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OBTAINING EYE FILMS BASED ON CHITOSAN

This work presents data on the study of the possibility of using the natural polysaccharide chitosan and a synthetic polymer of polyvinyl alcohol as a matrix for creating a polymer form in the form of a film with prolonged drug release. Eye films based on chitosan, as well as on the basis of chitosan and polyvinyl alcohol, have been developed by obtaining a composite injection. The immobilization of antibiotics in polyvinyl alcohol films leads to a pronounced prolongation of the antibiotic action, at the same time, it significantly increases the penetration of the drug into the tissues and eye fluids, providing the necessary therapeutic concentration for 1 day, which certainly becomes a significant advantage of antibiotic administration methods. To study the yield of drugs from polymer dosage forms, the method of UV spectroscopy was used.

The influence of the concentration of drugs on the dynamics of their release from polymer films in «in vitro» conditions was studied. It was found that their chitosan / PVA film has a longer release of the drug, which is indicative of a prolongation effect. The results which were obtained indicate the possibility of using a dosage form based on biocompatible high molecular weight compounds to create therapeutic systems with a diffusion mechanism of drug release.

Keywords: natural polymers, chitosan, polyvinyl alcohol, polymer eye films, medicinal product.

Introduction

Creation of innovative dosage forms of prolonged action based on natural and synthetic polymers containing immobilized drugs is a promising area of modern

chemistry of macromolecular compounds. The use of such dosage forms, called macromolecular therapeutic systems (Drug Delivery Systems), eliminates a number of disadvantages inherent in most traditional pharmaceuticals used in modern medicine, such as short-term pharmacological action and high toxicity [1–4].

The use of high molecular weight compounds as carriers of physiologically active substances allows you to achieve a better therapeutic effect due to long-term maintenance of the optimal concentration of the drug in the body, reduce the course dose, eliminate the irritating effect and overdose of drugs, makes it possible to create systems for controlled release and targeted transport of drugs to the field of pathology [5–7].

Among the polymer carriers used in immobilization processes, natural polysaccharides are of the greatest importance - high molecular weight compounds built from monosaccharide elementary units interconnected by glycosidic bonds and synthetic polymers. Polysaccharides include various derivatives of cellulose, dextran, chitosan, pectic and alginic acids, agarose, etc. This class of biopolymers is one of the most widespread in nature, characterized by availability, high biocompatibility, the presence of reactive functional groups that easily enter into various chemical reactions, as well as high hydrophilicity [8-11].

Much attention is paid to the use of chitosan and polyvinyl alcohol as a polymer carrier in pharmaceutical and ophthalmic practice.

Depolymerized chitosan with MM 3.5-250 kDa and SD 70 % can be used in the form of a complex with medicinal substances as a carrier providing sustained release of the medicinal substance. The modified chitosan complex is used as a delivery system in tablets, films, powders, matrix systems, as coatings or films on implants. To obtain drugs with prolonged release of a drug substance, structured chitosan is used [12–14].

Another effective material for the production of eye films turned out to be a synthetic water-soluble polymer, polyvinyl alcohol (PVA) [15]. Polyvinyl alcohol (PVA) is a polymer compound that cannot be obtained by polymerization of the corresponding monomer – vinyl alcohol CH_2CHOH, which does not exist in a free state.

Immobilization of antibiotics in PVA films leads to a pronounced prolongation of the antibiotic action and significantly increases the penetration of the drug into the tissues and eye fluids, providing the required therapeutic concentration for 1 day. In this respect, PVA films have a significant advantage over other methods of antibiotic administration. The experiment also showed the possibility of obtaining more elastic immobilized preparations of pilocarpine on PVA by introducing glycerol into the composition. Ophthalmic films with prolonged release of pilocarpine 20 μg or 40 μg are prescribed in cases where 3–4 times instillation of

pilocarpine per day is not enough to normalize intraocular pressure. Ophthalmic films with pilocarpine provide control of intraocular pressure for 1 day, while the induced myopia developing during the first hours decreases rapidly and usually does not exceed 0.5 diopters [16].

