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STUDY OF THE EFFECT OF PROPYLENE GLYCOL ON THE PROPERTIES OF POLOXAMER 338 SOLUTIONS

Oleksii Liapunov, Olena Bezugla, Nikolay Lyapunov, Oleksii Lysokobylka

The aim. *Study of the characteristics of 20 % solutions of poloxamer 338 (P338) in water and mixed solvents water – propylene glycol (PG) at various temperatures using rotational viscometry and the spin probe method.*
Materials and methods. *20 % m/m solutions of P338 in water and water – PG mixtures were the objects of research. The solutions were studied by rotational viscometry at 25 °C, 32 °C i 37 °C; the flow behaviour, low-yield stress (τ_0), hysteresis area (S_N) and dynamic or apparent viscosity (η) were determined. Spin probes based on fatty acids, which differ in molecular structure, solubility, and radical localisation, were added to the solutions. Electron paramagnetic resonance (EPR) spectra was obtained to determine their type and parameters.*
Results. *Depending on the content, PG affects the rheological properties of 20 % P338 solution. The ability of this solution to undergo thermally induced sol-gel transitions, resulting in the formation of gels with plastic flow behaviour at temperatures of 32 °C and 37 °C, is maintained at PG content of up to 20 %. At 37 °C and a 30 % PG content, an atypical thixotropic gel is formed. The rheological characteristics of gels containing 10–20 % PG at 32 °C and 37 °C are higher than those of gels without PG. The increase in the PG concentration from 0 to 40 % generally has little effect on the rotational correlation times (τ) and values of the order parameter (S) of the spin probes. In the case of the ammonium salt of 5-doxylstearic acid (5-DSA NH_4 salt), the anisotropic EPR spectra at a PG concentration of 40 % undergoes a transformation, becoming a triplet. This coincides with the loss of the ability of 20 % P338 solutions to thermally induced sol↔gel transitions. An increase in the concentration of PG (in contrast to ethanol) does not lead to the solvation of P338 micelle cores by the dispersion medium. The transformation of the EPR spectrum of the 5-DSA NH4 salt into a triplet is probably the result of the interaction between PG and the hydrophilic shell of micelles through the formation of hydrogen bonds.*
Conclusions. *The rheological properties of 20 % P338 solution are affected by the PG, depending on its content. The P338 solutions can undergo a thermally induced sol↔gel transition, provided that the PG content does not exceed 30 %. A correlation has been identified between alterations in the rheological properties of 20 % P338 solution and the corresponding change in the types of EPR spectra observed for the 5-DSA NH_4 salt, namely a transition from anisotropic spectra to triplet. As the PG content in the P338 solution increases up to 40 %, the solvation of micelle cores by the dispersion medium does not occur. It may be posited that the alteration in the structure of P338 micelles is a consequence of the interaction between PG and their hydrophilic shell*
Keywords: *poloxamer 338 (P338), propylene glycol (PG), solution, gel, viscosity, micelle, spin probe, EPR spectrum, spectrum parameters*

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1. Introduction

The poloxamers are block copolymers of ethylene oxide (PEO) and propylene oxide (PPO); the poloxamers are chemically similar in composition, differing only in the average molecular mass (M_r) and in the relative amounts of PPO and PEO [1, 2]. Poloxamers are nonionic surfactants [3] that form spherical micelles in aqueous solutions when the concentration exceeds the critical micelle concentration (CMC) and at the critical micelle temperature (CMT) [4].

The thermodynamics of micelle formation in poloxamer solutions was elucidated by R. Alexandridis et al. With the formation of micelles, the entropy of the system increases due to the destruction of the ice-like structure of water that occurs during the hydrophobic hydration of the PPO chains [5]. An increase in poloxamer content results in an increase in the volume fraction of micelles. Upon reaching the critical micelle volume fraction ($c \geq 0.53$), lyotropic liquid crystals are formed in aqueous solution, predominantly exhibiting cubic packing of spherical micelles, which induce the sol-to-gel transition [6, 7]. An increase in temperature promotes the transition of sol to gel, and vice versa. This indicates that such transitions in poloxamer solutions are thermally reversible [3, 6].

Based on the parameters of the EPR spectra of fatty acid-based spin probes it was demonstrated that with increasing temperature, the packing density of the PPO chains in the non-polar part of the poloxamer associates decreases. Conversely, a reduction in temperature results in an increase in the packing density of the PPO chains within the micelle cores. This results in an in-

crease or decrease in the volume fraction of micelles, which may be one of the mechanisms underlying thermally induced sol↔gel transitions [8].

Thermoresponsive polymers that undergo sol→gel transitions within the physiological temperature range have been widely used to develop prolonged-release drugs with different routes of administration, including intravaginal [9], transdermal [10], intra-articular [11], ophthalmic [12], and others, for use in the various fields of medicine.

During the development of medicinal products, in addition to poloxamers, the formulations should include other excipients serving various functions, such as co-solvents of active substances, penetration enhancers, etc.

The interactions of poloxamer 407 with various solvents and surfactants have been investigated by phase behavior studies and small-angle X-ray scattering (SAXS) [13]. The authors posit that organic solvents, depending on their polarity, are localised in different domains of P407 micelles. Some solvents (e.g. ethanol) may be located at the interface between the PEO-rich and the PPO-rich domains [13]. SAXS was employed to establish the structure of the liquid crystals obtained and to determine their characteristic length scales in ternary isothermal (25 °C) systems consisting of poloxamer 407, water, and one of the following solvents: ethanol, propylene glycol, glycerol, polyethylene glycol 400. It was demonstrated that the type of non-aqueous solvent has an impact on the stability of liquid crystalline phases in the studied systems [14].

It was demonstrated that ethanol when added to the 20 % solution of poloxamer 338 (P338) results in changes to the rheological properties of this solution. The ability of P338 to undergo a thermally induced sol→gel transition remains unaltered if the ethanol content does not exceed 5–10 % m/m. The rheological properties of the 20 % P338 solution exhibit a correlation with the observed change in EPR spectrum types for the 5-DSA NH_4 salt. As the ethanol content in the solution increases, the solvation of P338 micelle cores by the dispersion medium increases, accompanied by a decrease in the density and orderliness of the PPO chains packing in the micelle cores [15].

The molecular structure and characteristics of propylene glycol (PG) differ from those of ethanol [1, 2]. It was therefore of interest to investigate whether the ability of a 20 % P338 solution to undergo thermally induced sol↔gel transitions is dependent on the PG concentration.

Propylene glycol ((*RS*)-propane-1,2-diol ($C_3H_8O_2$); M_r 76.1; CAS [57-55-6]) is a clear, colorless, viscous, practically odorless liquid, miscible with water end ethanol (96 %) [1, 2]. PG is a polar substance; the hydrophilic-lipophilic balance (HLB) of PG, as determined by the Davis method, is 9.38, which is lower than that of glycerol and higher than that of ethanol and hexylene glycol [16]. The presence of two hydroxyl groups and a hydrophobic methyl group in its molecule enables PG to exhibit surface-active properties when dissolved in water [17]. The surface tension of PG and its mixtures with water is higher than the surface tension of ethanol and its aqueous solutions [17, 18].

There are numerous data on various characteristics of *water – propylyne glycol* mixtures (in different temperature intervals) in the scientific literature including values of density [17, 19, 20], dynamic viscosity [17, 20], molar volumes [17], refractive indices [20], sound speed [20], relative permittivity [21], thermal conductivity [22], etc. The dependence of density, viscosity, and molar volumes on the composition of the mixed solvent *water – propylene glycol* is not additive, which indicates the interaction between components of the mixture. The excess molar volumes are minimal at a PG concentration of about 30–40 % mol [22], excess viscosity is minimal at PG concentration of about 50 % mol [21], excess relative permittivity is maximal at about 60–65 % mol [21], and excess density is maximal at about 30 % mol [17]. This is a consequence of a change in the structure of the mixed solvent, which is dependent on its composition.

