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Research Article

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The study of the influence of α-lipoic acid, urea and tea tree oil on the rheological properties of the emulsion cream vehicle for use in diabetic foot syndrome

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ABSTRACT

The effects of active components (α-lipoic acid, urea and essential tea tree oil) on the structural mechanical (apparent viscosity, shear stress, type of flow) and physicochemical (colloid and thermal stability, pH) properties of the emulsion vehicle were studied in order to substantiate the optimal composition of cream. Analysis of the structural and mechanical properties of the developed samples was carried out on a rotary viscometer BROOKFIELD DV-II + PRO (USA) with a spindle SC4-21. By results of the research ascending and descending curves of the hysteresis loops (rheograms) were constructed and apparent viscosity - shear rate dependence was defined. Using the modern rotational viscometer «Rheolab QC», Anton Paar (Germany) with coaxial cylinders C-CC27/SS we determined the hysteresis areas of experimental emulsions that allowed choosing finally complex of emulsifiers. The influences of the components on the colloidal and thermal stability were studied. Attention was drawn that the addition of α-lipoic acid significantly affects the pH value, namely shifts the indicator to the acidic side. Under the investigations conducted optimum emulsion vehicle composition was selected for cream under develop for use in diabetic foot syndrome.

Key words: diabetic foot, emulsion o/w, α-lipoic acid, urea, tea tree oil, apparent viscosity, pH, colloid stability, thermal stability

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INTRODUCTION

Progressive diabetic neuropathy in diabetes leads to irreversible changes of neural structures, that entail the reduction of different kinds of sensitivity, poor nutrition of tissues, sebum secretion and sweating dysfunction, etc. [1]

Feet skin of patients with diabetes assumes the characteristics, such as excessive dryness, hyperkeratosis, violation of hydro-lipid balance and skin barrier [2]. Therefore, in the process of developing of topical medicinal and parapharmaceutical products for use in diabetic foot syndrome attention should be paid to the special requirements that specify not only to the active substances, but also to the drug vehicle. To achieve emollient action and to restore the hydro-lipid mantle o/w emulsion was chosen as the dosage form.

Previously by organoleptic, physicochemical and structural mechanical studies samples of the emulsion vehicles have been developed with different emulsifiers and their concentration [3]. Two types of emulsifiers were used: one of hydrophilic nature (1st kind) with HLB 8-13, and the other - of lipophilic nature (2nd kind) with HLB 3-6. Such system provides the greatest stability, high dispersion and necessary viscoplastic properties of emulsions. As emulsifiers of the 1st kind were used “Emulsifier № 1”, stearate PEG - 400, “Olivem 1000” with high HLB values as well as low irritation potential. Glycerol Stearate, wide-spread in the pharmaceutical industry in emulsion drugs development was used as the emulsifier of the 2nd kind [3, 4].

As the oily phase olive oil and shea butter were chosen for cream. Olive oil is recommended for dry skin care, it promotes its moisturizing and improving elasticity, exhibits antioxidant properties [5]. Shea butter is valued for its softening and regenerating properties, particularly when applied to chapped lips, hands and feet [6, 7]. Also, scientific research found anti-inflammatory activity of olive oil and shea butter [5, 8, 9].

Four compositions of cream vehicle with satisfactory values of the studied parameters (appearance, pH, colloidal stability and thermal stability as well as the structural and mechanical properties) were selected for the further investigations. It is known that the active components are substantially affect the rheological parameters as well as other parameters (pH, stability), that should be considered in soft dosage form developing [10 - 14]. Studying of structural and mechanical parameters is an important step towards the creation of a soft dosage form as it gives the opportunity to predict the behavior of a cream during the manufacturing operations, extrusion from the container (tube), application to the surface of the skin, etc. [15 - 17]. In this study, we elucidated the effects of α-lipoic acid, urea and tea tree oil on the rheological parameters of the developed cream bases.

