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Cryostructuring of Polymeric Systems. 61. Physicochemical Properties of Poly(vinyl alcohol) Cryogels Prepared on the Basis of Urea-Containing DMSO-Solutions of the Polymer and Evaluation of the Resultant Gel Materials as Potential Drug Carriers

Macroporous physical poly(vinyl alcohol)-based (PVA) cryogels were prepared originating from the dimethylsulfoxide solutions of the polymer that contained urea additives. The variables of the cryotropic gel-formation process were its temperature and the concentration of the added urea, which caused the increase in the rigidity and heat endurance of the resultant cryogels, as well as promoted widening of the macropores in the gel matter. Subsequent rinsing of the DMSO-swollen cryogels with the water excess resulted in the water-swollen PVA cryogels with simultaneous further increase in their rigidity. These gel matrices were tested with respect of their potential to operate as the polymeric carriers in the drug delivery systems. Loading of such water-swollen cryogels with a model drug, ε-amino caproic acid, and then studies of its release kinetics revealed that urea content in the initial PVA solutions used for the freeze-thaw-induced formation of the DMSO-swollen cryogels played the key role for the release characteristics of the drug-loaded water-swollen gel carrier. Namely, PVA cryogels prepared in the presence of a higher concentration of urea possessed the larger pores and, as a result, the drug release occurred somewhat faster.

Keywords: poly(vinyl alcohol) cryogels, dimethylsulfoxide polymer solutions, urea additives, cryogenic processing temperature, drug delivery cryogel carriers.

Introduction

Polymeric cryogels are the macroporous gel materials formed as a result of cryogenic processing (freezing — incubation in a frozen state — defrosting) of the molecular or colloidal solutions that contain certain low-molecular or high-molecular precursors [1–8]. Various polymeric cryogels are of both significant scientific and intensively developing applied interests. In particular, the latter assertion concerns the biomedical areas, where the use of different biocompatible cryogels has already revealed promising prospects [1, 7, 9–16]. One of the important types of these materials is the so-called drug delivery systems, e.g. the drug-carrying covers on wound and burns, and the respective cryogels are tested in details for such biomedical applications. Specific morphology of cryogels with the system of interconnected macropores allows loading the polymeric matrix with the drugs of a diverse chemical structure, aggregate state (soluble, solid and gaseous) and size (from the low-molecular weight substances to the polymeric ones and even nano/microparticles). Therefore, these gel materials are well-suitable for the drug delivery aims [1, 2, 9, 12–24]. With that, the polymeric matrix of similar delivery systems must be non-toxic, biocompatible and, if required, must be biodegradable. As regards the non-degradable (by the human organisms) cryogenically-structured polymeric carriers used in this field, the poly(vinyl alcohol)-based cryogels (PVACGs) [1, 4, 25–33] are of gross interest. Similar non-covalent macroporous gel materials [1, 4, 27, 34–41] are formed by the mechanism of interchain cross-linking via H-bonding. These cryogels posses excellent physico-mechanical properties, high heat endurance, and biocompatibility [1, 26–30, 39, 41]. Such combination of their useful characteristics opens wide possibilities for the biomedical applications of PVACGs [1, 14, 20, 27, 28, 33, 41–46].

The fabrication of PVACGs is a rather simple procedure, which includes the preparation of aqueous solution of this polymer, the addition, when it is required, soluble or insoluble (disperse filler) additives, then freezing the resultant feed liquid system at desired minus temperature for certain time period and subsequent thawing of frozen samples [1, 2, 35–30, 34–39]. The properties of thus prepared PVACGs depend on the molecular-weight characteristics of the initial polymer, its deacylation degree and chain tacticity, type and con-

centration of additives, when those are used, as well as on the regimes of all stages of the cryogenic processing and the number of freeze-thaw cycles [1, 2, 19, 20, 24–30, 36–40].

Apart from the PVACGs prepared from the aqueous solution of this gelling polymer, PVACGs are known to be formed based on its dimethylsulfoxide (DMSO) solutions [27, 34, 47–49]. In this case, it is found that some low-molecular solutes influenced on the physico-chemical properties of the resultant cryogels oppositely in comparison to the effects observed in aqueous media [50, 51]. Thus, it is revealed that such well-known chaotropes as urea or guanidine hydrochloride, the additives of which cause marked decrease in the gel strength and heat endurance of the PVACGs prepared from the aqueous polymer solutions [52, 53], in the DMSO media exhibit the antichaotropic (so-called *kosmotropic*) influence on the respective cryogels causing the considerable increase in their rigidity and fusion temperatures [51]. The studies of such phenomenon show that its main reason consisted in the urea-induced decrease in the solvation ability of DMSO with respect to PVA. As a result, this effect is the key factor responsible for strengthening of the structure formation upon the freeze-thaw gelation of this polymer in DMSO additionally containing additives like urea, which is capable of competing with PVA for the solvent. After the exhaustive rinsing of such PVACGs with water, i.e. after the removal of soluble additives and replacement of DMSO for H_2O, the elastic modulus and fusion temperature values of thus treated cryogels turned out to be higher significantly as compared to the PVACGs formed in the medium of pure water. In other words, it was possible to fabricate "aqueous" PVACGs possessing increased mechanical and thermal properties.

