DOI: 10.15825/1995-1191-2023-2-170-177

COMPARATIVE ANALYSIS OF THE PHARMACOKINETIC PARAMETERS OF TRANSDERMAL AND INJECTABLE FORMS OF NICOTINAMIDE

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In recent years, oxidative stress, characterized by excess free radicals in the body, has been called the cause of many diseases. There is an active search for drugs with antioxidant properties that are suitable for long-term maintenance therapy. Nicotinamide (NAM), an antioxidant, is used to treat a variety of diseases, usually in oral or injectable form. Given the peculiarities of the drug regimen (dose, prolonged administration), a new dosage form of NAM, a microemulsion-based transdermal patch (TP), containing 20 mg/10 cm^2 of NAM, has been proposed. The objective of this work is to compare the pharmacokinetic parameters of intramuscular and transdermal NAM administration in animal experiments for 24 hours. **Materials and methods.** We used laboratory samples of nicotinamide TP based on a microemulsion-based transdermal delivery emulsion (TDS) with different content of sodium docusate transfer activator**.** The pharmacokinetics of transdermal and intramuscular injections were studied in male Chinchilla rabbits weighing 3.5–4.0 kg. Plasma NAM levels of the experimental animals were determined by high-performance liquid chromatography using a specially designed method on NUCLEODUR PFP columns (5 μm, 250 × 4.6 mm) using the mobile phase acetonitrile: deionized water. The samples were preliminarily purified by solid-phase extraction using Chromabond C18 Hydra cartridges. **Results.** When administered intramuscularly, the maximum blood NAM level was 13.3±1 μg/mL; when NAM transdermal forms were applied in the same dosage with different contents of the transfer activator, the levels did not differ significantly – 3.1 and 3.2 μg/mL. It was shown that in transdermal administration of NAM, concentration of the active substance remained at a constant level for ~6 hours. The bioavailability of NAM with transdermal administration was calculated relative to intramuscular administration: 1.43 for TP with 9.8% docusate sodium and 1.84 with 3.3% docusate sodium. **Conclusion.** NAM has a higher bioavailability when administered transdermally at 20 mg than when administered intramuscularly in the same dose. With transdermal administration, NAM concentration can be maintained at a constant level for a long time, without the jumps that are typical of intramuscular administration.

Keywords: transdermal therapeutic system, transdermal patch, antioxidant, nicotinamide, pharmacokinetics.

INTRODUCTION

In recent years, the possibility of using antioxidants as both the main and adjuvant agents in the treatment of a number of diseases caused by oxidative stress, has been actively studied [1, 2]. This condition leads both to damage at the cellular level and disruption of the functioning of entire organs and systems, resulting in diseases such as cancer, atherosclerosis, chronic renal failure, diabetes and its characteristic complications, autoimmune diseases, hemorrhagic shock, heart attacks, ischemic conditions, etc. It is known that oxidative stress also accompanies surgical procedures associated with reversible vascular ischemia [3]. It is worth noting that graft rejection, as well as graft dysfunction caused by ischemia/reperfusion injury, is often associated with oxidative stress [3–5]. In practice, various methods of donor pretreatment and antioxidant treatment of donor organs are actively used. At the same time, antioxidant therapy is also indicated for recipients to improve graft performance. However, instrumental methods that are mostly used are rather difficult to implement [4, 6]. A combination of antioxidant approaches seems to be a rational way out [4]. There is evidence of the benefits of using both antioxidant enzymes and some vitamin preparations with antioxidant properties among organ recipients. Natural antioxidants are also capable of reducing damage under oxidative stress, which has been shown in experiments on a model of liver ischemia/reperfusion injury, but their use is limited by the need for long-term continuous administration and large doses [6]. For example, the use of vitamins E and C after cardiac transplantation is

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recommended to protect blood vessels, but no large-scale studies in this area have been conducted [7].

In literature, pancreatic islet transplantation is mentioned as a promising alternative therapy for diabetes [8], which at all stages is accompanied by the use of antioxidants that promote islet cell engraftment, improve vascularization, and exhibit immunosuppressive properties [9]. Earlier studies in beta cell transplantation noted the positive effect of antioxidant drugs, including vitamins E and C [8].

