ISSN 0974-3618 (Print)
0974-360X (Online)

www.rjptonline.org

RESEARCH ARTICLE

The Development of Industrial Technology of the Ointment Codenamed "Alergolik"

Rukhmakova O. A., Yarnykh T. G., Kovalenko S. N.
National University of Pharmacy, Ukraine, 61002, Kharkov, Pushkinskaya str. 53.
*Corresponding Author E-mail: **olynka22@rambler.ru**

ABSTRACT:
The article is dedicated to development of industrial technology of the ointment codenamed "Alergolik". To study the uniformity of distribution of medicinal substances and excipients in the drug the optimal time of the ointment's homogenization was found. The experiments showed that the ointment reaches homogeneity when it is stirring at 30 vol./min. by the frame stirrer during (20±2.5) min. Further stirring is impractical. Based on the complex of held biopharmaceutical, rheological and thermo gravimetric researches the rational technology of the ointment's preparation in industrial conditions was developed. The critical parameters in the process of production (mixing duration - (20±2.5) min., temperature of preparation - (50.0±5.0)°C, mixer mode - 30 vol./min.) were set.

KEYWORDS: Dermatitis, ointment, research, industrial technology, critical parameters.

INTRODUCTION:

Quite an important role in the pathogenesis of the most common skin disease pathogens plays fungal infections. Today, in the dermatological practice are more common manifestations of fungal and bacterial infections in patients with dermatitis [1].

Severe flow of chronic inflammatory diseases of the skin and their long-term treatment with immunosuppressive drugs, usually are accompanied by joining a secondary infection, including fungal. Joining this infection alters the clinical presentation and course of dermatitis, which in turn hinders its timely diagnosis and treatment management appointment. Therapy of fungal complications of dermatological diseases should be done systematically and locally. Among the drugs for local application are preferred, especially combined medicines with mild anti-inflammatory, antiallergic and antifungal effects [2].

Available range of ointments in the pharmaceutical market of Ukraine provides the use for the treatment of dermatitis with secondary fungal infection anti-inflammatory and antifungal agents of synthetic origin. As for drugs of natural origin with complex specified pharmacological activity, today there is only one available drug - ointment "Fladeks" containing polyphenols [3].

Therefore, the issue of expanding the range of herbal medicines to treat these skin lesions is extremely important and relevant. We as active substances in the soft dosage form of anti-inflammatory, antiallergic and antifungal action proposed to use dry extract of licorice root, terbinafine hydrochloride and Lavender oil. The aim of this work is to develop industrial technology of the ointment codenamed "Alergolik".

MATERIALS AND METHODS:

The process of ointments samples preparation carried out in accordance with the generally accepted rules of preparation ointments considering the nature, physical and chemical properties of medicinal substances and excipients [4, 6]. Dry extract of licorice root was introduced into the ointment in an aqueous solution at a ratio (1:5). Terbinafine hydrochloride was dissolved in

propylene glycol when heated in a water bath at a temperature of (40.0±2.0)°C. Lavender essential oil was pre-dissolved in the calculated amount of soybean oil.

As dermatitis with secondary fungal infection occurring with fairly severe dry skin and need of constant moisture, as bases of the ointment emulsion systems were examined [7, 8].

Determination of ointment samples homogeneity prepared by the technology provided, performed by the method of SPhU 1.1, P. 511.

Determination of appearance, color and odor was performed by the GOST 29188.90.

Investigation of thermal stability of the drug was carried out by the following procedure: 8.0-10.0 g of the ointment was placed in a thermostat with a temperature of 40-42°C for 7 days, then - in the refrigerator at a temperature 10-12°C for 7 days, and then kept for 3 days at room temperature. The stability was determined visually by the absence of separation.

Study of colloidal stability was performed by the method given in GOST 29188.3-91.