Considering these effects, we decided to use such preparation scheme, i.e. to fabricate "primary" PVACGs in the DMSO medium with urea additives, further to rinse thus formed gel systems by an excess of water, load the resultant "secondary" PVACGs with a model drug (ε-amino caproic acid (ε-ACA) in this case), and evaluate the release kinetics of this known hemostatic agent [54] from the cryogel carriers.

Therefore, the tasks of this study are as follows:

(i) to reveal the influence of the concentration of added urea and the temperature of the cryotropic gelformation on the physico-chemical characteristics of final cryogels;

(ii) to trace how the same preparation parameters are reflected on the drug release behavior.

Experimental

2.1 Materials

The following substances were used: poly(vinyl alcohol) (molecular weight of ca. 86 kDa, the deacetylation degree of 100 %; Acros Organics, USA), urea ("ultra pure" grade) and ε-amino caproic acid (>99.5 %) (both Sigma, USA). Dimethyl sulfoxide (>99 %; Komponent-Reaktiv, Russian Federation) was additionally purified by the freeze-out procedure.

2.2. Methods

2.2.1. Preparation of PVA cryogels

The preparation of the feed PVA solutions and then their cryogenic processing were carried out as described previously [51]. Briefly, a known amount of dry polymer was dispersed in a calculated volume of DMSO to reach a PVA concentration of 100 g/L. The mixture was incubated for 18 h at room temperature for swelling of the polymer, followed by the system heating for 1 h on a boiling water bath under stirring until the completion of PVA dissolution. Subsequently, the required amount of dry urea was added and dissolved in this liquid system after its cooling to room temperature.

Preparation of the "primary" PVACGs for the physico-mechanical tests was performed in the sectional duralumin moulds (inner diameter 15 mm, height 10 mm). The gel samples of the same composition for the measurements of their fusion temperatures (T_f) were formed in transparent polyethylene test tubes (inner diameter 10 mm), the 3-mL portions of the polymer solution were poured, and a stainless steel ball (diameter 3.5 mm, weight 0.275±0.005 g) was placed on the bottom of each tube. The containers and the tubes were put into the chamber of an FP 45 HP precision programmable cryostat (Julabo, Germany), where the samples were frozen and incubated for 12 h at the preset minus temperature. Then, the temperature was raised to 20 °C at a rate of 0.03 °C/min controlled by the cryostat microprocessor. Onwards, each cylindrical gel sample prepared in the duralumin moulds was subjected to the physico-mechanical tests (section 2.2.2) followed by immersing the sample in the vessel with 100 mL of pure water, where the cryogel was incubated with periodical stirring for 24 h. Such rinsing procedure was repeated 6 times to extract solutes from the samples and replace DMSO for water inside the gel bulk thus resulting in the transformation of the "primary" PVACGs to the "secondary" ones.

2.2.2. Physico-mechanical measurements

The compression Young's modulus (E) of the PVACG samples was determined from the linear portion of the stress–strain dependence using a TA-Plus automatic texture analyzer (Lloyd Instruments, UK) at a loading rate of 0.3 mm/min. Upon these experiments the applied load was automatically increased from 0 to 5 N. The tests were performed until reaching a 30 % of deformation. The measurements were performed for both "primary" and "secondary" PVACGs. The E values were measured for three parallel samples; the samples were examined in three to five independent experiments. The obtained results were averaged.

2.2.3. Heat endurance of PVA cryogels

Fusion temperatures (T_f) of the "primary" PVACGs were measured in accordance with the earlier reported procedure [29, 30, 50–52] by placing upside down the tightly corked polyethylene tube containing cryogel with the stainless steel ball (3.5 mm in diameter and 0.275±0.005 g in weight) at the bottom into the water bath. The bath temperature was increased at a rate of 0.4±0.1 °C/min. The gel fusion point was detected as the temperature when the ball fell down onto the stopper of the test tube after passing through the fused gel. The T_f values were measured for three parallel samples; the samples were examined in three independent experiments. The obtained results were averaged.

2.2.4. Optical microscopy studies

Macroporous morphology of the PVACG samples was investigated as described earlier [51] with use of an Eclipse 55i optical microscope (Nikon, Japan) equipped with an MMC-50C-M system (MMCSoft, Russian Federation) for digital image recording. In the as-prepared "primary" cryogels, DMSO was replaced by pure water, and the resultant "secondary" cryogels were cut for the 10-μm thick sections orthogonally to the axis of cylindrical samples using a SM-1900 cryomicrotome (Leica, Germany). Each section was placed on the microscope glass, which was then immersed into a 1 % aqueous solution of Congo red (the standard dye used for painting PVA-based materials [61], including the PVA cryogels [19, 24, 29, 30, 35, 36, 50–53]) for staining for 10 s, and then rinsed with pure water. The excess of liquid was removed with a filter paper. Then, the section was poured with a drop of fixing solution (solution of 1 g of gelatin in 12 mL of 50 % aqueous glycerol and 0.2 g of phenol as a bacteriostatic agent) and sealed with a cover glass. Prior to the studies, the samples were stored in a closed vessel at 4 °C.

