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Development of a nasal spray containing aminocaproic acid and a copolymer of *N*-vinylpyrrolidone and 2-methyl-5-vinylpyridine for use in the prevention of influenza and other viral respiratory infections

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Objectives. *Prevention of influenza and viral respiratory infections is one of the major public health problems today. The aim of the study was to develop the formulation and production conditions for a nasal spray that can be used in the prevention of influenza and other viral respiratory infections, based on aminocaproic acid and a copolymer of N-vinylpyrrolidone and 2-methyl-5-vinylpyridine.*

Methods. *The influence of pH and temperature on the transparency of the copolymer solution was investigated using a turbidimeter to determine the optimal pH for the dosage form. The pH value was determined using a pH meter equipped with a combined glass electrode. The presence or absence of opalescence in the solution was determined visually, whereas the dynamic viscosity of the solution was determined at 25.0±0.5°C using a rotational viscometer. The optimal temperature and mixing speeds were selected as part of the technological development process. Quantitation of the active substances in the resulting drug was conducted using a previously reported high performance liquid chromatography method. A preliminary evaluation of the drug's shelf life was performed via stability studies using the accelerated aging method.*

Results. *Drug stability was ensured when the pH range of the dosage form was between 5.5 and 6.2. The addition of a thickening agent is not advisable due to undesired interactions between the excipients and the active substances during storage. Ideally, the drug composition for nasal use was aminocaproic acid (1 wt %) and the copolymer (0.5 wt %) in aqueous solution. A phosphate buffer solution with pH 5.5 was selected as the solvent for the dosage form to ensure the stability of the drug solution and ease-of-use without any disruptions in the normal functioning of the cilia in the nasal cavity. The optimal technology for drug production was determined, and the control parameters for this process were highlighted. Drug stability studies conducted via the accelerated aging method revealed that the estimated shelf life of the dosage form was 2 years.*

Conclusions. *A new formulation and optimized production conditions were developed for a drug based on aminocaproic acid and a copolymer of N-vinylpyrrolidone and 2-methyl-5-vinylpyridine, in the form of a nasal spray, for the prevention of influenza and other viral respiratory infections.*

Keywords: *aminocaproic acid, copolymer of N-vinylpyrrolidone and 2-methyl-5-vinylpyridine, nasal spray, prevention of influenza, viral respiratory infections.*

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Создание назального спрея на основе аминокапроновой кислоты и сополимера *N*-винилпирролидона и 2-метил-5-винилпиридина для профилактики гриппа и ОРВИ

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Цели. *В настоящее время одной из первостепенных задач здравоохранения в мире является профилактика гриппа и острых респираторных вирусных инфекций. Целью работы являлась разработка состава и технологии получения лекарственного препарата на основе аминокапроновой кислоты и сополимера N-винилпирролидона и 2-метил-5-винилпиридина в форме назального спрея для профилактики этих социально значимых заболеваний.*
Методы. *Для определения устойчивости лекарственной формы в зависимости от pH и температуры определяли прозрачность раствора сополимера с помощью метода турбидиметрии; значение pH определяли с помощью pH-метра со стеклянным комбинированным электродом.В дальнейшем наличие или отсутствие опалесценции раствора определяли визуально. Определение динамической вязкости раствора проводили при температуре 25.0±0.5 °C методом ротационной вискозиметрии. В рамках разработки технологии подобраны оптимальные значения температуры и скорости перемешивания при растворении веществ. Количественное определение содержания активных веществ в полученном препарате проводили с помощью ранее разработанного способа с использованием ВЭЖХ. Предварительный срок годности полученного препарата устанавливали с помощью исследования стабильности методом ускоренного старения.*
Результаты. *Установлено, что необходимый диапазон pH разработанной лекарственной формы для обеспечения стабильности лекарственного препарата составляет 5.5–6.2. В ходе экспериментов было продемонстрировано, что добавление загустителя нецелесообразно вследствие его взаимодействия с активным веществом в процессе хранения, что недопустимо. Разработан состав лекарственного препарата в виде раствора для назального применения с содержанием 1 масс. % аминокапроновой кислоты и 0.5 масс. % сополимера 2-метил-5-винилпиридина и N-винилпирролидона в водном растворе. В качестве растворителя лекарственной формы подобрали фосфатный буферный раствор с значением pH 5.5 для обеспечения стабильности раствора препарата и комфортного применения без нарушения нормального функционирования ресничек в полости носа. Подобрана оптимальная технология получения лекарственного препарата, выделены контролируемые параметры для надлежащего проведения технологического процесса. В результате исследования стабильности спрея методом ускоренного старения установлен предполагаемый срок годности разработанного препарата, составляющий 2 года.*
Выводы. *Предложены новый состав и технология получения готового лекарственного препарата на основе аминокапроновой кислоты и сополимера N-винилпирролидона и 2-метил-5-винилпиридина в форме назального спрея для профилактики гриппа и ОРВИ.*

