

2018 № 1

Contents

Editorial Board

Contents

MOLECULAR DYNAMICS STUDY OF QUERCETIN AND SOME OF ITS SUCCINYL DERIVATIVES IN AQUEOUS SOLUTION

Lisnyak Yu. V., Martynov A. V.

Introduction. Numerous and diverse biological activity of flavonoid quercetin motivates interest to the peculiarities of its structure as a prerequisite for understanding its structure-function properties which are not fully understood today and remain an object of physico-chemical, biological and structural studies. In the solid state, quercetin is known to exist in two crystal forms, quercetin monohydrate and quercetin dihydrate. But there are only scarce data on its structure in the aqueous solution. High-throughput screening studies indicated that quercetin belongs to promiscuous inhibitors and is hypothesized to form aggregates comprising of many individual molecules. To investigate the peculiarities of structure and intermolecular interactions of quercetin as well as some of its succinyl derivatives in liquid phase we carried out molecular dynamics simulation of their behavior in the aqueous solution. **Methods .** Molecular dynamics simulations and the data analysis were performed by molecular modeling program YASARA Structure. Molecules of quercetin or its succinyl derivatives were randomly placed within a dodecahedral simulation cell. Simulation cell was filled with TIP3P water molecules to reach 10 % concentration of quercetin or its succinyl derivatives. Na⁺ and Cl⁻ counterions were added to neutralize the system and to reach ion mass fraction 0.9% NaCl. The molecular system was energy-minimized using AMBER14 force field with 8 Å force cutoff for dispersion interactions. To treat long-range electrostatic interactions the Particle Mesh Ewald algorithm was used. After a short steepest descent minimization, the procedure continued by simulated annealing minimization. The molecular dynamics simulations were run in NPT ensemble at 300 K and pH 7.4 using a multiple timestep of 2.5 fs for intra-molecular and 5 fs for inter-molecular forces. For each molecular system, trajectories were computed for 100 ns. **Results and discussion.** From the first nanoseconds of simulations, molecules of quercetin as well as succinyl-quercetins approached one another and began to self-organize into a compact aggregate that remained stable during further simulation time. Driving forces of the aggregate formation were the hydrophobic stacking interactions between aromatic systems of neighbor molecules. Due to a bulky succinyl substituent the aromatic systems of neighbor succinyl-quercetin molecules could not overlap optimally to ensure efficient stacking interactions that resulted in the higher mobility of the molecules in the aggregate and the possibility to form easily intermolecular H-bonds. Behavior of completely succinylated quercetin, 3,4',5,5',7-succinyl quercetin, in aqueous solution was essentially different. In this case, molecules remained free the majority of time and sometimes formed short-lived complexes between two or three molecules. The driving forces of the complex formation are hydrophobic and ionic intermolecular interactions. Hydrophobic interactions occurred between aliphatic residues, between aliphatic residues and aromatic systems, and also between aromatic systems. The later took place in T-shape ring arrangement. Ionic interactions between molecules of completely succinylated quercetin are mediated by their interactions with one or two Na⁺ ions. **Conclusions.** Results of our molecular dynamics simulations of the behavior of quercetin and some of its succinyl derivatives in aqueous solution are in line with the hypothesis of the self-organized aggregate formation by molecules of promiscuous inhibitor quercetin and reveal the peculiarities of the structure and intermolecular interactions within the aggregates in case of quercetin and the combinatorial mixture of its succinyl derivatives. These data may be useful for the search of new drugs based on quercetin as a lead compound.

Keywords: quercetin, succinylated quercetin, supramolecular aggregates, molecular dynamics.

EPIDEMIOLOGICAL FEATURES OF THE MEASLES IN KIROVOGRAD REGION in 2004 – 2015 16-20

Operchuk N.I.