We chose the water-soluble amide form of vitamin B_3, nicotinamide (NAM), a precursor of nicotinamide adenine dinucleotide (NAD), nicotinamide adenine dinucleotide phosphate (NAD^+) and their reduced forms as an antioxidant. NAD^+ derivatives play an enormous role in cellular homeostasis, generation, and inhibition of reactive oxygen species [10, 11].

The protective effect of NAM on insulin-producing β-cells has long been of particular interest; in addition, its stimulating effect on insulin secretion has been reported [12–17]. In addition to its protective effect in the treatment of diabetes, vitamin PP also plays a major role in islet cell repair [18]. The use of NAM in the therapy of diabetes can reduce the frequency or intensity of the most common complications of this disease, such as angiopathy, retinopathy, and neuropathy due to oxidative stress [11, 19–21]. The regenerative effect of NAM has been demonstrated in the restoration of liver tissue and its function in an experiment after partial hepatectomy [22]. The possibility of using NAM to reduce phosphate levels in hyperphosphatemic patients with renal failure who are on hemodialysis has been shown [23].

Constant, controlled rate of administration of appropriate drugs is an important condition for antioxidant therapy in transplantation [4]. A solution to this problem could be the use of reverse emulsions as part of transdermal therapeutic systems (transdermal patches, TP), which provide controlled continuous dosing of the active ingredient over a long period of time, delivering it to the target organs in unchanged form through the systemic circulation without first passing through the liver. The main advantages of TP include prolonged release of the active ingredient without jumps in its blood concentrations that can lead to adverse effects [24].

Given the physicochemical properties of nicotinamide (small molecular weight of 122.1 g/mol, hydrophilicity) [25] and the features of the regimen (long courses, oral or injected administration from 1 to 4 times a day, high doses, the need to divide the daily dose into several doses) [26], the authors developed a transdermal patch for nicotinamide (20 mg/10 cm^2) based on a microemulsion-based TDS [27]. The aim of this work is to carry out a comparative analysis of the pharmacokinetic parameters of nicotinamide in transdermal and intramuscular administration.

MATERIALS AND METHODS

Materials and equipment

Nicotinamide (molecular weight 122 g/mol Sigma, USA) in powder form was used as the active ingredient.

Laboratory samples of nicotinamide TP were made using materials and excipients approved for medical use and meeting the requirements of current regulatory documentation.

The microemulsion-based TDS for nicotinamide included the following components: deionized water, sodium dodecyl sulfate (AppliChem Panreac, Spain), apricot kernel oil (Desert Whale Jojoba Company Ltd, USA), α-tocopherol acetate (BASF SE, Germany), dioctyl sodium sulfosuccinate (docusate sodium) (Sigma, USA), and Decaglin PR (Decaglyn PR-20, Nikko Chemicals Co., Ltd., Japan).

To create the nicotinamide TP, the following auxiliary materials were chosen: elastic microbubble material Foam tape 9773 (3M, USA), sorbent base PALV-01 (Palma Group of Companies LLC, Russia), Skotchpak 9730 film (3M, USA).

Sodium citrate (NPO RENAM, Russia) was used to stabilize blood samples during *in vivo* studies.

All plasma samples, including calibration solutions, were purified from impurities using solid-phase extraction (SPE). Purification was performed using 3 mL Chromabond C18 Hydra cartridges (Macherey-Nagel, Germany) with a sorbent mass of 200 mg, which were prepared using solvents (acetonitrile (PanReac, Spain) and deionized water) used to create the mobile phase during chromatographic analysis.

Quantification of NAM in the samples by high-performance liquid chromatography (HPLC) was performed on a NUCLEODUR PFP column (5 μm, 250 × 4.6 mm Macherey-Nagel, Germany) with a NUCLEODUR PFP precolumn (4 × 3 mm, 5 μm Macherey-Nagel, Germany).

Equipment used in the work: DIAX 900 dispersant (Heidolph, Germany), UIS250V ultrasonic homogenizer (Heilscher, Germany), GH-200 analytical scales (AND, Japan), Rotina 38R centrifuge (Hettich, Germany), cleaning system Simplicity (Millipore, Germany), vacuum system with manifold and LiChrolut pump (Merck, Germany), Agilent 1260 Infinity chromatograph (Agilent Technologies, USA) equipped with diode matrix detector, column thermostat and Chem Station software (Agilent, USA).

Study design

The pharmacokinetics of NAM in transdermal and intramuscular injections was studied on male Chinchilla rabbits weighing 3.5–4.0 kg.

