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RESEARCH ARTICLE

The Study of Structural- Mechanical and Physicochemical Properties of the Drug Antimicrobial and Anesthetic Action

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Abstract

Introduction: This work is devoted to study of structural-mechanical and physicochemical properties of soft drugs with antimicrobial and anesthetic action. The purpose of this study was to study the effectiveness of physicochemical properties of soft drugs. Materials and methods: In the process of performing the work, pharmaco-technological, physicochemical, structural-mechanical, biopharmaceutical and biological research methods according to the State Pharmacopoeia of Ukraine were used. Results and discussion: The sample was considered stable if no stratification was observed in the tubes after centrifugation. If at least one of the tubes was observed stratification of the sample or the selection of sediment, the analysis was repeated with new portions. The type of emulsions was determined by dilution and staining methods. The study of local anesthetic activity was performed on a model of rabbit eye anesthesia. The experiment was performed on 25 male rabbits, which were divided into 5 groups of 5 rabbits each. Conclusions: The study of structural-mechanical and physico-chemical properties of drugs in the form of a cream is the basis for improving its therapeutic efficacy, mechanical stability and consumer properties.

Keywords: *Soft drugs, Antimicrobial action, Anesthetic action, Colloidal stability, Thermal stability, Emulsions, Rheogram.*

Introduction

In this work, the appearance and characteristic organoleptic properties of the samples (color, odor, consistency, etc.), as well as signs of physical instability (particle aggregation, coalescence, coagulation, delamination) were controlled. Determination of homogeneity was carried out according to the method of the State Pharmacopoeia of Ukraine (I edition, p. 511). Colloidal stability (for emulsion systems) is carried out according to GOST 29189-91 “Cosmetic creams.

General technical conditions". A laboratory centrifuge with a set of test tubes, a mercury thermometer with a range of measured temperatures from 0 to 100 °C and a division price of 1 °C, as well as a stopwatch and a water heater were used for the test. The tubes were filled to 2/3 volume (approximately 9 g) with the test samples and weighed to the nearest 0.01 g. The tubes were then placed in a water bath at a temperature of (42.5 ± 2.5) °C for 20 min, after which was wiped dry on the outside and placed in the sockets of the centrifuge. Centrifuged for 5 min at a speed of 6000 rpm (relative centrifugation power was about 5000 g). The sample was considered stable if after centrifugation in vitro no stratification was observed. If at least one of the tubes was observed stratification of the sample or the selection of sediment, the analysis was repeated with new portions. If at least one test tube with delamination was detected on retesting, the sample was considered unstable.

Thermal stability is carried out according to GOST 29189-91 “Cosmetic creams. General technical conditions". To determine took 5-6 glass tubes with a diameter of 15 mm and a height of 150 mm. The tubes were filled with 8-10 ml of test samples and placed in a thermostat brand TC-80M-2 with a temperature of (42.5 ± 2.5) °C for 7 days. After that, the samples were transferred for 7 days in a refrigerator with a temperature of (6 ± 2) °C and then for 3 days kept them at room temperature.

Stability was determined visually: if no stratification was observed in any test tube, the sample was considered stable.

Materials and Methods

Pharmaco-technological, physicochemical, structural-mechanical, biopharmaceutical and biological research methods according to the State Pharmacopoeia of Ukraine (SPU) were used. The pH level of the tested samples was determined potentiometrically using an ionomer EV - 74 universal at a temperature range of 18 - 25 °C. A sample of cream (gel) in the amount of 2.5 was added to a beaker with a capacity of 100 ml and added 50 ml of purified water (pH 6.2 - 7.0) with stirring with a glass rod for 10 minutes. Then the pH of the aqueous extract of the sample was measured potentiometrically.

Determination of the homogeneity of the content was performed according to the requirements of the article of the SPU (paragraph 2.9.6) "Homogeneity of the content of the active substance per unit dosage of the medicinal product", using test A [1]. The mass of the contents of the container was determined as follows: ten containers together with the contents were weighed, each separately, to the nearest 0.01 g, freed from the contents, washed with hot water, carefully removed residual water with filter paper and weighed again. The mass of the contents of each container should be according to the regulatory and technical documentation from 19.2 to 20.8 g. The tightness of the container was carried out according to the method: 10 tubes with the drug were selected and their outer surfaces were thoroughly wiped with filter paper. The tubes were placed in a horizontal position on a sheet of filter paper and kept in a thermostat at a temperature of (60 ± 3) °C for 8 hours.

