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INFLUENCE OF PHYSICOCHEMICAL PROPERTIES AND STRUCTURE OF MIXED SOLVENTS PROPYLENE GLYCOL – MACROGOL 400 ON THEIR *IN VITRO* RELEASE

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Aim. *To study the density and dynamic viscosity of the mixed solvents propylene glycol (PG) – macrogol 400 (M400), to calculate their excess values and excess activation parameters of viscous flow, to evaluate the features of the structure of the mixed solvents and their influence on the in vitro release of PG and M400.*
Materials and methods. *The mixed solvents PG – M400 were studied over the entire concentration range at temperatures from 293.15 to 313.15 K. The density and dynamic viscosity were determined, and the excess density, excess dynamic viscosity, activation parameters of viscous flow, and excess activation parameters of viscous flow were calculated. The in vitro release of PG and M400 from the mixed solvents was studied using vertical diffusion cells. The content of PG and M400 in the receptor medium was determined by gas chromatography using validated analytical procedures. The release rate, cumulative content, percentage of released PG or M400, coefficients of correlation and coefficients of determination were calculated.*
Results. *The isotherms of excess density and excess dynamic viscosity of the mixed solvents PG – M400 pass through a maximum. The enthalpy makes the main contribution to the free activation energy of the viscous flow. The excess free energy is positive and has small values; the values of the excess entropy and excess enthalpy are negative, and the isotherms have the minimum at PG concentrations of ~75 mol %. The release parameters of M400 are greater in binary mixtures where the M400 structure predominates. At PG content of ~75 mol %, the release parameters for PG and M400 are identical. With the increase in PG content above 75 mol %, when the PG structure predominates in the system, the release parameters of PG increase dramatically, and the release parameters of M400 decrease sharply.*
Conclusions. *The structure of the binary system PG – M400 depends on its composition. Based on the isotherms of excess activation of viscous flow, it is possible to differentiate the areas where the structure of PG or the structure of M400 dominates, or the mixed structure of the binary solvent prevails. The in vitro release parameters for PG and M400 depend on the structure of the mixed solvents. The greatest difference in the release parameters of PG and M400 is observed in the area where the structure of PG dominates*
Keywords: *propylene glycol, macrogol 400, solvent, density, viscosity, activation parameters of viscous flow, in vitro release*

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1. Introduction

Some hydrophilic non-aqueous solvents are excipients for medicinal products, in particular, for semi-solid preparations [1]. The most commonly used hydrophilic solvents in pharmacy are *ethanol, glycerin, isopropyl alcohol, liquid macrogols* (*macrogols* 200, 300, and 400), *propylene glycol* (*PG*), *dimethyl sulfoxide* (*DMSO*), *N-methylpyrrolidone* (*N-MP*), *diethylene glycol monoethyl ether* (*DME*), etc. The functional purpose of these solvents may be related to their use as co-solvents of active substances and other excipients [2], penetration enhancers [3], moisturisers [1], substances that provide antimicrobial preservative effect [4], osmotically active substances that absorb exudate [5], drug release modifiers [6], etc.

Typically, mixed solvents (mixtures of water with non-aqueous solvents or a mixture of two or more non-aqueous solvents) are used in semi-solid formulations. In such cases, the performance characteristics of mixed solvents depend on their composition and structure. For example, in mixed solvents, *N-MP – water*, the solubility of meloxicam increases sharply with an increase in the *N-MP* concent above 70 **%** w/w, when the structure of the mixed solvent with a predominance of the structure of a non-aqueous solvent prevails [7, 8]. In this regard, the study of mixed solvents can be carried out in two directions: first, the study of the properties and structure of mixed solvents depending on their composition [9], and second, the study of their performance characteristics.

For instance, the polythermal study (293.15–308.15 K) of the properties of binary solvents: *water – ethanol*, *water – ethylene glycol*, *water – diethylene glycol*, *water – triethylene glycol*, *water – polyethylene*

glycol (*PEG*) *200*, *water – PEG 300*, *water – PEG 400*, *water – PEG 600*, *water – glycerin* was conducted by Hoga H. E. et al. [10]. Densities, speeds of sound and viscosities for those binary mixtures were determined as a function of the composition. From obtained results, excess values and excess activation parameters for viscous flow were calculated. The results were used to discuss structural effects and intermolecular interactions between like and unlike molecules. In another work [11], excess enthalpies of mentioned above binary mixed solvents were determined using a microcalorimeter at 298.15 K. Intermolecular interactions were discussed based on the results of excess molar enthalpies. The experimental results were used to test the applicability of different models (Wilson, NRTL and UNIQUAC). The structural and thermodynamic properties of the binary mixtures of morpholine and PG were studied by Fakhri Z. and Azad M. T. [12]. The volumetric and ultrasonic studies of *PEG 400* and *PEG 4000* in aqueous solutions of glycerol at a different temperatures from 293.15 K to 308.15 K were carried out by Kaur K. and co-authors [13]. The evaluation of thermodynamic properties showed that the extent of interaction intensified with respect to the concentration of glycerol solution as well as with the molecular mass of *PEG*s. The densities and ultrasonic speeds for the binary mixture of *PEG 200* and *PEG 400* with *N,N-dimethylacetamide* (*DMA*) were measured over the entire mole fraction range and at temperatures 303.15 K, 313.15 K and 323.15 K [14]. The excess molar volume, excess ultrasonic speed and other characteristics were calculated. It was shown that strong hydrogen bonding occurs between *DMA* and *PEG* molecules; the molecular interactions are stronger in the case of *DMA* and *PEG 400* [14]. In the study conducted by Chaudhary N. et Nain A. K. [15], the excess parameters were evaluated from the experimentally measured data of density, speed of sound and refractive index for the binary mixtures of *PEG 400* with benzyl methacrylate over entire mole fraction range at the temperatures from 293.15 K to 318.15 K; the observed excess functions were used to discuss the intermolecular interactions between the components. Viscosity and molecular interactions for the binary mixtures *PEG 400 + DMSO* and *PEG 600 + water* within the temperature range 298.15 K to 308.15 K were studied, and molecular interactions in these mixtures were analysed by Upmanyu A. et al. [16].

