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## Regularities of Multicomponent Transport in Polymer Systems for Controlled Drug Release

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A mathematical model predicting the behavior of systems consisting of hydrophilic polymer, water, and a low-molecular compound has been developed. The model takes into account the process of swelling of polymers during water sorption, the existence of the embedded form of drug in polymer matrix and some other factors. The dependence of physico-chemical parameters on concentration of water, drug and on mechanical properties of polymer were confirmed by corresponding experimental results. Different ratios of kinetic parameters determined in this study enable us to predict the effect of matrix characteristics on controlled release of drugs.

**KEY WORDS** Controlled drug release, polymeric systems, kinetic parameters, matrix variables.

The study of the simultaneous transport of water and drug in swollen glassy polymers which is of great interest for two main reasons. First, the process of multicomponent transport in filled polymers is not yet fully understood,<sup>1,2</sup> and second, the results of the study in consideration are essential for developing the polymer matrix systems for controlled drug release.

A complete knowledge of the mechanism of interactions in the system consisting of polymer, solvent and low-molecular compound is required to regulate the kinetics of drug transport. Our previous investigation of such system<sup>1</sup> dealt with the dioxidine release from matrices of different hydrophilic character. The approach was based on the phenomenological equation of the solvent transport

$$\partial C_w / \partial t = D_w \nabla C_w - v_w C_w$$

where  $C_w$  is the concentration of solvent in polymer,  $D_w$  is its diffusion coefficient, and  $v_w$  is the velocity of local volume of solvent.

It was shown<sup>1</sup> that  $v_w$  was a function of drug concentration and this experimental result was attributed to differences in the stresses in the polymer resulting from drug loading. It is, however, unclear why the variation of stress affects the velocity of sorption mentioned above? The present work is the theoretical attempt to answer this question by using the model of transport of solvent in swelling glassy polymers which was suggested and successfully confirmed by experiments.<sup>3-5</sup>

Our other aim was to check the possibility to apply this approach for the modeling of simultaneous transport of solvent and low-molecular compound in glassy hydrophilic polymers.

## EXPERIMENTAL JUSTIFICATION OF THE MODEL

Before discussing the proposed model we should briefly review our previous experimental results which have been obtained in the study of the system consisting of the polymer, solvent, and drug.

Figure 1 shows the kinetic curves of water sorption by copolymers of N-vinylpyrrolidone (N-VP) with butyl- (PPB, Figure 1a) and methylmetacrylate (PPM-1, Figure 1b; PPM-2, Figure 1c). These copolymers are characterized by the different content of hydrophilic (N-VP) groups of 0.7 for (PPB), 0.4 for (PPM-1), for 0.2 (PPM-2) and different equilibrium concentration of water in the swollen polymer (0.46, 0.23, 0.07 g/g, respectively). The main feature of the kinetics of water sorption by copolymers of N-VP is the existence of a linear part of the kinetic curve, which is well-known to be the Case II of diffusion.<sup>4,6</sup> Noting the increase

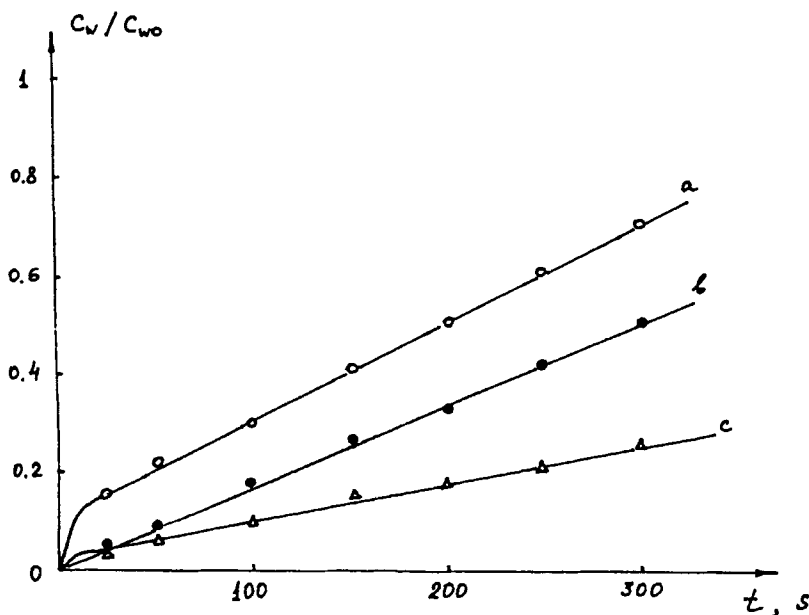


FIGURE 1 Kinetics of water sorption by copolymers of N-vinylpyrrolidone-PPB (a), PPM-1 (b) and PPM-2 (c),  $l = 100 \mu$ .

