Chimica Techno Acta
published by Ural Federal University
eISSN 2411-1414; chimicatechnoacta.ru

ARTICLE
2022, vol. 9(2), No. 20229206
DOI: 10.15826/chimtech.2022.9.2.06

Prolonging effects of polyvinyl alcohol on drug release

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This paper belongs to a Regular Issue.

Abstract

Polymers are currently of interest as drug delivery systems. The use of polymeric forms of medicinal substances will eliminate or reduce the disadvantages of traditional drugs. The purpose of this work was to assess the ability to prolong the action of polyvinyl alcohol in relation to the drug release when going from dilute to more concentrated solutions. It was established that an increase in the viscosity of the polymer in solution caused by an increase in its concentration results not only in a slowdown in the diffusion of drugs from the polymer solution, but also in a significant decrease in the amount of drugs firmly fixed on the polymer matrix. Since it is the adduct of the polyvinyl alcohol-drug interaction that provides the slow release of the drug from the polymer solution, a decrease in its amount leads to the fact that no enhancement of the prolonging action is observed. It is claimed that when moving from solutions to polymer films, the rate of drug release is also determined by the structure of the polymer matrix. The lower the density of the polymer film, the greater the diffusion coefficient of the drug release from the film. Thus, in the course of evaluating the ability to prolong the action of polyvinyl alcohol, it was shown that using some prolongation techniques, it is possible to achieve targeted regulation of the rate of drug release from polymer dosage forms.

Keywords

polyvinyl alcohol
prolongation
drug delivery
polymer film

Received: 11.04.22
Revised: 04.05.22
Accepted: 05.05.22
Available online: 11.05.22

1. Introduction

Almost all currently known dosage forms are produced using pharmaceutical aids. Until recently, the requirements of pharmacological and chemical inertness have been imposed on pharmaceutical aids [1–3]. However, it turned out that with their help it is possible to significantly influence the pharmacological activity of drugs and regulate the parameters of pharmacokinetics and pharmacodynamics [4–6]. For example, dimethyl sulfoxide added to eye drops accelerates the penetration of antibiotics into the eye tissue [7, 8]. The use of methylcellulose allows the drugs to be retained in tissues for a long time, prolonging their action [9].

Pharmaceutical aids affect not only the therapeutic efficacy of drugs, but also the physicochemical characteristics of dosage forms during their manufacture and storage. For example, the introduction of up to 1% polyvinylpyrrolidone into the composition of nitroglycerin tablets significantly reduces their porosity and, as a consequence, reduces the ability of nitroglycerin to evaporate [10]. As a result, the shelf life of the tablets in open packages increases from 2 weeks to several months. PVA nanofibers produced by o/w emulsion electrospinning were demonstrated to be suitable solid dispersion systems enabling robust controlled release of poorly water-soluble drugs in work [11].

One of the largest groups of pharmaceutical aids used are polymers, which mainly function as prolongates [12–14]. The use of prolonged dosage forms is caused by negative phenomena arising from the rapid clearance of drugs from the body. In this case, there is a need for frequent administration of drugs, which often leads to a sharp fluctuation in their concentration in the body and, in turn, causes toxicity, allergic reactions, irritation, etc. [6]. Rapid clearance of drugs from the body, in addition, causes the appearance of the forms of microorganisms resistant to these substances.

One of the promising polymers for medicine, in general, and the technology of dosage forms, in particular, is polyvinyl alcohol (PVA) [15–17]. PVA is a biodegradable semicrystalline synthetic polymer that has been used for biomedical applications for several years [18]. Crystalline structures can be controlled by modifying the chemical composition of OH groups [19]. For example, in the pharmaceutical area, PVA has been widely used to prepare solid dispersions to improve the solubility of drugs [18, 20]. On the basis of PVS, nanoparticles are also created that provide prolonged release of medicinal substances [21]. The effects of PVA on the release behavior of polymer nanoparticles from nanocomposite particles using amino acids were investigated [22]. PVA cross-linked microspheres are used in oral precision relief systems [23, 24]. Hydrogel composites based on PVS are of interest [25, 26]. In the work [25] Lomefloxacin drug was loaded into the hydrogels and its release profile was studied.

