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## ТЕХНОЛОГІЯ ЛІКАРСЬКИХ ПРЕПАРАТІВ

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*Recommended by Doctor of Pharmacy, professor N.P.Polovko*

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### DEVELOPMENT OF THE TECHNOLOGY OF “FITORYN-PLUS” NASAL GEL FOR TREATING ALLERGIC RHINITIS

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*Key words: technology; nasal gel; allergic rhinitis*

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*There are some available synthetic drugs of the foreign origin among symptomatic nasal medicines at the current pharmaceutical market. Most of them are produced in the form of drops or sprays, and it causes short duration of action of these drugs. Nowadays nasal gels attract great attention to the treatment of allergic rhinitis. The aim of the work is to develop a new nasal medicine based on biologically active plant substances in the gel form under the conditional name “Fitoryn-plus”. A dry extract of licorice root and essential oils of eucalyptus and Siberian pine were used as active ingredients of this nasal gel. In order to choose a structure-forming component of the gel base 9 model samples of gel systems were prepared, and the possibility of using carbomer (carbopol) 934, hydroxyethyl cellulose and sodium alginate was investigated. To neutralize aqueous dispersions of carbopol the ammonia solution, the solution of sodium hydroxide and triethanolamine were used. The gel was prepared at the room temperature using two variants of technology: by mixing the finished gel and solutions of active substances previously prepared (technology 1) and by introducing active substances into the dispersion medium before the gel thickening (technology 2). Based on the complex of organoleptic, physical and chemical, structural and mechanical studies conducted a gelling agent, a neutralizing agent, a hydrophilic nonaqueous solvent and their optimal concentrations in the drug composition have been chosen. It has been shown that thermal effects of the samples of the active substances, the gel base and “Fitoryn-plus” gel are similar in nature; it may be subjectively indicative of the absence of chemical interaction between the components of the drug and validate the technology developed.*

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Allergic rhinitis is a disease of the nasal epithelial membranes and is characterized by episodic disturbance of nasal breathing. Despite the fact that rhinitis is perceived by many patients as a temporary phenomenon, in doctors' opinion, it is the initial manifestation of systemic allergy.

Moreover, if this pathology is not treated, a chain of pathological processes in the lower respiratory system will start; and it can lead to development of some severe diseases such as asthma. Therefore, it is necessary to treat allergic (intermittent) rhinitis since the appearance of the first symptoms of this pathology [8, 10].

According to the World Health Organization, over the last ten years the number of patients suffering from allergic rhinitis has increased approximately twice, indicating the epidemic nature of the disease [5, 9].

The first symptoms that characterize intermittent rhinitis are formed from a few seconds to twenty minutes after direct interaction with the allergen. Patients suffering from allergic nasal pathology complain of nasal congestion and severe watery discharge from the nasal passages.

The main signs of allergic rhinitis include the following symptoms: frequent sneezing, itchy nose, scratchy throat, swelling of the face, watery eyes, headaches, hearing and smell disorders, etc. At the first signs of the disease

the systemic and symptomatic treatment is needed for adults and children [3, 7].

There are some available synthetic drugs of the foreign origin among symptomatic nasal medicines at the current pharmaceutical market. Most of them are produced in the form of drops or sprays, and it causes short duration of action of these drugs [2].

Nowadays nasal gels attract great attention to the treatment of allergic rhinitis; they provide retention of the active substances on the nasal mucosa, do not disrupt the movement of ciliated epithelium, maintain the natural moisture of the nasal mucosa and provide a prolonged therapeutic action [4, 6].

Therefore, the aim of our work is to develop a new nasal medicine based on biologically active plant substances in the gel form under the conditional name “Fitoryn-plus”.

#### **Materials and Methods**

A dry extract of licorice root and essential oils of eucalyptus and Siberian pine were used as active ingredients of the nasal gel proposed. Taking into account their solubility in well known solvents this dry extract of licorice root was introduced into the gel composition as an aqueous solution, and essential oils were as a solution in ethanol (96%).

