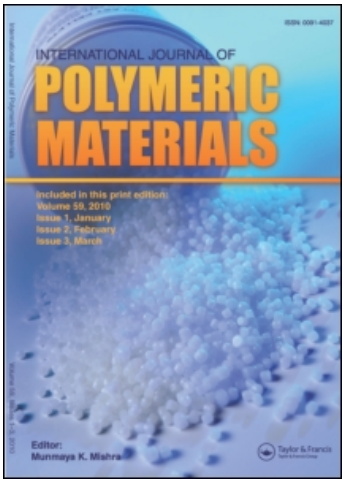

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Models of Simultaneous Transport of Water and Drugs in Hydrophilic Polymer Systems

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Different models have been developed in order to predict the behavior of systems consisting of hydrophilic polymer, water, and drug.

The first model deals with the so-called matrix system of controlled drug release and describes the simultaneous transport of water and drug in swelling glassy polymers. The dependencies of physical/chemical parameters on the concentation of water, drug and on the mechanical properties of the polymer are used for justification and prediction of corresponding experimental results.

The method of calculating the physical/chemical parameters is based on an experimental investigation of the structure of the polymer and the diffusion-kinetic process.

The main aim of the development of the other model is to predict the mechanism and velocity of drug release in "reservoir polymer systems" for which the sorption and diffusion properties of water transport through a polymer membrane are most important.

The main steps of drug release have been shown, and various dependencies of the diffusion coefficients have been studied in order to predict their influence on the mechanism and velocity of drug release.

KEY WORDS Transport, water, drugs, hydrophilic polymers

Changes in the hydrophilic character of polymeric materials due to plastification or degradation to varying extents may be applied to systems where a variation in the hydrophobic/hydrophilic balance is required. One such case is for the controlled release of a drug. Although the controlled release of a wide variety of drugs from different polymer systems has now been studied, there has been little work done on the general regularities of multicomponent transport in polymers containing solvent and solutes (particularly, drug).[1]

The present study is a part of research we gradually developed on the basis of a general theory for the transport of low-molecular weight compounds in polymers[2,3] and an experimental investigation of different kinds of systems for controlled release.[4,5] All such systems may be roughly divided into two types. They are matrix and reservoir polymer systems. The main feature of the first is the loading of a drug into a polymer matrix, while the second may be a drug, pill or powder coated by polymer. This clear distinction results in different applications for the same polymers, and even the same regularities of solvent sorption and transport.

Except for biodegradable polymers, which are not considered here, hydrophilic or moderately hydrophilic polymers are usually applied for the controlled delivery of drugs. Evidently, these polymers are more flexible and therefore more suitable

for variations in the velocity of aqueous solvent uptake followed by drug release. The main goal of the present paper is to apply our theoretical approach to systems of controlled drug release, which could be used in practice.

The Theory

The regularities of water sorption in respect to the corresponding behavior of hydrophilic polymer is the first point of the present paper. In general, we suppose that the polymer contains a low-molecular weight solute (drug), whose initial concentration can be significant or negligible depending on the type of polymer system.

We apply a differential stress model, which describes the effect of differential swelling stresses on the diffusion coefficient of the solvent as well as the effect of solvent and solute on the mechanical properties of the polymer such as viscosity, elastic moduli and the relaxation frequency.[2,3]

When combined with the corresponding model of solute desorption, the differential stress model describes the transport of solvent by the diffusion equation in this standard form:

$$\partial C_w/\partial t = (\partial/\partial x)(D_w \partial C_w/\partial x) < x < 1 \tag{1}$$

where

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

coupled with an equation describing the buildup and relaxation of the corresponding local differential swelling stresses along the plane of the film

$$\partial f/\partial t = (G_0 - G_\infty)\partial s/\partial t + \partial(sG_\infty)/\partial t + ((G_0 - G_\infty)^{-1}\partial(G_0 - G_\infty)/\partial t - \beta)(f - sG_\infty) \tag{3}$$

The effect of solvent and solute on swelling stresses is described through the corresponding dependencies of elastic moduli and stress relaxation