Ключевые слова: *аминокапроновая кислота, сополимер N-винилпирролидона и 2-метил-5-винилпиридина, назальный спрей, профилактика гриппа и ОРВИ.*

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INTRODUCTION

Despite great efforts to prevent influenza and other viral respiratory infections (VRIs), the incidence rate of these infections has been increasing annually. Often, the global epidemic of these infections claims the lives of thousands of people [1]. The problem is exacerbated by the mixed nature of these infections, high transmission rate, and rapid onset of drug resistance [2]. The effectiveness of treatment options for influenza and other VRIs is largely determined by the rational selection of drugs that focus more on managing the causes of the disease rather than merely alleviating the symptoms [3]. The main goal of pharmaceutical technology is to create efficient, safe, and high-quality drugs aimed at combating the most dangerous and widespread diseases. According to the World Health Organization, influenza and other VRIs are both highly common and severe diseases; up to 500 mln people worldwide are infected annually, of whom around 650 000 die. In Russia, between 27.3 and 41.2 mln cases are registered each year[1]. Despite these figures, only a small percentage of the global drug market for influenza and other VRIs are designed to have antiviral activity[2]. Therefore, developing novel drugs aimed at preventing and eradicating influenza and other VRIs is a priority task for researchers globally.

Based on the mechanism by which the influenza virus penetrates human host cells [4], nasal route of drug administration is considered the most promising and effective means of prophylaxis [5, 6]. In this study, a combination of active components– aminocaproic acid (ACA) and a copolymer of *N*-vinylpyrrolidone and 2-methyl-5-vinylpyridine (hereafter referred to as the copolymer) – is proposed as a basis for creating an effective therapeutic agent. An aqueous solution of ACA and the copolymer at a molar ration of 2:1 showed significant antiviral activity when administered nasally to outbred mice [7, 8]. In this study, we aimed to optimize the formulation and the production conditions of a nasal spray based on aminocaproic acid and the copolymer of *N*-vinylpyrrolidone and 2-methyl-5-vinylpyridine.

[1] The situation of influenza in Russia and the world. Ministry of Health of the Russian Federation. FSBI Research Institute of Influenza. D.I. Ivanovsky Research Institute of Virology. Available from: http://www.influenza.spb.ru/system/ [Accessed September 22, 2019] (in Russ.).

[2] Pharmacological Management of Pandemic Influenza A (H1N1) 2009 Part I: Recommendations of World Health Organization. Available from: https://www.who.int/csr/disease/swineflu/notes/h1n1_use_antivirals_20090820/en/ [Accessed September 17, 2019].

