

**CHEMISTRY AND TECHNOLOGY OF MEDICINAL COMPOUNDS
AND BIOLOGICALLY ACTIVE SUBSTANCES**

**ХИМИЯ И ТЕХНОЛОГИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ
И БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ**

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**On the use of aqueous solutions of polyvinyl methyl ether
for the embolization of blood vessels**

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Aqueous solutions of polyvinyl methyl ether were investigated in order to test whether it is possible to utilize them as bases for embolic agents used to deliberately block blood vessels. This may be necessary in the course of treatment of vascular abnormalities, tumors, as well as during the preparation of patients for surgery. The right branch of the binodal curve for the binary system “polyvinyl methyl ether–water” was drawn using the cloud point method and the lower critical mixing temperature (35.5 °C) was calculated. Furthermore, the exact concentration of polyvinyl methyl ether in aqueous solutions at which phase transition occurs (given the temperature of 35.5 °C) was found to be 30 wt %. The viscosity–velocity curves for the 30% solution of polyvinyl methyl ether, obtained by rheoviscometry in the temperature range of 5 to 36 °C, indicate that this aqueous solution has a low viscosity and behaves like a Newtonian fluid. However, at the temperature of 35 °C and higher, close to the phase transition, a significant deviation from its Newtonian behavior is observed due to precipitation of polyvinyl methyl ether as it forms a solid white mass. Through the use of the Arrhenius–Frenkel–Eyring equation, the activation energy of the viscous flow for polyvinyl methyl ether solutions was found to be 31 kJ/mol. Based on refractometry data, it was demonstrated that phase transition in aqueous solutions of polyvinyl methyl ether is reversible. This feature can facilitate medical equipment cleaning before introducing the embolic agent into a patient’s bloodstream. Finally, the investigation determined some parameters, in which the formation of embolic agents from a 30% polyvinyl methyl ether aqueous solution occurs (in situ in a blood vessel at a temperature of 35.5 °C).

Keywords: embolization, embolic agent, viscosity, polyvinyl methyl ether, aqueous solution.

О возможности применения водных растворов поливинилметилового эфира для эмболизации кровеносных сосудов

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Статья посвящена исследованию водных растворов поливинилметилового эфира с целью определения возможности их использования в качестве основы эмболизирующего состава для преднамеренной закупорки кровеносных сосудов при терапии сосудистых аномалий, опухолей и предоперационной подготовке пациентов. На основании экспериментальных данных, полученных с помощью метода точек помутнения, построена правая ветвь бинарной кривой бинарной системы поливинилметилвый эфир – вода и определено значение нижней критической температуры смешения (35.5 °C). Определена концентрация поливинилметилового эфира в водном растворе, при которой фазовый переход происходит при температуре 35.5 °C – она составляет 30% мас. Вязкостно-скоростные кривые 30%-го водного раствора поливинилметилового эфира, полученные с помощью метода реовискозиметрии в широком диапазоне температур 5–36 °C, свидетельствуют, что исследуемые растворы низковязки и проявляют ньютоновское поведение при течении. Однако уже при 35 °C и выше в области фазового перехода наблюдается значительное отклонение от ньютоновского поведения вследствие выпадения поливинилметилового эфира из раствора в виде белой твердой массы. В рамках уравнения Аррениуса–Френкеля–Эйринга оценена энергия активации вязкого течения водных растворов поливинилметилового эфира, которая составляет 31 кДж/моль. С помощью рефрактометрии было показано, что фазовый переход в исследуемых растворах имеет обратимый характер, что, в частности, облегчает очистку оборудования для введения эмболизирующего состава в организм пациента. В результате работы определены некоторые параметры, при которых формирование эмбола в кровеносном сосуде *in situ* происходит из 30%-го водного раствора поливинилметилового эфира при температуре 35.5 °C.

Ключевые слова: эмболизация, эмболизирующий агент, вязкость, поливинилметилвый эфир, водный раствор.

