ISSN 1027-5495. Functional Materials, 31, No.4 (2024), p. 609-618
doi:http://dx.doi.org/10.15407/fm31.04.609

# Polythermal studies of the water – propylene glycol systems by densitometry, viscometry and spin probes method

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*Received August 30, 2024*

Based on the determined values of density, dynamic viscosity and molar volumes, the thermodynamic activation parameters and excess thermodynamic activation parameters of viscous flow at temperatures from 293.15 K (20°C) to 313.15 K (40°C) were calculated for the mixed binary solvents *water – propylene glycol* (PG). Using the isotherms at 298.15 K, assumptions were made about the composition regions of binary solvents with different structural organizations. The structure of the mixed solvent has an impact on the various functional characteristics of the systems *water – PG*, and it could also influence the performance of medicinal products with a liquid dispersion medium. The density and excess density, as well as the dynamic viscosity and excess dynamic viscosity for systems *water – PG* were determined as a function of the PG concentration. Using the method of spin probes, it was demonstrated that changes in the dynamic viscosity of systems *water – PG* correlated with the alterations in the viscosity of the microenvironment of spin probe molecules. The viscosity of the microenvironment was also influenced by the interaction between molecules of dissolved spin probes and solvent molecules.

**Keywords**: water, propylene glycol (PG), density, dynamic viscosity, molar volume, thermodynamic activation parameter of viscous flow, spin probe, rotational correlation time, excess parameter

**Політермічні дослідження систем *вода – пропіленгліколь* методами денситометрії, віскозиметрії та спінових зондів.** *А.М.Ляпунова, А.П.Краснопьорова, О.П.Безугла, О.М.Ляпунов, Г.Д.Юхно, Т.М.Пухова*

За визначеними величинами густини, динамічної в'язкості й молярних об'ємів для розчинників *вода – пропіленгліколь* (PG) розраховані термодинамічні параметри та надлишкові термодинамічні параметри активації в'язкої течії при температурах від 293.15 К (20°С) до 313.15 К (40°С). За їх ізотермами при температурі 298.15 К зроблені припущення про області складів бінарних розчинників з різною структурною організацією, яка впливає на різні функціональні властивості систем *вода – PG* і потенційно може впливати на функціональні властивості лікарських засобів з рідким дисперсійним середовищем. Визначено залежність густини й надлишкової густини, а також динамічної в'язкості та надлишкової динамічної в'язкості для систем *вода – PG* від концентрації PG. Методом спінових зондів показано, що зміна динамічної в'язкості в розчинниках *вода – PG* корелює зі зміною в'язкості мікрооточення молекул спінових зондів. На величину в'язкості їх мікрооточення впливає також характер взаємодії молекул розчинених спінових зондів з молекулами розчинника.

## *1. Introduction*

Binary solvent mixtures *water – propylene glycol* (PG) are widely used in the pharmaceutical formulations due to the multifunctional nature of PG [1]. The selection of the specific composition of this mixed solvent for a given purpose must be supported by a rationale.

The volumetric properties of *water – PG* systems, including density, molar volumes, excess molar volumes [2, 3, 4, 5, 6, 7], dynamic viscosity [2, 5, 6], relative permittivity [5], thermal conductivity [6], surface tension [2], sound speed [6], and refractive indexes [10] have been the subject of extensive study. It has been demonstrated that the surface tension of a mixed solvent declines with an increase in PG content and temperature [2, 12]. The density reaches its maximum value at PG content of 70 % m/m and decreases with increasing temperature. The molar volume is observed to increase with growing PG concentration. The excess molar volume is found to be minimal at a PG concentration of approximately 35.59 % mol (70 % m/m) [3, 4, 6, 8]. The dynamic viscosity of the system increases in line with an increase in PG concentration, and conversely, decreases in line with an increase in temperature [5, 6]. Excessive dynamic viscosity is minimal at PG concentrations of approximately 35-50 % mol [5, 6, 8]. It has been demonstrated that the refractive index increases in conjunction with the PG content [10]. The speed of sound is observed to be at its maximum at PG concentration of about 75 % mol, and the variation of relative permittivity values is maximal at PG concentration of 65 % mol [11].

It should be noted that the density, molar volume, dynamic viscosity, and other characteristics of the binary solvent *water – PG* are not additive values; the excess values suggest the interactions between the components of this mixed solvent, which are predominantly associated with the formation of hydrogen bonds between water and PG [8]. Various aspects of the structure of the binary solvent *water – PG* depending on its composition and temperature have been characterized in the scientific literature. The microstructure variations for this binary solvent depending on PG content were studied by NMR [9]. It has been shown that the mole fraction of PG around 0.3 is critical for the structure of the mixed solvent. When the water structure predominates (mole fraction of PG< 0.15), alkyl protons of PG form weak C-H···O hydrogen bonds with surrounding water molecules, and its hydroxyls form strong O-H···O hydrogen bonds with water. When the PG structure predominates (mole fraction of PG > 0.3), the regions enriched in either hydrocarbons or hydroxyl groups are formed in the solution. This results in the formation of a microheterogeneous solution, where water is expelled into the areas enriched in hydroxyl groups [9].

Raman spectroscopy and stimulated Raman scattering (SRS) were used to investigate the hydrogen bonding network in binary solvents *water – PG* [10]. In the case of Raman spectroscopy, the strength of hydrogen bonds of water is weakened and then strengthened with the increase of PG volume fraction. SRS demonstrated that ice-like structures appeared near the methyl group and hydrogen bonds weakened. As the mole fraction of PG increased, the structure of hydrogen bonds in this binary system underwent a transition from $H_2O$-$H_2O$ to $H_2O$-PG when the mole fraction of PG was 0.4 [10].