The NMR method was used to study the change in the microstructure of a mixed solvent *water – propylene glycol* depending on its composition [23]. It was shown that PG molar fraction of about 0.3 is a critical point for the structure of the mixed solvent. In the region, where water prevails, water molecules are in the vicinity of PG, forming weak C–H···O H-bonds with PG alkyl protons and strong O–H···O H-bonds with PG hydroxyls. As the concentration of PG increases, PG molecules gradually aggregate in the order of CH_3, CH and CH_2. In the PG-prevailing region, the solution forms regions enriched in either hydrocarbons or hydroxyl groups, which results in the formation of microheterogeneous solution, where water is expelled from alkyl tails and accumulated in the region of PG hydroxyl's heads [23].

Raman spectroscopy and stimulated Raman scattering (SRS) were used to investigate the hydrogen bonding (HB) network in binary solutions *water – propylene glycol* [24]. Abnormal changes in hydrogen bonds were detected when the volume fraction of PG was 0.4. The strength of hydrogen bonds in water is weakened and then strengthened with the increase in PG volume fraction. The formation of ice-like structures in proximity to the methyl group and the weakening of hydrogen bonds were demonstrated by SRS. The structure of the hydrogen bond network in this binary system underwent a transition from H_2O-H_2O to H_2O-PG when the volume fraction of PG was 0.4 as PG increased [24].

Due to its functional characteristics, PG can be used as a humectant in concentrations reaching 15 % in topical formulations [1], as an antimicrobial preservative in liquid and soft medicinal products (15–30 %) [1, 25], as a solvent or co-solvent of active pharmaceutical substances and excipients in solutions for oral and parenteral use, as well as in topical preparations [1]. Additionally, it can serve as a penetration enhancer [26], cryoprotectant [23, 27], and a component of hydrophilic

ointment bases [28]. Due to its numerous functions and low toxicity, PG is a widely used excipient in the pharmacy [27].

Numerous scientific studies have been dedicated to the solubility of various active pharmaceutical substances in mixtures of water and PG [29], in particular: clotrimazole [29], atenolol [30], daidzein [31], sodium phenytoin [32], mesalazine [33], sodium sulfonamides [34], sulfadiazine, sulfamerazine and sulfamethazine [35], nicotinamide [36], paracetamol [37], sildenafil citrate [38], etc.

Consequently, in solutions/gels containing poloxamers, PG can be used as a co-solvent of active substances, antimicrobial preservative, rheological property modifier, penetration enhancer [39], etc. As previously demonstrated, it is rational to use both rotational viscometry and spin probe methods in the study of poloxamer solutions [8, 15]. It seems reasonable to use these methods to study the impact of PG on the rheological properties of poloxamer solutions (in particular, on the sol↔gel transitions) and the microstructure of poloxamer associates.

The aim. The objective of this work is to study the characteristics of 20 *%* solutions of poloxamer 338 (P338) in water and mixed solvents *water – propylene glycol* at different temperatures using rotational viscometry and the spin probe method.

2. Planning (methodology) of the research

The study is designed to use P338; this substance is solid and freely soluble in water [1, 2]. The research objects were 20 % P338 solutions with various PG concentrations from 0 to 50 % m/m. In other words, these were systems whose dispersion of medium structure, dependent on the PG content, changed toward the destruction of the water structure [24].

When 20 % aqueous solution of P338 is heated from 25 °C (the upper limit of the storage temperature for medicinal products) to 32 °C (the temperature at which dermatological preparations are applied) or 37 °C (the temperature of application of vaginal and rectal preparations), sol→gel transitions occur [8]. The objective of this study is to investigate the impact of PG on these sol→gel transitions.

One of the tasks was to study the rheological properties of 20 % P338 solutions using rotational viscometry to determine the effect of PG content and temperature. It was necessary to distinguish between the conditions under which P338 solutions behave as Newtonian liquids and those under which they form gels.

To detect changes in the supramolecular structures formed by P338 in its 20 % solutions, where the dispersion medium is water or mixed solvents *water – propylene glycol* (with various PG contents), the spin probe method was proposed [40–42]. The task was to evaluate changes in the rheological properties of solutions along with changes in the types and parameters of the electron paramagnetic resonance (EPR) spectra of spin probes.

It was of interest to establish the relationship between changes in the types and parameters of EPR spectra, as well as rheological properties and sol→gel transitions in P338 solutions depending on the PG content and temperature. Four spin probes were proposed for the study. Two of these probes were used to obtain information about P338 micelles at the interface between their polar and nonpolar parts. The other two probes were intended to assess the state of the hydrophobic core at different levels.

The results of these comprehensive studies could ascertain the potential for using PG in certain concentrations in 20 % P338 solutions, considering the effect of this solvent on thermally induced sol-gel transitions and the rheological properties of the solutions being researched. In addition, the study aimed to identify the correlation between changes in the rheological characteristics of P338 solutions and modifications in the microstructure of P338 associates, depending on the PG concentrations. The findings of these studies were intended to be evaluated in comparison with those pertaining to the influence of ethanol on the characteristics of 20 % P338 solutions [15].

3. Materials and methods

The following materials were used in the experiments: P338 (Kolliphor® P 338) and propylene glycol (Kollisolv® PG) from BASF, and purified water (hereafter referred to as water) [1]. The water content of the propylene glycol was preliminarily determined by the semi-micro method using Metrohm 870 KF Titrino plus automatic titrator. The water content of propylene glycol was found to be 0.08 %.

The solutions of P338 were the subjects of the study (Table 1).

Table 1

Composition of the solutions under study

Constituent	Concentration (% *m/m*) in solution:					
	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6
P338	20	20	20	20	20	20
Propylene glycol (PG)	0	10	20	30	40	50
Water	80	70	60	50	40	30

P338 was dissolved in water at a temperature of approximately 12 °C, PG was added, and the solutions were stirred and degassed. P338 solutions were tested at temperatures of 25 °C, 32 °C and 37 °C.

Rheological properties were studied by rotational viscometry (2.2.10) [1]. Rheograms, which are plots of the shear stress (τ_r) versus the shear rate (D_r)) were obtained using a rotating viscometer «Rheolab QC» with coaxial cylinders CC-27 (for gels) and DG-42 (for liquids) («Anton Paar GmbH»; software RHEOPLUS, 2.66 version). Rheograms were used to characterize the flow behaviour and to determine the dynamic viscosity (η) of Newtonian liquids or the apparent viscosity (η) of gels as well as the low-yield stress (τ_0) of gels and the hysteresis area (S_N), where applicable [1].

The viscosity (η) was calculated using the following equation:

$$\eta=\tau_r/D_r. \quad (1)$$

Electron paramagnetic resonance (EPR) spectroscopy was used for the research [38–40]. The following spin probes were used:

– probe 1: 4-Palmitamido-2,2,6,6-tetramethylpiperidine-1-oxyl (M_r 409.67; CAS [22977-65-7]);

– probe 2: 1-Piperidinyloxy,4-(hexadecyldimethylammonio)-2,2,6,6-tetramethyl-, iodide (M_r 551.65; CAS [114199-16-5]);

– probe 3: 5-DOXYL Stearic acid, ammonium salt (M_r 401.61; CAS: [2315262-05-4]) (5-DSA, NH_4 salt);

– probe 4: 16-DOXYL Stearic acid (M_r 384.57; CAS [53034-38-1]) (16-DSA).

Probe 1 and probe 4 simulated lipophilic surfactants. Probe 2 and probe 3 simulated cationic and anionic surfactants respectively. During the solubilisation of the probe molecules by P338 micelles, the free radicals of probe 1 and probe 2 are localised in the hydrophilic part and their alkyl chains are localised in the hydrophobic core. The doxyl radicals of probes 3 and 4 are located, respectively, near the 5th and 16th carbon atoms of the alkyl chains localised in the hydrophobic core of the micelles.