MATERIALS AND METHODS

The active reagents of the nasal spray formulation were ACA (*Polisintez*, Russia) at a concentration of 1 wt % and the copolymer at a concentration of 0.5 wt % in aqueous solution. The copolymer was of medium viscosity with a molecular weight of 27 kDa and 32 mol % pyridine units (*Institute of Pharmaceutical Technology*, Russia). In the process of developing the model formulations for this nasal spray, the concentration of the excipients and the optimal conditions required for drug preparation were determined. The following reagents were used in the formulation: sorbitol (*Chimmed*, Russia), polyethylene glycol (PEG) 4000 (TU 20.16.40-008-71150986-2019; *Norchem*, Russia), carboxymethyl cellulose (Na-CMC), 7LF (*Ashland*, United States), glycerin (GOST 6259-57; *Chimmed Sintez*, Russia), polysorbate 80 (*Oleon*, Belgium), polyvinylpyrrolidone (*AK Sintvita*, Russia), Avicel® RC 591 (*FMC*, United States; United States Pharmacopeia), Vivapur® MCG 811 P (*JRS Pharma*, Finland), PEG 1500 (PEG-32; *Clariant*, Switzerland), benzalkonium chloride (CAS 63449-41-2; *Sigma-Aldrich*, United States), and purified water (Pharmacopeia Article 2.2.0020.18). Buffer solutions were prepared in accordance with the Russian State Pharmacopeia XIV[3] by using the following components: potassium dihydrogen phosphate (CAS 7778-77-0; *Chimmed*, Russia), disodium hydrogen phosphate (CAS 7558-79-4; *Chimmed*, Russia), and sodium hydroxide (GOST 4328-77 Amend. 1, 2; *Chimmed Sintez*, Russia). Because the copolymer is both thermo- and pH-sensitive, the effects of pH and temperature on the transparency of the copolymer solution were studied using a WaterLiner WTM-86 turbidimeter (*Metronx*, Russia). The composition of the buffer system was also investigated. The pH of the solutions was measured using a pH meter (*Econix-Expert*, Russia) with an ESK-10601 combined glass electrode (*Izmeritelnaya Tekhnika*, Russia). Furthermore, when optimizing the conditions for producing the dosage form, the presence, or absence of opalescence in the solution was determined visually.

Studies were conducted on a selection of thickeners to determine the most effective distribution method for the drug in the nasal cavity and to increase the viscosity of the solution. The dynamic viscosity values were measured at 25.0±0.5°C using rotational viscometry with a Brookfield DV2T viscometer (*Brookfield Engineering Laboratories*, United States). Before

[3] The State Pharmacopeia of the Russian Federation. 14th ed. Moscow: Ministry of Health of the Russian Federation; 2018 (in Russ.).

the readings were noted, the temperature of the test sample was allowed to equilibrate for 15 min. The readings were conducted at shear rates ranging from 0.28 to 58.0 s^{-1}, which corresponded to 10–90% torque. The optimal dissolution time was determined, in addition to the ideal conditions for cooling and the influence exerted by the opalescence of the solution. The active substances in the prepared solution were monitored via high performance liquid chromatography [9] using a Dionex UltiMate 3000 (*Thermo Scientific*, Germany). For the analysis of the copolymer, a Luna column (150×4.60 mm); *Phenomene*x, United States) was filled with a C5 sorbent with a particle size of 5 μm and a pore diameter of 10 nm (mobile phase A: mixture of 0.1% phosphoric acid and acetonitrile in a volume ratio of 82:18 with the addition of 4.5 mM sodium pentanesulfonate solution; mobile phase B: acetonitrile). The ACA content was determined using a Nucleodur C18 Pyramid column (250×4.6 mm) filled with 5 μm spherical particles (mobile phase A: 30 parts by mass of methanol to 70 parts of a solution containing 1% H_3PO_4, 10 mM sodium pentanesulfonate, and 15 mM K_2HPO_4 in H_2O; mobile phase B: methanol). Sterility of the solution was ensured by filtration using a glass vacuum system (FilterSys AH0-1566 F; *Phenomenex*, UK) equipped with filters of pore sizes 0.45 and 0.22 μm (AF0-0514, AF0-0513; *Phenomenex*, UK). The shelf life of the drug was determined via the accelerated aging method using a climatic chamber (KK115; *Pol-Eko-Aparatura*, Poland); this investigation was conducted in accordance with the Russian State Pharmacopeia XIV (General Pharmacopeia Article 1.1.0009.15).