Table 1

The composition of model gel bases (%)

Model gel base	Carbopol 934 P	Hydroxyethyl-cellulose	Sodium alginate	Triethanolamine	Propylene glycol	Purified water
1	0.5	–	–	0.5	10.0	up to 100.0
2	1.0	–	–	1.0	10.0	up to 100.0
3	1.5	–	–	1.5	10.0	up to 100.0
4	–	1.0	–	–	10.0	up to 100.0
5	–	1.5	–	–	10.0	up to 100.0
6	–	2.0	–	–	10.0	up to 100.0
7	–	–	5.0	–	10.0	up to 100.0
8	–	–	7.0	–	10.0	up to 100.0
9	–	–	10.0	–	10.0	up to 100.0

In order to choose a structure-forming component of the gel base 9 model samples of gel systems were prepared, and the possibility of using carbomer (carbopol) 934, hydroxyethyl cellulose and sodium alginate as a gelling agent was investigated.

The solutions of ammonia, sodium hydroxide, as well as triethanolamine were used to neutralize the aqueous dispersions of carbopol. The appearance and colour of the model gel samples were estimated in the course of the experiment.

The gel was prepared at the room temperature using two variants of technology: by mixing the finished gel and the solutions of active substances previously prepared (technology 1) and by introducing active substances into the dispersion medium before the gel thickening (technology 2).

Determination of homogeneity of the samples was performed by the method of the State Pharmacopoeia of Ukraine (SPhU) [1]. The appearance, colour and odour was determined in accordance with the State Standard – GOST 29188.90.

The colloidal structure and thermal stability of the gel were visually assessed by the method of GOST 29188.3-91 at the room temperature (15-25°C), at 40°C and 5°C, as well as after cycles of freezing and thawing.

Determination of pH of aqueous extracts of the drug was conducted by the potentiometric method according to the SPhU [1].

Rheological studies were performed on a BROOKFIELD DV-II + PRO viscometer (USA) with the system of coaxial cylinders. Structural and mechanical properties were determined compared to “Loryzan” nasal gel widely used in the treatment of allergic rhinitis.

Water absorption kinetics of the drug was determined in experiments *in vitro* using the method of dialysis through a semipermeable membrane at (37.0±0.1)°C by changing the mass of the chamber with the sample.

Thermogravimetric analysis was performed on a Q-1000 derivatograph of the system of F.Paulik, J.Paulik, L.Efdey using the method of the SPhU [1]. Curves T (temperature), TG (change in weight), DTA (differential curve of thermal effects change) and DTG (differential curve of weight change) were recorded. As a reference aluminum oxide powder was used. The weight of the sample was 200 mg.

#### Results and Discussion

The optimal structure-forming component was selected on the basis of studies of physical and chemical stability of the gel model samples (Tab. 1). As a result of the studies conducted it has been found that model systems 1, 6 and 9 have too thin or, on the contrary, dense consistency, poorly applied to the mucosa and are almost not absorbed.

Model gel bases 2, 3, 7 and 8 both after preparation and after keeping for 30 days at 5°C, 20°C, 40°C and after 5 cycles of freezing / thawing (the temperature range was from -10°C to +45°C) were stable.

Samples of bases 4 and 5 did not withstand tests on colloidal and thermal stability. Therefore, for further study the gel systems 2, 3, 7 and 8 were chosen.

These gel samples were packed for storage at two temperature conditions – 8-15°C and 15-25°C. The results of the stability study of the bases developed while storing (within 30 days) are given in Tab. 2.

