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»

4 (64)

ОКТЯБРЬ – ДЕКАБРЬ 2018 г.

ИЗДАЕТСЯ С ОКТЯБРЯ 2003 ГОДА

ВЫХОДИТ 4 РАЗА В ГОД

АЛМАТЫ
2018

UTC 678.06:615.45

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RELEASE OF ANESTHETIC DRUGS FROM HYDROGEL BASED ON POLYHYDROXYETHYLMETHACRYLATE

Abstract. The release of anesthetic drugs from polymeric hydrogel based on polyhydroxyethylmethacrylate has been studied. The influence of various factors on process of release drugs from polymeric hydrogels was described. Anesthetic, evenly dissolved in polymeric matrix, was released in model media by the mechanism of diffusion with rate reduction.

Keywords: release, polymeric hydrogel, polyhydroxyethylmethacrylate, lidocaine, novocaine.

The large perspectives in the field of biotechnology are connected to polymeric hydrogels - the materials capable to absorb abnormal amount of water and dissolved the low-molecular substances. Despite of rather recent history hydrogels have already found wide application in various areas of biomedicine such as eye contact lenses, cosmetic artificial limbs, hygienic and dressing means, dental products and orthopedic materials [1-3]. Good compatibility with tissue of living organism, high permeability for various substances, transparency, hydrophilicity, nontoxicity are the basic advantages of hydrogels.

The wide application of hydrogels on the basis of synthetic polymer polyhydroxyethylmethacrylate (poly-HEMA) has received in the medicine. Polymeric gels based on poly-HEMA have high biocompatibility, elasticity similar to consistence to soft tissues of organism, have no antigenic and irritating properties [4]. Research of behaviour of materials from poly-HEMA in various environments has shown that catalytic active surroundings of organism do not cause destruction hydrogels for a long time.

The perspective and interesting field of HEMA-hydrogels application is systems of controlled delivery of medicinal substances. Earlier we have shown the possibility of application of such systems for treatment of infected cavities and purulent wounds.

Purpose of the present work is the study of various factors influenced on process of anesthetic drugs release from polymeric hydrogels based on poly-HEMA.

EXPERIMENTAL PART

Local anesthetics lidocaine and novocaine were used pharmaceutical grade purity. Hydroxyethylmethacrylate company "Aldrich" (USA) was used without further purification.

Polymeric hydrogels on a basis poly-HEMA were synthesized according to the below-mentioned procedure. Materials in form of soft elastic plate were received by polymerization of reacting mixture consisting from hydroxyethylmethacrylate (25-28 weight%), hydroxyethyldimethacrylate (1,2-2,5 %), water (65-70 %), ammonium persulphate (0,05 %) and drug (4-5 %). Reacting mixture was placed on Petri diches and heated at 90-100^{o}C within 2,5 h. As result the soft porous plate in form of disk in diameter 20-25 cm and thickness 0,4-0,5 cm containing dispersed drugs was received.

The release of drugs from polymer samples was studied under conditions *in vitro* at 37°C with help of the UV-spectroscopy. Spectra were recorded in quartz cuvette with thickness of 1 cm at spectrophotometer "Specord UV-VIS" (Japan).

RESULTS AND DISCUSSION

In order to estimate prolongation period of drugs the influence of different factors such as immobilization method, concentration of branching agent, content of water and drug on process of drug release from polymeric hydrogels was investigated. It was shown that drugs could be introduced into polymeric matrix not only during polymerization but also by way of sorbtion from water solutions. It is established that change of drug concentration in solution does not exert essential influence on sorbtion rate by hydrogel. At the same time, with increase of drug concentration in solution the increase of its limiting concentration in polymer was observed. The nature of drugs and its chemical structure rendered the certain influence on sorbtion process. The rate of diffusion was inversely proportional to the size of drug molecule.