The two most important factors affect the ability to prolong drug release. First, it is the high viscosity of PVA solutions, which provide a slow diffusion of drugs. Second, it is the ability of PVA functional groups to form complex compounds with drugs through hydrogen bonds [27–29]. In this case, it is a priori assumed that if in dilute solutions PVA is capable of interacting with drugs, then this fact will provide a high level of prolongation in the transition from liquid to soft dosage forms. However, an increase in the concentration of polymer in solution is accompanied not only by an increase in viscosity, which could contribute to the prolongation, but also by the structuring of the polymer. In its turn, the structure formation is accompanied by the aggregation of macromolecules and a hereto related decrease in the availability of polymer units for interaction with drugs [30], which makes the prolongation effect not so prominent.

In this regard, the purpose of this work was to assess the ability to prolong the action of PVA in relation to the drug release when going from dilute to more concentrated solutions. Three compounds of different chemical nature and mechanism of action–lidocaine (LD), cefazoline (CFZ) and dioxidine (DO)–which are presumably capable of forming complex compounds with PVA and are promising for creating liquid and soft dosage forms for the treatment of burns, purulent wounds of various etiologies, were taken as drugs.

2. Experimental

2.1. Materials

A sample of PVA grade 11/2 and M = 35 kDa produced by OOO “Reakhim”, sodium salt of cefazolin (CFZ) produced by OJSC Biosintez (Penza, Russia), lidocaine hydrochloride (LD) – PJSC Biokhimik (Saransk, Russia), dioxidin (DO) – OJSC Novosibkhimpharm "(Novosibirsk, Russia) were taken for the study. The drugs were used without any additional purification.

2.2. Equipment

UV-spectra were recorded on an UV-2600 Shimadzu spectrophotometer in bidistilled water solution at 298 K, wavelengths ranged from 190 to 500 nm (slit width 1.0 nm, medium scanning rate), with a quartz cuvette of 1 cm thickness.

IR- spectra were recorded on an IR Affinity-1S Shimadzu spectrophotometer with attachments for attenuated total internal reflection (ATIR).

Rheological studies were carried out on a Haake Mars III modular dynamic rheometer at 298 K in the mode of continuous shear deformation in the range of shear rates from 0.1 to 100 s^{-1}.

The physicomechanical properties were investigated on a Shimadzu AGS-X tensile testing machine (Shimadzu, Japan).

DSC curves were recorded on a NETZSCH-Gerätebau instrument (Germany) with a heating rate of 10°C/min.

2.3. Study of interaction of polyvinyl alcohol with drugs

To study the interaction of PVA with drugs, the UV spectra of individual compounds, as well as their mixtures, were investigated on a UV-2600 spectrophotometer. The concentration of PVA solutions used in the study was 10^{-4}–10^{-3} mol/l, CFZ and DO – 10^{-4} mol/l, LD – 10^{-3} mol/l.

The composition and the stability constant of the resulting complexes were determined by the method of molar ratios [31, 32].

2.4. Film preparation

The films were obtained by pouring a PVA solution onto the degreased surface of a Petri dish glass. The films were dried in two stages: first, in the open air, until the film was formed, and then in a vacuum cabinet at 30 °C until constant weight was obtained. The PVA concentration in the solution varied from 1 to 10%. In the case of preparation of drug-filled films, the drug dissolved in a small amount of water (2 ml) was added with stirring to the PVA solution immediately before the formation of the films. The drug content in the film was 0.01–0.1 mol/mol of the polymer.

2.5. Rheological investigations

Rheological investigations of PVA solutions, as well as their mixtures with drugs, were carried out on a Haake Mars III modular dynamic rheometer.

2.6. In vitro drug release

The drug loaded solution of PVA was added to dialysis membrane cellophane bags. The bags were immersed in a flask containing 150 ml of PVA solution of the same concentration as placed in the cellophane bags with a shaking speed of 100 r/min. The experiment was carried out in a thermostat at a temperature of 298 K. At specific time intervals, 1 ml of the solution was removed from the medi-

um and replaced with fresh solution. The drug concentration was determined by spectrophotometry in the UV region at a wavelength corresponding to the drug absorption maximum. PVA solution was used as a reference solution. The diffusion coefficient of the drug through a semi-permeable membrane was determined based on the Crank approach [33] by the formula:

$$G_s/G_\infty = \left[\frac{16D_s t}{\pi L^2}\right]^{0.5}, \quad (1)$$

where G_s is the concentration of the desorbed substance at time t, G_∞ is the value of G_s at $t\to\infty$, L is the semi-permeable membrane thickness.

