

УДК 615.4



FILMS IN RUSSIAN MEDICINE AND COSMETOLOGY: DEVELOPMENT HISTORY, CLASSIFICATION, TECHNOLOGY

Kishchenko V.M., Vernikovskiy V.V., Privalov I.M., Shevchenko A.M.

Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd Medical State University,
11, Kalinin ave., Pyatigorsk, Russia, 357532

E-mail: viktoriya.kishchenko@yandex.ru

Received 31 January 2020

Review (1) 5 April 2020

Review (2) 15 April 2020

Accepted 10 May 2020

Since the moment of their appearance in the second half of the 20th century, application forms have attracted the attention of the specialists involved in the skin application of pharmacologically active agents. Herewith, both localized exposure to the external integuments and the possibility of achieving a systemic effect, are of interest. The range of products used in modern films, is also wide – from pharmaceutical substances to biologically active components of cosmetics.

The aim of the present work is to study the current state of research in the field of the creation and improvement of medicinal and cosmeceutical films.

Materials and methods. The study was conducted on the base of patent information (fips.ru, findpatent.ru) and information and search databases – the State register of medicines (grls.rosminzdrav.ru) and the data from the Federal accreditation service (www.fsa.gov.ru), as well as scientific libraries (Google Scholar, eLIBRARY, PubMed) and reference literature.

Results. Native and foreign medicinal films have longer than a 50-year history of their existence in the pharmaceutical market. Modern scientists' interest in this application form, does not fade away due to a great number of its positive characteristics. In addition to pharmaceutical applications, films are widely used in cosmetics in the form of masks applied to the skin. Biologically active substances are widely used in cosmetics which, in recent years, has led to the emergence of a group of cosmeceutical products that combine medical and cosmetic films. The article also discusses film manufacturing technology, active substances, as well as polymers used for medicinal and cosmetic films presented in the Russian market.

Conclusion. The analysis of the literature data makes it possible to conclude that the development of films is promising in both medicine and cosmeceuticals.

Keywords: medicinal films, biologically active components, matrix, polymers, cosmetic films, cosmeceutics, classification of films, history of film development, film manufacturing technology

ПЛЕНКИ В РОССИЙСКОЙ МЕДИЦИНЕ И КОСМЕТОЛОГИИ: ИСТОРИЯ РАЗВИТИЯ, КЛАССИФИКАЦИЯ, ТЕХНОЛОГИЯ

Кищенко В.М., Верниковский В.В., Привалов И.М., Шевченко А.М.

Пятигорский медико-фармацевтический институт – филиал федерального государственного бюджетного образовательного учреждения высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации
357532, Россия, Ставропольский край, г. Пятигорск, пр. Калинина, 11

E-mail: viktoriya.kishchenko@yandex.ru

Получено 31.01.2020

Рецензия (1) 5.04.2020

Рецензия (2) 15.04.2020

Принята к печати 10.05.2020

Аппликационные формы с момента своего появления во второй половине XX века привлекают внимание специалистов, занимающихся вопросами кожного применения фармакологически активных средств. При этом интерес вызывает как оказание локализованного воздействия на наружные покровы, так и возможность достижения систем-

For citation: Kishchenko V.M., Vernikovskiy V.V., Privalov I.M., Shevchenko A.M. Films in russian medicine and cosmetology: development history, classification, technology. *Pharmacy & Pharmacology*. 2020;8(2):124-132. DOI: 10.19163/2307-9266-2020-8-2-124-132

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Для цитирования: Кищенко В.М., Верниковский В.В., Привалов И.М., Шевченко А.М. Пленки в российской медицине и косметологии: история развития, классификация, технология. *Фармация и фармакология*. 2020;8(2): 98-124-132. DOI: 10.19163/2307-9266-2020-8-2-124-132

ного эффекта. Широко также и диапазон применяемых в составе современных пленок средств – от фармацевтических субстанций до биологически активных компонентов косметических средств.

Цель. Настоящая работа посвящена изучению современного состояния российских исследований в области создания и совершенствования лекарственных и косметических пленок.

Материалы и методы. Исследование проводилось с использованием патентно-информационных (fips.ru, findpatent.ru) и информационно-поисковых баз – Государственного реестра лекарственных средств (grls.rosminzdrav.ru) и данных Федеральной службы по аккредитации (www.fsa.gov.ru), а также научных библиотек (Google Scholar, eLIBRARY, PubMed) и справочной литературы.