As it is seen from the data of Tab. 2, model samples 7 and 8 while storing for 30 days appeared to be un-

Table 2

The results of the stability study of gel samples 1, 2, 7 and 8 while storing

No.	Colour	Odour	Homogeneity	Colloidal stability (visually)	Thermostability (visually)
2	brown	pleasant	homogeneous	stable	stable
3	brown	pleasant	homogeneous	stable	stable
7	appearance of a black stain	specific	homogeneous	unstable	unstable
8	appearance of a black stain	specific	homogeneous	unstable	unstable

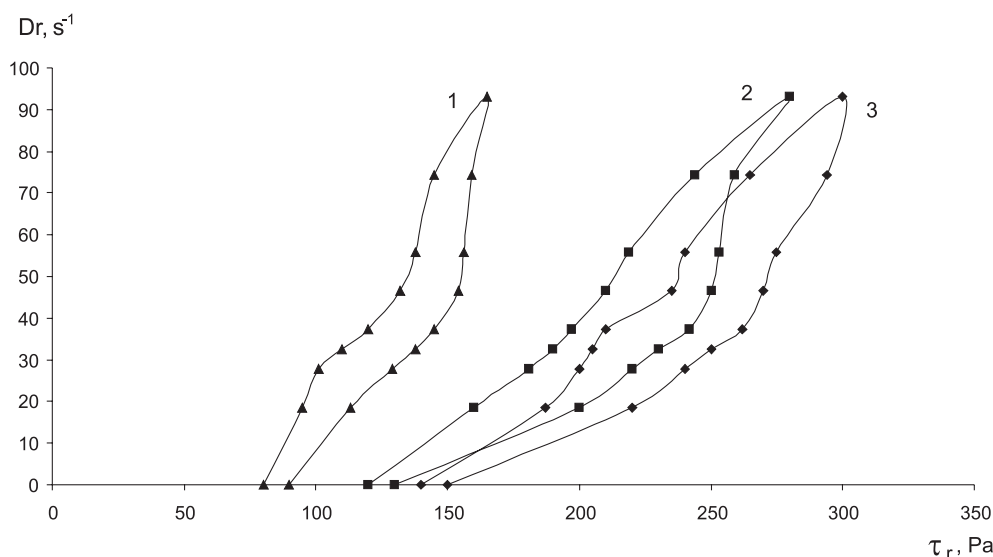


Fig. 1. Flow rheograms of the gel studied: sample 2-1, sample 3-2, and "Loryzan" gel – 3 at the temperature of  $(20.0 \pm 1.0)^\circ\text{C}$ .

stable. On the 15-th day of storage the appearance of a black stain was observed, indicating the microbial contamination of the bases developed. In addition, these samples of gel bases did not withstand tests on colloidal and thermal stability while storing. For further research the model gel samples 2 and 3 were selected.

When carrying out rheological studies of these samples it has been found that while increasing of the carbopol concentration in the systems studied there is a shift from plastic to pseudoplastic type of flow and the appearance of thixotropic properties.

Model samples of gel systems containing the gelling agent in the concentration of more than 1.5% had a dense heterogeneous gel-like structure; their further neutralization led to a sharp increase in the structural viscosity, formation of a dense gel, in which the active ingredients could not be introduced and distributed evenly.

Neutralization of aqueous dispersions of carbopol caused increase of rheological parameters and formation of transparent gels. The effectiveness of gelation (increase of the structural viscosity after neutralization) depended on the concentration of carbopol.

In the range of 1.0-1.5% gelation was more effective. With increase of the carbopol concentration in more than 1.5 % the structural viscosity increased slightly, confirming the feasibility of preparing a gel within the concentration range of 1.0-1.5% (Fig. 1).

As it is shown in Fig. 1, sample 3 has rheological parameters most closely resembling rheological parameters of "Loryzan" nasal gel, and it has been also confirmed by the calculated values of mechanical stability and dynamic dilution ratios (1.08 and 1.05, 72% and 70.5%, respectively).

Sample 2 is more liquid, and its width of "hysteresis loop" indicates the less distinct thixotropic properties.

