ТЕХНОЛОГІЯ ЛІКАРСЬКИХ ПРЕПАРАТІВ

Recommended by Doctor of Pharmacy, professor T.G.Yarnykh

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DEVELOPMENT OF THE FORMULATION OF "ARTPROMENT®" COMBINED GEL FOR APPLICATION IN SPORTS MEDICINE

O.S.Shpychak, O.I.Tikhonov

National University of Pharmacy

Key words: traumas of the locomotor system; combined gel; gel technology; sports medicine

Based on the data of pharmaco-technological and physico-chemical studies conducted the formulation of the gel with the anti-inflammatory and local anesthetic action under the conditional name "Arthroment®" has been theoretically and experimentally substantiated in the pharmacy and industrial conditions. It is intended for application in a complex treatment of mechanical injuries and post-traumatic inflammations of extremities soft tissues, diseases of the locomotor apparatus (tendons, muscles and joints), musculoskeletal injuries that are characteristic for sports medicine and sports during the rehabilitation period such as bruises, dislocations, sprains, ruptures of ligaments, tendons, etc. The objects of research were model samples of "Artproment®" gel, which includes such active pharmaceutical ingredients (APhI) in its composition as propolis phenolic hydrophobic drug, articaine hydrochloride, menthol (levomenthol) and rosemary oil, as well as the following excipients: a gelation agent (Ultrez-10 NF carbomer), a neutralizer (trometamol), a preservative, nonaqueous solvent (propylene glycol), ethanol and purified water. The results of the experimental research were used when developing the technological process flowchart for preparing "Artproment®" gel in the conditions of pharmacy production and standard operating procedure on the drug studied. Taking into account the physico-chemical properties and according to the research results on solubility of APhI in the composition of the drug the technological process flowchart for manufacturing the combined gel industrially and the project of manufacturing instructions have been developed; technological parameters of its manufacturing have been substantiated; the optimal amount of solvents required for performing each technological stage has been calculated taking into account the solubility of the gel components, consequence and phasing of their mixing, temperature and other parameters affecting the quality and stability of the drug; and the formulation of "Artproment®" combined gel has been tested in the pharmacy and industrial conditions.

Diseases of organs of the locomotor apparatus formed and progressed due to injuries obtained during physical exercises and sports are widely distributed among sportsmen of different age groups and are of socio-economic importance for sports medicine as a whole [11, 15, 20]. The question of pharmacotherapy of protracted and chronic injuries of sportsmen accompanied with unbearable pain, as well as their rehabilitation and rapid recovery of physical performance in the shortest possible time is particularly pointed [10, 16, 17].

At present there is a considerable list of medicines of local application for treating the pathology mentioned above in the arsenal of a practicing doctor in sports medicine; however, most of them act only for a short period of time or exhibit undesirable side effects [21]. Taking into consideration the advantage of medicines for local application, in particular in the form of gels, as well as the nature of inflammatory processes and diseases of the locomotor apparatus, the topical problem of medicine and pharmacy is creation of a new effective drug of domestic manufacture with the anti-inflammatory and local anesthetic action for treating the given pathology.

Our efforts are under way to develop a new complex drug in the form of gel under the conditional name "Artproment®" on the basis of synthetic substances and compounds of the natural origin, in particular apiculture products, for treating traumas and diseases of the locomotor apparatus that mainly occur in sports medicine [5, 6].

In the previous studies the rational composition of the drug in the form of combined gel was developed, the study of structural-mechanical and technological properties of model samples was conducted with the purpose of selecting the base for the gel under research, the choice of a gelation agent and its concentration have been substantiated, as well as the indicators of quality control were determined, they were included to the project of quality control methods on the drug developed [7, 8].

Based on the results of pre-clinical experimental studies of the specific pharmacological action, the marked

Table

Solubility of active pharmaceutical ingredients of "Artproment®" combined gel in some solvents

No.	Solvent	Solubility of API			
		PPHD	Articaine hydrochloride	Menthol	Rosemary oil
1	Purified water	Practically insoluble	Readily soluble	Practically insoluble	Practically insoluble
2	Glycerine	Moderately soluble	Practically insoluble	Slightly soluble	Practically insoluble
3	PEO-400	Slightly soluble	Practically insoluble	Slightly soluble	Practically insoluble
4	Propylene glycol	Readily soluble	Practically insoluble	Slightly soluble	Practically insoluble
5	96% Ethanol	Moderately soluble	Readily soluble	Readily soluble	Readily soluble

analgesic and local anesthetic action of "Artproment®" combined gel, as well as its anti-edema action expressed at the level of 40-50% have been determined and its safety has been experimentally substantiated [9].

