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THE SUBSTANTIATION OF THE TECHNOLOGY FOR PREPARING THE CREAM WITH SILVER CITRATE

Aim. To substantiate the **technology** for preparing a veterinary cream with silver citrate and study the **effect** of the conditions of preparation on the quality of the finished product.

Materials and methods. The studies were carried out with the cream samples obtained by different methods. Emulsification was carried out using a Polytron® System PT 2500 homogenizer manufactured by Kinematica AG, Switzerland. The samples were subjected to microscopic and rheological studies.

Results. Using a Rheolab QC rheometer (Anton Paar, Austria) and the system of coaxial cylinders C-CC27/SS it was determined that by all rheological indicators the cream samples were not significantly different and had the similar profile of their rheological behavior. The samples had a low flow boundary calculated by the Casson mathematical model. It indicates easy extrusion from the tube and application on the animal's skin surface. The samples prepared using the complete mixing technology appeared to be the most resistant to mechanical impact based on the viscosity values at infinite shear rate according to the Casson model. The samples prepared by the phase inversion technology had a lower value of the hysteresis loop area.

Conclusions. The effect of the technology for preparing the cream and the rate of emulsification on disperse and structural-mechanical parameters has been studied. It has been found that at the rate of emulsification of 5.000 rpm there are no significant changes using both the complete mixing technology and the phase inversion technology. The effect of the temperature on the disperse system stability has been studied, and the temperature range for transporting and filling the cream into tubes has been determined.

Key words: cream emulsion; veterinary drug; silver citrate; rheology; dispersion analysis; technology.

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ОБҐРУНТУВАННЯ ТЕХНОЛОЇ ВИГОТОВЛЕННЯ КРЕМУ ЗІ СРІБЛА ЦИТРАТОМ

Мета: обґрунтування технології виготовлення ветеринарного крему зі срібла цитратом та дослідження впливу умов виготовлення на якість готового продукту.

Матеріали та методи. Дослідження проводили зі зразками крему, одержаними різними методами. Емульгування здійснювали за допомогою гомогенізатора Polytron®SystemPT 2500, Kinematica AG (Швейцарія). Виготовлені зразки піддавали мікроскопічним та реологічним дослідженням.

Результати дослідження. За допомогою реометра Rheolab QC, AntonPaar (Австрія) з використанням системи коаксіальних циліндрів C-CC27/SS встановлено, що за сукупністю реологічних показників зразки крему суттєво не відрізняються і мають схожий профіль реологічної поведінки. Зразки мають низьку межу плину, розраховану за математичною моделлю Кассона, що свідчить про легке видавлювання з труби та нанесення на поверхню шкіри тварини. Найбільш стійкими до механічного впливу, виходячи зі значень в'язкості при нескінченній швидкості зсуву за Кассоном, були зразки, виготовлені за технологією повного змішування. Зразки, виготовлені за технологією інверсії фаз, мають меншу величину площі петлі гістерезису.

Висновки. Здійснено дослідження впливу технології виготовлення крему та швидкості емульгування на дисперсні та структурно-механічні показники, за якими встановлено, що при швидкості емульгування 5000 об/хв за технологіями повного змішування та інверсії фаз не спостерігається суттєвих змін. Досліджено вплив температури на стабільність дисперсної системи й встановлено температурний інтервал, при якому рекомендовано здійснювати транспортування та фасування крему в труби.

Ключові слова: крем емульсійний; ветеринарний препарат; срібла цитрат; реологія; дисперсний аналіз; технологія.

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ОБОСНОВАНИЕ ТЕХНОЛОГИИ ПРИГОТОВЛЕНИЯ КРЕМА С ЦИТРАТОМ СЕРЕБРА

Цель: обоснование технологии ветеринарного крема с цитратом серебра и исследование влияния условий изготовления на качество готового продукта.

Материалы и методы. Исследования проводились с образцами крема, полученными разными методами. Эмульгирование осуществляли с помощью гомогенизатора Polytron®System PT 2500, Kinematica AG (Швейцария). Приготовленные образцы подвергали микроскопическим и реологическим исследованиям.

