

## RESEARCH ARTICLE

### Development of gel composition and technology based on pyrimidine substance

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#### ABSTRACT

**Background:** This work was conducted in the framework of quality by design project involving the production of a pharmaceutical gel. Preliminary work included the identification of the quality target product profiles from historical values for previously laboratory batches, which were used to construct a D-optimal experimental design. Fungal disease of mycoses has long been known, since the days of antiquity. Our research gel high pharmacological effect (antifungal) in comparison with the drugs “Flucytosine” and “Fucis”. **Aims and Objectives:** The purpose of this study is to develop the optimal composition and rational gel technology under the conventional name “Anticandid” on the basis of the substance piperidinyethanone with an antifungal effect. **Materials and Methods:** Thermogravimetric analysis and rotational viscometry, which affect the process of the formation of carbopol, were taken. Based on the physicochemical properties and technological properties of the gel, an optimal solvent system is selected that corresponds to the maximum solubility of the drug substances and ensures polymer swelling. At the same time, the materials dimexide (DMSO), propylene glycol (PG), carbol-floor, and triethanol were taken into account, which improve the process of solubility and gelling. **Results:** The results were obtained, which, when the active substance is administered in the dissolved state, is the most therapeutic effect on the gel base. At the same time, active pharmaceutical ingredients (APIs) were dissolved in different solvents with gradual heating. The ratio of solvents DMSO-PG-water (1:4:1) at which the developed dosage form will be more structured, stable, and thixotropic is established. **Conclusion:** Fungal skin diseases are one of the most frequently discussed problems in various dermatological forums and in the pages of scientific journals. The relevance of this topic is determined by the high prevalence of this pathology, which, according to the literature, accounts for 37-42% of all skin diseases. The results of the studies on the study of the microbiological, physicochemical properties of APIs, and carbopol Ultrez 20 for the development of optimal composition are taken into account. It was found that the gel model with an active substance content of 3% is more effective and has high antifungal activity.

**KEY WORDS:** Optimal Formulation; Efficient Technology; Antifungal Action; Gel; Active Pharmaceutical Ingredient; A Substance Derived 4*H*-pyrido [4',3':5,6]pyrano[2,3-*d*]pyrimidine

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#### INTRODUCTION

Fungal infections of the skin (ringworm) and nails (onychomycosis) make up a large part of human infectious pathologies. They are a problem in more social than medical nature and can adversely affect the quality of life of patients. If incorrect or ineffective treatment of certain forms of fungal

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infections is becoming resistant to even the most modern methods of treatment, which can lead not only to distribution but also to chronic fungal process. Currently, described and studied more than 69,000 species of fungi, human pathogens found about 400 species of fungal infections, a quarter of which is the most common. To prevent this, very unpleasant disease will only thoroughly be personal hygiene and public prevention.<sup>[1-4]</sup>

By the type of action, the fungal cells are distinguished fungicidal and fungistatic agents. According to a source producing distinguish two groups antimycotics: Antibiotics and synthetic agents. The most promising is synthetic antimycotics, the specificity of which is caused by their direct effects on the fungal cell, its structure, and metabolism. Efficacy of synthetic antimycotics, used in the treatment of superficial dermatomycosis, largely depends on the degree of lipophilicity of the compound as well as the properties of the ointment base, promoting a better release of the substance and its penetration into the deeper layers of the skin and its appendages to the site of localization of the pathogen.<sup>[5-8]</sup> Over the past 25 years, have been major advances in the synthesis of a large group of new specific antifungals - pyrimidine derivatives.

Currently, pyrimidine derivatives are basic antifungal agents. They are characterized by high activity against dermatophytes, molds, and yeast-like organisms; fungistatic and antimicrobial action type; fairly good penetration into the stratum corneum of the epidermis; negligible toxicity; and lack mushrooms natural resistance to these drugs.<sup>[9,10]</sup>

For outdoor, antifungals characterized by seasonality of demand. The warm season is the most favorable for the development of fungal infections. Pretty high temperatures and as a consequence, the increased humidity, visits to places significant crowds - all factors that contribute to, and further spread of skin and nail fungal infections. During this period, regularly observed increased demand for antifungal drugs. Pharmaceutical institutions should be in time to respond to consumer demands: To prevent the emergence, to ensure the availability of a wide range within the group, and to provide the necessary advice to interested buyers.