The amount of the drug that passed through the membrane by the time t (G_s) was estimated from the calibration curve. The moment when a constant drug concentration (G_∞) was established in the solution was considered the moment when equilibrium was established.

2.7. In vitro drug release from polymer films

The kinetics of the drug release from the films into the aqueous medium at 298 K was studied by UV spectrophotometry of aqueous solutions in the region of the drug absorption maximum. Diffusion coefficients were calculated using equation (1). In this case, L was understood to be the thickness of the film.

2.8. Determination of density of polymer films

The density of PVA and PVA-drug films was determined by the pycnometric method according to the standard procedure.

3. Results and discussion

3.1. Characterization of complexes polyvinyl alcohol-drugs

The prolonging effect of polymers is, in fact, largely determined by their ability to form strong compounds such as complexes or salts with drugs. UV-spectroscopic study of dilute PVA solutions in the presence of the studied medicinal substances confirms the existing interaction between them. Thus, absorption maxima in UV spectra of CFZ and LD in the aqueous solution are observed at 272 nm (CFZ) and 262 nm (LD). There are three absorption maxima in the UV spectra of DO – at 235, 266, and 280 nm. When the equivalent amount of PVA not absorbed in the UV region at a concentration of 10^{-4}–10^{-2} mol/l is added to the solution, the intensity of the absorption peak changes, while the absorption maximum shifts by about 3–5 nm bathochromically (Figure 1).

The phenomena observed indicate the effect of the polymer on the electronic system of the drugs and the formation of the interaction adducts. By the difference in the values of the wavelengths Δλ corresponding to the absorption maximum of the complex and the individual drug, it is possible to estimate the binding energy in the complex compound by the Planck formula:

$$\Delta E = \frac{hc}{\Delta\lambda}, \quad (2)$$

where ΔE is the binding energy, h is Planck's constant, c is the speed of light.