The release of drugs from polymeric hydrogels in water was studied by means of method of UV-spectroscopy. It was established that process of release occurs on the mechanism of diffusion with reduction of rate. It was shown that values of diffusion coefficients of drugs was not differ both at their introduction in polymer by sorbtion and at introduction during polymerization. Drugs were not interacted chemically with polymeric matrix and dissolved in water filling pores of hydrogel. Typical curves of novocaine release are presented at figure 1.

The values of the diffusion coefficients of novocaine release are summarized in the table. The rate of drug release from hydrogels can be regulated by changing of the physical structure of polymer. With the increase of water content in poly-HEMA the release rate of drugs increases. The most suitable to the use as the carrier of drugs is hydrogel with the content of water from 65 up to 75 %. The increase of the water content is higher than those limits results in deterioration of durability and uniformity of hydrogel. The polymers consisting amount of water less than 65 % became rigid and fragile.

The influence of concentration of branching agent on rate of diffusion of lidocaine hydrogel was investigated. It was shown that this dependence had extreme character (figure 2). At increase of concentration diethyl ether of dimethacrylic acid up to the certain limit (from 1,0 up to 2,5 wt %) the diffusion

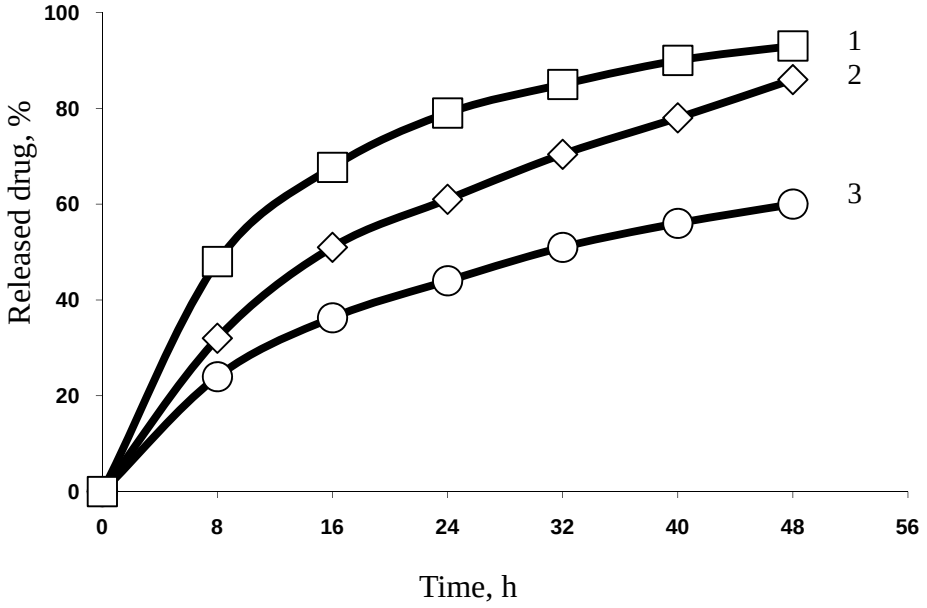

Figure 1 – Release of novocaine from poly-HEMA hydrogels at different H_2O content: 1 – 75, 2 – 70 , 3 – 65 %

Diffusion coefficients of novocaine release from poly-HEMA hydrogels

H_2O content: (wt.%)	D, $\cdot 10^{-6}$, cm^2/s
60,0	3,4
65,0	4,1
70.0	4,2
75,0	4,4
80,0	5,8

coefficient of drug decreases. Concentration of branching agent in these limits is optimum as it provides the optimum pore sizes within the limits of 10^{-5} - 10^{-3} cm. The time of dosed and prolonged release of drugs achieved up to 1,5-2,0 days The increase of concentration of branching agent higher than 2,5 wt %, resulted in sharp increase of rate of drug diffusion from hydrogel. I this case the desorbtion of drug occured only from surface of hydrogel. With increase of drug content in polymer the release rate insignificantly reduces.