The rabbits were obtained from a nursery belonging to KrolInfo Ltd. The producer provided a veterinary certificate for the last animal health monitoring. All the experimental animals were specially bred and were not

previously involved in research. Quarantine was for 14 days. All manipulations didn't cause any pain to the animals and were conducted according to the rules adopted in the European Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes (ETS 123) Strasbourg, 1986) and in accordance with the Russian legislation: GOST 33215-2014 (Guidelines for accommodation and care of laboratory animals: Environment, housing and management) and GOST 33216-2014 (Guidelines for accommodation and care of laboratory animals: Species-specific provisions for laboratory rodents and rabbits).

Plasma NAM levels in transdermal and intramuscular administration was studied according to the developed design. The animals were divided into three groups at random. The first group of animals (n = 5) received NAM once intramuscularly at a dose of 20 mg. In the second (n = 7) and third groups (n = 5), we examined the pharmacokinetic parameters of the transdermal therapeutic system with the drug at the same dose but with different levels of the transdermal carrier of dioctyl sodium sulfosuccinate (3.3% and 9.8% respectively) in the microemulsion-based transdermal delivery system.

In groups 2 and 3, transdermal patch was applied to a pre-shaved dorsal skin area at the base of the neck. The drug was applied to healthy skin not earlier than one day after the hair removal procedure.

Blood sampling of the experimental animals was performed before administration of the drug, as well as at discrete time intervals from the marginal ear vein, into tubes with 3.8% sodium citrate solution. Blood sampling times for TP were 40, 50, 60 minutes, then every hour for 8 hours, 12, 15, 18, and 24 hours of application. For the injectable form: 5, 10 minutes, then for 1 hour every 10 minutes, then every hour for 8 hours after intramuscular injection of NAM.

Test tubes containing the blood samples from experimental animals were centrifuged for 5 minutes at 1500 rpm at room temperature, then the plasma was carefully collected.

HPLC for quantification of nicotinamide in the plasma of the experimental animals

Sample preparation

Eppendorf tubes were filled with 500 μL of blood plasma samples and diluted with distilled water in a 1 : 1 ratio. After stirring, the contents of the tubes were transferred to a previously activated SPE cartridge. The sample was passed at a rate of 1–1.5 mL/min, adjusting the rate using the manifold valve. A three-fold wash with water (1 mL each) was then performed, after which NAM was eluted with the mobile phase (acetonitrile:deionized water, 20:80, 1 mL). The eluate was then analyzed on a liquid chromatograph.

When preparing calibration solutions, 20 μL of a standard solution of NAM with a known concentration (6.25; 12.5; 25; 125; 250 μg/ml) was added to 480 μL of plasma, then 500 μL of deionized water was added, and SPE of calibration solutions was performed as described above.

Since NAM is present in all tissues of the animal body, to correctly estimate the amount of NAM in the studied samples, its background values were taken into account by performing plasma studies before applying the patch and subtracting the values obtained when processing the obtained data.

Quantification of nicotinamide

Quantification of NAM in blood plasma after SPE was performed by HPLC under the following conditions:

Mobile phase: acetonitrile:deionized water.
Elution mode: gradient (Table 1).
Mobile phase flow rate: 1 mL/min.
Column thermostat temperature: 40 °C.
Volume of injected sample: 20 μL.
Detection wavelength: 262 nm.
Chromatographic time: 30 min.
NAM retention time: ~11.8 minutes.

Calculation of pharmacokinetic parameters

Pharmacokinetic research method allows to give a number of quantitative characteristics of the processes of absorption, metabolism (biotransformation), distribution and removal of drugs from the body. For this purpose, the following parameters were calculated [28]:

– C_{max}, maximum concentration of the drug in blood plasma (μg/mL).
– T_{max}, time to reach maximum drug concentration (hour).
– AUC, the total area under the drug concentration curve from the time of its entry into the body until its complete removal from the body (h·mcg/mL).
– AUMC, the total area under the curve of the product of time and drug concentration in the body from the moment of its entry into the body until its complete removal from the body (h^2·mcg/mL);

Table 1

Composition of the mobile phase

Time (minutes)	Ratio of the components of the mobile phase (%)	
	Acetonitrile	Deionized water
0	0	100
5	0	100
6	5	95
11	5	95
16	30	70
21	30	70
24	0	100
30	0	100

– $T_{1/2}$, drug half-life – the period of time required for the concentration of the drug in the body to be reduced by one-half (hour);
– MRT, mean residence time – the average time that the drug spends in the body (hours);
– β, elimination rate constant (h^{-1});
– F, bioavailability.