Introduction.The incidence of measles in Ukraine remains an actual problem. Measle is related to vaccine - controlled infections. However, low levels of immunization of the child population by planned measles vaccine, insufficient provision of immunobiological drugs (vaccines) in recent years, anti-vaccine companies contribute to the increase of the measles morbidity in Ukraine. Prominent scientist L.V. Gromashevsky spoke about measles, which is a "disease of unique distribution". In the implementation of the Program for the elimination of measles, an important role is assigned to laboratory diagnostics as an integral part of epidemiological surveillance, which assures laboratory confirmation of all cases of measles disease. The purpose of the study: to analyze the peculiarities of the epidemic situation of measles in the Kirovograd region, the state of laboratory diagnosis of measles. Materials and methods: Data from the official statistical reporting of the state institution "Kirovograd Regional Laboratory Center of the Ministry of Health of Ukraine" (forms №1, № 2, № 40), demographic annual indicators of the State Statistics Service of Ukraine and the Main Department of Statistics in Kirovograd region. Results and discussion: The epidemiological analysis of measles incidence in the Kirovograd region in the period 2004-2015 and the results of laboratory diagnosis of cases in measles in this period of observation have been carried out. The peculiarities of manifestation of the epidemic process of measles in the Kirovograd region require a detailed study also because Kirovograd region is the only region in Ukraine with rich natural reserves of uranium ore. The presence of uranium raw materials on the territory of the region in turn increases the natural radiation background. The technological process of which enhances natural ionizing radiation technogenously. The effect of technogenic contamination by natural radionuclide of the environment and the increased natural radiation background on the human immune state, as well as the manifestations of the epidemic process of the measles, the influence on the properties of viruses is not excluded. From 2004 to 2015, the incidence of measles in Ukraine ranged from 0.06 (2009) to 90.7 per 100 thousand population (2006). During this period, there were two peaks of the measles in Ukraine: in 2006 - 90.7 per 100 thousand and in 2012 - 27.9 per 100 thousand populations. During 2007-2010, the incidence of measles in Ukraine gradually decreased (2.15, 0.11, 0.06, and 0.08 per 100 thousand populations, respectively). The dynamics of measles morbidity in the Kirovograd region for the period 2004-2015 is characterized by unstable levels. The trend of the morbidity of the population of the region repeats the course of measles morbidity in Ukraine with a slight decrease or excess. In this period, the incidence rates of the Kirovograd region were lower than the Republican figures in 2005 (by 49%); 2007 (by 67%); 2008 (by 9.0%); 2011 (by 76%); 2013 (by 67%) according to similar indicators in Ukraine. In 2010 and 2015, the incidence of measles in the Kirovograd region was not recorded. In all other years of the observation period, the incidence rates of measles in the Kirovograd region were higher than in Ukraine as a whole. In the region, one peak of the incidence of growth was observed in 2006, when the incidence rate in the Kirovograd region (147.9 per 100 thousand populations) exceeded the similar indicator in Ukraine (90.7 per 100 thousand populations) in 1, 63 times. During this time, 1,741 inhabitants of the region suffered from measles, including - 472 (21, 1%) children and 1269 (78.9%) adults. If the share of children's population in the overall incidence of measles in the Kirovograd oblast amounted to 85.7% in 2007; in 2013

