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DEVELOPMENT OF WATER SOLUBLE DRUG FORMS OF MEXIDOLE BASED ON POLYVINYLPYRROLIDONE

Abstract. The new water soluble polymeric drug forms of ophthalmic drug mexidole based on synthetic polymer polyvinylpyrrolidone have been developed. By means equilibrium dialysis method the interaction of mexidole with polyvinylpyrrolidone was studied. The dynamic of drug release into physiological solution was investigated. It was concluded the possibility of the polymer application for prolongation action of mexidole.

Key words: polymeric forms, mexidole, polyvinylpyrrolidone, drug release.

Introduction. One of ways of development prolong forms of drugs is formation of their complexes with water-soluble polymers. Use of such polymeric drugs at injected introduction allows to reduce collateral toxic action of drugs and also to receive long therapeutic effect at unitary injection. One of the perspective directions in the field of drug delivery systems is development of complexes of drugs with various water-soluble polymers. Rigid requirements of medicine (biocompatibility, solubility in water or physiological solution, ability to completely remove from organism, etc.) sharply narrow the circle of polymers used as drug carriers [1-3].

Various natural and synthetic polymers like cellulose derivatives, pectin, dextran, alginates, polyvinyl alcohol are used for the preparation of therapeutic prolonged forms of drugs [4]. These polymers are physiologically inert, hydrophobic, soluble in water, available and cheap. For these purposes it is considered the most expedient application of polymers which have properties of blood substitutions. Among the high-molecular compounds having such properties, the wide spreading found polyvinylpyrrolidone.

One of the most important issues in the ophthalmology is drug treatment of age-related macular, aimed to stimulate the functioning portions of the retina, rather than restoring the affected areas [5, 6]. Currently used pharmacological substances do not provide sufficiently stable effect on the treatment. Risk factor may be low levels of antioxidants in the body. Mexidole is a succinic acid salt (succinate) belonging to the synthetic antioxidants group. In ophthalmology mexidole initially was used for the treatment of diabetic retinopathy and chronicopticneuropathy. However, alongside with a number of positive properties, mexidole has certain drawback. It is low-molecular substance and its pharmacological effect is kept quickly[7, 8].

With the purpose of elimination these drawbacks, the research on development of new the polymeric water soluble forms of mexidole based on polyvinylpyrrolidone are described.

EXPERIMENTAL PART

Polyvinylpyrrolidone (PVP) were purchased from Sigma Chemicals, St.louis, USA. Mexidole was used pharmaceutical grade.

For detailed understanding of character and nature of binding and the interaction between drug and macromolecules were studied by means equilibrium dialysis method. The release behaviour of mexidole from polymeric solutions was examined by dialysis method in a modelling biological medium at 37°C. The amount of drug released was determined spectrophotometrically by measuring the absorbance maximum UV spectra were recorded on a Jasco UV-VIS (Japan) spectrophotometer.

RESULTS AND DISCUSSION

Polyvinylpyrrolidone has found wide application in medicine as blood substitute, bases for ointments, prolonger of action of many medicinal substances. The basic advantages of this polymer is solubility in water and other solvents, absence of toxic and allergenic action, high ability to complexation. Two commercial preparations are issued on the basis of PVP: plasma substitute "Gemovinyl" and deintoxicator "Gemodez". The first is 3,5 % solution of mean-molecular weight polymer, and the second - 6 % solution of low-molecular polymer. To the purposes of prolongation, the polymer with molecular weight 15 000 - 40 000 was applied. That provides long stay of polymer and binding drug in living organism.

The determining role in binding of PVP with various low-molecular substances is played hydrogen bonds and hydrophilic interactions. Presence in structure of drug the appropriate groups capable form weak complexes with PVP, gives the basis to use this polymer for prolongation of therapeutic action of drug.

