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PREPARATION OF HYDROGELS BASED ON ISOPROPYLACRYLAMIDE COPOLYMERS AS DRUG DELIVERY CARRIERS

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Abstract.

Thermosensitive hydrogels based on *N*-isopropylacrylamide (NIPAM) and ethylene glycol vinyl ether (EGVE) were synthesized and investigated as potential biomaterials for controlled drug delivery applications. The hydrogels were prepared by free-radical copolymerization using different molar ratios of NIPAM and EGVE to tailor their physicochemical properties. The influence of copolymer composition on the swelling behavior and temperature-responsive characteristics of the polymer networks was systematically examined. Equilibrium swelling experiments demonstrated that increasing the EGVE content in the initial monomer mixture significantly enhanced the water uptake capacity of the hydrogels due to the higher hydrophilicity of the polymer matrix. In contrast, increasing the proportion of NIPAM strengthened the thermoresponsive behavior, resulting in a more pronounced thermocollapse near the lower critical solution temperature (LCST), which is characteristic of poly(NIPAM)-based materials. The loading and interaction of the synthesized hydrogels with streptocide were also evaluated to assess their drug encapsulation capability. The results indicated that the hydrogels effectively absorbed and retained the model drug while maintaining their temperature-sensitive properties. Owing to their tunable swelling behavior, reversible thermal response, and satisfactory drug-loading performance, the developed NIPAM–EGVE hydrogels show considerable promise as controlled drug delivery carriers and as hydrogel-based ointment matrices for pharmaceutical and biomedical applications.

Keywords: thermosensitive hydrogels, N-isopropylacrylamide, ethylene glycol vinyl ether, drug delivery, swelling behavior.

1. Introduction

In recent years, thermosensitive polymer hydrogels have attracted considerable interest in the fields of biomedicine and pharmaceutics. Owing to their ability to respond to changes in environmental temperature, these materials are widely investigated as controlled drug delivery carriers, wound dressing materials, and transdermal therapeutic systems. Hydrogels based on N-isopropylacrylamide (NIPAAm) possess a lower critical solution temperature (LCST), enabling them to change their volume in response to temperature variations and thereby regulate the rate of drug release.At present, one of the important scientific directions is the regulation of thermosensitive hydrogel properties through the copolymerization of hydrophilic and hydrophobic monomers. It has been established that the structure and swelling properties of NIPAAm-based copolymers depend on the content of hydrophilic fragments in their composition [1]. In addition, the biocompatibility and high-water absorption capacity of hydrogels allow them to be used as materials like soft biological tissues [2]. Recent studies have demonstrated that polymers based on ethylene glycol derivatives can provide prolonged and controlled drug release [3].

In medicine, particularly in the treatment of burns and skin wounds, the demand for biocompatible and effective wound dressing materials is continuously increasing. Thermosensitive hydrogels are considered promising systems for such applications because they maintain a moist environment at the wound site and ensure gradual drug release [4]. Studies conducted over the last decade have investigated the ability of NIPAAm-based hydrogels to form complexes with antibiotics and antiseptic agents, demonstrating their effectiveness in controlled drug delivery systems [5-7]. Furthermore, it has been shown that the swelling behavior and thermocollapse properties of hydrogels in salt solutions depend on their structural characteristics [8].

Therefore, the synthesis of hydrogels based on N-isopropylacrylamide and ethylene glycol

vinyl ether, as well as the investigation of their interactions with drugs, are of considerable scientific and practical importance. In the present work, the swelling properties, temperature responsiveness, and streptocide complex formation ability of thermosensitive NIPAAm–EGVE-based hydrogels were investigated.

2. Materials and methods

2.1 Characteristics of starting materials and solvents

N-isopropylacrylamide (NIPAAm) was supplied by "Kohjin" (Japan). The monomer was purified by recrystallization from hexane at 40 °C to remove the inhibitor. The obtained product was kept in air for several days and then dried under vacuum (m.p. = 335–338 K; b.p. = 362 K).

Ethylene glycol vinyl ether (EGVE), with a purity of 99.5%, was dried over freshly calcined potassium carbonate for one week and subsequently distilled three times under vacuum (m.p. = 341.15 K; b.p. = 412 K/96 kPa; nD20 = 1.4360).

Azobisisobutyronitrile (AIBN), analytical grade, was recrystallized twice from absolute ethanol (b.p. = 372 K (experimental data); b.p. = 374 K (reference data)).

N,N′-methylenebisacrylamide (MBAA) (Reanal, Hungary) was used as a crosslinking agent without further purification.