The spin probes were added to the studied solutions at the concentration of 10^{-4} mol/l. The EPR spectra were recorded using the «ESR Spectrometer CMS8400» («Adani»; software EPRCMD). The type of EPR spectra (triplet, anisotropic spectrum, superposition spectrum etc.), the peak heights, and the linewidth at the low-field (ΔH_{+1}) and central (ΔH_0) components were determined. The rotational correlation times of the spin probes (τ_{+1}, τ_{-1}, $\tau_{\pm1}$) and the anisotropy parameter (ε) in the case of the triplet spectra were calculated using the equations [41, 42]:

$$\tau_{+1}=\left(\sqrt{\frac{h_0}{h_{+1}}}-1\right)\cdot\Delta H_0/2\cdot10^8; \quad (2)$$

$$\tau_{-1}=\left(\sqrt{\frac{h_0}{h_{-1}}}-1\right)\cdot\Delta H_0/3.6\cdot10^9; \quad (3)$$

$$\tau_{\pm1}=\left(\sqrt{\frac{h_{+1}}{h_{-1}}}-1\right)\cdot\Delta H_{+1}\cdot6.65\cdot10^{-10}; \quad (4)$$

$$\varepsilon=\frac{\sqrt{h_0/h_{+1}}-1}{\sqrt{h_0/h_{-1}}-1}, \quad (5)$$

where h_{+1}, h_0 and h_{-1} are the peak-to-peak heights at the low-field, central and high-field components of EPR spectrum; ΔH_{+1} and ΔH_0 are the linewidth at low-field and central components, respectively.

The rotational correlation time of the spin probe (τ) is directly proportional to the effective radius of the molecule (R) and the microviscosity of its local surrounding (η) and inversely proportional to the absolute temperature (T) [40, 41]:

$$\tau=\left(4\cdot\pi\cdot R^3\cdot\eta\right)/3\cdot k\cdot T. \quad (6)$$

The A_N constant, which characterises the polarity of the radical's environment, in the case of triplet spectra was determined as the distance (in mT) between the central and high-field components [42]. In the case of the EPR spectra for probe 3 and probe 4, the A_N constant and the order parameter (S) were calculated after determination the hyperfine splitting constants $A_{\|}$ and $A_{\perp}$ according to the equations [40]:

$$A_N=\left(A_{\|}+2A_{\perp}\right)/3; \quad (7)$$

$$S=\frac{A_{\|}-A_{\perp}}{A_{\|}+2A_{\perp}}*1.66. \quad (8)$$

The parameter (ν), which characterizes the semi-amplitude of the molecular motion, was determined by the order parameter (S) using the calibration graph [40].

A circulating thermostat Julabo F12-ED («Julabo Labortechnik GmbH») was used to maintain the necessary temperature.

4. Research results

4. 1. Study of the effect of propylene glycol on the rheological properties of P338 solutions

At 25 °C, 20 % P338 solutions behave as Newtonian fluid, irrespective of the PG content (Fig. 1). The dynamic viscosity of the solutions depends on the PG content, with the highest value observed at PG concentration of 20 % (Table 2).

At 32 °C, 20 % P338 solutions without PG and with PG content of 10 % and 20 % transform into gels with a plastic flow, high values of the low-yield stress and apparent viscosity. Upon increasing the temperature to 37 °C, the rheological parameters of these gels demonstrate an increase (Fig. 1, Table 2). The rheological parameters of gels containing 20 % PG are nearly 50 % higher at 32 °C and approximately 30 % higher at 37 °C than those observed for gels with only water as the dispersion medium (Table 2).

At PG content of 30 % and temperature of 37 °C, an atypical gel is formed; this gel is characterized by high value of low-yield stress, pseudoplastic flow and large hysteresis area (S_N=10819 Pa·s^{-1}), which indicates its thixotropic properties (Fig. 1, *d*). At PG contents of 40 % and 50 % in the 20 % P338 solutions, and temperatures from 32 °C to 37 °C, the formation of gels is not observed. Instead, the solutions exhibit Newtonian behaviour (Fig. 1). It should be noted that with an increase in temperature at PG content up to 30 %, the viscosity of P338 solutions increases, however, at PG contents of 40 % and 50 %, the dynamic viscosity of solutions decreases (Table 2).

It has been shown that 20 % P338 solutions containing PG can undergo a thermally induced sol↔gel transition, provided that the PG content is not more than 30 %.

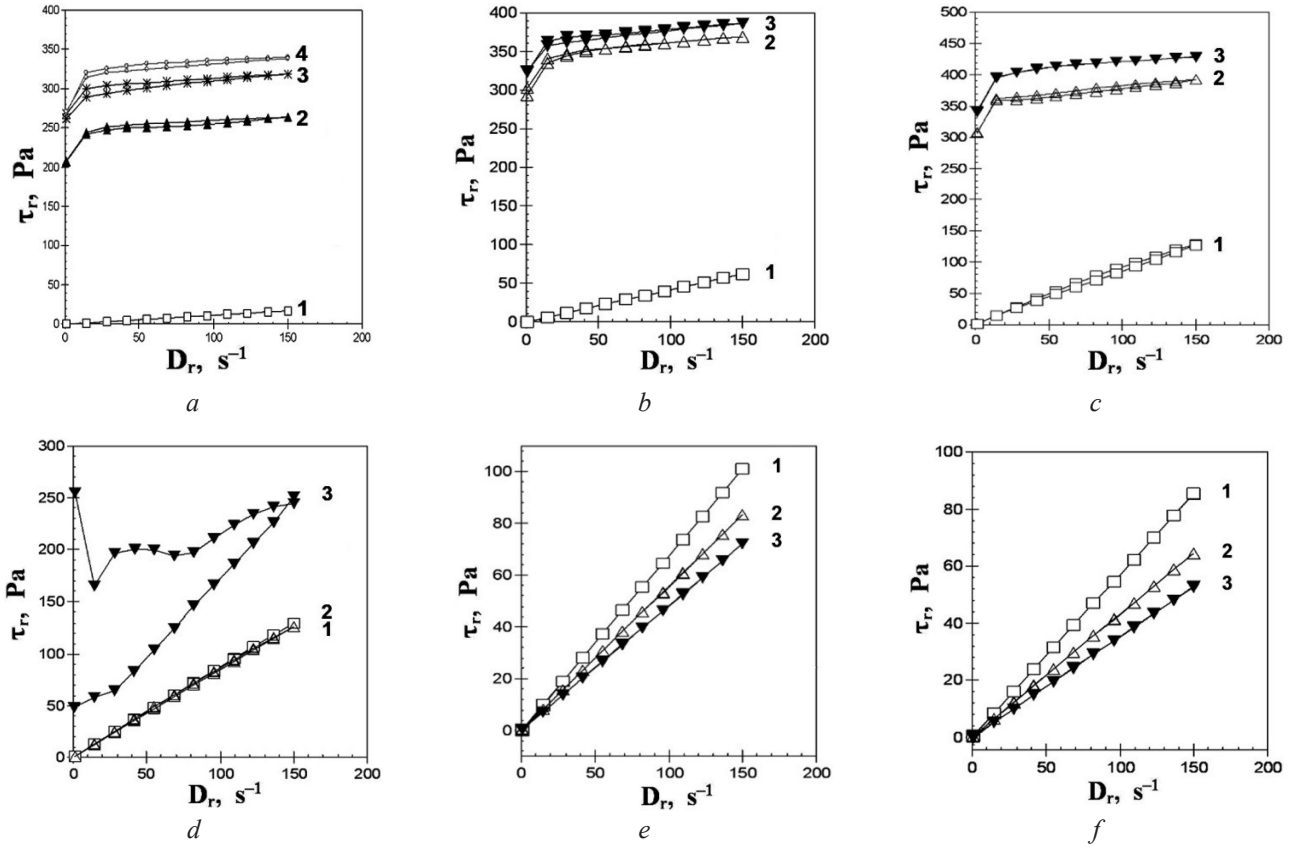

Fig. 1. Rheograms of 20 % P338 solution with various propylene glycol contents: *a* – 0 %; *b* – 10 %; *c* – 20 %; *d* – 30 %; *e* – 40 %; *f* – 50 %, at: 1 – 25 °C; 2 – 32 °C; 3 – 37 °C

