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Investigation of rheological properties of the ointment bases at justification of the ointment composition for herpes treatment

Short title: Investigation of the ointment for herpes

Tanya Ivko[1], Vita Hrytsenko[2], Lydmila Kienko[2], Larisa Bobrytska[2], Halyna Kukhtenko[2], Tamara Germanyuk[1]
[1]National Pirogov Memorial Medical University, Vinnytsya, Ukraine
[2]National University of Pharmacy, Kharkiv, Ukraine

Corresponding Author Information
Tanya Ivko
+380982640560
ivkot1981@gmail.com
orcid.org/0000-0003-2873-1473
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ABSTRACT
INTRODUCTION: The combined drugs are leading among pharmacotherapeutic agents, including the treatment of herpetic infections, which require complex treatment. We have developed a soft dosage form in the form of an ointment, which includes acyclovir and miramistin, which has antimicrobial, anti-inflammatory and local immunoadjuvant action.The aim of the work was to investigate the rheological properties of the ointment bases in order to substantiate the composition of a soft dosage form with the antiviral effect with the content of active ingredients miramistin and acyclovir.
METHODS: The objects of the study were model heterogeneous and homogeneous compositions of the bases, made using a wide range of excipients. Structural and mechanical studies were carried out using the "Rheolab QC" rotary viscometer by Anton Paar (Austria) with coaxial cylinders CC27/S-SN29766. The rheological parameters were studied at a temperature of 25±0.5ºC. The samples were thermostated using a thermostat MLM U15c. The batch of sample weighed about 15.0±0.5 g was placed in the container of an external stationary cylinder, the required temperature of the experiment was set, the time of thermostating was 20 min. The device is equipped with RheoPlus 32 V3.62 software.
RESULTS: The rheological behavior of model compositions is analyzed with help of such indicators as: yield strength, hysteresis square, the coefficients of dynamic flow, mechanical stability. It was found that all samples have a non-Newtonian pseudoplastic type of flow. The model of spreading optimums is used to evaluate consumer properties. According to the set of rheological parameters, it is advisable to use the sample based on paraffin and vaseline oil for further research.
DISCUSSION AND CONCLUSION: Conclusion: The results will be used in the development of the soft dosage form for the treatment of herpes viral diseases.
Keywords: Ointment bases, soft dosage forms, rheology, structural and mechanical properties

INTRODUCTION

Soft dosage forms are dispersed systems with a viscous-plastic dispersed medium characterized by a non-Newtonian type of flow[1]. Their viscosity at a given temperature and shear stress varies nonlinearly depending on the shear rate[2-3].
When developing composition of soft dosage drugs, much attention is paid to the study of their

rheological properties, and the structural and mechanical parameters determine the stability of viscose-dispersed systems[4]. A comprehensive study of rheological characteristics is of both theoretical and practical interest, as they can be an effective and objective criterion for quality control at the stage of creation, production, storage and use of drugs[5-6]. The rheological properties affect the release of medicinal substances, therapeutic efficacy of drug, consumer requirements (the process of extrusion from tubes, convenience and ease of lubrication on the skin) and production characteristics (the process of dispersion, packaging)[7-9].

Soft dosage forms are complex systems that contain a base and active ingredients[10]. Properly selected base provides the necessary speed and completeness of medicinal substances release, comfort in use and stability during storage of drug[11-12]. Therefore, the study of the structural and mechanical properties of ointment bases is important step in the development of soft dosage forms[13-15].

Today the combined drugs are leading among pharmacotherapeutic agents, including the treatment of herpetic infections, which require complex treatment. Choice of drug combination allows to expand the range of action of the drug and the complex influence on the disease, enhance the activity of the every ingredient, as well to improve tolerability and reduce side effects[16-19.]

Herpetic infections occur in the form of mono-, mixed and coinfections and can be asymptomatic (latent), in an acute, chronic persistent form with a recurrent course, as well as in the form of an atypical chronic active infection [20]. Currently, the combined drugs are leading among pharmacotherapeutic agents, including the treatment of herpetic infections, which require complex treatment. Drug combination choice allows to expand the range of action of the drug and the complex influence on the disease, activity of the every ingredient, as well to improve tolerability[21-26]. We have developed a soft dosage form in the form of an ointment, which includes acyclovir (TEVA Pharmaceutical and Chemical (Hang-zhou) Co., Ltd, China) and miramistin (Infamed LLC, Russia), which has antimicrobial, anti-inflammatory and local immunoadjuvant action.