Relative bioavailability was determined by comparing the total areas under the drug concentration curve from the time of entry into the body to complete removal from the body in transdermal and intramuscular injections. It was calculated by the formula:

$$F = \frac{AUC_{(TP)} \times D_{(injection)}}{AUC_{(injection)} \times D_{(TP)}},$$

where AUC is the area under the kinetic curve, D is the drug dose.

Pharmacokinetic parameters were calculated using a model-independent method.

Statistical processing of results

Normal distribution of experimental data was proved using the Shapiro–Wilk test on a small number of samples ($n \geq 5$). Significance of differences was determined using Student's t test (standard software package Microsoft Excel 2010). Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

A comparative analysis of the pharmacokinetic parameters of NAM in intramuscular and transdermal administration in rabbits was performed.

The averaged pharmacokinetic curves of NAM obtained by application of TP with different levels of transdermal carrier of docusate sodium (9.8% and 3.3%) and intramuscular injection (at the same dose of 20 mg) are presented in Fig.

As can be seen from Fig., for intramuscular administration of NAM, the maximum concentration (drug) in the blood was reached after 20 minutes, 13.3 ± 1.0 μg/mL. Then there was a sharp decrease to 5.3 ± 0.7 μg/mL by 2 hours after drug administration. By 8 hours of the experiment, the concentration was 0.30 ± 0.35 μg/mL.

When transdermal forms of NAM were applied with the same dosage with different carrier content, increase in blood concentrations was slower than with intramuscular injection, as shown in Fig. By the first hour, 2.2 ± 0.85 μg/mL and 1.4 ± 0.44 μg/mL drug were detected in the blood when the transdermal patch was applied with 3.3% and 9.8% carrier, respectively.

With this method of administration, the maximum NAM concentration in the blood for the patch with different transfer activator content did not differ significantly (~3.1 and 3.2 μg/mL), remaining constant within the statistical error for about 6 hours.

For TP with lower carrier content, the decrease in NAM concentration began after 7 hours of application, and after 15 hours NAM was no longer detectable in the blood. In the case of application of forms with more carrier, a gradual decrease in NAM levels was traced: the beginning of the decrease was noted after 8 hours of application, the drug concentration was 0.55 ± 0.35 μg/mL at 15 hours, and no NAM was detected in the blood plasma at 24 hours.