In further research when choosing a neutralizing agent to the gel system 3 the solutions of ammonia and sodium hydroxide, as well as triethanolamine were introduced. Samples neutralized with the ammonia solution and the sodium hydroxide solution darkened over

Table 3

The results of studying pH of the model samples of "Fitoryn-plus" gel

No.	The content of triethanolamine	pH value
3-a	1.0%	$5.85 \pm 0.05$
3-b	1.5%	$6.40 \pm 0.05$

time. While using the ammonia solution salting-out was also observed. Therefore, triethanolamine was used further since its addition did not change physical and chemical properties of the gel during the experiment. The optimal concentration of the neutralizing agent in the drug composition was determined when studying pH of its model samples (Tab. 3).

As it can be seen from the table data, the model sample of the drug containing 1.5% of triethanolamine has the pH value that is the most close to the normal pH value of the human nasal mucosa, which is 6.0-7.0.

Propylene glycol was introduced to the composition of the nasal drug studied in order to provide a moderate osmotic activity, prevent dryness and irritation of the nasal mucosa. In addition, it is known that a positive moment of introduction of hydrophilic nonaqueous solvents into gels provides stability of their composition during the technological process.

We prepared model samples of gels containing propylene glycol from 10% to 30% and studied the kinetics of water absorption of these samples in quintuplicate. The concentration 10% was identified as the optimal concentration of propylene glycol (Fig. 2).

As it is shown in Fig. 2, the sample of "Fitoryn-plus" gel containing 10% of propylene glycol provides a moderate osmotic activity of the drug for 7 h, and it may indicate the absence of the irritating action. With introduction of propylene glycol in higher concentrations the osmotic activity of the samples reached 60-75%. It is not acceptable for nasal gels from the biomedical point of view.

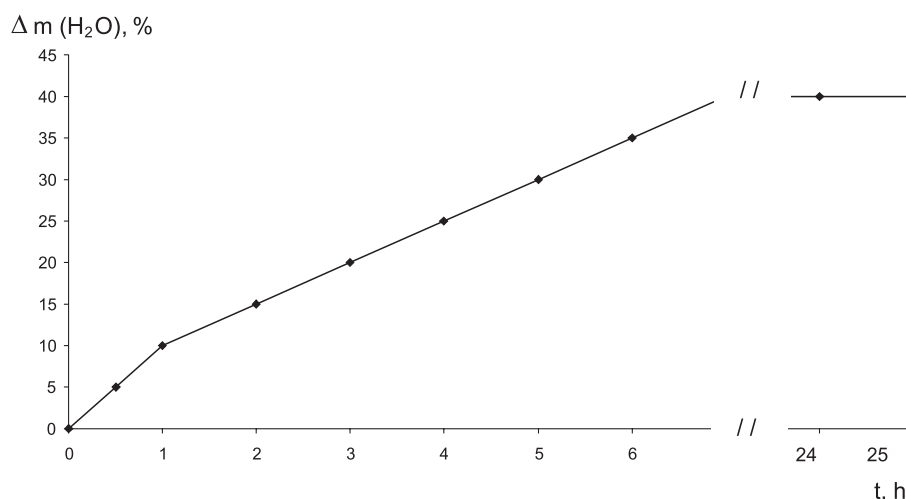


Fig. 2. The osmotic activity of "Fitoryn-plus" nasal gel containing 10% of propylene glycol.

Table 4

#### Physical and chemical properties of the samples of "Fitoryn-plus" gel

Medicine	Colour	Odour	Homogeneity	pH	Colloidal stability	Thermal stability
Gel by technology 1	brown	specific pleasant	+	6.70±0.05	+	+
Gel by technology 2	brown	specific pleasant	+	6.65±0.05	-	-

Considering all experimental data the samples of "Fitoryn-plus" gel by technology 1 and 2 were prepared.