There should be no leakage of the drug from any of the tubes on the filter paper. If leakage is observed from only one tube, the test is performed with an additional 20 tubes, if more than one tube, the test results are considered unsatisfactory. The test results are considered satisfactory if no leakage is observed from the first 10 tubes, or leakage was observed for only one of the 30 tubes.

The osmotic activity of the samples was studied using a semipermeable membrane (cellophane film grade B 8079, GOST 7730-79) at a temperature of 34 ± 1 ˚C. Measurements of the mass of the inner cylinders were performed after 0.5; 1; 2; 4.8; 12; 24 h on analytical scales (ADV - 200 M) with an accuracy of 0.001 g, pre-wiping them from the outside. The tests were performed at a temperature of 34.0 ± 1.0 ˚C using a thermostat TC-80M-2. Periodically, the volume of purified water in the dialysis chamber was brought to the initial level. The mass difference between the two weighings was used to determine the amount of liquid absorbed.

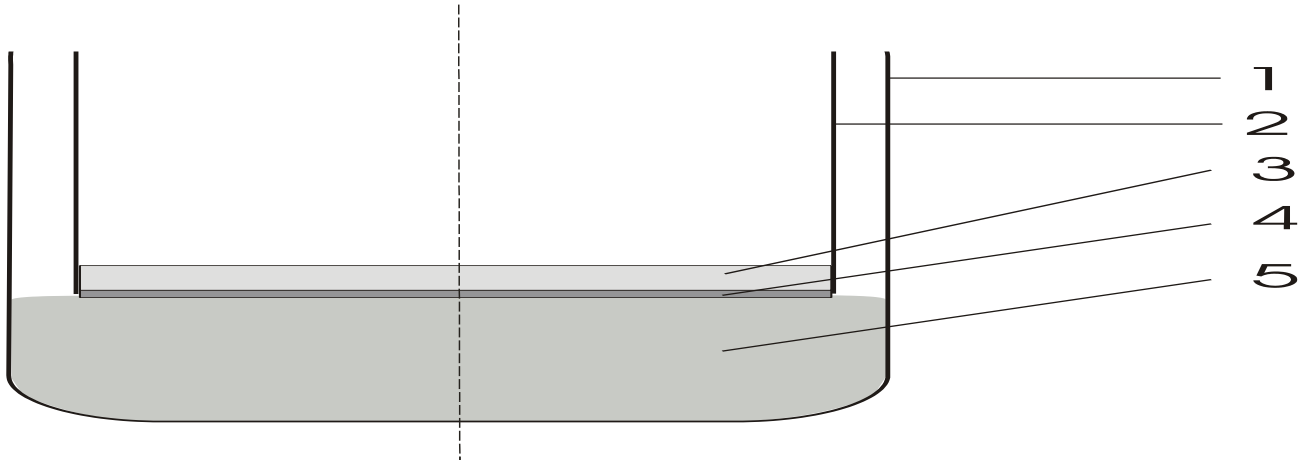

Fig. 1. Dialysis scheme: 1 - dialysis chamber; 2 - internal cylinder; 3 - sample sample; 4 - semipermeable membrane; 5 - purified water

Results and Discussion

The type of emulsions was determined by dilution and staining methods.The method of dilution is that, when making a few drops of the test sample in water, emulsions of different types behave differently.

Direct emulsion systems (o/w type) quickly form a turbid layer around the introduced droplets, and large particles are crushed into smaller ones. If the emulsion sticks to the spatula and is almost not distributed in water, forming non-wettable globules, it

belongs to the second type of emulsion (w/o). However, it should be recognized that this method is unreliable: type II emulsions can be partially distributed in water, especially if the content of the aqueous phase is high, and the emulsion contains surfactants. Therefore, when approaching the critical point of phase inversion, or in the case of complex emulsions, this method does not guarantee accurate results [2, 3].

Another method - staining with lipophilic and hydrophilic dyes - is widely used in practice and gives more accurate results. The studies used a variety of this method, which consists in staining the test sample, followed by microscopic examination. For this purpose, a drop of the test sample and a drop of dye solution (methyl orange) were thoroughly mixed and placed on a glass slide, which was carefully covered with a cover glass.

Given the hydrophilic nature of the dye, the color of the aqueous or oily phases of the sample was used to draw conclusions about the type of emulsion. Another variant of this method was also used in the work, which is based on the properties of cobalt salts (cobalt chloride) to turn red in the presence of water.