2.2.5. Loading of PVACGs with a model drug substance and its release from the gel carrier

The volumes of the cylindrical samples of "secondary" PVACGs (V_{sec}) were measured. Each sample was immersed into a vial with aqueous ε-ACA solution of necessary volume ($V_{\varepsilon\text{-ACA}}$) so that the sum volume 'cryogel+liquid' turned out to be equal to 4 mL. Since the V_{sec} values depended on the urea concentration in the feed PVA solutions, the ε-ACA concentrations in the loading solutions were prepared with the intention to reach after the equilibration approximately the same ε-ACA amount (m_{eq}) being entrapped in these gel carriers (Table).

The release of ε-ACA from the amino-acid-loaded PVACGs was registered using the conductometry technique (a F30 conductometer, Mettler-Toledo, Switzerland). Each sample of the ε-ACA-saturated cryogel was placed into a beaker with 30 mL of pure water, and the values of electrical conductivity were measured under the instructions given in the manual for this instrument. The concentration of the amino acid in the respective solutions was found from the preliminary obtained calibration plot.

Table

Composition of the systems used in the loading-release experiments

Urea concentration in the feed PVA solution, mol/L	V_{sec}, mL	$V_{\varepsilon\text{-ACA}}$, mL	ε-ACA concentration in the loading solution, mg/L	m_{eq} [a], mg
0	1.29	2.71	23.3	29.9
2	1.01	2.99	30.0	30.0
4	0.79	3.21	37.9	29.9

[a] After the equilibration of the 'cryogel+liquid' system

Results and Discussion

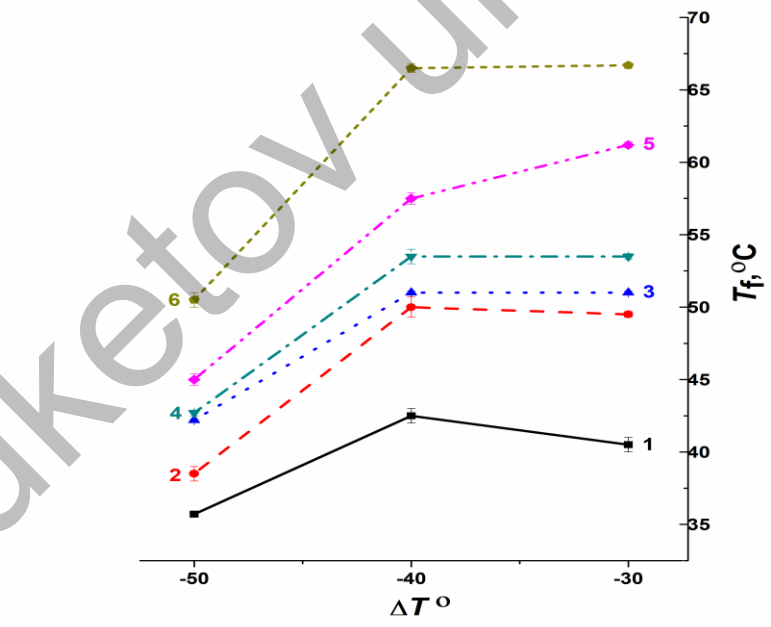
3.1. Preparation of "primary" and "secondary" PVACGs

As indicated in the 'Introduction', the subjects of this study are the PVA cryogels possessing both the increased durability and the potential ability to operate as the efficient biocompatible carriers for the drug

delivery systems like the covers on wounds or burns. To achieve the former goal, we selected the approach based on the earlier found kosmotropic influence of urea introduced in the feed DMSO solutions of PVA to be gelled cryogenically [51]. The respective PVACGs were prepared (section 2.2.1) starting from the urea-free (reference samples) and the urea-containing DMSO solutions of the polymer. Its concentration was 100 g/L in all the cases, and the content of urea was one of the following series: 0, 1.0, 1.5, 2.0, 3.0 or 4.0 mol/L. Such solutions were cryogenically solidified at the desired freezing temperature (T_{fr}): either –11.6 °C, or –21.6 °C, or –31.6 °C. Since the DMSO crystallization point (T_0) is +18.4 °C [55], in terms of the ΔT values equal to the T_{fr}–T_0 [50, 51], this parameter had the following moduli: ΔT = –30°, –40° and –50°, respectively. Such ΔT values testify that feed polymeric solutions were frozen at the temperatures 30, 40 or 50 degrees lower than the crystallization point of a neat DMSO. After storing frozen and then thawing the "primary" PVACGs were obtained (section 2.2.1). Subsequent measurement of their characteristics allowed us tracing the influence of such varying parameters as the urea concentration and the freezing temperature on the physico-chemical properties of these DMSO-swollen cryogels. Further change of DMSO for water resulted in the target "secondary" water-swollen PVACGs, which were then loaded with a model drug (ε-ACA), and its release kinetics was evaluated.