Introduction

Today, the treatment of major issues in blood vessels by embolization has become rather popular. It is a virtually noninvasive procedure wherein vessels are intentionally blocked [1–4]. Embolization is used to treat various conditions such as aneurysms, cases of angiodysplasia, uterine fibroids, various cancers, injuries with severe blood loss, as well as for the preparation of patients for surgery (to limit blood loss) [1]. To perform embolization, a catheter is used to deliver substances into the blood vessel. These substances may be different in nature, structure and composition; they may be liquid or solid, but their role is to form a thrombus (clot) which prevents free blood flow.

Some of the first materials that were used for blood vessel blockage were fragments of muscle tissue, fat tissue or brain meninges, as well as hemostatic sponges and stainless steel granules [5, 6]. Modern cardiovascular medicine uses embolization based on gelatin sponges, synthetic polymers, and microspheres of various composition, balloons, occluders and coils. However, the development of current treatment standards requires novel embolic agents, based on polymers and co-polymers [5, 6]. It is worth noting that liquid agents, which form solid emboli in blood vessels *in situ*, have some advantages when compared to solid agents [7]. For example, liquids are easier to introduce into a vessel and localize in a certain area; the risk of vessel damage is also lower. Most liquid embolic agents contain

toxic solvents that may affect the human body and cause negative side effects [8]. This can be avoided by using water-based agents; their development is very important [9]. A promising reagent for this purpose is an aqueous solution of polyvinyl methyl ether (PVME) [10]. It is a synthetic polymer with high solubility in cold water, but it precipitates at temperatures above 35 °C. Materials based on PVME are highly adhesive to various surfaces, particularly plastic and metal, and they are used in production of glues and varnishes, letterpress ink and sealants [11]. The purpose of the current study was to evaluate the possibility of creating PVME-based aqueous embolic agents.

Materials and Methods

We used aqueous solutions of polyvinyl methyl ether (PVME) (Sigma-Aldrich, US) at concentrations ranging from 5 to 50 wt %.

The cloud point temperature for PVME solutions was measured using the following setup. The specimen was fixed between two glass cover slips next to the sensor bulb of a mercury-in-glass thermometer, which was thermostated. The temperature was elevated or decreased gradually at the speed of 1 °C/min. In the first scenario, the cloud point temperature was determined at the moment when clouding started to occur, and in the second – when the specimen became transparent again. We have analyzed PVME solutions with the following concentrations: 5, 10, 20, 30, 35, 40, 45, 50 wt %.

The dynamic viscosity of PVME aqueous solutions was measured using a Brookfield DV2TLV viscometer (SC4-16 module) at the following temperatures (°C): 5, 10, 15, 20, 25, 30, 33, 34, 35, 36. The shear rate was in the 25–50 s⁻¹ range. We used Rheocalc software to process the data.

The refractive index for 30% and 50% PVME solutions was measured on an URL-1 refractometer in the 25–40 °C range, with gradual (by 3 °C) increase/decrease in temperature.

Results and Discussion

The phase transition in aqueous solutions of PVME results in a change from the original liquid fluid into solid matter, which may be used as an embolus. The temperature of this transition highly depends on the polymer's concentration. Thus, to optimize this embolic agent, it is necessary to investigate the phase diagram of the PVME–water system and to determine the concentration at which the phase transition occurs, at 35 °C or a higher temperature (human body temperature). Based on the data obtained via cloud point method, we have created the binodal curve of the phase diagram for the PVME–water system (Fig. 1).

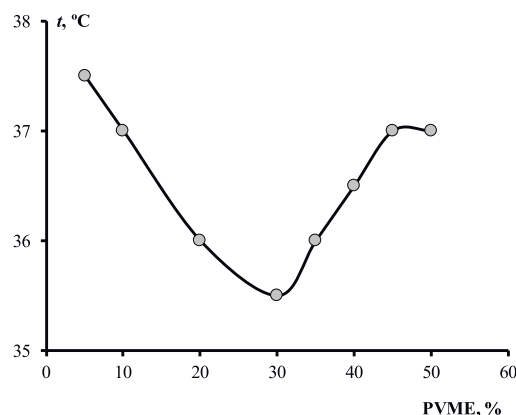


Fig. 1. Phase diagram (binodal) for the binary system PVME–water.