The range of exterior antifungals is still dominated by imported products. Currently registered in Kazakhstan about 20 trade names of antifungal drugs for external use. At the same time, on the preparations, local production accounts for only 7% of sales in value terms. In the past three years, clearly procaking tendency to increase sales of Russian products, however, is dynamic rather modest in terms of value growth of about 2%.<sup>[11,12]</sup>

Considering the above, we have developed a mild formulation based on substances derived 4*H*-pyrido[4',3':5,6]pyrano[2,3-*d*]pyrimidine derivatives with antifungal activity.

## Objective

The purpose of this study is to develop the optimum composition of the gel and rational technologies under the code name "Anticandid" on the basis of substances derived 4*H*-pyrido[4',3':5,6]pyrano[2,3-*d*]pyrimidine antifungal activity.

## MATERIALS AND METHODS

We studied the segment of antifungal drugs, presented in the modern pharmaceutical market in Kazakhstan. For the study, drugs were chosen from the following groups according to ATS-classification: D01A1 "Antifungal preparations for external use," D01A2 "antifungal dermatological preparations systemic," and D01A3 "Antifungal drugs for the treatment of scalp".

Total on, the market of Kazakhstan is antifungal preparations of 13 active ingredients. 8 enterprises of Kazakhstan produce antifungal medicinal preparations 5 active substances: Itraconazole, ketoconazole, terbinafine, fluconazole, and clotrimazole.

The pharmaceutical market of antifungal drugs which depends on the import Kazakhstan - The share of imported antifungal products reaches 88%.

On the basis of the physicochemical properties of the gel (poorly soluble in water) and technological properties structurant - Carbopol Ultrez 20 (swelling) chosen optimal solvent system dimexide [DMSO]-PG-water (1:4:1) corresponding to the maximum solubility drug and polymer provides swelling.

Rotational viscometer method identified the factors influencing the process of structure formation Carbopol Ultrez 20: Polymer concentration, degree of neutralization, and the temperature. It is found that the developed drugs have thixotropic properties and are structured and stable systems.<sup>[8-14]</sup>

Selection of the concentration of active pharmaceutical ingredient (API) selected by the results of studies of antifungal activity in various embodiments of the gel *in vitro* experiments agar diffusion method. It is found that the gels of samples with an active compound content of 3.0% and 5.0% are promising for further work on creating formulations with antimicrobial properties and antifungals.

## RESULTS

The invention relates to medicine, namely, to the development of a medicinal composition in the form of a gel for external use, having an antifungal activity based on a new synthetic substance, 2-(6-hydroxymethyl-9-methyl-

2-(4-fluorophenyl)-5*H*-pyrido[4',3':5,6]pyrano[2,3-*d*]pyrimidin-4-ylsulfanyl)-1-*N*-piperidinyl-ethanone from the class 4*H*-pyrido[4',3':5,6]pyrano[2,3-*d*]pyrimidines. The object of the present invention is to expand the range of antifungal agents using a new synthetic substance, 2-(6-hydroxymethyl-9-methyl-2-(4-fluorophenyl)-5*H*-pyrido [4',3':5,6]pyrano[2,3-*d*] pyrimidin-4-ylsulfanyl)-1-*N*-piperidinyl ethanone, which has a pronounced antifungal activity.

For the aim of optimal composition and rational technology of gel, the following studies were carried out:

1. Preparation of API solution;
2. Preparation of the carrier substrate of the API;
3. Study of the swelling capacity of IUS (high-molecular compounds) or RAP (Rare cross-linked acrylic polymers);
4. Study of the effect of polymer concentration on the rheological characteristics of carbopol gels of the brand Ultrez 20;
5. The effect of neutralizing agent on the process of gel formation;
6. The influence of temperature on the process of gel formation;
7. Justification of the composition and technology of obtaining the gel "Anticandid";
8. Study of the structural and mechanical properties of the gel "Anticandid" which provides ease, high pharmacological activity, as well as uniformity of LV distribution in skin areas. When developing gels with an antifungal effect, it is necessary to take into account that they should have the appropriate melting point. At high temperatures, the gels are liquefied and can flow out of the containers, not fixing when applied to the surface. To achieve this aim, it was necessary to solve a practical problem - to study the influence of temperature on the process of gel formation. To determine the temperature of the samples of gels, on the basis of RAP, the amount of 25.0 g was placed in a measuring container of a rotational viscometer "Rheotest-2" and thermostat for 20 min. At each test, temperature is in the range from 20°C to 90°C in steps of 10°C. After that, the viscosity of the gels was measured and the plots of viscosity versus temperature.