The gels obtained by the technologies proposed had gel-like homogeneous consistency with a specific pleasant odour, brown colour, pH = 6.0-7.0. The study of thermal and colloidal stability proved stability of the system prepared only by technology 1 (Tab. 4).

Therefore, technology 1 (introduction of active ingredients to the finished gel) was determined as the rational technology for preparing "Fitoryn-plus" gel.

Then the thermogravimetric studies were conducted with the samples of the active ingredients, the gel base and the gel developed. When analyzing thermogravimetric curves of these samples it has been found that

essential oils of Siberian pine and eucalyptus are stable up to the temperature of (50.0±1.0)°C, and at the temperatures ranging from 53°C to 84°C their losses in mass are up to 3%, the process of the sample destruction ends at the temperature of 200°C.

A dry extract of licorice root is stable up to the temperature of (37.0±1.0)°C, within the temperature range from 37°C to 130°C there is a gradual loss in its mass (Fig. 3).

The base starts melting at the temperature of (37.0±1.0)°C.

The process of decomposition of the gel takes place in two stages (Fig. 4). At the first stage the significant moisture loss in weight is not observed up to 37°C. The second (37-100)°C stage is characterized by the rapid

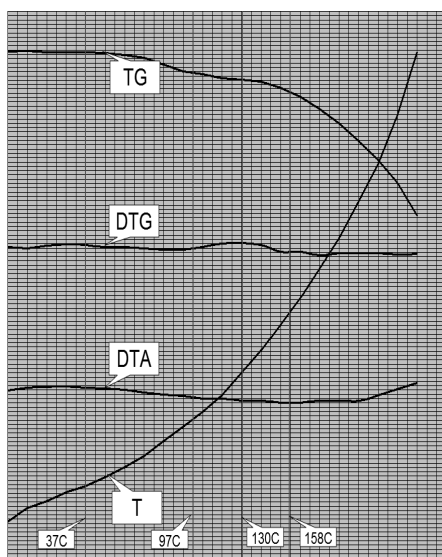


Fig. 3. Thermogravimetric curves of a dry extract of licorice root.

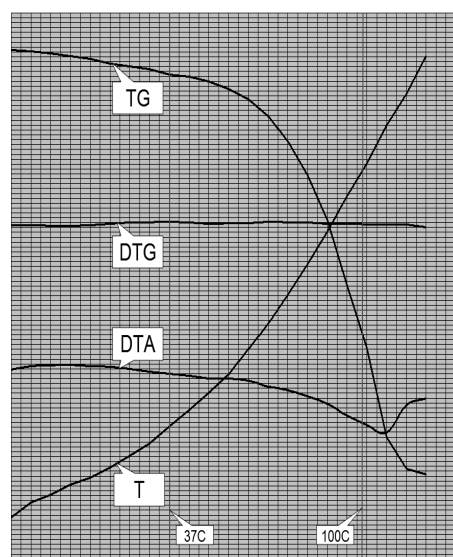


Fig. 4. Thermogravimetric curves of "Fitoryn-plus" gel.

and continuous process of destruction accompanied by significant exothermic effects.

Therefore, based on the thermogravimetric studies conducted it has been found that thermal effects of the samples are similar in nature; it may indicate a subjective absence of chemical interaction between components of the gel prepared according to the technology proposed.

#### CONCLUSIONS

1. The rational technology of the nasal gel under the conditional name "Fitoryn-plus" for treating allergic rhinitis has been developed.

2. The complex of organoleptic, physical and chemical, structural and mechanical studies was conducted; based on it a gelling agent, a neutralizing agent, a hydrophilic nonaqueous solvent and their optimal concentrations in the drug composition have been chosen.

3. It has been shown that thermal effects of the samples of the active substances, the gel base and "Fitoryn-plus" gel are similar in nature; it may be subjectively indicative of the absence of chemical interaction between the components of the drug and validate the technology developed.