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

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

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

The change in area caused by unconstrained solvent uptake is given by

$$A(C_w) = A(0) \cdot (1 + k_s C_w), \tag{4}$$

while the actual area of a thin film is constrained to a uniform value $\bar{A}$, which is a function of time only. This leads to the creation of the following expression for

local strains

$$s = \tilde{A}(t)/A(x, t) - 1 \tag{4a}$$

and corresponding local stresses f, which must add up to zero net overall stress. Hence, we have

$$\int_0^1 f(x, t)\, dx = 0 \tag{5}$$

The general regularities of water uptake in hydrophilic polymers in the presence of a solute are reported in Reference 6, where the different parameters involved in Equation (1) have been varied. These regularities are summarized and illustrated in Reference 6 as follows: the acceleration of water sorption coupled with minor changes in the shape of the kinetic curve are the main results of the strong dependence of D_w on C_w. Because C_w and f influence D_w in opposite directions their effects tend to cancel at low values of overall water uptake (M_{wt}), while there is a substantial deviation between the cases of a strong dependency of D_w on C_w and f at high M_{wt} values. The acceleration of water sorption is a consequence of an increase of the initial relaxation frequency (β_0).

The influence of relative drug mobility on water uptake is negligible, while the effect of the presence of drug may be significant if we consider its influence on the mechanical properties of polymer.

A strong dependence of the elastic moduli on the concentration of water, nearly results in case-II diffusion of water unter $M_{wt} = 0.6 \cdot M_{w\infty}$, while non-linear uptake was observed at higher values of M_{wt}. A strong dependence of elastic moduli on solute concentration is characterized by Fickian water uptake.

A study of the variation of the parameters appearing in the expression for the relaxation frequency enables one to draw the following conclusions.

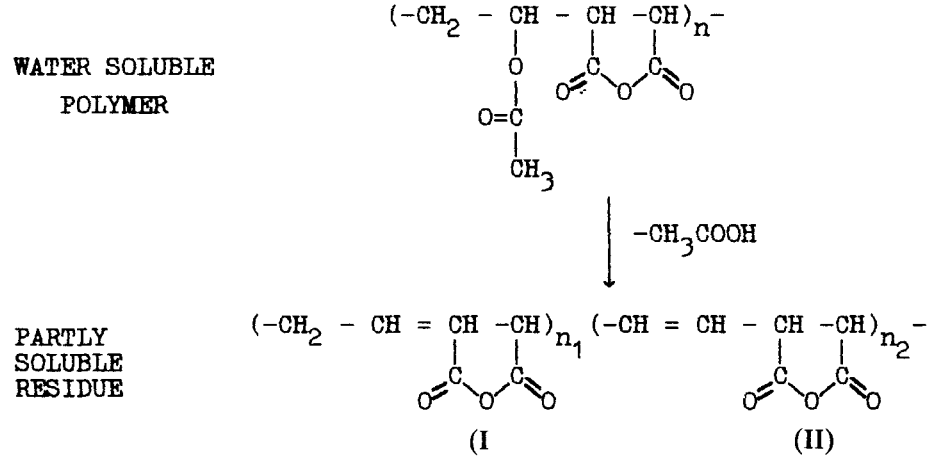
Because of solute desorption, deceleration of water uptake was observed for the case of a strong dependence of stress relaxation on the concentation of solute in comparison with the case of the same initial value of β corresponding to unfilled dry polymer.

A strong dependence of β on the concentation of solvent causes a further deceleration of water uptake at lower values of $M_{wt} \leq 0.6 \cdot M_{w\infty}$. At higher values of M_{wt} the deviation of the kinetic curve for water sorption above the Fickian curve was observed. This leads to a higher velocity of water uptake in comparison with the case of a strong dependence on the content of solute.