C.
(P.)
1
2-5
6-15

- 62.5%; in 2005 - 53.6%; then in 2006 - 25.2%; in 2011 - 28.6%; in 2014 - 36.8%. The laboratory confirmation of a clinical diagnosis in the early stages of the development of the outbreak improving the effectiveness of epidemiological surveillance of the measles promotes. 214 samples of blood serums from patients with suspected measles and a clinical diagnosis of "Measles" were received to the virological laboratory of the Kirovograd Regional Laboratory, accounting for 12.3% of all reported cases of measles in 2004-2015. 214 samples (100%) were investigated for the detection of antibodies to the IgM class of the virus of the measles. In the study of blood serum antibodies of the class IgM found in 42.5% (91 people). The levels of immunization against the measles population in the Kirovograd region since 2009 were insufficient and below 95%. The plan for vaccination against measles in children in 1 year is fulfilled: on 75.9% (2009), 52.8 (2010); 62.3% (2011); 89.8% (2012); 80.7% (2013); 86.5% (2014); to 39.6% (2015). The plan of the revaccination plan for children 6 years of age is secured by 71.6% (2009); 31.5% (2010); 31.0% (2011); 89.2% (2012); 77.9% (2013); 73.0% (2014); 27.4% (2015). Conclusions. Despite the fact that the intensity of the epidemic process of measles in the Kirovograd region during the last epidemic peak was significantly lower than in Ukraine in general, the marked tendency to increase the incidence among children and insufficient coverage of children by vaccination and revaccination is an unfavorable prognostic sign. This refers to the risk of further growth of the intensity of the epidemic process at the expense of those age groups of the population who must be protected in accordance with the vaccination calendar, and the loss of the measles infection as a "managed" status. The current situation requires immediate action to restore immunization in the country in full.

Keywords: measles, epidemiology, Ukraine, Kirovograd, year 2004-2015

ANTISEPTIC SPRAY BASED ON STABILIZED SILVER PARTICLES: AN ANALYSIS OF ANTISEPTIC PROPERTIES AND COMPREHENSIVE COMPARISON

21-27

Manuilov A.M., Martynov A.V.

Introduction. It's known that some antiseptic sprays based on alcohols can provoke the formation of multi-resistant strains of pathogenic microorganisms. In addition, alcoholic antiseptics has a number of restrictions to use, for example, they can't to be used in even the presence of micro-trauma on the skin, their ingression into the body and mucous membranes is unacceptable. Alternative can be natural antiseptics based on colloidal silver or silver nanoparticles, as well as silver in ionic form. However, such antiseptics has low efficacy against the most dangerous strains. Company Modern Biochem Technologies Ltd. announced the development of a portable device that generates a natural and safe antiseptic Dew, based on stabilized silver particles. Antiseptic Dew surpasses the vast majority of antiseptics based on silver, and is not inferior in effectiveness to antiseptics based on alcohols. This work is devoted to testing the declared characteristics of Dew and its comparison with antiseptics based on colloidal silver, silver nanoparticles and isopropyl alcohol. **Materials and methods.** To test the antiseptic effect of these agents, we used four test strains from the American Type Culture Collection: E. Coli ATCC 25922, Staphylococcus Aureus ATCC 25923, Candida Albicans ATCC 885-653 and Proteus Vulgaris ATCC 4636 with billion concentration of colony forming units in 1 ml ($10^8 - 10^9$ CFU/mL, ln CFU/mL = 19.57 ... 20.72). Sowing and screening of cultures were performed on sterile Petri dishes according to the standard procedure. Antiseptic Dew was prepared by prototype provided by Modern Biochem Technologies. The antiseptics of comparison were purchased in Kharkiv, Ukraine. The treatment of contaminated surfaces was performed using mechanical pump sprayers. In accordance with the internal protocol, 1 ml of antiseptic was sprayed from the distance of 10 cm onto the infected surface. To determine the silver content in the Dew, we were used atomic-absorption spectrometer MGA-925MD. Samples for analysis were prepared in accordance with the standard protocol for operation on MGA-925MD. **Results & Discussion.** For the research we conducted more than 200 microbiological tests. Based on the results of these tests, we can conclude that Dew is indeed superior to other silver-based antiseptics. Also, we can note that in one case, Dew surpassed the effectiveness of the antiseptic based on isopropyl alcohol, but in the second case was slightly less effective. Dew is effective against all four test strains, and the decrease in microbial load after treatment is very substantially - from 10^9 CFU/mL to $0-10^1$ CFU/mL. The concentration of silver in Dew does not exceed 1.45 ppm and is on average 20 times lower than that of the other tested antiseptics based on silver. **Conclusion.** Based on the data obtained, we conclude that Dew is a promising antiseptic. Note that the prototype generated the antiseptic with stable characteristics throughout the study. Antiseptics of comparison were shown their effectiveness against test strains, however in one case Dew was surpassed them all in efficiency. In conclusion, we note that we recommend conducting in-depth tests, primarily aimed at determining the effect of Dew in vivo. We also recommend testing Dew on hospital-strains or other resistant strains.