One of the important factors affecting the therapeutic action of the drug developed and its quality, as well as providing the satisfactory consumer characteristics, is development of the rational scientifically based formulation. Therefore, the technological process of manufacture should consist of the optimally planned systemic approach to complex experimental research conducted at the stage of the pharmaceutical development of the drug studied, and it influences on the final result of its quality and stability during storage [14].

The aim of this work is the experimental development of the scientifically based formulation of the combined gel with the anti-inflammatory and local anesthetic action under the conditional name "Artproment®" for application in a complex treatment of mechanical injuries and post-traumatic inflammations of extremities soft tissues, diseases of the locomotor apparatus (tendons, muscles and joints), musculoskeletal injuries that are characteristic for sports medicine and sports during the rehabilitation period such as bruises, dislocations, sprains, ruptures of ligaments, tendons, etc., in the pharmacy and industrial conditions.

Experimental Part

The objects of research were model samples of "Artproment®" gel including such active pharmaceutical ingredients (APhI) in its composition as propolis phenolic hydrophobic drug ((PPHD) batch No. 391011) "Zdorovya" Pharmaceutical company, Ltd., Kharkiv; articaine hydrochloride (batch No. 159.166) Societa Italiana Medicinali Scandicci (SIMS), Italy; menthol *(levomenthol)* batch No. NE-432-2009) Vaishali Pharmaceuticals, India; and rosemary oil (batch No. 1611211) Zolotoniska Perfumery-Cosmetic Factory, OJSC, Zolotonosha; as well as the following excipients: a gelation agent – Ultrez-10 NF carbomer (batch No. 0101078466) "Lubrizol", Belgium, a neutralizer – trometamol (batch No. 8386D050) "Merck KGaA", USA, a preservative, nonaqueous solvent – propylene glycol (batch No. ACG/QD-111122A) "Arrow Chemical Group Corp.", China, ethanol and purified water [5, 6, 7].

In order to determine the optimal technological parameters the standard laboratory equipment required for manufacturing soft medicines (stirred minireactor, homogenizer, etc.) was used. The formulation of the gel developed was tested in the pharmacy and industrial conditions; its experimental substantiation was based on the results obtained from organoleptic, physico-chemical and pharmaco-technological studies.

Results and Discussion

To solve the goal set at the first stage of the experimental research it was necessary to obtain a stable gel system, which was prepared by dispersion of a gelation agent – Ultrez-10 NF carbomer in 1/3 part of purified water at the room temperature and constant stirring for one hour with a previously dissolved preservative in it. It is known from the literary sources that the main advantage of Ultrez-10 NF carbomer is the fact that it requires no special conditions for its dissolution and increase of the temperature conditions [1, 12, 18]. However, according to some data in order to avoid the formation of lumps when preparing the aqueous solutions of carbomer the powder should be layered on the surface of water through the sieve [4].

After obtaining the aqueous solution of carbomer trometamol was added several times and mixed gradually in order to obtain the gel base [13], as well as to neutralize the solution obtained (to prevent the formation of air bubbles). It should also be noted that in industrial conditions after neutralization of carbomer solution with trometamol the gel obtained is placed under vaccume in the reactor to remove air bubbles [4].

For rational introduction of API and excipients to the composition of the gel base we studied solubility of active substances in some solvents permitted to medical use. The results of the APhI solubility of "Artproment®" combined gel are given in Table.

When dissolving PPHD in different solvents (Table) it has been found that according to the quality parameters for this substance described in FS 42U-34-20-95 and AND-DV-SP-090 of "Zdorovya" Pharmaceutical company, Ltd., Kharkiv PPHD is a hydrophobic substance, which is soluble in 96% ethanol and practically insoluble in water. However, the results of the experiment have shown that the given substance is more readily soluble in propylene glycol than in 96% ethanol; it has been considered when developing the formulation of the drug under research.