3.2. Thermal and physico-mechanical properties of the PVACGs under study

Since PVACGs are physical gel materials, the spatial network of which is maintained by the thermo-dissociating interchain H-bonds between the OH-groups of neighboring chains, the fusion temperature of PVACGs is the indicator of both the amount of such non-covalent bonds and their cooperativity within the microcrystallinity zones performing as the knots of the supramolecular polymeric network [25–30, 37]. In this respect, the elevation of the fusion temperature values (T_f) of PVACGs formed in the DMSO medium with increasing concentration of added urea (Fig. 1) points to some increase in the total amount of interchain H-bonds responsible for the heat endurance of the physical gels, in general [56], and of the PVA cryogels under consideration in the present study, in particular. In other words, the data of Fig. 1 confirm the earlier observed the antichaotropic influence [51] of urea on the freeze-thaw gelation of PVA in the DMSO medium.



Urea concentration: 0 (curve 1), 1.0 (curve 2), 1.5 (curve 3), 2.0 (curve 4), 2.0 (curve 5) and 4.0 (curve 6) mol/L

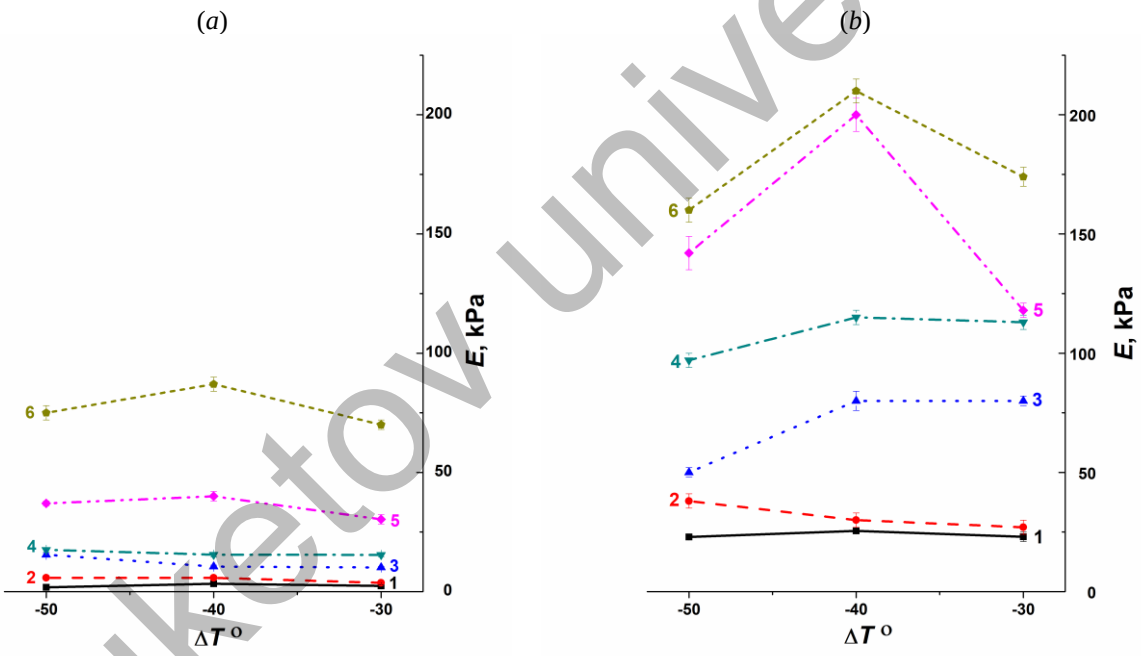
Figure 1. The values of the gel fusion temperature (T_f) of the "primary" PVA cryogels prepared on the basis of the urea-free and the urea-containing DMSO solutions of the polymer as dependent on the temperature of the cryotropic gelation process

The dependences in Fig. 1 demonstrate that both the urea-free and the urea-containing PVACGs prepared at the cryogenic processing temperatures ΔT = –30° and –40° possessed higher heat endurance in comparison with the cryogels prepared at ΔT = –50°, thus indicating the decreased gel-formation efficiency with lowering the freezing temperature. Such a trend is known to be inherent in the PVA cryotropic gelation of

the urea-free aqueous solutions [27, 29], i.e., similar effect is common for the freeze-thaw gel-formation of this polymer in both the aqueous and the organic media.

In turn, the graphs in Figure 2 (plots *a* and *b*) combine the experimental data on the rigidity (in the terms of Young's modulus — *E*) of the "primary" and the "secondary" PVACGs. Thus, it is possible to compare their physico-mechanical properties depending on the ΔT values for the samples that contained various amount of urea in the composition of initial DMSO solutions of the PVA, as well as to demonstrate pictorially a paramount increase in the gel strength caused by the transition from the DMSO-containing "primary" cryogels to the aqueous "secondary" ones. The analysis of these results revealed the following trends with the respect of the factors capable of exerting major effects on the elasticity of the cryogels under discussion.