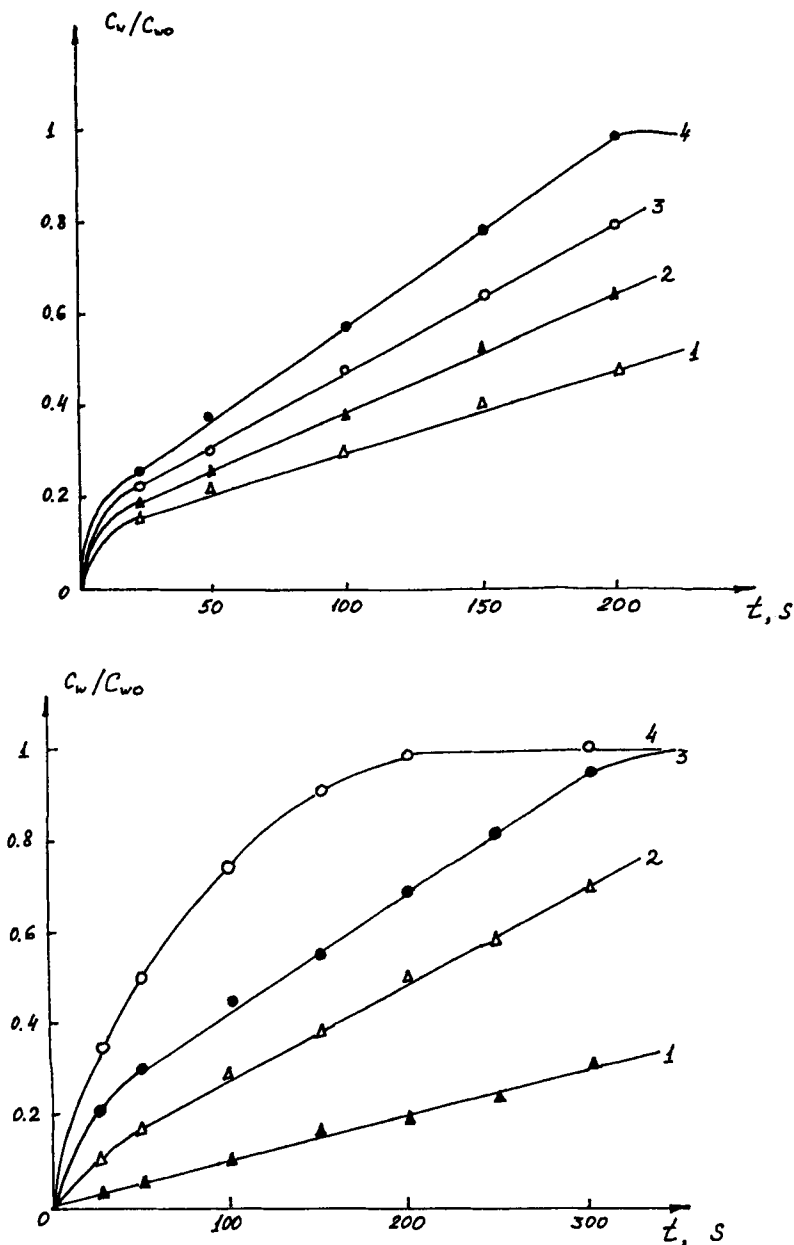


FIGURE 2 Kinetics of water sorption by hydrophilic polymers containing different amount of low-molecular compound. PPB-dioxidine (a) 0 (1), 0.05 (2), 0.1 (3), 0.2 (4) g/g; PVA-NaAc (b) 0 (1),  $7.5 \cdot 10^{-3}$  (2), 0.02 (3), 0.04 (4) g/g.  $l = 100 \mu$ .