The study of physicochemical characteristics and evaluation of the structure of binary mixtures *water – PG* depending on its composition and temperature holds significant scientific and practical value. Interest in this problem has been maintained for decades. A substantial number of studies have been conducted to determine the dynamic viscosity of binary systems *water – PG*; however, these investigations did not include the calculation of the thermodynamic activation parameters of their viscous flow [2, 5, 6]. In one of the publications, it was demonstrated that the maximum excess Gibbs free energy of activation occurred at PG concentration of 35.58 % mol within a temperature range of 30 °C to 45 °C [8]. However, the polythermal determination of dynamic viscosity, along with the calculation of the thermodynamic activation parameters for viscous flow, would permit the estimation of the structure of binary solvent mixtures *water – PG* as well as the identification of concentration regions with specific intermolecular interactions [13].

Over the years, many authors have determined the same physicochemical characteristics (e.g., density, viscosity, molar volumes, surface tension, etc.) of binary solvents *water – PG* and used the data obtained from their studies for various purposes (e.g., to compare experimental and calculated data [2]). Using data from scientific publications to calculate the thermodynamic activation parameters of viscous flow at the stage of pharmaceutical development is not acceptable for some reasons. These reasons include variations in the compositions of binary solutions studied by different authors, differences in the temperatures at which the experiments were conducted, as well as discrepancies in the experimental data obtained, particularly, regarding the values of dynamic viscosity [2, 5]. For instance, the authors of the publication [2] reported that the dynamic viscosity of pure PG at 298.15 K (25 °C) is 39.436 mPa·s, whereas the value provided in the paper [5] is 43.428 mPa·s, resulting in the discrepancy of 9.2 %. At 308.15 K (35 °C), the values of dynamic viscosity mentioned in these publications are 20.267 mPa·s and 24.247 mPa·s, respectively, which represents a discrepancy of 16.4 %. According to paper [2], the surface tension of PG at 25 °C is 41.31 mN·m$^{-1}$. However, as evidenced in article [12], this value is 35.8 mN·m$^{-1}$, representing a discrepancy of 15.4%.

The aim of this study was to examine the excess activation parameters of viscous flow in order to assess the structures of binary solvents *water – PG*.

## 2. Experimental

### Materials

The binary systems containing water for injections (hereinafter water; conductivity 1.0 µS·cm$^{-1}$ at 20 °C) and a non-aqueous solvent propylene glycol – PG (Dow Chemical Company; batch F820NB1PD1) over the whole concentration range were under study (Table 1). The constituents of the binary systems (namely PG and water) met the requirements of the relevant monographs of the European Pharmacopoeia [14]. The water content of PG was preliminarily determined by the semi-micro method using an automatic titrator 870 KF (Metrohm AG; software Firmware 58700025).

Binary solvents were prepared gravimetrically using an analytical balance (AUW 120D, Shimadzu). The water content of the PG, which was determined to be 0.08 % m/m, was taken into account when preparing the mixed solvents.

The Ubbelohde viscometers were used to measure the dynamic viscosity (η) of the solvents. Measurements were carried out at temperatures from 293.15 K to 313.15 K (from 20 °C to 40 °C with 5 °C step). A Julabo F12-ED refrigerating/heating circulator (Julabo Labortechnik GmbH) was used to maintain the necessary temperature with an accuracy of ±0.1°C. The dynamic viscosity (η, mPa·s) was calculated according to the equation:

$$\eta = k \cdot t \cdot \rho \qquad (1)$$

where $k$ is the constant of the viscometer (mm$^{2}$·s$^{-2}$); $t$ is the flow time of the liquid to be examined (s), and ρ is the density of the liquid to be examined (mg·mm$^{-3}$).

The density (ρ) of the binary solvents was measured at the abovementioned temperatures using a densitometer DMA 500 (Anton Paar GmbH; software version V1.003) with an internal Peltier thermostat. The measurements were done at least in triplicates.

Molar volumes ($V_M$) for the binary systems were calculated according to the equation:

$$V_M = (M_1 \cdot X_1 + M_2 \cdot X_2) / \rho \qquad (2)$$

where $M_1$ and $M_2$ are molar masses of water and PG, respectively; $X_1$ and $X_2$ are mole fractions of water and PG, respectively, and $\rho$ is the density of the binary system.

The density and dynamic viscosity values for 100 % PG were obtained by extrapolation, taking into account 0.08 % m/m (0.34 % mol) water content of the PG under study.

Polythermal studies of the dynamic viscosity of binary solvents *water – PG* enabled the calculation of the thermodynamic activation parameters of viscous flow: the Gibbs energy of activation ($\Delta G^{\neq}_{\eta}$), the entropy activation ($\Delta S^{\neq}_{\eta}$) and the enthalpy of activation ($\Delta H^{\neq}_{\eta}$).

The values of Gibbs free energy of activation for viscous flow ($\Delta G^{\neq}_{\eta}$) were calculated from the Eyring equation [15]:

$$\eta = \frac{h \cdot N}{V_M} \exp\left[\frac{\Delta G^{\neq}_{\eta}}{RT}\right] \qquad (3)$$

where $\eta$ is the dynamic viscosity, mPa·s; $h$ is the Plank's constant; $N$ is the Avogadro constant; $V_M$ – is the molar volume, l/mol; $R$ is the universal gas constant, and $T$ is the temperature, K.

The values of $\Delta S^{\neq}_{\eta}$ were estimated by differentiating the free energy of activation for viscous flow with respect to the temperature, and the values of $\Delta H^{\neq}_{\eta}$ were obtained by the fundamental thermodynamic relationship:

$$\Delta G^{\neq}_{\eta} = \Delta H^{\neq}_{\eta} - T\Delta S^{\neq}_{\eta} \qquad (4)$$

The EPR spectrometry was used for the study [16]. The spin probes employed were TEMPO ($C_9H_{18}NO$; $M_r$ 156.25; CAS number [2564-83-2]) and TEMPOL (4-hydroxy-TEMPO) ($C_9H_{18}NO_2$; $M_r$ 172.24; CAS number [2226-96-2]).

