ЕҢБЕК ҚЫЗЫЛ ТУ ОРДЕНДІ
«Ә. Б. БЕКТҰРОВ АТЫНДАҒЫ
ХИМИЯ ҒЫЛЫМДАРЫ ИНСТИТУТЫ»
АКЦИОНЕРЛІК ҚОҒАМЫ

ҚАЗАҚСТАННЫҢ ХИМИЯ ЖУРНАЛЫ

ХИМИЧЕСКИЙ ЖУРНАЛ КАЗАХСТАНА

CHEMICAL JOURNAL of KAZAKHSTAN

АКЦИОНЕРНОЕ ОБЩЕСТВО
ОРДЕНА ТРУДОВОГО КРАСНОГО ЗНАМЕНИ
«ИНСТИТУТ ХИМИЧЕСКИХ НАУК
им. А. Б. БЕКТУРОВА»

3 (63)

ИЮЛЬ – СЕНТЯБРЬ 2018 г.

ИЗДАЕТСЯ С ОКТЯБРЯ 2003 ГОДА

ВЫХОДИТ 4 РАЗА В ГОД

АЛМАТЫ
2018

UTC 678.06:615.45

E. O. BATYRBEKOV[1], A. E. BORISOVA[2], M. B. UMERZAKOVA[1]

[1]A. B. Bekturov Institute of Chemical Sciences JSC, Almaty, Republic of Kazakhstan,
[2]Kazakh-British Technical University, Almaty, Republic of Kazakhstan

WATER SOLUBLE POLYMERIC DRUG FORM OF LOCAL ANESTHETIC BASED ON POLYVINYL ALCOHOL

Abstract. The new water soluble polymeric drug form of local anesthetic novocaine on the based synthetic polymer polyvinyl alcohol has been developed. By means equilibrium dialysis method the interaction of novocaine with polyvinyl alcohol 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 novocaine.

Key words: polymeric form, local anesthetic, novocaine, polyvinyl alcohol, drug release.

Introduction. One of perspective directions in the field of drug delivery systems is development of complexes of drugs with various water-soluble polymers. Application of such complexes allows to lower of toxic action of drugs and also to receive long therapeutic effect. 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. For these purposes it is considered the most expedient application of polymers which have properties of blood substitutions [1, 2]. Among the high-molecular compounds having such properties, the wide spreading has found polyvinyl alcohol [3, 4].

One of the most important tasks in the field of chemistry of medico-biological polymers is the development of polymeric forms of anesthetic drugs. The existing arsenal of antipain drugs are small and many of them have a number of disadvantages, namely short duration of the anesthetic and toxic effects on the body associated with overdose of the drug. In many cases, especially in disaster medicine, to eliminate pain syndrome it is necessary to maintain the effective concentration of the analgesic drugs in the body for long time. A prolonged effect can be achieved by immobilizing anesthetic drugs to macromolecular carriers [5-8].

In the present study the polymeric water soluble forms of novocaine based on polyvinyl alcohol are described.

EXPERIMENTAL PART

Polyvinyl alcohol (PVA) were purchased from Sigma Chemicals, St.louis, USA. Novocaine 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 novocaine 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

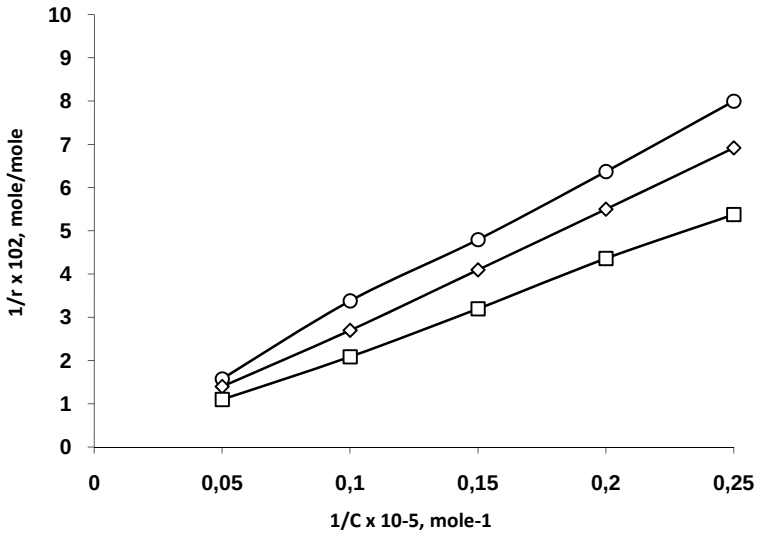
Polyvinyl alcohol has found wide application in medicine as blood substitute, bases for ointments, prolonger of action of many medicinal substances. The basic advantages of this polymer are solubility in water and other solvents, absence of toxic and allergenic action, high ability to complexation. To the purposes of prolongation, the polymer with molecular weight 15000-20000 was applied. That provides long stay of polymer and binding drug in living organism.