Keywords: spray, antiseptic, silver, antimicrobial

CORRECTION OF LARGE INTESTINE DYSBIOSIS IN PATIENTS WITH ACUTE HEPATITIS B

28-31

Sklyar A.I., Kalinichenko S.V., Melent'yeva K.V., Torianyk I.I., Popova N.G.

Introduction. Viral hepatitis is one of the global challenges for modern medicine. Among them, hepatitis B (GB) remains one of the most widespread viral diseases of the present day. According to the WHO estimates, more than 1/3 of the world's population (2 billion people) has serological evidence of current or transmitted HBV infection, of which 350 million are chronically infected. Separate studies have identified the state of the colon biocenosis in patients with acute hepatitis and found that dysbiotic lesions of varying degrees are found in patients with viral hepatitis in 73.3% - 96% of cases [6-8]. Disturbances of the quantitative and qualitative composition of the microflora reduce the detoxification function of the intestine and increase the toxic load on the liver, which, in turn, negatively affects the development of the basic pathological process. **The aim of the work** was to determine the degree of dysbiotic changes in the microflora of the large intestine and to evaluate the effectiveness of their correction with a symbiotic drug in patients with acute hepatitis B. **Materials and methods.** To perform the task, 108 patients with acute hepatitis B, aged 18-69 being on hospital treatment at Kharkiv Regional Clinical Hospital of Infectious Diseases, have been examined. The diagnosis has been set on the basis of clinical anamnestic, epidemiological, laboratory and instrumental data. The etiologic verification of the diagnosis has been performed by detecting specific serological markers of hepatitis B (HBsAg, HBeAg, anti-HBc IgM, by the ELISA method). The diagnosis of GHB and its clinical and pathogenetic variants of the course, form and degree of severity have been determined according to the International Statistical Classification of Diseases and Related Security Problems Health (ICD-10, version 2006). According to the purpose of study the patients have been divided into groups as follows: group A - the main one, where patients have additionally been taking symbiotic besides who the basic treatment; group B - patients to whom basic therapy has been applied. Thus, 2 groups of 54 patients have been formed. The control group, which did not differ from the groups of patients by age and gender, has been made up of 17 clinically healthy persons. For patients of group A patients we have been using symbiotic — Bifilact Extra, TM "Ariadna", Ukraine, certificate of registration No. 05.08.07 / 4089 of 02.10.2000 containing *Lactobacillus acidophilus* and *Bifidobacterium bifidum*. Determination of the qualitative and quantitative composition of microbiocenosis of the large intestine has been carried out in accordance with current normative documents as per generally accepted methods. The degree of dysbiotic disturbances was determined by V.M. Bondarenko in 2007. Microbiological studies of the material have been conducted in dynamics before the treatment and 7 days after the end of the course of treatment with the symbiotic. Statistical processing of the data was carried out using the Statistics-10 software package, Microsoft Office Excel 2003. **Results.** In all patients, there was an acute cyclic course of HBV infection with clinically expressed jaundice in the background of cytotoxic syndrome. By results of researches of the species composition of the microflora of the colon in jaundice period of AHB, a violation of the microecology of this biotope of different degrees was found in 96.3% of patients. It turned out that the degree of dysbiotic shifts did not depend on the severity of hepatitis. About half of patients had dysbiosis of grade III. Analyzing the species composition and population level of the microflora of the colon in patients with acute hepatitis