Результаты исследования. С помощью реометра Rheolab QC, AntonPaar (Австрия) с использованием системы коаксиальных цилиндров C-CC27/SS установлено, что по совокупности реологических показателей образцы крема имеют схожий профиль реологического поведения. Образцы имеют низкую границу течения, рассчитанную по математической модели Кассона, что свидетельствует о легком выдавливании из тубы. Наиболее устойчивыми к механическому воздействию, исходя из значений вязкости при бесконечной скорости сдвига по Кассону, были образцы, приготовленные по технологии полного смешивания. У образцов, приготовленных по технологии инверсии фаз, обнаружена меньшая величина площади петли гистерезиса.

Выводы. Проведено исследование влияния технологии изготовления крема и скорости эмульгирования на дисперсные и структурно-механические показатели, которым установлено, что при скорости эмульгирования 5000 об/мин по технологиям полного смешивания и инверсии фаз не наблюдается существенных изменений. Исследовано влияние температуры на стабильность дисперсной системы и установлен температурный интервал, при котором рекомендуется осуществлять транспортировку и фасовку крема в тубы.

Ключевые слова: крем эмульсионный; ветеринарный препарат; серебра цитрат; реология; дисперсный анализ; технология.

Statement of the problem. Among the problems of veterinary medicine mastitis of cattle is of the most epizootiological and economic significance. The prevalence of mastitis in livestock is rather wide, especially where there is a high level of mechanization and automation of production, and intensive exploitation of animals. The main causes of mastitis are disadvantages of the organizational and economic, technological, technical, selective and genetic and veterinary and sanitary nature [1]. In case of noncompliance with the rules of the technological discipline the opportunistic microflora, which is present in livestock premises, accumulates in a large number, changes its species composition, increases virulence and becomes pathogenic, can cause diseases of animals. Infectious mastitis is transmitted when milking cows using objects polluted by contaminated microorganisms with milk. Contagious pathogenic microorganisms are obligate parasites that are unstable in the environment; the udder of cattle is a reservoir for them. Animals may become diseased at any time of the year, at different periods of lactation and in the dry period [2]. Complexity in the treatment of cows suffering from mastitis is determined by many factors, the main of which is the high level of resistance of pathogens to antibacterial drugs widely used. The unreasonable, haphazard use of antimicrobial drugs in veterinary medicine leads to a rapid selection and distribution of antibiotic resistance [3]. Despite the achievements of modern science and practice in the diagnosis, treatment, prevention of subclinical mastitis the number of cows with this pathology in recent years has significantly increased. Thus, the solution of the problem of prophylaxis and treatment of cattle mastitis lays by

developing of an anti-mastitis agent with the antimicrobial action is relevant.

Analysis of recent research and publications. In Ukraine, such researchers as V. P. Koshevoi, V. B. Borisevich dealt with the issues of pathology of veterinary obstetrics and gynecology. Nowadays scientists V. A. Yablonskii, S. P. Khomin, and V. Y. Lyubetskii conduct research on the improvement of productive longevity of animals [4]. Among the scientists involved in veterinary pharmacy problems T. A. Groshvoi, T. H. Kalyniuka, T. H. Yarnykh, O. I. Tikhonov should be mentioned, they continue pharmaceutical development of veterinary drugs for the prophylaxis and treatment of animals [5]. Works of the technological direction by such scientists as I. M. Pertsev, V. I. Chueshov, L. L. Davtyan, O. A. Ruban, and V. V. Hladysheva elucidate the effect of the technology of semi-solid dosage forms on their structural-mechanical parameters and the disperse system stability [6, 7].

Identification of aspects of the problem unsolved previously. The quality of any veterinary medicinal product depends not only on the reasonable composition of active substances and excipients, but also on the proper conditions for their industrial production. In the manufacture of semi-solid dosage forms the order of mixing the components, temperature, speed and time conditions substantiated at the stage of pharmaceutical development of a medicinal product must be strictly observed. In our previous studies the composition of an antimicrobial cream with silver citrate to care for the udder of cattle was developed [8]. It is advisable to continue the scientific experiment with the aim of substantiating the technology of manufacturing a veterinary cream containing silver citrate and studying the effect of the

conditions of preparation on the quality of the finished product.