The determining role in binding of polyvinyl alcohol 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 PVA, gives the basis to use this polymer for prolongation of therapeutic action of drug. Interaction of drug with PVA was studied by means of various physical and chemical methods.

UV-spectroscopic researches are shown that at mixing water solutions of drug and polymer precise change in spectral characteristics novocaine at 202 nm as increase of the maximum of absorption. This process proceeded in time, increase of optical density occur within 6-8 hours. The given effect is caused complexation of molecules novocaine with OH-group of polymer due to formation of hydrogen bonds. Viscosimetric measurements also testified about complexation of drug and polymer. So, the intrinsic viscosity of 0,5 % solution of PVA at dilution water changes linearly, and at dilution the same solution of 0,5 % solution novocaine occurs sharp increase of the given viscosity in the field of small concentration of polymer, characteristic for polyelectrolites. The given effect testifies to increase of the linear sizes of macromolecules result of its association with novocaine. Measurement of viscosity of solutions at various mole ratio of components has shown, that at the ratio close to equimolar (0,8-0,9 mole novocaine on 1 part PVA), the sharp increase of viscosity testifying to formation of a complex of structure 1:1.

For more detailed investigation of interaction novocaine with PVA 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 PVA, quantitative characteristics of process of interaction (coefficient of distribution, binding constant, thermodynamic parameters) were determined. The coefficient

of distribution novocaine 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 versus 1/C, where "a" is the parameter describing the share of macromolecules, formed complex, C - concentration or unbound drug (figure). This dependence represented a straight line which corner of inclination corresponded 1/Kc.



Dependence on novocaine versus interaction with PVA at the temperature:
□ – 25°C, ◊ – 37 °C, ○ – 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 PVA decrease.

Table 1 – Thermodynamic parameters of novocaine interaction with PVA

Temperature, °C	$K_в \cdot 10^{-2}$, L/mole	Free Energy, kJ/mol	Enthalpy, kJ/mol	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.

Table 2 – Dynamic of novocaine release from PVA into physiological solution

Ratio Drug:Polymer	Quantity 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

Received data indicate that at the presence of polymer the diffusion of novocaine through membrane is reduced. So, for 8 hours at molar ratio polymer:drug = = 1:1 preparation is diffused on 78 %, while from water solution novocaine is released on 96 %. On the basis of the received data the diagrams of logarithmic dependence of amount released novocaine in time were drawn and constants of rate of drug diffusion through the membrane are calculated (figure 2).

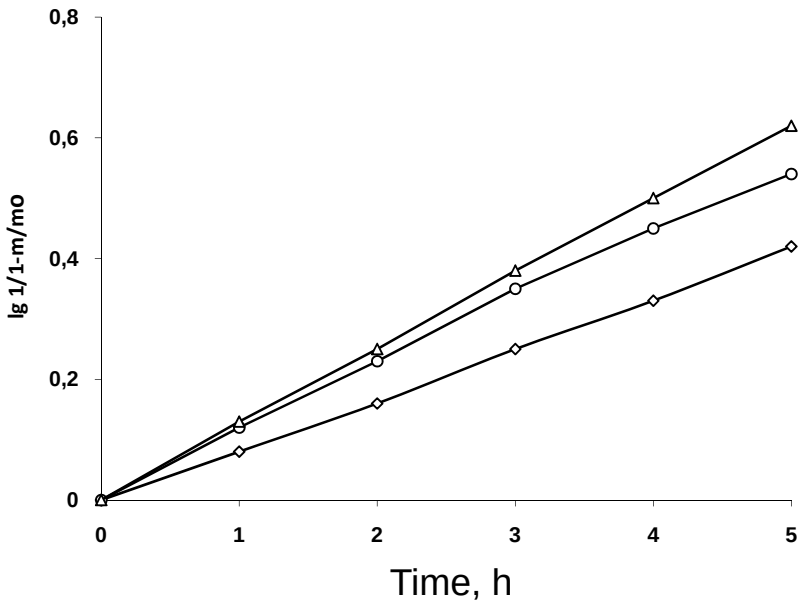


Figure 2 – Dynamic of novocaine release from PVA solution at different ratio polymer:drug. ◊ – 4:1, ○ – 2:1, Δ – 1:1.

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 5,06·10-5 s^{-1}, accordingly. Kinetic curve of diffusions show, that the greatest prolonging effect achieved at a ratio PVA:drug equal 1:4.