Результаты. В России и за рубежом лекарственные пленки насчитывают более чем 50-летнюю историю своего существования на фармацевтическом рынке. Интерес современных ученых к данной аппликационной форме не угасает благодаря большому количеству положительных характеристик. Помимо фармацевтической сферы применения пленки получили широкое распространение в косметике, где применяются в качестве масок, наносимых на кожу. В косметических средствах широко применяются биологически активные вещества, что в последние годы привело к появлению группы косметической продукции, объединяющей медицинские и косметические пленки. Также в статье рассмотрены методы получения пленок, действующие вещества и полимеры, применяемые для лекарственных и косметических пленок, представленных на российском рынке.

Заключение. Проведенный анализ данных литературы позволяет сделать вывод о перспективном развитии пленок в российской медицине и косметике.

Ключевые слова: пленки лекарственные, биологически активные компоненты, матрица, полимеры, пленки косметические, косметика, классификация пленок, история развития пленок, технология изготовления пленок

INTRODUCTION

Application (from the Latin. *applicatio* – application) as a way to use medicines and cosmetics and medical products, has been known since ancient times. Application preparations are considered dosage forms and other products applied to the skin, mucous membranes or wound surfaces and somehow fixed on them. This method of application, depending on the active ingredients used, excipients and design features of the application preparation, makes it possible to achieve both localized and systemic effects on the human body. The latter gives a possibility to consider application preparations not from the point of view of being traditional dosage forms, but as delivery systems [1]. One of the promising directions for the development of local-regional and transdermal drug delivery systems is self-fixing application dosage forms and, in particular, films.

The aim of the present work is to study the current state of research in the field of the creation and improvement of medicinal and cosmeceutical films.

MATERIALS AND METHODS

The study was conducted on the base of information (fips.ru, findpatent.ru) and information and search databases – the State register of medicines (grls.rosminzdrav.ru) and data from the Federal accreditation service (www.fsa.gov.ru), as well as scientific libraries (Google Scholar, eLIBRARY, PubMed) and reference literature. The search depth of literary sources was 21 years, and the patent search depth was 17 years. The following search terms were used during the search for materials: “medicinal films”, “films”, “cosmetic films”, “films”.

RESULTS AND DISCUSSION

The history of films as a production form of medicines and cosmetics, has more than 50 years. For the first time in our country, films as a dosage form appeared in the 60s of the XX-th century, and their scope was limited to the ophthalmic practice [2]. In the foreign pharmaceutical market, a “film” dosage form was officially introduced in 1970 as a substitute for rapidly dissolving tablets [3]. In native pharmacy, the official definition of the “film” dosage form first appeared in the State Pharmacopoeia of the XIII-th edition in the general pharmacopoeial article on ophthalmic dosage forms, where “ophthalmic films” were highlighted as “solid ophthalmic dosage forms for topical application” [4]. However, in already the XIV-th edition of the State Pharmacopoeia, films as a separate general pharmacopoeial article, were highlighted as an independent dosage form. According to the definition of the current pharmacopoeia, films are a solid dosage form, represented by thin plates of a suitable size, containing one or more active substances and some auxiliary substances, including film-forming ones. The scope of application of films as a dosage form of drugs was expanded; depending on the method of administration and the route of administration, ophthalmic films and films for oral use are distinguished [5].

As any dosage form, films have a number of positive and negative features (advantages and disadvantages) that determine the scope of their application (Table 1) [6].

Table 1 – Advantages and disadvantages of films as a dosage form

Advantages	Disadvantages
<p>Technological:</p> <ul style="list-style-type: none"> • film production does not require complex equipment; • the possibility of combining various groups of active substances; • ease of use because of the reduction of administration (with a prolonged release); • sufficient mobility for patients' self-use. <p>Pharmacological:</p> <ul style="list-style-type: none"> • prolongation possibility of active substances' action; • maintaining a constant concentration of active substances; • possible reduction in a therapeutically active dose; • if necessary, the dose of the active substance can be increased by applying an additional film; • reducing or eliminating side effects; • an active substance penetrates into the systemic bloodstream with a reduced effect of the first hepatic pass. 	<ul style="list-style-type: none"> • It is difficult to include considerable amounts of active substances in the composition of films; • low in some cases, the rate of passive diffusion requires the use of special auxiliary substances – penetrators; • active substances of natural origin can form competent complexes with auxiliary substances reducing their pharmacological activity; • restraint of selection and a high cost of packaging; • during storage, films can change their properties if packaging has been chosen incorrectly (loss of moisture, dampness).