The pH of ointment was found using the method of extraction, which is as follows: 1.0 g of the ointment was placed in a conical flask of 150 ml; 100 ml of purified water was added and stirred for 10 minutes with a glass rod. The resulting solution was filtered through a filter "blue ribbon". We determined the pH of the aqueous extraction by the procedure performed by SPhU, p. 2.2.3 "Potentiometric determination of pH". Rheological study of the drug and its base committed using viscometer BROOKFIELD DV-II + PRO (USA) with a system of coaxial cylinders [5].

The kinetics of water absorption was determined in experiments *in vitro* by dialysis through a semi permeable membrane at (37.0±0.1)°C by changing the weight of the camera with the sample.

Thermogravimetric analysis was performed on derivatograph Q-1000 system F. Paulik, J. Paulik, L. Efdey by the methodology of SPhU 1.1, p. 2.2.34. Recorded curves T (temperature), TG (change in weight), DTA (differential thermal curve of change effects), DTG (differential curve of weight). As the standard aluminum oxide powder was served as an inert substance. The weight of the sample was 200 mg.

RESULTS AND DISCUSSION:

It is known that one of the important indicators of the quality of soft drugs in developing their technology is the study of the rheological properties. The viscosity of ointment in the process of production depends on uniformity of distribution of medicinal substances at the base and dosing accuracy. In addition, the study of rheological parameters of ointments is important in determining the optimum parameters of the process of manufacturing the drug, such as temperature, mixing and homogenizing modes, which is particularly important for emulsion systems.

In order to justify the temperature regimes in production of ointment "Alergolik" its structural and mechanical studies at different temperatures were performed (Fig. 1).

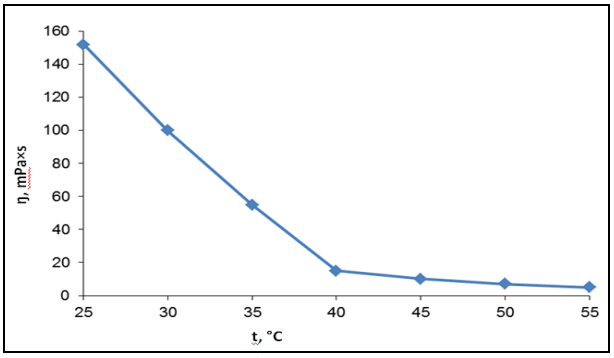

Fig. 1. The dependence of structural viscosity of the ointment "Alergolik" from the temperature

Fig. 1 shows that when the temperature of samples changes from 25°C to 50°C structural viscosity of the ointment at gradient shear rate 27.9 s^{-1} is reduced in more than 20 times. At the next increase of temperature to 55°C the system is close to Newtonian flow type, consistency of the ointment becomes liquid.

Analyzing the results, we can conclude that the structural viscosity of the ointment has significant dependence on temperature. Due to the fact that at a temperature ≥ 55°C ointment has low values of rheological parameters, in its preparation and dosage sedimentation of medicinal substances is possible, which can lead to inhomogeneity and stratification of medicinal substances.

When the temperature decreases to 45°C the structural and mechanical properties of the ointment increase sharply, there are thixotropic properties. Thus, during the manufacturing process homogenization of the ointment "Alergolik" should be performed at a temperature ranging (50.0±5.0)°C.

To determine the mode of mixing in the manufacture of the ointment we conducted a study of the influence of mixing time on the structural viscosity of the system (Fig. 2). Research were conducted at the set temperature

(50.0±5.0)°C, mode of mixers was 30 vol./min. Sampling was conducted every 5, 10, 15, 20, 25 and 30 minutes.

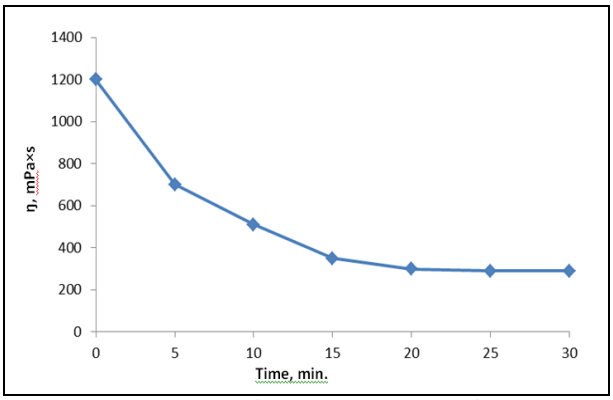

Fig. 2. The dependence of structural viscosity of the ointment "Alergolik" from the time of mixing

As it is shown in Fig. 2, ointment with stirring loses its structural strength. Thus, while stirring the drug for 20 minutes structural viscosity decreases by almost in 75 %. This further mixing does not significantly influence the structural viscosity of the ointment.

