DOI: 10.33184/dokbsu-2021.1.2

Studying kinetics of release medicinal substances from chitosan films

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The kinetics of controlled release of medicinal substances from chitosan films has been investigated. Correlation between values of coefficients diffusion and shares of medicinal substance connected with a polymeric chain has been established. It was shown that the greater proportion of the medicinal substance connected with a polymeric chain, the lower the value of diffusion coefficients and the index defining process of diffusion in the chitosan films, and the slower transport of medicinal substance from a polymeric matrix.

Keywords: chitosan, medicinal substance, diffusion, the abnormal character.

Introduction

Last time the considerable interest to studying of the diffusion phenomena in polymers is observed. The reason is that the diffusion plays a primary role in such processes as dialysis, permeability of biomembranes and tissues, prognostication of the protective properties of polymeric coatings, etc. [1]. Studies of the diffusion of substances from polymer matrix are also necessary in development of medicinal polymeric films with controllable release of medicinal substances.

The aim of our study was to examine the fundamental aspects of processes of diffusion of medicinal substance in polymeric films based on a natural polysaccharide chitosan and to determine opportunities of monitoring of a release of medicinal preparations.

Experimental

We used a sample of chitosan (ChTS) manufactured at Bioprogress ZAO (Russia) by alkaline deacetylation of crab chitin (degree of deacetylation ~84%) with M_{sd} = 113 000. As the medicinal substance (MS) served antibiotics of the amino glycoside (kanamitsin, KM) and cefalosporin series (ceftriaxone, CFT).

To form chitosan acetate film samples a 1% polymer solution in 1% acetic acid was poured on a glass surface. An antibiotic aqueous solution was added to the chitosan solution imme-

diately before film formation. The drug content in a film was as high as 0.01, 0.05, or 0.1 mol/mol chitosan. Throughout all experiments, the film thickness was constant and equal to 100 μm. The film samples were subjected to isothermal annealing at 120°C for a fixed period of time.

The kinetics of drug release under thermally controlled conditions (T = 36°C) was studied via placement of a sample in a cell with distilled water. An antibiotic released into the aqueous phase was recorded with a spectrophotometer at a wavelength corresponding to the maximum of drug absorption in the UV region. The amount of drug, G_s, released from the film up to time t was estimated from the calibration curve. The time at which a constant concentration of drug, G_∞, was established was taken as the instant of equilibrium attainment. The weight fraction of a drug capable of diffusion, α, was estimated as the ratio of the maximum amount of the antibiotic released from a film to the amount of drug introduced in the film.

The mechanism of mass transfer was analyzed through an equation describing the kinetics of release:

$$G_s/G_\infty = kt^n, \quad (1)$$

Where G_∞ is value of G_s at $t \to \infty$, k is a constant related to the parameters of polymer–diffusate interaction, and n is a parameter characterizing the mechanism of transport of a low-molecular mass substance in the film. Exponent n in Eq. (1) was found from the tangent of the slope of the ln (G_s/G_∞)–ln t dependence.

The interaction of MS with ChTS was studied by UV spectroscopy. UV spectra of all the samples were recorded in 1 cm thick quartz cuvettes relative to water with a Specord M-40 spectrophotometer in the range 220–350 nm.

To determine the weight fraction of a drug bound to a polymer matrix, β, the products of the interaction of chitosan with the antibiotic were isolated via double precipitation from a solution in acetic acid into a NaOH solution followed by washing of the precipitate with ethanol. The precipitate was dried up to a constant weight. The content of the drug bound with the chitosan matrix was determined by UV spectroscopy.

Results and discussion

Now the established fact that at controlled release of MS from polymeric systems diffusion processes dominate is standard.

Figure 1 shows typical experimental curves of CFT release from chitosan films with different drug contents. All kinetic curves level off with a clearly defined limit value corresponding to equilibrium drug yield G_∞.

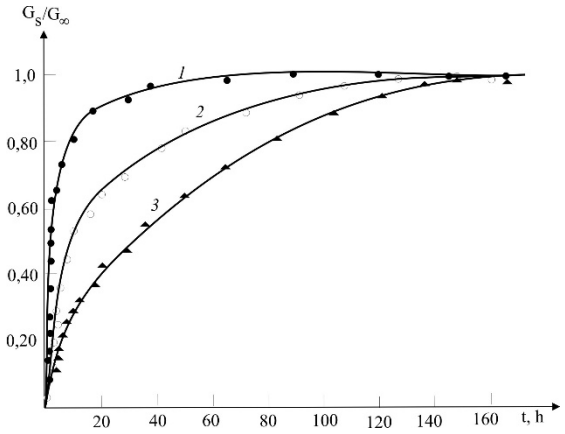

Fig. 1. Kinetic curves of drug release for ChTS-CFT films with CFT contents of (1) 0.01, (2) 0.05, and (3) 0.1 mol/mol chitosan. The isothermal annealing time is 30 min.