However, as Table 1 shows, in some cases, positive features of this dosage form can be also its disadvantages. For example, the size of the dosage form allows it to be quite mobile and convenient to use, but since a film is a compact form, due to its size, it cannot include a large number of active substances. Films can also contain combinations of active substances in their composition, which is undoubtedly their positive feature. However, in this case, the selection of the composition is complicated by the fact that not only the active substances must be indifferent to each other, but also the base polymer in the manufacturing process, is more likely to bind the active substances and thus prevent their release.

The analysis of the literature data has shown that the most developed classification issues are for films as a medicinal form, while in the case of cosmetic films, the classification has not been given a sufficient attention.

A growing interest of researchers and a vast scope of applications of "film" medicinal form, dictated the need to create classifications by various features.

For example, a detailed classification of films was presented by Professor E.A. Korzhavykh. According to the author, medicinal films can be classified according to four main characteristics:

1. by the route of administration: buccal, vaginal, ocular, dental, dermatological, intraocular;
2. by composition: collagen, fibrin, phyto-films;
3. by properties of the polymer: insoluble and rapidly dissolving;
4. by other features: impregnated, spray and modified release films.
5. One of the highlighted groups is a group of modified release films.

A prolonged release of active components from the films is achieved through the use of certain polymers and their combinations. Thus, the results of a biopharmaceuti-

cal study of remineralizing films with trimecaine hydrochloride and chlorhexidinebigluconate on four bases (sodium-carboxymethylcellulose, sodium alginate, Blanose 7MF, Blanose 7M8SF) and remineralizing films with calcium chloride, sodium phosphate bi-substituted, sodium fluoride based on methylcellulose, have been published. The results of this study showed that the rate of release of active substances from different bases is not the same: the base with sodium alginate had a prolonged release of the active substances, and Blanose 7M8SF provided an accelerated release, since this polymer base had a high swelling ability and, therefore, rapid dissolution [8]. A rapid release of active substances from the polymer base can be one of the advantages of films. An accelerated release, for example, is relevant for oral dispersed drugs containing nitroglycerin or loratidine [3, 9].

A mathematical analysis of the process of releasing the active component from a hydrophilic matrix (in particular, based on chitosan) placed in water, was carried out by A.O. Syromyasov and co-authors. As a result, the following mathematical model of the diffusion of substances from the same hydrophilic film, which takes into account the influence of various factors on this process, was proposed: the dependence of the properties of the matrix on the concentration of the active component in it, due to the phenomenon of partial binding of the active component inside the matrix, and the dependence of the properties of the matrix on the time associated with its swelling and possible dissolution in an aqueous medium [10].

Since their inception, the films have undergone significant modifications, for example, in terms of releasing an active component. Thus, the issues related to the development of new compositions and improvement of technologies, are some of the "pressing issues" of modern pharmacy [11, 12].

Currently, native scientists have developed a significant number of compositions of polymer medicinal films with various effects: antimicrobial, antiviral, immunomodulating, affecting the cardiovascular system and also used for local anesthesia [9, 13, 14]. Modern films may contain herbal remedies, enzymes and other medicines as active ingredients for the treatment of ophthalmic, dental, dermatological, otorhinolaryngological, gynecological, oncological diseases, burns, wounds, alcoholism, drug addiction, depression, angina pectoris, etc. [2, 15–18].

The greatest interest of researchers is attracted to the films for use in the oral cavity, containing active ingredients of natural, synthetic origin or a combination thereof. So, the composition was developed and the technology for producing dental films with bischofite having anti-edematous action was standardized [19].

A study on the creation of two-layer dental films with analgesic, anti-inflammatory and antimicrobial effects was conducted. As active ingredients, in the composition of these films, the authors used novocain, norsulfazolum-natrium and kalanchoe juice; a number of polymers were used to create model matrix formulations of the dosage form: gelatin, methyl cellulose, polyvinyl alcohol and sodium carboxymethyl cellulose. To select the optimal basis, the film formers were compared among themselves on the basis of their organoleptic properties. The study showed that the optimal basis for Novocain is a 3% solution of methyl cellulose, and for norsulfazole, a 6% solution of polyvinyl alcohol is most suitable [20].