B in the jaundice period, there was elimination or severe deficiency of bifidobacteria and lactobacilli and the vegetation of opportunistic bacteria. But the most common cause of local microecology was *Candida* spp, it was determined in 30,8 % of the total number of identified pathogenic microorganisms. In addition, the proportion of *Candida* spp in violation of the microecology of the large intestine increased in the dynamics of the disease to 42,3%, which was evidenced in the period of convalescence. The appointment of a symbiotic resulted in a reduction in the clinical manifestations of dysbiosis in 63,0 % of patients compared to patients receiving baseline therapy. The appointment of a symbiotic resulted in a reduction the length of stay of patients of mild severity and patients of average severity in the hospital compared to patients receiving baseline therapy, $p < 0,05$. **Conclusions.** By results of researches of the species composition of the microflora of the colon in jaundice period of AHB, a violation of the microecology of this biotope of different degrees was found in 96,3% of patients. About half of patients had dysbiosis of grade III. The appointment of a symbiotic resulted in a reduction in the clinical manifestations of dysbiosis in 63,0 % of patients compared to patients receiving baseline therapy. The appointment of a symbiotic resulted in a reduction the length of stay of patients of mild severity and patients of average severity in the hospital compared to patients receiving baseline therapy.

Keywords: acute hepatitis B, large intestine, microbiocenosis, complex treatment, symbiotic.

THE ROLE OF EPSTEIN-BARR VIRUS AND HUMAN ENDOGENOUS RETROVIRUSES IN THE PATHOGENESIS OF MULTIPLE SCLEROSIS 32-37

Zelenska A. D., Tupotilov O. V., Kolyada T. I.