Thus, to study the mixed solvents, polythermal determination of parameters (density, dynamic viscosity, ultrasonic speed, etc.) should be performed, which makes it possible to calculate quasi-thermodynamic functions [9]. The determination should be carried out over the entire range of mole fractions, and excess parameters should be calculated [7, 10]. The results of their analysis can be used to evaluate the intermolecular interactions between components in the system.

The most frequently studied functional characteristic of mixed solvents is their ability to dissolve various active substances. Generally, the solubility of active substances is studied depending on the temperature, composition and structure of the solvents. In this case, a correlation is made between experimental data and values calculated by different models. The thermodynamic dissolution functions should be calculated, which make it possible to evaluate the process of dissolution and compare it when using mixed solvents with different composition.

There are numerous publications regarding studies of the dissolution of a number of active substances in various mixed solvents: meloxicam in mixtures *ethylene glycol – water* and *PG – ethanol* [17]; mesalazine in ternary systems *ethanol – PG – water* [18]; nicotinamide in mixtures *water – ethanol* and *water – PG* [19]; caffeine in mixtures *N-MP – PG* [20]; lifitegrast in mixed solvents containing *DME, glycerin, PEG 400, PG* and *water* [21]; carvedilol in the ternary system *water – choline chloride – PG* [22]; paracetamol in mixed solvents *water – ethanol* and *water – PG* [23]; ketoconazole in mixtures *ethanol – PG* [24]; acetaminophen in mixed solvents containing *ethanol, PG* and *water* [25]; curcumin in four mixed solvents: *water – ethanol*, *water – n-propanol*, *water – isopropyl alcohol*, *water – PG* [26]; sodium phenytoin in mixed solvents *PG – water* [27]; sulfapyridine in mixed solvents *water – PG* [28] and sulfadiazine in binary mixtures *PEG 400 – water* [29]; deferiprone in mixed solvents *water – ethylene glycol*, *water – PG* and *water – PEG 400* [30]; amlodipine besylate in mixed solvents *PEG 400 – water* [31]; fluphenazine decanoate in aqueous solutions of *PEG 400* or *PEG 600* [32].

In addition to the nature of the active substance and its interaction with the solvent, solubility is also affected by the nature of intermolecular interactions in the solvent itself (hydrogen bonds, conformational states, etc.), which is especially relevant in the case of mixed solvents. Therefore, the scientific rationale for choosing optimal solvents for active substances should also take into account the results of the evaluation of the physicochemical properties of these solvents.

Some water-soluble ointments for the local treatment of purulent wounds in the inflammatory phase contain a mixture of *PG* and *M4*00 in a mass ratio of 6:4 [33]. Among the numerous studies of mixed solvents, there are no data on the properties of the binary solvent *PG – M400*. One of the scientific articles presents the results of studies of the toxicological properties of a mixed solvent containing 5 % *N-MP*, 45 % *PG*, and 50 % *PEG 400* when administered intravenously to rats. This ternary solvent was well tolerated in rats at a dose of up to 2 ml/kg/day for 14 days and at a dose of 1 ml/kg/day for 28 days [34].

The idea of using the binary solvent *PG – M400* together with highmolecularmass macrogols and poloxamers in ointments for local wound treatment is based on the following considerations. Generally, a water-soluble ointment base containing *M400* in combination with highmolecularmass macrogols is commonly used [33]. It is obvious that when applying an ointment with such a base, due to the low rate of release of M400, the processes of water/exudate diffusion to the ointment prevail. *In vivo*, exudate absorption is accompanied by nonspecific dehydration of all tissues, including granulation tissue. If the ointment base contains two solvents with different molecular

weights, *the PG* release rate is higher, and this solvent quickly penetrates into the tissues, resulting in an osmotic equilibrium between the biological object and the ointment. This equilibrium is then maintained by *M400*, which is released and penetrates into tissues more slowly [35]. The addition of a low-molecular-mass solvent into the ointment base made it possible to eliminate the non-specificity of the dehydrating effect of the ointments *Miramistin®-Darnitsa* and *Oflocain®-Darnitsa*. The ointment base provides the absorption of purulent exudate by those preparations in the absence of dehydrating effects on viable tissues, in particular, granulation tissue [33].