Materials and methods

Methods for obtaining new polymeric eye films based on chitosan. 1.5 % chitosan was dissolved by heating in 0.1 M hydrochloric acid. Place the beaker on a magnetic stirrer until the complete dissolution of chitosan. The calculated amount of the immobilized 5-fluorouracil preparation (125 mg / g and 250 mg / g) was added to the obtained filtered polymer solution with stirring. The solution was poured into a Petri dish and placed on a horizontal surface for 2-3 days at room temperature. The resulting dry films were carefully removed from the mold and immersed in 5% NaOH solution to neutralize residual hydrochloric acid, and then washed with ethanol to remove excess NaOH. Film size 1 * 8 * 0.35mm^3.

Obtaining a polymer eye film based on chitosan and PVA. 1.5 % chitosan was dissolved by heating in 0.1 M hydrochloric acid. Place the beaker on a magnetic stirrer until the complete dissolution of chitosan. In a separate glass, 8 % PVA was dissolved in distilled water. Added to a 1.5 % chilled solution of chitosan. The polymer ratio is 75:25, respectively. The calculated amount of the immobilized 5-fluorouracil preparation (125 mg / g and 250 mg / g) was added to the obtained filtered polymer solution with stirring. The solution was poured into a Petri dish and placed on a horizontal surface for 2-3 days at room temperature. The resulting dry films were carefully removed from the mold and immersed in 5 % NaOH solution to neutralize residual hydrochloric acid, and then washed with ethanol to remove excess NaOH. Film size 1 * 8 * 0.35mm^3.

UV spectra of aqueous solutions of medicinal substances were recorded on an Evolution 300 UV / VIS spectrophotometer (USA) in a quartz cuvette with a thickness of 10 mm. The drug concentrations were determined using calibration curves plotted from the absorption maxima characteristic of 5-FU. UV spectroscopic study of the release of drugs from polymer dosage forms was carried out by determining the change in absorption at a fixed wavelength at different time intervals.

The thermal properties of the films were studied by thermogravimetric analysis (TGA) using a Mettler Toledo TGA / SDTA 851 instrument (Switzerland). Thermogravimetry is a method that allows you to determine the change in the mass of a substance during its controlled temperature treatment. TGA was carried out in the temperature range from 50 to 500 ° C with a heating rate of 5 °C / min.

To determine the kinetics of drug release from the polymer form, a special device was used, which consisted of a metal basket, a thermostatted glass, and a

mechanical stirrer. The yield of the preparations was studied under in vitro conditions. For this, a certain number of films were placed in a metal basket immersed in 50 ml and 70 ml of water (respectively), Ringer- Locke solution, or physiological saline at room temperature or at 37 ° C. A constant stirring rate of the release medium (100 rpm) was provided using a magnetic stirrer, and temperature control was maintained using a flow cell. At regular intervals, 2 ml of the solution was taken to determine the drug content using UV spectroscopy.

The diffusion coefficients of drugs from the dosage form were calculated using equation (2).

$$M_t/M_0 = 4(Dt/\pi l^2)^{0.5} \quad (1)$$

$$D = (M_t/M_0)^2 \, l^2\pi/4t \quad (2)$$

where: D – diffusion coefficient, m 2 / sec;l – membrane thickness, m;

t – time, sec;

M_t – the amount of diffused drug during time t;

M_0 – the equilibrium amount of the drug.

Results and discussion

The most widely used dosage forms in ophthalmology are eye drops (solutions, suspensions), ointments and gels, and eye films.

The search for new dosage forms that allow less frequent administration of a drug without reducing the therapeutic effect is of great scientific and practical interest. The use of prolonged forms of the drug reduces the possibility of drug overdose and the negative effect of frequent instillation, and also frees the patient and medical personnel from frequent manipulations. In this regard, the development and application of ophthalmic medicinal films (OMF) would be a rational solution to the problem of prolonged therapeutic action and dosed intake of effective antibiotics into the eye tissues.

Polymer eye films occupy a special place in the field of medical grade polymers. Unlike other dosage forms, medicinal films allow you to prolong the effect of eye agents, more accurately dose their amount, and reduce the consumption and toxic effect of the drug.

In order to determine the prolonging properties, the release of 5-FU from chitosan and chitosan / PVA films was studied at various drug concentrations (50, 100, and 150 mg / g) under in vitro conditions (Figure 1.2, respectively). Table 1 shows the release data for 5-FU from the chitosan film.