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS), the development of which is associated with the action of a large number of pathogenetic factors which role can vary significantly at different stages of the disease. Although the etiology of MS still remains unclear, in recent years the hypothesis of the pathogenetic role of Epstein-Barr virus (EBV) and human endogenous retroviruses, such as MSRV / HERV-W, is actively considered. EBV has a unique ability to infect, activate, and latently persist within B lymphocytes during human life. Immune control of EBV infection in healthy organisms is realized through humoral and cellular mechanisms – EBV virions are destroyed by neutralizing antibodies, and proliferating and lytically active EBV-infected B cells are the targets of specific CD8+ T cells. At the same time, EBV remains latent for most of the life of the infected individual, expressing a single gene (EBNA1) within memory B cells. EBNA1 protein is not well recognized by CD8+ T cells, allowing infected memory B cells to avoid detection. In addition to epidemiological data, association of EBV with MS is indicated by a significant increase in IgG titres to EBV antigens, mainly to EBNA1, in serum of patients a few years before the onset of clinical manifestations of the disease. Although the data on the presence of EBV in the CNS remain controversial due to a number of methodological difficulties, a number of studies have shown the presence of EBV-infected B cells in the CNS, as well as effector CD8+ T cells specific for them in meningeal inflammatory infiltrates and white matter lesions in brain samples of MS patients. At the same time, the EBV bystander damage hypothesis which considers CNS damage in multiple sclerosis as a result of EBV-targeted cytotoxic reactions of CD8+ T cells, does not explain the autoimmune nature of MS, although secondary autoimmune responses could develop as a result of sensitization to CNS antigens released after a cytotoxic response directed to EBV elimination causing bystander neuronal damage. It also does not explain why the EBV-targeted T cell immune response sufficient to cause bystander CNS damage does not eliminate EBV-infected B cells from the CNS. It was found that subpopulations of EBV-specific CD8+ T cells in MS patients show signs of depletion, increasing with the duration of the disease, which apparently allows EBV-infected B cells to accumulate in the CNS and leads to the formation of a vicious circle, in which the initially defective T cell response is aggravated by depletion of T cells as a result of a constant high viral load in CNS. M. Pender has proposed a hypothesis of the pathogenesis of MS according to which MS is caused by the accumulation in the CNS of autoreactive EBV-infected B cells that are capable of self-sustaining proliferation, production of pathogenic antibodies in the CNS, and providing costimulatory and survival-promoting signals to autoreactive CD4+ T cells. But it remains unclear what type of CD8+ T cells is dominant in CNS lesions in patients with MS - specific to EBV, specific to myelin proteins, or both types of cells. However, the delay between seroconversion in the EBV-positive status in late EBV infection and the development of MS may indicate the presence of additional factors in the development of the disease. In recent years, a number of studies indicate a possible pathogenetic role of endogenous human retroviruses (HERV) in MS. In infectious mononucleosis, the increased expression of MSRV/HERV-W in peripheral blood mononuclear cells has been observed, moreover, a direct correlation has been found between levels of IgG to EBNA-1 and levels of MSRV-specific mRNA expression. Binding of the EBV caused activation of MSRV / HERV-W in peripheral blood mononuclear cells and in astrocytes. Activation of MSRV/HERV-W was also revealed in inflammatory context and in neuropathogenic processes in MS. In the peripheral blood mononuclear cells culture of MSRV-positive individuals, expression of MSRV was activated by the action of pro-inflammatory cytokines such as TNF- α , IL-6, and IFN- γ , and significantly decreased by IFN- β . At the brain level, HERV-Wenv activates Toll-like receptors (TLR4) of oligodendroglial precursor cells, which results in the production of pro-inflammatory cytokines as well as inducible nitric oxide synthase (iNOS), and a decrease in myelin protein expression. Within chronic brain lesions in MS, HERV-Wenv was detected in microglia / macrophages near TLR4-positive oligodendroglial precursor cells. Immunohistochemical detection of HERV-Wenv protein in postmortem brain samples of MS patients showed its elevated levels only in active lesions in astrocytes and microglia, and the intensity of staining correlated with the degree of active demyelination and inflammation. Thus, EBV infection and activation of retroviruses are considered as important elements in the pathogenesis of MS. Within the framework of the "viral hypothesis", the most important tasks are the verification of data indicating the possible etiological role of EBV, the study of the pathogenetic mechanisms associated with MSRV/HERV-W at different stages of MS development, as well as the identification of immunological and genetic factors associated with the defective control of EBV-infected B cells and, as a result, their migration and accumulation in the CNS. Thus, EBV infection and activation of retroviruses are considered as important factors in the pathogenesis of MS. Late EBV infection may be the initiating trigger of the pathological process leading to the development of MS years later, and HERV-W / MSRV affect as active cofactors of the neuropathogenesis of the MS accompanying the course of the disease. **The aim of the review** was to consider the latest evidence of possible mechanisms of the involvement of EBV and human endogenous retroviruses in the pathogenesis of multiple sclerosis.

Keywords: multiple sclerosis, Epstein-Barr virus, human endogenous retroviruses, immunopathogenesis.

STUDY OF THE INFLUENCE OF A GEL FORMER (THICKENER) TYPE ON THE SORPTION KINETIC OF LONG-LIVING RADIONUCLIDES AND HEAVY METALS BY NATURAL ZEOLITE PASTE FROM AN AQUEOUS SOLUTION IN VITRO 38-44

Rybachuk V.D., Krasnopyorova A.P., Yuhno G.D.

Introduction. The deterioration of the population health, due to the chemicalization of many aspects of life, requires the development and introduction of new healing technologies. One of the modern areas of efferent therapy is the oral administration of sorbents. An alternative to solid dosage forms, in some acute cases, is using enterosorbents in the form of paste, but in the Ukrainian pharmaceutical market, the range of such medicines has only several positions. The promising sources for the creation of such medicines is the natural zeolite. The aim of our study was to investigate the influence of a gel former (thickener) type on the sorption kinetics of long-living ^{90}Sr and ^{137}Cs radionuclides and Pb^{2+} and Hg^{2+} heavy metals by natural zeolite paste from an aqueous solution in vitro. **Materials and methods.** As objects for the study we used experimental pastes containing 25% natural zeolite each and different gel formers: 7% silicon dioxide, 3% apple pectin and 0.5% sodium alginate. As sorption medium, we used solutions 7.25 mg/l $\text{Hg}(\text{NO}_3)_2 \cdot \text{H}_2\text{O}$ and 6.74 mg/l $\text{Pb}(\text{NO}_3)_2$ and radionuclide solutions ^{90}Sr ($1.8 \times 10^7 \text{ Bq/dm}^3$) and ^{137}Cs ($3.2 \times 10^7 \text{ Bq/dm}^3$). The sorption capacity for heavy metals was investigated by a limited volume method at pH

