

## Study of viscosity and quasi-thermodynamic activation parameters for viscous flow in the system water-(propylene glycol-macrogol 400)

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The results of a polythermal study of the dynamic viscosity ( $\eta$ ) of the ternary system containing water and the mixture of propylene glycol (PG) and macrogol 400 (M400) are presented. The values of  $\eta$  for the ternary system vary widely depending on its composition and temperature. The isotherms of  $\eta$  are nonlinear. The isotherms of excess dynamic viscosity ( $\eta^E$ ) are asymmetric, which indicates a different structure of the ternary system depending on the water content. The absolute values of the  $\eta^E$  on the relevant isotherms decrease with increasing temperature. The quasi-thermodynamic activation parameters of viscous flow are positive regardless of the ternary system composition. Changes in their values indicate the destruction of water structure under the influence of PG and M400. The dependencies of the excess quasi-thermodynamic activation parameters of viscous flow on the mole fraction of non-aqueous solvent (PG - M400) make it possible to differentiate the areas of compositions with different structures: structure of water, structure of mixed solvents with the dominance of water structure or non-aqueous solvent, and structure of non-aqueous solvent. The structure of the ternary mixed system can affect the properties of heterogeneous disperse systems with a liquid dispersion medium.

**Keywords:** water, propylene glycol, macrogol 400, viscosity, activation parameters of viscous flow.

**Дослідження в'язкості та квазітермодинамічних параметрів активації в'язкої течії системи вода - (пропіленгліколь - макрогол 400).** *О.П.Безугла, А.П.Краснопльорова, А.М.Ляпунова, Г.Д.Юхно, М.О.Ляпунов*

Наведено результати політермічного дослідження динамічної в'язкості ( $\eta$ ) потрібної системи, що містить воду та суміш пропіленгліколю (PG) і макроголу 400 (M400). Величини  $\eta$  потрібної системи змінюються в широких межах залежно від її складу і температури. Ізотерми  $\eta$  є нелінійними. Ізотерми надлишкової динамічної в'язкості ( $\eta^E$ ) є асиметричними, що вказує на різну структуру потрібної системи залежно від вмісту води. Абсолютні значення  $\eta^E$  на відповідних ізотермах з ростом температури зменшуються. Квазітермодинамічні функції активації в'язкої течії позитивні незалежно від складу потрібної системи. Зміни їх величин свідчать про руйнування структури води під впливом PG і M400. Залежності надлишкових квазітермодинамічних функцій активації в'язкої течії від мольної частки неводного розчинника (PG і M400) дозволяють розрізнити області складів з різною структурою: структурою води, структурою змішаних розчинників з домінуванням структури води або неводного розчинника, структурою неводного розчинника. Структура потрібної змішаної системи може впливати на властивості гетерогенних дисперсних систем з рідким дисперсійним середовищем.

## 1. Introduction

Currently, mixed solvents are widely used in the composition of bases-vehicles for medicinal products, in particular, mixtures of water with propylene glycol (PG) and macrogol 400 (M400) [1]. The choice of the composition of such mixed solvents should be based on the results of physicochemical studies. Viscosity is one of the key parameters of liquid systems, which is quite easy to determine. In addition, viscosity can be used to understand intermolecular interactions by calculating the quasi-thermodynamic activation parameters of viscous flow. All this makes it possible to consider studies of viscosity as one of the most informative methods of physicochemical analysis of liquid multicomponent systems [2]. The results of the study of the binary systems water-PG, water-M400 are described in the number of publications [3–5]. The aim of this work was to determine the viscosity, calculate the activation parameters of viscous flow, and evaluate the structure of the ternary system water-(PG-M400) for use in semi-solid preparations.

## 2. Experimental

### Materials

We studied ternary systems containing purified water (hereinafter water) and a mixed non-aqueous solvent PG-M400 with the constant ratio between PG and M400 equal to 60:40 %w/w. The average molecular weight ( $M_r$ ) of the PG-M400 mixed solvent was 112.57. Non-aqueous solvents (PG and M400) were purchased from BASF (Germany) and met the requirements of the relevant monographs of the European Pharmacopoeia [6].