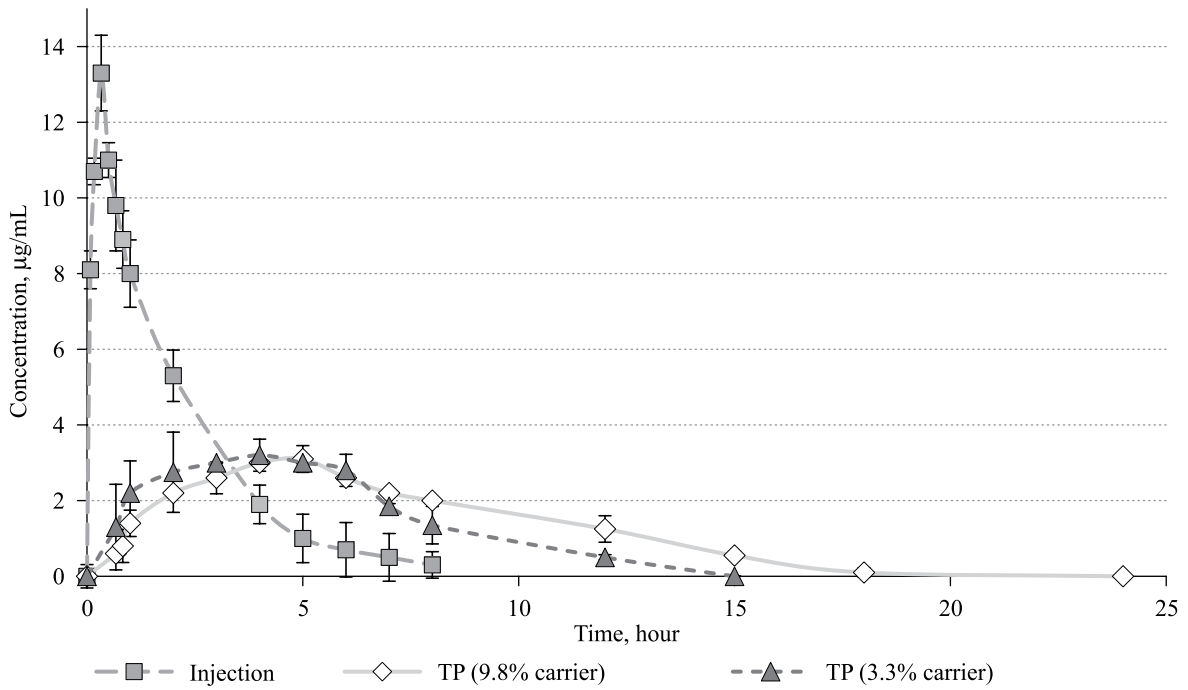

Fig. Averaged dynamics of plasma NAM levels in experimental animals with intramuscular and transdermal administration. Differences in the values of points (Δ) and (◊) are not statistically significant ($p > 0.05$)

Table 2

Pharmacokinetic parameters of nicotinamide with transdermal and intramuscular administration in rabbits

Parameters	Method of administration		
	Intramuscular, n = 5	Transdermal	
		Transdermal carrier content	
		3.3%, n = 7	9.8%, n = 5
C_{max}, μg/mL	13.3	3.2	3.1
T_{max}, h	0.33	4	5
β, 1/h	0.495	0.301	0.187
$T_{1/2}$, h	1.4	2.3	3.7
AUC, h·μg/mL	27.01	49.75	38.58
AUMC, h^2·μg/mL	50.12	320.89	245.5
MRT, h	1.9	6.5	6.4

Thus, with the transdermal method of nicotinamide delivery, there was a more uniform and prolonged drug entry into the blood, while the concentration remained at a constant level for ~6 hours.

The calculated pharmacokinetic parameters for single transdermal and intramuscular administration of NAM to experimental animals are presented in Table 2.

The average time that NAM spends in the body (MRT) in the transdermal patch groups in both cases was more than 6 hours. In the case of intramuscular injection, MRT was 1.9 hours. Thus, a transdermal nicotinamide therapeutic system can increase the mean residence time of the drug in the body by about 3 times compared to intramuscular injection.

The drug half-life $T^{1/2}$ was 3.7 and 2.3 hours for the drug forms with a higher and lower content of the transdermal transfer activator, respectively. This parameter was lower by almost 2.5 times – 1.4 hours – when NAM was administered intramuscularly.

Calculation showed that NAM had a higher bioavailability when administered transdermally than when injected intramuscularly (1.43 for TP with 9.8% carrier and 1.84 with 3.3% carrier).

Thus, the results of the *in vivo* studies and a comparative analysis of the pharmacokinetic parameters of NAM in transdermal and intramuscular administration showed the promise of the transdermal route of administration of the studied antioxidant.

CONCLUSION

In the course of this work, the pharmacokinetics of intramuscular and transdermal routes of NAM administration *in vivo* were studied using transdermal patches with different contents of the transdermal carrier activator of dioctyl sodium sulfosuccinate.

Application of the NAM 20 mg transdermal therapeutic system has been shown to provide higher bioavailability than intramuscular administration of this drug at the same dose. At the same time, the maximum drug concentration in the blood is 4 times lower and its residence time in the body is more than 3 times longer, which may promote prolonged drug effect. Changes in the drug concentrations in the blood for transdermal patch occur gradually over several hours in contrast to its sudden jump when NAM is administered intramuscularly. This is a definite advantage of the transdermal nicotinamide system in case of long-term use for prophylaxis and maintenance therapy.

The authors declare no conflict of interest.