Streptocide (tablet form, Kazakhstan) was used in its as-received pure form without additional purification.

2.2 Polymer synthesis

NIPAAm–EGVE copolymers were synthesized via free-radical copolymerization at 333 K in the presence of AIBN. Monomer mixtures with different initial compositions were calculated and prepared as 50–70% aqueous solutions. The prepared solutions were transferred into molybdenum-glass ampoules and purged with argon gas for 10–15 minutes (depending on volume) to remove dissolved oxygen. The ampoules were then placed in an LOIP LT-910 thermostat and kept at the specified temperature until complete gel formation.

After synthesis, the hydrogels were thoroughly washed with distilled water for a long period to remove unreacted monomers and to separate sol and gel fractions.

2.3 Physicochemical methods of investigation

To study complex formation with the drug, equilibrium-swollen, tablet-shaped hydrogel samples were immersed in a streptocide solution, and the kinetics of interaction were monitored over time. In addition, the release of streptocide from the hydrogel was investigated by maintaining the samples in solution for approximately one week.To remove excess streptocide from the obtained complexes, the samples were placed in different buffer solutions, and changes in their volume and optical density were recorded over time.

The relative swelling kinetics of the polymer hydrogels were evaluated using a B-630 cathetometer by monitoring changes in the V/V_0 ratio over time, where V_0 and V correspond to the initial synthesis volume and the equilibrium-swollen volume of thesample, respectively. FTIR spectra of the EGVE–NIPAAm copolymer and the EGVE–NIPAAm–drug composite were recorded using a "Satellite FTIR Mattson" (USA) spectrometer in the range of 4000–400 cm^{-1}.

The equilibrium swelling degree of the polymer hydrogels was calculated using the following equation:

$$\alpha = (m-m_0)/ m_0 \quad (1)$$

where m is the mass of the equilibrium-swollen polymer sample, and m_0 is the mass of the dry gel.

The mass of the dried sample was determined after vacuum drying in a desiccator until a constant weight was achieved. Mass measurements were carried out using an ISO 9001-certified Sartorius analytical balance (Germany). The swelling degree was determined in several parallel experiments, and the average value was calculated.

The gel fraction yield of the studied hydrogels was calculated using the following equation:

$$G = m_0 / m_{synth} \times 100\% \quad (2)$$

where *G* is the gel fraction yield (%), m_0 is the mass of the dried gel (g), and *m synth* is the mass of the synthesized gel (g).

The sol fraction was calculated as:

$$S = 100 - G \quad (3)$$

where *S* is the sol fraction (%).

The amount of dry polymer content was determined after vacuum drying the samples to constant mass. Determination of streptomycin concentration

The concentration of streptomycin in solution was determined using a "UV-2401-PC Shimadzu" (Japan) UV spectrophotometer at λ = 235 nm, corresponding to the maximum absorption in the ultraviolet region.

2.4 Sorption studies

For the investigation of model substance sorption, crosslinked NIPAAm–EGVE copolymer samples were immersed in streptomycin solution. The amount of sorbed streptomycin was determined from the difference between the initial and final concentrations in solution, using a pre-established calibration curve plotted in D–C coordinates.

To investigate drug release from the hydrogel, streptomycin-loaded hydrogel samples were placed in a cell containing either distilled water or isotonic solution at room temperature. The cell was continuously stirred using a magnetic stirrer. At predetermined time intervals, aliquots of the solution were taken, and the concentration of released streptomycin was monitored by UV spectrophotometry through optical density measurements.

The amount of drug released at time *t* (W) was calculated using a calibration curve according to equation (4):

$$W = C / C_0 \times 100\% \quad (4)$$

where *C* is the concentration of streptomycin in the surrounding solution at time τ, and C_0 is the initial concentration of streptomycin in the hydrogel.

Membrane diffusion study

For drug release experiments, a dialysis membrane with a molecular weight cut-off of 3500 Da (Medicell International Ltd.) was used. The system was thermostated at 37 °C, and drug release from the hydrogel was monitored using UV spectrophotometry. The concentration of streptomycin in aqueous solutions was determined from a calibration curve (λ = 235 nm) based on optical density as a function of concentration (C, mol/L).

3. Results and discussion

Currently, a wide range of imported and high-cost pharmaceuticals are widely used in the treatment of various skin diseases and burns. To replace these medicines, the production of biomedical materials—particularly wound dressing materials-based on domestic raw materials and the determination of their optimal formulation remains one of the most relevant challenges.

