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CREATION OF FILM COVERINGS ON A BASIS OF CHITOSAN THE PROLONGED ACTION

Key words: chitosan, modification, medicinal preparation, the state of polymer matrix.

Features of a complex formation of polymer of a natural origin chitosan with antibiotics are studied. Medicinal film coatings on the basis of chitosan and antibiotics both of cephalosporin series and of aminoglycoside one have been considered. It has been shown that the antibiotics release from a film will be determined by the amount of antibiotics connected with chitosan by hydrogen bonds, on the one hand, and by the state of the polymer matrix, on the other.

Ключевые слова: хитозан, модификация, лекарственное вещество, состояние полимерной матрицы.

Изучены особенности комплексообразования полимера природного происхождения хитозана с антибиотиками. Рассмотрены лекарственные пленочные покрытия на основе хитозана и антибиотиков цефалоспоринового и аминогликозидного ряда. Было показано, что высвобождение антибиотиков из пленок будет определяться с одной стороны количеством антибиотика, связанного с хитозаном, а с другой стороны, и состоянием полимерной матрицы.

Introduction

Decrease in efficiency of therapy by the antibiotics, being observed recently, is caused, generally distribution of strains of bacteria steady against them. Polymeric derivatives of antibiotics can help with the solution of this task. Advantages of use of polymeric derivative antibiotics are obvious in that case when polymer carrier of medicinal substance is in a soluble form. However, it isn't less important to consider that case when polymer carries out a matrix role - the carrier of medicinal substance. In this work some approaches to creation of film antibacterial coverings on a basis of chitosan (ChT) of the prolonged action suitable for treatment of surgical, burn and slow wounds of various etiology are considered. The choice as the ChT carrier isn't casual as this polymer possesses the whole range of the unique properties doing it by irreplaceable polymer [1,2,3] for medicine. In the present study we've considered some approaches to creating antibacterial ChT-based coatings of prolonged action suitable for treating surgical, burning and slowly-healing wounds of different etiology.

Experimentals

The objects of investigation were a ChT specimen produced by the company "Bioprogress" (Russia) and obtained by acetic deacetylation of crab chitin and antibiotics both of cephalosporin series – cephazolin sodium salt (CPhZ), cephotoxim sodium salt (CPhT), and of aminoglycoside series – amikacin sulfate (AMS), gentamicin sulfate (GMS). The investigation of the interaction of medicinal preparations with ChT was carried out according to the techniques described in [4,5].

ChT films were obtained by means of casting of the polymer solution in acetic acid onto the glass surface with the formation of chitosan acetate (ChTA). The polymer mass concentration in the initial solution was 2 g/dl. The acetic acid concentration in the solution was 1, 10 and 70 g/dl. Aqueous antibiotic solution was added to the ChT solution immediately before films formation. The content of the medicinal preparation in the films was 0.1 mol/mol ChT. The film thickness in all the experiments was maintained constant and equal to 0.1mm. The kinetics of antibiotics release from ChT film specimens into aqueous medium was studied spectrophotometrically at the wave length corresponding to the maximum absorption of the medicinal preparation.

In order to regulate the ChT ability to be dissolved in water the anion nature was varied during obtaining ChT salt forms. So, a ChT-CPhZ film is completely soluble in water. The addition of aqueous sodium sulfate solution in the amount of 0.2 mol/mol ChT to the ChT-CPhZ solution makes it possible to obtain an insoluble ChT-CPhZ-Na_2SO_4 film. On the contrary, a ChT-AMS film being formed at the components ratio used in the process of work, isn't soluble in water. Obtaining a water-soluble film is possible if amikacin sulfate is transformed into amikacin chloride (AMCh). In this case the obtained ChT-AMCh film will be completely soluble in water. Thus, the following film specimens have been analyzed in the investigation: ChT-CPhZ and ChT-CPhT (soluble forms); ChT-CPhZ-Na_2SO_4 (insoluble-in-water form); ChT-AMCh (soluble form); ChT-AMS and ChT-GMS (insoluble-in-water forms).

With the aim of determining the amount of medicinal preparation held by the polymer matrix there was carried out the synthesis of adducts of the ChT-antibiotic interaction in the mole ratio 1:1 in acetic acid solution. The synthesized adducts were isolated by double re-precipitation of the reaction solution in NaOH solution with the following washing of precipitated complex residue with isopropyl alcohol. Then the residue was dried in vacuum up to constant mass. The amount of preparation strongly held by chitosan matrix was determined according to the data of the element analysis on the analyzer EUKOEA – 3000.

The results discussion

On the basis of the chemical structure of the studied medicinal compounds [6] one can suggest that they are able to combine with ChT forming polymer adducts of two types – ChT-antibiotics complexes and polymer salts produced due to exchange interaction. As a result some quantity of medicinal substance will be held in the polymer chain. The interaction taking place between the studied medicinal compounds and ChT was

demonstrated by UV- and IR-spectroscopy data. The interaction energies evaluated by the shift in UV-spectra are about 7-12 kj/mole, which allows us to speak about the formation of complex ChT-antibiotic compounds by means of hydrogen bonds.