The study of articaine hydrochloride solubility has shown that this APhI is more readily soluble in purified water than in 96% ethanol. Thus, we have decided to prepare the aqueous solution of the substance, which unlike the alcohol solution does not form a white pre-

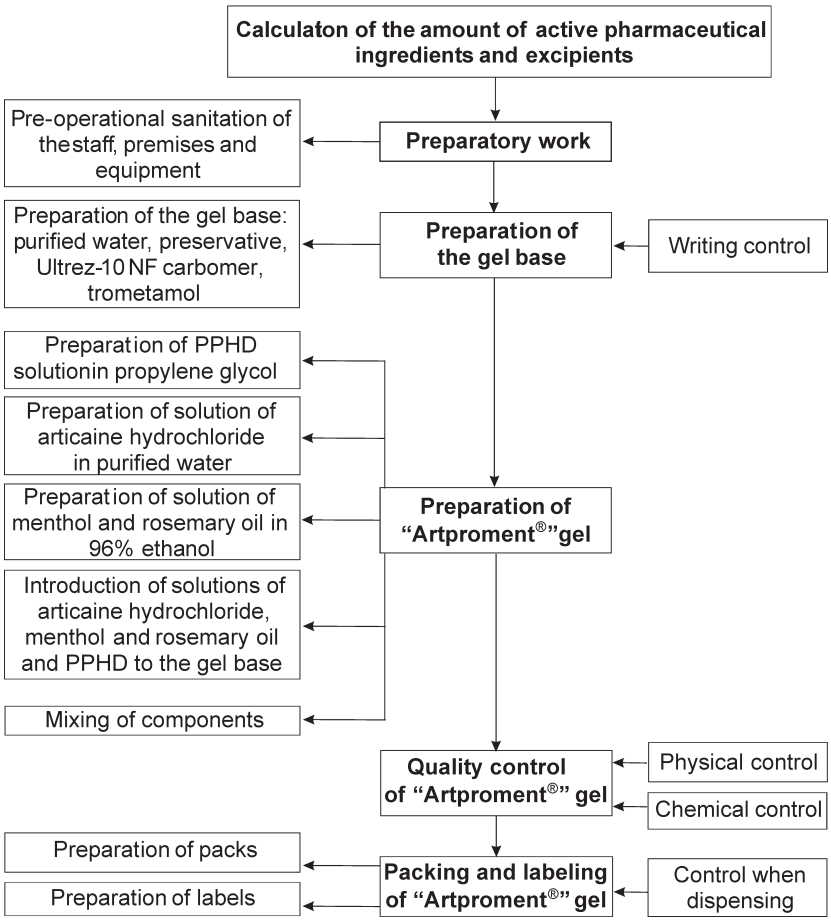

Fig. 1. The technological process flowchart for manufacturing "Artproment®" combined gel in the pharmacy conditions.

cipitate in the form of insoluble particles of the substance.

As menthol is readily soluble in the alcohol solution [2], it is dissolved in 96% ethanol; then rosemary oil is added with constant stirring till obtaining a homogeneous transparent solution since it is practically insoluble in water and hydrophilic solvents.

The results of the experimental research were used when developing the technological process flowchart for manufacturing "Artproment®" combined gel in the pharmacy conditions (Fig. 1) and the standard operating procedure on the drug under research. Taking into account the physico-chemical properties and the study of APhI solubility in the composition of the drug the technological process flowchart for manufacturing "Artproment®" gel in the industrial conditions has been also developed. It consists of the stage of preparatory work, the stages of the main production process, the stages of packing, labeling and delivery of the finished product to the warehouse; their brief description is given further.

It should also be noted that while making the technological process flowchart for the drug developed the optimal amount of solvents that are necessary to perform each technological stage has been calculated taking into account solubility of the gel components, sequence and phasing of their mixing, temperature and other parameters affecting the drug quality and stability.

The technological process flowchart for manufacturing "Artproment®" in the industrial conditions is presented in Fig. 2 where the critical parameters and critical stages, indicators that are directly controled in the process of manufacture of the combined gel are given.

The stage of preparatory work for manufacture consists of preparation of the premises, equipment and apparatuses, staff, raw material and materials, checking the necessary documentation. The raw material used for preparing the gel is subject to the initial control, after that it is brought on the site using transport trolleys and transferred to stages 1-5.

Stage 1. Preparation of PPHD solution

Load propylene glycol and PPHD previously weighed into the collector using balances into the reactor using vapour, heat the mixture with constant stirring to the temperature (60±5)°C. Continue stirring to the complete dissolution of PPHD for (10±2) min, then cool the reactor to the room temperature.