For investigation of interaction mexidole with PVP the method of equilibrium dialysis was used, allowing establish degree of binding between components in solution not only qualitative, but also quantitatively. Experiments carried out in water solution at various temperatures, using acetylcellulose dividing membrane. Drug, diffused from one cell through membrane, contacted with polymer which is taking place in other cell. Changing concentration of drug in various experiments with constant concentration of PVP, quantitative characteristics of process of interaction (coefficient of distribution, binding constant, thermodynamic parameters) were determined. The coefficient of distribution mexidole at equilibrium dialysis characterizes itself the relationship of drug amount in dialysed cell and outside solution. Constant of binding determined according to Klotz equation [9] by the diagram of dependence 1/a from 1/C, where a - parameter describing the share of macromolecules, formed the complex, C - concentration free or unbound drug (figure 1). This dependence represented a straight line which corner of inclination corresponded 1/Kc.

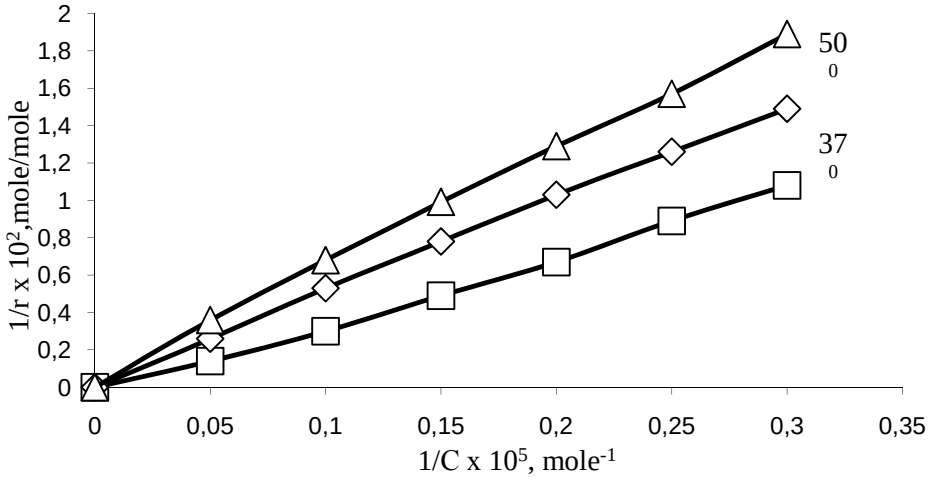

Figure 1 – Dependence on mexidole interaction with PVP at different temperature.
□ – 25 °C, ◊ – 37 °C, Δ – 50 °C

Values of thermodynamic parameters of interaction at various temperatures are presented in table 1. The data indicate clearly that with increase of temperature parameters of drug the binding with PVP decrease.

Table 1 – Thermodynamic parameters of interaction of mexidole with PVP

Temperature, °C	$K_в \cdot 10^{-2}$, L/mole	Free Energy, kJ/mole	Enthalpy, kJ/mole	Entropy, E.u.
25	41,4	-9,22	-5,47	12,65
37	38,2	-9,39	-4,12	15,32
50	38,1	-9,48	-3,32	18,71

Process of complex formation has exothermic character, negative values of change testify to it enthalpy and free energy, and also positive change of entropy. Low absolute values thermodynamic parameters indicated the prevailing value of hydrogen bonds in process. Alongside with them existence of hydrophobic interactions between components in the complex is possible.

The release of drug from polymeric solution was investigated. Experiments carried out at various ratio polymer:drug – from 1:1 up to 4:1. For comparison the amount of drug, released through membrane in absence of polymer was determined. Results of investigation are presented in table 2.

Received data indicate that at the presence of polymer the diffusion of mexidole through membrane is reduced. So, for 8 hours at molar ratio polymer:drug = 1:1 preparation is diffused on 78 %, while from water solution mexidole is released on 96 %. On the basis of the received data the diagrams of

Table 2 – Dynamic of mexidole release from PVP into physiological solution

Ratio Drug:Polymer	Quantity of released drug, %				
	1 h	2 h	3 h	4 h	6 h
1:0	24	45	71	82	94
1:1	19	35	59	74	75
1:2	14	31	53	69	79
1:3	12	28	47	65	72
1:4	11	25	44	61	68