of the velocity of water sorption to be a function of content of hydrophilic groups in copolymer we are turning our attention to Figure 2 which shows that the load of drug also promotes the increase of the velocity of water uptake. The similar tendencies were observed in the study of water transport process in polyvinylalcohol

(PVA). It was observed that the sorption parameters of solvent are functions of sodium acetate content in the polymer.<sup>7</sup>

On the other hand, the hydrophilic character of the polymer matrix affects the mechanism of drug release.<sup>1</sup> For instance (Figure 3), the kinetic curves of dioxidine release out of more hydrophilic PPB have a steady-state portion, and the release velocity (for the case of PPB) is equal to the velocity of water sorption. The diffusion mechanism of drug release was also observed for moderately hydrophilic copolymer of PPM-2. Finally, the kinetic curve of release for the case of PPM-1 was more complicated and it did not have a steady-state or Fickian parts. Investigations have shown that the diffusion coefficient of dioxidine in moderately hydrophilic films of PPM-2 was an increasing function of the initial content of the drug in the matrix. This copolymer was also characterized by the existence of an embedded form of drug which did not get released during interaction of matrix with water. We explained this<sup>1</sup> by inaccessibility of polymer for molecules of solvent which is the general feature of interaction between the water and moderately hydrophilic polymers.<sup>8,9</sup> There is, however, another explanation. The initial content of drug in PPM-2 is usually much higher than its solubility in polymer and its solubility in water present in the polymer. As the drug is released its insoluble part dissolved and became mobile. At present we have sufficient data (Figure 3, curve c) to conclude that this explanation is more appropriate than the one made in Reference 1.

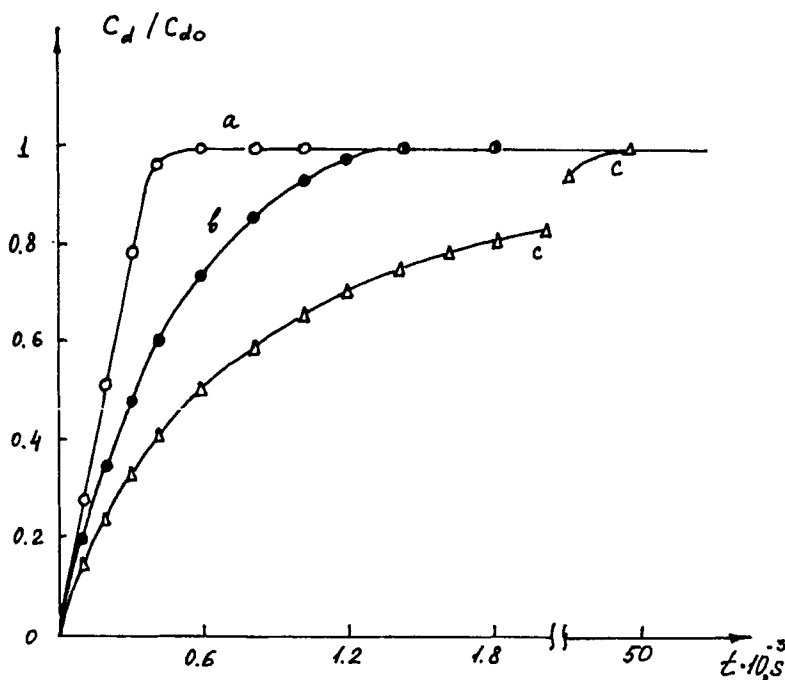


FIGURE 3 Kinetics of drug release out of copolymers of NVP. PPB (a), PPM-1 (b), PPM-2 (c).  $C_d$  is the mean concentration of drug desorbed to aqueous solution,  $C_{d0}$  is the initial concentration of drug in polymer.

Experimental results presented above were interpreted by mathematical modeling.

### THE MODEL OF SIMULTANEOUS TRANSPORT OF SOLVENT AND LOW-MOLECULAR COMPOUND IN SWOLLEN COPOLYMERS

The main parameters used are as follows:  $C_w$  is solvent (water) concentration in polymer;  $C_s$  is the concentration of low-molecular compound (salt) in polymer;  $C_{ss}$  is the concentration of its soluble form in polymer;  $a_s$  is the activity of salt in polymer;  $C_s^0$  is the concentration of saturated solution of salt in water ( $a_w = 1$ );  $S$  is the salt solubility in polymer;  $D_w$  is the Fickian diffusion coefficient of water in polymer;  $D_{Ts}$  is the thermodynamic diffusion coefficient of salt in polymer;  $l$  is the thickness of polymer film;  $f$  is the mechanical stress;  $s$  is the swelling strain;  $G_0$ ,  $G_x$  are the initial and final elastic moduli;  $\beta$  is the frequency of stress relaxation.