First, this work confirms previous study [51] on kosmotropic-like "action" of urea additives on the PVA cryotropic gel-formation in the DMSO medium. If in the case of the formation of cryogels via the freeze-thaw processing of the aqueous urea-containing PVA solutions, the increase in the urea concentration gave rise to the crucial decrease in the gel strength because of the urea-induced inhibition of the interchain PVA-PVA H-bonding [52, 53] while in the DMSO medium the effects were opposite. This result is stipulated by the competition of urea with PVA for the solvent, since the urea forms rather stable H-bonds with DMSO thus promoting the partial change of the PVA-DMSO solvate interactions for the additional interchain PVA-PVA H-bonding [51]. In particular, with increasing the initial urea concentration from 0 to 4 mol/L the *E* values of the respective "primary" PVACGs grew from 1.8-3.3 kPa up to 70-87 kPa, i.e. more than about 30-fold (Fig. 2*a*). Also, Figure 2*b* illustrates that this trend was retained for the "secondary" cryogels.



Urea concentration: 0 (curve 1), 1.0 (curve 2), 1.5 (curve 3), 2.0 (curve 4), 2.0 (curve 5) and 4.0 (curve 6) mol/L

Figure 2. The values of the elastic modulus of the "primary" (*a*) and the "secondary" (*b*) PVA cryogels prepared on the basis of the urea-free and the urea-containing DMSO solutions of the polymer as dependent on the temperature of the cryotropic gelation process

Second, the influence of the cryogenic stages temperature (i.e. ΔT values) within its range from –30° to –50° on the rigidity of the resultant "primary" PVACGs (Fig. 2*a*) had a weakly expressed bell-like character being more evidently pronounced with an increase in the urea concentration in the initial DMSO solutions of PVA (Fig. 2*a*). For the PVACGs prepared in the urea-free aqueous media such bell-like temperature dependences are well-known (e.g., see [29]). The reason is the competition of different factors that influence on the characteristics of the resultant PVACGs. Thus, at the same polymer concentration in an initial solution, the lower is the temperature of frozen system the higher is the PVA concentration in the unfrozen liquid microphase [57–59]. This effect promotes the polymer–polymer interactions and the formation of cryogels. However, a regular increase in viscosity and the retardation of the thermal mobility of chains and their seg-

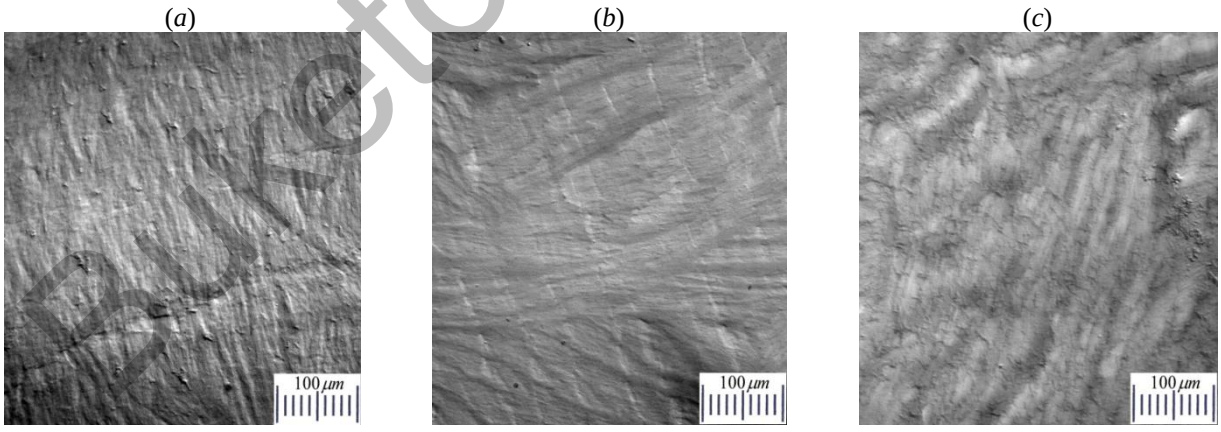
ments with a decrease in the temperature act as factors that inhibit gelation. As a result, the bell-like dependence of the physicochemical characteristics for such cryogels on the temperature of freezing–storage of the cryogenically-structuring polymer system is observed.