Varying the mass ratio between *PG* and *M400* would make it possible to obtain medicines with optimal properties for the treatment of various pathological processes when a different ratio between the processes of penetration and dehydration is required [35]. In this case, an *in vitro* release test for *PG* and *M400* may serve as a suitable model for the research [36].

The aim of this study was to study the density and dynamic viscosity of mixed solvents *PG – M400*, to calculate their excess values and excess activation parameters of viscous flow, to evaluate the features of the structure of the mixed solvents and their influence on the *in vitro* release of *PG* and *M400*.

2. Planning (methodology) of the research

It was planned to study *PG* and *M400*, as well as mixed solvents *PG – M400* in the entire range of mole fractions.

The kinematic viscosity and density of the solvents should be determined, and their dynamic viscosity should be calculated in the temperature range from 293.15 K to 313.15 K, in particular, at 25 °C, 32 °C, and 37 °C (storage temperature, temperatures when using medicines in dermatology, as well as in proctology and gynaecology, respectively). The parameters of viscous flow activation: Gibbs free energies, entropy and enthalpy values should be calculated [9]. Excess density, excess dynamic viscosity, and excess activation parameters of viscous flow should be calculated, and possible intermolecular interactions between components in binary solvents, depending on their composition, should be evaluated.

At the next stage, the effect of the composition of binary solvents on the *in vitro* release of *PG* and *M400* from these mixed solvents should be studied by the dialysis using vertical diffusion cells. The quantitative determination of *PG* and *M400* in the receptor medium was planned to be carried out by gas chromatography (GC) according to validated analytical procedures [35, 37]. The release parameters should be calculated, and their dependence on the composition of the binary solvent should be evaluated. The range of compositions and structures of binary solvents when *PG* release predominated *M400* release should be determined. This would make it possible to scientifically substantiate the composition of the dispersion medium for ointments with water-soluble bases, which are able to absorb exudate but do not damage granulation tissues [35].

3. Materials and methods

The objects of the study were PG and M400 (Sigma-Aldrich, Germany), which met the requirements of the relevant monographs of the European Pharmacopoeia [38], as well as mixed solvents *PG – M400* in the entire range of mole fractions. Solvent compositions are given in Table 1.

Table 1

Compositions of the studied mixed solvents *PG – M400*

Content, % w/w		Content, mol %	
PG	M400	PG	M400
0	100	0	100
1.02	98.98	5.00	95.00
2.13	97.87	10.00	90.00
3.33	96.67	15.00	85.00
4.66	95.34	20.00	80.00
7.73	92.27	30.00	70.00
9.52	90.48	35.00	65.00
11,53	88.47	40.00	60.00
16.35	83.65	50.00	50.00
22.67	77.33	60.00	40.00
31.32	68.68	70.00	30.00
36.96	63.04	75.00	25.00
43.88	56.12	80.00	20.00
52.55	47.45	85.00	15.00
63.75	36.25	90.00	10.00
78.78	21.22	95.00	5.00
90,00	10.00	97.88	2.12
95.00	5.00	98.98	1.02
100	0	100	0

Mixed solvents were prepared by mass using an analytical balance (AUW 120D, Shimadzu). In order to calculate the mole fractions, the average molecular weight (M_r) of the used *M400* was determined to be 389.4 [37]. The molecular weight of *PG* is 76.1 [38].

The Ubbelohde viscometers were used to measure the kinematic viscosity (ν) of the solvents. Measurements were carried out in the temperature range from 293.15 K to 313.15 K. A Julabo F12-ED refrigerating/heating circulator (Julabo Labortechnik GmbH) was used to maintain the necessary temperature. The density (ρ) of the solvents was measured at certain temperatures using a density meter DMA 500 (Anton Paar GmbH, Austria; software version V1.003) [39].

The dynamic viscosity (η) was calculated according to the equation:

$$\eta=\nu\cdot\rho. \quad (1)$$

Excess dynamic viscosity (η^E) was calculated as the deviation of the experimental data (η_{exp}) from the additive values using the following equation:

$$\eta^E=\eta_{exp.}-\Sigma\eta_i\cdot x_i, \quad (2)$$

where η_{exp} is the dynamic viscosity of the ternary system; η_i is the dynamic viscosity, and x_i is the mole fraction of the components.

The excess density (ρ^E) was calculated similarly to the calculation of the excess dynamic viscosity.

Using the data on the density (ρ) and composition of the binary solvents, their molar volumes (V_M) were calculated by the equation:

$$V_M = \left(M_{r1} \cdot X_1 + M_{r2} \cdot X_2\right) / \rho, \quad (3)$$

where V_M is the molar volume of the mixture, l/mole; M_{r1} and M_{r2} – molar weights of the first and second components; X_1 and X_2 – mole fractions of the first and second components.

Gibbs free energy of activation $\left(\Delta G_\eta^{\neq}\right)$ was estimated from the Eyring equation [9]:

$$\eta = \frac{h \cdot N}{V_M} \exp\left[\frac{\Delta G_\eta^{\neq}}{RT}\right], \quad (4)$$

where η is the dynamic viscosity, mPa·s; h is the Plank constant; N is the Avogadro constant; V_M is the molar volume, l/mole; R is the universal gas constant; T is the absolute temperature, K.