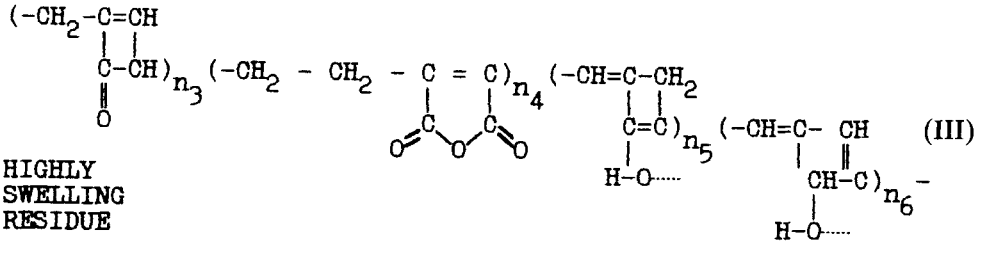
The aforesaid regularities have been used to describe the simultaneous transport of water and drug in matrix and reservoir systems of controlled release. The main point of application of the theory is the proper selection of the dependencies of transport and mechanical parameters.

Modelling of drug release in matrix system. Among different applications of theoretical research to the modelling of systems of controlled release we take the example of the alteration of drug release by controlled polymer degradation. The

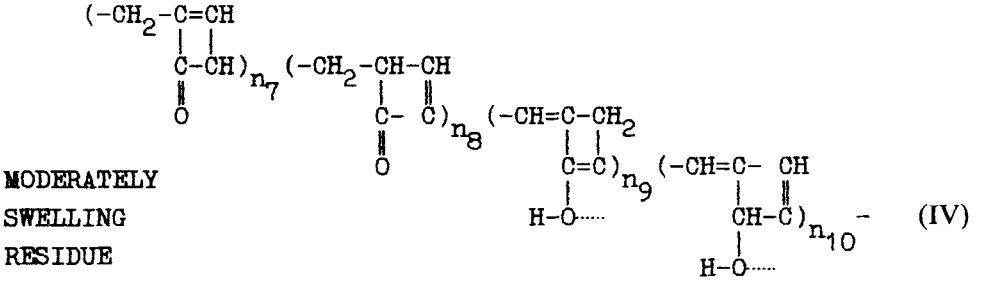
thermal degradation of a copolymer of maleic anhydride with vinyl acetate has been studied by thermal volatilisation analysis (TVA).[8] Under isothermal investigation at 205°C, structural rearrangements of the copolymer occurred following an initial loss of acetic acid and a further elimination of carbon dioxide. The formation of conjugated double bonds and hydroxyl groups as well as the development of insolubility due to intermolecular dehydration are the most important among these rearrangements. These data must also be related to the time of degradation. The first stage of degradation is represented as follows



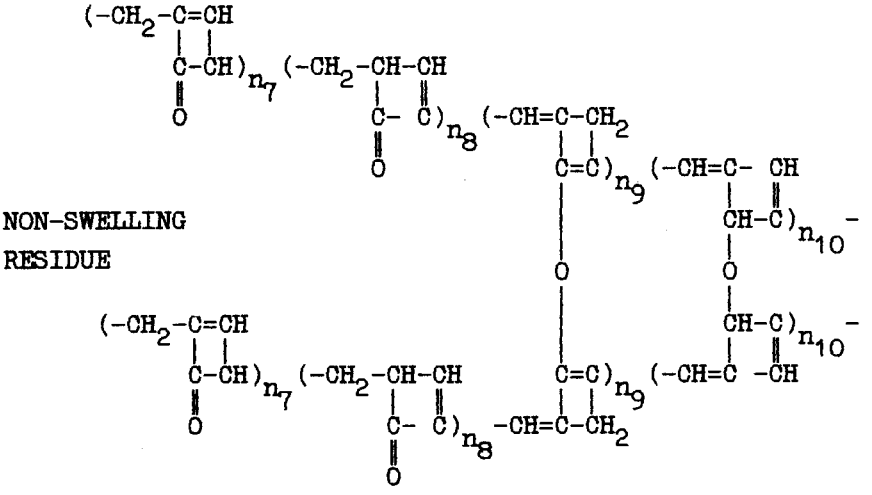
The next step includes a rearrangement of structures (I) and (II) with or without the elimination of carbon dioxide, giving a complex chain structure which may be represented as shown below.



The last step of the isothermal degradation is a total breakdown of the anhydride ring, leading to a chain structure such as



The ring structure built into the backbone reduces flexibility and provides one reason for the reduction in solubility. A second contributing factor is the cross-linking, for which the simplest explanation is the dehydration between pairs of OH groups.