EXPERIMENTAL SECTION

Objects of study were the o/w emulsion drug vehicles selected in previous studies with the following composition (Table-1).

According to Table-1 oily phase consists of natural emollients: olive oil (RHLB 8) (Xian Jiatian Biotech Co., Ltd., China) and shea butter (RHLB 7) (Athena (Guangzhou) Cosmetics Manufacturer Co., Ltd., China). The concentration of the oil phase was 30 % as according to literature data recommended for emulsions for very dry, calloused skin care. [4]

As the 1st kind emulsifiers were used "Emulsifier № 1" with HLB 10 (sodium salts of sulfuric acid esters of high alcohols and free higher alcohols of the same faction in the ratio 3:7, OOO SPE “Electrogasokhim”, Ukraine), Stearate PEG-400 with HLB 13,4 (OOO SPE “Electrogasokhim”, Ukraine), “Olivem 1000” with HLB 12 (Cetearyl Olivate and Sorbitan Olivate, HallStar Italia Srl, Italy), as an emulsifier of the 2nd kind - Glycerol Stearate with HLB 3,6-4 (OOO SPE “Electrogasokhim”, Ukraine) [3, 10].

The selection of the emulsifier system was based on the HLB concept, where the required HLB of the oil mixture is equivalent to the HLB of the emulsifiers [18]. Singly α-lipoic acid (Chengde Miracle Pharmaceutical Co. Ltd, China), urea (“Kharkovreakhim” Ltd., Ukraine) and tea tree oil (*Melaleuca alternifolia Maid*, Cassegrain Tea Tree Oil Pty Ltd, Australia) were incorporated to each of the experimental emulsions.

Table-1 The composition of the test emulsion vehicles

	Concentration of the component, % w/w			
Olive oil and Shea butter	Up to 30,0			
Stearate PEG-400 and Glycerol Stearate	10,0	-	-	-
"Olivem 1000" and Glycerol Stearate	-	10,0	-	-
"Emulsifier №1" and Glycerol Stearate	-	-	8,0	10,0
Purified water	Up to 100,0			

The samples were prepared using an electronic laboratory scales CERTUS Balance CBA-300-0, 005 (Taiwan) and the homogenizer POLYTRON PT 2500 E-kinematica (Switzerland). The pH of the samples was determined by potentiometric method with pH ionometer MI-150 "Izmerytelnaya technica" (Russian Federation), the colloidal stability with a laboratory centrifuge MPW-210 company "Mechanika precyzyjna" (Poland), a mercury thermometer, as well as a stopwatch, and a water-bath DZKW-D-4 (China).

Rheological parameters (apparent viscosity, shear stress, etc.) were measured using a viscometer BROOKFIELD DV-II + PRO (USA), spindle SC 4-21. The following technique was used: about 8.0 - 8.5 g of sample of cream was placed in the chamber, after spindle was immersed in the cream and was driven in rotational movement (20, 30, 35, 40, 50, 60, 80 and 100 r/min) from small deformation rates and then in reverse order. At the same time parameters (shear rate (Dr, c-1: 18.6, 27.9, 32.5, 37.2, 46.5, 55.8, 74.4, 93), shear stress (τ, Pa), apparent viscosity (η, mPa·s)) were fixed on the viscometer display.

For a more detailed study of emulsions we carried out additional research of rheological parameters using modern rotational viscometer «Rheolab QC», Anton Paar (Germany) with coaxial cylinders C-CC27/SS. According to computed hysteresis area the mechanical stability of structured systems can be understood: the lower it is the greater the mechanical stability of the system is [19-24]. The technique consists of the following: sample mass 17,0 (±0,5) g was placed in external fixed cylinder container, temperature of the experiment (20 °C) was set. Experimental

conditions (shear rate of the inner cylinder (0.1 to 350 s^{-1}), the amount of experiment points at the flow curve of the sample (35) and the duration of the measurement at each point of the curve (1 s)) were set by using the software the device equipped with as well as hysteresis areas were calculated (Pa/s).