Entropy values $\left(\Delta S_\eta^{\neq}\right)$ were found by differentiating the free energy of activation for viscous flow by temperature, and the values of the enthalpy $\left(\Delta H_\eta^{\neq}\right)$ were estimated by the fundamental thermodynamic relationship:

$$\Delta G_\eta^{\neq} = \Delta H_\eta^{\neq} - T\Delta S_\eta^{\neq}. \quad (5)$$

The excess quasi-thermodynamic activation parameters of viscous flow $\left(\Delta Y_\eta^{\neq E}\right)$ were calculated similarly to the calculation of the excess dynamic viscosity.

In order to study the release of *PG* and *M400* from binary solvents, the vertical diffusion cells (weight of test liquid was 3.0 g, the volume of receptor medium (*water R*) was 60 ml; membrane area was 7.065 cm^2) and cellulose membranes (GOST 7730-89) were used; the membranes were pre-soaked in the receptor medium for 24 hours. The experiments were performed at a temperature of 32 °C (skin temperature) [36]. A Julabo F12-ED refrigerating/heating circulator (Julabo Labortechnik GmbH) was used to maintain the necessary temperature. The dialysate was stirred by a magnetic stirrer with a mixing rate 600 rpm. Samples (1.0 ml) were collected from the receptor chamber at 0.5, 1, 2, 3, 4, 5, and 6 h after the application of test liquid and the volume withdrawn was replaced with *water R*. The amount of *PG* and *M400* released at each time point per unit area of the membrane (mg/cm^2) was determined. The results were processed and evaluated using accepted approaches [40, 41].

Quantitative determination of *PG* and *M400* in the dialysate was performed by GC [38, 39] according to validated methods [35, 37] using Shimadzu GC-2014 gas chromatograph with FID detector and IOC-20 autosampler (Shimadzu; software: GC solution version 2.30.00).

Analytical procedure for the quantitative determination of PG.

Test solution. Filtered sample (dialysate).

Reference solution. Dissolve 400 mg of PG CRS (State Pharmacopoeia of Ukraine CRS; cat. No. P0347) in 8 ml of *water R*, dilute to 10 ml with the same solvent and filter using membrane filter with a 0.45 μm pore size.

Chromatographic conditions:

– column: glass, 110 cm×3.2 mm, packed with stationary phase *ethylvinylbenzene–divinylbenzene copolymer R* (80–100 mesh);

– carrier gas: *nitrogen for chromatography R*;

– flow rate: 25 ml/min;

– temperature: termostat – 220 °C; injection port – 250 °C; detector – 250 °C;

– detection: flame ionisation;

– injection: 1 μl;

– run time: ~ 4 min;

– retention time: *PG* about 2.4 min.

System suitability (reference solution): column performance calculated by the *PG* peak should be at least 300 theoretical plates; symmetry factor should be from 0.8 to 2.0; relative standard deviation for areas of *PG* peaks should not exceed 3.0 %.

Analytical procedure for the quantitative determination of M400.

Test solution. Filtered sample (dialysate).

Reference solution. Dissolve 100 mg of M400 (Sigma-Aldrich, cat. No. 202398) in 80 ml of *water* R, dilute to 100 ml with the same solvent and filter using a membrane filter with a 0.45 μm pore size.

Chromatographic conditions:

– column: fused silica Optima 5, 30 m×0.32 mm, packed with stationary phase polydimethyldiphenylsiloxane R (film thickness 0.25 μm) (Macherey-Nagel, cat. No. 726314.30);

– carrier gas: *nitrogen for chromatography R*;

– linear velocity: 50 cm/min;

– split ratio: 1:30;

– temperature: termostat – 150 °C (1 min)→270 °C (5 °C/min; 40 min); injection port – 270 °C; detector – 270 °C;

– detection: flame ionisation;

– injection: 1 μl.

System suitability (reference solution): resolution should be at least 5.0 between the peaks due to any two oligomers of *M400*; symmetry factor for any oligomer peak should be from 0.8 to 1.5; relative standard deviation for the sum of areas of all peaks due to *M400* oligomers should not exceed 4.0 %.

The compositions of the solvents used to study the *in vitro* release of *PG* and *M400* are given in Table 2.

Table 2

Compositions of mixed solvents *PG – M400* used to study *in vitro* release of *PG* and *M400*

Content, % w/w		Content, mol %	
PG	*M400*	*PG*	*M400*
0	100	0	100
15.0	85.0	47.5	52.5
30.0	70.0	68.7	31.3
50.0	50.0	83.7	16.3
60.0	40.0	88.5	11.5
100	0	100	0

4. Research results

4. 1. Study of some physicochemical properties of solvents

Densimetry and viscometry are the most informative methods for the physicochemical analysis of liquid multicomponent systems [42]. As can be seen from Fig. 1, the density of the binary solvents *PG – M400* gradually decreases with increasing *PG* concentration. The density depends more on the solvent composition than on the temperature (Fig. 1). The density isotherms are nonlinear and convex with respect to the abscissa axis. With increasing temperature, the density decreases, but the convexity remains. The type of isotherms indicates that the system under study is not ideal [42]. To determine the peculiarities of the interaction between *PG* and *M400*, the values of the excess density were calculated (Fig. 2).