A drop of test emulsion was applied to the filter paper treated with 20 % cobalt chloride solution and dried. If the dispersion medium of the system is aqueous, then at the point of contact of the sample with the paper, the blue color turns to pink. The emulsion type w/o (dispersion medium which is hydrophobic) does not cause discoloration and leaves greasy spots. However, with a complex composition of emulsions, the results of this method may also be inaccurate.

The study of structural and mechanical (rheological) properties of the cream and gel was performed using the device "Rheotest-2" (Germany) at different temperatures. The temperature was measured with a laboratory thermometer with a partition price of 0.1 ˚C. Thermostating was performed using an ultrathermostat, which is included in the device.

The tangential shear stress was calculated using the formula:

$$\tau_r = Z \cdot L,$$

Where: τ_r-tangential shear stress, Pa;

Z-device constant (depending on the type of cylinder);

L-the indicator of the device.

After calculating the shear stress at certain shear rates, the structural viscosity of the test samples was calculated using the formula:

$$\eta = \tau / D_r,$$

Where: D_r – shear rate, sec^{-1};

η – structural viscosity, Pa*sec;

τ_r – tangential shear stress, Pa.

Next, thermogravimetric analysis was performed on a Q-1000 derivatograph of the system F.Paulik, I.Paulik, L.Efdei with a platinum-platinum-rhodium thermocouple when heating the samples in ceramic crucibles from 20 to 300 °C in air. The heating rate was 5 °C per minute. The standard was hardened alumina. The weight of the samples was 50 mg. Recorded curves: T (temperature changes); TG (weight changes); DTA (differentiated curve of change of thermal effects); DTG (differentiated curve of weight change) [4, 5]. The study of local anesthetic activity was performed on a model of rabbit eye anesthesia.

The experiment was performed on 25 male rabbits, which were divided into 5 groups of 5 rabbits each. Animals of the 1st group were given 0.1 g of gel with a content of 1 % anesthesia for the lower eyelid; animals of the 2nd group were given the same amount of gel containing 3% anesthesia; 3rd group - 5 % anesthesia; 4th group - 7 % anesthesia; 5th group - 10 % anesthesia.

Thirty seconds after the start of the experiment, the conjunctiva was irritated by running the horse's hair over the surface of the eye from the outer corner in the direction of the pupil, causing the eye to squint. Irritation was repeated every 10 seconds. The rate of local anesthesia was determined by the time from the laying of the test sample to the disappearance of the reaction to eye irritation.

The duration of action of the anesthetic was determined by the time of recovery of the eye's response to irritation. Limited rheograms of the cream flow are shown in

Fig. 2, which shows that the lubricity of the developed drug in the form of a cream is satisfactory: the yield curves do not exceed the rheological optimum. The extrusion capacity can be judged by the amount of shear stress. The study was performed in the range of tangential stresses at shear rates from 3.0 to 1312.0 s-1.

The rheogram of the cream flow studied by us does not go beyond the area limited by the region of the optimum of the rheology of extrusion, this indicates a good consistency of the developed sample. The obtained curves are nonlinear, which indicates a non-newtonian type of flow of the developed drug.

