UDK 541.64:615.014

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POLYMERIC FORMS OF CLOPHELINE BASED ON NATURAL POLYSACCHARIDES

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The new polymeric forms of clopheline based on natural polysaccharides have been developed. By means equilibrium dialysis method the interaction of clopheline with sodium salts of carboxymethylcellulose, pectic and alginic acids was studied. The dynamic of drug release into physiological solution was investigated. It was concluded the possibility of natural polysaccharides application for prolongation action of clopheline.

One of ways for development of prolonged forms of drugs is formation of their complexes or salts 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 [1, 2]. Among the big circle of the water-soluble polymers intended for these purposes, the greatest interest represents natural polysaccharides. These polymers are physiologically inert, hydrophilic, good soluble in water, accessible and cheap [3, 4].

One of the most widespread diseases of the cardiovascular system is arterial hypertension. This illness suffers about 22-23 % of the population in the age of 35-55 years and about 15 % have boundary levels of arterial pressure. Presence arterial hypertension is one of the major factors resulting in death as a result of insult or heart attack of myocardium.

The most effective drug for hypertension treatment is clopheline, representing hydrochloride of 2-(2,6-dichlorphenilamino)-imidazoline [5]. The main pharmacological feature of clopheline is strongly pronounced hypothensive action at very small doses (0,000075 g). Clopheline is not toxic and has extraordinary big therapeutic breadth. Clopheline has found wide application in clinical practice for treatment of various forms of arterial hypertension. Favorable hypothensive effect was achieved at 50-80 % of patients. Clopheline also widely used in ophthalmology for decrease intraocular pressure at glaucoma and stops of bleeding at eye traumas [6].

However, alongside with a number of positive properties, clopheline has certain drawbacks. It is low-molecular substance and its pharmacological effect is kept quickly and accompanied by sharp decrease of arterial pressure at the initial moment after reception. For increase of pharmacological duration of action there is a necessity of repeated dose of drug, which results in its excessive concentration in an organism and to occurrence of toxic-allergic reactions. The sudden discontinuance of clopheline doses or significant reduction of dose can result in development of «syndrome of cancellation» which is shown by fast increase of pressure, tachycardia, headache, nausea and other symptoms of a hypertonic crisis.

With the purpose of elimination these drawbacks, the researches on development of new highly effec-

tive medicinal forms of clopheline with long hypertensive action are widely conducted. Such medicinal forms allow to provide constant concentration of drug at the therapeutic level during a long time [7–9].

In the present study the polymeric forms of clopheline based on natural polysaccharides such as sodium salts of carboxymethylcellulose (CMC), pectic (PAc) and alginic (AAc) acids are described.

Materials and methods. Sodium alginate, pectic acid and carboxymethylcellulose were purchased from Sigma Chemicals, St.louis, MO. Clopheline was used pharmaceutical grade.

For detailed understanding of character and nature of binding, the interaction between drug and macromolecules was studied by means equilibrium dialysis method. Such interaction can be one of the major factors determining rate of drug release and, hence, prolongation of action. In researched systems the complex formation can occur due to electrostatic interaction of clopheline ion with carboxyl-anion of polysaccharides and also due to hydrophobic interactions between molecule of drug and polymeric chain. Experimental data were shown that the degree of binding linearly grows with increase of concentration of polymers in solution. It is caused that with increase content of macromolecules the number of the functional groups capable to formation of ionic bonds with drug is increased. From the received dependences the values of binding constant were calculated. These values were equal for CMC - 5,71, and for pectic and alginic acids - 3,74 and 3,86, accordingly.

The release behaviour of clopheline from SPU 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 at 278 nm. UV spectra were recorded on a Jasco UV-VIS (Japan) spectrophotometer.

Results and its discussion. In table 1 values of coefficient of clopheline distribution at dialysis equilibrium are presented. This parameter characterizes the ratio of free drug amount to drug amount bound with polymer. The observed data show that the increase of polymer concentration in solution resulted of reduction value of coefficient of distribution, testifying about more full clopheline interaction with polymers.

Table 1. **Values of coefficient of distribution clopheline at dialysis equilibrum**

Ratio	Polymer		
Clopheline : Polymer	CMC	PAc	AAc
1:1	0,48	0,54	0,56
1:2	0,36	0,43	0,44
1:3	0,29	0,35	0,32
1:4	0,22	0,28	0,28

Comparison of values of binding constants and also coefficients of distribution for the investigated polymers shows that interaction of clopheline with CMC occurs more strongly that with pectic and alginic acids. It is caused by that CMC has more strong acidic properties due to different location of carboxyl groups in elementary links of these polysaccharides.

The formation of salt bonds between positively charged ions of drug and polymeric chain of polysaccharides is found out at viscosimetric titration of water solutions of polymeric Na-salts by the solution of drug. The addition of growing quantities of drug to solutions of polymers is accompanied on initial site of curve by downturn of the reduced viscosity, that is testified about electrostatic interaction between cation of drug and carboxyl-anion of polymers.

Full charge at association decreases, that is results in reduction of intramolecular forces of electrostatic pushing away and reduction of the sizes of macromolecules, and, hence, and to reduction of viscosity of system. Formation of polymeric salts proves to date of IR-spectroscopy. So, in spectrum of the product of interaction of drug with investigated polysaccharides there are intensive strips at 1420 and 1610 sm^{-1}, characteristic for salts of carboxylic acids.