Objective statement of the article. These studies were performed to identify possible risks in the production of veterinary preparations in the form of a cream, as well as to analyze the criticality of the impact of risks on their quality and management. The substantiation of these manufacturing parameters is the necessary information for scaling the production of a veterinary drug in the process of transfer in the conditions of industrial production and standardization of the technology [9].

Presentation of the main material of the research. The object of research was the samples of the cream containing silver citrate, dexpanthenol and compositions containing such excipients as petroleum jelly, isopropyl myristate, isopropyl palmitate, octyl dodecanol, dimethicone, cetyl stearyl alcohol, emulsifier No. 1, and purified water. The components were selected in the quantities, in which the heterogeneous disperse system was the oil-to-water (o/w) emulsion.

Today there are a number of manufacturing technologies for emulsion systems, such as addition of the internal phase to the external one, addition of the external phase to the internal one, mixing of both heated phases, alternate addition of both phases to the emulsifier, emulsification by precipitation, etc. The choice of the manufacturing technology depends on the physicochemical properties of the drug components [10]. In the work the method of mixing of both heated phases was used. It consists in that the internal phase (oil) is prepared by addition of components of the oil phase and emulsifiers, followed by melting to obtain a homogeneous solution. The external phase (water) is heated separately to the same temperature as the internal phase. The temperature to which the phase is heated is determined by the melting points of the emulsifiers, it is 48-52 °C for cetyl stearyl alcohol and 50-60 °C – for emulsifier No. 1. Further, the phases are mixed and homogenized at high mixing rates (emulsification). A variation of this technology is a method of the phase inversion, in which addition of one phase to another is not complete, but partial. Under these conditions at first the emulsion is opposite from the desired one, and then gradually the desired disperse

system is obtained. In our case, there was a partial addition of the external phase (the dispersion medium – purified water), and emulsions of w/o and o/w were alternately obtained.

In the manufacture of emulsion systems the critical parameter is the rate and the time of emulsification, in which the required dispersion of the heterogeneous system is achieved. The system dispersion affects the physical stability and consistency. For the purpose of studying the effect of the emulsification rate and time on the quality of the samples of the veterinary cream obtained the speed was varied between 5.000 rpm, 7.000 rpm, and 10.000 rpm within 15 min when preparing samples according to the given technologies. Emulsification of the samples was performed using a Rolutron® SuteMem RT 2500 homologizer (Kimematis AG, Switzerland). The samples were subjected to microscopic and rheological studies.

The method of microscopic studies. To study the microscopy of the samples a Lumam P1 microscope equipped with a digital DMC 300 digital camera, and the ScopePhoto software were used. On the slide glass a small drop of emulsion (cream) was placed, it was taken with a glass rod from the middle part of the samples prepared. A drop of the sample was covered with a cover glass. Then the cover glass was gently squeezed with a stick to obtain a homogeneous thin layer, which was transparent when viewed with the naked eye. The slide glass with the sample prepared was placed on the microscope stage. To view the samples a lens with a 20x magnification and 1.6 times intermediate magnification was used. The samples were viewed in light of a halogen lamp. Photomicrographs were obtained using the ScopePhoto software. Automatic settings of white balance and brightness were used. On photomicrographs a comparison scale (50 µm) was applied using a calibrated system. To study the effect of the manufacturing technology and the rate of emulsification on dispersion of the emulsions obtained the microscopic studies were performed.

The results of these studies are given in Fig. 1 and 2. The degree of dispersion of emulsion creams is an important indicator that determines their stability and consistency. The dispersion of components of emulsion creams according to literary sources may vary from 0.1 to 10 µm [11, 12].

