of incomplete catalysis of glucose, which manifested by a decrease in the synthesis of ATP, an increase in the level of SR, which are generated as a result of defection of the electron transport mechanism.*

The therapy of NAC and Mel or their combination was accompanied by the protection of the rats` brain cells with DM 1 from the toxic effect of SR, preventing disturbance of mitochondrial function that indicate neuroprotective action. NAC and Mel are perspective drugs for the prevention and treatment of diabetic neuropathy

Keywords: *diabetes mellitus, brain, oxidative stress, N-acetylcysteine, melatonin, mitochondria, superoxide*

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DETERMINATION OF THE CONTENT OF AMINO ACIDS IN THE ROOTS OF THE SOPHORA FLAVESCENS

p. 47-51

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Shrubby sophora (Sophora flavescens L.) genus of the Fabaceae family is a perennial plant that is common in Russia, Japan, Korea, Northeast, North and Central China. The roots of this plant contain 1–2 % of alkaloids (allomatrin, anagirin, isomatrin, matrine, sofofarpin, soforamin, soforanol), triterpene saponins (soyasaponin I), flavonoids (soforaflavosides I, II, III, IV, biosanin A, kuraridin, kurarin, Cushenols A, B, C, D, I, K, L, M, (–) – maakianin, neokurarinol, norkurarinone) and amino acids (proline, aspartic acid, glycine, argenine). Plant amino acids form a large group of organic compounds and have unique biological and pharmacological properties. Therefore, in recent years, scientists have paid great attention to the study of the amino acid composition of medicinal plants.

The aim *of our work was to determine the content of amino acids in the roots of shrubby Sophora (Sophora flavescens L.).*

Materials and methods: *the study was performed by high performance liquid chromatography (HPLC). Identification of amino acids was performed by comparing the retention time with a mixture of amino acid standards (Agilent 5061-3334). The content of bound amino acids was determined by the difference between the content of free amino acids and their total content.*

Results and discussion: *as a result of the study, the content of 15 amino acids was found and determined in the free and bound state of shrubby Sophora roots, of which 6 are irreplaceable (threonine, valine, methionine, leucine, isoleucine, phenylalanine).*

In a free state, proline (3.61 μg/mg) and aspartic acid (0.73 μg/mg) in the bound state – glycine (1.25 μg/mg), arginine (0.87 μg/mg) accumulated in large quantities, serine (0.84 μg/mg) and glutamic acid (0.80 μg/mg). In the free state, in the minimal quantities were accumulated methionine (0.024 μg/mg), glycine (0.040 μg/mg) and threonine (0.046 μg/mg), in the bound state – proline (0.079 μg/mg), aspartic acid (0.229 μg/mg) and methionine (0.231 μg/mg). An amino acid such as lysine was not found in the roots of shrubby Sophora.

Conclusions: *using the HPLC method, we determined the content of 15 free and bound amino acids in the roots of shrubby Sophora, of which 6 are irreplaceable. Monoaminomonocarboxy, monoaminodicarboxy, diaminomonocarboxylic, aromatic and heterocyclic amino acids were found in the series of bound acids. Considering that amino acids contribute to the rapid absorption and potentiation of the action of other biologically active substances (phenolic compounds, polysaccharides, organic acids, macro- and microelements) contained in plant raw materials, the study of the amino acids of the roots of Sophora flavescens L. is promising for use in official medicine and gives the opportunity to create new drugs of combined action based on the specified type of medicinal plant materials*

Keywords: *shrubby Sophora, roots, amino acid composition, essential amino acids, high performance liquid chromatography*

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ANTIPYRETIC ACTIVITY OF THE NEW 2-(((3-MERCAPTO-5-METHYL-4H-1,2,4-TRIAZOL-4-YL) IMINO)METHYL)-5-R-BENZOATES

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Temperature rise is an important defensive mechanism of the body that activates immune system and increases phagocytosis, suppressing viral and microbial growth. Antipyretic activity, which involves the increase of thermolysis through angiectasis of skin vessels and heightened sweat production, is largely connected with a relaxing effect on the diencephalon's thermoregulation centers' irritation that may be altered due to disease.

Body temperature higher than 39 °C poses a threat to human health, including people of any age, from kids to adults of all ages.

Despite analgesics' high effectiveness, their use is not entirely safe. The use of aspirin impairs blood coagulation and increases the risk of inflammatory processes in gastroenteric tract and causes angiasthenia.

The search and study of the new highly effective antipyretic medicines is greatly relevant nowadays.

***The aim of this work** is to conduct a pharmacological screening over the new antipyretic drugs, specifically the derivatives of 2-(((3-mercapto-5-methyl-4H-1,2,4-triazol-4-yl)imino)methyl)-5-R-benzoate that were obtained for the first time.*

Materials and methods.

The objects of the research were the new 2-(((3-mercapto-5-methyl-4H-1,2,4-triazol-4-yl)imino)methyl)-5-R-benzoate derivatives.

The experimental fever was caused in white nonlinear rats by administrating 2,4-dinitrophenol (2,4-DNP), a dividing agent in oxidative phosphorylation, at the dose of 20 mg/kg. Acetylsalicylic acid was administrated to the reference group of animals at the dose of 100 mg/kg.

The substances of research were administrated in 30 minutes ($T_{0.5}$) after rats received 2,4-DNP, body temperatures were recorded during 1 hour (T_1). The initial rectal temperature (T_0) was recorded prior the abdominal injection of 2,4-DNP. Acetylsalicylic acid was used as a reference substance at the dose of 100 mg/kg.

Results and discussion.

The results of the experiment established that in 30 minutes after the abdominal injection of 2,4-DNP, body temperature in the population of rats (n=133) was in range from 37.36 °C to 38.37 °C on average ($_{\Delta}T$=0.88 °C).

As for the reference substance acetylsalicylic acid, it caused a 3 % decrease of body temperature in rats with a modeled pathology ($_{\Delta}T$=–1.2 °C, p≤0.05) with relation to the reference group.

The results demonstrated that antipyretic activity of some of the substances was better than that of the reference substance. Hence, substances IV, V, and VIII decreased body temperature in rats by more than 0.39 %.

Among the studied entities, substances IV and V are the most promising; they decreased body temperature in rats by 4.66–4.95 %, or by 1.19–2.10 °C, with relation to the reference group.

Conclusions

New 2-(((3-mercapto-5-methyl-4H-1,2,4-triazol-4-yl)imino)methyl)-5-R-benzoate derivatives were obtained. Ammonium 2-(((3-mercapto-5-methyl-4H-1,2,4-triazol-4-yl)imino)methyl)-5-R-benzoate is the most active substance. Introduction of inorganic cations leads to the loss of activity. Introduction of piperedinium leads to a slight increase of activity, but still it is weaker than that of the reference substance

***Keywords:** 1,2,4-triazole derivatives, organic synthesis, biological activity, antipyretic activity, antipyretics, hyperthermia*

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