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Development of the optimal composition of the rectal ointment with Hedysarum alpinum dry extract

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Abstract

Diseases caused by Herpes Simplex viruses are worldwide spread. Long-term treatment of these diseases with known and widely used medicines leads to drug-resistant virus strains occurring. For this reason, research and development of novel anti-HSV medicines is a critical task now. There are two ways to invent and develop a new drug - design, and synthesis of new molecules for therapeutic purposes and production pharmacologically active plant-derived natural products. Hedysarum alpinum is one of those plants that contain a complex of bioactive substances which are pharmacologically active against HSV and have an immunostimulatory effect.

The purpose of the study is to develop a formulation and technology to obtain a semisolid dosage form which contains Hedysarum alpinum dry extract. The study includes results of choosing excipients and appearance, osmotic activity and aggregate stability tests. As a result of the study, a composition of the dosage form was selected.

Keywords: Herpes simplex virus, semisolid dosage form, ointment, Hedysarum alpinum.

INTRODUCTION

According to the WHO information, more than 3.7 billion people (67% of the population) of the world under the age of 50 are infected with various types of herpes viruses [5]. There are two types of herpes simplex virus (HSV) - type 1 herpes simplex virus (HSV-1) and type II herpes simplex virus (HSV-2). HSV-1 is transmitted mainly through oro-oral contact and causes orolabial herpes. HSV-2 is almost always sexually transmitted and causes genital herpes. However, according to the latest WHO data, HSV-1 also causes genital herpes [5]. As a result, it was revealed that more than half a billion people aged 15 to 49 years had a genital infection caused by either HSV-1 or HSV-2. There is no full recovery from these types of viruses and usually in the body HSV-1 is in a latent state. When it is activated, symptoms present with painful blisters or ulcers with different localization [6,7].

Among the various dosage forms for rectal treatment of HSV there is a promising ointment. It has several advantages over suppositories: the possibility of external use with little common effect on the body; the maximum concentration of the active substances at the site of the skin or mucous damage, where the risk of common side effects is minimal, and the ointment is convenient to use [2,4].

Recently, much attention has been paid to the creation of new drugs based on medicinal plant materials (MPM). Such drugs due to the complex of biologically active substances (BAS) have a wide therapeutic spectrum, as well as a milder effect. In our opinion, drugs based on medicinal plants of the genus Hedysarum L. (Fabaceae) [3,4] are very promising.

Despite the widespread use of these plants, analysis of existing dosage forms with Hedysarum L. shows their limitations, which is a prerequisite for the creation of modern standardized formulations with it.

MATERIALS AND METHODS

During the development of the ointment composition, we should take into account not only the properties of base components, which should provide comfort and the most complete and rapid biologically active substances release, but also the features of the introduction of Hedysarum alpinum dry extract.

Among water-soluble carriers of active substances in semi-solid dosage forms, polyethylene glycols (PEG) with various degrees of polymerization and molecular weight are common. When creating ointment compositions it is recommended to combine PEGs with different molecular weight. As a rule, PEGs are non-toxic, stable, easily release medicinal substances, have an antibacterial effect, as well as high osmotic activity, which can cause irritation during applying to the skin and mucous. [1]. This effect can be eliminated by introducing lipophilic components into such bases, transforming them into diphilic systems — olive oil and solid fat, type A.

There were used OC-20 emulsifiers stabilizing the oil/water emulsion and T-2 emulsifier stabilizing the water/oil emulsion as stabilizers [1].

All factors affecting the homogeneity of the extract distribution in the base, the parameters of the emulsification process (nature and amount of emulsifier, temperature, speed and method of homogenization, and structuring conditions) were taken into account.

The technology for obtaining ointments with dry Hedysarum alpinum extract consisted of following stages: preparation of the base (emulsion system), introduction of the dry extract solution into the base, homogenization, structuring with repeated homogenization, packing and packaging.

Osmotic properties of ointments were studied on a simplified dialysis model (according to Kruvchinsky) with a device consisting of a glass tube with a diameter of 30 mm, one end of which was tightened with a Kuprofan hemodialysis film 0.45 mm thickness with a 0.025 mm pore size [8]. An ointment portion weighed 2.0 g was applied to the inner surface of the film and weighed. Then they were placed in a vessel with purified water for 2-3 mm and thermostatically at 37 ° C. Every hour, the tube was removed and weighed. An increase in the mass of the tube indicated the amount of liquid absorbed by the ointment in comparison with the initial mass. In parallel, in the control experiment, 2 ml of purified water was placed in tubes on one of the films.

Dialysis was carried out until a constant, unchanging mass of the system under study was established for 10 h.

The magnitude of the osmotic activity was estimated gravimetrically when the dialysis unit was weighed every hour from the start of the experiment. The amount of absorbed water was calculated by the formula:

$$P = \frac{(M_n - M_0) - (M_n^k - M_0^k)}{M} \times 100\%, \text{ где}$$

P - the value of osmotic activity,%;

Mn is the mass of the dialysis unit with a sample of the dosage form at a given time, g;

M_0 is the mass of the dialysis unit with the sample of the dosage form before the start of the experiment, g;

M_n^k is the mass of the dialysis block in the control experiment at a given time, g;

M_0^k is the mass of the dialysis block in the control experiment before the start of the experiment, g;

M is the mass of the sample dosage forms,

RESULTS

The compositions of the experimental samples of the ointment are presented in table 1.

The obtained samples of ointments were a homogeneous mass of light yellowish color, phase separation was not observed.