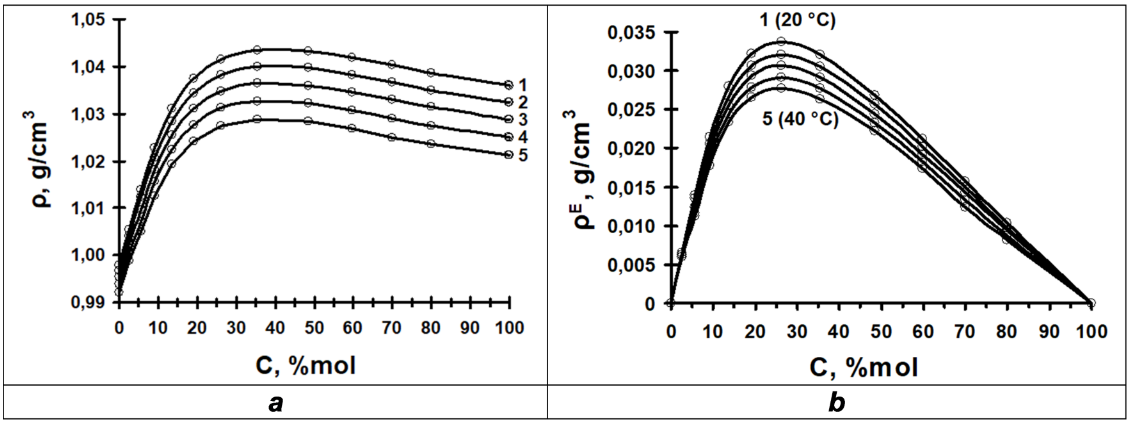


Fig. 1. Density (ρ) (***a***) and excessive density ($\rho^E$) (***b***) for *water – PG* mixtures as a function of PG concentration (C) at: 1 – 20°C, 2 – 25°C, 3 – 30°C, 4 – 35°C, 5 – 40°C

In contrast to the TEMPOL probe, the TEMPO probe molecule is devoid of a hydroxyl group. This can result in different interactions of these probes with water and PG.

The spin probes were added to the binary systems at the concentration of $10^{-4}$ mol/l. The EPR spectra were recorded using the «ESR Spectrometer CMS8400» («Adani»; software EPRCMD) at 25 ºC and 35 ºC. Using the EPR spectra obtained the rotational correlation times of the spin probes ($\tau_{-1}$) were calculated by equation [16]:

$$\tau_{-1} = \left( \sqrt{\frac{h_0}{h_{-1}}} - 1 \right) \cdot \Delta H_0 \,/\, 3{,}6 \cdot 10^9 \qquad (5)$$

where $h_0$ and $h_{-1}$ are the peak-to-peak heights at the central and high-field components of the EPR spectrum; and $\Delta H_0$ is the linewidth of the central component (Gs).

The excess values (deviations of the experimental values from the additive values – $\nu^E$) were calculated using the formula:

$$\nu^E = \nu - (\nu_1 \cdot X_1 + \nu_2 \cdot X_2) \qquad (6)$$

where $\nu$ is the experimentally determined value for a binary solvent; $\nu_1$ and $\nu_2$ are the experimentally determined values for water and PG, respectively; $X_1$ and $X_2$ are the mole fractions of water and PG, respectively.

For the binary systems *water – PG*, as well as for the same systems containing 1.0 % m/m of the nonionic surfactant macrogol 20 cetostearyl ester (Kolliphor® CS 20, BASF), the surface tension was determined by the bubble pressure method at 25 °C. These measurements were performed to demonstrate the effect of the structure of the mixed binary solvent on the functional properties of the surfactant.

## *3. Results and discussion*

The experimental data on density, dynamic viscosity, and molar volumes for the binary systems *water – PG*, essential for calculating the Gibbs free energy of activation for viscous flow ($\Delta G^{\neq}_{\eta}$) by Eyring's equation [15] are presented in Table 1. The density of the binary systems was observed to increase with rising PG concentration up to 35.47 % mol (69.89 % m/m) and a gradual decline in density was noted with further rising PG concentration (Fig. 1***a***). The values of the excess density were positive, exhibiting a maximum at a PG concentration of 35.47 % mol (Fig. 1***b***). As the temperature increased, the values of density and excess density decreased, reaching a maximum at the same PG concentration (Fig. 1).

The dynamic viscosity of water and PG differed significantly at varying temperatures: at 20°C – by a factor of 57, while at 40°C – by a factor of 28.4 (Table 1). The experimental results demonstrated that the dynamic viscosity of binary systems increased with higher PG concentrations and decreased with rising temperature (Fig. 2***a***). The dynamic viscosity isotherms were nonlinear at temperatures ranging from 20 ºC to 40 ºC (Fig. 2***a***), which is characteristic for systems that do not follow Raoult's law. The values of excess dynamic viscosity were negative and reached a minimum at a PG content of 48.52 % mol (69.89 % m/m) (Fig. 2***b***). With increasing temperature, the excess dynamic viscosity decreased, but the extreme deviation from the additive value persisted at a PG concentration of 48.52 % mol (Fig. 2). Based on data from scientific publications, it is not feasible to accurately establish the PG concentration at which the minimum value of excess dynamic viscosity is observed [5, 6, 8].