Table 2

Rheological parameters of 20 % P338 solutions with various PG contents (*C*) at different temperatures (*t*)

C, % *m/m*	*t*, °C	τ_0, Pa	η, (Pa·s) at D_r:		
			14.6 s^{-1}	41.6 s^{-1}	82.3 s^{-1}
0 %	25	~0	0.11*		
	32	207.1	16.60**	6.00**	3.09**
	37	267.3	20.60**	7.35**	3.78**
10 %	25	~0	0.41*		
	32	301.7	23.40**	8.45**	4.35**
	37	323.3	24.91**	8.89**	4.56**
20 %	25	~0	0.99*		
	32	307.2	24.86**	8.80**	4.60**
	37	341.8	27.21**	9.81**	5.08**
30 %	25	~0	0.88*		
	32	~0	0.89*		
	37	254.5	11.36**	4.80**	2.40**
40 %	25	~0	0.67*		
	32	~0	0.56*		
	37	~0	0.48*		
50 %	25	~0	0.57*		
	32	~0	0.43*		
	37	~0	0.35*		

*Note: * – dynamic viscosity; ** – apparent viscosity.*

4. 2. Study of 20 % P338 solutions with various contents of propylene glycol using the spin probe method

The EPR spectra of the lipophilic spin probe 1 in P338 solutions are typical triplets; the low-field components of these spectra are more intense than the central components (Fig. 2). This indicates the rapid rotation of the molecules of probe 1 around the long axis, which makes it impossible to calculate the value of τ_{+1} using equation (2). The values of the anisotropy parameter (ε) calculated by equation (5) are negative (Table 3).

Upon increasing the PG content from 0 to 40 % and the temperature from 25 °C to 37 °C, the EPR spectra of probe 1 were triplets (Fig. 2).

The molecules of lipophilic probe 1 are solubilized by P338 micelles, as evidenced by the EPR spectra, which are triplets; in water, the EPR spectra of probe 1 are singlets [43]. Upon solubilization, the alkyl chains of probe 1 molecules are localized in the lipophilic core of P338 micelles, and nitroxyl radicals are in the hydrophilic part formed by hydrated polyethylene oxide (PEO) chains (near the interface between PEO and PPO), as evidenced by the values of the A_N constant above 1.6 mT (Table 3). At PG contents of up to 40 %, the A_N values range from 1.61 to 1.65 mT (Table 3). At 32 °C and 37 °C, the PG content has practically no effect on the values of the A_N constant of the EPR spectra of probe 1 and, consequently, on the polarity of the environment of its nitroxyl radical. At 25 °C, a slight tendency for the values of the A_N constant to increase from 1.62 mT to 1.65 mT is observed with an increase in the PG content of up to 40 % (Table 3).

The influence of PG content and temperature between 25 °C and 37 °C on the anisotropy parameter ε of the EPR spectra of probe 1 is minimal (Table 3).

The rotational correlation times (τ_{-1}, $\tau_{\pm1}$) of probe 1 in P338 micelles are within the range of fast rotations [41, 42]. However, at 25 °C and regardless of the PG content, the values of τ_{-1} and $\tau_{\pm1}$ of probe 1 in P338 solutions are like the values of τ_{-1} and $\tau_{\pm1}$ of probe 1 in white soft paraffin (Table 3) [8]. At 37 °C, the values of τ_{-1} and $\tau_{\pm1}$ of probe 1 in P338 solutions are comparable to the values of τ_{-1} and $\tau_{\pm1}$ of probe 1 in liquid paraffin at 25 °C (Table 3) [8]. This suggests that an increase in temperature by 12 °C results in the melting of the micelles' cores at the interface between their polar part and lipophilic core.

With an increase in the PG content from 0 to 40 %, there is a tendency to increase the values of $\tau_{\pm1}$; the PG content has a lesser effect on the τ_{-1} (Table 3). Therefore, an increase in the PG content contributes to an increase in the $\tau_{\pm1}$ values of probe 1, in contrast to ethanol, which, with rising concentration, contributes to their decrease [15].

The EPR spectra of probe 2 in P338 solutions are triplets (Fig. 3). As the PG content is increased from 0 to 40 % and the temperature is elevated from 25 °C to 37 °C, the EPR spectra of probe 2 remain triplets (Fig. 3), in which the central component is more intense than the low-field component (Fig. 3). This makes it possible to calculate the value of τ_{+1} using equation (2). In this instance, the values of the anisotropy parameter (ε) calculated by equation (5) are positive (Table 4).

At PG content of up to 40 %, the values of A_N are in the range from 1.62 mT to 1.64 mT (Table 4). The values of A_N in the case of the EPR spectra of probe 2 practically do not depend on the PG content and temperature from 25 °C to 37 °C; i.e., these factors do not significantly influence the polarity of the nitroxyl radical environment of probe 2.

The rotational correlation times (τ_{+1}, τ_{-1}, $\tau_{\pm1}$) of probe 2 indicate its rapid rotation; their values decrease with increasing temperature from 25 °C to 37 °C (Table 4). An increase in the PG content to 40 % has a negligible effect on the values of τ_{-1} and $\tau_{\pm1}$, whereas there is a tendency for the value of τ_{+1} to decrease. Thus, the values of τ_{+1} are observed to be lower at PG content of 40 % compared to the values of τ_{+1} in the case of 20 % aqueous solution of P338 by 40.3 % at 25°C, by 47 % at 32 °C, and by 44.1 % at 37 °C (Table 4). Therefore, PG at concentrations of 30–40 % (equivalent to PG concentrations of 37.5 % and 50.0 % in the mixed solvent *PG – water*) exerts a certain influence on the structure of P338 micelles at the interface between their polar and non-polar domains.

In the molecule of spin probe 3, the doxyl radical is located approximately at the level of the 5th carbon atom of the alkyl chain. In 20 % aqueous solution of P338, the EPR spectra of this probe are anisotropic at 25 °C, 32 °C, and 37 °C (Fig. 4).

The anisotropic EPR spectra of probe 3 indicate a high level of organization in the microenvironment of doxyl radicals. At temperatures of 25 °C, 32 °C and 37 °C The EPR spectra of probe 3 are anisotropic when the concentration of PG in 20 % P338 solution is not more than 20 % (Fig. 5). At 25 °C and 32 °C, the EPR spectra of probe 3 in 20 % P338 solution containing 30 % PG remain anisotropic (Fig. 4, *a, b*, EPR spectra 4). However, at 37 °C, the EPR spectra of probe 3 in this solution exhibit a resemblance to a superposition of two spectra. At PG content of 40 %, the EPR spectra of probe 3 in 20 % P338 solution are triplet (Fig. 4).