At the Department of Chemistry and Technology of Organic Substances, Natural Compounds and Polymers at Al-Farabi Kazakh National University, thermosensitive linear and crosslinked copolymers based on ethylene glycol vinyl ether (EGVE) and N-isopropylacrylamide (NIPAAm) have been synthesized via radical copolymerization. The main regularities of their formation and their physicochemical properties have been comprehensively studied [9]. For the preparation of crosslinked copolymers, diethylene glycol divinyl ether was previously used as a crosslinking agent. It was established that the rate of copolymerization of linear polymers is higher, and that NIPAAm units are significantly more reactive compared to EGVE units. The present study represents a continuation of these investigations.The aim of this work is to obtain hydrogels based on

copolymers of N-isopropylacrylamide and ethylene glycol vinyl ether for use as a base for ointment formulations. Unlike the study reported in [9], N,N′-methylenebisacrylamide (MBAA) was used for the first time as a crosslinking agent. Hydrogels were synthesized by varying the molar ratio of monomers in the initial mixture and adjusting the aqueous phase content in the range of 50–70%. An optimal synthesis route was selected based on the experimental results.The gel fraction yield demonstrates that, as the content of the hydrophilic EGVE monomer in the initial monomer mixture (IMM) increases, both the gel yield and the degree of crosslinking of the hydrogels decrease (Fig. 1a). This indicates that the hydrophobic NIPAAm monomer exhibits higher reactivity compared to the hydrophilic EGVE monomer.As the proportion of EGVE in the initial monomer mixture increases, the decrease in crosslinking density leads to an increase in the swelling degree of the hydrogels in water, as shown in Fig. 1b. This confirms that water acts as a better solvent for NIPAAm–EGVE polymer hydrogels with higher EGVE content.

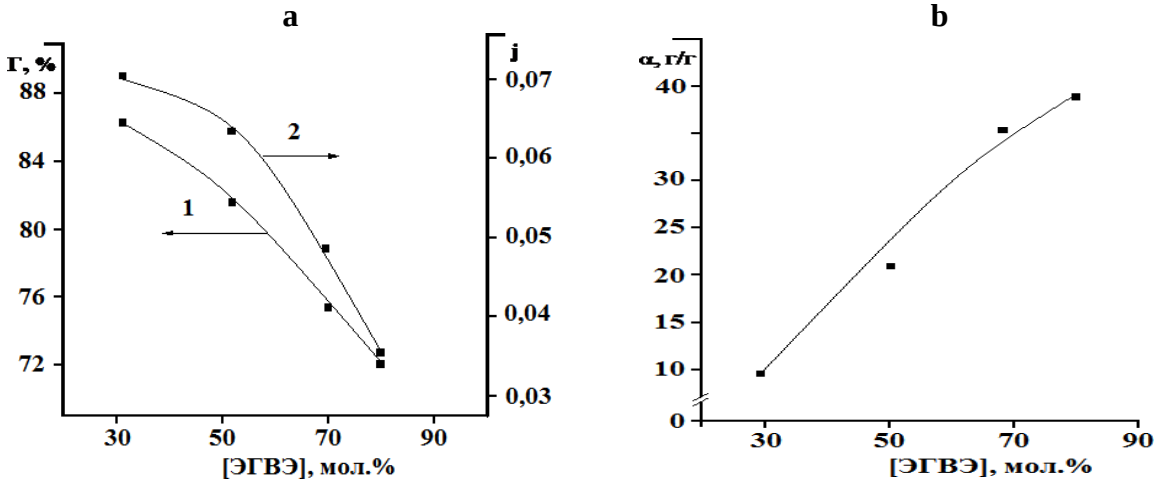

Figure 1 - Dependence of (a) gel fraction and crosslinking degree, and (b) swelling degree in water on the content of EGVE in the initial monomer mixture (IMM)

The curves shown in Figure 2 indicate that the swelling degree is strongly dependent on the copolymer composition. An increase in the content of the hydrophobic NIPAAm component in the initial monomer mixture leads to a decrease in the swelling degree of the resulting hydrogels in water, whereas an increase in the hydrophilic EGVE content results in a corresponding increase in swelling. This behavior can be explained by the reduction in the crosslinking density of the polymer network (Fig. 2).

Compared with the results reported in [9], the hydrogels obtained in this study exhibit noticeably higher swelling capacities. This improvement is attributed to the use of N,N′-methylenebisacrylamide (MBAA) as a crosslinking agent during synthesis, which provides more favorable network formation conditions.