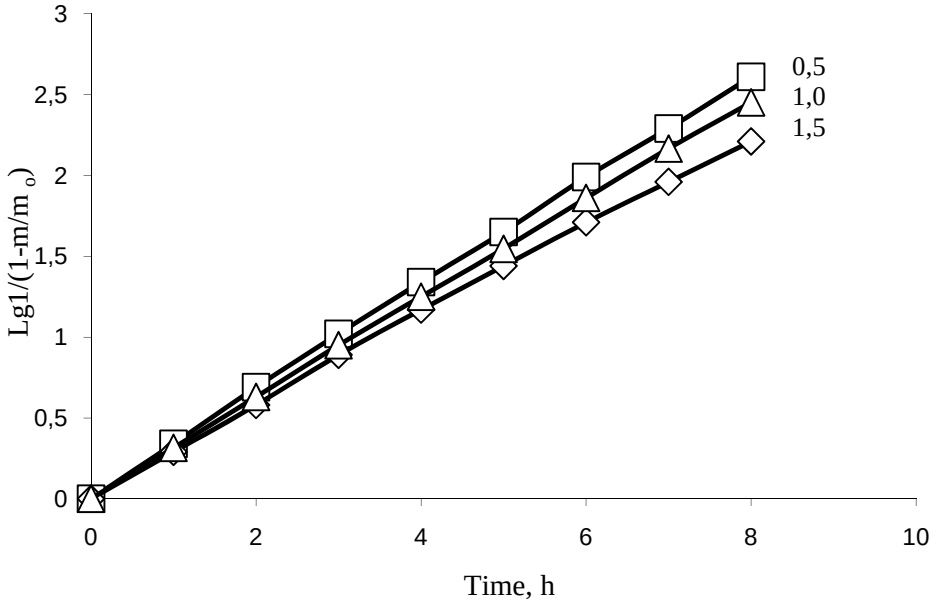

Figure 2 – Dynamic of mexidole release from PVP solution at different ratio polymer:drug.
◊ – 4:1, □ – 2:1, Δ – 1:1

logarithmic dependence of amount released mexidole f in time were drawn and constants of rate of drug diffusion through the membrane are calculated (figure 2).

It is shown that with increase molar ratio of reagents from 1:1 up to 1:4, the value of constant of diffusion decreases and makes 5,93; 5,61; 5,33 and $5{,}06 \cdot 10^{-5}$ s^{-1}, accordingly. Kinetic curve of diffusions show, that the greatest prolonging effect is achieved at a ratio PVP:drug, equal 1:4.

Thus, the investigations have shown that ophthalmic drug mexidole in water solutions forms with synthetic polymer polyvinylpyrrolidone the complexes due to hydrogen bonds and hydrophobic interactions. Long therapeutic action of polymeric water-soluble complexes was established. The opportunity of creation

on polyvinylpyrrolidone basis the injected medicinal forms prolonged therapeutic actions were shown.

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Резюме

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ПОЛИВИНИЛПИРРОЛИДОН НЕГІЗІНДЕ ЖАҢА СУДА ЕРИТІН МЕКСИДОЛДЫҢ ДӘРІЛІК ТҮРЛЕРІН ӘЗІРЛЕУ

Поливинилпирролидонның синтетикалық полимерінің негізіндегі мексидол жаңа суда еритін полимерлік дәрілік түрлері әзірленді. Теңестіру диализдың әдісімен мексидол поливинилпирролидонмен әрекеттестік зертелді. Препараттың физиологиялық ерітіндісіне босатып шығу зертелді. Мексидолдың әсер ету уақытын ұзарту үшін полимер қолдану мүмкіндігі туралы тұжырым жасалды.

Түйін сөздер: полимерлік түрлері, мексидол, поливинилпирролидон, дәрілік босатып шығу.

Резюме

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РАЗРАБОТКА ВОДОРАСТВОРМЫХ ЛЕКАРСТВЕННЫХ ФОРМ МЕКСИДОЛА НА ОСНОВЕ ПОЛИВИНИЛПИРРОЛИДОНА

Разработаны новые водорастворимые полимерные лекарственные формы мексидола на основе синтетического полимера поливинилпирролидона. Методом равновесного диализа изучено взаимодействие мексидола с поливинилпирролидоном. Исследована динамика высвобождения препарата в физиологический раствор. Сделано заключение о возможности использования полимера для пролонгирования действия мексидола.

Ключевые слова: полимерные формы, мексидол, поливинилпирролидон, высвобождение лекарства