Third, the transformation of the "primary" PVACGs to the respective "secondary" ones resulted in the significant growth of the gel strength. For example, if the values of the elastic modulus for the urea-free "primary" PVACGs varied within the range from 1.8 to 3.3 kPa (curve 1, Fig. 2*a*), for the "secondary" cryogels these values grew up to the range of 23–26 kPa (curve 1, Fig. 2*b*), i.e. almost 10-fold. For the urea-containing "primary" PVACGs their *E* values, depending on the urea concentration and the temperature of cryogenic processing, were over the range of 4–87 kPa (curves 2–5, Fig. 2*a*), whereas after the samples transformation to the respective "secondary" aqueous cryogels their elastic moduli increased by many times and reached the level of 27–210 kPa (curves 2–5, Fig. 2*b*). Such reinforcement effects were found [51] to be induced by the replacement of the DMSO medium, which was a thermodynamically better solvent for PVA, by a poorer solvent — water [60]. As a consequence of such medium change, some fraction of the polymer-solvent interactions was replaced by the polymer-polymer ones, thus leading to the increase in the density and the rigidity of the 3D supramolecular network of the "secondary" PVACGs as compared with the "primary' ones.

3.3. Microstructure of the PVACGs under study

Since the PVACGs are the heterophase macroporous gel matrices [1, 4, 25–33], their integral physicomechanical properties are stipulated not only by the rigidity of the polymeric phase (the walls of macropores) but also by the macroporous morphology of these gel materials. On the other hand, it is significant to compare the drug release characteristics of the drug-loaded "secondary" PVACGs fabricated from the DMSO-swollen "primary" cryogels that, in turn, were prepared in the presence of different amount of urea additives.

The first stage of such comparison was the microstructural study of the respective cryogels (section 2.2.4). The results of these experiments are illustrated by the optical microphotographs in Fig. 3, where the macroporous morphology is shown for the thin sections of the "secondary" PVACGs prepared originating from the initial polymer solutions, either the urea-free one (*a*), or those containing urea at the concentration of 2.0 (*b*) and 4.0 mol/L (*c*). The dark areas in these black-and-white images are the elements of the polymeric phase (the pore walls stained with the 'Congo red' dye), and the light areas are the macropores filled with water. The "secondary" water-swollen cryogels rather than the "primary" DMSO-swollen samples were investigated since the polymeric walls of macropores in the 'primary' cryogels were almost transparent, so the peculiarities of their texture in the thin sections were in fact indiscernible with an optical microscope. In addition, it turned out that the DMSO-swollen PVACGs were practically not stained with Congo red dye usually employed to contrast the thin sections of the water-swollen PVA cryogels [19, 24, 27, 29, 30, 53].



Urea concentration: 0 (*a*), 2.0 (*b*), and 4.0 (*c*) mol/L

Figure 3. Optical images of the microstructure registered for the Congo-red-stained thin sections of the "secondary" PVACGs derived from the respective "primary" samples prepared on the basis of the urea-free and the urea-containing DMSO solutions of the polymer by their cryotropic gelation at $\Delta T = -40^{o}$

Qualitatively, Figure 3 demonstrates clear differences between the character of macroporous morphology of the cryogels prepared from the urea-free (*a*) and the urea-containing (*b, c)* feed PVA solutions. If the PVACG formed by the freeze-thaw gelation of the urea-free PVA solution had the pores of an anisometric

shape and no more than ~10 μm in cross-section, the presence of the urea additives in the initial PVA solutions caused a noticeable increase in the diversity of the pore shapes and sizes, especially with the urea concentration increase. With that the lamellar structures (up to 10–20 μm in the cross-section) of pore walls were arisen in the PVACG formed in the presence of 2.0 mol/L content of urea (Fig. 3*b*), and in the case of cryogel prepared with 4.0 mol/L of urea the porous texture of the matrix became more diffuse with widening of the pore size to the level of about 20–35 μm (Fig. 3*c*). It turn, the polymeric phase of such PVACG were stained stronger in the comparison to the image (*b*), thus indicating to the increased density of the polymeric network within the pore walls of this sample.

In general, the data of Figure 3 testified that the cross-section of the macropores in the PVACGs is increased with the growth of urea concentration in the DMSO solutions of PVA to be freeze-thaw structured. Therefore, such an effect should be manifested in the drug-release behavior of the soluble substances preliminary loaded in the PVACG-based drug carrier.

3.4. Loading and release of ε-ACA in and from the PVACGs

There are two principle options to insert some soluble substance to the polymer gel matrix intended for the use as a potential drug delivery system [17]. The first one is the introduction of the substance of interest in the mixture of precursors prior to the system gelation, thus resulting in the substance entrapment in the gel matrix after the completion of its formation. The main disadvantage of such approach is the lack of real possibility to rinse the resultant gel from the sol-fraction (e.g., the residues of precursor components that did not embed in the 3D polymeric network), since the entrapped target solute will be simultaneously washed-away. The second option includes the preliminary preparation of the gel matrix, its rinsing to remove the sol-fraction, and only then the loading of thus treated polymeric carrier with the solute of interest. In this study, we implemented the latter approach as the model drug compound the ε-amino caproic acid was used (section 2.2.5). Since for the microstructure of prepared in the present study PVAGCs, the concentration of urea in the feed solutions to be structured cryogenically was more significant factor than the freezing temperature (Fig. 3). the ε-ACA loading/release experiments were carried out using "secondary" PVA cryogels derived from the corresponding "primary" gel samples formed under the identical thermal conditions, namely at $\Delta T = -40^{o}$. Thus, the feed DMSO solutions of PVA either did not contain the urea (reference system), or its concentrations were 2.0 or 4.0 mol/L.