REFERENCES

1. *Olefir YuV, Romanov BK, Kukes VG, Sychev DA, Prokofiev AB, Parfenova OK et al.* The role of oxidative stress in the pathogenesis of socially significant human diseases and ways of its drug correction. *Medical News of North Caucasus*. 2021; 16 (4): 450–455. [In Russ, English abstract]. https://doi.org/10.14300/mnnc.2021.16109.
2. *Vetsheva MS, Sviridova V, Podkorytova LO.* Antioxidant therapy in various deseases. Preventing opportunities (a literature review). *Kremlin medicine. Clinical Bulletin*. 2022; 1: 71–77. [In Russ, English abstract]. doi: 10.26269/y0z6-xs61.
3. *Ma A, Qi S, Chen H.* Antioxidant therapy for prevention of inflammation, ischemic reperfusion injuries and allograft rejection. *Cardiovasc Hematol Agents Med Chem*. 2008; 6 (1): 20–43. doi: 10.2174/187152508783329966. PMID: 18220719.
4. *Shi S, Xue F.* Current Antioxidant Treatments in Organ Transplantation. *Oxid Med Cell Longev.* 2016; 8678510. doi: 10.1155/2016/8678510; PMID: 27403232; PMCID: PMC4926011.
5. *Gori F, Fumagalli J, Lonati C, Caccialanza R, Zanella A, Grasselli G.* Ascorbic acid in solid organ transplantation: A literature review. *Clin Nutr.* 2022; 41 (6): 1244–1255. doi: 10.1016/j.clnu.2022.04.004; PMID: 35504167.
6. *Elias-Miró M, Jiménez-Castro MB, Rodés J, Peralta C.* Current knowledge on oxidative stress in hepatic ischemia/reperfusion. *Free Radic Res*. 2013; 47 (8): 555–568. doi: 10.3109/10715762.2013.811721; PMID: 23738581.
7. *Patel J.* Vitamin therapy after heart transplantation. *Expert Review of Cardiovascular Therapy*. 2015; 13 (10): 1071–1074. doi: 10.1586/14779072.2015.1086268.
8. *Mohseni Salehi Monfared SS, Larijani B, Abdollahi M.* Islet transplantation and antioxidant management: a comprehensive review. *World J Gastroenterol*. 2009; 15 (10): 1153–1161. doi: 10.3748/wjg.15.1153; PMID: 19291814; PMCID: PMC2658860.
9. *Eguchi N, Damyar K, Alexander M, Dafoe D, Lakey JRT, Ichii H.* Anti-Oxidative Therapy in Islet Cell Transplantation. *Antioxidants (Basel)*. 2022; 11 (6): 1038. doi: 10.3390/antiox11061038; PMID: 35739935; PMCID: PMC9219662.
10. *Makarov MV, Trammell SAJ, Migaud ME.* The chemistry of the vitamin B_3 metabolome. *Biochem Soc Trans*. 2019;