Table 1. Density (ρ), dynamic viscosity (η) and molar volume (Vm) of water, PG and *water – PG* mixtures at various PG concentrations (C) and different temperatures (T/t)

| T, K | t, °C | C, % m/m | C, % mol | $\rho$, g·cm$^{-3}$ | η, mPa·s | Vm, cm$^3$·mol$^{-1}$ |
|---|---|---|---|---|---|---|
| 293.15 | 20.0 | 0 | 0 | 0.9979 | 1.026 | 18.06 |
| | | 9.98 | 2.56 | 1.0054 | 1.425 | 19.40 |
| | | 19.98 | 5.58 | 1.0140 | 2.047 | 20.97 |
| | | 29.96 | 9.20 | 1.0228 | 3.045 | 22.84 |
| | | 39.95 | 13.61 | 1.0311 | 4.366 | 25.14 |
| | | 49.92 | 19.10 | 1.0374 | 6.356 | 28.06 |
| | | 59.93 | 26.15 | 1.0416 | 9.256 | 31.88 |
| | | 69.89 | 35.47 | 1.0435 | 13.531 | 37.01 |
| | | 79.92 | 48.52 | 1.0432 | 20.541 | 44.29 |
| | | 86.24 | 59.74 | 1.0419 | 27.599 | 50.60 |
| | | 90.79 | 70.01 | 1.0403 | 35.063 | 56.41 |
| | | 94.41 | 79.98 | 1.0387 | 42.526 | 62.07 |
| | | 99.92 | 99.66 | 1.0361 | 58.254 | 73.26 |
| | | 100.00 | 100.00 | 1.0360 | 58.526 | 73.46 |
| 298.15 | 25.0 | 0 | 0 | 0.9968 | 0.918 | 18.08 |
| | | 9.98 | 2.56 | 1.0040 | 1.252 | 19.43 |
| | | 19.98 | 5.58 | 1.0123 | 1.760 | 21.00 |
| | | 29.96 | 9.20 | 1.0206 | 2.586 | 22.89 |
| | | 39.95 | 13.61 | 1.0283 | 3.666 | 25.21 |
| | | 49.92 | 19.10 | 1.0343 | 5.193 | 28.15 |
| | | 59.93 | 26.15 | 1.0382 | 7.393 | 31.99 |
| | | 69.89 | 35.47 | 1.0400 | 10.702 | 37.14 |
| | | 79.92 | 48.52 | 1.0397 | 15.911 | 44.44 |
| | | 86.24 | 59.74 | 1.0382 | 21.253 | 50.78 |
| | | 90.79 | 70.01 | 1.0367 | 26.758 | 56.60 |
| | | 94.41 | 79.98 | 1.0350 | 32.317 | 62.29 |
| | | 99.92 | 99.66 | 1.0325 | 43.422 | 73.52 |
| | | 100.00 | 100.00 | 1.0324 | 43.614 | 73.71 |
| 303.15 | 30.0 | 0 | 0 | 0.9954 | 0.830 | 18.10 |
| | | 9.98 | 2.56 | 1.0025 | 1.117 | 19.46 |
| | | 19.98 | 5.58 | 1.0097 | 1.538 | 21.06 |
| | | 29.96 | 9.20 | 1.0182 | 2.146 | 22.94 |
| | | 39.95 | 13.61 | 1.0255 | 3.085 | 25.28 |
| | | 49.92 | 19.10 | 1.0311 | 4.291 | 28.23 |
| | | 59.93 | 26.15 | 1.0348 | 6.045 | 32.09 |
| | | 69.89 | 35.47 | 1.0364 | 8.577 | 37.27 |
| | | 79.92 | 48.52 | 1.0360 | 12.394 | 44.59 |
| | | 86.24 | 59.74 | 1.0345 | 16.261 | 50.96 |
| | | 90.79 | 70.01 | 1.0330 | 20.466 | 56.80 |
| | | 94.41 | 79.98 | 1.0315 | 24.667 | 62.51 |
| | | 99.92 | 99.66 | 1.0288 | 32.914 | 73.78 |
| | | 100.00 | 100.00 | 1.0287 | 33.056 | 73.98 |
| 308.15 | 35.0 | 0 | 0 | 0.9939 | 0.755 | 18.13 |
| | | 9.98 | 2.56 | 1.0007 | 1.001 | 19.49 |
| | | 19.98 | 5.58 | 1.0072 | 1.353 | 21.11 |
| | | 29.96 | 9.20 | 1.0156 | 1.862 | 23.00 |
| | | 39.95 | 13.61 | 1.0225 | 2.663 | 25.35 |
| | | 49.92 | 19.10 | 1.0277 | 3.615 | 28.33 |
| | | 59.93 | 26.15 | 1.0312 | 5.020 | 32.20 |
| | | 69.89 | 35.47 | 1.0326 | 7.045 | 37.40 |
| | | 79.92 | 48.52 | 1.0322 | 10.099 | 44.76 |
| | | 86.24 | 59.74 | 1.0308 | 13.171 | 51.14 |
| | | 90.79 | 70.01 | 1.0290 | 16.104 | 57.03 |
| | | 94.41 | 79.98 | 1.0275 | 19.204 | 62.75 |
| | | 99.92 | 99.66 | 1.0251 | 25.224 | 74.05 |
| | | 100.00 | 100.00 | 1.0250 | 25.328 | 74.24 |
| 313.15 | 40.0 | 0 | 0 | 0.9921 | 0.691 | 18.16 |
| | | 9.98 | 2.56 | 0.9988 | 0.904 | 19.53 |
| | | 19.98 | 5.58 | 1.0050 | 1.203 | 21.16 |
| | | 29.96 | 9.20 | 1.0125 | 1.624 | 23.07 |
| | | 39.95 | 13.61 | 1.0194 | 2.319 | 25.43 |
| | | 49.92 | 19.10 | 1.0242 | 3.112 | 28.42 |
| | | 59.93 | 26.15 | 1.0274 | 4.300 | 32.32 |
| | | 69.89 | 35.47 | 1.0287 | 5.856 | 37.55 |
| | | 79.92 | 48.52 | 1.0284 | 8.269 | 44.92 |
| | | 86.24 | 59.74 | 1.0269 | 10.631 | 51.33 |
| | | 90.79 | 70.01 | 1.0249 | 12.902 | 57.25 |
| | | 94.41 | 79.98 | 1.0235 | 15.183 | 62.99 |
| | | 99.92 | 99.66 | 1.0213 | 19.553 | 74.32 |
| | | 100.00 | 100.00 | 1.0212 | 19.628 | 74.52 |