MATERIALS AND METHODS

The objects of the study were ointment bases (Table 1). The ointment bases have been developed using excipients that are widely used in soft dosage technology.

The ointment bases were obtained at National University of Pharmacy, Department of Industrial Technology of Drugs. As excipients used: propylene glycol (BASF SE, Germany)[27], proxanol-268 (NPF “Perftoran” OJSC, Russia), polyethylene oxide-400 (Dow Chemical, Germany)[28], vaseline oil (Borma wachs, Italy)[27], paraffin (LLC “Novokhim”, Ukraine), cetostearyl alcohol (Guangzhou Yiming Chemical Material Co., Ltd., China) [29], twin-80 (MN & Gustav Heess Ukraine, Ukraine), carbopol 934 (Kylin Chemicals Co., Ltd., China), triethanolamine (LLC “Novokhim”, Ukraine)[27], corn oil (Nordolio, Italy), eucerit (LLC NPP “Electrogazokhim” Ukraine), aristoflex AVC (Clariant, Switzerland), vaseline (Balea, Germany)[27], emulsifier “Solid-2” (LLC NPP “Electrogazokhim”, Ukraine), isopropylmyristate (MN & Gustav Heess Ukraine, Ukraine)[23], hydroxyethylcellulose (LLC “Linkchem”, Ukraine).

The rheological (structural-mechanical) properties of the bases were determined with the means of “Rheolab QC” rotary viscometer by (Anton Paar, Austria) with coaxial cylinders CC27/S-SN29766. The rheological parameters were studied at a temperature of 25±0.5ºC. The samples were thermostated using a thermostat MLM U15c.

The batch of sample weighed about 15.0±0.5 g was placed in the container of an external stationary cylinder, the required temperature of the experiment was set, the time of thermostating was 20 min. The device is equipped with

RheoPlus 32 V3.62 software. Measurements of the rheological flow curve were performed in 3 stages:

1. Linear increase at the rate of shear velocity from 0.1 s^{-1} to 350 s^{-1} with 105 measurement points and duration of the measurement point is 1 s;
2. Constant shift at a speed of 350 s^{-1} for 1 s of duration;
3. Linear decrease at the rate of shear velocity from 350 s^{-1} to 0.1 s^{-1} with 105 measurement points and duration of the measurement point for 1 s.

The range of the shear rate gradient 0.1-350 s^{-1} corresponds to the range speed of 0.075-270 revolutions per minute.
The device allows measuring the tangential bias voltage (□) in the range 0.5-3.0 10^4 Pa, the gradient of the shear rate ($\dot{\gamma}$) from 0.1 to 4000 s^{-1}, the viscosity (□) is from 1 to 10^6 Pa sec.
Using RheoPlus 32 V3.62 software, the hysteresis square (A, Pa/sec) was calculated; points (yield) strength (τ_0, Pa), and viscosity at the infinite shear rate (η_∞, Pa·s) using the Casson model[5-6]:

$$\tau^{\frac{1}{2}} = \tau_0 + (\eta \cdot \dot{\gamma})^{\frac{1}{2}}$$

where τ_0 – yield strength, Pa;
η – dynamic viscosity, Pa·s;
$\dot{\gamma}$ – shear rate, s^{-1}
The Casson model describes an imperfectly plastic type of flow, in which there is a disproportionate relationship between shear rate and stress and most closely corresponds to the nature of the flow of the studied ointment bases.
A coefficient of dynamic flow was determined at the speed rates of 3.4 and
10.2 s^{-1}, corresponding to the velocity of the palm while soft dosage form distributing over the surface and the viscosity of the system at the velocity rates of 27.0 and 155 s^{-1}, which display velocity of the processing procedure while manufacturing. Based on the results obtained, the values of coefficients of the dynamic flow of the system have been calculated by the formulas[5-6]:

$$K_{d1} = \frac{\eta_{3.4} - \eta_{10.2}}{\eta_{3.4}} \cdot 100\%$$

$$K_{d2} = \frac{\eta_{27} - \eta_{155}}{\eta_{27}} \cdot 100\%$$

where K_{d1}, K_{d2} – the dynamic flow coefficients;
η – apparent viscosity at specified shear rates
For more complete study of samples, the parameters of their mechanical stability (MS) have been calculated. It is known that the optimal value of MS is 1[15]. The MS value is defined as the ratio of the strength of the structure to failure (τ_1) to the strength value after fracture (τ_2) at a shear rate 3,4 s^{-1} according to the formula[5-6]:

$$MS = \frac{\tau_1}{\tau_2}$$

RESULTS AND DISCUSSION
To study the structural and mechanical properties of the experimental samples, complete rheograms of the dependence of the shear stress (□) from the shear rate gradient (γ) were constructed (Figure 1). For a comprehensive assessment of the behavior of the ointment bases during step-by-step destruction and subsequent restoration (Figure 1) also shows the dependence of viscosity from the shear rate. Sample values of the shear stress and viscosity of the model bases are given (Table 2).
The profile of rheological behavior depends from the composition of the ointment base and varies in a wide range of structural and mechanical parameters (Figure 1). All samples have a pseudoplastic type of flow, the viscosity of the samples decreases disproportionately with increasing shear rate. The samples are exposed to the flow in different ways, which is expressed in the value of the yield strength calculated by the mathematical Casson equation and is 105.8 Pa - 1.3 Pa - 49.3 Pa -12.6 Pa - 104.5 Pa - 77.2 Pa - 65.9 Pa - 0.3 Pa for the samples respectively № 1 - № 2 - № 3 - № 4 - № 5 - № 6 - № 7 - № 8. The yield strength is an indicator that shows at what force the dispersed system begins to flow. In accordance with the value, it is possible to draw a conclusion about how easily the system will be squeezed out, whether the self-flow of the system will be observed and about the adhesive properties of the drug. Thus, the sample № 8 has low rheological parameters, the system has a pronounced ability to self-flow due to insufficient concentration of gelling agent [4-6].
The plan of the experiment envisages a stepwise increase in the rate of destruction of the dispersed system, the flow of which is reflected in the ascending curve, and a subsequent decrease in the rate

