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E. O. BATYRBEKOV[1], M. B. UMERZAKOVA[1], A. E. B0RISOVA[2]

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

RELEASE OF ANESTHETIC DRUGS FROM POLYMERIC FILMS

Abstract. The release of anesthetic drug from polymeric medicinal films with the prolonged therapeutic action is studied. Local anesthetic lidocaine is used as anesthetics agent. The films are obtained by watering of polyvinyl alcohol solution of different concentration on the horizontal glass surface with their subsequent drying during 2-3 days. Kinetics of drug release from films in model biological environments is investigated. Lidocain, evenly dissolved in polymeric matrix, is released by the mechanism of diffusion with rate reduction. The clinical tests of polymeric anesthetic films are conducted at treatment of periodontal pathology.

Keywords: release, polymeric films, polyvinyl alcohol, lidocaine, periodont treatment.

Medical films have found wide application in the clinic of ophthalmology, dentistry, cardiology and the treatment of wounds and burns [1, 2]. Film therapeutic system is obtained by dissolving polymer carrier and drug substance in common solvent, the resulting solution was poured onto substrate, heated and molded film by evaporation of solvent. The obtained film was cut into samples of the required size. The simplicity of this technological scheme is obviously, another advantage consists in the possibility of using a broad range of drugs. As materials for manufacture of film dosage forms use variety of synthetic and natural polymers. To control the rate of release of drugs from medicinal films used either their limited permeability through polymer membrane (membrane systems), or slow diffusion of the drug dissolved in polymer matrix (solid system).

Dosage forms, traditionally used in therapeutic dentistry, have several disadvantages, the main of which can be attributed the short period of therapeutic action, the inability to ensure the sustainability concentration of drug in oral cavity, discomfort and duration of treatment. A promising direction is development new drug forms, capable of continuously release the drug in the local area, to have high adhesion to wet and hard tissues, to ensure dosing accuracy and constancy of concentration of drug for long time. Successful therapy of inflammatory periodontal diseases is only possible while maintaining constant concentration of drug long time within the ideal "therapeutic corridor" between the lower borders of toxic and effective concentrations [3-6].

An example of adhesive mucosal dosage form is medicinal films obtained on the basis of biocompatible polymers. Medical films containing various pharmacological drugs are already used in dental practice. Prolonged effect in such films is achieved by immobilization of local anesthetics on various polymeric

carriers. Application of essentially new medicinal forms on the basis of polymeric films opens new era in pain therapy.

In this work release of local anesthetic lidocaine from polymeric films in model biological environments is studied. The application of polymeric medicinal films with the prolonged therapeutic action for treatment of periodontal diseases is briefly described.

Experimental part

Local anesthetic lidocaine was used pharmaceutical grade purity. Polyvinyl alcohol (PVA) with MM 70 000 company "Aldrich" (USA) was used without further purification.

Polymer films were obtained from the corresponding solution of polymer and drug substance by evaporation of the solvent (water). Amount of 10,0 % PVA in distilled water kept on magnetic stirrer at 80°-90°C until complete dissolution. After obtaining homogeneous solution it cooled to room temperature and was added a calculated amount of substance of lidocaine. After mixing the resulting solution was poured onto a glass substrate and dried in the box, installed horizontally level, at room temperature to constant weight. Received dosage form had the appearance of thin elastic transparent film, which with the help of die cut standard discs with a diameter of 0.45-0.5 cm or squares with thickness of 0.2-0.5 mm. The calculation of dose of drug was carried out at the minimum dose.

The release of drug 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).

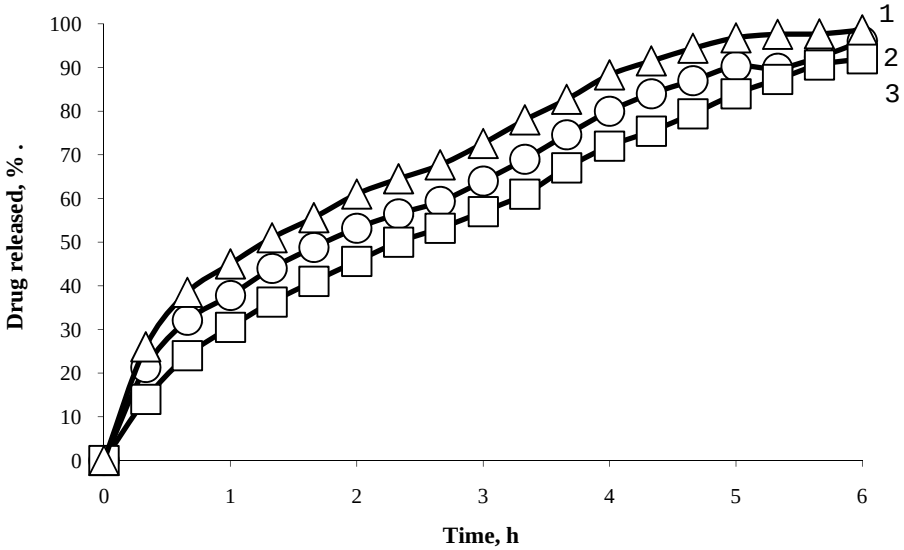
Results and discussion

Polyvinyl alcohol represents considerable interest as drug carrier in developing the anesthetizing films. This polymer has been widely used in medicine as plasma substitutes, stabilizer for suspensions, film-forming agent for capsules and tablets, component of ointment [7].