Other parameters will be involved to the text.

The Maxwell model of stress relaxation which takes into account the relations between the viscosity ( $\eta$ ), elastic modulus, and the frequency of relaxation represents the basis of the present model. J. Petropoulos<sup>4</sup> was one of the first who applied Maxwell model for swelling processes in glassy polymers when he described the transport of solvent by equation

$$\partial C_w / \partial t = \partial / \partial x (D_w) \partial C_w / \partial x \quad 0 < x < 1 \quad (1)$$

where

$$D_w = D_{w0} * \exp(k_{w1} C_w + k_{w2} f) \quad (2)$$

$$\begin{aligned} \partial f / \partial t = & (G_0 - G_x) \partial s / \partial t + \partial (s G_x) / \partial t \\ & + ((G_0 - G_x)^{-1} \partial (G_0 - G_x) / \partial t - \beta) (f - s G_x) \quad (3) \end{aligned}$$

$$s = (1 + k_s C_w)^{-1} - 1$$

Expressions (2) and (3) are written in form which is more convenient for calculation than the procedure we used in Reference 4. For this reason the record of (2, 3) is slightly differed from the original record.<sup>4</sup>

The most significant point of present study is the selection of parameter dependence on concentrations of solvent and low-molecular compound which appear in the Equation (1) and expressions (2), (3). Therefore, we should present a detailed justification for the selected dependences.

First, the proposed dependencies of diffusion coefficients of solvent and low-molecular component are in agreement with the free volume theory. For this reason the concentration of salt does not appear in expression (2) as a separate factor. Nevertheless it is obvious that diffusion coefficient of water depends on  $C_s$  due to

the existence of  $f(C_s)$  dependence. We also accept the justification of authors of paper<sup>4</sup> for the expressions for initial and final elastic moduli.

$$G_0 = G_{00}g(C_w, C_s)$$

$$G_\infty = G_{\infty 0}g(C_w, C_s)$$

The proposal about the decrease of elastic modulus as concentration of solvent in polymer increases has been confirmed by experimental comparison of mechanical properties of the films containing water in equilibrium with vapours and those which were dried at lower pressure. The considerable difference between elastic moduli of highly hydrophilic PPB and moderately hydrophilic PPM-2 should be mentioned. Corresponding properties of PPM-1 were intermediate as well as those we indicated in our previous study.<sup>1</sup> On the other hand, the load of drug to polymer matrix led to the increase of elastic modulus. This enabled us to conclude that the influence of solvent and lower molecular compound are opposite for this set of polymers. In fact, the empirical polynomial dependencies of mechanical parameters of polymer on concentrations of solvent, additives, fillers, etc.<sup>10,11</sup> can also be theoretically justified. For this reason, the exponential expressions for dependencies in question could be more appropriate.

$$G_0 = G_{00} \exp(-k_{g1}C_w + k_{g2}C_s)$$

$$G_\infty = G_{\infty 0} \exp(-k_{g1}C_w + k_{g2}C_s)$$

Here, we propose that all kinetic constants are positive.

Rather unexpected results have been obtained during the study of the frequency dependence of stress relaxation on  $C_w$  and  $C_s$ . It has been shown that an increase of either water or drug content accelerated the transition of supermolecular structure in all investigated polymers. This means that both components affect the relaxation properties of polymers in the same direction. Usually, the increase in the frequency of relaxation indicates phenomena as plastification, where the fall of viscosity ( $\eta$ ) is more pronounced than the decrease of elastic modulus. This is represented by

$$\beta = G/\eta$$

For our system this trend was observed only for the process of water sorption. On the other hand, direct dependence of  $G$ ,  $\eta$  (and  $\beta$ ) on concentration of additives does not exist. For example, copolymers PPB, PPM-1, PPM-2 have the same viscosity and moduli which are differed by orders. However, further study in details of unusual dependencies  $\beta(C_s)$ ,  $G(C_s)$  is required for their explanation.