RESULTS AND DISCUSSION

Optimization of the pH values and the components of the buffer solution

The composition and conditions required to produce a nasal spray based on aminocaproic acid and the copolymer of *N*-vinylpyrrolidone and 2-methyl-5-vinylpyridine were developed after a comprehensive research. Phosphate buffered saline (PBS) was used as the base for the spray, and a series of buffer solutions with different pH values (5.0–6.6) was prepared in accordance with the Russian State Pharmacopeia XIV (General Pharmacopeia Article 1.3.0003.15). The copolymer (0.5 wt %) was then added to each solution, and the stability of the solutions was determined at different temperatures (25–45°C) using turbidimetry. The effects of the pH value and temperature on the transparency of the copolymer solution in the buffer are presented in Table 1. The solutions were considered "transparent" when the turbidity index was up to 3.0 nephelometric turbidity units.

The results clearly showed that the turbidity of the copolymer solution at 30°C and pH 6.3 was high, implying instability of the formulation. Thus, the optimal pH range for the dosage form was determined to be between 5.5 and 6.2. For the PBS samples, the results of the pH optimization experiments are presented in Table 2 [10]. The most stable PBS samples had a pH value of 5.5.

Optimization of the excipients

Several studies were conducted to increase the viscosity of the spray solution through the use of an appropriate thickener, to prolong drug effectiveness. Afrin, a commercially available nasal spray [11], was chosen as the control sample as it contained thickeners with a measured viscosity of 500±50 mPa×s at 25ºC. Samples with various concentrations of the excipients, all of which had been approved for medical use and were used in commercial nasal dosage forms, were used to determine the optimal characteristics (Table 3). The samples were compared on the basis of two parameters: the pH value and the viscosity of the solution at 25.0°C. The test was conducted at a shear rate of 22.4 s^{-1}.

As we can see from Table 3, the ideal pH and viscosity parameters were only observed in samples 4 and 5. When subsequent observations of these samples were conducted over the course of a month, sample 4 showed only a slight decrease in viscosity, whereas sample 5 exhibited a decrease in viscosity that was below the required threshold (see Figure).

From the results of the rheoviscometry experiments, it was clear that there was a noticeable decrease in the dynamic viscosity of the solution after prolonged storage with the thickener Vivapur®. In the absence of Vivapur®, however, the dynamic viscosity of the solution remained almost constant. This was

Table 1. Effect of pH and temperature on the transparency of the solutions

Temperature, ºC	pH								
	5.0	5.5	6.0	6.1	6.2	6.3	6.4	6.5	6.6
25	2.9	0.8	0.9	0.9	0.8	0.8	0.8	1.4	14.3
30	2.3	1.1	1.0	1.0	0.9	3.4	157	685	–
40	2.4	1.3	1.7	1.0	2.0	326	609	678	–
45	2.6	1.3	4.4	14.8	280	742	817	–	–

indicative of pronounced intermolecular interaction between Vivapur® and the other components of the solution, which, in turn, disrupted the stability of the system during storage. Because the chemical interaction between the active components and the excipients was undesired, we decided to exclude Vivapur® from the final composition. Thus, the optimal distribution of the drug across the mucous membrane of the nasal cavity was accomplished by optimizing the spray nozzle rather than by lowering the viscosity of the solution.

The stability of the dosage form over the course of its entire shelf life was ensured by adding benzalkonium chloride (0.15 mg/mL), the commonly used preservative in commercial nasal spray formulations. The optimal combination of reagents for the model mixture is shown in Table 4.

Next, the optimization of the laboratory conditions was conducted by the *Institute of Pharmaceutical Technologies*, Russia. The rapid dissolution of the copolymer was achieved only at low pH values and at low temperatures of the buffer solutions. The copolymer was dissolved in cold purified water with constant stirring, followed by refrigeration as part of the protocol for optimization process.