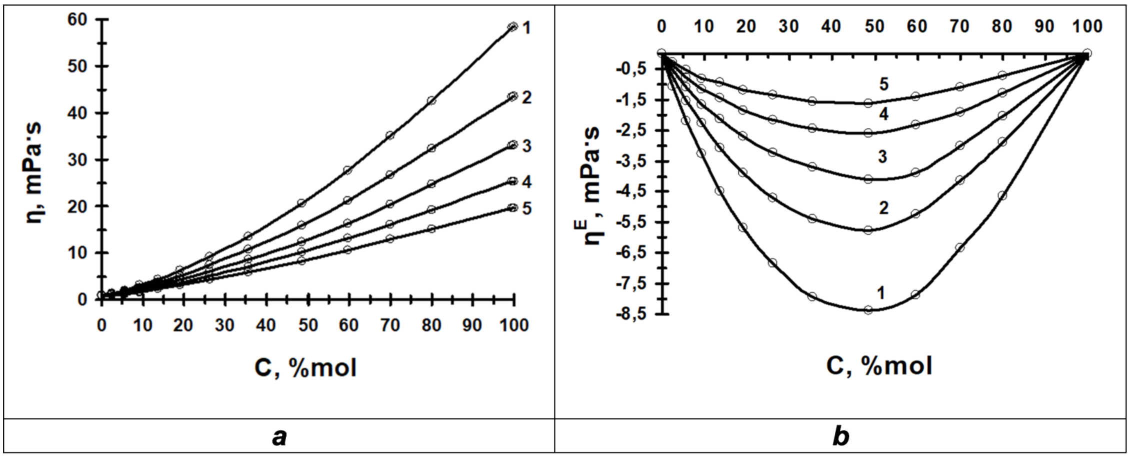


Fig. 2. Dynamic viscosity (η) (***a***) and excess dynamic viscosity ($\eta^E$) (***b***) for *water – PG* mixtures as a function of PG concentration (C) at: 1 – 20°C, 2 – 25°C, 3 – 30°C, 4 – 35°C, 5 – 40°C

The molar volumes of water and PG differed by approximately 4.1 times. In binary systems *water – PG*, the molar volume increased with an increase in the PG concentration (Table 1). As evidenced by the literature, the excess molar volume is negative and exhibits a minimum at PG concentration of ~35.59 % mol (70 % m/m) at temperatures from 20°C to 45°C [3, 8].

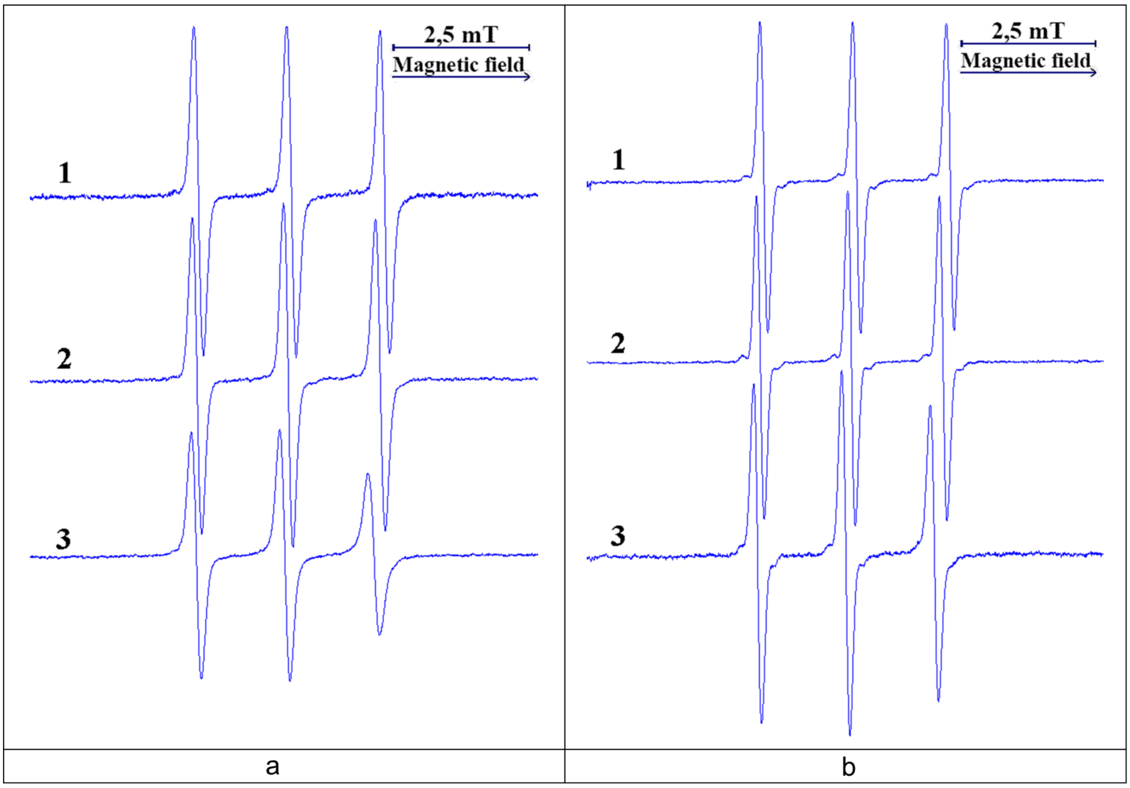
A review of the relevant literature can support the validity of our experimental findings. A comparison of the values for density, dynamic viscosity, and molar volume of binary mixtures is challenging due to the discrepancy in the PG concentrations under consideration. Therefore, it is reasonable to compare data for 100 % PG at specific temperatures. At 25°C (298.15 K), the value of PG density obtained by our research team was 1.0324 $g\cdot cm^{-3}$ (Table 1); this value differs by 0.00001 $g\cdot cm^{-3}$ from the value of 1.03241 $g\cdot cm^{-3}$ reported by K. Nakaniashi et al. [4], by 0.0004 $g\cdot cm^{-3}$ from the value of 1.0328 $g\cdot cm^{-3}$ reported by J. Jimeneze et al. [3], and by 0.0001 $g\cdot cm^{-3}$ from the value of 1.0323 $g\cdot cm^{-3}$ obtained by I.S. Khattab et al. [2]. At 25°C, the value of the dynamic viscosity of PG obtained by our research team was 43.614 mPa·s (Table 1), differing by 0.43% from the value of 43.428 mPa·s determined by J. George and N.V. Sastry [5]. At the same temperature, the molar volume of PG obtained in this study was 73.71 $cm^3\cdot mol^{-1}$ (Table 1), differing by 0.04 $cm^3\cdot mol^{-1}$ (0.05 %) from the value of 73.67 $cm^3\cdot mol^{-1}$ reported in [3] and is consistent with the molar volume presented in paper [2]. These comparisons demonstrate the accuracy of the results obtained by our research team and their suitability for further calculations of $\Delta G^{\neq}_{\eta}$.