Hydrogels are widely recognized as “smart materials,” as discussed in detail in the literature review. This is primarily due to their high biocompatibility with the human body and their extensive application in controlled drug release systems. Owing to their high-water absorption capacity and soft consistency, they are also used as one of the key components in ointment formulations. Their temperature-dependent drug release behavior is governed by thermosensitive polymer networks. Therefore, investigating the temperature responsiveness of the synthesized copolymers was significant.

To study the thermosensitive behavior of the hydrogels, the effect of temperature on their swelling capacity, specifically on the relative volume change of the copolymers, was investigated. During the thermally induced collapse studies, equilibrium-swollen hydrogel samples in the form of cylinders (3–5 mm in diameter and 2–3 mm in thickness) were placed in a temperature-controlled aqueous cell. The temperature varied from 25 °C to 60 °C in six measurement steps. Changes in the

relative volume of the polymer hydrogels were recorded using a V-630 cathetometer (measurement accuracy ±0.1 mm) and evaluated as the V/V_0 ratio.

As shown in Figure 3, an increase in temperature leads to a reduction in the volume of the NIPAAm–EGVE polymer networks, indicating a thermally induced contraction state. This behavior is attributed to the enhancement of hydrophobic interactions involving NIPAAm units, which stabilize a more compact conformation of the copolymer macromolecular chains. Furthermore, increasing the NIPAAm content in the polymer network results in a higher amplitude of thermally induced contraction, and the transition from the swollen to the collapsed state occurs at lower temperatures as the system becomes more hydrophobic.

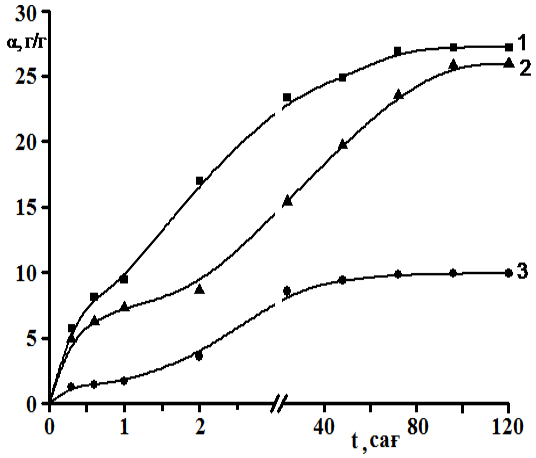

Figure 2 - Swelling kinetics of NIPAAm–EGVE hydrogels in water.

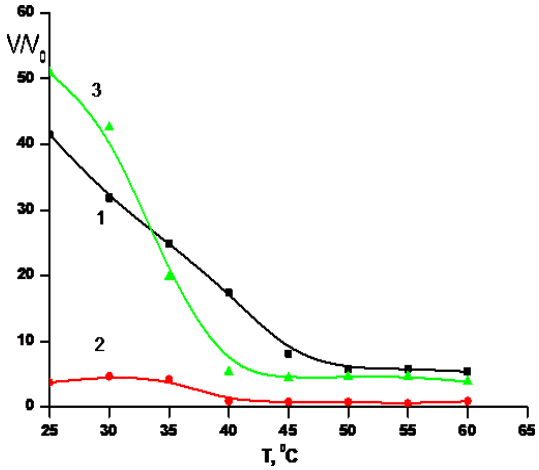

Figure 3 - Effect of temperature on the relative volume of NIPAAm–EGVE copolymer

Burns are injuries to body tissues caused by exposure to high temperatures or certain chemical agents.

The severity of a burn is determined by the depth and area of the injury. First aid in burn cases is primarily aimed at eliminating the effect of the external damaging factor and treating the affected area [10].

Burn injuries are among the most widespread types of trauma worldwide. In the Republic of Kazakhstan alone, approximately 17,000 cases of burn injuries are registered annually. This figure reflects only those patients who seek medical assistance, while an additional 30% receive ongoing treatment. Each year, around 200 people die because of burn-related injuries.

The healing process of burn wounds is generally divided into three stages, depending on the therapeutic approach:

- Phase I – Inflammatory phase. Main characteristics include swelling, significant exudate formation, microbial invasion of the wound area, necrosis development, and disruption of microcirculation.
- Phase II – Regeneration phase (granulation). This stage involves wound cleansing from exudate, reduction of edema, and formation of new connective tissue.
- Phase III – Final maturation phase of connective tissue regeneration. This stage is characterized by the formation of new epithelial tissue on the wound surface.