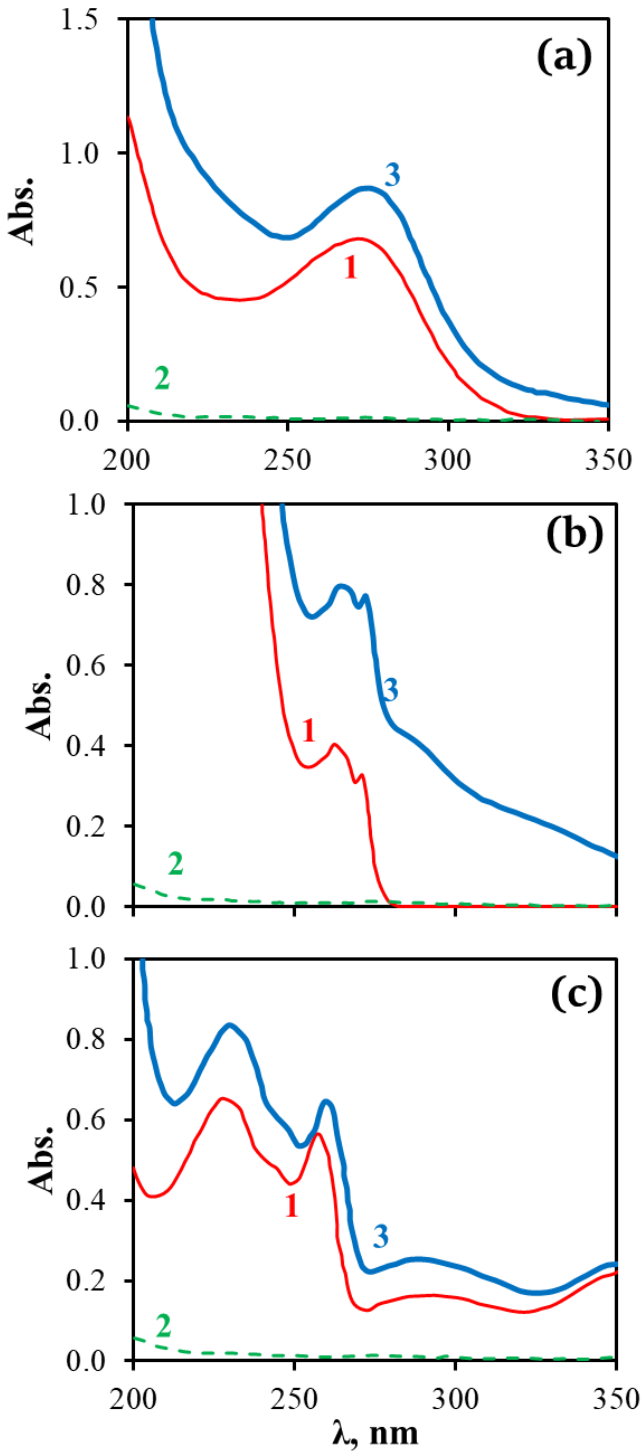

Figure 1 UV spectra of drug (1), PVA (2), and PVA-drug (3) for CFZ (a), LD (b) and DO (c).

The value of the binding energy in the complexes of PVA with the drugs studied, estimated from the shift of absorption maxima in UV spectra, is about 10–15 kJ/mol.

The small values of the bond energies suggest that complex formation occurs via hydrogen bonds. The composition of the reaction adducts obtained for all studied systems, determined by the method of isomolar series and the method of molar ratios, is equal to 1. The values of the stability constant for PVA-drug systems are $5.7 \cdot 10^3$, $6.5 \cdot 10^3$ and $5.1 \cdot 10^3$ l/mol when using DO, CFZ and LD, respectively.

Thus, the adducts of the PVA-drug interaction in an extremely dilute solution can be characterized as compounds with medium stability.

3.2. In vitro drug release

The presence of interaction in the PVA-drug system, in principle, is capable of providing a certain level of drug action prolongation due to the attachment to the polymer chain. Indeed, as can be seen from curve 1 in Figure 2, the release of the drug (in this case, CFZ) from a dilute PVA solution occurs rather slowly.

However, the situation changes when going from extremely dilute solutions to more concentrated ones. The kinetic curves of the release of CFZ from PVA solutions shown in Figure 2 can be divided into two ranges. In the first initial short range, the release of free CFZ, not fixed on the polymer chain, occurs through diffusion. In the second range, CFZ attached to the macromolecule is released slowly due to the disintegration of the PVA-CFZ complex. In this case, the kinetic curves reach the limit corresponding to the equilibrium drug yield. From the difference between the optical density value corresponding to the equilibrium drug yield and the optical density corresponding to the amount of CFZ introduced into the solution, it is possible to determine the value of equilibrium β_{equ} fixed on the macromolecular chain. Generally, the higher the PVA concentration in the solution, the lower the value of the amount of the drug β_{equ} fixed on the polymer chain (Figure 3). This fact allows us to assume that with an increase in the viscosity of the PVA solution, the effect of prolongation can actually be leveled.

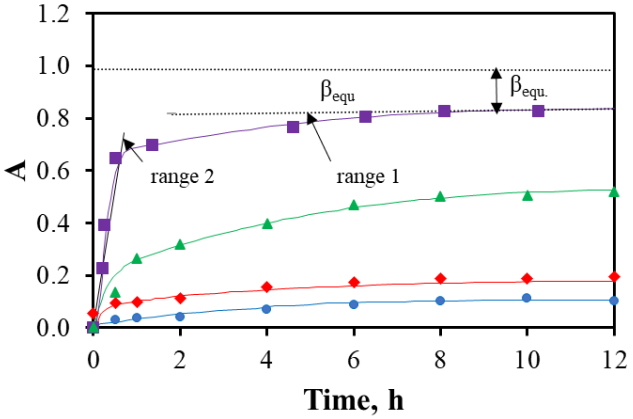

Figure 2 Kinetic curves of the release of CFZ from a PVA solution with a concentration of $4 \cdot 10^{-3}$ (1), $4 \cdot 10^{-1}$ (2), 1 (3) and 4 (4) g/dl. The content of CFZ in the solution is 10^{-4} mol/l. The dotted line shows the optical density value corresponding to the amount of CFZ introduced into the solution.