Mixed ternary systems with different composition were prepared by mass using an analytical balance (AUW 120D, Shimadzu).

Ubbelohde viscometers were used to measure the kinematic viscosity ( $\nu$ ) of the solvents and pycnometers were used to determine their density ( $\rho$ ) [6]. Measurements were carried out at temperatures from 20°C to 55°C. A Julabo F12-ED refrigerating/heating circulator (Julabo Labortechnik GmbH) was used to maintain necessary temperature with an accuracy of  $\pm 0.1^\circ\text{C}$ . The dynamic viscosity ( $\eta$ ) was calculated according to the equation:

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

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

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

where  $\eta_{exp}$  is the dynamic viscosity of the ternary system;  $\eta_i$  is the dynamic viscosity;  $x_i$  is the mole fraction of the components.

Gibbs free energy of activation ( $\Delta G_\eta^\ddagger$ ) was estimated from the Eyring equation [7]:

$$\eta = \frac{h \cdot N}{V_M} \exp \left[ \frac{\Delta G_\eta^\ddagger}{RT} \right], \quad (3)$$

where  $\eta$  is the dynamic viscosity, mPa·s;  $h$  is the Planck constant;  $N$  is the Avogadro constant;  $V_M$  is the mole volume, l/mole;  $R$  is the universal gas constant;  $T$  is the absolute temperature, K.

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

$$\Delta G_\eta^\ddagger = \Delta H_\eta^\ddagger - T\Delta S_\eta^\ddagger. \quad (4)$$

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

## 3. Results and discussion

The dynamic viscosity of the ternary system under study varied significantly depending on its composition and temperature (Fig. 1). Thus, the dynamic viscosity at the transition from the structure of water to the structure of the mixed non-aqueous solvent (PG-M400) increased at 20°C by 66.1 times from 1.01 to 66.77 mPa·s. With an increase in the temperature of the ternary system from 20°C to 55°C, the dynamic viscosity decreased by 5.1 times. At the same time, dynamic viscosity isotherms at all temperatures were nonlinear, which is typical for systems that do not obey Raoul's law. In general, the dynamic viscosity isotherms were typical for systems water-glycol [4].

The properties that are additive in the absence of interaction between the components of the system are of great importance for interpreting the results of physico-

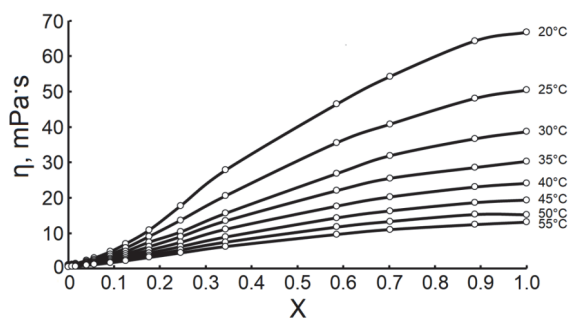


Fig. 1. Dynamic viscosity ( $\eta$ ) of the ternary system water - (PG -M400) vs mole fraction ( $X$ ) of the mixed non-aqueous solvent (PG - M400) in the temperature range from 20°C to 55°C.

chemical studies of liquid systems. The deviations of the viscosity experimental data from the additive values for the studied ternary system indicate the dependence of the nature of intermolecular interactions on the mole fraction of the mixed non-aqueous solvent (PG-M400) (Fig. 2).

The isotherms of excess dynamic viscosity are asymmetric (Fig. 2). At 25–35°C they have a minimum at near 0.1 mole fraction of a non-aqueous solvent (PG-M400), and the values of the excess viscosity are negative. With an increase in temperature, the  $\eta^E$  values increase in the area of minimum on the isotherms, and at 55°C the minimum practically disappears. With an increase in the mole fraction of the non-aqueous solvent (PG-M400) above approximately 0.2, the values of the excess dynamic viscosity become positive (Fig. 2). These values increase with an increase in the mole fraction of the mixed non-aqueous solvent, pass through a maximum at its content of about 0.6–0.7 mole fractions and decrease with further increase in its content. With increasing temperature, the positive deviations  $\eta^E$  on the isotherms decrease, which indicates a weakening of the interaction between solvent molecules.