In order to develop an optimal composition of rectal ointment with a Hedysarum alpinum dry extract, we studied the osmotic activity of the ointment compositions. The results are presented in Table 2.

From the results of the study, presented in Table 2, it can be seen that the osmotic activity of ointments depends on the composition of excipients. In the ointment compositions on polyethylene glycol (PEG) basis, the highest osmotic activity was established. With the introduction of type A solid fat to the base, the osmotic activity of ointments is significantly reduced, and even if the amount of solid fat varies from 15 to 20%, the osmotic activity decreases by 10%.

At the same time, studies have not established the effect of the type and amount of surface-active substances (surfactants) on the osmotic activity of the ointment with the dry Hedysarum alpinum extract.

Based on the foregoing, for further research we selected ointment formulations No. 2 and 3.

Compositions 2 and 3 differ in emulsifiers. Since the resulting diphilic emulsion type system is a transitional form between a direct emulsion (oil in water) and an inverse emulsion (water in oil), it is necessary to determine the type of emulsifier for its stabilization. It should be noted that the emulsifier T-2 (composition 3) is an emulsifier of type II with a hydrophilic-lipophilic balance value (HLB) of 5.5; and the emulsifier OC-20 (composition 2) is of type I with an HLB of 14-16.

Since the main criterion for the stability of a disperse system is its stability, both during production and during storage, the next step in our research was to study the effect of surfactant type on increasing the stability of the ointment composition.

The investigated samples of rectal ointments with Hedysarum alpinum dry extract were prepared according to the developed and previously described technological scheme.

The quality of the obtained samples was evaluated by the aggregative stability index by centrifuging at 3000 rpm for 5 minutes immediately after preparation, as well as after storage at various temperatures (20, 45, and 50 ° C) for 24 hours. Aggregative stability was evaluated by the ratio of the separation of the lipophilic and hydrophilic phases.

The results presented in Table 3 indicate that the ointment composition with the OS-20 emulsifier is stable both during preparation and during storage. Use as a surfactant emulsifier T-2, belonging to type II, gives the system stable during preparation, but stratified during storage at elevated temperature.

Consequently, the use of a type I emulsifier (OC-20) in amount 5% makes it possible to obtain a highly stable diphilic system for rectal ointment with Hedysarum alpinum dry extract.

Table 1. Compositions of experimental samples of the ointment with Hedysarum alpinum dry extract

Components, %	Sample's composition								
	1	2	3	4	5	6	7	8	9
Olive oil	30	30	30	30	30	30	30	30	30
PEG -1500	58	40	40	45	45	50	50	55	55
PEG – 400	6,6	4,6	4,6	4,6	4,6	5,6	5,6	6,6	6,6
Solid fat type A	-	20	20	15	15	10	10	5	5
Emulsifier T-2	5	-	5	5	-	4	-	3	-
OC-20	-	5	-	-	5	-	4	-	3
Dry extract	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1
Nipagin	0,3	0,3	0,3	0,3	0,3	0,3	0,3	0,3	0,3

Table 2. Osmotic activity of ointment compositions

Absorbtion time, hours	Quantity of absorbed water, % Compositions number, №№								
	1	2	3	4	5	6	7	8	9
1	18,9±2,6	5,5±2,5	5,4±2,4	11,5±2,6	12,5±2,3	17,9±2,5	12,4±2,5	16,2±2,1	23,6±2,3
2	26,8±2,7	6,6±1,9	8,7±2,9	13,7±2,8	23,8±2,8	23,0±3,2	25,7±2,7	27,4±2,5	28,4±2,2
3	28,5±3,7	7,8±2,9	8,9±2,1	18,9±3,2	25,6±2,8	27,7±2,5	37,8±2,9	32,7±2,8	31,9±2,9
4	31,8±3,1	11,5±2,9	10,3±2,6	25,3±2,6	36,5±3,2	38,7±3,3	38,8±2,9	45,6±2,3	45,3±3,2
5	47,4±2,9	15,7±2,8	16,6±2,7	36,5±3,6	37,2±2,5	39,3±2,9	49,3±2,3	57,7±3,3	58,3±2,7
6	65,2±4,6	19,8±2,6	21,8±2,7	37,5±2,1	38,1±3,2	41,9±2,8	49,9±3,1	59,9±2,1	62,1±1,1

Table 3. Agregative stability depending on the emulsifier

№ состава	Agregative stability			
	After producing	After 24 hour storage in temperature:		
		+ 20^0 C	+5 ^{0}C	+45^0 C
2	-	-	-	-
3	-	+	+	+

DISCUSSION

An emulsion-type diphyl system was obtained, which is a transitional form between oil-water and water-oil emulsions. As known, in terms of its microstructure, the diphilic system has a bilayer structure in which the hydrophilic and lipophilic phases are connected and alternate with each other, depending on the type of emulsifier entering the system. As a rule, they can be obtained on the basis of a combination of emulsifiers. PEGs as a part of the ointment combination have a solubilizing and emulsifying activity and also, contribute to the formation of stable pseudo-emulsions of both types.

The choice of this type of system was made due to the fact that polyethylene glycols have an irritating effect, accompanied by a burning sensation, which can be leveled by the introduction of lipophilic components.

The main requirement for this type of systems is stability during storage. For stabilization, surfactants of the first and second type are used. According to the stability studies results, high stability was shown by the composition, where OC-20 of the first type was used as a surfactant.

CONCLUSION

Based on a comprehensive study, the optimal composition and technology of producing rectal ointment with Hedysarum alpinum dry extract was established.

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