During the first phase, prevention of secondary infection is critical. In the second phase, the focus is wound cleansing, where the hygroscopic properties (ability to absorb moisture from the environment) of dressing materials play an important role [11].

In this context, polymeric hydrogels have been widely discussed in literature as promising materials for the development of soft contact lenses, controlled and prolonged drug release systems, and transdermal therapeutic systems. Their high-water content in equilibrium state makes their structure highly like human tissues, which provides excellent biocompatibility.

In this study, NIPAAm–EGVE-based hydrogels were investigated as potential drug carriers

and as a base material for ointment formulations, with particular emphasis on their interaction with drug substances. Streptocide was selected as the model drug. Streptocide is a broad-spectrum antibacterial agent. Its mechanism of antimicrobial action is associated with antagonism toward para-aminobenzoic acid (PABA), a structurally similar compound. Streptocide is taken up by microbial cells, where it competes with PABA and inhibits its incorporation into dihydrofolic acid. It also competitively inhibits the enzyme dihydropteroate synthase, which is responsible for the incorporation of PABA into dihydrofolic acid. As a result, the synthesis of dihydrofolic acid is disrupted, leading to a decrease in the formation of tetrahydrofolic acid, which is essential for the synthesis of purines and pyrimidines. This ultimately inhibits microbial growth and reproduction, producing a bacteriostatic effect [45].

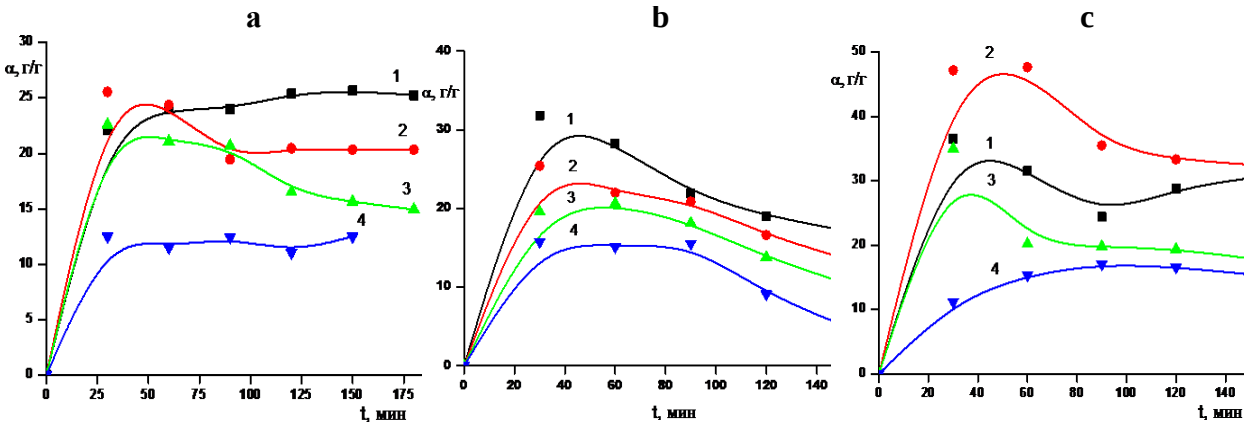

Figure 4 - Swelling kinetics of NIPAAm–EGVE hydrogels in different media. Initial monomer feed ratio (IMM): [NIPAAm]:[EGVE] = 30:70 (a); 50:50 (b); 70:30 (c), mol.%. NaCl concentrations: 0.45 (1); 0.9 (2); 1.8 (3); and alcohol (4).

In this work, the swelling kinetics of the NIPAAm–EGVE crosslinked network in streptocide solutions with different NaCl concentrations, as well as in alcohol, was investigated (Fig. 4). It was found that, regardless of the composition of the NIPAAm-based copolymer, the hydrogels did not swell in alcohol, which is attributed to the precipitation effect of alcohol on the linear structure of the hydrogel network [9].

It was also observed that increasing the concentration of NaCl leads to different swelling behaviors of the hydrogel. As the concentration of low-molecular solutes increases, the swelling degree of the hydrogel decreases, which is explained by the thermodynamically unfavorable interactions between the hydrophobic groups in the copolymer and the surrounding medium.

This is further confirmed by the fact that increasing the proportion of NIPAAm units in the copolymer results in a greater decrease in swelling in saline solutions. However, in systems with a high content of NIPAAm units and at high salt concentrations, the hydrogel exhibits an initial swelling within the first 1.5–2 hours, passing through a maximum. This initial swelling is attributed to the adsorption of low-molecular species on the hydrogel surface, leading to surface contraction of the polymer network. As a result, NaCl ions can penetrate the internal pores of the hydrogel network, causing a temporary increase in swelling during the initial stage.