The preparation of a control form for the aforementioned samples was conducted visually (i.e., a transparent homogeneous solution was obtained without

Table 2. Change in pH values of 0.5% copolymer solutions during storage at 25ºC depending on the initial pH value of the PBS

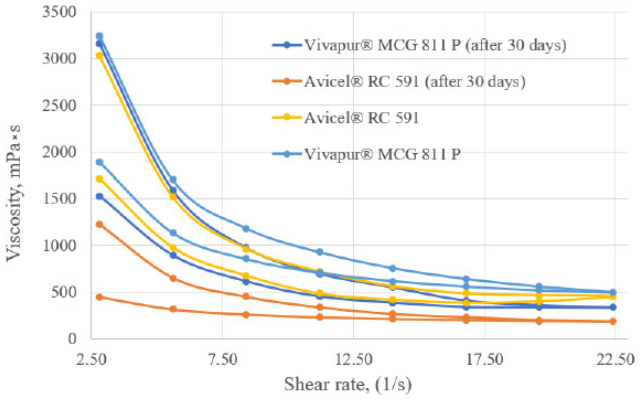
Shelf life, days	Samples PBS				
	pH 5.0	pH 5.2	pH 5.5	pH 5.8	pH 6.0
0	5.3	5.5	5.7	5.9	6.3
7	5.4	5.4	5.8	5.7	6.3
30	5.5	5.4	5.8	5.6	6.3

Table 3. Optimization of the excipients

Name of the component in the sample	Compositions of the nasal spray, with the content of substances, mg/mL								
	1	2	3	4	5	6	7	8	9
Sorbitol	50		–	–	20	10	5	–	–
PEG 4000	–	10	–	–	10	–	–	3	–
Na-CMC	–	–	25	–	–	30	–	15	–
Glycerin	1.5	1	–	–	–	–	1.2	–	0.5
Polysorbate 80	0.01	–	0.05	0.1	–	–	0.2	–	–
Povidone K29-32	–	5.5	–	–	4	–	10	5	5
Avicel® RC 591	10	–	–	–	20	–	–	–	15
Vivapur® MCG 811 P	–	–	–	20	–	–	–	10	–
PEG 1500	–	15	–	10	–	5	–	–	–
Parameters									
Viscosity, mPa×s at a shear rate of 22.4 s^{-1} and temperature of 25°C	374	275	1315	498	452	1117	989	2546	1245
pH	6.8	6.2	5.3	6.0	6.0	5.5	5.0	5.4	6.0

visible mechanical impurities and opalescence) as well as via quantitative analysis of the condition parameters for the active reagents. Based on the data shown in Table 5, the optimal process was set as follows:

1. Prepare the buffer solution with pH 5.5 from solutions 1 and 2 and then filter it through a 0.45 μm filter.
2. Cool the buffer solution to 15±2°C.
3. Fill the reactor with the buffer solution.
4. Add and dissolve the copolymer with subsequent sedimentation at 3–6°C for 24 h.
5. Add and dissolve ACA and benzalkonium chloride.



Viscosity–velocity curves of samples 4 and 5 at 25ºC.

6. Sterilize via filtration and then bottle the solution into 10 mL polymer bottles equipped with polymer based spray nozzles.

Thermal sterilization, in this case, was not possible because of the thermosensitivity of the copolymer. Additionally, sterilization using an autoclave resulted in precipitation within the solution. Therefore, filtration was selected as the preferred method of sterilization.

The shelf life of the nasal spray was determined by quantifying the stability of three series of spray samples (Table 6) in polymer based bottles with spray nozzles using the accelerated aging method at 40±2ºC and 75±5% humidity for 180 days. This experiment was performed in accordance with the Russian State Pharmacopeia XIV, as these conditions were nearly similar to those of aging of the dosage form for 2 years under natural conditions. During this analysis, the pH, microbiological purity, and the quantitative content of the active substances were monitored [12].

From the results of the study, it was clear that the values of the controlled indicators remained within the reference range and that the deviation values corresponded to the measurement error calculations. The shelf life of the drug was estimated to be 2 years. As a confirmatory test, three series of drug samples were subjected to the same natural conditions.