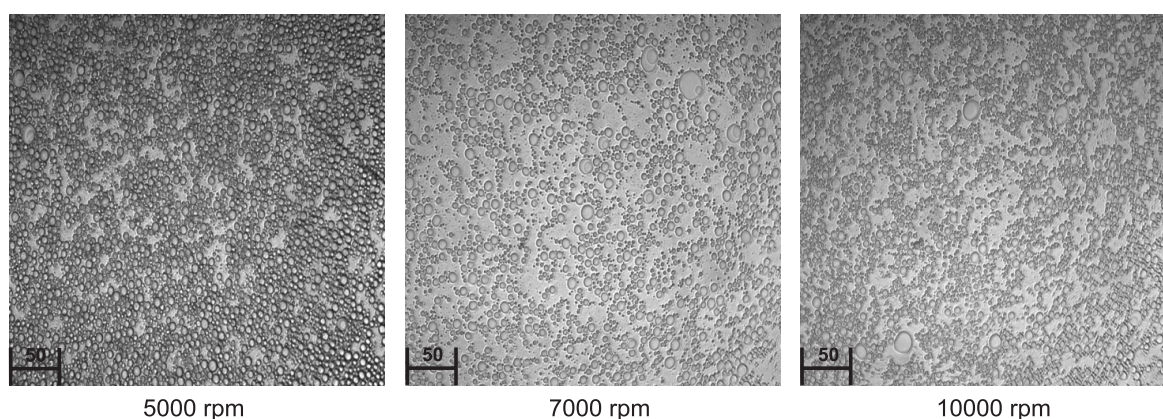


Fig. 1. Photomicrographs of the cream samples obtained by the complete mixing technology

Analyzing the above micrographs it is evident that the tendency of decreasing the particle size of the internal phase with the increase in the rate of emulsification is traced. In the samples prepared at the emulsification rate of 5.000 rpm the droplets of the internal phase have a size of 5-10 microns with the same compaction throughout the emulsion volume. In the samples of emulsions obtained at the emulsification rate of 7000 rpm and 10000 rpm by the size of oil particles the emulsions are divided into two fractions: 2-5 μm and 5-10 μm with single droplets at 15 μm . The sample prepared by the phase inversion at 10.000 rpm has homogeneity of oil droplets with the sizes of 2-5 microns and the same compaction. It should be noted that when increasing the rate of emulsification the formation of foam with a greater intensity occurs. The cause for this can be emulsifier No.1, which belongs to anionic surfactants known for their high ability to foaming and used as foaming agents.

Determination of rheological or structural-mechanical properties of the samples. The studies

were performed using a Rheolab QC rheometer (Anton Paar, Austria) using the C-CC27/SS Coaxial Cylinder system. The device meets the ISO 3219 requirements. Measurements of the rheological curve were carried out in three stages: 1) the linear increase of the shear rate from 0.1 s^{-1} to 350 s^{-1} with 115 measuring points and the measuring point duration of 1 s; 2) a constant displacement at the shear rate of 150 s^{-1} , one point of measurement with duration of 1 s; 3) the linear decrease in the shear rate from 350 s^{-1} to 0.1 s^{-1} with 115 measuring points and the measuring point duration of 1 s. The temperature of the study of rheological properties was 25°C .

The results of the rheological studies are shown in Fig. 3, 4 and in Tab. 1. By all rheological indicators the samples are not significantly different and have the similar profile of their rheological behavior. The samples have a low flow boundary (τ_0 , Pa) calculated by the Casson mathematical model. It indicates easy extrusion from the tube and application on the animal's skin surface. The samples prepared