with the same step. The flow of the system is described by a descending curve.
The ascending curve is located above the descending one; this arrangement of curves is called positive thixotropy, because there are also such dispersed systems that have antitixotropic or reopective properties. In such systems, the ascending and descending curves are opposite. The studied ointment bases are restored to varying degrees, the surface area between the ascending and descending curves indicates the thixotropy of the system or the ability to recover [11,15]. On the one hand, the smaller the area of the hysteresis loop, the faster the system recovers, and on the other hand, the larger the area, the easier the system is distributed on the surface and on a larger surface area. The first aspect is important in the production process and speaks of the reproducibility of the structured system after the technological process of processing, and the other is important as a consumer indicator of quality. The hysteresis square for the base № 1 is 38780.5 Pa/sec, № 2 - 30887.8 Pa/sec, № 3 - 40.2 Pa/sec, № 4 - 17242.8 Pa/sec, № 5 - 49174, 4 Pa/sec, № 6 - 49521.1 Pa/sec, № 7 - 82587.0 Pa/sec and the base № 8 - 319.5 Pa/sec.
During the period of destruction of structured systems by means of increasing speed of rotation of the internal cylinder there is a rarefaction of systems which never comes to the end because some share of communications is restored back even at high speeds. The viscosity at the infinite shear rate calculated by the Casson model is 0.39 Pa·s - 0.54 Pa·s -0.83 Pa·s - 0.72 Pa·s - 0.88 Pa·s - 0, 34 Pa·s - 0.44 Pa·s - 0.65 Pa·s, respectively, for the samples № 1 - № 2 - № 3 - № 4 - № 5 - № 6 - № 7 - № 8 (Table 3). According to this indicator, the most resistant to the applied shear force is the sample № 8 based on hydroxyethylcellulose. Emulsion samples are liquefied to the greatest extent.
The behavior of dispersed systems during step destruction is also evaluated by the coefficients of dynamic flow and mechanical stability. The coefficient of dynamic flow Kd_1 at shear rates of 3.4 and 10.3 s^{-1} varies in the range from 34.8 % to
95.9 %. The coefficient of dynamic flow Kd_2 is in the range of even higher values, because systems at higher shear rates are destroyed to a greater extent. The coefficient of mechanical stability, calculated at γ 3,4 s-1, serves as a measure of the assessment of the restoration of the structure after the full cycle of destruction-restoration. The closer the calculated value is to 1, the faster the system recovers, and speaks of high instantaneous thixotropic properties. From table 2 we see that the lowest value of the mechanical stability index has a sample №8 made using hydroxyethylcellulose. For gel systems, this behavior is typical, because during the increasing speed of rotation of the cylinder is the elongation of the molecules of macromolecular matter, and after the cessation of the driving force, the structured orientation of the molecule is restored. In emulsion dispersed systems, which include samples №3, №4, №5, №6, the change in viscoplastic properties is due to the sol-gel transition, and such systems are restored over time. Homogeneous hydrophobic dispersed systems (samples №2, №7) recover more slowly, the reason for this may be a violation of thermodynamic equilibrium in the system as a result of forced mixing of one layer relative to another, the viscosity of hydrophobic systems is sensitive to temperature changes.
Samples №6 and №7 (Fig. 1) have an unstable flow at high shear rates, which can be interpreted as an unstable structure that can stratify over time.
The sample № 2 (based on paraffin and vaseline oil) has a stable homogeneous flow over the entire range of the shear rates, the system is easily propelled, characterized by good consumer properties according to the optimum lubrication. According to the set of the rheological parameters, we consider it expedient to use the sample of the ointment base № 2 for further research on the development of the composition of the ointment with antiviral effect.

CONCLUSION

1. The structural and mechanical activity of the ointment bases was studied with help of the rotary viscometer "Rheolab QC" by Anton Paar (Austria) with coaxial cylinders CC27/S-SN29766.
2. It was found that all samples have a non-Newtonian pseudoplastic type of flow.
3. It is established that the ointment base № 2, which includes vaseline oil and paraffin, exhibits a homogeneous rheological flow.

PROSPECTS FOR FURTHER RESEARCH

Further research will focus on the development of composition of ointments with the antiviral

effect.
Conflicts of interest: No conflict of interest was declared by the authors.

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Table 1. The composition of the ointment bases

Ingredients	**Numbers of bases / contents of components, g**							
	№1	**№2**	**№3**	**№4**	**№5**	**№6**	**№7**	**№8**
Propylene Glycol	24.0	-	10.0	-	-	10.0	-	-
Proxanol-268	54.0	-	-	-	-	-	-	-
Polyethylene oxide-400	22.0	-	10.0	-	12.0	10.0	-	-
Vaseline oil	-	85.0	-	-	25.0	-	5.2	-
Paraffin	-	15.0	-	-	-	-	-	-
Cetostearyl alcohol	-	-	-	-	25.0	-	-	-
Twin-80	-	-	-	-	2.0	-	-	-
Carbopol 934	-	-	1.5	-	-	-	-	-
Triethanolamine	-	-	1.5	-	-	-	-	-
Corn oil	-	-	10.0	20.0	-	-	-	-
Emulsifier № 1	-	-	6.0	-	-	-	-	-
Aristoflex AVC	-	-	-	2.0	-	-	-	-
Vaseline	-	-	-	-	-	55.0	93.6	-
Emulsifier T-2	-	-	-	-	-	10.0	-	-
Isopropylmyristate	-	-	-	-	-	-	1.2	-
Hydroxyethylcellulose	-	-	-	-	-	-	-	2.0
Purified Water to	-	-	100.0	100.0	100.0	100.0	-	100.0

Table 2. The parameters of the shear stress and the structural viscosity of the ointment bases at the appropriate shear rate