= 2 and pH = 6. The concentration of lead was determined by atomic absorption spectroscopy (atomic absorption spectrophotometer C-115 PCS) in a flame of acetylene-air ($\lambda = 283.3$ nm). The concentration of mercury was determined by the flame atomization method using mercury device PR-115 ($\lambda = 253.7$ nm). The sorption capacity of the samples against radionuclides was studied by the static sorption method at pH values 2.0, 5.5 and 8.0. The radioactivity were measured by a α - β -automaton NRR-610 "Tesla" radiometer. Concentration of ions and radioactivity of solutions were controlled after 0.5, 1, 2, 3, 4 and 5 hours of experiment. The equilibrium capacity of sorbents coefficient (A_{eq} , mg/g), the coefficient of sorption (K_s , %) and the coefficient of distribution of (K_d , l/g) were calculated for evaluation the process.

Results and discussion. The process of sorption includes two main stages – fast and slow. The first stage is responsible for the process of saturation of microcrystals by ions on the surface of the sorbent. The second stage, which indicates the complete saturation of sorbent surface by the ions with the subsequent slow diffusion ions inside the sorbent. For most of the investigated objects, the achievement of the adsorption equilibrium in the heterophasic system took place within first 30-60 minutes of the experiment. The sorption activity of samples against heavy metals and radionuclides varied widely and depended on a number of factors, such as the type of gel formers, pH of the solution, nature and physico-chemical properties of the ions (hydration energies, charge and radius of the ions). Significant influence on the sorption gave the pH value of the solutions. The complex nature of this dependence we explain by the influence of the acidity of the solution on the physico-chemical properties and the structure of the sorbents, as well as on their sorption-active centres. In this connection, it can be assumed that under other equal conditions, the exchange capacity of the studied sorbents in the stomach environment will be minimal, and will grow in the moderately alkaline environment of different parts of the intestine. The K_d value of studied samples against heavy metals allowed us to compare the sorption and selective properties of samples and arrange the metal ions in order of decreasing their relative affinity to sorbents as $Hg^{2+} > Pb^{2+}$. This difference in selectivity can be explained by the difference in an electronic configuration, as well as by a radius and a value of hydration energy of ions. The obtained K_d and K_s of radionuclides showed that samples better absorb ^{137}Cs radionuclide at all pH values. The sorption characteristics of ^{90}Sr are much lower, but they increase sharply with increasing pH values. The highest affinity with respect to ^{137}Cs and ^{90}Sr radionuclides was demonstrated by samples with silicon dioxide as a gel former. The greatest activity against all metals also showed the composition of the paste containing silicon dioxide as a gel former. Its sorption coefficient for lead and mercury ions were 93.2-99% and 95.8% respectively, and for ^{90}Sr and ^{137}Cs radionuclides were 19-65% and 64-91% respectively. **Conclusions.** The influence of the type of gel formers (thickeners) on the sorption kinetics of long-living radionuclides and heavy metals by natural zeolite paste (clinoptilolite) from an aqueous solution in vitro was studied. The best results samples with silicon dioxide have demonstrated. The obtained results will be taken into account in the further development of medicines with natural zeolite (clinoptilolite) in the paste form.

Keywords: natural zeolite, paste, sorption, radionuclides, heavy metals, gelling agents

INVESTIGATION OF THE PHARMACO-TECHNOLOGICAL PROPERTIES OF SOLID DISPERSIONS OF THIOCTIC ACID, OBTAINED BY MICRONIZATION

45-51

Kovalevska I.V, Ruban O.A.