Stage 2. Preparation of solution of articaine hydrochloride

Weigh articaine hydrochloride into the collector using balances and load into the reactor, measure the required amount of purified water, load into the reactor, after that switch on the blade paddle mixer and mix till complete dissolution of articaine hydrochloride.

Stage 3. Preparation of solution of menthol and rosemary oil

Weigh menthol into the collector and add ethanol, load into the reactor, switch on the mixer and mix to form a homogeneous solution. Then weigh rosemary oil into the collector, load into the reactor to the alcohol

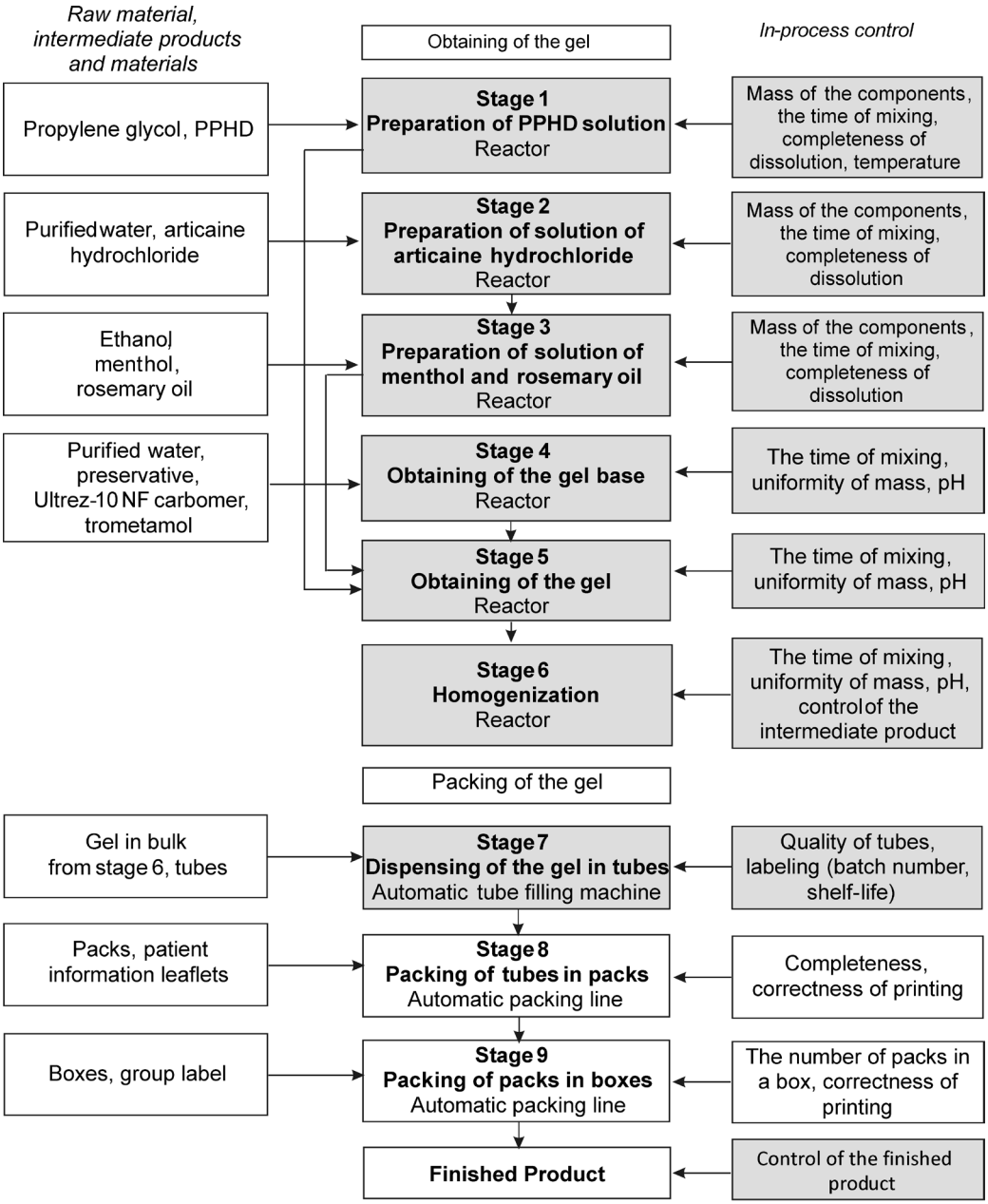

Fig. 2. The technological process flowchart for manufacturing "Artproment®" combined gel in the industrial conditions.

solution of menthol and again mix carefully using the mixer. After obtaining the ethanol solution of menthol and rosemary oil, load the solution of articaine hydrochloride previously prepared in another reactor from stage 2 using vacuum, switch on the blade paddle mixer and mix to form a homogeneous mass.