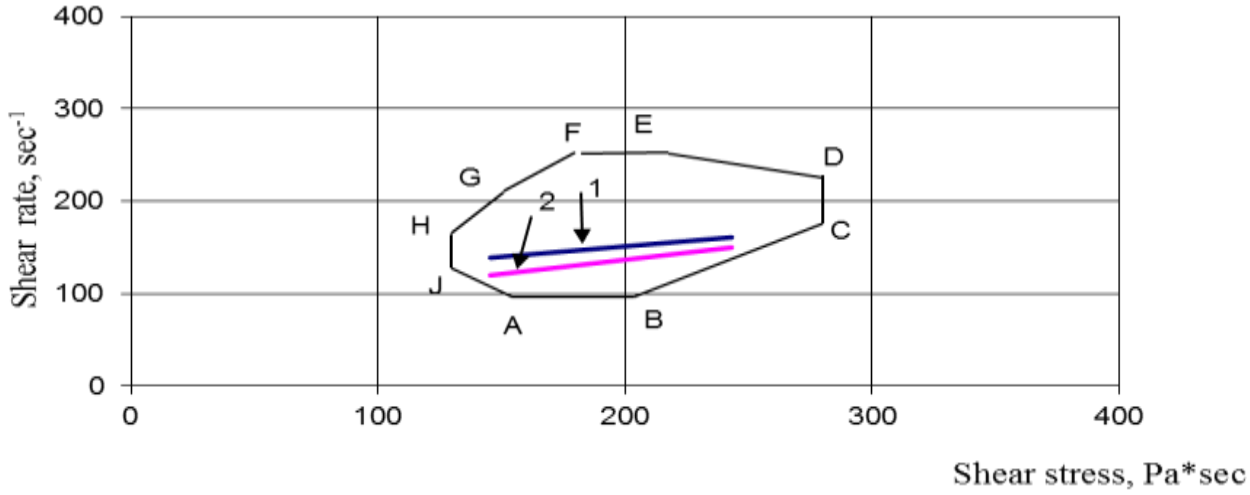

Fig. 2: Limited rheogram of the cream flow at a temperature of 34 ^{0}C: 1- after 2-3 s; 2 - in 15 s for cream

The constructed curves of the cream flow indicate that its flow does not begin immediately, but only after some applied voltage required to break the elements of the structure. During the period of decreasing voltage, the viscosity of the sample is gradually restored. This confirms the plastic-viscous and thixotropic properties of the treated drug.

It is characteristic that during the period of reduction of the shear stress the restoration of the structure is delayed. On the rheograms, the descending and ascending curves form "hysteresis loops", which confirms the thixotropy of the studied creams. After calculating the value of the effective viscosity, we obtained a graph of the viscosity versus shear rate (Fig. 3).

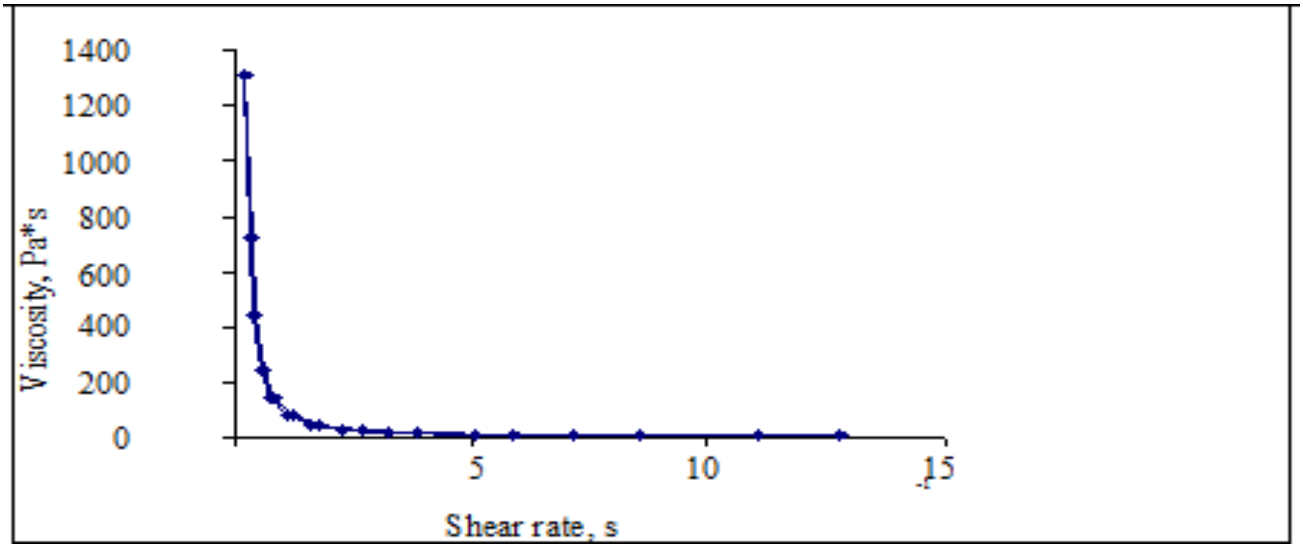

Fig. 3: Dependence of the viscosity of the developed cream on the shear rate

Conclusion

As the degree of destruction of the structure of both the base and the cream increases, the viscosity decreases sharply and, reaching its lowest value, practically does not change. In the region of high shear rates, the change in

viscosity is described by a rectilinear relationship. Thus, based on the obtained results, it can be concluded that the studied sample of cream has thixotropy, can be diluted during application, well lubricated and capable of extrusion from tubes. In addition, the consistency of the test cream sample is satisfactory.

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