OPTIMIZATION OF COMPOSITION AND PRODUCTION TECHNOLOGY OF ALPIZARIN LINIMENT

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In the class of drugs possessing antiviral properties, a special place is occupied by medicinal plant preparations producing a softer action as compared to that of synthetic drugs. Alpizarin is an original domestic preparation developed at the State Research Institute of Medicinal and Aromatic Plants (Moscow), based on the biologically active substances extracted from the herbs of tick trefoil (*Hedisarum alpina* or *Hedisarum luteum*). This preparation is not found in foreign pharmacopoeias. The acting agent in alpizarin is mangiferin, a xanthine glycoside possessing antiviral, antiinflammatory, antimicrobial, and immunostimulant properties. The advantages of alpizarin over the other known antiviral drugs is high tolerance and the absence of allergic reactions, mutagen properties, and local irritant action.

The clinical investigation of alpizarin revealed no side effects, and no negative changes in the composition of blood, urine, or bile. The drug is equally well tolerated upon peroral, subcutaneous, and intraperitoneal administration. Pronounced antiherpes activity, low toxicity, and the absence of teratogenic and immunosuppressive action allows alpizarin to be widely and effectively used in practice.

Modern medicinal preparations usually represent complex multicomponent systems including a large set of auxiliary substances. Both Russian and international pharmacy is continuously searching for new substances capable of carrying drugs. In recent years, there is a tendency to replacing hydrophobic bases in soft medicinal forms (SMFs) by hydrophilic ones, which are usually characterized by lower toxicity and more complete release of the acting agents.

This study was aimed at optimizing the composition and developing the technology of alpizarin liniment with allowance for modern trends.

MATERIALS AND METHODS

A parent substance for the development of a desired liniment, intended for the treatment of viral infections, is alpizarin. As noted above, the active agent in alpizarin is the xanthine glycoside mangiferin. The parent substance of alpizarin is slightly and slowly (within 24 h) soluble in a water – acetone (1 : 1) mixture (the solution can exhibit slight opalescence) and is practically insoluble in 96% ethanol, water, and chloroform [1]. The structure forming component in the preparation is rarely crosslinked acrylic acid, either of the arespol type (TU-2219-005-29053342–97) or MARS-06 type (TU-06-02-221–96), capable of forming a hydrogel matrix.

The structure and mechanical properties of a hydrogel base and the SMF of alpizarin were characterized by rheological techniques using a rotation viscometer RV Type Rheotest-2 (Germany) with an amount of sample in the container of about 20.0 g. Each sample was measured in three runs at room temperature with a time interval of 30 min, and the rotation speed of the inner cylinder was gradually increased from 0.333 to 145.8 rpm (with 12 steps). Upon reaching the maximum possible tangent shear stress, the rotation velocity was sequentially decreased. The tangent shear stress developed in an SMF (liniment) sample studied was determined in the two stiffness intervals of a load gauge with different sensitivities characterized by the corresponding gauge constant. The experimental data were computer processed using a Rheotest program package [2].

The tangent shear stress T [N/m] was calculated by the formula

$$T = z\,a,$$

where a is the instrument scale reading and z is gauge constant [M/(m · division)].

The dynamic viscosity η [Pa · sec] was determined, proceeding from the tangent shear stress and the strain rate, by the formula

$$\eta = T/Dr\,,$$

where Dr is the strain rate gradient [$\sec^{-1}$].

During the rheological experiments, it is interesting to trace changes in the structure and mechanical properties of SMFs in the two intervals of the strain rate corresponding to

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Dr = 3.0 – 5.4 and 27.00 – 145.8 sec^{-1}. The first interval corresponds, on the average, to the real velocity of the human hand during liniment application and the second, to the average rate developed in the course of technological processes. The corresponding dynamic liquefaction coefficients K_d [%] were calculated by the formulas

$$K_{d1} = \frac{\eta_{3.0} - \eta_{5.4}}{\eta_{3.0}} \times 100\%,$$

$$K_{d2} = \frac{\eta_{27.0} - \eta_{145.8}}{\eta_{27.0}} \times 100\%,$$

where K_{d1} [%] is the dynamic liquefaction coefficient at Dr = 3.0 – 5.4 sec^{-1}, $\eta_{3.0}$ [Pa · sec] is the effective viscosity at Dr = 3.0 sec^{-1}, $\eta_{5.4}$ [Pa · sec] is the effective viscosity at Dr = 5.4 sec^{-1}, K_{d2} [%] is the dynamic liquefaction coefficient at Dr = 27.00 – 145.8 sec^{-1}, $\eta_{27.0}$ [Pa · sec] is the effective viscosity at Dr = 27.0 sec^{-1}, and $\eta_{145.8}$ [Pa · sec] is the effective viscosity at Dr = 145.8 sec^{-1}.