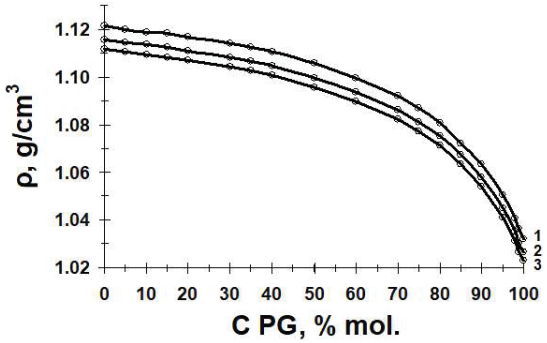

Fig. 1. Density of mixed solvents *PG – M400 vs PG* concentration at: 1 – 25 °C; 2 – 32 °C; 3 – 37 °C

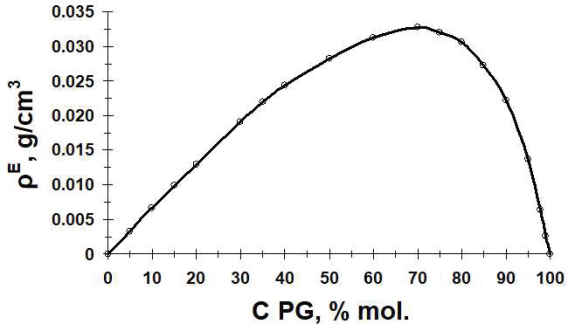

Fig. 2. Representative isotherm of excess density for binary solvents *PG – M400* at 32 °C

The deviations of the experimental density data from the additive values are positive, and the excess density isotherms are extreme (Fig. 2). This indicates that intermolecular interactions depend on the composition of the mixed solvent. The positive deviations of the density from the additive values can be explained by the destruction of hydrogen bonds in each of the solvents and the formation of mixed associates of *PG* and *M400* molecules, mainly due to hydrogen bonds between hydroxyl groups of *PG* and electronegative oxygen atoms in *M400* molecules. The isotherms of excess density show a maximum at a *PG* content of 70 mol %, when associates involving 0.7 mol % *PG* and 0.3 mol % *M400* are formed.

The dynamic viscosity of the binary solvents decreases gradually with increasing *PG* content (Fig. 3); the viscosity also decreases with increasing temperature, indicating that intermolecular interactions are weakened.

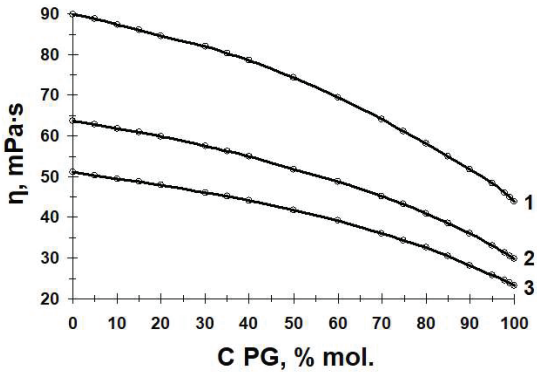

Fig. 3. Dynamic viscosity (η) of binary solvents *PG – M400 vs PG* concentration at: 1 – 25 °C; 2 – 32 °C; 3 – 37 °C

The dynamic viscosity isotherms are nonlinear; this is typical for systems that do not obey Raoul's law [42]. The deviations of the dynamic viscosity from the additive values are positive, and the isotherms of excess dynamic viscosity are extreme (Fig. 4). At 25 °C, a maximum is observed at *PG* content of 50 mol %, and at 32 °C and 37 °C, the maximums occur at *PG* content of 60 mol %.

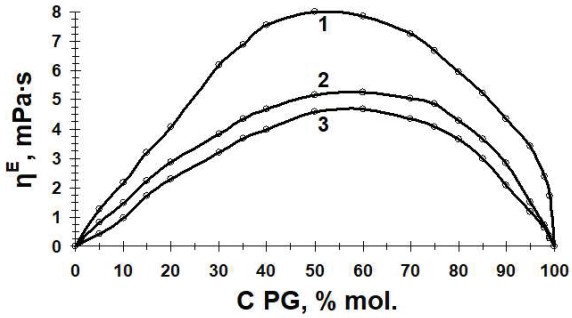

Fig. 4. Excess dynamic viscosity of binary solvents *PG – M400 vs PG* concentration at: 1 – 25 °C; 2 – 32 °C; 3 – 37 °C

Deviations of the dynamic viscosity from the additive values indicate intermolecular interactions of different strengths in the studied system. Excessive dynamic viscosity is not a measure of the interaction between the components of a binary solvent, but it can be assumed that when the interaction is stronger, the greater the difference between the additive and experimental values of dynamic viscosity (η_{ad} and η_{exp}, respectively). Thus, at 25 °C, the η_{exp} value for a solvent containing 50 mol % *PG* and 50 mol % *M400* is 74.2 mPa·s, and the η_{ad} value is 66.855 mPa·s. The difference between these values is 7.345 mPa·s, i.e., 9.9 % of the η_{exp} value. For comparison, the maximum difference at 25 °C between the η_{exp} and η_{ad} values for the system *water – PEG 400* is 57 % [43]. That is, the interaction between *PG* and *M400* in a non-aqueous solvent is weaker than the interaction between molecules of *water* and *M400*.