Stage 4. Obtaining of the gel base

To obtain the base measure the required amount of purified water into the reactor and from the collector take the preservative previously weighed on balances, then switch on the mixer and mix the mixture for 3 min. Perform dissolution of the preservative at the room temperature. In the same reactor load gradually by small portions a gelation agent (carbomer) previously weighed on balances from the collector and allow to stand for one hour. In an hour mix a dispersed gel in the reactor with the mixers switched on till the formation of a homogeneous dispersion, which is controlled visually for uniformity and absence of sticky lumps.

To prepare the gel carry out neutralization of carbomer dispersion directly in the reactor with constant stirring (the rate of rotation of mixers – 800 rpm). To achieve gelation with the help of vacuum load gradually the required amount of trometamol solution in several stages(individual portions) [19]. After introduction of each portion of trometamol mix the mass in the reactor with gate-impeller and blade paddle mixers for 2-3 min and determine the pH level.

Mix the mixture obtained for 20 min with simultaneous adding of vacuum till the formation of a homogeneous, colourless, transparent gel base, control for uniformity and again determine the pH level.

Stage 5. Obtaining of the gel

To the reactor with the base with the help of vacuum load the mixtures of dissolved substances previously prepared at stages 2 and 3, switch on the gate-impeller mixer and mix thoroughly to obtain the homogeneous gel, then add the solution of PPHD previously prepared to propylene glycol from another reactor using vacuum.

Stage 6. Homogenization

Switch on the gate-impeller mixer and perform homogenization of the mixture obtained for 20 min to form a homogeneous gel with simultaneous vacuumizing in order to avoid the aeration process in the drug obtained [3]. Pump the gel obtained into the collector using a pump, take test samples from its various areas, control the mass of the gel obtained on balances, carry out analysis of the drug intermediate product and transfer to the stage of dispensing of the gel in tubes.

Stage 7. Dispensing of the gel in tubes

From the collector transfer the gel into the bin of the automatic tube filling machine using vacuum and dispense in tubes with a bouchon 30.0 g each. Control accuracy of the dose by balances, machine performance, correctness of printing and labeling on the tube (batch number, shelf-life).

Stage 8. Packing of tubes in packs

Pack the tubes with the patient information leaflet in packs using automatic packing line. Control the completeness of the pack (tube, patient information leaflet, bouchon).

Stage 9. Packing of packs in boxes

Perform packing of packs in boxes on the automatic packing line. Form the batch of the finished product on the basis of one loading of the reactor-homogenizer.

CONCLUSIONS

1. Based on the pharmaco-technological and physico-chemical studies conducted the formulation of "Artproment®" combined gel with the anti-inflammatory and local anesthetic action has been theoretically and experimentally substantiated. It is intended for application in a complex treatment of mechanical injuries and post-traumatic inflammations of extremities soft tissues, diseases of the locomotor apparatus (tendons, muscles and joints), musculoskeletal injuries that are characteristic for sports medicine and sports during the rehabilitation period such as bruises, dislocations, sprains, ruptures of ligaments, tendons, etc.

2. According to the research results the technological parameters for manufacturing the combined gel (conditions of preparation, sequence of mixing, temperature conditions, etc.) have been substantiated; on their basis the technological process flowcharts for its manufacturing in the pharmacy and industrial conditions have been developed.

3. The results of the experimental research have been used when developing the projects of manufacturing instructions and standard operating procedure on "Artproment®" gel, and the technology of its manufacturing has been tested in the pharmacy and industrial conditions.