RESULTS AND DISCUSSION

The first step was to prepare model samples. As a result of previous biological studies optimal concentration of α-lipoic acid and urea (2 % w/w and 10 % w/w respectively) have been determined. By microbiological investigations was proved the optimal concentration of tea tree oil (3 % w/w). In these concentrations the substances were incorporated into the investigated bases. Totally for the study 12 samples were prepared:

1 - emulsion base + α-lipoic acid (samples № 1.1, 2.1, 3.1, 4.1);
2 - emulsion base + urea (samples № 1.2, 2.2, 3.2, 4.2);
3 - emulsion base + tea tree oil (samples № 1.3, 2.3, 3.3, 4.3).

Before the study rheological parameters of the samples were tested for colloidal and thermal stability and pH measurements 10 % aqueous solution of the samples were carried out (Table-2).

As Table-2 shows addition of the active components does not affect the stability of emulsions. It was no phase separation observed after centrifugation (6000 and 8000 rpm) and the effects of temperature (42,5 ± 2,5) °C and (6 0 ± 2,0) °C (recommended temperature modes according to the SPhU) of all the samples [19].

Addition of active substances affected pH level. Observed that the inclusion of α-lipoic acid shifts the pH value of the emulsions to the acid side (with 7.24 - 8.07 to 4.01 - 4.33). Addition of tea tree oil decreases the pH value close to neutral (6.81 - 6.98), and the inclusion of urea affects the pH slightly, except sample № 1.2: with the addition of urea to the emulsion based on emulsifier Stearate PEG - 400 pH changed from (8,07 ± 0,05) to (6,61 ± 0,02).

Table-2 Physicochemical and structural mechanical properties of model emulsions (n=3)

pH (10% aqueous solution)	4,05 ±0,04	4,16 ±0,05	4,19 ±0,03	4,27 ±0,06	6,61 ±0,02	8,16 ±0,05	7,37 ±0,04	7,25 ±0,06	6,3 ±0,05	6,83 ±0,02	6,86 ±0,05	6,91 ±0,07
Colloidal stability at 6000 rpm	+	+	+	+	+	+	+	+	+	+	+	+
Colloidal stability at 8000 rpm	+	+	+	+	+	+	+	+	+	+	+	+
Thermal stability	+	+	+	+	+	+	+	+	+	+	+	+
Apparent viscosity at 20 rpm (mPa·s)	5000	11500	11000	8000	12500	15000	10600	13000	11000	14000	11000	12800
Hysteresis Area, (Pa/s)	3483,9	8224,5	5413,4	9108,4	7797,2	7309,6	4749,6	7779,2	6135,5	10155,3	5836	8753,7