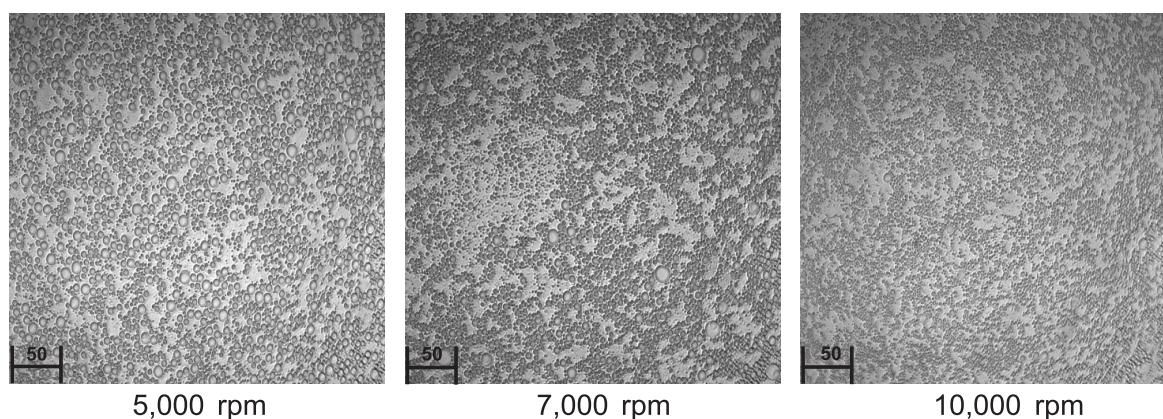


Fig. 2. Photomicrographs of the cream samples obtained by the phase inversion technology

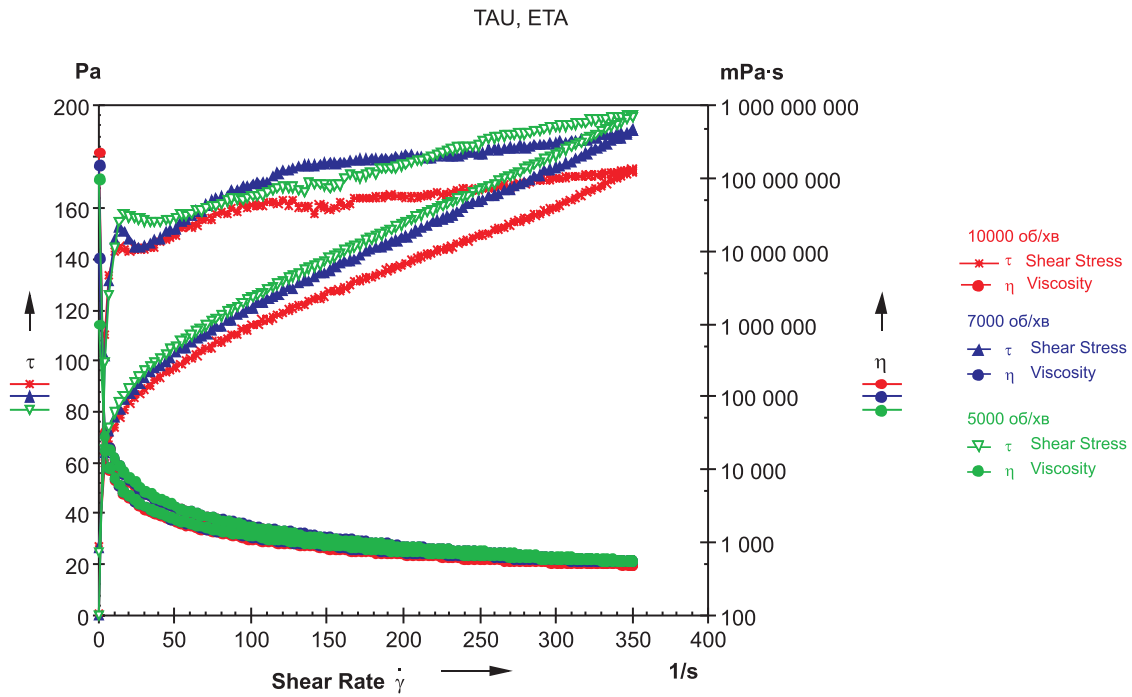


Fig. 3. The flow rheograms and viscosity curves of the samples prepared by the complete mixing technology

using the complete mixing technology are the most resistant to mechanical impact based on the viscosity values at infinite shear rate according to the Casson model. The samples prepared by the phase inversion technology have a lower value of the hysteresis loop area.