As far as present investigation is concerned it follows from the results obtained that

$$\beta = \beta_0 \exp(k_{d1}C_w + k_{d2}C_s)$$

The equation proposed in Reference 2 which takes into account that the solubility of salt in water and in polymer could be lower is the salt content in the matrix is used for describing the transport of low-molecular compound in the system in consideration.

$$\partial C_s / \partial t = \partial / \partial x (D_{Ts} \cdot S) \partial a_s / \partial x \text{ for } C_s \leq S \quad 0 < x < 1 \quad (4)$$

$$C_s = C_{s0} \text{ for } C_s > S$$

where

$$D_{Ts} = D_{Ts0} \exp(-k_{w3}/C_w)$$

in agreement with the free volume theory.

The following boundary and initial conditions were selected for the present study.

$$C_w(0, t) = C_w(1, t) = C_{w0}$$

$$C_s(0, t) = C_s(1, t) = 0$$

$$C_w(x, 0) = 0$$

$$C_s(x, 0) = C_{s0}$$

where  $C_{w0}$  is the equilibrium concentration of water in polymer, and  $C_{s0}$  is the initial content of low-molecular compound in polymer.

We should mention again that the present theoretical study was based on experimental results discussed above. However, our approach is also applicable for other systems provided the expressions for dependencies of diffusion coefficients the boundary and initial conditions, are properly modified and adjusted for conditions of the new systems.

## RESULTS AND DISCUSSION

To verify the reliability of the presented calculation procedure we made test calculations of water uptake for different values of  $D_w$ ,  $\beta$ ,  $G_0$  and of other parameters for which similar calculations were made in Reference 4. The results obtained were the same, but for present study our main focus was on the dependencies of kinetic parameters of water sorption and the release of low-molecular compound on constants  $\bar{k}_{w1}$ ,  $\bar{k}_{w2}$ ,  $\bar{k}_{d1}$ ,  $\bar{k}_{g1}$ ,  $\bar{k}_{g2}$ , which depend on properties of polymer, water solubility, and salt content. Values of other parameters were selected in agreement with the experimental results and data described in literature. They were:  $k_s = 0.1$  (this means that the strain under swelling was equal to 10% or less);  $\bar{D}_{Ts0} = 100$  (the diffusion coefficient of low molecular component is two orders of magnitude higher than the diffusion coefficient of water in the polymer);  $\bar{k}_{w3} = 4.6$ ;



( $\bar{D}_{T_5}(\bar{C}_w = 1)/\bar{D}_{T_{50}} = 10^{-2}$ , (the values of diffusion coefficients of water and low molecular component were of the same magnitude); and, finally,  $\bar{G}_{10}$  and  $\beta_0$  were selected to be equal to 1.

It was shown (Figure 4) that the increase of  $k_{w1}$  (and decrease of  $k_{w2}$ ) accelerated