Table 4. Composition of the solution of the nasal spray per 1 mL

Ingredient	Quality standard	Quantity, mg
Active substances		
Aminocaproic acid (ACA)	Pharmacopeia Article of the Manufacturer LS-000113-280909, Amend. 1, 2	10.00
Copolymer of 2-methyl-5-vinylpyridine and *N*-vinylpyrrolidone	Normative Documentation Project	5.00
Excipients		
Potassium dihydrogen phosphate	Russian State Pharmacopeia XIV	9.45
Disodium hydrogen phosphate	Russian State Pharmacopeia XIV	1.28
Benzalkonium chloride	European Pharmacopeia; Russian State Pharmacopeia XIV	0.15
Purified water	Russian State Pharmacopeia XIV	Up to 1.00

Table 5. Optimization of the production conditions

Parameter	Conditions				
Experiment number	**E1**	**E2**	**E3**	**E4**	**E5**
Temperature, °C	5	10	15	20	25
Dissolution time before opalescence, min	10	12	15	25	45
Conclusion: the optimal temperature for mixing is 5–15ºC					
Experiment number	**E6**	**E7**	**E8**	**E9**	**E10**
Mixer speed, rpm	30	40	50	80	100
Dissolution time before opalescence, min	>30	>30	13	>30	>30
Conclusion: the optimal mixing speed is 50 rpm					
Experiment number	**E11**	**E12**	**E13**	**E14**	**E15**
Refrigeration until complete dissolution of the copolymer, h	12	15	20	24	30
The presence of opalescence, +/–	+	+	+	–	–
Copolymer content in the solution, mg/mL	4.68	4.80	4.97	5.04	5.01
Conclusion: the optimal storage time of the copolymer in the refrigerator is 24 h					
Experiment number	**E16**	**E17**	**E18**	**E19**	**E20**
Dissolution of ACA and benzalkonium chloride at ambient temperature, °C	10	12	15	20	25
Dissolution time, min	3	3	3	3	3
Conclusion: ACA and benzalkonium chloride dissolve equally well between 10 to 25°C					
Experiment number	**E21**	**E22**	**E23**	**E24**	**E25**
Dissolution of ACA and benzalkonium chloride with mixing, stirrer speed, rpm	50	80	100	150	300
Dissolution time, min	3	3	2	2	2
Conclusion: the rate of dissolution of ACA and benzalkonium chloride varies insignificantly					

Table 6. Selected data on the stability of the nasal dosage form in polymer package

Specification	Standard	Shelf life, days	Batch		
			130318	210518	191118
pH	5.5–6.2	0	5.7	5.8	6.0
		180	5.8	5.8	5.9
Microbiological purity	Category 2	0	Complies	Complies	Complies
		180	Complies	Complies	Complies
Quantitative assay					
ACA, mg/mL	9.5–10.5	0	9.89	10.05	10.12
		180	9.89	10.05	10.11
Copolymer, mg/mL	4.75–5.25	0	5.03	5.15	4.96
		180	5.03	5.13	4.96

CONCLUSIONS

In this study, we developed the composition and conditions needed to produce a nasal spray for the prophylactic treatment of influenza and other VRIs. The nasal spray contains 1 wt % aminocaproic acid and 0.5 wt % copolymer of 2-methyl-5-vinylpyridine and *N*-vinylpyrrolidone. Accelerated aging studies showed that the estimated shelf life of the drug is 2 years.

The author declares no conflicts of interest.

REFERENCES

1. Svyatchenko S.V., Durymanov A.G., Kolosova N.P., Gudymo A.S., Goncharova N.I., Torzhkova P.Y., Bulanovich Y.A., Epanchintseva A.V., Danilenko A.V., Marchenko V.Y., Sysoeva A.V., Susloparov I.M., Tregubchak T.V., Ryzhikov A.B., Maksyutov R.A., Ilicheva T.N. Severe cases of seasonal influenza in Russia in 2017-2018. *Journal of microbiology epidemiology immunobiology.* 2019;(4):58-64 (in Russ.). https://doi.org/10.36233/0372-9311-2019-4-58-64

2. Kiselev O.I., Marynich I.G., Sominina A.A. (eds.). *Gripp i drugie respiratornye virusnye infektsii: epidemiologiya, profilaktika, diagnostika i terapiya* (Influenza and other respiratory viral infections: epidemiology, prevention, diagnosis and therapy). Saint Petersburg: Borges; 2003. 245 p.