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#### РОЗРОБКА ТЕХНОЛОГІЇ НАЗАЛЬНОГО ГЕЛЮ «ФІТОРИН-ПЛЮС» ДЛЯ ЛІКУВАННЯ АЛЕРГІЧНОГО РИНИТУ

**О.А.Рухмакова, Т.Г.Ярних**

**Ключові слова:** технологія; назальний гель; алергічний риніт

На сучасному фармацевтичному ринку серед симптоматичних назальних засобів наявними є переважно синтетичні лікарські препарати закордонного виробництва. Значна їх частина випускається у формі крапель або спреїв, що обумовлює короткочасність дії. Все більшу увагу на сьогоднішній день у лікуванні алергічного риніту привертають назальні гелі. Метою роботи є розробка назального засобу на основі речовин рослинного походження у формі гелю під умовною назвою «Фіторин-плюс». В якості діючих речовин було використано сухий екстракт кореня солодки та ефірні олії сосни сибірської та евкаліпту. З метою вибору структуроутворюючого компонента досліджена можливість використання карбомера (карбополу) 934 Р, гідроксіетилцелюлози та натрію альгінату. Для нейтралізації водних дисперсій карбополу використані розчини амоніаку, натрію гідроксиду та триетаноламін. Приготування гелю здійснювалось при кімнатній температурі за двома варіантами технології: шляхом змішування готового гелю і приготовлених розчинів діючих речовин (технологія №1) та шляхом введення діючих речовин до дисперсійного середовища перед загущенням гелю (технологія №2). На підставі комплексу проведених органолептичних, фізико-хімічних і структурно-механічних досліджень були обрані гелеутворювач, нейтралізуючий агент, гідрофільний неводний розчинник та їх оптимальні концентрації у складі препарату. Показано, що термічні ефекти зразків діючих речовин, гелевої основи і гелю «Фіторин-плюс» мають подібний характер, що може суб'єктивно свідчити про відсутність хімічної взаємодії між компонентами препарату і підтверджувати правильність розробленої технології.

#### РАЗРАБОТКА ТЕХНОЛОГИИ НАЗАЛЬНОГО ГЕЛЯ «ФИТОРИН-ПЛЮС» ДЛЯ ЛЕЧЕНИЯ АЛЛЕРГИЧЕСКОГО РИНИТА

**О.А.Рухмакова, Т.Г.Ярних**

**Ключевые слова:** технология; назальный гель; аллергический ринит

На современном фармацевтическом рынке среди симптоматических назальных средств имеются преимущественно синтетические лекарственные препараты зарубежного производства. Значительная их часть выпускается в форме капель или спреев, что обуславливает кратковременность действия препаратов. Большое внимание сегодня в лечении аллергического ринита привлекают назальные гели. Цель работы – разработка назального

средства на основе веществ растительного происхождения в форме геля под условным названием «Фиторин-плюс». В качестве действующих веществ использованы сухой экстракт корня солодки, эфирные масла сосны и эвкалипта. С целью выбора структурообразующего компонента исследована возможность применения карбомера (карбопола) 934 P, гидроксипропилцеллюлозы и натрия альгината. Для нейтрализации водных дисперсий карбопола использованы растворы аммиака, натрия гидроксида и триэтанолламин. Приготовление геля осуществлялось при комнатной температуре по двум вариантам технологии: путем смешивания готового геля и приготовленных растворов действующих веществ (технология №1) и путем введения действующих веществ в дисперсионную среду перед сгущением геля (технология №2). На основании комплекса проведенных органолептических, физико-химических и структурно-механических исследований были выбраны гелеобразователь, нейтрализующий агент, гидрофильный неводный растворитель и их оптимальные концентрации в составе препарата. Показано, что термические эффекты образцов действующих веществ, гелевой основы и геля «Фиторин-плюс» имеют сходный характер, что субъективно свидетельствует об отсутствии химического взаимодействия между компонентами препарата и подтверждает правильность разработанной технологии.