Medical and biologic tests of poly-HEMA hydrogel have shown that received material did not render toxic, irritating and allergenic actions on the organism of experimental animals (white rats, guinea pigs). Clinical tests established that the bandage from hydrogel was antitraumatic, easily modeled to

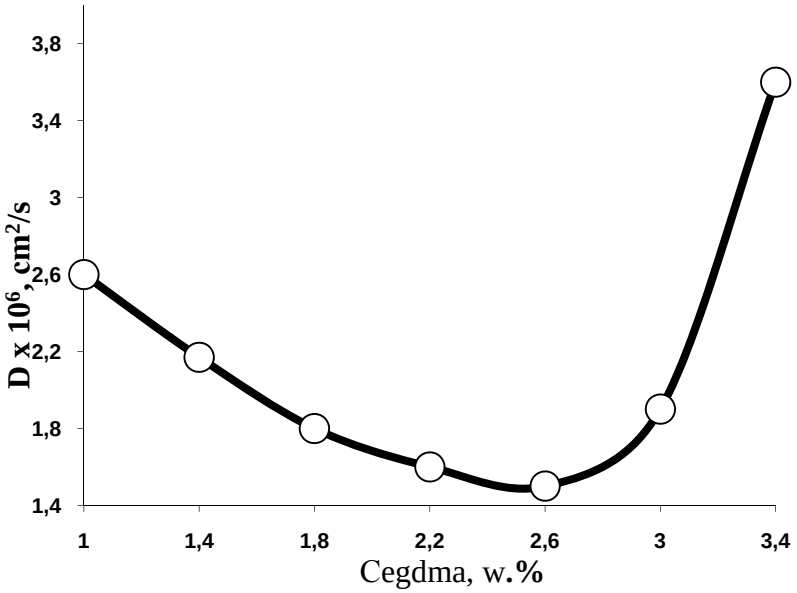

Figure 2 – Dependence diffusion coefficient
of lidocaine release versus concentration of branching agent

wounds, absorbs purulent liquid. Moreover, it promoted the long release of drug into wounds resulted in their fast sanitation.

Conclusion. The researches have shown the opportunity of regulation of drug release from hydrogels based on hydroxyethyldimethacrylate depending on chemical compound and physical structure of polymer. The sustained drug release from gels provides prolonged therapeutic effect. The developed polymeric materials with controlled anesthetic action have shown the high efficiency for pain treatment.

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

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Резюме

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ПОЛИГИДРОКСИЭТИЛМЕТАКРИЛАТ НЕГІЗІНДЕГІ
ГИДРОГЕЛЬДЕРДЕН АНЕСТЕТИКТЕРДІ БӨЛУ

Полигидроксиэтилметакрилат негізіндегі полимерлік гидрогельден анестетиктердің бөлінуі зерттелінді. Полимерлік гидрогельден дәрілік заттардың шығуына әртурлі факторларның әсері көрсетілген. Полимер бойында еріген дәрілік зат жылдамдығың баяулай отырын диффузия механизмі бойынша модельді ортаға шығады.

Түйін сөздер: босату, полимерлі гидрогель, полигидроксиэтилметакрилат, лидокаин, новокаин.

Резюме

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ВЫСВОБОЖДЕНИЕ АНЕСТЕТИКОВ ИЗ ГИДРОГЕЛЕЙ
НА ОСНОВЕ ПОЛИГИДРОКСИЭТИЛМЕТАКРИЛАТА

Изучено высвобождение анестетиков из полимерных гидрогелей на основе полигидроксиэтилметакрилата. Описано влияние различных факторов на процесс высвобождения лекарственных препаратов из полимерных гидрогелей. Анестетик, равномерно растворенный в полимерной матрице, высвобождается в модельные среды по механизму диффузии с уменьшением скорости.

Ключевые слова: высвобождение, полимерный гидрогель, полигидроксиэтилметакрилат, лидокаин, новокаин.