After storing samples of the ointment for 24 hours at a rest, it was found that they almost completely restored their original structural strength. The data suggest a properly chosen mode of mixing the drug.

As an important factor affecting the homogeneity of active ingredients distribution in the ointment's base is the time of mixing of the drug, we conducted a quantitative determination of glycyrrhizin acid (GA) of dry extract of licorice root, terbinafine hydrochloride and lavender oil in the samples of the ointment "Alergolik" that were taken from the upper and lower layers of the capacity. The research results are presented in Table 1.

Table 1. The effect of mixing time on the homogeneity of active ingredients distribution

Mixing time, min.	Quantitative content of GA equivalent to 1.0 mg of the ointment		Quantitative content of terbinafine hydrochloride equivalent to 1.0 mg of the ointment		Quantitative content of lavender oil equivalent to 1.0 mg of the ointment	
	upper layer	lower layer	upper layer	lower layer	upper layer	lower layer
5	10.11	15.23	4.58	6.62	3.25	6.15
10	11.65	14.98	4.96	6.12	3.98	5.98
15	12.98	13.21	5.01	5.11	4.67	5.45
20	13.12	13.12	5.07	5.07	5.01	5.01
25	13.15	13.17	5.02	5.05	4.86	5.15
30	12.96	12.87	4.98	4.97	4.51	4.96

Notes: n = 5; P = 95 %

According to information received, ointment reaches homogeneity when it stirring at 30 vol. / min. by frame stirrer during (20±2.5) min. Further stirring is impractical. After processing technology of the ointment "Alergolik" its study of the organoleptic, physical, chemical properties and stability were conducted. The resulting ointment has a light brown color, pleasant odor, pH 5.0-6.0, homogeneous and stable.

When analyzing thermograms of the active ingredients, ointment base and ointment "Alergolik" it was found that lavender oil is stable to a temperature of (50.0±1.0)°C, and at temperature ranging from 53°C to 84°C a loss of weight is 3 %, ending of the sample destruction is at 200°C.

Dry extract of licorice root is stable to a temperature of (40.0±1.0)°C; at temperature ranging from 40°C to 130 °C there is a gradual loss in its weight.

Terbinafine hydrochloride is thermally stable substance up to a temperature (202.0±1.0)°C. At temperature ranging from 202°C to 209°C there is the melting of the sample with its weight loss of about 1 % from the original sample.The base begins to melt at a temperature of (45.0±1.0)°C.

The process of decomposition of the ointment comes in three stages. At the first stage - up to 50°C there is no moisture loss in the weight. Second (50-85°C) and third (110°C) stage are characterized by rapid continuous process of destruction and accompanied by significant exothermic effects.

Based on thermogravimetric studies have found that thermal effects of samples are of such character that can subjectively indicate no chemical interaction between the components of the drug, prepared according to the proposed technology. So as a result of the research of rheological, physical, chemical and pharmaco-technological properties of the ointment in the process of manufacturing the influence on quality indicators of the drug following technical factors: temperature, stirring speed and time was studied.

Based on the research we set the basic technological parameters of manufacturing the ointment "Alergolik":

- homogenization of the drug at the temperature of (50.0±5.0)°C, with a stirring speed of frame mixer 30 vol. / min. during (20±2.5) min.
- dosing of the ointment - temperature is

(50.0±5.0)°C.

Technological scheme of ointment's production is shown in Fig. 3. Critical parameters of each stage of production process of the ointment are presented in the Table 2.