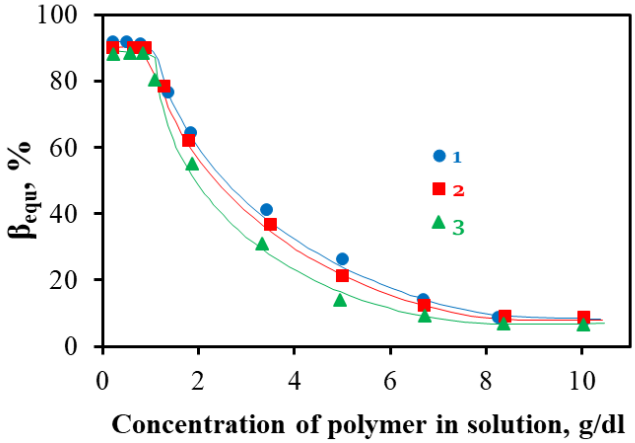

Figure 3 Dependence of the amount of CFZ (1), DO (2) and LD (3) firmly attached to the polymer chain on the concentration of PVA in solution.

For all the drugs studied, the nature of the dependence of β_{equ} on the concentration is the same. There is a concentration range within which the amount of drug firmly held by macrochains is maximal and practically does not depend on the concentration of PVA. With an increase in the concentration of PVA in the solution, the values of β_{equ} begin to decrease up to a minimum value, reaching the limit at a PVA concentration of the order of 8–10 g/dl.

A decrease in the amount of the drug retained by macromolecules is likely to be associated with a decrease in the availability of polymer units for interaction with drugs due to changes in the supramolecular state of the polymer that occur with an increase in the PVA content in the solution.

3.3. Rheological investigations of polymer solutions

The data of rheological measurements unambiguously indicate that an increase in the concentration of polymer in the solution is accompanied by an increase in viscosity. Moreover, this increase in viscosity is not monotonic. Figure 4 clearly distinguishes three regions. Region I is the so-called region of dilute solutions, in which macromolecules do not interact with each other. The viscosity in this area increases with increasing concentration according to the linear law $\eta \sim C^1$ [34–36]. Region II is the region of concentrated solutions with a fully formed fluctuation network of entanglements of macromolecules. In this region, the viscosity increases with an increase in concentration according to the power law $\eta \sim C^n$, where $n \sim 5$. The intermediate region of semi-diluted solutions is characterized by an intensive rearrangement of the supramolecular structure and the formation of a fluctuation network [37, 38].

Despite the fact that the addition of drugs at a concentration of up to 0.5 mol/l does not change the viscosity either in dilute or in more concentrated solutions (Figure 4), the changes in the structural-physical state of PVA in solution are directly reflected in the character of the

interaction of PVA with the drugs analyzed in the work (Figure 3). And, since from the structural-physical point of view PVA solutions are not equivalent, the value of β_{equ} also changes unequally. Solutions with a PVA concentration of less than 0.5 g/dl are the solutions of non-interacting macromolecules that are maximally available for interaction with a drug. It is in this region that β_{equ} reaches its highest values, which remain constant while the solution is diluted. PVA solutions with a concentration of about 10 g/dl and more represent a continuous fluctuation network, in which the availability of PVA links for interaction with a drug is minimal. In this region, the values of β_{equ} are the lowest. The intermediate region of semi-diluted solutions is characterized by significant changes in the values of β_{equ}. Consequently, an increase in the viscosity of the polymer in the solution caused by an increase in its concentration leads to a decrease in the fraction of the drug that is firmly attached to the polymer chain. In the case when the amount of a strongly attached drug is not large, there is a rapid release of a part of the drug that is not associated with the polymer chain but the remaining part of the drug, which is attached to the chain, is released at a rate corresponding to the rate of decomposition of the PVA-drug adduct.