Thermodynamic parameters of interaction, received from Klotz dependence [10] at various temperatures, are presented in table 2. It is shown, that the binding of drugs proceeds with allocation of heat, and for Na-CMC the contribution of electrostatic forces in complexation is more significant, since exothermity of the process in this case is higher. Additional confirmation of presence of such interaction is reduction of value of enthalpy at increase of ionic force of system (in Ringer-Lock). However, this fact practically has not effected for value of free energy, the basic contribution in which is put entropy. Besides, the decrease of enthalpy can characterize also hydrophobic interactions, which become more stable with increase of temperature. For systems Na-pectic acid and Na-alginic acid the increase of ionic

Table 2. **Thermodynamic parameters of complexation clopheline with polysaccharides**

Temperature, ^{0}C	$K_в x10^{-2}$, L/mole	Free Energy, kG/mole	Enthalpy, kG/mole	Entropy, E.u.
Na-pectic acid				
25	28,2	- 18,76	- 6,14	42,4
37	27,4	- 20,22	- 5,13	46,8
50	26,0	- 21,02	- 4,12	50,4
Na- alginic acid				
25	33,2	- 19,04	- 7,45	42,8
37	32,4	- 20,06	- 6,68	44,6
50	31,2	- 21,46	- 6,06	48,2
Na-CMC				
25	186,2	- 25,08	- 11,62	48,4
37	174,4	- 25,54	- 9,84	50,6
50	166,4	- 26,26	- 7,64	54,8

Table 3. **Dynamic of clopheline release from polymeric complexes into physiological solution**

Polymer	Ratio Cf:Polymer	Quantity of released drug, %				
		1 h	2 h	4 h	6 h	8 h
–		23	46	72	84	96
CMC	1:1	16	28	43	54	61
	1:2	11	24	36	42	46
	1:3	8	14	22	34	38
	1:4	6	12	19	27	31
AAc	1:1	18	29	47	59	68
	1:2	15	29	44	51	60
	1:3	13	22	40	46	52
	1:4	11	19	36	42	45
PAc	1:1	14	28	46	58	64
	1:2	12	25	42	52	56
	1:3	10	22	37	48	52
	1:4	8	20	38	44	48

force not influences so significantly on thermodynamic parameters of complexation. The obtained facts are testified that electrostatic forces alongside with hydrophobic interactions are played the significant role in formation of these complexes.

For estimation of prolonging properties of polymeric salts the dynamic of drug release into physiological solution is investigated by method of equilibrium dialysis [11,12]. For comparison, the amount of drug passed through membrane from solution in absence of polymer was determined. Results of investigation presented in table 3.

Apparently from the received data, release of drug from polymeric solutions occurs more slowly than from water solutions. So, for 8 hours at molar ratio polymer:drug equal 1:1, drug diffused at 60-70 % while from water solution the drug diffused through membrane to 96 %. The increase of the concentration of drug is resulted in delay of release rate. Most brightly this effect is shown in case of CMC. So, at molar ratio CMC:drug equal 4:1 for 8 hours the drug is released at 31 % , whereas from solutions of the PAc and AAc at the same ratio drug diffused at 45-55 %. The difference of drug release rate from salts with different polysaccharides is stipulated for difference of spatial orientation of their macromolecules.

As is known, the polymeric chair of cellulose is characterized by the rigid strictly ordered distribution of units, and also presence of significant number of hydrogen bonds between rings of macromolecules. At interaction of such polymer with molecules of drugs the ordered structure of macromolecules is kept. It creates some kind of «depot», as complicates diffusion of drug from polymeric solution. To the contrary, pectic substances and alginic acids have non-uniform structure due to small amount of branches and are characterized by smaller degree of orderliness and orientation of macromolecules. These polymers lesser degree binds with drug and are not capable «to grasp» it in the structure. Therefore release of drug from these polysaccharides occurs the greater rate. On the basis of the received results diagrams of logarithmic dependence of amount of released drug in time were constructed and constants of rate of drug diffusion through membrane, submitted in table 4 are designed. As for research of drug release the method of equilibrium dialysis which gives the comparative data was used, the amount of released drug and the designed constants of rate diffusion were compared to released amount of drug in absence of polymer.

Table 4. **Constants of rates of clopheline diffusion through membrane from polymeric complexes**

Ratio Cf : Polynmer	Kdiff x 10^5, s^{-1}		
	CMC	PAc	AAc
1:1	3,86	4,98	5,22
1:2	2,44	4,86	4,78
1:3	1,81	4,22	4,16
1:4	1,26	3,60	3,64

Apparently from the table, value of diffusion constant rate of drug from polymeric salts in 3-6 times are lower, than at free drug (Kdiff. = 8,92 x 105 s-1). The increase of the content of polymeric carrier in system results in reduction of diffusion constant values.

Thus, the obtained data show that binding of drug with natural polymers such as Na-salts carboxymethylcellulose, pectic and alginic acids results to gradual release of drug and allows to prolong its action. On the basis of these water-soluble polymers it is possible to receive injectable drug delivery systems with long hypertensive action.

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Резюме

Табиғи полисахаридтар негізінде клофелин препаратының жаңа полимерлік дәрілік түрлері алынды. Теңестіру диализ әдісімен клофелиннің карбоксиметилцеллюлозаның, пектинның және альгин қышқылының натрий тұзымен әрекеттесуі зерттелді. Препараттың физиологиялық ерітіндісіне бөлініп шығу динамикасы зерттелді. Табиғи полисахаридтарды клофелиннің әсер ету уақытысын создыру үшін қолдануға болатындығы көрсетілді.

Резюме

Разработаны новые полимерные лекарственные формы клофелина на основе природных полисахаридов. Методом равновесного диализа изучено взаимодействие клофелина с натриевыми солями карбоксиметилцеллюлозы, пектовой и альгиновой кислот. Исследована динамика высвобождения препарата в физиологический раствор. Сделано заключение о возможности использования природных полисахаридов для пролонгирования действия клофелина.

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Поступила 2.03.07г.