"+" = stable system

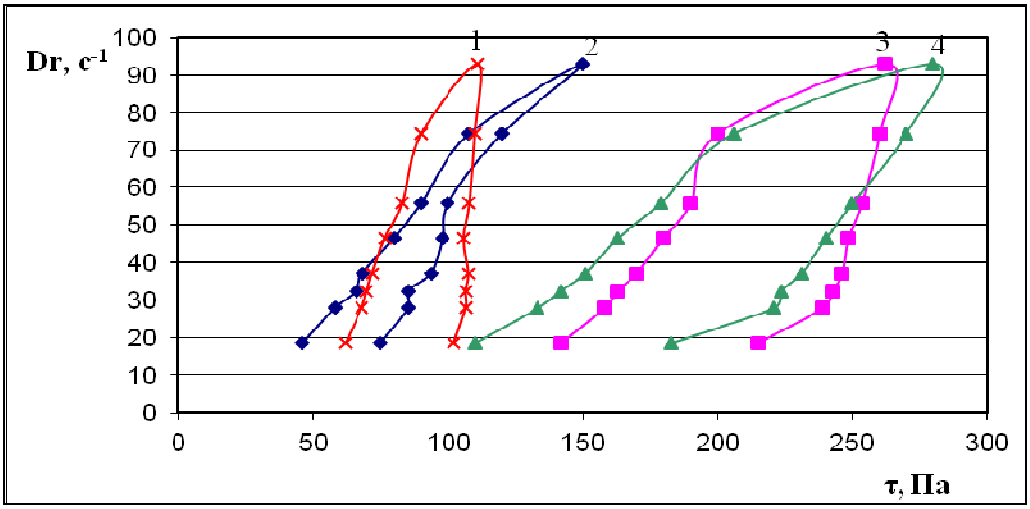

Fig-1 Rheograms of investigated emulsions: 1 - cream base № 1 based on Stearate PEG-400; 2 - sample of cream № 1.1; 3 – sample of cream № 1.2; 4 - sample of cream № 1.3

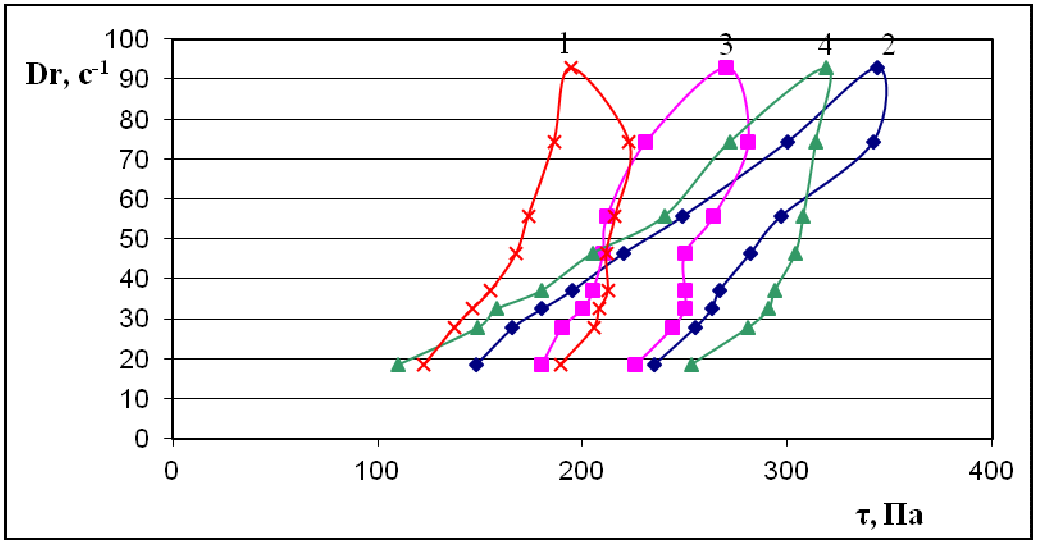

Fig-2 Rheograms of investigated emulsions: 1 - cream base № 2 based on "Olivem 1000"; 2 - sample of cream № 2.1; 3 - sample of cream № 2.2; 4 - sample of cream № 2.3