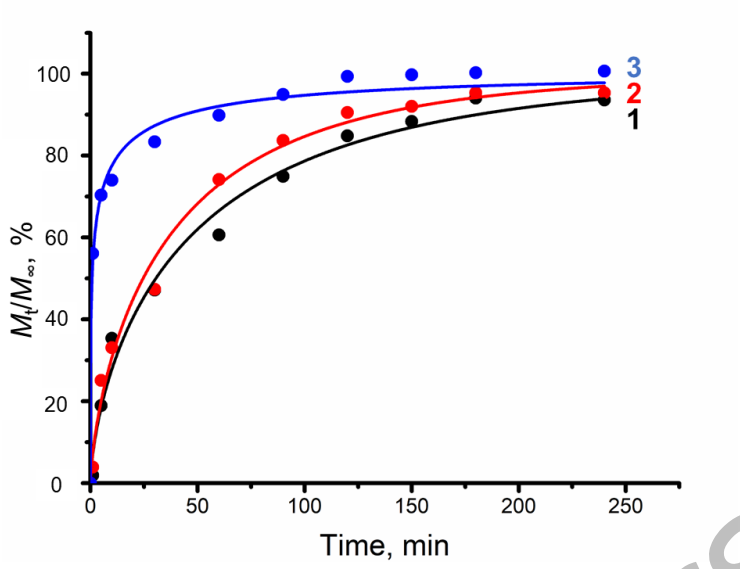
During these experiments the release kinetics was analyzed in terms of the Weibull's function [61] depicted as the solid lines of the plot in Fig. 4:

$$M_t/M_\infty = 1 - \exp(-a \times t^{\,b}),$$

where M_t is the amount of the released substance at time t; M_∞ is the solute amount entrapped in the gel carrier (in our case this value is equal to that of m_{eq} in Table); M_t/M_∞ is the solute fraction (in per cent) released from the matrix for time t; the parameters a and b are some constants. The latter ones are calculated automatically by the ORIGIN PRO software (OriginLab Corp., Northampton, USA) after uploading the Weibull's equation and the experimental data in this computer program.

Such kind of the kinetic data presentation is known to be a useful variant for the analysis of the drug release mechanism from various polymeric matrices [62]. In the case of ε-ACA release from the "secondary" PVACGs, this approach showed good correlation of the experimental values (round symbols in Fig. 4) with the Weibull's approximation. In addition, on a qualitative level, the obtained data turned out to be in a sufficient accordance with the microstructural features of the respective cryogel drug carriers. Namely, the larger was the size of gross pores inside the gel matrix (i.e. the larger was the PVA-free space of the pores within the macroporous cryogel), the faster was the drug release. Most likely, this trend was stipulated by the significant widening of the macropores in the resultant cryogels upon the increase in the urea concentration in the initial PVA solution (Fig. 3).

Thus, the late stage (>60 %) of the ε-ACA release in the case of drug carrier with the largest pores (PVACG formed originating from the feed solution with urea concentration of 4.0 mol/L; curve 3 in Fig. 4) reached for 5–10 min after start of release experiments. For the drug carrier based on the cryogel formed from the feed PVA solution with urea concentration of 2.0 mol/L (curve 2 in Fig. 4) this time period elongated up to 50–60 min, and for the drug carrier formed in the urea-free system this was already about 1.5 h (curve 2 in Fig. 4). These data evidently demonstrate that urea content in the initial PVA solutions, which is used for the freeze-thaw-induced formation of "primary" cryogels, plays a key role for the release characteristics of the drug-loaded "secondary" PVACGs.



Urea concentration: 0 (curve 1), 2.0 (curve 2) and 4.0 (curve 3) mol/L

Figure 4. Kinetic profiles of ε-ACA release from the drug-loaded "secondary" PVACGs transformed from the "primary" cryogels prepared by the cryotropic gel-formation at ΔT = –40° of the urea-free and the urea-containing DMSO solutions of the polymer

Conclusions

Urea is a well-known chaotropic agent capable of efficiently inhibiting the formation of H-bonds in aqueous media. Since the H-bonding processes are the main ones responsible for the gel-formation in the frozen water-PVA systems, the urea additives introduced in the feed aqueous PVA solutions cause significant deteriorative effects with respect of the rigidity and heat endurance of the resultant cryogels [52, 53]. On contrast, in such organic solvent, as dimethylsulfoxide, the additives of this chaotropes exhibit the opposite (i.e. the kosmotropic-like) influence causing the increase in the elastic modulus and fusion temperature of the resultant PVACGs [51]. Exactly the latter phenomenon was used in the present study to prepare the PVACGs possessing high mechanical strength and thermal resistance, following by the evaluation of such polymeric materials as potential carriers for the drug delivery systems.