47 (1): 131–147. doi: 10.1042/BST20180420; PMID: 30559273; PMCID: PMC6411094.
11. *Maiese K.* Nicotinamide as a Foundation for Treating Neurodegenerative Disease and Metabolic Disorders. *Curr Neurovasc Res*. 2021; 18 (1): 134–149. doi: 10.2174/1567202617999210104220334; PMID: 33397266; PMCID: PMC8254823.
12. *Dedov II, Gorelysheva VA, Smirnova OM, Romanovskaya GA, Filippov IK.* Effects of antioxidants on lipid peroxidation and beta-cell function in patients with newly detected insulin-dependent diabetes mellitus. *Problems of Endocrinology*. 1995; 41 (5): 16–20. [In Russ]. https://doi.org/10.14341/probl199541516-20.
13. *Gorelysheva VA, Smirnova OM, Dedov II.* Nicotinamide in the treatment of insulin-dependent diabetes mellitus at the debut of the disease. *Problems of Endocrinology*. 1996; 42 (6): 26–30. [In Russ]. https://doi.org/10.14341/probl12057.
14. *Fadeeva NI, Balabolkin MI, Mamaeva GG, Kravchenko TV, Mishchenko BP, Knyazeva AP.* Primenenie nikotinamida i drugikh antioksidantnykh preparatov v kompleksnoy terapii sakharnogo diabeta 2-go tipa. *Diabetes mellitus*. 2001; 4 (1): 21–23. [In Russ]. https://doi.org/10.14341/2072-0351-6103.
15. *Bondar' IA, Klimentov VV.* Antioksidanty v lechenii i profilaktike sakharnogo diabeta. *Diabetes mellitus*. 2001; 4 (1): 47–52. [In Russ]. https://doi.org/10.14341/2072-0351-6108.
16. *Pandey A, Tripathi P, Pandey R, Srivatava R, Goswami SH.* Alternative therapies useful in the management of diabetes: A systematic review. *J Pharm Bioallied Sci.* 2011; 3 (4): 504–512. doi: 10.4103/0975-7406.90103.
17. *Alenzi FQ.* Effect of nicotinamide on experimental induced diabetes. *Iran J Allergy Asthma Immunol.* 2009; 8 (1): 11–18. PMID: 19279354.
18. *Banerje M, Kanitkar M, Bhonde RR.* Approaches towards endogenous pancreatic regeneration. *Rev Diabet Stud*. 2005; 2 (3): 165–176. doi: 10.1900/RDS.2005.2.165; PMCID: PMC1783561; PMID: 17491691.
19. *Ahmad AARAA, Sakovich VN.* The study of the clinical efficacy of nicotinamide-containing drugs in patients with initial forms of diabetic retinopathy. *Problems of environmental and medical genetics and Clinical Immunology*. 2013; 1 (115): 153–161. [In Russ, English abstract].
20. *Chandrasekaran K, Najimi N, Sagi AR, Yarlagadda S, Salimian M, Arvas MI et al.* NAD+ Precursors Repair Mitochondrial Function in Diabetes and Prevent Experimental Diabetic Neuropathy. *Int J Mol Sci*. 2022; 23 (9): 4887. doi: 10.3390/ijms23094887. PMID: 35563288; PMCID: PMC9102948.
21. *Jung KI, Han JS, Park CK.* Neuroprotective Effects of Nicotinamide (Vitamin B_3) on Neurodegeneration in Diabetic Rat Retinas. *Nutrients*. 2022; 14 (6): 1162. doi: 10.3390/nu14061162. PMID: 35334819; PMCID: PMC8950738.
22. *Wan HF, Li JX, Liao HT, Liao MH, Luo L, Xu L et al.* Nicotinamide induces liver regeneration and improves liver function by activating SIRT1. *Mol Med Rep*. 2019; 19 (1): 555–562. doi: 10.3892/mmr.2018.9688. Epub 2018 Nov 22. PMID: 30483782.
23. *Lenglet A, Liabeuf S, El Esper N, Brisset S, Mansour J, Lemaire-Hurtel AS et al.* Efficacy and safety of nicotinamide in haemodialysis patients: the NICOREN study. *Nephrol Dial Transplant.* 2017; 32 (5): 870–879. doi: 10.1093/ndt/gfw042. PMID: 27190329.
24. *Arefev AS, Zhukova IV.* Transdermal therapeutic systems, their types and advantages. *Innovative scientific research*. 2022; 1–3 (15): 13–20. doi: 10.5281/zenodo.6368638. – EDN CBFERX. [In Russ, English abstract].
25. Femb.ru [Internet]. Federal'naya elektronnaya meditsinskaya biblioteka. Gosudarstvennaya farmakopeya Rossiyskoy Federatsii, XIV izdanie, tom 3. Nikotinamid. FS.2.1.0143.18 [data obrashcheniya: 17.04.2023]. Dostupno na: https://docs.rucml.ru/feml/pharma/v14/vol3/1211.
26. Vidal.ru [Internet]. Spravochnik lekarstvennykh sredstv Vidal [data obrashcheniya: 17.04.2023]. Dostupno na: https://www.vidal.ru/drugs/molecule/735.
27. *Kuznetsova EG, Ryzhikova VA, Salomatina LA, Kuryleva OM, Sevastianov VI.* Percutaneous Delivery System for Nicotinamide Transdermal Therapeutic System. *Perspektivnye materialy*. 2023; 7: 12–24. [In Russ, English abstract].
28. *Belousov YuB.* Klinicheskaya farmakologiya i farmakoterapiya. M.: MIA, 2010. 872.

The article was submitted to the journal on 11.05.2023

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Russian Journal of Transplantology and Artificial Organs
Shumakov National Medical Research Center of Transplantology and Artificial Organs
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Издание зарегистрировано в Госкомпечати РФ, № 018616 от 23.03.99 г.

Подписано к печати 5.07.23.

Тираж 1000 экз.

ООО «Издательство «Триада».
ИД № 06059 от 16.10.01 г.
170034, г. Тверь, пр. Чайковского, 9, оф. 514,
тел./факс: (4822) 42-90-22, 35-41-30
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Заказ 27052