The asymmetric dependence of  $\eta^E$  on the composition of the ternary system (Fig. 2) may indicate different specifics of interactions between molecules of water and non-aqueous solvents at different water contents. The positive deviations of the excess dynamic viscosity are probably due to the predominance of the interaction between water molecules and the PG and M400 polar groups. The negative values of  $\eta^E$  may indicate the effect of hydrophobic hydration of PG and M400 molecules [4, 8]. The  $\eta^E$  isotherms indicate that the nature of intermolecular interactions in the ternary system

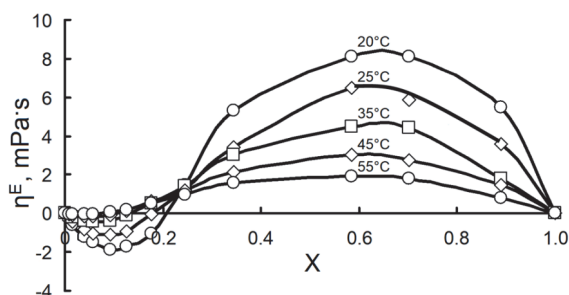


Fig. 2. Excess dynamic viscosity ( $\eta^E$ ) of the ternary system water - (PG -M400) vs mole fraction ( $X$ ) of the mixed non-aqueous solvent (PG -M400) in the temperature range from 20°C to 55°C.

under study varies significantly depending on the composition and temperature [2]. It can be assumed that the greater the  $\eta^E$  value, the stronger the interaction between water and glycols.

One of the elementary acts of the viscous flow of associated liquids is the movement of individual molecules, which requires the breaking of a certain number of hydrogen bonds [7]. A certain free activation energy of viscous flow ( $\Delta G_{\eta}^{\ddagger}$ ) is necessary for this process.

For a viscous flow to occur, a molecular vacancy must form, into which a flowing molecule can move. The total activation energy of the viscous flow is the sum of the energies required to create vacancies in the liquid and move flowing molecules into these vacancies. The ratio of the enthalpy and entropy constituents of  $\Delta G_{\eta}^{\ddagger}$  can be determined from the nature of the  $\Delta G_{\eta}^{\ddagger}$  isotherm. According to the data shown in Fig. 3, the main contribution into  $\Delta G_{\eta}^{\ddagger}$  is made by the enthalpy.

There are two regions with different slope angles on the plots of the quasi-thermodynamic functions of viscous flow activation ( $\Delta Y_{\eta}^{\ddagger}$ ) versus the composition of the ternary system (Fig. 3). With an increase in the content of the non-aqueous solvent (PG-M400) to 0.2 – 0.3 mole fractions, a greater increase in the values of the quasi-thermodynamic functions is observed. In this range of the ternary system compositions, the non-aqueous solvent structure is more influenced by the structure of water. A further increase in the mole fraction of the non-aqueous solvent does not lead to a significant increase in the  $\Delta Y_{\eta}^{\ddagger}$  values.

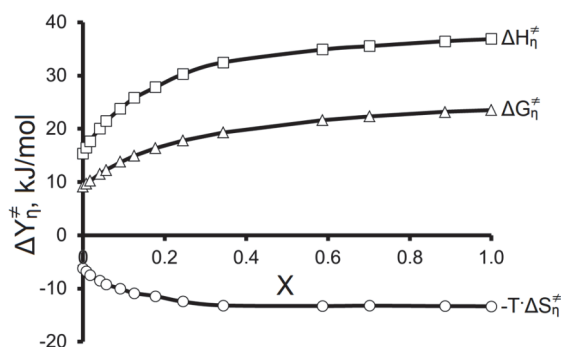


Fig. 3. Activation parameters of viscous flow for the ternary system water - (PG -M400) vs mole fraction (X) of the mixed non-aqueous solvent (PG -M400) at 298.15 K.

The values of the free activation energy ( $\Delta G_{\eta}^{\ddagger}$ ) of the viscous flow activation process are positive regardless of the composition of the ternary system under study. The increase in the  $\Delta G_{\eta}^{\ddagger}$  values in the transition from the water structure to the mixed structure can be explained by an increase in the energy required for the formation of vacancies in the liquid.