Gradient of shear rate, ($\dot{\gamma}$, s^{-1})	Shear stress with increasing (τ_1, Pa) / decreasing (τ_2, Pa) shear rate gradient ($\dot{\gamma}$, s^{-1})															
	№1		**№2**		**№3**		**№4**		**№5**		**№6**		**№7**		**№8**	
	τ_1	τ_2	τ_1	τ_2	τ_1	τ_2	τ_1	τ_2	τ_1	τ_2	τ_1	τ_2	τ_1	τ_2	τ_1	τ_2
0,1	118	52,9	43,7	0,745	8,31	21,4	2,16	29,8	128	66,1	106	37,9	381	16,6	0,178	2,04
3,4	365	104	189	6,68	162	121	130	82,9	164	106	371	74,4	399	79	18,3	17
6,8	320	114	219	9,53	206	167	144	93	178	130	320	81,2	416	87	28,3	26,6
10,2	312	122	230	11,7	225	196	149	99,9	194	149	314	86,3	467	91,7	35,1	33,6
13,6	310	127	234	13,7	244	217	151	105	209	165	317	90,3	511	95,9	40,8	39,6
16,9	310	132	233	15,5	259	233	157	110	228	178	319	94,3	550	99,7	45,7	44,5
27,0	316	147	222	20,9	296	260	175	121	275	207	319	104	621	111	57,8	57,2
155,0	403	282	171	83,5	381	386	246	185	607	415	381	202	433	204	122	124
350,0	490	488	199	196	419	418	282	283	742	737	386	380	380	384	167	167
	Structural viscosity with increasing (η_1, Pa·s) / decreasing (τ_2, Pa) shear rate gradient ($\dot{\gamma}$, s^{-1})															
	η_1	η_2	η_1	η_2	η_1	η_2	η_1	η_2	η_1	η_2	η_1	η_2	η_1	η_2	η_1	η_2
0,1	1820	546	437	7,54	4340	5870	3100	2900	859	661	1530	386	4 620	166	1,81	19,7
3,4	103	30,1	54,3	1,93	49,1	35,9	38,6	24,7	46,9	30,7	105	21,5	112	22,9	5,28	4,91
6,8	46,4	16,7	31,9	1,4	30,4	24,9	21,4	13,8	26	19	46,4	11,9	60,3	12,8	4,14	3,9
10,2	30,5	11,9	22,5	1,15	22,2	19,5	14,7	9,9	19	14,6	30,7	8,48	45,5	9	3,44	3,3
13,6	22,8	9,41	17,2	1,01	18,1	16,1	11,2	7,84	15,4	12,2	23,3	6,66	37,5	7,08	3,01	2,92
16,9	18,3	7,8	13,7	0,916	15,4	13,8	9,31	6,51	13,5	10,5	18,8	5,57	32,4	5,89	2,7	2,63
27,0	11,7	5,45	8,21	0,774	11	9,66	6,51	4,49	10,2	7,67	11,8	3,86	22,9	4,1	2,14	2,12
155,0	2,61	1,82	1,1	0,539	2,46	2,5	1,59	1,2	3,92	2,68	2,5	1,3	2,8	1,32	0,787	0,799
350,0	1,4	1,39	0,569	0,561	1,2	1,19	0,805	0,807	2,12	2,11	1,1	1,08	1,09	1,1	0,476	0,476

Table 3. Structural and mechanical parameters of the ointment bases are calculated

Indicator	**№1**	**№2**	**№3**	**№4**	**№5**	**№6**	**№7**	**№8**
Hysteresis square, Pa/s	38780,5	30887,8	40,2	17242,8	49174,4	49521,1	82587,0	319,5
Yield strength at Casson τ_0, Pa	105,8	1,3	49,3	12,6	104,5	77,2	65,9	0,3
Structural viscosity at the infinite shear rate at Casson η_∞, Pa·s	0,39	0,54	0,83	0,72	0,88	0,34	0,44	0,65
The coefficient of dynamic flow Kd_1, %	70,4	58,6	27,1	61,9	59,5	70,8	95,9	34,8
The coefficient of dynamic flow Kd_2, %	77,7	86,6	77,6	75,6	61,6	78,8	97,7	63,2
Mechanical stability at γ 3,4 s^{-1}	3,51	27,84	1,34	1,56	1,55	4,99	5,05	1,08