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РОЗРОБКА ТЕХНОЛОГІЇ КОМБІНОВАНОГО ГЕЛЮ «АРТПРОМЕНТ®» ДЛЯ ЗАСТОСУВАННЯ В СПОРТИВНІЙ МЕДИЦИНІ

О.С.Шпичак, О.І.Тихонов

Ключові слова: *травми органів рухового апарату; комбінований гель; технологія гелів; спортивна медицина*

На підставі проведених фармакотехнологічних та фізико-хімічних досліджень теоретично обґрунтовано та експериментально розроблено в аптечних умовах та в умовах промислового виробництва технологію виготовлення комбінованого гелю протизапальної та місцевоанестезуючої дії під умовною назвою «Артпромент®» для застосування в комплексному лікуванні механічних пошкоджень і посттравматичних запалень м'яких тканин кінцівок, захворювань органів рухового апарату (сухожиль, м'язів та суглобів), м'язово-скелетних травм, характерних для спортивної медицини і спорту в реабілітаційному періоді: забиття, вивихи, розтягнення, розриви зв'язок, сухожиль та ін. Об'єктами дослідження були модельні зразки гелю «Артпромент®», до складу якого входять активні фармацевтичні інгредієнти (АФІ): фенольний гідрофобний препарат прополісу, артикаїну гідрохлорид, ментол (левоментол) та розмаринова олія, а також допоміжні речовини: гелеутворювач (карбомер Ultrez-10 NF), нейтралізатор (трометамол), консервант, неводний розчинник (пропіленгліколь), етанол та вода очищена. Результати експериментальних досліджень були використані при розробці блок-схеми технологічного процесу виготовлення гелю «Артпромент®» в умовах аптечного виробництва та технологічної інструкції на досліджуваний препарат. З урахуванням фізико-хімічних властивостей та за результатами вивчення розчинності АФІ, що входять до складу лікарського засобу, було розроблено блок-схему технологічного процесу виробництва комбінованого гелю в промислових умовах та проект технологічного регламенту, обґрунтовані технологічні параметри його виготовлення, розраховано оптимальну кількість розчинників, необхідних для проведення кожної технологічної стадії з урахуванням розчинності компонентів гелю, послідовності і поетапності їх змішування, температурних та інших параметрів, що впливають на якість і стабільність препарату, а технологія комбінованого гелю «Артпромент®» апробована в аптечних і промислових умовах.

РАЗРАБОТКА ТЕХНОЛОГИИ КОМБИНИРОВАННОГО ГЕЛЯ «АРТПРОМЕНТ®» ДЛЯ ПРИМЕНЕНИЯ В СПОРТИВНОЙ МЕДИЦИНЕ

О.С.Шпичак, А.И.Тихонов

Ключевые слова: *травмы органов двигательного аппарата; комбинированный гель; технология гелей; спортивная медицина*

На основании проведенных фармакотехнологических и физико-химических исследований теоретически обоснована и экспериментально разработана в аптечных условиях и в условиях промышленного производства технология изготовления комбинированного геля противовоспалительного и местноанестезирующего действия под условным названием «Артпромент®» для применения в комплексном лечении механических повреждений и посттравматических воспалений мягких тканей конечностей, заболеваний органов двигательного аппарата (сухожилий, мышц и суставов), мышечно-скелетных травм, характерных для спортивной медицины и спорта в реабилитационном периоде: ушибы, вывихи, растяжения, разрывы связок, сухожилий и др. Объектами исследования были модельные образцы геля «Артпромент®», в состав которого входят активные фармацевтические ингредиенты (АФИ): фенольный гидрофобный препарат прополиса, артикаина гидрохлорид, ментол (левоментол) и розмариновое масло, а также вспомогательные вещества: гелеобразователь (карбомер Ultrez-10 NF), нейтрализатор (трометамол), консервант, неводный растворитель (пропиленгликоль), этанол и вода очищенная. Результаты экспериментальных исследований были использованы при разработке блок-схемы технологического процесса изготовления геля «Артпромент®» в условиях аптечного производства и технологической инструкции на исследуемый препарат. С учетом физико-химических свойств и по результатам изучения растворимости АФИ, входящих в состав лекарственного средства, разработана блок-схема технологического процесса производства комбинированного геля в промышленных условиях и проект технологического регламента, обоснованы технологические параметры его изготовления, рассчитано оптимальное количество растворителей, необходимых для проведения каждой технологической стадии с учетом растворимости компонентов геля, последовательности и поэтапности их смешивания, температурных и других параметров, влияющих на качество и стабильность препарата, а технология комбинированного геля «Артпромент®» апробирована в аптечных и промышленных условиях.