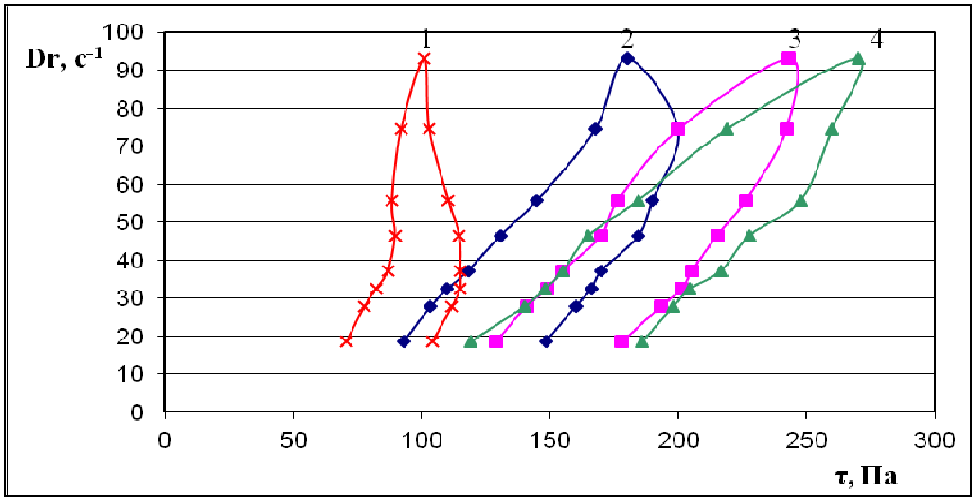

Fig-3 Rheograms of investigated emulsions: 1 - cream base № 3 based on "Emulsifier №1" with the total concentration of emulsifiers 8%; 2 - sample of cream № 3.1; 3 - sample of cream № 3.2; 4 - sample of cream № 3.3

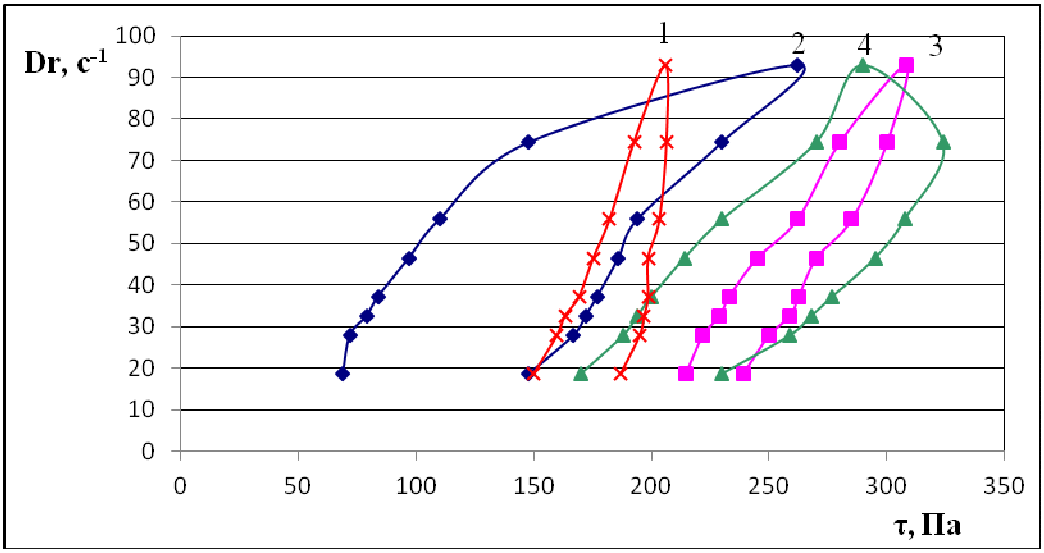

Fig-4 Rheograms of investigated emulsions: 1 - cream base № 4 based on "Emulsifier №1" at a total concentration of 10% of emulsifiers; 2 - sample of cream № 4.1; 3 - sample of cream № 4.2; 4 - sample of cream № 4.3

During the structural and mechanical studies some changes were revealed in rheological parameters after incorporation of active components to the studied emulsions. Rheograms (Fig 1 - 4) show that the studied emulsions are non-Newtonian fluids with plastic type flow. It is noted that the addition of active components did not change the type of model emulsions flow.