The urea concentration on the feed DMSO solutions of PVA and the temperature of the cryogenic processing were the variables during the performed systematic studies. As a result, it was shown that the amount of urea introduced in the initial polymer solution to be freeze-thaw-gelled had exerted the crucial influence on the physico-chemical characteristics and macroporous morphology of both the DMSO-swollen "primary" PVACGs and, after replacement of the organic liquid by water, the water-swollen "secondary" cryogels. Subsequently, the latter ones were examined as potential drug vehicles in the ε-ACA loading/release experiments. The obtained data allowed to draw conclusion that by the variation of the initial urea concentration in the DMSO/PVA solutions used for the preparation of "primary" PVACGs it is possible to influence on the rigidity, heat endurance, and macroporous morphology of the resultant cryogels, and to govern the release behavior of the drugs uploaded in the bulk of the "secondary" PVA-cryogel-based delivery carriers.

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Conflicts of Interest

The authors declare no conflict of interest.

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Полимерлі жүйелерді криоқұрылымдау. 61. ДМСО құрамында мочевина бар полимерлі ерітінділер негізінде дайындалған поливинил спирті криогельдерінің физикалық-химиялық қасиеттері және алынған гельдік материалдарды потенциалды дәрілік тасымалдаушылар ретінде бағалау

Поливинил спирті (ПВС) негізіндегі макрокеуекті физикалық криогельдер құрамында мочевина қоспалары бар диметилсульфоксид полимер ерітінділерінен алынды. Криотропты гельдеу процесінің айнымалылары оның температурасы мен қосылған мочевина концентрациясы болды, бұл алынған криогельдердің қаттылығы мен жылуғатөзімділігінің жоғарылауын қамтамасыз етеді, сонымен қатар гель массасындағы макрокеуектердің кеңеюіне ықпал етеді. ДМСО-дан ісінген криогельдерді судың артық мөлшерімен жуғаннан кейін судан ісінген ПВС криогельдерінің пайда болуына, олардың қаттылығының бір мезгілде жоғарылауына әкелді. Бұл гельдік матрицалар дәрілік заттарды жеткізу жүйелерінде полимерлі тасымалдаушылар ретінде жұмыс істеу қабілетіне сыналған. Суда ісінген осындай криогельдерді модельдік препаратпен — ε-аминокапрон қышқылымен толтыру, содан кейін оның шығарылу кинетикасын зерттеу ДМСО-да ісінген криогельдерді мұздату-еріту арқылы туындаған бастапқы ПВС ерітінділеріндегі мочевина құрамы суда ісінген, құрамында дәрілік зат бар тасымалдаушы гельдің шығарылу сипаттамасында маңызды рөл атқарғанын көрсетті. Атап айтқанда, мочевина концентрациясы жоғары болған жағдайда дайындалған ПВС криогельдері үлкен тесіктерге ие болды, бұл препараттың біршама жылдамырақ шығарылуына әкелді.

Кілт сөздер: поливинил спиртінің криогельдері, диметилсульфоксидті полимер ерітінділері, мочевина қоспалары, криогенді өңдеу температурасы, дәрілік заттарды жеткізуге арналған криогельді тасымалдаушылар.

Д.А. Мичуров, О.Ю. Колосова, В.И. Лозинский

Криоструктурирование полимерных систем. 61. Физико-химические свойства криогелей поливинилового спирта, приготовленных на основе мочевиносодержащих растворов полимера в ДМСО, и оценка полученных гелевых материалов как потенциальных носителей лекарственных средств

Макропористые физические криогели на основе поливинилового спирта (ПВС) получали из диметилсульфоксидных растворов полимера, содержащих добавки мочевины. Переменными криотропного процесса гелеобразования являлись его температура и концентрация добавляемой мочевины, что обусловливало повышение жесткости и теплостойкости полученных криогелей, а также способствовало расширению макропор в гелевой массе. Последующая промывка набухших от ДМСО криогелей избытком воды приводила к образованию набухших от воды криогелей ПВС с одновременным дальнейшим увеличением их жесткости. Эти гелевые матрицы были протестированы в отношении их способности работать в качестве полимерных носителей в системах доставки лекарственных средств. Наполнение таких набухших в воде криогелей модельным препаратом — ε-аминокапроновой кислотой, а затем изучение кинетики его высвобождения показало, что содержание мочевины в исходных растворах ПВС, использованных для индуцированного замораживанием-оттаиванием криогелей, набухших в ДМСО, играло ключевую роль в характеристиках высвобождения набухшего в воде геля-носителя, содержащего лекарственное средство. А именно, криогели ПВС, приготовленные в присутствии более высокой концентрации мочевины, имели более крупные поры, в результате чего высвобождение лекарственного вещества происходило несколько быстрее.

Ключевые слова: криогели поливинилового спирта, растворы полимеров диметилсульфоксида, добавки мочевины, температура криогенной обработки, криогелевые носители для доставки лекарственных средств.

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