To obtain hydrogel-based ointment matrices from isopropylacrylamide copolymers, the interaction patterns between the drug substance and the polymer network were investigated.

For studying complex formation with the drug (DS), equilibrium-swollen tablet-shaped hydrogel samples were immersed in a streptocide solution, and the kinetics of the interaction were monitored over time (Fig. 5). The experiments were carried out using UV spectrophotometry.

The obtained results showed that complex formation between the drug and the copolymer increases with both (i) the percentage of NIPAAm units in the hydrogel composition and (ii) the ionic strength of the medium. This behavior is explained by the fact that, in addition to coordination interactions between streptocide and the polymer matrix, hydrophobic interactions also contribute

significantly to complex formation.

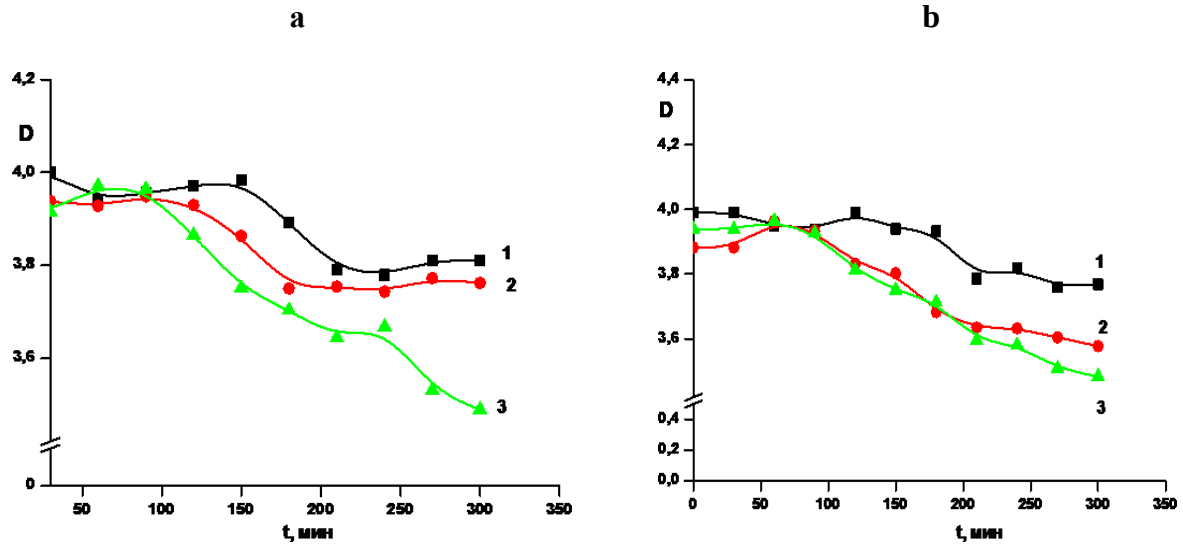

Figure 5 - Sorption kinetics of drug substance by NIPAAm–EGVE hydrogels. Initial monomer feed ratio (IMM): [NIPAAm]:[EGVE] = 30:70 (1); 50:50 (2); 70:30 (3), mol.%. Drug concentration: 0.1% (a); 0.05% (b).

4. Conclusion

In this work, water-swellable copolymers based on N-isopropylacrylamide (NIPAAm) and ethylene glycol vinyl ether (EGVE) were successfully synthesized. The influence of temperature on the hydrogel systems was investigated. It was found that increasing the proportion of NIPAAm units in the copolymer composition accelerates the thermally induced collapse (thermocollapse) behavior of the hydrogels.

To evaluate the potential application of the obtained hydrogels as ointment bases, their interaction with a model drug substance was studied. Streptocide was used as the model drug. It was established that an increase in the NIPAAm content in the hydrogel composition leads to enhanced ability of the polymer network to form complexes with the drug substance.

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Author Contributions

Conceptualization: Asel Toktabayeva, Formal analysis: Raikhan Rakhmetullayeva, Investigation: Asel Toktabayeva, Methodology and Supervision: Raikhan Rakhmetullayeva, Writing – original draft: Asel Toktabayeva, Writing – review & editing: Raikhan Rakhmetullayeva.

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Data availability statement: The data presented in this study may be obtained on request from the corresponding author.

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