Thus, taking into account all results of the dispersion analysis and rheological studies, which have not determined critical deviations when using different manufacturing technologies for emulsions and the emulsification rates as the final product, it is possible to use both

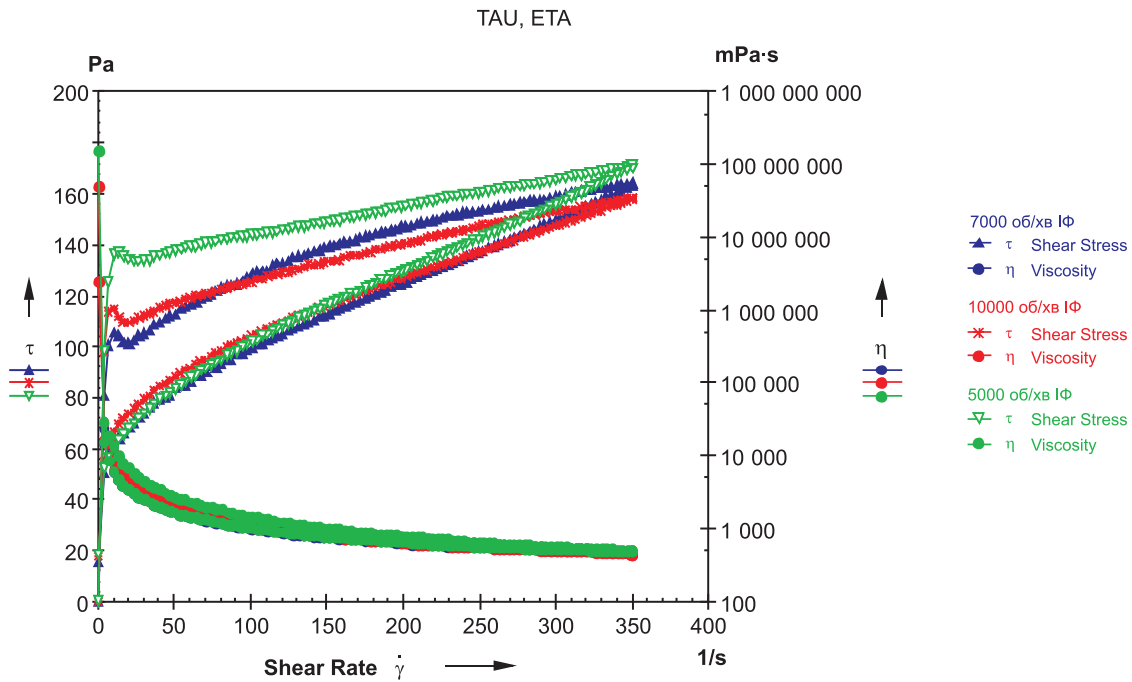


Fig. 4. The flow rheograms and viscosity curves of the samples prepared by the phase inversion technology

Table 1

THE STRUCTURAL-MECHANICAL PARAMETERS OF THE CREAM SAMPLES PREPARED BY DIFFERENT TECHNOLOGIES WITH THE TOTAL CONCENTRATION OF EMULSIFIERS OF 10 %

The emulsification rate	The flow boundary by Casson, τ_0 , Pa	Viscosity at the infinite shear rate by Casson, η_{∞} , Pa·s	The hysteresis loop area, A, Pa/s
<i>The samples prepared by the complete mixing technology</i>			
5.000 rpm	71.726	0.098	10176.4
7.000 rpm	72.606	0.090	11482.2
10.000 rpm	72.512	0.080	11017.4
<i>The samples prepared by the phase inversion technology</i>			
5.000 rpm	55.168	0.089	10701.1
7.000 rpm	60.985	0.072	7533.8
10.000 rpm	56.334	0.084	5821.0

manufacturing technologies at the emulsification rate of 5.000 rpm.

After emulsification the mass in the reactor is cooled to a temperature of (25 ± 2) °C while stirring periodically with a scraper and blade stirrer at the rotation speed of 45 rpm.