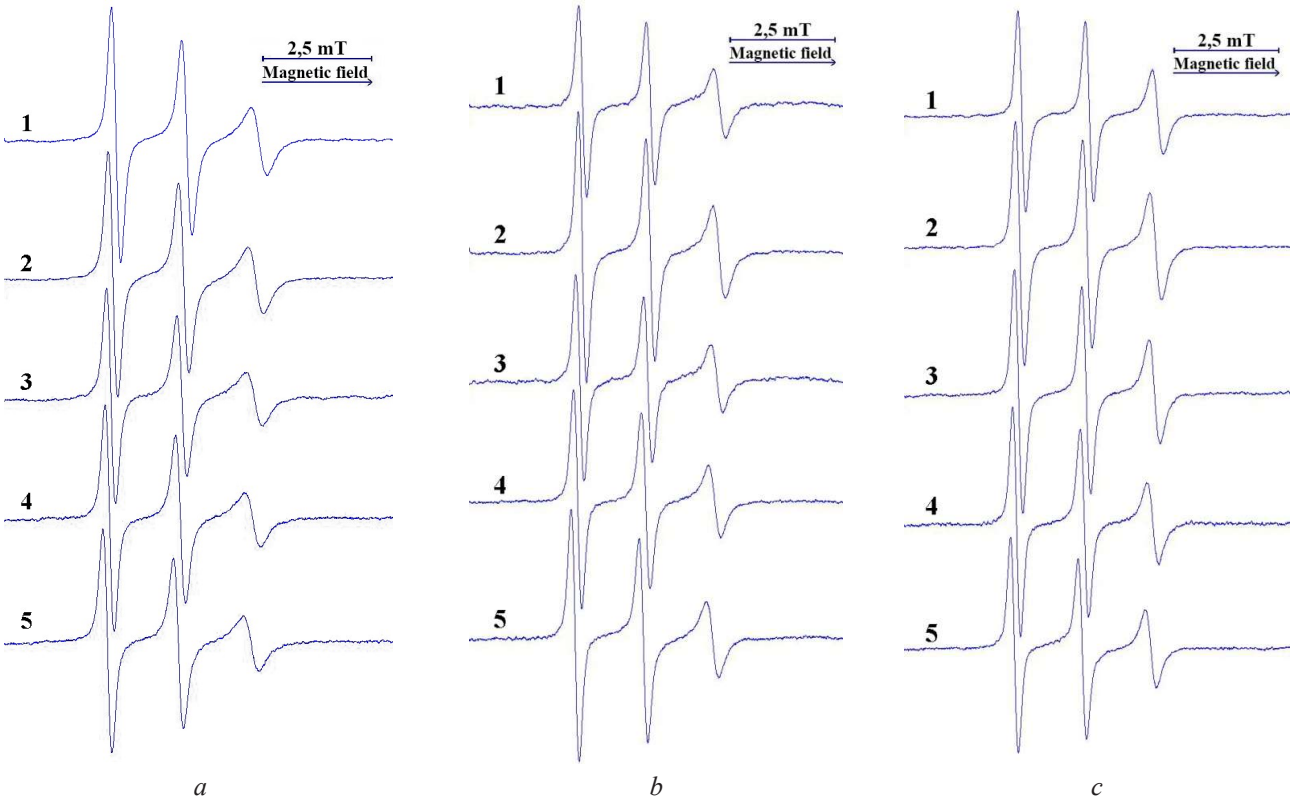

Fig. 2. EPR spectra of probe 1 in 20 % P338 solution with various PG contents: 1 – 0 %; 2 – 10 %; 3 – 20 %; 4 – 30 %; 5 – 40 %, at: *a* – 25 °C; *b* – 32 °C; *c* – 37 °C

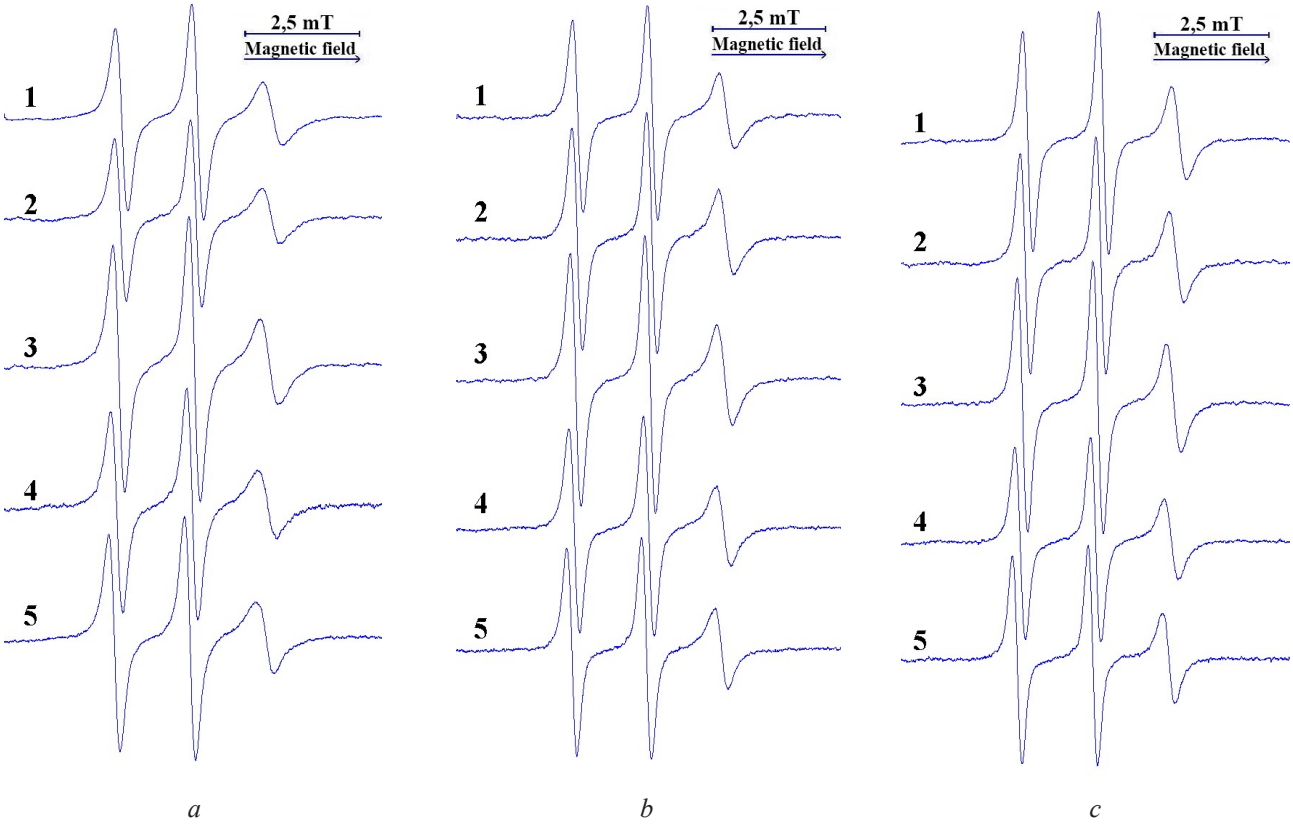

Fig. 3. EPR spectra of probe 2 in 20 % P338 solution with various PG contents: 1 – 0 %; 2 – 10 %; 3 – 20 %; 4 – 30 %; 5 – 40 %, at: *a* – 25 °C; *b* – 32 °C; *c* – 37 °C