It is evident from this figure that PVME solutions do have the lowest critical mixing temperature, 35.5 °C. The PVME–water system is a transparent liquid fluid (Fig. 2a) at points below the binodal, and it is a solid white substance (Fig. 2b) when above the binodal. The solid form is able to be lodged in a blood vessel.

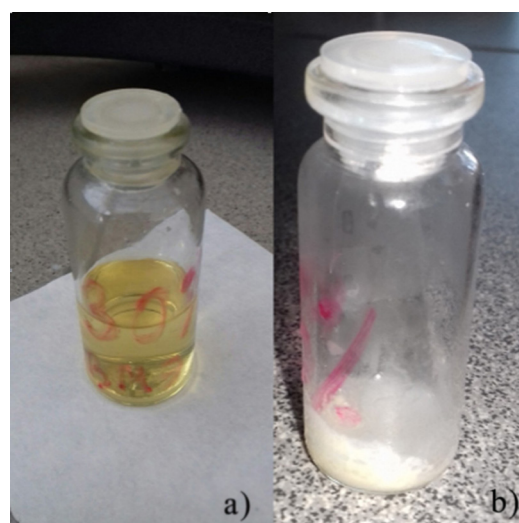


Fig. 2. A typical view of the PVME–water system, below (a) and above (b) the binodal curve.

The lowest critical mixing temperature is observed when the concentration of PVME is 30 wt %, according to the binodal (Fig. 1). If this solution is introduced into a blood vessel, clouding is guaranteed to occur, since the human body temperature is 36.5–37.0 °C.

One of the most important characteristics of an embolic agent is its viscosity, which determines the embolization technique, particularly the diameter of the catheter and the mode of introduction into the blood system. That is why the next step of this work

sought to investigate the rheological parameters of the 30% PVME solution. Its viscosity was analyzed in a wide range of temperatures, from 5 to 36 °C. The experimental viscosity–velocity curves (Fig. 3) show that the solutions tested are lowly viscous and almost Newtonian. However, at 35 °C and 36 °C, a significant scattering of experimental values was observed. This indicates that the substance deviates from the Newtonian behavior when close to phase transition.

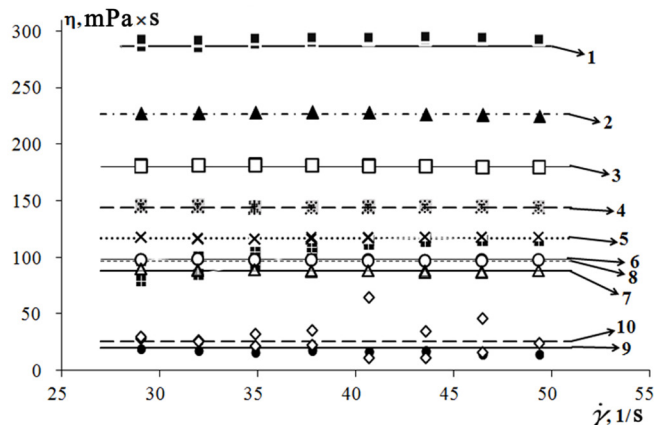


Fig. 3. Viscosity–velocity curves for 30% aqueous solution of PVME at the following temperatures, °C:

1 – 5, 2 – 10, 3 – 15, 4 – 20, 5 – 25,
6 – 30, 7 – 33, 8 – 34, 9 – 35, 10 – 36

The analysis of the data obtained at different temperatures allows for the estimation of the activation energy of viscous flow using the Arrhenius–Frenkel–Eyring equation:

$$\ln \eta = \ln A - \frac{E_{act}}{RT}, \quad (1)$$

where η is the dynamic viscosity coefficient, A – pre-exponential factor, E_{act} – activation energy of viscous flow, R – universal gas constant, T – temperature.

The anamorphosis of the temperature dependency for the dynamic viscosity coefficient of the 30% PVME solution is shown in Fig. 4.