According to the Stokes-Einstein equation, the rotational correlation time of the spin probe ($\tau_{-1}$) is directly proportional to the radius of the molecule (R) and the viscosity of its local surrounding (η) and inversely proportional to the absolute temperature (T) [16]:

$$\tau = \left(4\cdot\pi\cdot R^3\cdot\eta\right)/\,3\cdot \mathrm{k}\cdot \mathrm{T} \qquad (7)$$

It was of interest to establish a correlation between the change in dynamic viscosity in the binary systems *water – PG* and the viscosity of the local microenvironment around molecules of other dissolved substances. For this purpose, two spin probes – TEMPOL and TEMPO – were used. Both probes are soluble in water, PG, and mixed solvents *water – PG*. However, they differ in their chemical composition: the molecule of the TEMPOL probe contains a hydroxyl group, while the molecule of the TEMPO probe does not. It can be assumed that this difference will have an impact on the interactions of the probes with water and PG molecules.

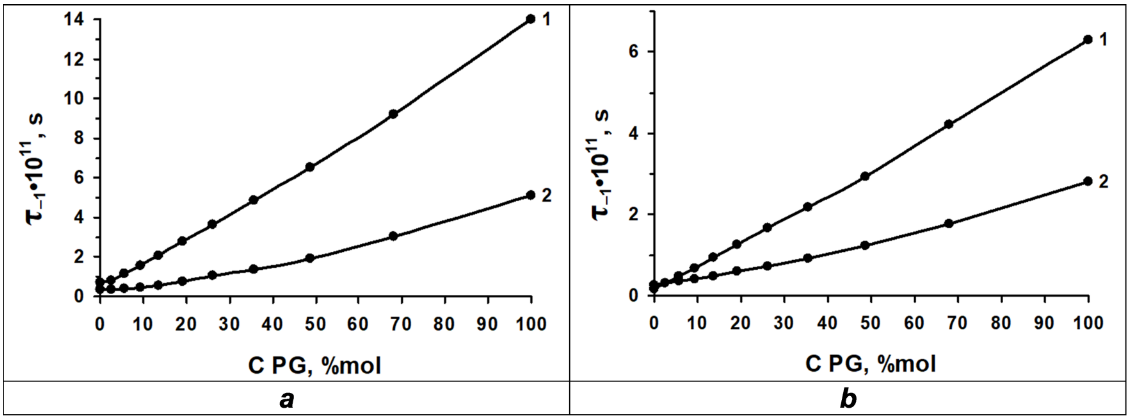
The EPR spectra of the abovementioned probes in water, in mixed solvents *water – PG*, and in PG were all triplet, regardless of the concentration of PG (Fig. 3). The EPR spectra of both probes in water indicated that probes exhibited rapid isotropic rotation. The rotational correlation times ($\tau_{-1}$) at 25°C were $0.33\cdot10^{-11}$ s for the TEMPO probe and $0.70\cdot10^{-11}$ s for the TEMPOL probe. As the concentration of PG increased, the intensity of the high-field component of the spectra decreased in relation to the intensity of the central component; and the $\tau_{-1}$ increased at both 25°C and 35°C (Fig. 4). At 25°C in propylene glycol (PG), the rotational correlation time ($\tau_{-1}$)



a

b

Fig. 3. Representative EPR spectra of spin probes TEMPOL (***a***) and TEMPO (***b***) in water (1), *water – PG* mixture (1:1) (2) and PG (3) at 25°C



***a***

***b***

Fig. 4. Rotational correlation time ($\tau_{-1}$) of spin probes TEMPOL (1) and TEMPO (2) in water – PG systems as a function of PG concentration at 25°C (a) and 35°C (b)

for the TEMPO probe was $5.1 \cdot 10^{-11}$ s, while for the TEMPOL probe it was $14.0 \cdot 10^{-11}$ s. This indicates that the $\tau_{-1}$ value for the TEMPO probe was 15.5 times higher in PG compared to water, while for the TEMPOL probe, it was 20 times higher. In PG at 25°C, the $\tau_{-1}$ value for the TEMPOL probe was found to be 2.75 times higher than that for the TEMPO probe, which lacks a hydroxyl group in its molecule.

The excess rotational correlation times for the TEMPOL and TEMPO spin probes in binary systems *water – PG* were found to be negative, with extremes observed at a PG concentration of 48.64 % mol (Fig. 5), which corresponded to the PG concentration in the case of negative extremes for the dynamic viscosity (Fig. 2***b***). As the temperature increased from 25°C to 35°C, the rotational correlation times for both probes decreased (Fig. 4). Conversely, the excess rotational correlation times increased (Fig. 5), indicating a weakening of the interaction between the molecules of the spin probes and the solvents.