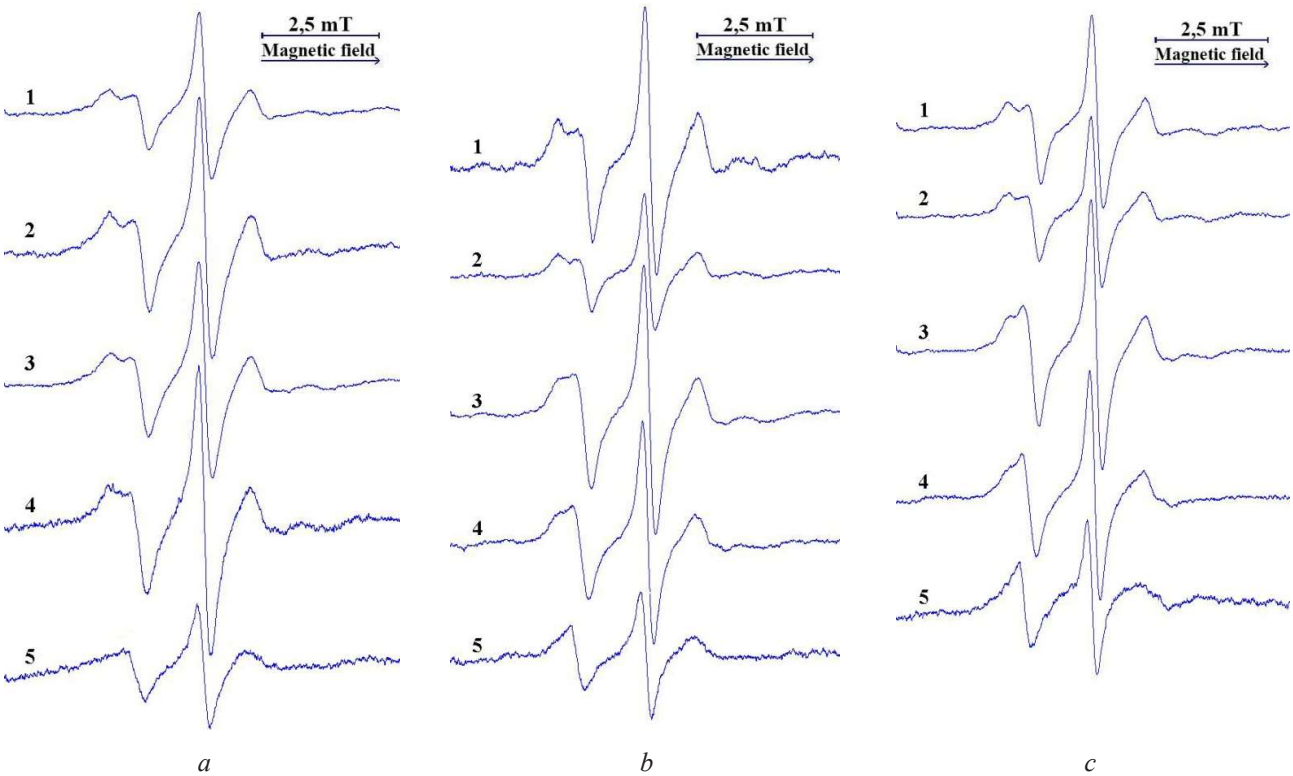

Fig. 4. EPR spectra of probe 3 in 20 % P338 solution with various PG contents: 1 – 0 %; 2 – 10 %; 3 – 20 %; 4 – 30 %; 5 – 40 %, at: *a* – 25 °C; *b* – 32 °C; *c* – 37 °C

An increase in the PG content in 20 % of P338 solutions has a negligible effect on the order parameter (*S*), whereas at PG concentrations of 20–30 %, there is a tendency for its decrease and, consequently, an increase in the

semi-amplitude of molecular motion (parameter ν). Additionally, a decrease in the order parameter S is observed with a temperature increase from 25 °C to 37 °C (Table 5).

Table 3

Parameters of EPR spectra of spin probe 1 in 20 % P338 solutions with various PG contents (*C*) at different temperatures (*t*)

C, % *m/m*	*t*, °C	A_N, mT	τ_{-1}, ns	$\tau_{\pm1}$, ns	ε	Spectrum type
0	25	1.62	0.48	1.42	–0.18	triplet
10	25	1.62	0.46	1,43	–0.18	triplet
20	25	1.64	0.46	1,44	–0.19	triplet
30	25	1.64	0.49	1,61	–0.18	triplet
40	25	1.65	0.50	1.59	–0.17	triplet
0	32	1.61	0.32	0.92	–0.15	triplet
10	32	1.62	0.33	1.00	–0.17	triplet
20	32	1.62	0.32	1.01	–0.19	triplet
30	32	1.62	0.34	1.06	–0.19	triplet
40	32	1.62	0.36	1.27	–0.16	triplet
0	37	1.62	0.27	0.67	–0.12	triplet
10	37	1.62	0.26	0.80	–0.20	triplet
20	37	1.61	0.27	0.83	–0.18	triplet
30	37	1.62	0.29	0.90	–0.19	triplet
40	37	1.62	0.32	0.93	–0.16	triplet

Table 4

Parameters of EPR spectra of spin probe 2 in 20 % P338 solutions with various PG contents (*C*) at different temperatures (*t*)

C, % *m/m*	*t*, °C	A_N, mT	τ_{+1}, ns	τ_{-1}, ns	$\tau_{\pm1}$, ns	ε	Spectrum type
0	25	1.62	1.29	0.68	1.37	0.10	triplet
10	25	1.63	1.10	0.59	1.39	0.09	triplet
20	25	1.63	0.98	0.61	1.38	0.09	triplet
30	25	1.62	0.80	0.54	1.11	0.08	triplet
40	25	1.64	0.77	0.63	1.32	0.07	triplet
0	32	1.62	0.66	0.45	0.97	0.08	triplet
10	32	1.62	0.57	0.42	0.93	0.08	triplet
20	32	1.62	0.47	0.43	0.93	0.06	triplet
30	32	1.63	0.46	0.46	1.00	0.06	triplet
40	32	1.63	0.35	0.43	1.05	0.05	triplet
0	37	1.62	0.59	0.40	0.86	0,08	triplet
10	37	1.62	0.44	0.38	0.88	0,06	triplet
20	37	1.63	0.44	0.41	0.84	0,06	triplet
30	37	1.62	0.34	0.32	0.86	0.06	triplet
40	37	1.62	0.33	0.38	0.86	0.05	triplet

The tendency for the A_N constant of the EPR spectra of probe 3 to increase with rising PG content and temperature (from 25 °C to 37 °C) is practically absent. This is probably due to the lack of solvation by the dispersion medium of the lipophilic core of P338 micelles at the level of the 5th carbon atom of the alkyl chain of probe 3, because of the influence of PG and temperature increase (Table 5).

The EPR spectra of the lipophilic spin probe 4 (16-DSA) in P338 solutions are triplets; the low-field and high-field components of these spectra are less intense than the central component (Fig. 5). As the PG content increases from 0 to 40 % and the temperature rises from 25 °C to 37 °C, the EPR spectra of probe 4 consistently remains as triplets (Fig. 5).

Table 5

Parameters of EPR spectra of spin probe 3 in 20 % P338 solutions with various PG contents (*C*) at different temperatures (*t*)

C, % *m/m*	*t*, °C	A_N, mT	*S*	ν, °	Spectrum type
0	25	1.47	0.47	53.8	anisotropic
10	25	1.48	0.47	53.8	anisotropic
20	25	1.48	0.47	53.8	anisotropic
30	25	1.48	0.45	55.0	anisotropic
40	25				triplet
0	32	1.48	0.42	56.9	anisotropic
10	32	1.47	0.40	58.0	anisotropic
20	32	1.46	0.39	58.5	anisotropic
30	32	1.46	0.38	59.0	anisotropic
40	32				triplet
0	37	1.48	0.39	57.5	anisotropic
10	37	1.47	0.38	59.5	anisotropic
20	37	1.49	0.38	59.5	anisotropic
30	37				transformation to superposition
40	37				triplet

In the molecule of spin probe 4, the doxyl radical is located near the 16th carbon atom of the alkyl chain. It was of interest to compare the rotational parameters of probes 3 and 4. Consequently, the parameters for the EPR spectra of probe 4 were calculated using equations (2), (3), (4) and (5) as well as equations (6) and (7) (Tables 6, 7).

With an increase in the PG content in 20 % P338 solutions, there is practically no tendency to decrease the order parameter (*S*) and, consequently, to increase the semi-amplitude of molecular motion (parameter ν), as determined from the EPR spectra of spin probe 4 (Table 6). As the temperature rises from 25 °C to 37 °C, there is a tendency for the order parameter *S* to decrease and for the parameters ν and A_N to increase (Table 6).

In 20 % P338 solutions containing up to 20 % PG, the order parameter S in the case of EPR spectra of probe 3 (5-DSA NH_4 salt) is about 4–5 times higher than in the case of EPR spectra of probe 4 (16-DSA). In the case of the EPR spectra of probe 4, the values of the parameter ν are markedly higher than in the case of the EPR spectra of probe 3 (Tables 5, 6). The calculated values of the constant A_N for the EPR spectra of probe 4, as per equation (6), are slightly lower than the corresponding parameter for the EPR spectra of probe 3 (Tables 5, 6). This suggests that the surrounding polarity of the doxyl radicals in the micelle core at the 16th carbon atom of probe 4 is lower.