One of the elementary acts of the process of viscous flow of associated liquids is the movement of individual molecules, which requires the breaking of a certain number of hydrogen bonds [9]. A certain free activation energy of viscous flow $\left(\Delta G_{\eta}^{\neq}\right)$ is necessary for this pro-

cess. The total activation energy of the viscous flow is the sum of the energies required to create vacancies in the liquid and to move flowing molecules into these vacancies. The ratio of enthalpy and entropy constituents of $\Delta G_\eta^{\neq}$ can be determined by the character of the $\Delta G_\eta^{\neq}$ isotherm. According to the data shown in Fig. 5, the main contribution into $\Delta G_\eta^{\neq}$ was made by the enthalpy.

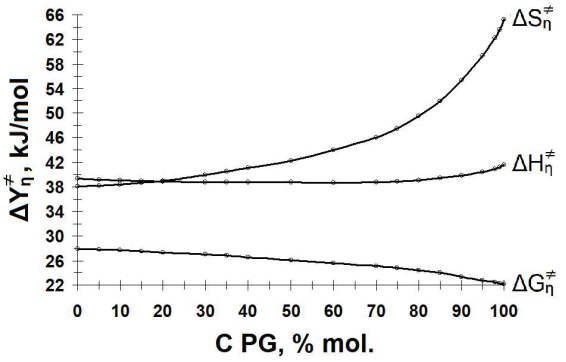

Fig. 5. Activation parameters of viscous flow for binary solvents *PG – M400 vs PG* concentration at 25 °C

The values of the viscous flow activation process $\left(\Delta G_\eta^{\neq}\right)$ for the studied system are positive and decrease with increasing *PG* content (Fig. 5). The addition of *M400* to *PG* in concentrations up to 20–30 mol % leads to a decrease in $\Delta H_\eta^{\neq}$ values; at higher concentrations, *M400* has almost no effect on $\Delta H_\eta^{\neq}$ values. The decrease in $\Delta S_\eta^{\neq}$ values with increasing *M400* content indicates that the structure of *PG* is more ordered compared to its mixtures with *M400*. The addition of *M400* to *PG* leads to the destruction of the ordered structure of *PG*. The greatest decrease of $\Delta S_\eta^{\neq}$ occurs when the M400 content increases to approximately 30–40 mol %.

The quasi-thermodynamic activation parameters of viscous flow are mole-additive [42]. This made it possible to calculate their deviations from additive values for the studied system of solvents (Fig. 6).

The excess values of $\Delta G_\eta^{\neq E}$ are positive and not high. Minor deviations from additivity may be due to a number of mutual compensating factors [42]. At the same time, deviations from additive values for $\Delta H_\eta^{\neq}$ and $\Delta S_\eta^{\neq}$ are negative and pass through a minimum at PG content of 70–75 mol % (Fig. 6).

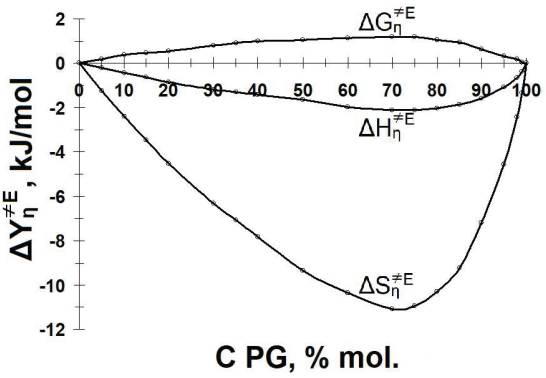

Fig. 6. Excess activation parameters of viscous flow for binary solvents *PG – M400 vs PG* concentration at 25 °C

4. 2. Study of PG and M400 release

Water and a mixed hydrophilic solvent separated by a semipermeable membrane cause two multidirectional processes:

1) release of PG and M400 into the chamber with water;

2) diffusion of water into the chamber with hydrophilic solvent [6].

The process of water diffusion is not discussed in this paper.

The plots (Fig. 7, 8) and the values of the correlation coefficients (Tables 3, 4) indicate that the dependences of the released amount of *PG* and *M400* per unit area of the membrane versus the square root of time were linear for all studied formulations, which made it possible to determine the release rates [40, 41].

In the case of single-component solvents, the *PG* release rate was greater than *M400* release rate by approximately 1.9 times. The cumulative content of *PG* in the dialysate was 2.0 times higher compared to this parameter for *M400*. The released amount of *PG* was approximately 2.0 times greater compared to the released amount of *M400* (Table 3).