As can be seen from the data in Table 1, the rate of the drug release increases with an increase in the PVA concentration in the solution, since as the content of PVA in the solution increases, the amount of the free drug increases. The values of the diffusion coefficient undergo similar changes. If with an increase in the concentration of PVA in solution the value of β_{equ} tended to zero, in concentrated solutions the yield of the drug would only be determined by the concentration of the free drug not bound by the polymer chain. In this case, during the transition from liquid to soft dosage forms of protective film coatings the prolongation effect due to the formation of the PVA-drug adduct would be virtually absent. However, since the value of β_{equ} goes to the non-zero limit, the drug yield from concentrated solutions is determined by two factors – the amount of the free drug and the stability constant of the PVA-drug complex.

Thus, the effect of prolonging the action of PVA does not increase with an increase in its content in the solution. An increase in the viscosity of the polymer in solution, caused by an increase in its concentration, leads not only to a slowdown in the diffusion of the drug from the polymer solution, but also to a significant decrease in the amount of drugs firmly fixed on the polymer matrix. Since it is the PVA-drug interaction adduct that provides the slow release of the drug from the polymer solution, a decrease in its amount leads to the fact that no enhancement of the prolonging action is observed.

Table 2 presents the physicochemical and physicomechanical characteristics of the PVA films obtained from solutions of various concentrations.

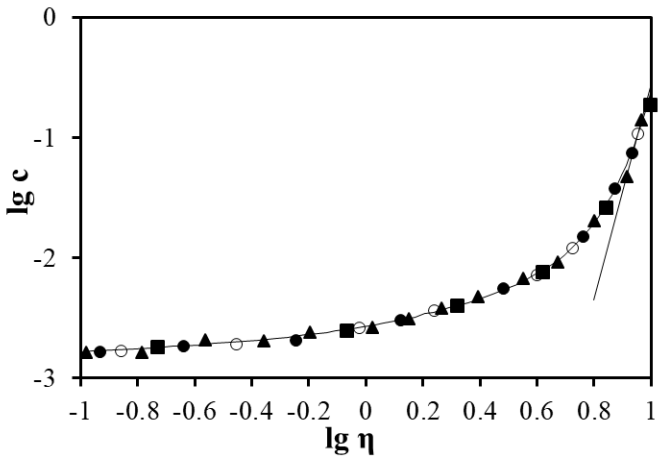

Figure 4 Dependence of the dynamic viscosity of PVA on its concentration in solution in logarithmic coordinates in the absence (•) and in the presence of DO (▾), LD (■), CFZ (□) taken at a concentration of 0.1 mol/l.

Table 1 Results of processing the kinetic curves of the drug release from PVA solutions.

Drug	PVA concentration in solution, g/dl	*V*, %/min	$D_a \cdot 10^9$, cm²/s
CFZ	$4 \cdot 10^{-3}$	0.10	0.04
	$4 \cdot 10^{-1}$	0.18	0.27
	1.0	0.49	1.18
	2.0	1.25	3.40
	4.0	1.92	5.35
	8.0	2.15	6.02
	10.0	2.18	6.11
LD	$4 \cdot 10^{-3}$	0.13	0.11
	$4*10^{-1}$	0.19	0.30
	1.0	0.67	1.70
	2.0	1.75	4.86
	4.0	1.98	5.53
	8.0	2.26	6.35
	10.0	2.28	6.40
DO	$4 \cdot 10^{-3}$	0.14	0.15
	$4 \cdot 10^{-1}$	0.15	0.18
	1.0	0.56	1.38
	2.0	1.58	4.36
	4.0	1.82	5.06
	8.0	2.00	5.59
	10.0	2.10	5.88

3.4. In vitro drug release from polymer films

When film materials are obtained from PVA solutions, from the technological point of view it is much more convenient to obtain them not from diluted but from more concentrated solutions. Consequently, the process of film formation will be carried out under conditions when the amount of the drug firmly fixed on the polymer matrix β_{equ}, is small. This means that most of the drug will freely diffuse through the polymer film.

So, the rate of this process will be determined not only by the value of β_{equ} and K_{est} but also by the characteristics of the polymer film itself. In this regard, it becomes possible to additionally regulate the rate of the drug release from the polymer film.

Table 2 Characteristics of PVA films obtained from solutions of different concentrations.