Table 1 gives the data on the amount of antibiotics determined in polymer adducts obtained from acetic acid solution.

Table 1 - The amount of antibiotics determined in reaction adducts

C_{CH_3COOH}, g/dl in the initial solution	The antibiotics used	The amount of antibiotics in reaction adduct, % mass.
1	CPhZ	10,1
	CPhT	15,9
	AMS	61,5
	GMS	59,4
10	CPhZ	5,88
	CPhT	57,5
	AMS	55,8
	GMS	31,3
70	CPhZ	3,03
	CPhT	3,7
	AMS	41,3
	GMS	40,1

Attention should be paid to the fact that the amount of medicinal preparation in the adduct of the ChT-medicinal preparation reaction is considerably higher in the case of antibiotics of aminoglycoside series than in the case of antibiotics of cephalosporin series. This can be connected with the fact that CPhZ and CPhT anions interact with ChT polycation forming salts readily soluble in water. In the case of using AM and GM sulfates because of two-base character of sulphuric acid one may anticipate the formation of water-insoluble "double" salts – ChT-AM or ChT-GM sulfates due to which additional quantity of antibiotics is held on the polymer chain.

Table 2 gives the data on the value of the rate of AM and GM release from film specimens formed from acetic acid solutions of different concentrations. The rate was evaluated only for water-insoluble films because at using soluble films the antibiotic release was determined not by medicinal preparation diffusion from swollen matrix but by film dissolving.

Table 2 - Transport properties of chitosan films in relation to medicinal preparation release

Acetic acid concentration g/dl	The antibiotics used	Release, % mass./h for chitosan specimens
1	AMS	0,5
	GMS	0,4
10	AMS	0,8
	GMS	0,5
70	AMS	1,5
	GMS	1,3

Attention must be given to the fact of interaction between the rate of antibiotics release from chitosan films and their amount which is strongly held in ChT chain. For example, at increasing the concentration of acetic acid used as a solvent the amount of medicinal preparation connected with the polymer chain decreases in all the cases considered by us. Correspondingly, the rate of antibiotics release from films insoluble in water, increases.

The influence of the amount of medicinal preparation strongly held in ChT matrix, on the rate of medicinal substance release from the film must be most pronounced at comparing the rates of release of antibiotics of aminoglycoside series and cephalosporin one. However, ChT-CPhZ and ChT-CPhT films are soluble in water while ChT-AMS and ChT-GMS ones do not dissolve in water and it isn't correct to compare them. At ChT transition into insoluble form (by adding sodium sulfate) the rate of release of antibiotics of cephalosporin series decreases considerably (Fig. 1, curve 1) as compared with a soluble form but still it is higher than that in the case of antibiotics of aminoglycoside series (Fig. 1, curve 2). It should be also noted that the rate of antibiotics release from soluble ChT-CPhZ film (Fig. 1, curve 3) is also higher than in the case of ChT-AMCh film (Fig. 1, curve 4). Thus, considerable difference between the rate of release of aminoglycoside series antibiotics and that of cephalosporin series antibiotics is evidently explained by the difference in the amount of ChT-antibiotics adduct.

Thus, at forming film coatings one should proceed from the fact that a medicinal preparation can be distributed in the polymer matrix in two ways. One part of it connected with polymer chain, for example, by complex formation is rather strongly held in that polymer chain.

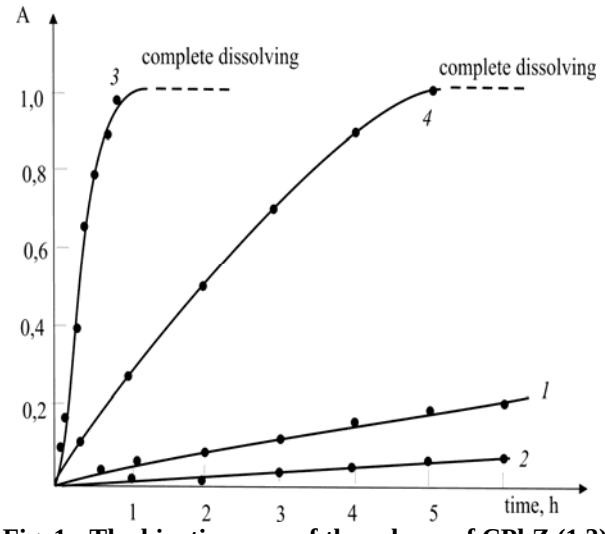

Fig. 1 - The kinetic curve of the release of CPhZ (1,3) and AM (2,4) from soluble (1,2) and insoluble (3,4) films

The rest of it is concentrated in polymer free volume (in polymer pores). The rate of release of antibiotics from the film will be determined by the amount of antibiotics connected with ChT by hydrogen bonds, on the one

hand, and by the state of the polymer matrix including its ability to dissolve in water, on the other hand.

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