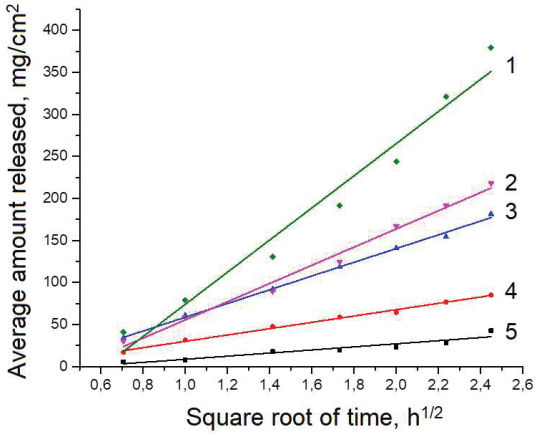

Fig. 7. *PG* release rate plots obtained from the *in vitro* experiments for solvents *PG – M400* at *PG* content of: 1 – 100 mol %; 2 – 88.5 mol %; 3 – 83.7 mol %; 4 – 68.7 mol %; 5 – 47.5 mol %

Table 3

Parameters of *PG* release from binary solvents *PG – M400*

Parameter	*PG* content (% w/w/mol %)				
	15.0/47.5	30.0/68.7	50.0/83.7	60.0/88.5	100
Release rate (*R*), mg/cm²/h$^{-1/2}$	18.43	37.66	81.74	108.23	191.24
Cumulative amount (*A*) (at the time point 6 h), mg/cm²	301.32	601.44	1281.84	1539.12	2680.5
Correlation coefficient *r*	0.95566	0.99677	0.99844	0.99456	0.98413
Coefficient of determination R^2	0.91329	0.99355	0.99688	0.98915	0.96851
Released amount (at the time point 6 h), %	66.96	66.83	85.46	85.51	89.35

The release of *PG* and *M400* depends on their concentration in mixed solvents (Fig. 9, 10), as well as on the structure of the mixed solvent. With an increase in the PG content to approximately 70 mol % (30.0 % w/w), the parameters of *PG* release increase slowly, and parameters of *M400* release slowly decrease (Fig. 9, 10). Meanwhile, the values of release parameters for M400 are greater than for PG.

In the case of a mixture containing 75 mol % PG and 25 mol % M400 (approximately 37 % w/w PG and 63 % w/w M400), when the structure of mixed solvent prevails, the release parameters of PG and M400 are identical (Fig. 9, 10). With a further increase in the *PG* content, the parameters of its release begin to increase sharply, and the parameters of M400 release begin to decrease drastically (Fig. 9, 10).

Table 4

Parameters of M400 release from binary solvents *PG – M400*

Parameter	M400 content (% w/w / mol %)				
	40.0/11.5	50.0/16.3	70.0/31.3	85.0/52.5	100
Release rate (*R*), mg/cm²/h$^{-1/2}$	33.05	45.19	60.54	72.99	100.15
Cumulative amount (*A*) (at the time point 6 h), mg/cm²	425.64	601.62	934.20	1061.76	1333.08
Correlation coefficient *r*	0.96056	0.98450	0.97815	0.98444	0.99590
Coefficient of determination R^2	0.92268	0.96924	0.95678	0.96912	0.99182
Released amount (at the time point 6 h), %	35.47	40.11	44.49	41.64	44.44

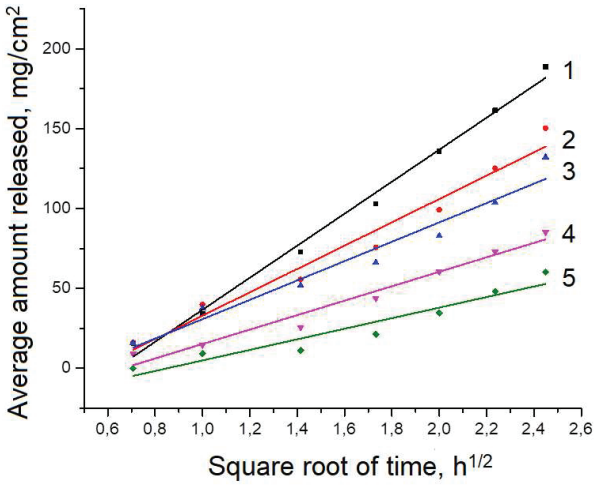

Fig. 8. M400 release rate plots obtained from the *in vitro* experiments for solvents *PG – M400* at M400 content of: 1 – 100 mol %; 2 – 52.5 mol %; 3 – 31.3 mol %; 4 – 16.3 mol %; 5 – 11.5 mol %