The results on physico-chemical research and the production of dental films based on collagen and gelatin, have been published; they contain 30% chlorhexidine in their composition. It has been established that the gelation process is influenced by concentration, the initial temperature of gelation, the rate of the cooling process and the content of auxiliary additives [21]. The gelation rate increased if the process started at a lower temperature. In the free cooling mode (from 38° C in the air to the ambient temperature of 24° C), the structure of the gelatin solution changed with the endpoint of gelation. The gelatin mass precipitation time during solidification was 60 minutes. The structure formation of collagen from a thin layer of a solution in the initial period was determined by the nature of the evaporation of pure solvents. This process is quite lengthy – the authors indicate that in 100 minutes only 23% of the liquid phase was removed from the total mass [21].

For the prevention and treatment of periodontal disease, a medical-preventive film with a matrix based on polyvinyl alcohol and vitamin D3 as the active component, has been developed. For this composition, the studies of the physical integrity of the developed composition have been conducted. They showed that the physical integrity of the film increases by 10% with the joint introduction of a film former (polyvinyl alcohol), plasticizer (glycerine) and vitamin D3 as the active sub-

stance. The effect of vitamin D3 on the functional activity of the cells isolated from the periodontal pocket, was also studied. The studies have shown that vitamin D3 released from the film, significantly limited the production of inflammatory mediators [22].

To correct gingivitis, periodontosis and periodontitis, compositions of medicinal films with chaga melanin (*Inonotus obliquus* (Ach. ex Pers.) Pil.) and chlorhexidine based on the composition of polymers – polyvinyl alcohol and zoster polysaccharide, were developed. The developed dental films were subjected to tests on the indicator of “the moisture content” and the time of dissolution. The results of the experiments showed that the optimal moisture content values for dental films, were in the range of 6–12%. It was also established that the introduction of chlorhexidine into the composition reduced its solubility by 8% [23]. A polyvinyl alcohol-based matrix was also used to develop the composition of dental medicinal films containing magnesium chloride and zinc-substituted calcium hydroxyapatite as active substances [24].

For the deposition of drugs on the surface of the nasal mucosa and maxillary sinus, an adhesive polymer soluble film containing a composition of lidocaine hydrochloride and polysorb MP, was developed. A blend of polymers oxypropylmethylcellulose and pectin, was chosen as a matrix. Clinical studies of the specific activity of the proposed composition conducted on a group of patients, are of interest. As a result, it was determined that the developed film contributes to a faster epithelization of the nasal mucosa and maxillary sinus [25]. The results on the development of an optimal film composition based on phytocomposition (a mixture of dry extracts of calendula and yarrow) with the addition of propolis tincture for the treatment of traumatic lesions of the oral mucosa, have been published; in this composition gelatin was used as a film-forming agent with the addition of glycerol as a plasticizer [26].

Medicinal films are also used in pediatric dental practice. So, the compositions and technologies of films with anesthetic and anti-inflammatory effects have been developed. In these compositions, the active ingredients were the substance of trimecaine and the aqueous extraction from chamomile flowers; the matrix was a composition of sodium carboxymethylcellulose, gelatin, and polyethylene oxide-600 [27, 28].

Besides the dental field, films are also widely used in ophthalmology. For example, the study results of the choice of the ophthalmic films composition with a liquid extract of aloe for the correction of inflammatory diseases of the conjunctiva oculi have been published. Polyvinylpyrrolidone, carboxymethylcellulose, polyethylene oxide-400 were used as polymers to create the film base. The optimal composition selection makes it possible to evaluate the following parameters: a moisture content, linear dimensions, pH, as well as the attractiveness of the film appearance. As a result of the studies, it was found

out that the best characteristics had been obtained for the film based on carboxymethylcellulose [29].

Medicinal films are used not only for the treatment of humans, but also for the correction of diseases in animals. For treating animals' eyes, polymeric drug films with moxifloxacin and a base of a polyvinyl alcohol and arabinogalactan composition, have been proposed. A study of the kinetics of the drug release from the model bases carried out by a spectrophotometric method showed that the studied composite base has a more pronounced prolonging effect compared to a film based on pure polyvinyl alcohol [30, 31].