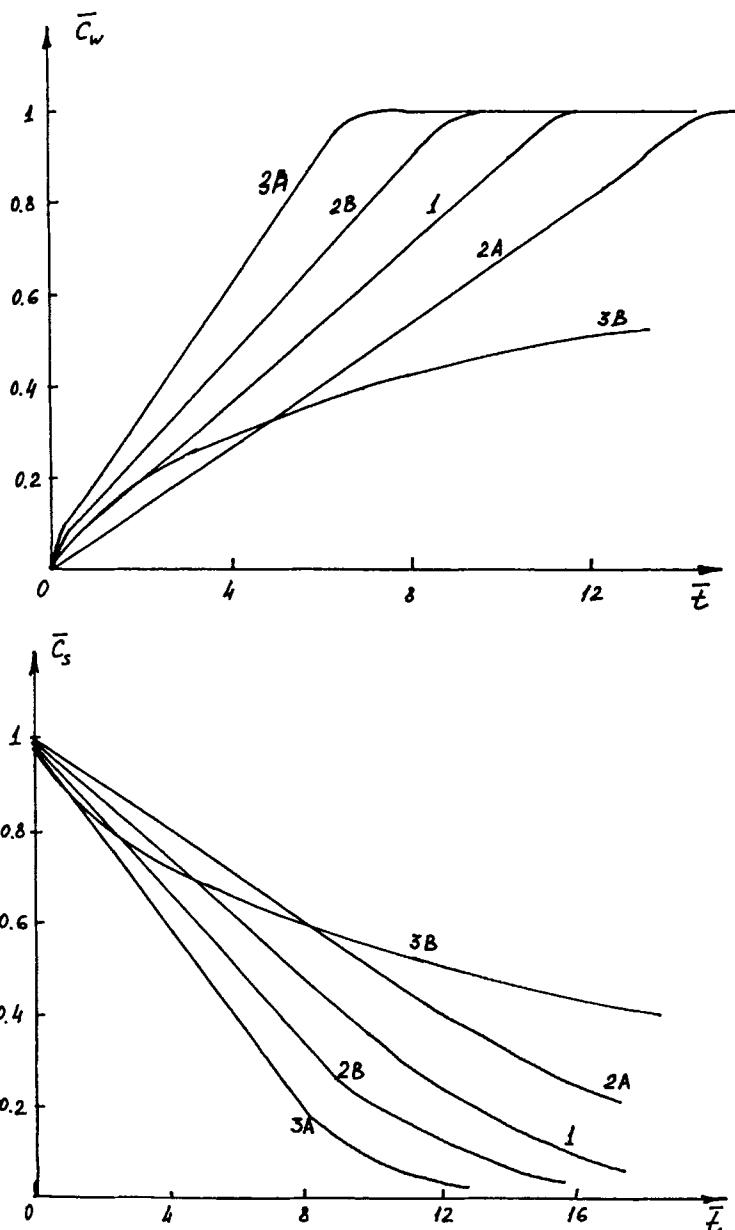


FIGURE 4 Calculated kinetics curves of water sorption (a) and release of low-molecular compound (b) at different values of constants which characterize transport properties of solvent.  $\bar{k}_{w2} = 1$  ( $\bar{k}_{w1} = 1$  (1), 0.1 (2A), 10 (3A));  $\bar{k}_{w1} = 1$  ( $\bar{k}_{w2} = 0.1$  (2B), 10 (3B)),  $D_{T50} = 100$ ,  $\bar{k}_{g1} = \bar{k}_{g2} = \bar{k}_{d1} = \bar{k}_{d2} = 1$ .