It has been experimentally established that 1 g of triethanolamine (pH 7.0) is consumed to completely neutralize 1 g Carbopol Ultrez 20 in a DMSO-PG-water (1:4:1) solvent system. For organic amines, a sharp increase in the values of the effective viscosity of the system is characteristic with an increase in the pH of the system to 5. In the range of pH values from 5 to 11, the effective viscosity of the bases remains practically unchanged, which can be explained by the complexation of the polyacid with the amines to be studied. Physical-chemical methods of analysis selected the optimal diluent, consisting of PEG, DMSO, and water in the ratio (1:4:1), and 1 g of triethanolamine (pH 7.0) was chosen as the neutralizing agent.

Based on the rheological studies of the gel under the conventional name "Anticandid" and their analysis, it was found that samples No. 3 and No. 5, with an active substance content of 3% and 5%, have a positive effect on the structural and mechanical properties of the soft dosage form. They have optimal structural and mechanical characteristics and are a thixotropic system, sufficiently stable and plastic, capable of spreading onto the skin and providing the necessary stability of the system in the process of technological operations. Samples with active substance content of 3% and 5% are promising for further work on the development of drugs with antifungal action.

The choice of API concentration was chosen based on the results of the study of the antifungal activity of various gel variants in *in vitro* experiments by the method of diffusion into agar (well method).

Taking into account, the results of studies on the study of microbiological (antifungal activity), physicochemical properties (solubility) of API, and technological properties of carbopol Ultrez 20, we selected the composition of the gel "Anticandid" (Table 1).

## DISCUSSION

In view of results of the research on microbial (antifungal activity), physical-chemical properties (solubility) API, and

**Table 1:** Selection of models of gel under the conventional name "Anticandid"

Gel composition	Gel model									
	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10
API	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0	10.0
DMSO	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5
PG	45.5	45.75	50.0	50.25	50.5	50.75	60.0	60.25	60.5	60.75
Carbopol Ultrez 20	0.25	0.5	1.0	1.25	1.5	1.75	2.0	2.25	2.50	2.75
Triethanolamine	0.25	0.5	1.0	1.25	1.5	1.75	2.0	2.25	2.50	2.75
Purified water	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0