PVA concentration in the film, g/dl	T_g, °C	T, °C	ΔH, J/g	w_{cr}, %	α_{cr}, %	E, MPa	σ_{break}, MPa	l_{break}, MPa
1	52	227	86.2	55.0	33.5	2404	57.8	86.3
2	44	226	85.4	54.5	33.0	3965	65.3	146.7
3	42	225	85.5	54.5	32.6	4672	87.4	150.6
5	40	224	84.7	54.0	32.4	5277	90.5	153.8
7	43	224	80.4	51.3	30.0	5513	88.5	110.0
10	45	223	71.8	45.8	28.3	4850	83.3	65.8
20	50	224	70.8	45.1	27.5	4167	73.4	50.1

w_{cr} – from DSC data; α_{cr} – from IR-spectra data.

For example, by varying the concentration of the polymer in the initial solution films with different densities can be obtained. From the data shown in Table 3, it can be seen that the values of the density of the films obtained from the initial different concentration of the polymer in the solution (in the presence of the drug as well) pass through a minimum corresponding to the concentration value of 5 g/dl. It is important that, according to the change in density, the values of the drug release rate from the film and the diffusion coefficient also change.

Table 3 Summary data on the results of processing the kinetic curves of drug release from the PVA films and data on the film density.

Drug	drug concentration, mol/mol PVA	PVA concentration in fillm, g/dl	ρ, g/cm³	$D_a \cdot 10^9$, cm²/s
–	–	1	1.142	–
		2	1.120	–
		5	1.050	–
		10	1.156	–
CFZ	0.01	1	–	1.11
		2	–	2.72
		5	–	3.22
		10	–	1.98
	0.10	1	1.159	1.14
		2	1.134	2.80
		5	1.072	3.41
		10	1.167	1.92
LD	0.01	1	–	1.54
		2	–	2.83
		5	–	3.92
		10	–	3.46
	0.10	1	1.154	1.89
		2	1.129	2.90
		5	1.063	3.68
		10	1.163	3.05
DO	0.01	1	–	1.24
		2	–	1.98
		5	–	2.90
		10	–	2.81
	0.10	1	1.150	1.27
		2	1.125	1.32
		5	1.057	1.41
		10	1.160	0.98

Analysis of the data given in Table 3 unambiguously proves the fact that varying the polymer concentration in the initial solution is an additional factor regulating the rate of drug release. Previously, this kind of impact of the supramolecular organization of the polymer matrix on diffusion processes was discovered in the works [30, 39, 40] for the films of physiologically active polymers – chitosan polysaccharides, sodium salt of chitosan succinamide and sodium salt of carboxymethylcellulose.

It is noteworthy that the diffusion coefficients for the film samples for all considered cases are lower than those for solutions of the corresponding concentrations (Table 1). Obviously, a sharp increase in viscosity when going from solutions to solid film samples, in this case, has a decisive effect on the value of the diffusion coefficients.

Thus, the assessment of the ability to prolong the action of one of the physiologically active polymers, polyvinyl alcohol, showed that using some prolongation technological methods, involving the creation of compounds of medicinal and auxiliary substances, as well as an increase in the viscosity of the dispersion medium when the drugs are enclosed in film shells, it is possible to achieve direct regulation of the rate of release of medicinal drugs from polymer dosage forms.

4. Conclusions

It was shown that mixing aqueous PVA solutions with the solutions of cefazolin, lidocaine, and dioxidine is accompanied by the formation of reaction adducts which are complex compounds of medium stability formed by means of hydrogen bonds.

It was found that the range of PVA concentrations in a solution of 0.5–10 g/dl is characterized by an intense rearrangement of the supramolecular structure, which results in a significant decrease in the amount of the drug which can be firmly fixed on the macromolecular chain under the equilibrium conditions. As a result, no increase in the prolonging effect of PVA with an increase in its content in the solution and a corresponding increase in viscosity is observed.

It was proven that when going from solutions to polymer films, the yield of drugs is largely determined by the structure of the polymer matrix, in particular, by its density. The lower the density of the polymer film, the greater

the diffusion coefficient of the drug release from the film. The diffusion coefficient values for the film samples for all considered cases are lower than those for the solutions of corresponding concentrations.

Supplementary materials

No supplementary data are available.

Funding

This research had no external funding.

Acknowledgments

None.

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Investigation: Sh.A.S., L.R.Yu., Z.E.M.
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Conflict of interest

The authors declare no conflict of interest.

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