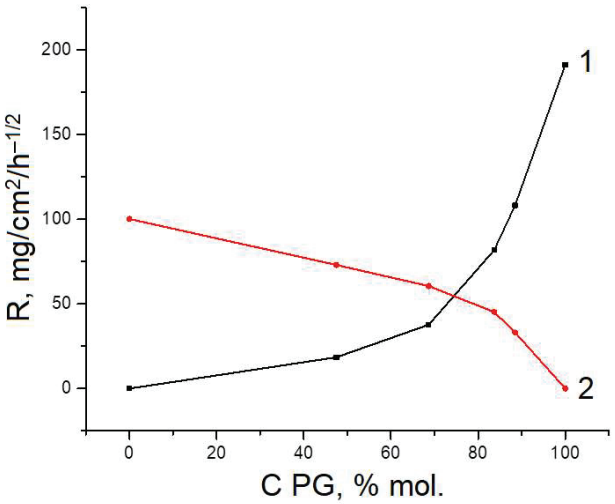

Fig. 9. Release rates of *PG* (1) and M400 (2) *vs PG* concentration

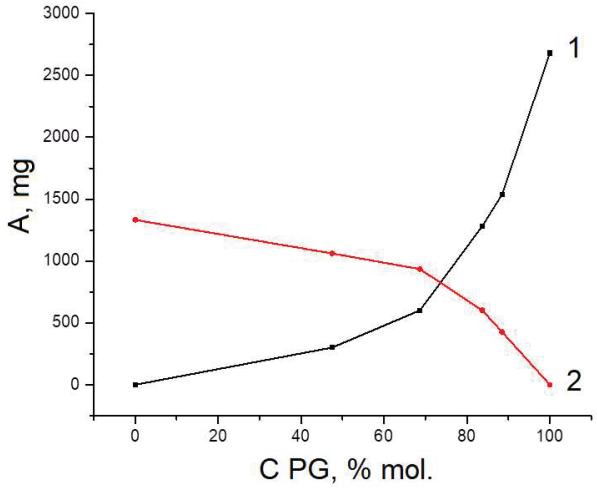

Fig. 10. Cumulative amount of *PG* (1) and M400 (2) *vs PG* concentration

5. Discussion of research results

Based on the results of the study of excess density (Fig. 2) and excess activation parameters of viscous flow (Fig. 6), it can be concluded that with a change in the composition of the binary system *PG – M400*, its structure changes, mainly due to the formation of hydrogen bonds between molecules of *PG* and *M400*. On the one hand, when *M400* is added to *PG*, hydrogen bonds between *PG* molecules are destroyed. This is evidenced by a decrease in $\Delta H_{\eta}^{\neq E}$ and a sharp decrease in $\Delta S_{\eta}^{\neq E}$ with an increase in the *M400* content to approximately 25–30 mol % (Fig. 6). On the other hand, the addition of *PG* to *M400* to approximately 70 mol % *PG* also leads to a change in the structure of *M400*, as evidenced by a gradual decrease in $\Delta H_{\eta}^{\neq E}$ and a more pronounced decrease in $\Delta S_{\eta}^{\neq E}$ (Fig. 6). It can be assumed that the interaction of *M400* molecules with *PG* molecules results in a conformational transformation of the *M400* chain associated with the transition of the helical conformation to the zigzag conformation [44]. These two trends cause minima in the plots of $\Delta H_{\eta}^{\neq E}$ and $\Delta S_{\eta}^{\neq E}$ versus *PG* concentration. At a molar ratio of *PG* and *M400* of approximately 0.7:0.3 (31.3 % w/w *PG* and 68.7 % w/w *M400*), the

mixed structure of the binary solvent *PG – M400* predominates to the greatest extent.

It was of interest to study the effect of the structure of binary solvents on the *in vitro* release of *PG* and *M400*. When each of the solvents was studied separately, the release parameters for *PG* were approximately 2 times higher than the release parameters for *M400* (Tables 3, 4), although the molecular weights of these solvents differ by a factor of 5. It can be assumed that the release of *PG* from a single-component solvent is limited due to the rigid network between *PG* molecules created by hydrogen bonds.

The release parameters of *M400* are higher in the case of the binary solvents in which the structure of *M400* predominates. At the same time, an increase in the concentration of *PG* and, accordingly, a decrease in the concentration of *M400* leads to a slow decrease in the release parameters of *M400* and a gradual increase in the release parameters of *PG* (Fig. 9, 10). At *PG* content of about 75 mol % the release rate and cumulative content for both components become the same.

With a further increase in the *PG* concentration and a decrease in the *M400* content, the structure of *PG* begins to predominate in binary mixtures. At the same time, the release parameters of *PG* increase sharply, and the release parameters of *M400* decrease sharply (Fig. 9, 10). With an increase in the *PG* concentration above 75 mol %, it was found that the greater the difference in the concentrations of *PG* and *M400*, the greater the difference in the release parameters of *PG* and *M400*.

Therefore, the concentration of each component and, as a result, the structure of the binary mixture affect the *in vitro* release of solvents. If the structure of *PG* predominates in the system, then this solvent is released significantly more intensively than *M400*, which is a prerequisite for its rapid penetration into the biological object. As a result, an osmotic equilibrium is created between the biological object and the medicinal product (ointment). This equilibrium should then be maintained by *M400*, which is released more slowly and also penetrates into tissues. Based on the results of the study, it can be assumed, that the introduction of *PG* and *M400* in a certain ratio into the composition of ointment base is a factor that makes it possible to eliminate the non-specificity of the dehydrating effect of ointment bases *in vivo*. At the same time, water-soluble ointment bases can provide absorption of exudate in the absence of dehydrating effects on viable tissues, in particular, on granulation tissue.

Study limitations. The results of studies on the physicochemical properties and structure of mixed *PG – M400* solvents are presented briefly, which is due to the purpose of this work and its applied value.

Prospects for further research. The research results can be used during the development of semi-solid preparations for use in various fields of medicine: surgery, combustiology, proctology, gynaecology, etc. It is promising to conduct similar studies with other solvent systems, in particular, with ternary systems.

6. Conclusions

The structure of the binary system *PG – M400* depends on its composition. Based on the isotherms of excess activation of viscous flow, it is possible to differentiate the areas where the structure of PG or the structure of M400 dominates or the mixed structure of the binary solvent prevails. The *in vitro* release parameters for PG and M400 depend on the structure of the mixed solvents. The greatest difference in the release parameters of PG and M400 is observed in the area where the structure of PG dominates.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this paper.

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The study was performed without financial support.

Data availability

Data will be made available on reasonable request.

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