The medical films on the basis of PVA containing different doses of anesthetic drug lidocaine are developed. The effect of various physical-chemical factors on the process of drug release in model biological environment is studied. Dependence of lidocaine release at various drug loading is presented in figure.

Lidocaine is uniformly dispersed in polymer matrix and released in model environment on the mechanism of diffusion with rate reduction. The process of diffusion is described by Fick law and follows first order kinetics, i.e. the amount of drug released per unit time is proportional to its concentration in polymer. It is shown that drug diffused from polymer at 85-90% for 5-6 hours.

With the increase of film thickness, the diffusion of drugs slows down. So if the system is 1.0 mm thick the 50% of drug released per 1,0-1,5 h, at a film thickness of 2.5 mm the same amount of anesthetic diffuses for 4.0-4.5 h. It is found that with increase of drug loading from 100 to 300 mg per 1 g of polymer diffusion coefficients is reduced.



Release of lidocaine from PVA-films at various drug loading:
25 mg/1 g of PVA (1), 50 mg /1g of PVA (2), 100 mg /1 g of PVA (3)

Release parameters of lidocaine from PVA-films

Loading, мg/g	Time of 50% release, h	Time of max release, h	$D \cdot 10^{-7}$, cm^2/s
25	1,5	5,0	2,9
50	2,0	5,5	2,6
100	2,5	6,0	2,2

Clinical observations on patients with periodontal disease inflammatory and inflammatory-destructive nature showed significant advantages of using polymer film forms of lidocaine. Clinical efficacy was confirmed in statistically significant reduction of terms of treatment of patients with generalized periodontal disease, improvements of the test of Kulagina, gingival index of Loe, hygienic condition of the mouth, a higher percentage of remission of the disease in the early and late periods.

The main advantage of film is long and effective therapeutic effects of small drug doses in the area of pathology. The regulation process is carried out by slow diffusion of oral fluid in polymer, followed by swelling, biodegradation and slow release of the drug from swelling polymer. The sustained drug release from films provides prolonged therapeutic effect. Using variety of techniques, it is possible in a wide range to change the physical-chemical properties of the matrix and respectively the kinetics of release of drug substance. The one of advantages of

new dosage form of lidocaine should also be attributed to the lack of irritating action on the mucous membrane of the mouth, absence of allergic reactions and change the function of salivary glands, whereas the imposition of hardening of the gingival dressing is always associated with salivation, unpleasant taste of the dressing and aesthetic discomfort.

The analysis of direct, immediate and remote results of treatment and long-term observation of patients who have taken courses of treatment using medicinal films, expanded range of therapeutic and preventive measures, give experimental and clinical substantiation of their use in dental practice.

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Резюме

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

ПОЛИМЕРЛІК ҚАБЫРШАҚТАН АНЕСТЕТИКТЕРДІ БОСАТУ

Емдік әсері ұзақ полимерлік қабыршақтан анестетиктерді босату зерттелді. Ауруды сездірмейтін дәрі ретінде лидокаин қолданылады. Қабыршақ үлгілері әртүрлі концентрациядағы поливинил спирт ерітіндісінің көлденең шыны бетке құйып, оны ары қарай 2-3 күн шамасында кептіру арқылы алынады. Анестетиктің қабыршақтан модельді биологиялық ортаға босату кинетикасы анықталды. Полимерлі қалыпта бірыңғай еріген дәрілік зат жылдамдықтың төмендеуімен диффузия механизмі бойынша модельді ортаға шығады. Қабынған түрдегі пародонт ауруын

емдеуге арналған полимерлі ауруды сездірмейтін қабыршақтар клиникалық бақылаудан өткізілді.

Түйін сөздер: босату, полимерлі қабыршақтар, поливинил спирті, лидокаин, парадонт емдеу.

Резюме

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

ВЫСВОБОЖДЕНИЕ АНЕСТЕТИКОВ ИЗ ПОЛИМЕРНЫХ ПЛЕНОК

Изучено высвобождение анестетиков из полимерных пленок с пролонгированным лечебным действием. В качестве обезболивающего агента использован местный анестетик – лидокаин. Образцы пленок получали поливом раствора поливинилового спирта различной концентрации на горизонтальную стеклянную поверхность с последующим их высушиванием в течение 2-3 сут. Исследована кинетика высвобождения местного анестетика из пленок в модельные биологические среды. Установлено, что лекарственные вещества, равномерно растворенные в полимерной матрице, высвобождаются в модельные среды по механизму диффузии с уменьшением скорости. Проведены клинические испытания полимерных обезболивающих пленок при лечении патологии пародонта.

Ключевые слова: высвобождение, полимерные пленки, поливиниловый спирт, лидокаин, лечение пародонта.