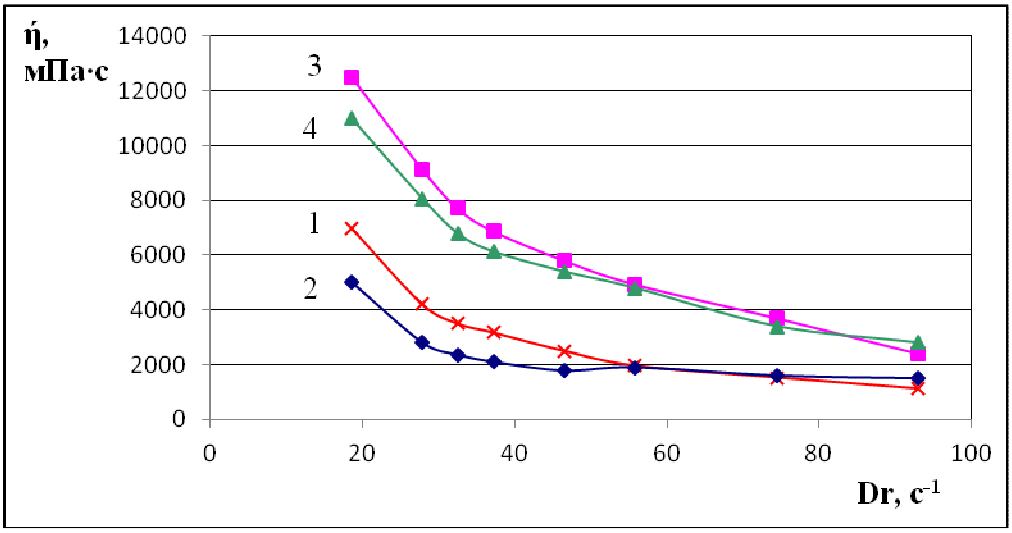

Fig-5 Apparent viscosity - shear rate diagram: 1 - cream base № 1 based on emulsifier Stearate PEG-400; 2 - sample of cream № 1.1; 3 - sample of cream № 1.2; 4 - sample of cream № 1.3

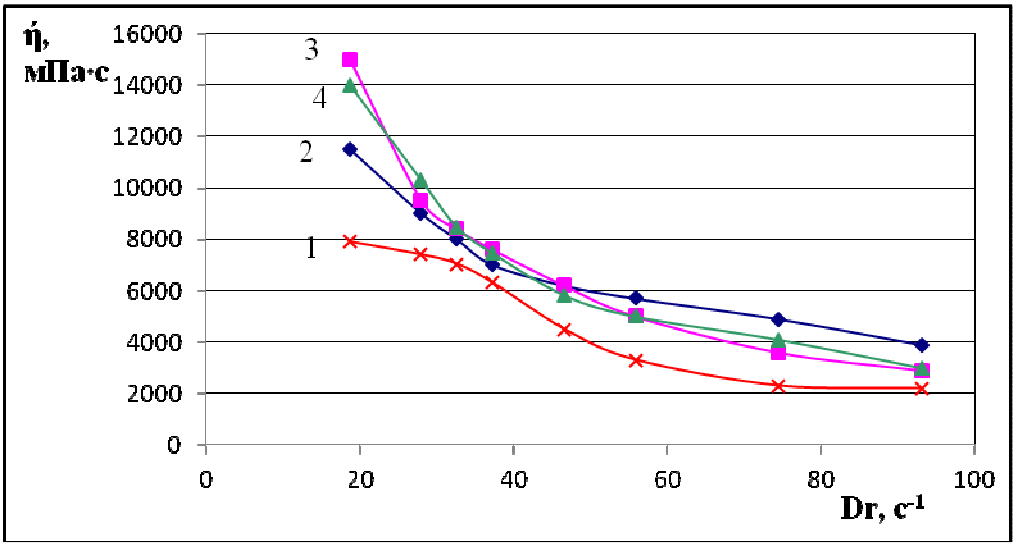

Fig-6 Apparent viscosity - shear rate diagram: 1 - cream base № 2 based on "Olivem 1000"; 2 - sample of cream № 2.1; 3 - sample of cream № 2.2; 4 - sample of cream № 2.3

Rheograms of the test samples (from Fig-1 to Fig-4) also demonstrate the presence of thixotropic properties because of hysteresis loops. At the moment of shear stress reduction restoration of the structure retards, which is typical for emulsions, the structure of which requires more time to restore after physical impact. Hysteresis areas of emulsions №№ 1, 2, 3, 4 were 3657.2; 9869.2; 2695.3; 5484.0 (Pa/s) respectively. Hysteresis area increase after introduction of active substances to the test bases, which was observed in all the samples except № 1.1, 2.2, 4.2, indicates a thixotropy enhancement (Table-2). However, a significant increase in thixotropy (samples №№ 1.2, 1.3, 4.1, 4.3) can undermine the rheological properties of creams during storage.