Table 2. Key critical parameters of p ointment "Alergolik" production

The name of the stage of manufacturing process	The name of the process parameter	The value of the process parameter
Preparation of the dry extract of licorice root solution	completeness of dissolution mode of mixer temperature	According to the product. recipes (visually) 30 vol./min. 15-25 ºC
Preparation of terbinafine hydrochloride solution in propylene glycol	completeness of dissolution mode of mixer temperature	According to the product. recipes (visually) 30 vol./min. 35-40 ºC
Preparation of the solution of lavender essential oil in soybean oil	completeness of dissolution mode of mixer temperature	According to the product. recipes (visually) 30 vol./min. 15-25 ºC
Preparation of ointment's base	mode of mixer time of mixing temperature homogeneity	30 vol./min. (20±2.5) min. (50.0±5.0) °C According to the product. recipes (visually)
Mixing of components, homogenization	temperature of preparation mode of mixer time of mixing homogeneity control of intermediate product	(50.0±5.0) ºC 30 vol./min. (20±2.5) min. According to the product. Recipes (visually) according to the product. recipes
Packing of the ointment	completeness temperature of packaging drug mass	According to the product. recipes (visually) (50.0±5.0) ºC 24.0-26.0 g

Table 3. Physical, chemical and technological parameters of the ointment "Alergolik"

Objects of research	Indicators				
	Viscosity, Pa × s	Mechanical stability	Coefficient of dynamic dilution	pH	Microbiological pirity
"Alergolik"	Laboratory samples				
	7.95±0.2	1.21±0.01	76.15±0.35	5.62±0.05	+
	Experimental (industrial) samples				
	7.86±0.4	1.19±0.02	76.25±0.15	5.71±0.05	+

Notes: *n = 5, P = 95 %*

Technological scheme of the ointment "Alergolik" production is consistent with the given descriptions of the process. Testing of laboratory technology of the developed ointment in industrial conditions confirmed the identity of laboratory and pilot samples and complete reproducibility of laboratory technology (Table 3).

CONCLUSIONS:

1. To study the uniformity of distribution of medicinal substances and excipients in the drug the optimal time of the ointment's homogenization was found. The experiments showed that the ointment reaches homogeneity when it is stirring at 30 vol./min. by the frame stirrer during (20±2.5) min. Further stirring is impractical.
2. Based on the complex of held biopharmaceutical, rheological and thermogravimetric researches the rational technology of the ointment's preparation in industrial conditions was developed. The critical parameters in the process of production (mixing duration - (20±2.5) min., temperature of preparation - (50.0±5.0) °C, mixer mode - 30 vol./min.) were set.

REFERENCES:

1. Bieber, T. Atopic dermatitis. Mechanisms of disease (review) / T. Bieber // The England journal of medicine. – 2008. – Vol. 14, No 3. – P. 1483–1495.
2. Buys, L. Treatment options for atopic dermatitis / L. Buys // American Family Physician. – 2007. – Vol. 4, № 4. – P. 523–528.
3. Rukhmakova, O. A. Characteristics of children's inflammatory skin diseases of immune nature and areas of their treatment / O. A. Rukhmakova, T. G. Yarnykh // Nauka i Studia. – 2013. – Vol. 109, № 41. – P. 5–10.
4. USP Pharmacists' Pharmacopeia. – II ed. – Rockville : The United State Pharmacopeial, 2008. – 1519 p.
5. Brummer, R. Rheology Essentials of Cosmetic and Food Emulsions / R. Brummer. – London: Applied Science Publishers, 2006. – 180 p.
6. Compounding Around the World / J. Vail, A. M. Naddeo, R. Kinget et al. // International Journal of Pharmaceutical Compounding. – 2008. – Vol. 51, № 2. – P. 102–115.
7. Development of pediatric medicines: points to consider in pharmaceutical development. – London, European Medicines Agency, 2010. – 32 p.
8. Guideline on Pharmaceutical Development of Medicines for Pediatric Use. – London, European Medicines Agency, 2011. – 38 p.