RESULTS AND DISCUSSION

Polymers of acrylic and methacrylic acids find increasing application as liniment bases in Russian pharmacy and abroad. Arespol also represents a polymers of this type. In optimizing the composition and developing the SMF technology for alpizarin liniment, the main point is to establish the therapeutic concentration of the parent substance in the preparation. In order to select an effective alpizarin concentration in the liniment, we have performed a series of tests on animals in the VILAR Laboratory of Pharmacology. The results of these experiments showed that a justified alpizarin content in the liniment intended for the treatment of herpes simplex virus and zoster is 2%.

From the biopharmaceutical standpoint, the optimum form of an active agent in the liniment base is solution. For this reason, the first stage of the investigation was devoted to determining the solubility of alpizarin in various solvents according to the method stipulated by the State Pharmacopoeia (RSP-XI). The results of this investigation showed that the optimum solvent system is a mixture of poly(ethylene glycol) PEG-400 and water in 3 : 2 ratio at a temperature of 50°C. The drug was dissolved in this solvent system by heating on a water bath.

Once the alpizarin solution is available, another important point is the hydrogel base preparation. In our liniment, the base forming component is arespol. The main factors influencing the structure and mechanical properties of gel systems are the solvent nature, polymer concentration, the type of a neutralizing agent, auxiliary components, temperature, and others. The swelling ability of the base polymer was studied in the aforementioned solvent system (PEG – water) best suited for the dissolution of alpizarin.

The results of these experiments showed that the PEG – water (3 : 2) mixture favors an increase in polymer swelling and, hence, this solvent system offers the optimum performance by simultaneously providing sufficiently good polymer swelling and drug solubility. The rheological properties of the liniment base depend on the polymer concentration. The gels obtained using arespol taken in a concentration from 2.0 to 3.0% were characterized by a high viscosity. Data on the concentration dependence of the effective viscosity of gel systems show that η increases with the polymer concentration [3, 4]. Based on the results of experiments, we have selected a polymer concentration of 1%, which provided gel systems with optimum rheological viscosity [5].

Our study of the influence of the type of a neutralizing agent on the gel viscosity showed that aqueous disperse systems of arespol in the pH interval from 3.0 to 5.0 are not structured. On approaching the neutral pH range, the effective viscosity tends to increase as a result of hydrodynamic volume of the swelling polymer particles. We have also established that stability of the gel system depends on the order of introduction of triethanolamine and sodium hydroxide solution, so that neutralizing agents should be introduced after the polymer swelling.

Investigations of the osmotic activity of the gel base showed that the main factors influencing this property of the liniment base are the nature and concentration of the active osmotic component. The base containing 1% of arespol and 60% of PEG ensures a dehydrating (drying) action in skin rush and herpes ulceration during the entire period of treatment.

In order to provide for a softer action, we have introduced an oil phase (castor oil) into the liniment composition. As is known, castor oil produces a positive wound-healing action and is well absorbed by the skin. In order to find the optimum composition, we have studied the effect of the oil added in a concentration of 5, 10, and 15% on the rheological properties and structural stability of the liniment. The effect was characterized by determining the rheological parameters. An analysis of the hysteresis loops on the rheogram of the arespol – castor oil system showed that the optimum castor oil content for the liniment under consideration is 10%. In this case, a relatively narrow hysteresis is evidence of a small mechanical stress relaxation time and weak interactions between the structure forming bonds. Adding Tween-80 to the emulsion base increased the system stability and improved the appearance. The experimentally selected arespol to Tween-80 ratio is 1 : 1.

Thus, based on the results of investigations, we suggest the following liniment composition: alpizarin, 1.0 g; PEG, 60.0 g; castor oil, 10.0 g; Tween-80, 1.0 g; nipagin, 0.1 g, and water to 100.0 g. The technology of liniment preparation includes three stages: stage 1, arespol hydrogel preparation; stage 2, introduction of the alpizarin – nipagin solution with stirring into the hydrogel; stage 3, introduction of Tween-80 and castor oil and homogenization of the total mixture.

The rate of alpizarin release from the proposed liniment and commercial Vaseline based ointments was studied by the method of equilibrium dialysis via a semipermeable membrane. It was established that the amount of alpizarin released from the liniment it about two times that released from the Vaseline base.

We have also characterized the new liniment with respect to toxicity. The tests on rabbits showed that the liniment applied onto a depilated skin area did not change the general state and behavior of animals.

REFERENCES

1. V. I. Glyzin, G. G. Nikolaeva, and T. D. Dargaeva, *Natural Xanthones* [in Russian], Nauka, Novosibirsk (1986).
2. K. V. Alekseev, V. N. Li, M. T. Alyushin, et al., *Farmatsiya*, No. 4, 22 – 25 (1986).
3. V. A. Kemenova, R. I. Mustafin, K. V. Alekseev, et al., *Farmatsiya*, No. 1, 67 – 72 (1991).
4. K. V. Alekseev, V. N. Li, V. N. Demishev, et al., *Farmatsiya*, No. 5, 15 – 18 (1987).
5. S. J Warren and I. W. Kellaway, *Pharm-Dey-Technol.*, **3**(2), 199 – 208 (1999).