Probe 4 displays rapid rotation, as evidenced by the values of rotational correlation times (τ_{+1}, τ_{-1}, $\tau_{\pm1}$) [41]. An increase in the PG content from 0 to 40 % has a negligible impact on the parameters of the EPR spectra of probe 4 (Table 7). However, a notable decline in τ values is observed as the temperature rises from 25 °C to 37 °C (Table 7). The values of the anisotropy parameter (ε) are slightly different at 25 °C, 32 °C and 37 °C, yet display minimal dependence on the PG content (Table 7).

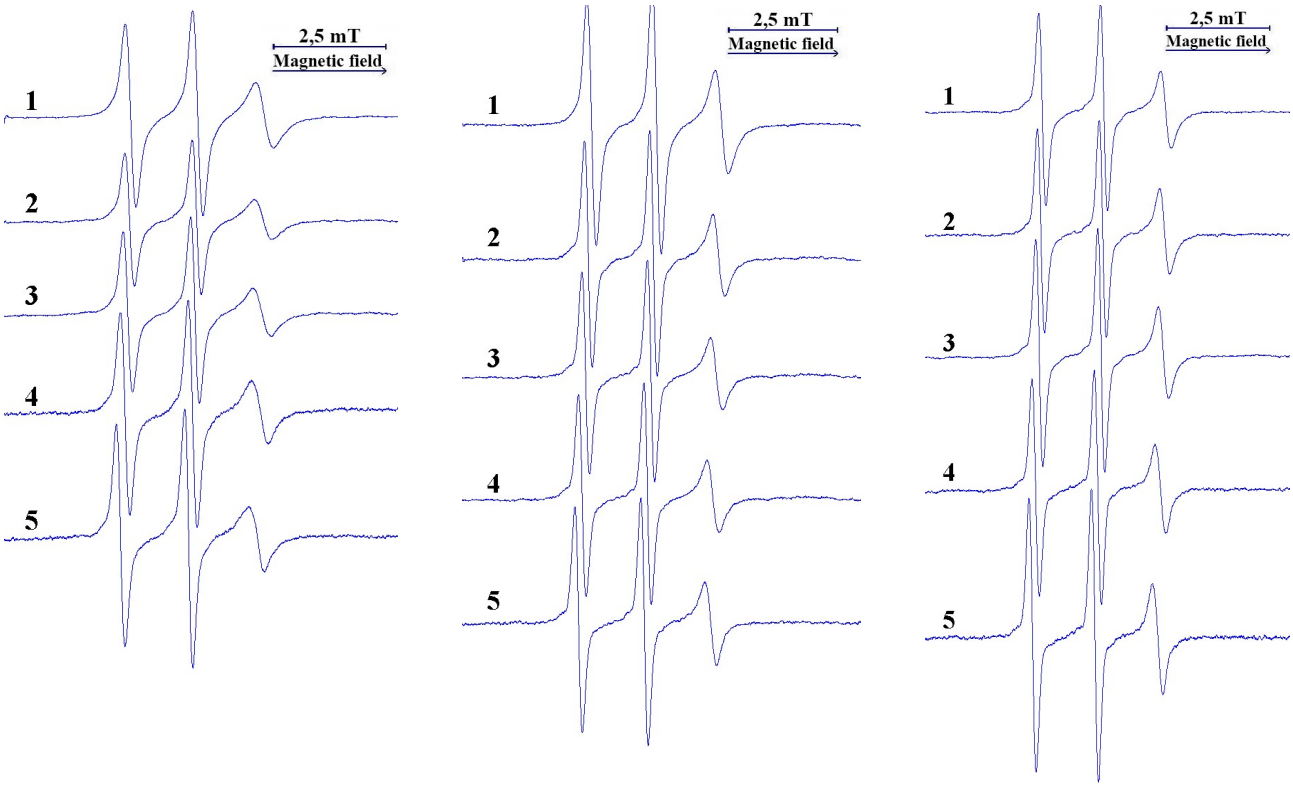

Fig. 5. EPR spectra of probe 4 in 20 % P338 solution with various PG contents: 1 – 0 %; 2 – 10 %; 3 – 20 %; 4 – 30 %; 5 – 40 %, at: *a* – 25 °C; *b* – 32 °C; *c* – 37 °C

Table 6

Parameters of EPR spectra of spin probe 4 in 20 % P338 solutions with various PG contents (*C*) at different temperatures (*t*)

C, % *m/m*	*t*, °C	A_N, mT	*S*	ν, °	Spectrum type
0	25	1.41	0.12	78.5	triplet
10	25	1.38	0.13	77.5	triplet
20	25	1.41	0.12	78.5	triplet
30	25	1.42	0.12	78.5	triplet
40	25	1.44	0.10	80.0	triplet
Mean value	25	1.41±0.05	0.12±0.02	78.6±1.9	–
0	32	1.42	0.10	80.0	triplet
10	32	1.43	0.09	81.8	triplet
20	32	1.44	0.08	82.5	triplet
30	32	1.40	0.08	82.5	triplet
40	32	1.40	0.08	82.5	triplet
Mean value	32	1.42±0.04	0.09±0.02	81.9±2.3	–
0	37	1.43	0.08	82.5	triplet
10	37	1.44	0.08	82.5	triplet
20	37	1.44	0.08	82.5	triplet
30	37	1.45	0.08	82.5	triplet
40	37	1.45	0.08	82.5	triplet
Mean value	37	1.44±0.02	0.08±0	82.5±0	–

The values of the constant A_N, defined as the distance (in mT) between the central and high-field components of the EPR spectra of probe 4 [41, 42], practically do not tend to increase with increasing the PG content from 0 % to 40 % (Table 7). The polarity of the microenvironment of the doxyl radical at the level of the 16th carbon atom of the alkyl chain of probe 4 does not increase under the influence of PG. This indicates that there is no solvation of P338 micelle cores by the dispersion medium.

As the temperature rises from 25 °C to 37 °C, there are discernible trends towards a slight increase in the A_N parameter, a decrease in the rotational correlation times of probe 4, and a slight decrease in the anisotropy parameter ε (Table 7).

Table 7

Parameters of EPR spectra of spin probe 4 in 20 % P338 solutions with various PG contents (*C*) at different temperatures (*t*)

C, % *m/m*	*t*, °C	A_N, mT	τ_{+1}, ns	τ_{-1}, ns	$\tau_{\pm1}$, ns	ε
0	25	1.46	0.66	0.48	1.04	0.08
10	25	1.46	0.79	0.55	1.25	0.08
20	25	1.46	0.72	0.50	1.03	0.08
30	25	1.47	0.67	0.57	1.15	0.07
40	25	1.47	0.85	0.58	1.11	0.08
Mean value	25	1.46±0.01	0.74±0.17	0.54±0.09	1.12±0.19	0.08±0.01
0	32	1.47	0.52	0.40	0.86	0.07
10	32	1.47	0.41	0.40	0.87	0.06
20	32	1.47	0.42	0.36	0.80	0.06
30	32	1.46	0.45	0.38	0.81	0.07
40	32	1.49	0.49	0.40	0.85	0.07
Mean value	32	1.47±0.02	0.46±0.10	0.39±0.04	0.84±0.07	0.07±0.01
0	37	1.47	0.33	0.31	0.68	0.06
10	37	1.47	0.32	0.34	0.63	0.05
20	37	1.47	0.37	0.35	0.67	0.06
30	37	1.49	0.39	0.35	0.75	0.06
40	37	1.49	0.33	0.35	0.63	0.05
Mean value	37	1.48±0.02	0.35±0.06	0.34±0.04	0.67±0.10	0.06±0.01

Note: the type of these EPR spectra is given in Table 6.

5. Discussion of research results

20 % aqueous solution of P338 undergoes a sol→gel transition when the temperature is increased from 25 °C to 32 °C; the rheological parameters of the gel increase as the temperature is raised to 37 °C (Fig. 1, *a*, Table 2) [8]. The incorporation of propylene glycol into a 20 % P338 solution results in alterations to its rheological characteristics at various temperatures, with the extent of these changes contingent upon the concentration of PG.