The graph (Fig. 4) shows that at 35–36 °C, a sharp deviation from equation (1) occurs, clearly due to phase transition. The polymer forms a solid white precipitate (Fig. 2b). However, the data for the temperatures below the phase transition point enables the calculation of the activation energy of viscous flow for the PVME solution. Its level is at 31 kJ/mol, and the pre-exponential factor $\ln A = -2.71$. Knowing these parameters, the viscosity of PVME in a wide range of temperatures – from storage conditions to

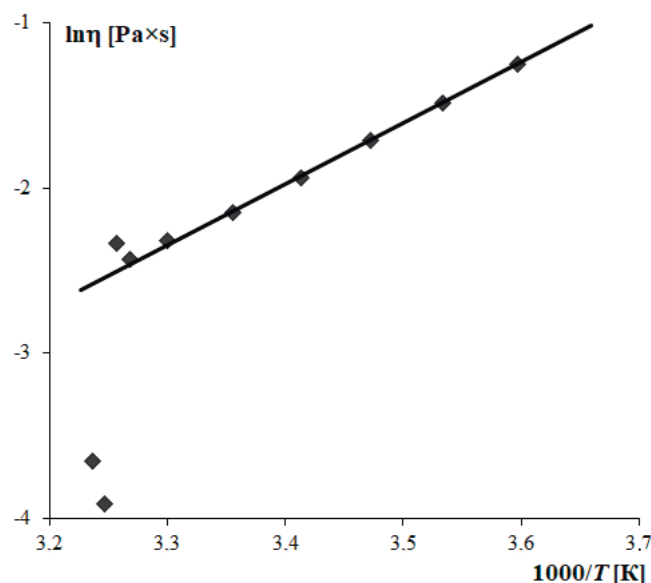


Fig. 4. Temperature dependency of the viscosity for the 30% aqueous solution of PVME based on equation (1).

the phase transition point – can be predicted.

The important feature of embolic agents based on PVME aqueous solutions is the reversibility of phase transition. The temperature dependency of the refractive index (Fig. 5) shows that PVME is dissolved in water in a reversible manner. This may facilitate the cleaning of medical equipment used for the introduction of an embolus into a blood vessel. At the same time, it is safe for the patient as the temperature of a living human body cannot be lower than 35 °C.

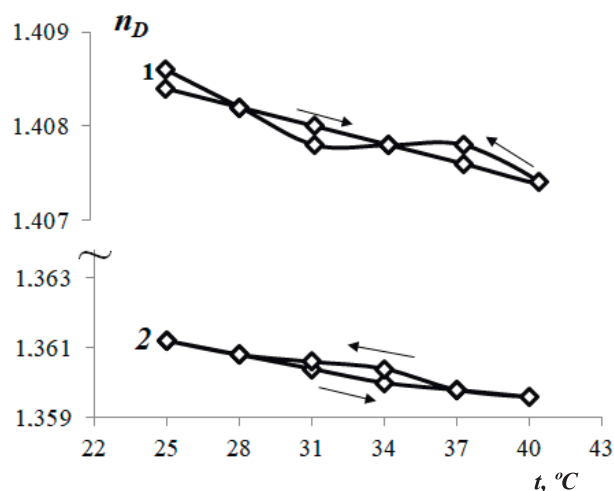


Fig. 5. Refractive index of PVME solutions depends on temperature: 1 – 50% PVME, 2 – 30% PVME.

Conclusion

Rheoviscometry and refractometry were used to analyze aqueous solutions of polyvinyl methyl ether (PVME). The potential of such solutions to be used as embolic agents was demonstrated, as they undergo phase transition at 35–36 °C. The cloud point method was used to create the right branch of the binodal for the phase

diagram of the PVME–water system. This has helped to determine the optimal PVME concentration, 30 wt %, at which the phase transition occurs and an embolus is formed at a temperature of 35 °C. The reversible character of the clouding–solubilization process in the analyzed system was also demonstrated.

The authors declare no conflict of interest.

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