The  $\Delta H_{\eta}^{\ddagger}$  values are positive regardless of the composition of the ternary system. The  $\Delta H_{\eta}^{\ddagger}$  value is proportional to the enthalpy of vaporization ( $\Delta H_{ev}$ ) [2]; the increase in  $\Delta H_{\eta}^{\ddagger}$  values when transition from structure of water to a mixed structure was probably due to an increase in the  $\Delta H_{ev}$  of the mixture and, consequently, an increase in the energy required to form vacancies in the liquid.

The changes in the  $\Delta Y_{\eta}^{\ddagger}$  values indicate that the mixed non-aqueous solvent (PG-M400) destroys the structure of water.

The quasi-thermodynamic activation parameters of viscous flow are mole-additive [2]. This makes it possible to calculate their deviations from additive values for the system under study (Fig. 4). The excess quasi-thermodynamic parameters of viscous flow activation ( $\Delta Y_{\eta}^{\ddagger E}$ ) are positive and are characterized by the presence of maxima on the isotherms in the region of approximately 0.25 – 0.35 mole fractions of the mixed non-aqueous solvent (PG-M400). The maxima  $\Delta H_{\eta}^{\ddagger E}$  and  $-T \cdot \Delta S_{\eta}^{\ddagger E}$  on the isotherms indicate the predominant effect of the breaking the structure of the water under influence of a non-aqueous solvent up to ~ 25 – 35 mol % (67.0 – 76.6 % w/w) and stabilization of the structure of the non-aqueous solvent with a further increase in its content to 100 %.

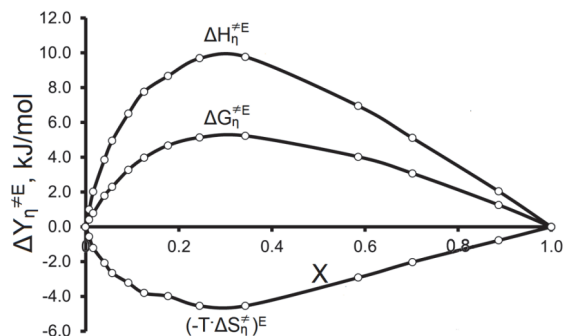


Fig. 4. Excess activation parameters of viscous flow for the ternary system water- (PG -M400) vs mole fraction (X) of the mixed non-aqueous solvent (PG -M400) at 298.15 K.

According to the plots of  $\Delta Y_{\eta}^{\ddagger E}$  versus the mole fraction of the non-aqueous solvent (PG - M400), it is possible to approximately distinguish areas of compositions with different dominant structural organization: this is the structure of water at the content of the non-aqueous solvent not higher than ~ 4.0 mol% (~ 20.8 % w/w); the structure of the mixed solvent with the dominance of the structure of water at the content of the non-aqueous solvent in the range of ~ 4.0 mol% to 18.0 mol% (~ 20.8 – 57.3 % w/w); the structure of the mixed solvent with the dominance of the structure of the non-aqueous solvent at its content from ~ 18.0 mol% to 70.0 mol% (~ 57.3 – 93.6 % w/w); the structure of the non-aqueous solvent at its content over 70.0 mol%.

#### 4. Conclusions

The structure of mixed solvents can affect the performance characteristics of drugs, which are heterogeneous dispersed systems with a liquid dispersion medium stabilized by surfactants. Solvents that destroy the structure of water can contribute to the stability of such dispersed systems [9]. Probably, in viscoplastic o/w emulsions, the content of a mixed non-aqueous solvent (PG-M400) in the dispersion medium should not exceed 60 % w/w. At a higher content of this mixed non-aqueous solvent, its structure dominates, which might lead to a significant weakening or elimination of hydrophobic interactions [10]. In this case, emulsifiers lose their ability to stabilize emulsions.

In the case of higher content of the mixed non-aqueous solvent in emulsions, another stabilizing factor not related to hydrophobic interactions is required. Such a factor may be gel formation in the disperse medium of o/w emulsions or a high viscosity of the lipophilic medium in w/o emulsions, which will prevent flocculation and coalescence of emulsion globules.

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