Conclusion. Thus, the investigations have shown that local anesthetic novocaine in water solutions forms with synthetic polymer polyvinyl alcohol the complexes due to hydrogen bonds and hydrophobic interactions. Long therapeutic action of polymeric water-soluble complexes was established. The opportunity of creation on polyvinyl alcohol basis the injected medicinal forms prolonged the rapeutic actions were shown.

The research was carried out according to the scientific and technical program No. BR05234667 within the framework of program-targeted financing CS MES RK.

REFERENCES

[1] Drug Delivery Systems: Fundamentals and Techniques / Ed. by Johnson P. and Lioyd-Jones J.G. Weinheim, NY: VCH; Chichester: Ellis Horwood,1987. 282 p.

[2] Batyrbekov E.O, Ismailova A.B., Baiyrkhanova A.O., Utelbaeva Z.T. Polymeric water soluble drug forms of fluorouracil based on polyvinylpyrrolidone // Chemical journal of Kazakhstan. 2014. N 1. P. 112-117.

[3] Aleyamma A.J., Sharma Ch.P. Polyvinyl Alcohol as a biomaterial // Blood compatible materials and devices / Ed.by Sharma Ch.P. & Szycher M.Technomic Publ. 1991. P. 123-130.

[4] Vidyalakshmi K., Rashmi K.N., Kumar T.M. Prarnod., Siddaramaiah. Studies on formulation and in vitro evaluation of PVA / chitosan blend films for drug delivery // J. Macromol. Set. A. 2004. Vol. 41, N 10. P. 1115-1122.

[5] Woolfson D.A., McCafferty D.F., Moss G.P. Development and characterisation of bioadhesive drug delivery system for percutaneous local anaesthesia // Internat. Journal of Pharmaceutics. 1998. Vol 169, N 1. P. 83-94.

[6] Okamoto H., Taguchi H., Iida K., Danjo K. Development of polymer film dosage forms of lidocaine for buccal administration // Journal of Controlled Release. 2001. Vol. 77. P. 253-260.

[7] Danjo K., Higuchi F., Otsuka A. Release of lidocaine from polymer dosage forms // Chem. Pharm. Bull. (Tokyo). 1995. Vol. 43. P. 1759-1763.

[8] Oguchi M., Shikama N., Sasaki S., Gomi K., Katsuyama Y., Ohta Sh., Hori M., Takei K., Arakawa K., Sone S. Mucosa-Adhesive. Water-Soluble Polymer Film for Treatment of Acute Radiation-Induced Oral Mucositis // Intern. Journal of Radiation Oncology, Biology, Physics. 1998. N 5. P. 1033-1037.

[9] Klotz I.M., Walker F.M., Pivan R.B. The binding of Organic Ions by Proteins // J. Amer. Chem. Soc. 1946. Vol. 68, N 8. P. 1486-1490.

Резюме

Е. О. Батырбеков, А. Е. Борисова, М. Б. Өмерзакова

ПОЛИВИНИЛ СПИРТІНЕ НЕГІЗДЕЛГЕН
ЖЕРГІЛІКТІ АНЕСТЕТТИКТЕРДІҢ СУДА ЕРИТІН ДӘРІЛІК ТҮРЛЕРІ

Поливинил спиртінің синтетикалық полимеріне негізделген новокаинның жергілікті анестетиктерінің жаңа суда еритін полимерлі дәрілік формалары әзірленді.

Новокаиннің поливинил спиртімен өзара әрекеттесуі тепе-теңдік диализ әдісімен зерттелді. Физиологиялық тұзды дәрі-дәрмектерді босату динамикасы зерттелді. Новокаин әсерін ұзарту үшін полимерді қолдану мүмкіндігі туралы қорытынды жасалды.

Түйін сөздер: полимерлік түрлері, жергілікті анестетик, новокаин, поливинил спирті, дәрінің бөлінуі.

Резюме

Е. О. Батырбеков, А. Е. Борисова, М. Б. Умерзакова

ВОДОРАСТВОРМЫЕ ЛЕКАРСТВЕННЫЕ ФОРМЫ МЕСТНОГО АНЕСТЕТИКА НА ОСНОВЕ ПОЛИВИНИЛОГО СПИРТА

Разработаны новые водорастворимые полимерные лекарственные формы местного анестетика новокаина на основе синтетического полимера поливинилового спирта. Методом равновесного диализа изучено взаимодействие новокаина с поливиниловым спиртом. Исследована динамика высвобождения препарата в физиологический раствор. Сделано заключение о возможности использования полимера для пролонгирования действия новокаина.

Ключевые слова: полимерные формы, местный анестетик, новокаин, поливиниловый спирт, высвобождение лекарства.