3. Dondurey E.A., Obraztsova E.V., Semiletko Y.S., Ovchinnikova N.V., Golovacheva E.G., Osidak L.V., Afanasyeva O.I. ARVI antiviral therapy in children in modern clinical practice. *Meditsinskiy sovet = Medical Council.* 2019;(2):183-187 (in Russ.). https://doi.org/10.21518/2079-701X-2019-2-183-187

4. Cheshik S.G. Influenza. *Detskie infektsii = Infant Infections.* 2005;(4):56-63 (in Russ.).

5. Ghori M.U., Mahdi M.H., Smith A.M., Conway B.R. Nasal Drug Delivery Systems: An Overview. *Am. J. Pharm. Sci.* 2015;3(5):110-119.

6. Degenhard M.A., Gerallt W.U., Birkhoff M.S. Intranasal Drug Administration — An Attractive Delivery Route for Some Drugs. *Drug Discovery and Development – From Molecules to Medicine. IntechOpen.* 2015;(13):300-318. http://dx.doi.org/10.5772/59468

СПИСОК ЛИТЕРАТУРЫ

1. Святченко С.В., Дурыманов А.Г., Колосова Н.П., Гудымо А.С., Гончарова Н.И., Торжкова П.Ю., Булановичч Ю.А., Епанчинцева А.В., Даниленко А.В., Марченко В.Ю., Сысоева А.В., Суслопаров И.М., Трегубчак Т.В., Рыжиков А.Б., Максютов Р.А., Ильичева Т.Н. Тяжелые случаи заболевания гриппом на территории Российской Федерации в эпидемическом сезоне 2017-2018. *Журнал микробиологии, эпидемиологии и иммунобиологии (ЖМЭИ)*. 2019;(4):58-64. https://doi.org/10.36233/0372-9311-2019-4-58-64

2. Киселев О.И., Маринич И.Г., Соминина А.А. (под ред.). Грипп и другие респираторные вирусные инфекции: эпидемиология, профилактика, диагностика и терапия. СПб.: Боргес; 2003. 245 с.

3. Дондурей Е.А., Образцова Е.В., Семилетко Ю.С., Овчинникова Н.В., Головачёва Е.Г., Осидак Л.В., Афанасьева О.И. Противовирусная терапия ОРВИ у детей в современной клинической практике. *Медицинский Совет.* 2019;(2):183-187. https://doi.org/10.21518/2079-701X-2019-2-183-187

4. Чешик С.Г. Грипп. *Детские инфекции.* 2005;(4):56-63.

5. Ghori M.U., Mahdi M.H., Smith A.M., Conway B.R. Nasal Drug Delivery Systems: An Overview. *Am. J. Pharm. Sci.* 2015;3(5):110-119.

6. Degenhard M.A., Gerallt W.U., Birkhoff M.S. Intranasal Drug Administration — An Attractive Delivery Route for Some Drugs. *Drug Discovery and Development – From Molecules to Medicine. IntechOpen.* 2015;(13):300-318. http://dx.doi.org/10.5772/59468

7. Karpova A.S., Kochkina Y.V., Kedik S.A. The antiviral activity study of complex drug with aminocapronic acid for prevention of influenza and ARVI. *Razrabotka i registratsiya lekarstvennykh sredstv = Drug Development & Registration.* 2019;8(2):22-26 (in Russ.).
https://doi.org/10.33380/2305-2066-2019-8-2-22-26

8. Evseeva A.S., Kochkina Yu.V., Krasilnikov I.V., Kedik S.A., Eremin D.V., Suslov V.V. Antiviral and immunomodulating combination based on aminocaproic acid and a copolymer of 2-methyl-5-vinylpyrilin and *N*-vinylpyrrolidone: patent 2669810 RF. Appl. 21.06.2017, publ. 16/10/.2018. Bull. Number 29 (in Russ.).

