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MACROMOLECULAR COMPOUNDS AND POLYMERIC MATERIALS

Thermal Modification of Chitosan Films as a Way to Control Their Transport Properties

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Abstract—The possibility of using heat treatment (~120°C) for controlling the drug release from chitosan films prepared from acetic acid solutions and containing antibiotics cefazolin and cefotaxime was examined.

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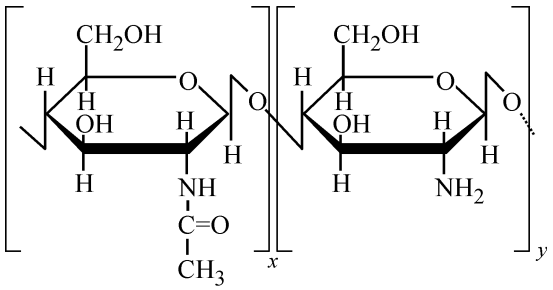
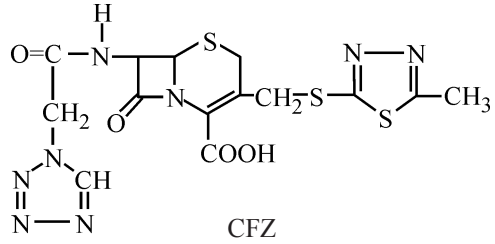
The development of new procedures for local treatment of wounds and burns using polymeric coatings with preset properties is given much attention today [1]. To ensure the reliable therapeutic effect, the coatings should meet a number of special requirements including atraumaticity, high sorption ability, protection from external infection, and possibility of controllable drug release. Unique properties of chitosan (CT) polysaccharide, such as biocompatibility with tissues of a living body, bacteriostatic properties, capability to enhance regenerative processes in wound healing, biodegradability, and excellent chelating ability [2, 3], in combination with the film-formation ability make CT a promising material for film coatings of prolonged effect for protection and treatment of surgery wounds and burns. The structural formula of chitosan units is shown below:



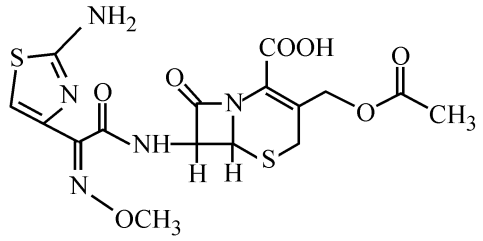
The goal of this study was the development of medicinal chitosan films with controllable transport properties with respect to the immobilized drugs, cefazolin and cefotaxime antibiotics.

EXPERIMENTAL

As investigation objects we used a CT sample [TU (Technical Specification) 9289-067-00473124–03, Bioprogress Private Company (Russia)] prepared by base deacetylation of crab chitin (degree of deacetylation ~84%, M_η = 90000) and antibiotics of the cephalosporin series: cefazolin (CFZ) and cefotazime (CFT):



CFZ



CFT

Chitosan films were prepared by casting a polymer solution in acetic acid onto glass surface. The gravimetric concentration of the polymer in the initial solution was 2 g dl^{-1}. The acetic acid concentration in solution was 1

or 70 g dl^{-1}. Aqueous solution of an antibiotic was added to a CT solution immediately before film formation. The film thickness was kept constant in all the experiments, 0.1 mm. The kinetics of the CFZ and CFT release from CT film samples into aqueous medium was monitored spectrophotometrically by the optical density D at λ = 270 and 262 nm, respectively (absorption maxima of the antibiotics). To make the film insoluble in water, it was heat-treated at ~120°C for 15–200 min. The drug content in the film was 0.1 mol mol^{-1} CT. The IR spectra were recorded on Specord M-80 and Shimadzu spectrometers (KBr pellets, films) in the range 700–3600 cm^{-1}. The UV spectra of all the samples were measured in 1-cm quartz cells against water on a Specord M-40 spectrophotometer in the range 220–350 nm.

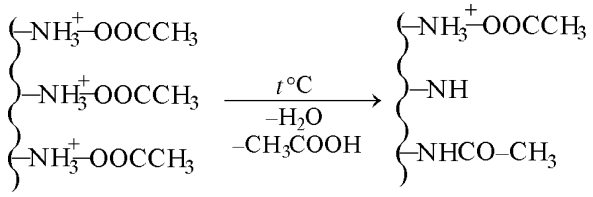
In the development of materials for prolonged therapy, one of the major problems determining the therapeutic efficiency is control of the rate of the drug release into the wound. If a drug is not covalently bonded to the polymeric matrix, its release is due to diffusion from the swollen polymeric system into the environment. Therefore, two principal approaches are mainly used for controlling the drug release kinetics: (1) variation of the conditions under which the structure of the polymeric matrix is formed and (2) modification of the formed structure of the polymeric matrix. In the first case, formation of structures characterized by different packing densities and, correspondingly, different volumes of interstructural regions can be ensured, e.g., by varying the quality of the solvent used or the time parameters of film preparation.