The diffusion coefficients of low-molecular mass components in films were determined with the use of Fick's second law [2]:

$$\frac{\partial c_s}{\partial t} = D_s \frac{\partial^2 c_s}{\partial x^2} \quad (2)$$

The solutions to the above equation for long ($G_s/G_\infty > 0.5$) and short ($G_s/G_\infty \leqslant 0.5$) experiments have dissimilar forms.

$$\text{At } G_s/G_\infty \leqslant 0.5 \; {G_s}/{G_\infty} = [16 D_s t/\pi L^2]^{0.5} \quad (3а),$$

$$\text{and, at } G_s/G_\infty > 0.5 \; {G_s}/{G_\infty} = 1 - [8/\pi^2 \exp(-\pi^2 D_s t/L^2] \quad (3б),$$

where $G_s(t)$ – concentration of the desorbed substance at time t and G_∞ – Gs value at $t \to \infty$, L – thickness of the film sample.

In case of the molecular diffusion submitting to the classical equation of Fick, it is necessary to expect equality of coefficients of $D_s^a = D_s^b$ [3]. However, apparently from the data presented in table 1, for all analyzed cases, value of diffusion coefficients calculated at an initial and final stage of diffusion don't coincide.

It indicates to a deviation of the mechanism of diffusion from classical type and allows assuming the so-called pseudo-normal mechanism of diffusion of MS from a chitosan matrix.

The type of the kinetic curves constructed in coordinates of $G_s/G_\infty - t^{1/2}$ also testifies to pseudo-normal type of diffusion of MS. In case of simple diffusion, the dependence of release of MS from film samples in coordinates $G_s/G_\infty - t^{1/2}$ would have to be straightened at all times of experiment. However, the linear site is observed only on $G_s/G_\infty < 0.5$ then the rate of release of an antibiotic significantly decreases.

Table 1. Parameters of MC desorption from chitosan films

Film composition	Drug concentration in film, mol/mol ChTS	Annealing time, min	$D_s^{а}*10^{11}$, cm^2/sec	$D_s^{б}*10^{11}$, cm^2/sec	n	α
ChTS-KM	1:0.01	30	27.80	2.25	0.32	0.96
		60	26.70	2.02	0.26	0.91
		120	24.50	1.90	0.24	0.89
	1:0.05	30	26.60	1.97	0.20	0.84
	1:0.1	30	25.80	1.63	0.17	0.75
ChTS-CFT	1:0.01	30	94.70	8.35	0.40	0.95
		60	88.90	6.83	0.38	0.93
		120	82.30	6.10	0.33	0.92
	1:0.05	30	68.80	6.93	0.33	0.91
	1:0.1	30	52.10	6.01	0.30	0.90

Table 2. Mass fraction β of an antibiotic in the reaction adducts obtained from 1% acetic acid

Antibiotic	MS concentration in a film, mol/mol ChTS	β
KM	1.00	0.58
	0.10	0.26
	0.05	0.19
	0.01	0.05
CFT	1.00	0.17
	0.10	0.10
	0.05	0.07
	0.01	0.03

At MS diffusion from films abnormally low values of the parameter n estimated on a tangent of angle of an inclination in coordinates of $\ln(G_s/G_\infty)$ – ln t take place. Increases in the drug concentration and isothermal annealing time are accompanied by an additional decrease in n. The change in the α value is symbate to that of n.

All the specific features inherent in the anomalous (non-Fick) diffusion are well described in terms of the relaxation model [4]. In contrast to the Fick diffusion, in which an instantane-

ous attainment of the surface concentration of the sorbate and its change is assumed, the relaxation model presumes variation of the concentration in the surface layer (i.e., variable boundary conditions) in accordance with the first-order equation [5]. One of the main reasons causing change of boundary conditions call a non-equilibrium of the structural-morphological organization of a polymeric matrix [4]. It is noteworthy that the anomalously small values of n have also been observed by other researchers and attributed to the strong interaction of the MS with the polymer [6].

The data on the fraction β of the antibiotic bound into polymeric adducts formed in acetic acid solutions are presented in Table 2.

It can be seen that the fact that KM can “cross-link” chitosan chains results in that in the substantialy larger amount of the MS firmly bound macromolecules, compared with CFT.

Thus, the structural changes in the polymer matrix, including those resulting from its modification via the interaction with drugs, are most probably responsible for the deviations of the mechanism of the mass transfer processes from the classical Fick’s mechanism.

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The article is recommended for publication by the Department of High Molecular Compounds and General Chemical Technology of the Bashkir University (dr. chem. sciences, prof. Kulish E. I.)

Изучение кинетики высвобождения лекарственных веществ из хитозановых пленок

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Исследована кинетика контролируемого высвобождения лекарственных веществ из хитозановых пленок. Установлена корреляция между значениями коэффициентов диффузии и долей лекарственного вещества, прочно удерживаемой полимерной цепью. Показано, что чем больше доля лекарственного вещества, связанного с полимерной цепью, тем меньше значение коэффициентов диффузии и показателя, определяющего процесс диффузии в хитозановых пленках, и тем медленнее происходит транспорт лекарственного вещества из полимерной матрицы.

Ключевые слова: хитозан, лекарственное вещество, диффузия, аномальный характер.