In industrial production at the stage of obtaining a semi-finished product of the bulk cream the mass is stored for a certain time at room temperature until the results of the intermediate control are obtained. In the case of receiving positive results the mass is transferred to the stage of dispensing. While transferring the cream mass is exposed to the mechanical impact during pumping and dosing on high-performance tube filling lines. At the same time, the mass can be heated to facilitate transportation and dosing, as well as to reduce losses. The mechanical impact and temperatures on the disperse system already structured is a critical parameter of the manufacturing process.

In order to study the effect of the temperature on the structural-mechanical parameters

of the half-finished product of the bulk cream the rheological studies were conducted. The results of these studies are shown in Fig. 5 and Tab. 2.

Taking into account that the preliminary studies determined the total concentration of emulsifiers of cetyl stearyl alcohol and emulsifier No. 1 in the amount of 8-10 % the probability of destruction is greater with the use of emulsifiers as the main structure-forming components, at the lower boundary of concentrations, i.e. 8 %. Therefore, the subsequent rheological studies were performed for the sample containing 8 % of emulsifiers. For greater informativity and clarity Fig. 5 shows only the flow curves and viscosities calculated by the Casson model. As can be seen from the above data, when the temperature rises from 20°C to 35°C, slight changes in the rheological behavior of the samples are observed. At a temperature of 35 °C and above, the flow boundary decreases, and the area of the hysteresis loop increases. A decrease of the flow boundary

Table 2

THE STRUCTURAL-MECHANICAL PARAMETERS OF THE SAMPLE WITH THE TOTAL CONCENTRATION OF EMULSIFIERS OF 8 %

Temperature, t, °C	The flow boundary by Casson, τ_0 , Pa	Viscosity at the infinite shear rate by Casson, η_{∞} , Pa·s	The hysteresis loop area, A, Pa/s
20	35.96	0.118	755.01
25	34.51	0.095	580.42
30	33.56	0.090	870.22
35	27.48	0.062	1457.26
40	17.13	0.056	1964.31
45	9.37	0.027	1399.56
50	2.72	0.018	1960.35