Introduction. Thioctic acid is used in the treatment of diseases that are characterized by lack of mitochondrial activity, which is responsible for the formation of free radicals. Widespread use of thioctic acid is due to the chemical structure. The thioctic acid exhibits biological activity in both hydrophilic and hydrophobic environments. Thioctic acid is an enzyme cofactor and a powerful antioxidant, it regulates the transcription of numerous genes, participates in regulation of glucose and lipid metabolism, increases insulin sensitivity, and forms complexes with heavy metals. Thioctic acid has a high pharmacological potential, which is confirmed by the evidence base of clinical trials. An analysis of the literature on the oral use of thioctic acid indicates that solid dosage forms can be used for long-term therapy. This route of administration is limited by factors such as reduced solubility in acidic environments and enzymatic degradation. For this reason, the search for various compositions of auxiliary substances and methods of obtaining drugs is an urgent task of pharmaceutical technology. **Material & methods.** Objects of study were solid dispersions of thioctic acid (SDTA) on the basis of cellulose derivatives: microcrystalline (MCC), HPMC (hydroxypropyl methylcellulose) and polyvinylpyrrolidone (PVP) as compared to thioctic acid (TA). The samples were made by solid phase method using micronization in a laboratory shredder at a ratio of 1: 1. Pharmacological and technological parameters were determined according to generally accepted methods. **Results & discussion.** In appearance the resulting mixtures had lemon color, without inclusions and the formation of conglomerates, with homogeneous sized particles. According to the pharmaco-technological studies, the samples do not have a satisfactory flowability. The values of the Carr index and the ratio of Hausner make it possible to conclude that there is a large force of cohesion between the particles, a significant aeration of the material. As can be seen from the data presented in the table, micronization in the medium of MCC, PVP and HPMC has led to a change in the density of stacking, which is characteristic of powders with an anisodiametric form of particles, but the strength of the internal friction coefficient has practically not changed, as evidenced by the indicators of the natural slope. The value of porosity suggests a significant degree of the Van der Waals forces action between the particles of the SD. All samples of solid dispersions can be attributed to fragile materials: BW was 5.57 kgf / mm². When stored in a static state, there was a partial agglomeration. The results show that all samples of solid dispersions are well moistened with purified water, as opposed to a sample of thioctic acid. An analysis of the marginal wetting angle indicates that the surfaces of samples of solid dispersions are hydrophilic. According to the microscopic analysis it was established that the influence of external forces has changed the form of the thioctic acid: from the plate with the factor of the form 0,85 to the uncertain form. In samples with microcrystalline cellulose and hydroxypropyl methylcellulose there is a mixture of crushed thioctic acid crystals and carrier. The form factor has dropped to 0.45. The investigation of the dissolution of the obtained solid dispersions showed that the addition of MCC to thioctic acid even reduces the amount of matter passing into the solution, as opposed to solid dispersions with PVP and HPMC (24% and 37% respectively). The difference in the values of dissolution can be due to both the nature of chemical bonds, and the nature of electrostatic attraction, due to the polarity and the emergence of hydrogen bridges. The investigation of the dissolution of the obtained solid dispersions showed that the addition of microcrystalline cellulose to thioctic acid even reduces the amount of matter passing into the solution, as opposed to solid dispersions with PVP and HPMC. The difference in the values of dissolution can be due to both the nature of chemical bonds, and the nature of electrostatic attraction, due to the polarity and the emergence of hydrogen bridges. **Conclusion.** Thus, the results indicate an increase in the dissolution of thioctic acid in the solid dispersion with PVP in 2.6 times, with HPMC in 1.3 times, which may be the basis for research on the development of solid dosage forms of thioctic acid.

Keywords: Thioctic acid, solid dispersions, pharmaceutical technology, micronization