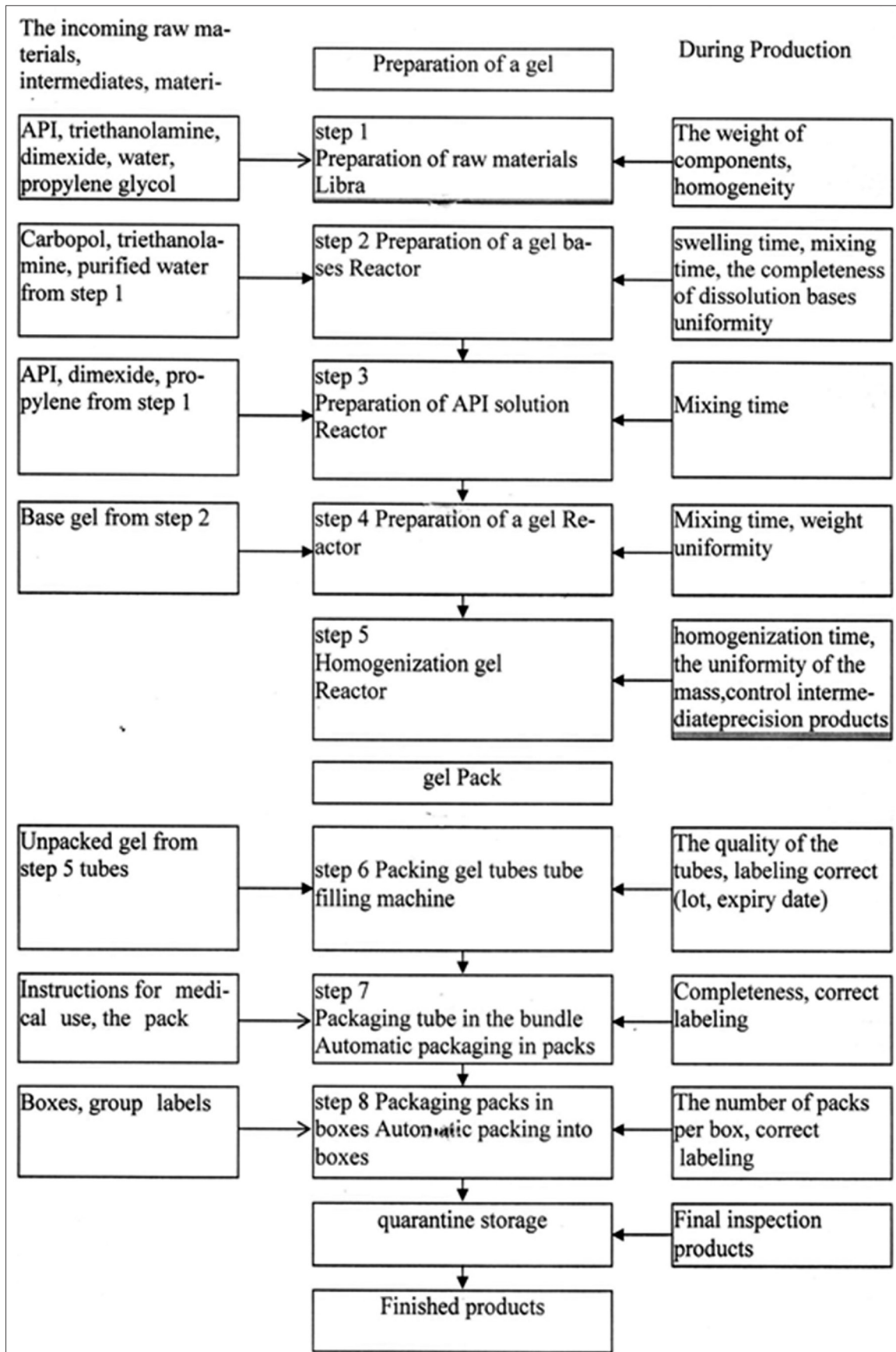


Figure 1: Block diagram of the manufacturing process of gel "Anticandid" 3%

**Table 2:** The gel of the gel under the code name “Anticandid” based on substances derived 4*H*-pyrido[4',3':5,6]pyrano[2,3-*d*]pyrimidine

Active substance	
The API	3.0%
Excipients	
DMSO	3.0%
PG	50.0%
Carbopol Ultrez 20	1.0%
Triethanolamine	1.0%
Purified water	42.0%

API: Active pharmaceutical ingredient, DMSO: Dimexide, PG: Propylene glycol

technological properties of Carbopol Ultrez 20, we selected gel composition was “Anticandid” (Table 2).

The content of DMSO and PG is set in the research of the solubility of APIs and supported by experimental studies on the swelling and the rheological properties of the gel Carbopol Ultrez 20. The mixture was solvents DMSO-PG-water (1:4:1) in the selected ratio, on the one hand, provides the complete dissolution of the API. On the other hand, it compensates for the fall of Padania viscosity characteristics of the system. The selected amount of water is sufficient for a selected amount of swelling Carbopol Ultrez 20. Included in the composition of triethanolamine neutralizing agent plays a role and enables gel base with constant rheological performance in a wide pH range.

Based on the studies defined technology for production of the gel composition, which is as follows: By weighing the required amounts of API, DMSO, PG, Carbopol Ultrez 20, triethanolamine, and purified water. API is dissolved in a mixture of DMSO and PG with constant stirring. Carbopol Ultrez 20 was dispersed in water. After swelling Carbopol Ultrez 20, it is introduced into a dispersion of triethanolamine and stirred to obtain a homogeneous gel. The gel is administered API solution in a mixture of DMSO and PG and stirred to obtain a homogeneous colorless gel. Technological scheme of the production of gel “Anticandid” is shown in Figure 1.

The technological process of the industrial production of the gel “Anticandid” includes the following steps:

1. Preparation of raw materials. The weight of components, homogeneity
2. Preparation of gel bases. Swelling time, mixing time, the completeness of dissolution homogeneity of the substrate
3. Preparation of API solution. The mixing time, the homogeneity of mass
4. Preparation of gel. The mixing time, the homogeneity of mass
5. The homogenization of the gel. Homogenization time, weight uniformity, control of intermediate products

6. Packing gel tubes. The quality of the tubes, labeling correct (lot, expiry date)
7. Packaging tubes in bundles. Completeness, accuracy of marking
8. Packaging of packs in boxes. The number of packs per box, the correct labeling.

## CONCLUSIONS

Fungal skin diseases are one of the most frequently discussed problems in various dermatological forums and in the pages of scientific journals. The relevance of this topic is determined by the high prevalence of this pathology, which, according to the literature, accounts for 37-42% of all skin diseases. In view of the study of microbiological studies (antifungal activity), physical-chemical properties (solubility) API, and technological properties Carbopol Ultrez 20 designed optimal composition and gel technology, code-named “Anticandid” based on substances derived 4*H*-pyrido[4',3':5,6]pyrano[2,3-*d*]pyrimidine.

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