Table 1 – Parameters of 5-FU release from chitosan films

Time, min	C1, %	C2, %	C3, %	Average concentration

1	2	3	4	5
0	0	0	0	0,0
15	6,178	21	21	16,06
30	24,849	30,5	30,5	28,6
60	24,906	37,5	38	33,47
90	25,043	44	43	37,35
150	40,662	46	46,5	44,38733
180	51,897	55	54,5	53,80
210	54,568	56	57,5	56,02
240	55,515	58,5	59,5	57,84
270	59,954	64,4	64,5	62,95
300	67,72	69,5	69,5	68,91
330	72,975	74	75	73,99
360	72,884	80	80	77,63
390	80,006	84	83,5	82,50
420	91,785	88,7	89	89,83
450	100	95	95	96,67

The process was studied by UV spectroscopy based on the characteristic absorption maximum of the drug at λ = 266 nm. The amount of 5-FU was determined by the calibration graph of the dependence of optical density on concentration. Freshly prepared Ringer-Locke solution was used as the release medium.

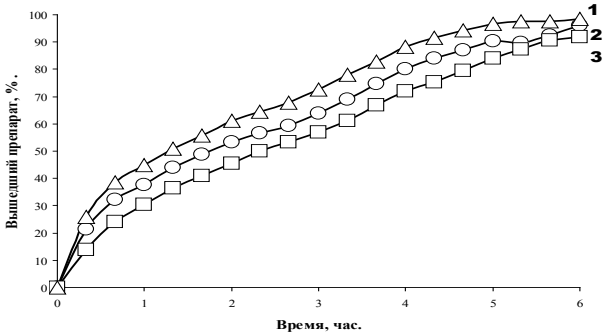

Figure 1 – Release of 5-FU from chitosan films at various drug concentrations, mg / 1 g: 1-50; 2-100; 3-150

The values of the diffusion coefficients for the films, calculated at the initial stage of release, are in the range of 7.5–8.3 x 10-6 cm^2 / s for all three concentrations, which indicates that there is no significant effect of drug loading on the rate of drug release from the films.

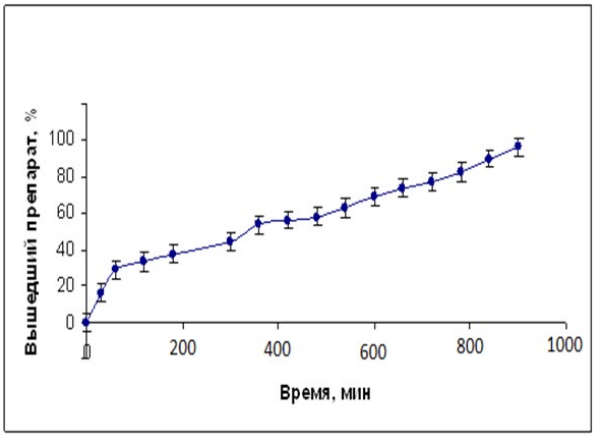

Figure 2 – Release of 5-fluorouracil from chitosan / PVA films

It was found that the drug from chitosan films completely diffuses into the Ringer – Locke solution within 6-7 hours, and from chitosan / PVA films within 14-15 hours without undergoing any changes. It was shown that these chitosan films containing 5-FU have a short-term therapeutic effect, which necessitates its frequent administration.

In order to determine the sterilization ability of polymer films, their thermal stability was studied. Figure 3 shows the TGA diagram of chitosan/ PVA films containing 5-FU.

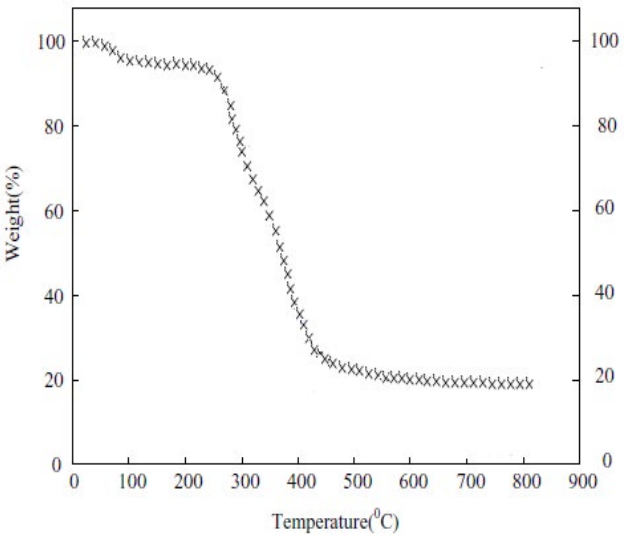

Figure 3 – TGA diagram of chitosan / PVA of films containing 5-FU

Analysis of the TGA diagram of polymer films showed that thermal destruction of the films begins at a temperature of 200 ° C. In general, the process of destruction takes place in the temperature range 200°–380 °C.