It is known [4] that the acetic acid concentration in solution appreciably affects the degree of protonation of CT amino groups α and, correspondingly, the viscosity of CT solutions. At equimolar ratio of acetic acid and CT, α does not exceed 0.5–0.7. Correspondingly, in dilute acetic acid (1–2 wt %) CT solutions are characterized by low viscosity and compact shape of the macromolecules. An increase in the acetic acid concentration is accompanied by an increase in the solution viscosity.

Along with the influence of the acetic acid concentration on the degree of CT protonation, it should be also taken into account that solutions with different acetic acid concentrations are solvents of different thermodynamic quality with respect to CT. 70% acetic acid solutions exhibit the highest affinity for CT [5]. Therefore, the absolute viscosity reaches a maximum specifically for CT solutions in 70% acetic acid. This significant difference in the structure of the initial solutions is apparently preserved in the structure of films formed from these solutions, which may be reflected in their transport properties.

However, a chitosan film in the salt form, formed from acetic acid solutions, contains protonated NH_3^+ groups and dissolves in water. Therefore, it is impossible to evaluate the possible influence of the structure of the polymeric matrix on the drug release from the film without using a second approach, modification of the chitosan film.

Heat treatment of films is accompanied by removal of the acetic acid bound by the amino groups and can lead to amidation with the formation of chitin units. As a result, the affinity of the film for water will decrease [6]. The reactions presumably occurring in the course of heat treatment are described by the following scheme:



The fact of formation of amide groups in the heat-treated films is confirmed by significant enhancement in the IR spectra of the amide I band in the range 1630–1550 cm^{-1}. Furthermore, the intensity of stretching vibration bands of hydroxy groups decreases, and a shoulder characteristic of stretching vibrations of amino groups appears at 3500–3000 cm^{-1}. These data indicate that, indeed, the degrees of both amidation and acetic acid elimination gradually increase upon heat treatment.

Since heat treatment of the films makes them insoluble in water, too long heat treatment hinders the release of antibiotics from the polymeric matrix and correspondingly decreases the rate of drug release from the films. By varying the heat treatment conditions, it is possible to vary also the transport properties of the films. Indeed, as seen from Fig. 1, from the water-soluble film that was not subjected to heat treatment, the drug completely passes into the solution within 15–30 min (curve *1*), which is comparable with the time of the film dissolution in water.

The heat-treated films behave differently: The drug release from the film considerably decelerates. As seen from Fig. 1, curves *2–4*, during the first 1–20 h the drug is released at a constant rate, after which the release decelerates, and on the 7th–10th day the drug

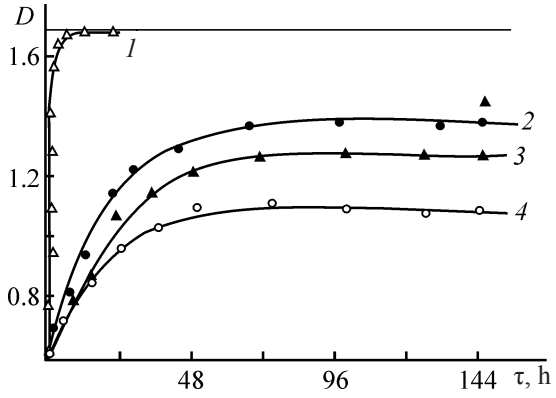


Fig. 1. Kinetic curves of CFZ release from a film prepared from 1% acetic acid. Heat treatment of the film: (*1*) none, (*2*) for 15 min, (*3*) for 30 min, and (*4*) for 60 min. (*D*) Optical density and (τ) time. The horizontal line corresponds to the release of the whole amount of CFZ, 0.1 mol mol^{-1} CT, from the film.

concentration in the aqueous phase reaches a constant value. The longer the heat treatment time, the lower the release rate and the limiting egress of the antibiotic from the film (see table, Fig. 2).