Despite the active research conducted by native scientists on the development of medicinal films, this form of production is presented very modestly in the pharmaceutical market. The State register of medicines contains only five registered medicines produced in this form. These are two versions of films with nitroglycerine "Trinitrolong" glued to the gum, intended for the prevention and relief of angina attacks. It is based on a matrix of a polymer that is bio-soluble for medicinal films, which is a copolymer of acrylamide, N-polyvinylpyrrolidone and ethylacrylate. Two other drugs are oral dispersed films with sildenafil "Invida ODP" and "Dynamico Forward", intended for the correction of an erectile dysfunction. As a film-forming agent, in these medicines a food polysaccharide pullulan is used. In these cases, the film form is a kind of analog of tablets, having the advantage over the latter in the form of a simple technology that makes possible a more flexible regulation of the release kinetics. As for the fifth drug registered in the form of films, these are eye films "Taurine", used for the correction of dystrophy and injuries of the cornea, also created on the basis of a matrix of biopolymer soluble for medicinal films.

The simplicity and high manufacturability of films, provides the possibility to use them not only as medicines, but also as dressings. At different times, scientists conducted research in the market of dressings and medicinal films, thus showing the relevance of their use and the continuing interest in improving this form of medicines production [2, 18, 32, 33].

Currently, in Russia films are used not only in the native medical practice; in the native cosmetic market they have also taken a fairly stable position. So, according to the Russian Accreditation dated August 21, 2019, in the perfumery and cosmetic market, cosmetics included more than 162,000 product names (100%). The subgroup of "skin care products" consisted of more than 22,700 items, which represented approximately 14% of all cosmetics. In turn, among the skin care products, "face masks" stand out (more than 3500 items, or 2.2% of the total number of cosmetics); among them "mask-films" were allocated in the amount of about 0.01% of the total the number of cosmetics in the Russian market. Despite such a small share in relative indices, in absolute terms, there are more than 150 types of film masks in the Russian cosmetic market, which is

many times greater than the number of drugs sold in this form in Russia.

Being not medicinal products, cosmetic masks-films can contain the same biologically active substances as medicinal forms, but in a much lower concentration, thereby having a favorable effect on the skin. Such masks help to eliminate dryness and peeling of the skin, regulate the work of the sebaceous glands, etc. At the same time, they do not have a toxic effect on the consumer's body due to the content of active substances in concentrations much lower than in drugs (in most cases, the concentration is about 0.5% or less) [34–36]. The use of biologically active components in cosmetics has led to the emergence of the term "cosmeceuticals", which refers to cosmetic products containing components that have a pronounced biological activity. More than 20 years ago, this term combining the concepts of "pharmacy" and "cosmetics", was introduced by an American dermatologist Albert Kligman. Cosmeceuticals differ from cosmetics mainly in the following: they do not mask skin imperfections, but eliminate the cause of their appearance. Cosmeceutical agents can also affect the hypodermis, while cosmetic ones are usually able to penetrate no further than the derma [37, 38].

The analysis of the range of biologically active substances included in the composition of cosmeceuticals, has shown that they are mainly of natural origin, while synthetic compounds are practically not used. The components of animal origin included in cosmetic products are, for example, a number of bee products, such as bee pollen, which has an antioxidant, anti-inflammatory, anti-carcinogenic, anti-bacterial, anti-fungal effect [39]; drone brood, which slows down the aging process of the skin; Royal jelly, used as a means with a high regenerative index [40]. A fairly common active component is snail mucin, which can be used for the treatment of various types of burns, dermatitis, eczema, diaper rash and wounds [41–43]. A study of a product research of cosmetic masks with collagen acting not only as a film-forming agent but also as an active ingredient, has been published [46]. However, in addition to these rather specific components, cosmeceutical films contain components found in almost every cosmetic product – guanine, keratin, etc. [44, 45].

In addition to biologically active substances of animal origin, vegetable components are widely used in cosmetics: rose water, extracts of chamomile, cornflower, calendula, etc., as well as vegetable oils (including essential oils). Products derived from aloe vera and tree aloe, are among the most commonly found in the composition of dermatological masks-films. Aloe juice and extracts are used in the cosmetic industry to stimulate skin regeneration and prevent dermatitis of various origins.

In cosmetics, a study of the application frequency of polymers containing natural mineral salts was conducted; it showed that polyvinylpyrrolidone, xanthan gum,

cellulose derivatives and carbomers are the most applicable for these compositions [47].