Addition of α-lipoic acid, urea and tea tree oil is also showed an impact on the rheological parameters (apparent viscosity and lower yield stress). Before the inclusion of active substances viscosity of the cream bases was 7000 - 9300 mPa·s at 20 rpm. Incorporation of urea and tea tree oil in all cases led to an increase in the rheological parameters values (Table-2), which is associated with the strengthening of dispersion coagulation structure.

Effect of α-lipoic acid on rheological parameters of emulsion vehicles was not identic. With the inclusion of α-lipoic acid values of the lower yield stress and apparent viscosity increased in the samples № 2.1 and № 3.1 (Fig-2, Fig-3), but decreased in the samples № 1.1 and № 4.1 (Fig-1, Fig-4, Fig-5, Fig-8). A significant decrease in viscosity of the sample № 1.1 (Fig-5) may indicate changes in the emulsifier Stearate PEG-400 properties in acidic media.

The data obtained were plotted as viscosity versus shear rate (from Fig-5 to Fig-8).

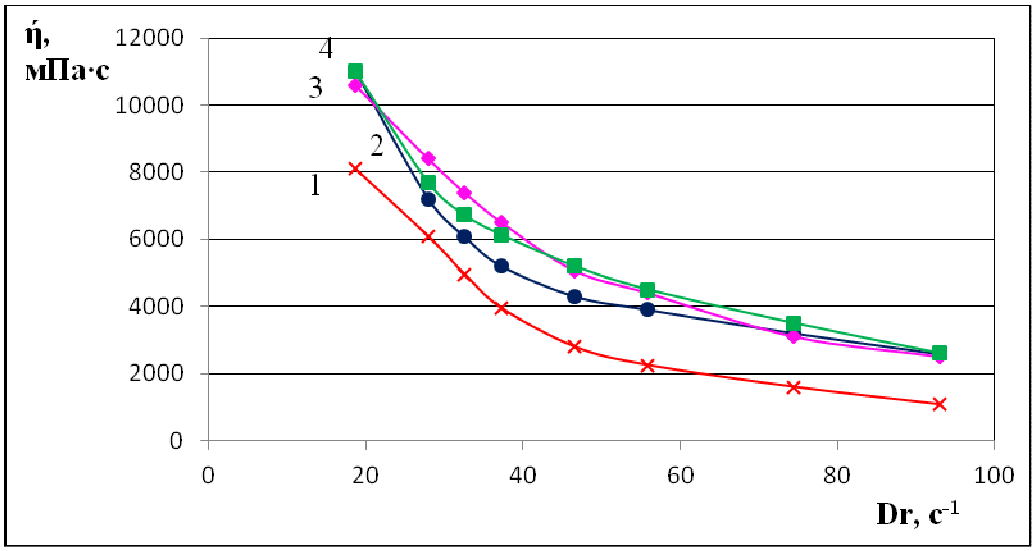

Fig-7 Apparent viscosity - shear rate diagram: 1 - cream base № 3 based on "Emulsifier №1" with the total concentration of emulsifiers 8%; 2 - sample of cream № 3.1; 3 - sample of cream № 3.2; 4 - sample of cream № 3.3