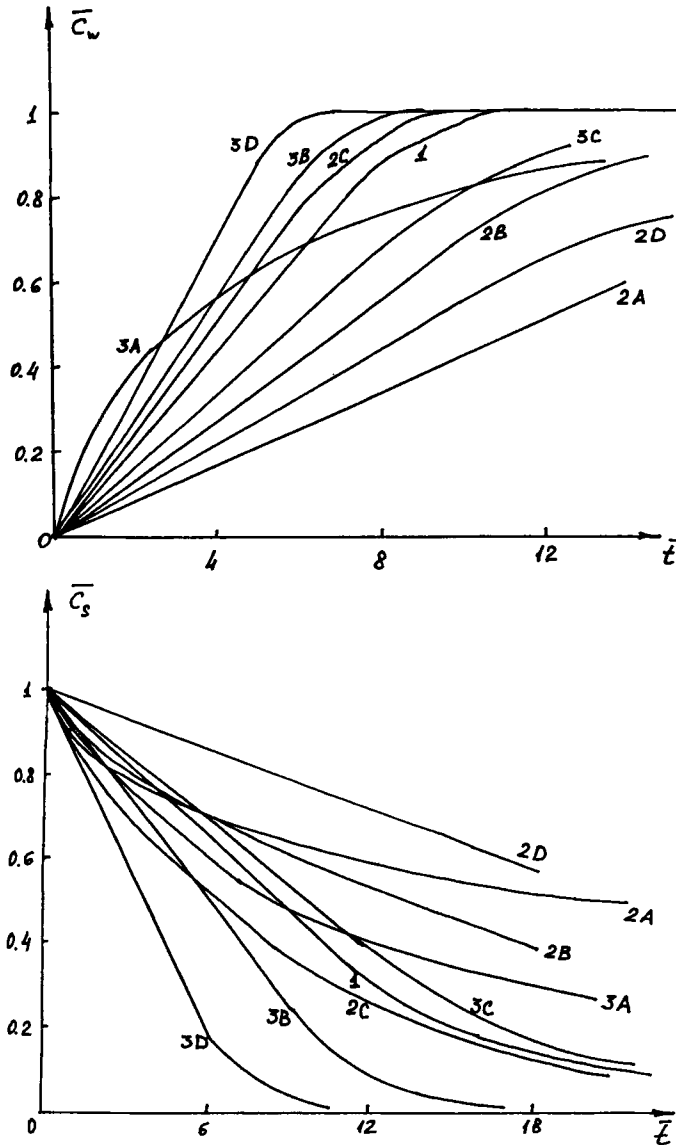


FIGURE 5 Calculated kinetics curves of water sorption (a) release of low-molecular compound (b) at different values of constants which characterize the influence of hydrophilic character of polymer and solubility of low-molecular compound on mechanical properties of matrix.  $\bar{k}_{g1} = 1, \bar{k}_{g2} = 1, \bar{k}_{d1} = 1, (\bar{k}_{d2} = 1 (1), 0.1 (2A), 10 (3A)); \bar{k}_{g1} = 1, \bar{k}_{g2} = 1, \bar{k}_{d2} = 1, (\bar{k}_{d1} = 0.1 (2B), 10 (3B)); \bar{k}_{g1} = 1, \bar{k}_{d1} = 1, \bar{k}_{d2} = 1, (\bar{k}_{g2} = 0.1 (2C), 10 (3C)); \bar{k}_{g2} = 1, \bar{k}_{d1} = 1, \bar{k}_{d2} = 1, (\bar{k}_{g2} = 0.1 (2D), 10 (3D)), D_{T50} = 100, \bar{k}_{w1} = \bar{k}_{w2} = 1.$

the water uptake and slightly increased the velocity of drug release. Usually we did not observe the change of the mechanism of transport processes except with the high values of  $\bar{k}_{w2}$  ( $\bar{k}_{w2} \geq 10$ ), when Fickian diffusion of water simultaneously with its deceleration was noted. This result could be explained by the increase of modulus  $G_{\infty 0}$  resulting from corresponding changes of mechanical properties of polymer.

We were concerned primarily with the comparison of the results of computation with the experimental data of the kinetic of water sorption and drug release. Theoretically, the dependence of these processes on water solubility and initial concentration of drug was studied on the basis of variations of constants  $\bar{k}_{d1}$ ,  $\bar{k}_{d2}$ ,  $\bar{k}_{g1}$  and  $\bar{k}_{g2}$ .

Different ratios of these parameters enable us to describe all experimental curves obtained as it can be seen in Figure 5. The most important effects are: a) the acceleration of water sorption in the area of Case II diffusion as water solubility in polymer is increasing; b) the similar behaviour of water sorption following the increase of the content of the drug in polymer; c) the transition from Case II to the Fickian diffusion of water at high values of  $\bar{k}_{d2}$ , corresponding to higher concentrations of drug and characterizing its influence on the relaxation time.

It was mentioned above that the last effect was observed earlier<sup>7</sup> in the experimental study of water sorption by PVA containing different amount of sodium acetate (Figure 2b), and at that time it was not explained.

The modeling of desorption of low-molecular compounds by Equation (4) in combination with the equation of transport of solvent (1) has shown that the three experimentally observed cases for the kinetics of drug release could be explained as follows: i) the Fickian diffusion corresponds to moderately swollen polymers ( $C_{s0} > S$ ) and lower velocities of water sorption; ii) the highly swollen polymers ( $C_{s0} > S$ ) are characterized by either Case II release and higher velocity of water sorption; iii) the intermediate case between Fickian and the Case II diffusion follows moderate velocity of water sorption described by the Case II and values of  $C_{s0}$  closed to  $S$ .

We should also emphasize that the processes of drug release out of highly hydrophilic polymers can be described by Fick's law, but this case must correspond only to Fickian diffusion of water in such polymers. That is why we concluded that the water sorption by highly hydrophilic polymers is the limiting stage of the release of low molecular compounds contained in this polymer. In particular it is the limiting stage of the drug release.

The results we discussed in present paper do not cover all consequences from the proposed model. The reason is that the system is rather complicated. Therefore we look forward to applying the proposed theoretical approach to other systems as an important goal of our further research.

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