Figures 3a and 3b show changes occurring in the UV spectra of CT–CFZ and CY–CFT films upon heat treatment. As can be seen, with an increase in the heat

Influence of conditions of preparation and modification of chitosan films on their transport properties: initial rate of the release of antibiotics from the film and their limiting egress
Antibiotic

Anti-biotic	c_{acid}, wt %	Heat treatment time, min	Initial release rate,[a] (wt %) h^{-1}	Limiting egress,[a] wt %
CFZ	1	15	2.80	80
		30	2.55	76
		60	2.20	65
		120	2.0	57
	70	15	2.85	84
		30	2.65	79
		60	2.35	66
		120	2.1	57
CFT	1	15	2.85	81
		30	2.60	77
		60	2.20	64
		120	2.00	56
	70	15	2.90	84
		30	2.70	78
		60	2.35	67
		120	2.15	57

* Weight percentage relative to the initial amount of drug introduced into the film.

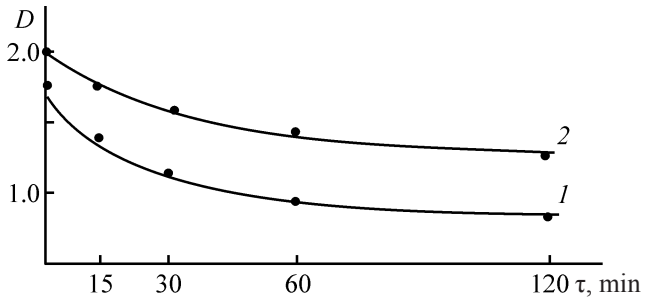


Fig. 2. Optical density *D* of solutions, corresponding to the limiting egress of (*1*) CFZ and (*2*) CFT from films formed in 1% acetic acid, as a function of the time τ of heat treatment of the films.

treatment time the absorption band is shifted to longer wavelengths by 30–40 nm and its intensity changes, which suggests changes in the polymeric matrix. Heat treatment of the individual drugs is not accompanied by changes in their electronic spectra.

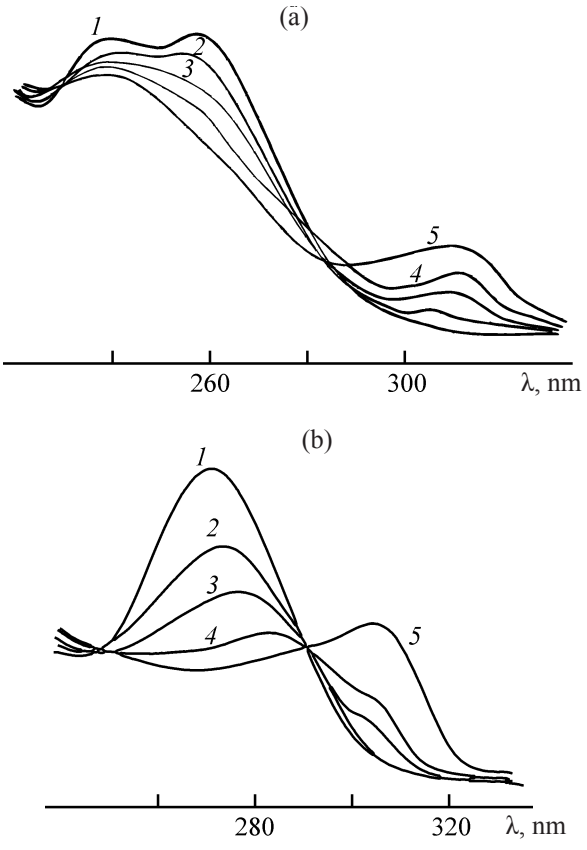


Fig. 3. UV spectra of the (*1*) initial film and films heat-treated for (*2*) 15, (*3*) 30, (*4*) 60, and (*5*) 120 min. (λ) Wavelength. Film: (a) CT–CFT and (b) CT–CFZ.

As the modified film is insoluble in water, it becomes possible to follow the influence of the structure of the polymeric matrix on the rate and extent of the drug release from the film. As seen from the table, from the films prepared from 70% acetic acid the antibiotics are released somewhat faster than from the films prepared from 1% acetic acid. The limiting egress of the drugs from the films changes correspondingly. This result is quite understandable in view of the fact that the density and ordering of the films formed from solutions in concentrated acetic acid are lower than those of the films formed from 1% acetic acid [5].

Thus, we found ways allowing control of the rate and extent of drug release by varying the time of heat treatment of the films and concentration of acetic acid in the initial solution.

CONCLUSIONS

(1) For both systems studied, chitosan–cefazolin and chitosan–cefotaxime, an increase in the time of heat treatment of the film at ~120°C is accompanied by gradual and regular decrease in the rate and extent of antibiotic release.

(2) The rate and extent of drug release from films is determined, apart from the heat treatment time, by the acetic acid concentration in the initial solution, governing the supramolecular structure of the films. An increase in the acetic acid concentration favors more complete release of antibiotics from the films.

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