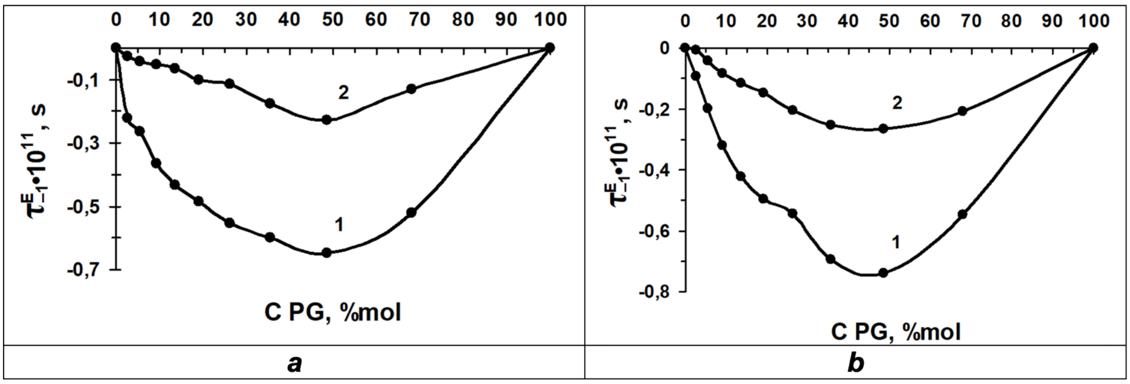


Fig. 5. Excess rotational correlation time of spin probes TEMPOL (*a*) and TEMPO (*b*) in *water – PG* systems as a function of PG concentration at 25°C (1) and 35°C (2)

According to the results of the study by the spin probes method, it can be concluded that changes in the dynamic viscosity in mixed solvents *water – PG* correlate with changes in the viscosity of the microenvironment surrounding the molecules of the substances dissolved in these solvents. The viscosity of the microenvironment is influenced by the nature of the interaction between the molecules of the dissolved substance and the solvent molecules. This is probably evidenced by the difference in the values of the correlation rotational times for the spin probes TEMPO and TEMPOL; the presence of a hydroxyl group in the TEMPOL molecule allows it to form strong hydrogen bonds, which probably contributes to these differences.

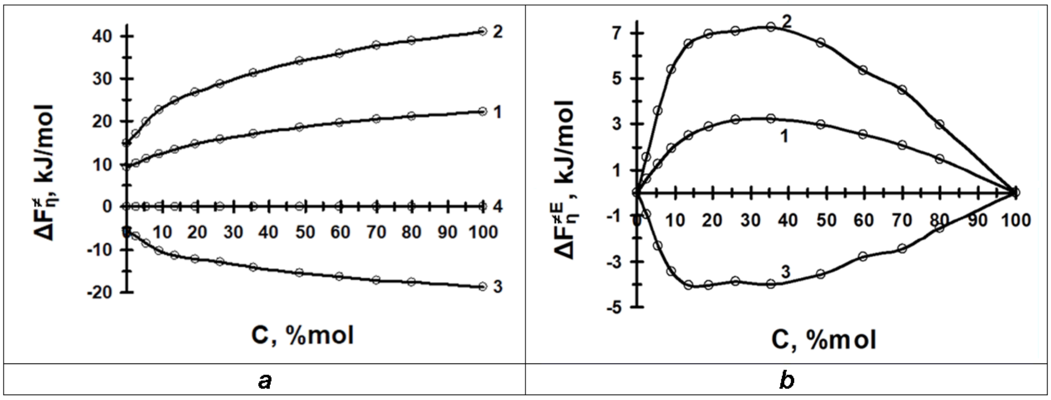
The Gibbs energy of activation for viscous flow ($\Delta G_\eta^{\neq}$) was found to be positive for the binary solvents *water – PG* across the entire range of the compositions (Fig. 6***a***). The values of enthalpy ($\Delta H_\eta^{\neq}$) and entropy ($\Delta S_\eta^{\neq}$) of activation for viscous flow were also positive. The entropy values ($\Delta S_\eta^{\neq}$) were very small, indicating that the process of viscous flow for the systems *water – PG* as well as the interaction between the components were primarily attributed to the enthalpy term ($\Delta H_\eta^{\neq}$) (Fig. 6***a***). Thus, at 25°C, the $\Delta H_\eta^{\neq}$ value was 31.35 kJ/mol, while the $\Delta S_\eta^{\neq}$ value was about 0.05 kJ/mol, which is 627 times less. For clarity, Fig. 6***a*** illustrates the plot of ($-T\Delta S_\eta^{\neq}$) as a function of PG concentration.

Two regions, characterized by differing slope angles, can be discerned in the plots of the thermodynamic activation parameters of viscous flow ($\Delta F_\eta^{\neq}$) *versus* the composition of the binary system (Fig. 6***a***). An increase in the non-aqueous solvent PG content to 13.61 % mol resulted in a more pronounced alteration of the thermodynamic parameters than was observed with a further increase in PG concentration.

The thermodynamic activation parameters of viscous flow are mole-additive [13]. This made it possible to calculate their excess values, i.e., deviations from additive values for the studied solvent system *water – PG (*Fig. 6***b***). The excess Gibbs energies of activation for viscous flow were found to be positive, exhibiting a maximum on the isotherm at the PG content of 35.47 % mol (equivalent to 69.89 % m/m). Additionally, extremes as plateaus can cab be observed on the isotherms of $\Delta H_\eta^{\neq E}$ and $-T\Delta S_\eta^{\neq E}$ within the range of PG concentrations from 13.61 % mol to 35.47 % mol (equivalent to approximately 40-70 % m/m) (Fig. 6***b***).

An evaluation of the change in the excess thermodynamic parameters of viscous flow activation suggests that when the PG content reaches 13.61 % mol (~40 % m/m), the water structure is destroyed due to the influence of PG. However, it can be assumed that the water structure prevails at least up to a PG concentration of 9.20 % mol (~30 % m/m) inclusive. Conversely, the addition of water to PG results in the destruction of the non-aqueous solvent structure when the PG content is reduced to 35.47 % mol (~70 % m/m). In the range of PG concentrations from 13.61 % mol (~40 % m/m) to 35.47 % mol (~70 % m/m), it is probable that mixed structures are present. A further increase in PG concentration results in the predominance and stabilization of the non-aqueous solvent structure.