Thus, it has been established that polymer films containing 5-fluorouracil can be sterilized in an autoclave.

Conclusion

Thus, the obtained polymer dosage form in the form of a film can be used in scientific research practice as a theoretical material in the development of other effective polymer forms with a controlled and prolonged therapeutic effect.

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Материал 14.12.20 баспаға түсті.

ХИТОЗАН НЕГІЗІНДЕ КӨЗ ПЛЕНКАЛАРЫН АЛУ

Бұл жұмыста табиғи полисахарид хитозанды және поливинил спиртінің синтетикалық полимерін матрица ретінде дәрілік заттың ұзақ уақыт бөлінуімен қабықша (пленка) түрінде жасау үшін матрица ретінде пайдалану мүмкіндігін зерттеу туралы мәліметтер зерттеліп, келтірілген. Хитозан негізінде, сондай- ақ хитозан мен поливинил спирті негізінде көзге арналған қабықшалар композициялық инъекцияны алу арқылы жасалған. Поливинил спиртінің пленкаларындағы антибиотиктердің иммобилизациясы антибиотик әсерінің айқын ұзаруына әкеледі, сонымен бірге препараттың денеге және көз сұйықтығына енуін едәуір арттырады, бір тәулік ішінде қажетті терапевтік концентрацияны қамтамасыз ететіні анықталды, бұл сөзсіз антибиотиктерді енгізу әдістерінің маңызды артықшылығы болып табылады. Полимерлі дәрілік формалардан дәрілік заттардың шығуын зерттеу үшін УФ-спектроскопия әдісі қолданылды.

Дәрілік заттар концентрациясының олардың «in vitro» жағдайдағы полимерлі қабықшалардан бөліну динамикасына әсері зерттелді. Олардың хитозан/ поливинил спирті пленкасында препарат ұзағырақ бөлінетіні анықталды, бұл өз алдына ұзарту әсерін көрсетеді. Алынған нәтижелер дәрілік заттардың бөлінуінің диффузиялық механизмі бар терапевтік жүйелер құру үшін био- үйлесімді жоғары молекулалық қосылыстарға негізделген дәрілік форманы қолдану мүмкіндігін дәлелдеп, көрсетеді.

Кілтті сөздер: табиғи полимерлер, хитозан, поливинил спирті, көзге арналған полимерлі қабықшалар, дәрілік зат.

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ПОЛУЧЕНИЕ ГЛАЗНЫХ ПЛЕНОК НА ОСНОВЕ ХИТОЗАНА

В настоящей работе представлены данные по изучению возможности использования природного полисахарида хитозана и синтетического полимера поливинилового спирта в качестве матрицы для создания полимерной формы в виде пленки с пролонгируемым высвобождением лекарственного препарата. Разработаны глазные пленки на основе хитозана, а также на основе хитозана и поливинилового спирта путем получения композиционного введения. Иммобилизация антибиотиков в пленках поливинилового спирта приводит к выраженному пролонгированию действия антибиотика, вместе с тем, в значительной степени увеличивает проникновение препарата в ткани и жидкости глаз, обеспечивая необходимую терапевтическую концентрацию в течение 1 суток, что безусловно становится значительным преимуществом способами введения антибиотиков. Для изучения выхода препаратов из полимерных лекарственных форм привлекли метод УФ-спектроскопии.

Изучено влияние концентрации препаратов на динамику их высвобождения из полимерных пленок в условиях «in vitro». Установлено, что для хитозановой / ПВС пленки наблюдается более длительный выход лекарственного препарата, свидетельствующий об эффекте пролонгации. Полученные результаты свидетельствуют о возможности использования лекарственной формы на основе биосовместимых высокомолекулярных соединений для создания лечебных систем с диффузионным механизмом высвобождения лекарственных средств.

Ключевые слова: природные полимеры, хитозан, поливиниловый спирт, полимерные глазные пленки, лекарственный препарат.

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