Polymers of natural, semi-synthetic and synthetic origins, are used as a matrix for creating films; it gives a possibility to divide films into the following groups [48]:

- of animal origin (collagen, gelatin, elastin, chitosan);
- of vegetable (alginates, cellulose);
- of microbial origin (agar-agar, dextrin, pullulan);
- semi-synthetic (methyl cellulose, sodium carboxymethylcellulose, (hydroxypropyl)ethyl cellulose, modified starches);
- synthetic (polyvinylpyrrolidone, polyvinyl alcohol, polyethylene oxides, polyacrylamides).

Most often, in films as drugs manufacturing, cellulose derivatives (methyl cellulose, etc.), gelatin and agar are used [29, 49, 50]. In cosmeceutical masks-films, sodium alginate and polyvinyl alcohol are most often found as base polymers [51].

In addition to the auxiliary substances making up the base, films include plasticizers (glycerin, propylene glycol, polyethylene glycol, castor oil, tweens), preserving agents (ethyl alcohol, nipagin, benzalconium chloride), penetrators (dimethyl sulfoxide, dimethylformamide), odor and taste flavoring agents, pH regulators, solubilizers (tween 80, polyethylene glycol 1500, glycyram) and others. They provide optimal technological, chemical, physico-chemical and pharmacological parameters.

In addition to form-forming and auxiliary ingredients, medicinal and cosmetic films combine manufacturing processes of film matrices. Currently, the following methods of forming films are used:

- spraying;
- pouring;

- extrusion.

A pulverization method consists in the distribution of the polymer base over the substrate with constant drying in an intensive flow of warm air using a spray gun. The films obtained in this way, dry up faster, but the film mass can be also distributed unevenly, and at the drying stage, the finished films may not correspond to the organoleptic characteristics. In films manufacturing by the method of pouring, the polymer solution is distributed on the substrate, and then dried up either in chamber driers or at the room temperature. The disadvantage of this method is uneven drying of the film: during the drying process, the layer located on the surface dries quickly and prevents the removal of moisture from the underlying layers, which can result in an uneven film. This disadvantage can be avoided by using the equipment set up at the level of the form, as well as dryers to speed up the drying process. During extrusion molding, the film mass is pressed under pressure through the forming nozzle, obtaining a film of the required thickness [5], but the disadvantage of this method is the formation of inclusions of air bubbles in the film mass. This disadvantage can be corrected by including the vacuum stage in the production process.

CONCLUSION

A review of the studies made it possible to draw a conclusion about the rapid improvement of the films and their sufficient representation in the classification of medicines and cosmetics. The initial data from literary sources allow us to conclude that films are not only relevant and highly-demanded, they are also a popular dosage form. However, in the pharmaceutical market they are extremely limited. Based on a number of proven advantages of films, it can be assumed that this form is optimal for use in cosmetology.

FINANCIAL SUPPORT AND SPONSORSHIP

This study did not have any financial support from outside organizations.

AUTHOR'S CONTRIBUTION

All authors equally contributed to the research work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS

Victoria M. Kishchenko – post-graduate student of the Department of Pharmaceutical Technology with a course in medical biotechnology at Pyatigorsk Medical and Pharmaceutical Institute, a branch of the FSBEI HE VolgSMU of the Ministry of Health of the Russian Federation. ORCID 0000-0002-6947-7662. E-mail: viktoriya.kishchenko@yandex.ru

Vladislav V. Vernikovsky – Candidate of Sciences (Biology), associate Professor of the Department of Pharmaceutical Technology with a course in medical biotechnology of Pyatigorsk Medical and Pharmaceutical Institute, a branch of the FSBEI HE VolgSMU of the Ministry of Health of the Russian Federation. ORCID 0000-0002-0324-1999. E-mail: v.v.vernikovsky@mail.ru

Igor M. Privalov – Candidate of Sciences (Biology), associate Professor of the Department of Pharmaceutical Technology with a course in medical biotechnology of Pyatigorsk Medical and Pharmaceutical Institute, a branch of the FSBEI HE VolgSMU of the Ministry of Health of the Russian Federation. ORCID 0000-0001-9797-4060. E-mail: igor.privacy@gmail.com

Aleksandr M. Shevchenko – Doctor of Sciences (Pharmacy), associate Professor, the head of the Department of Pharmaceutical Technology with a course in medical biotechnology of Pyatigorsk Medical and Pharmaceutical Institute, a branch of Volgograd State Medical University. ORCID 0000-0002-7541-2558. E-mail: nplfarmak-50@ya.ru