It should be noted that the maximum excess density of the binary systems *water – PG* was observed at a PG concentration of 26.15 % mol (~60 % m/m); this concentration was close to PG content at which $\Delta G_\eta^{\neq E}$ was maximal.



*a* *b*

Fig. 6. Thermodynamic parameters of viscous flow (1 – $\Delta G^{\neq}_{\eta}$, 2 – $\Delta H^{\neq}_{\eta}$, 3 – $-T\Delta S^{\neq}_{\eta}$, 4 – $\Delta S^{\neq}_{\eta}$) (a) and excess quasi-thermodynamic parameters of viscous flow (1 – $\Delta G^{\neq E}_{\eta}$, 2 – $\Delta H^{\neq E}_{\eta}$, 3 – $-T\Delta S^{\neq}_{\eta}$) (b) for water – PG systems as a function of PG concentration (C) at 25°C (298.15 K)

The extremes of excess dynamic viscosity and excess rotational correlation time for TEMPOL and TEMPO spin probes were noted at a PG concentration of 48.52 % mol (~80 % m/m); at this concentration, a transition from mixed structures to the predominance of the non-aqueous solvent structure occurred. The excess molar volumes reached the minimum at a PG concentration of approximately 35.59 % mol (70 % m/m) [3, 4, 6, 8]; this concentration coincided with the PG content when $\Delta G^{\neq E}_{\eta}$ was maximal, and marked the transition from a mixed structure to a nonaqueous solvent structure occurred.

It can be assumed that the structure of mixed solvents *water – PG* has an impact on their functional properties. The following examples illustrate this point. As demonstrated in the referenced paper [17], the solubility of the hydrophobic substance betamethasone 17-valerate exhibited a slight increase with an increase in the PG concentration up to 30 % m/m (9.21 % mol), i.e. in the PG concentration range where the water structure predominates (Fig. 6***b***). A significant enhancement in the solubility of betamethasone 17-valerate was observed at PG content exceeding 40 % m/m (13.64 % mol), when the transition to mixed structures for binary solvents *water – PG* occurs (Fig. 6***b***). It was demonstrated by *in vitro* experiments using human skin that PG enhanced the penetration of both betamethasone 17-valerate and hydrocortisone 17-butyrate. The penetration mechanisms were different at PG concentrations of up to 40 % m/m (up to 13.64 % mol) and at 80 % m/m (48.65 % mol), when the PG structure predominated in the mixed solvent.

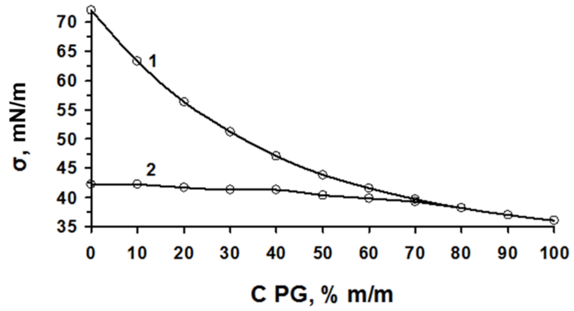


Fig. 7. Surface tension for *water – PG* systems (1) and for *water – PG* systems containing 1.0 % m/m macrogol 20 cetostearyl ether (2) as a function of PG concentration at 25°C

According to the results of the study, the surface tension of mixed solvents *water – PG* decreased as the PG content increased, reaching a value of 36.1 mN·m$^{-1}$ (Fig. 7). This result is very close to the literature value of 35.8 mN·m$^{-1}$ [12], showing only a 0.84 % difference.

The surface tension of 1 % macrogol 20 cetostearyl ether solutions in the mixed solvent *water – PG* was dependent on the presence of the surfactant provided that the PG concentration did not exceed 70 % m/m (35.59 % mol). This concentration was determined to be the point at which the transition to a non-aqueous solvent structure occurred (Fig. 6***b***). As the PG content was increased beyond this point, the surface tension of the system was conditioned by this non-aqueous solvent (Fig. 7).

As evidenced in the literature [18], the efficacy of antimicrobial preservation of binary solvent system *water – PG* was inadequate at a PG concentration of 25 % m/m (7.32 % mol), particularly against the *Aspergillus niger*. The inadequate efficacy of PG as an antimicrobial preservative can likely be attributed to the predominance of the water structure in the solution at a PG concentration of 7.32 % mol (Fig. 6***b***).

At a PG concentration of 40 % m/m (13.64 % mol), which corresponds to mixed structures *water – PG*, solutions of poloxamer 338 lost their ability to undergo thermally induced sol ↔ gel transitions – when heated from 25°C to 37°C, they remained Newtonian liquids [19].

## 4. Conclusions

Based on the determined values of density, dynamic viscosity and molar volumes, the thermodynamic activation parameters and excess thermodynamic activation parameters of viscous flow at temperatures from 293.15 K (20°C) to 313.15 K (40°C) were calculated for the mixed binary solvents *water – PG*. Using the isotherms at 298.15 K, assumptions were made about the composition regions of binary solvents with different structural organizations. The structure of the mixed solvent has an impact on the various functional characteristics of the systems *water – PG*. It is conceivable that it could also influence the performance of medicinal products with a liquid dispersion medium. Characteristics that may be impacted include, in particular, the solubility of active substances, their release from the dosage form and their bioavailability; the efficacy of antimicrobial preservatives in medicinal products; the surface-active properties of surfactant solutions and the physical stability of dispersed systems with a liquid dispersion medium; the ability of poloxamer solutions to undergo thermally induced sol ↔ gel transitions, etc.

The density and excess density, as well as the dynamic viscosity and excess dynamic viscosity for systems *water – PG* were determined as a function of the PG concentration. Using the method of spin probes, it was demonstrated that changes in the dynamic viscosity of systems *water – PG* correlated with the alterations in the viscosity of the microenvironment of spin probe molecules. The viscosity of the microenvironment was also influenced by the interaction between molecules of dissolved spin probes and solvent molecules.

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