9. Evseeva A.S., Vorfolomeeva E.V., Kochkina Yu.V., Kedik S.A., Vostrov I.A. A method for the quantitative determination of aminocaproic acid when it is combined with a copolymer of 2-methyl-5-vinylpyridine and *N*-vinylpyrrolidone by HPLC: patent 2700167 RF. Appl. 09/13/2018, publ. 09/13/2019. Bull. Number 26 (in Russ.).

10. Kravchenko I.A. *Sposoby vvedeniya lekarstvennykh preparatov v organizm. Intranazal'noe vvedenie lekarstvennykh preparatov* (Methods of introducing drugs into the body. Intranasal administration of drugs). Odessa: Astroprint; 2009. 164 p. ISBN 978-966-190-128-4 (in Russ.).

11. Kundoor, V., Dalby, R.N. Effect of Formulation- and Administration-Related Variables on Deposition Pattern of Nasal Spray Pumps Evaluated Using a Nasal Cast. *Pharm. Res*, 2011;28(8):1895-1904.
https://doi.org/10.1007/s11095-011-0417-6

12. Sakaeva I.V., Bunyatyan N.D., Kovaleva E.L., Sakanyan E.I., Mitkina L.I., Prokopov I.A., Shelekhina E.S., Mitkina Y.V. The main approaches to the study of drug stability: domestic and international experience. *Vedomosti Nauchnogo centra ekspertizy sredstv medicinskogo primeneniya = The Bulletin of the Scientific Centre for Expert Evaluation of Medicinal Products.* 2013;(3):8-11. (in Russ.).

7. Карпова А.С., Кочкина Ю.В., Кедик С.А. Изучение противовирусной активности комплексного препарата с аминокапроновой кислотой для профилактики гриппа и ОРВИ. *Разработка и регистрация лекарственных средств.* 2019;8(2):22-26.
https://doi.org/10.33380/2305-2066-2019-8-2-22-26

8. Евсеева А.С., Кочкина Ю.В., Красильников И.В., Кедик С.А., Еремин Д.В., Суслов В.В. Противовирусная и иммуномодулирующая комбинация на основе аминокапроновой кислоты и сополимера 2-метил-5-винилпирилина и *N*-винилпирролидона. Патент РФ № 2669810. Заявка от 21.06.2017, опубл. 16.10.2018 г. Бюлл. № 29.

9. Евсеева А.С., Ворфоломеева Е.В., Кочкина Ю.В., Кедик С.А., Востров И.А. Способ количественного определения аминокапроновой кислоты при её совместном присутствии с сополимером 2-метил-5-винилпиридина и *N*-винилпирролидона методом ВЭЖХ. Патент РФ № 2700167. Заявка от 13.09.2018; опубл. 13.09.2019 г. Бюлл. № 26

10. Кравченко И.А. Способы введения лекарственных препаратов в организм. Интраназальное введение лекарственных препаратов. Одесса: Астропринт; 2009. 164 с. ISBN 978-966-190-128-4

11. Kundoor, V., Dalby, R.N. Effect of formulation- and administration-related variables on deposition pattern of nasal spray pumps evaluated using a nasal cast. *Pharm. Res.*, 2011;28(8):1895-1904.
https://doi.org/10.1007/s11095-011-0417-6

12. Сакаева И.В., Бунятян Н.Д., Ковалева Е.Л., Саканян Е.И., Митькина Л.И., Прокопов И.А., Шелехина Е.С., Митькина Ю.В. Основные подходы к изучению стабильности лекарственных средств: отечественный и международный опыт. *Ведомости Научного центра экспертизы средств медицинского применения.* 2013;(3):8-11.

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