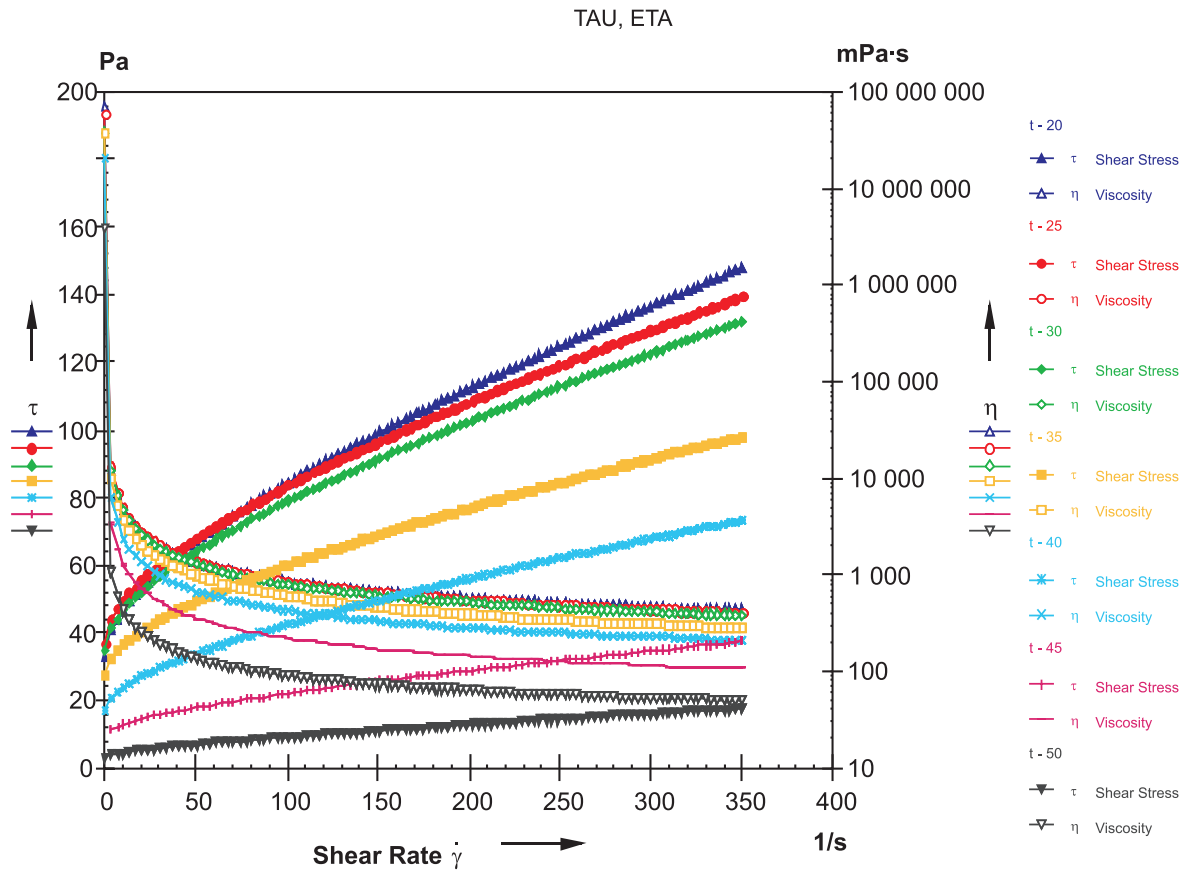


Fig. 5. The flow curves and viscosity curves for the cream samples calculated by Casson

indicates the flow ability, while an increase in the hysteresis area shows the poor restoration of the destructured disperse system.

Thus, the process of transportation and dosing of the cream in tubes, if necessary, is possible when the mass is heated to a temperature not exceeding 30°C since the cream is fusible. At the same time, it should be noted that when dispensing the cream in a high-performance tube filler (more than 100 tubes per minute) the mass spontaneous heating is possible due to the high gradient of the shear rate while dosing when a decrease in structural viscosity is observed. Therefore, to maintain the physical stability of the cream developed the process of dosing should be conducted at a temperature of 25-30°C.

Conclusions and prospects for further research

The effect of the technology for preparing the veterinary cream with silver citrate and the rate of emulsification on its disperse and structural-mechanical parameters has been studied. According to the microscopic studies it has been

found that there is a tendency to reduce in the particle size of the internal phase of the drug with an increase in the rate of emulsification. In the samples prepared at the emulsification rate of 5.000 rpm the droplets of the internal phase have a size of 5-10 microns with the same compaction throughout the emulsion volume. In the samples of emulsions obtained at the emulsification rate of 7000 rpm and 10000 rpm by the size of the oil particles the emulsions are divided into two fractions: 2-5 μm and 5-10 μm with single droplets at 15 μm . The sample prepared by the phase inversion at 10.000 rpm differs by homogeneity of oil droplets with the sizes of 2-5 μm and the same compaction. It has been found that at the rate of emulsification of 5.000 rpm there are no significant changes in both the complete mixing technology and the phase inversion technology.

Using a Rheolab QC rheometer (Anton Paar, Austria) and the system of coaxial cylinders C-CC27/SS it has been determined that by all rheological indicators the cream samples are not significantly different and have the similar

profile of their rheological behavior. The samples have a low flow boundary (τ_0 , Pa) calculated by the Casson mathematical model. It indicates easy extrusion from the tube and application on the animal's skin surface. The samples prepared using the complete mixing technology are the most resistant to mechanical impact based on the viscosity values at infinite shear rate according to the Casson model. The samples

prepared by the phase inversion technology have a lower value of the hysteresis loop area.

The effect of the temperature on the disperse system stability has been studied, and the temperature range, which is recommended for transporting and filling the cream into tubes, has been determined.

Conflict of Interests: authors have no conflict of interests to declare.

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