It can be observed that the thermally induced sol-gel transitions occur with increasing temperature to 32 °C and 37 °C even at PG contents of 10 % and 20 % (Fig. 1, *b, c,* Table 2). In the case of ethanol (96 %), the thermally induced sol→gel transitions with increasing temperature to 32 °C and 37 °C occur at an ethanol content of only 5 % [15]. This indicates that the thermally induced sol→gel transition can occur in a 20 % P338 solution at a PG content four times higher than the ethanol content.

When heated to 32 °C, 20 % P338 solutions containing 10 % or 20 % of PG form gels with a plastic flow type, high values of the low-yield stress and apparent viscosity. As the temperature and PG content increase, the rheological parameters of these gels also increase (Fig. 1, Table 2). A 20 % P338 solution containing 30 % PG at 32 °C displays Newtonian fluid behavior, with the formation of a gel occurring only at 37 °C (Fig. 1, *d*, Table 2). The resulting gel is characterised by high low-yield stress, a zone of pseudoplastic flow, and thixotropic properties (Fig. 1, *b, c, d*). In terms of rheological properties, this gel differs significantly from gels with plastic flow behavior containing 10 % and 20 % PG.

Solutions of P338 containing 15–30 % ethanol behave as Newtonian liquids at 32 °C and 37 °C; the dynamic viscosity of the solution with 30 % ethanol decreases as the temperature increases [15]. The same rheological behaviour is observed for P338 solutions containing 40 % and 50 % PG (Fig. 1, *e, f*, Table 2).

It was important to assess the parameters and type of the EPR spectra of spin probes 1, 2, 3 and 4 localised within P338 micelles as a function of PG concentration and temperature.

The EPR spectra of probes 1 and 2 in P338 solutions are triplets (Fig. 2, 3). The rotational correlation times of these probes in P338 micelles indicate that these probes undergo rapid rotation [41, 42]. As the temperature is increased from 25 °C to 37 °C, the rotational correlation times of probes 1 and 2 decrease. This is likely due to the transition from a soft to a liquid consistency of micelles at the interface of their polar part and hydrophobic core (Tables 3, 4). An increase in the PG content from 0 to 40 % results in an increase in the values of $\tau_{\pm1}$ of probe 1. The PG concentration has little effect on the values of τ_{-1} of probe 1, as well as τ_{-1} and $\tau_{\pm1}$ of probe 2 (Tables 3, 4). As the PG content is increased from 0 to 40 %, a slight tendency for a decrease in the τ_{+1} values of probe 2 is observed (Table 4). In contrast, ethanol with increasing concentration contributes to a significant decrease in the rotational correlation times of probes 1 and 2 [15]. The rise in the PG concentration from 0 to 40 % has a negligible impact on the A_N constant of the EPR spectra of probes 1 and 2 (Tables 3, 4); at 25 °C, there is a slight tendency for the A_N constant to increase from 1.62 mT to 1.65 mT when the PG content reaches 40 % (Table 3). The findings of the studies demonstrate that the impact of PG on the structure of P338 micelles at the interface between the hydrophilic PEO shell and the hydrophobic PPO core is markedly distinct from ethanol [15].

In a 20 % aqueous solution of P338, the EPR spectra of spin probe 3 are anisotropic at temperatures from 25 °C, 32 °C and 37 °C and at PG concentrations up to 20 % (Fig. 4). At 30 % PG content, the EPR spectra are anisotropic only at 25 °C and 32 °C. At 37 °C, the EPR spectrum of spin probe 3 undergoes a transformation, becoming similar to the superposition of two signals or approaching a triplet.

This particular EPR spectrum is characteristic of a gel with thixotropic properties (Fig. 1, *d*). At PG content of 40 %, the EPR spectra of probe 3 are triplet, and P338 solutions are Newtonian fluids (Fig. 1, *e*).

The rise in the PG concentration has a negligible impact on the order parameter (*S*) calculated from the EPR spectra of probe 3, as well as on the A_N constant (Table 5). However, at a certain concentration of PG, the EPR spectra of probe 3 undergo a transformation. It seems reasonable to suggest that this transformation is not a result of PG interacting with the core of P338 micelles, but rather the result of PG molecules forming strong hydrogen bonds with the hydrophilic PEO part of the micelles [44]. This is probably evidenced by the tendency for the value of $\tau_{\pm1}$ of probe 1 to increase in conjunction with an increase in the PG content from 0 to 40 % (Table 3). The interaction of PG with P338 micelles is markedly distinct from their interaction with ethanol. With an increase in ethanol concentration, the S parameter decreases significantly, while the values of the A_N constantly increase. This, probably, suggests that ethanol interacts with the core of P338 micelles [15].

The EPR spectra of probe 4 are triplets characterised by a significantly lower order parameter and indicate a faster rotation than that observed for probe 3 (Fig. 4, 5, Tables 5–7). As the temperature increased from 25 °C to 37 °C, the rotational parameters of probe 4 (τ_{+1}, τ_{-1}, $\tau_{\pm1}$, ε, *S*) demonstrate a decrease, while the parameter ν exhibits an increase, and the A_N constant slightly tends to grow (Tables 6, 7). The PG content in the range of 0 to 40 % does not affect the rotational parameters of probe 4; their values observed at different PG concentrations exhibit a discrepancy within the limits of the determination error (Tables 6, 7) [41, 42]. It can be stated that PG at a concentration of up to 40 % does not penetrate the cores of P338 micelles. Conversely, ethanol at increasing concentrations has been observed to contribute to a notable decrease in the values of τ, the parameter S, and an increase in the A_N constant of the EPR spectra of probe 4; this suggests the solvation of P338 micelle cores by ethanol or a mixed solvent *water-ethanol* [15].

The EPR spectra of probes 1, 2, and 4 exhibit no significant alterations with increasing PG content in 20 % P338 solution. Therefore, using these spectra it is not possible to elucidate the observed changes in the rheological properties of P338 solutions, particularly the sol↔gel transitions. However, with increasing PG concentration in 20 % P338 solutions, significant changes are observed in the EPR spectra of probe 3. It should be noted that in the case of 20 % P338 solutions, where sol↔gel transitions occur, the EPR spectra remain anisotropic at 25 °C, 32 °C and 37 °C (Fig. 4). Regarding probes 1, 2, 3, and 4, the previously defined sequence of EPR spectrum types is maintained: a triplet for probes 1 and 2, an anisotropic spectrum for probe 3, and a triplet for probe 4 (Fig. 2–5). That is, the cores of P338 micelles remain anisotropic in viscosity [8, 15].

Practical relevance. The results provide a theoretical basis for the pharmaceutical development of novel medicinal products that are thermally reversible solutions/gels.

Study limitations. The present research is constrained by the fact that the impact of propylene glycol content on solution properties at a P338 concentration of only 20 % and within a narrow temperature range of 25 °C to 37 °C was studied.

Prospects for further research. Further studies on 20 % solutions of P338, whose dispersion medium contains water and another hydrophilic non-aqueous solvent (glycerol, macrogol 400, *N*-methyl pyrrolidone, etc.) in varying proportions, would be beneficial to gain an understanding of the impact of different solvents on the rheological properties of those solutions and the structure of P338 micelles. Furthermore, similar studies might also be promising for solutions of other poloxamers [1].

6. Conclusions

It has been demonstrated that the rheological properties of 20 **%** P338 solution are affected by the PG, depending on its content. The P338 solutions can undergo a thermally induced sol↔gel transition, provided that the PG content does not exceed 30 **%**. A correlation has been identified between alterations in the rheological properties of 20 **%** P338 solution and the corresponding change in the types of EPR spectra observed for the 5-DSA NH_4 salt, namely a transition from anisotropic spectra to triplet. As the PG content in the P338 solution increases up to 40 **%**, the solution of micelle cores by the dispersion medium does not occur. It may be posited that the alteration in the structure of P338 micelles is a consequence of the interaction between PG and their hydrophilic shell.

Conflict of interests

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

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Data availability

Data will be made available on reasonable request.

Use of artificial intelligence

The authors confirm they did not use artificial intelligence technologies when creating the current work.

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