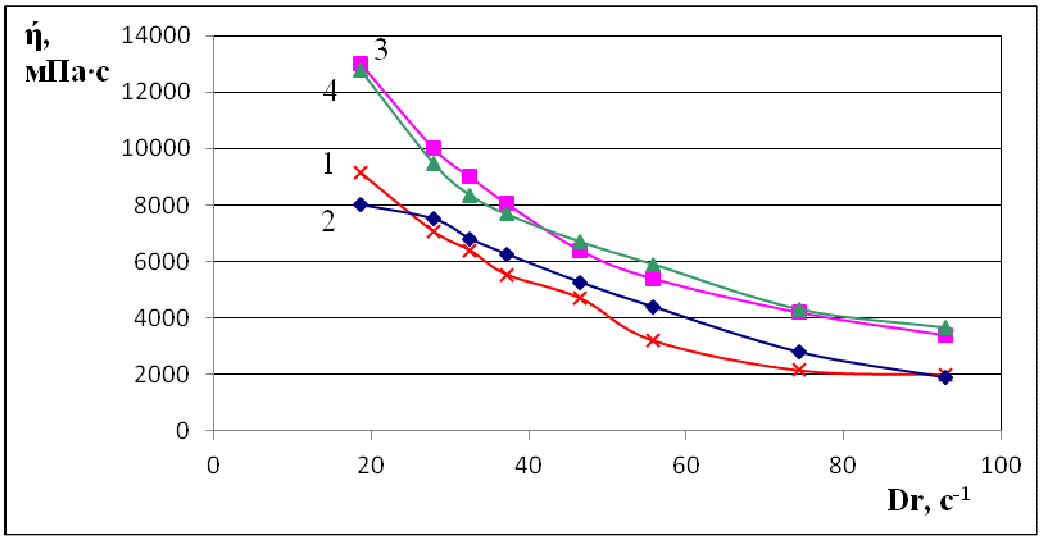

Fig-8 Apparent viscosity - shear rate diagram: 1 - cream base № 4 based on "Emulsifier №1" at a total concentration of 10% of emulsifiers; 2 - sample of cream № 4.1; 3 - sample of cream № 4.2; 4 - sample of cream № 4.3

Investigation of the apparent viscosity versus shear rate dependence for the model emulsions showed that the viscosity of the samples gradually decreases with shear rate increase. Especially intensive apparent viscosity decreases in a larger deformation range from 20 to 40 s^{-1} in the samples based on the emulsifiers Stearate PEG-400 and "Olivem 1000" (Fig-5, Fig-6) and from 20 to 50 s^{-1} in the samples based on the "Emulsifier №1" (Fig-7, Fig-8). Further apparent viscosity does not change so rapidly and at a strain rate over 60 s^{-1} is described by the linear dependence. This is due to the fact that there is structural destruction at high strain rates, which nevertheless does not extend fully because of a certain amount of connections capable of reversibly recovering even at high speeds.

Established apparent viscosity versus shear rate dependences indicate more effortless distribution of investigated emulsions based on stearate PEG-400 and "Olivem 1000" on the skin during application. Incorporation of active ingredients resulted in an increase of the apparent viscosity but slightly affected the character of viscosity - shear rate reducing (the form of curves).

CONCLUSION

Thus, investigations have shown that the selected active components of the cream for use in diabetic foot syndrome can significantly affect the main characteristics of the emulsion bases. The type of flow of emulsions has not changed after α-lipoic acid, urea and tea tree oil were included. The test emulsions are non-Newtonian fluids with a plastic type of flow. However, there was an increase in values of rheological parameters (apparent viscosity, the lower yield point). Also, most of the samples had thixotropic properties enhancement (the hysteresis area growth).

It was revealed that the inclusion of α-lipoic acid shifts the pH of the emulsions to the acidic side. This is reflected adversely on the properties of the emulsifier Stearate PEG-400. There was decrease of rheological parameters after α-lipoic acid inclusion into the emulsion based on Stearate PEG-400.

Due to the physicochemical, structural and mechanical studies conducted emulsion vehicle № 2 with the complex of emulsifiers "Olivem 1000" and Glycerol Stearate was chosen for possessing the most optimal features for developed cream for use in diabetic foot syndrome.

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