(V)

All structures mentioned above are consistent with data obtained by UV-VIS, IR, NMR, and GCM-spectroscopies.

The behavior of the initial copolymer in the presence of water and the way in

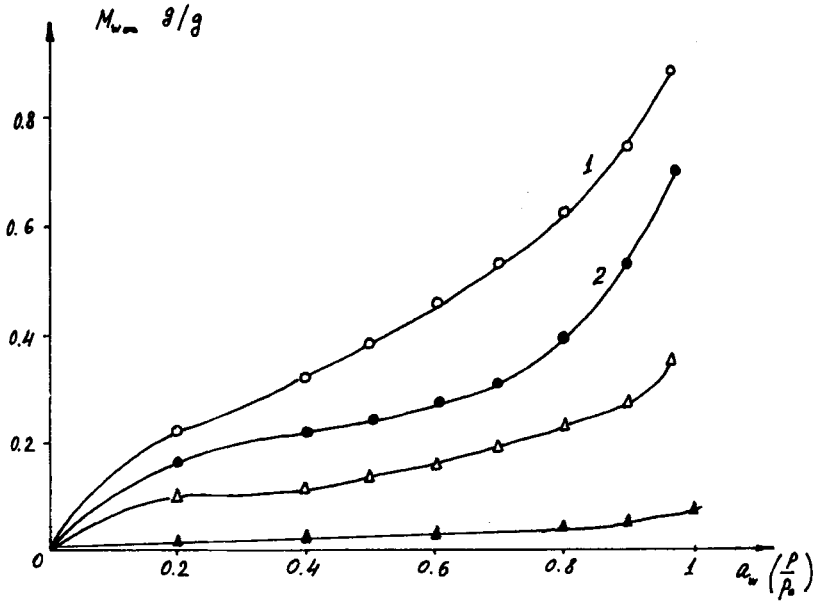


FIGURE 1 Isotherms for the sorption of water by a MAn-VAc copolymer (1) and its residues after thermal degradation at 10 (2), 20 (3) and 30 (4) minutes.

which sorption of water is altered by controlled degradation was a secondary objective of this study.

The process of water sorption was studied with an initial sample of MAn-VAc copolymer and with its residues after thermal degradation at 10 (structure I + II), 20 (III), 30 (IV) minutes. The isotherms of water sorption, shown in Figure 1, indicate the different hydrophilic nature of the samples. The residue, after 30 min of degradation, sorbs water as a typical swelling polymer while the initial copolymer appears to be water soluble.

The dependence on concentration of the diffusion coefficients of water in undegraded and partially degraded MAn-VAc copolymer (Figure 2) confirm different hydrophilic character of these materials. These dependencies put in model were used for the prediction of the regularities of controlled release of a drug.

We studied a multilayer system which included a polyamide coated blend of copolymer with drug.

Redistribution of the drug following preparation of such a composition defines a multistage process for its further release. This release includes desorption from the moderately hydrophilic polyamide, being in contact with solvent, followed by diffusion with swelling and dissolving of the second layer.

Taking into account these stages we use equation[3,11] to describe the process for the release of the drug, for which solubility in the polymer may be limited

$$\begin{aligned} \partial C_s \partial t &= \partial/\partial x(D_s \cdot S)\partial a_s/\partial x && \text{for } C_s \leq S \\ & && 0 < x < 1 \\ C_s &= C_{s0} && \text{for } C_s > S \end{aligned} \tag{6}$$

where

$$D_s = D_{s0} \cdot \exp(-k_{w3}/(1 + k_{w4}C_w)) \tag{7}$$

coupled with initial and boundary conditions

$$-D_s \cdot \partial C_s(0, t)/\partial x = j_d$$

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

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

$$1 = 1(t)$$

where j_d is the flux of drug released from the polyamide, 1 is the thickness of the hydrophilic polymer, which is defined through a corresponding dependence of $\bar{A}(t)$.

Among the parameters responsible for drug release from the system under study, the diffusion coefficient is the most important. The permeability of the partially degraded copolymer of MAn-VAc to the drug has been studied by the method

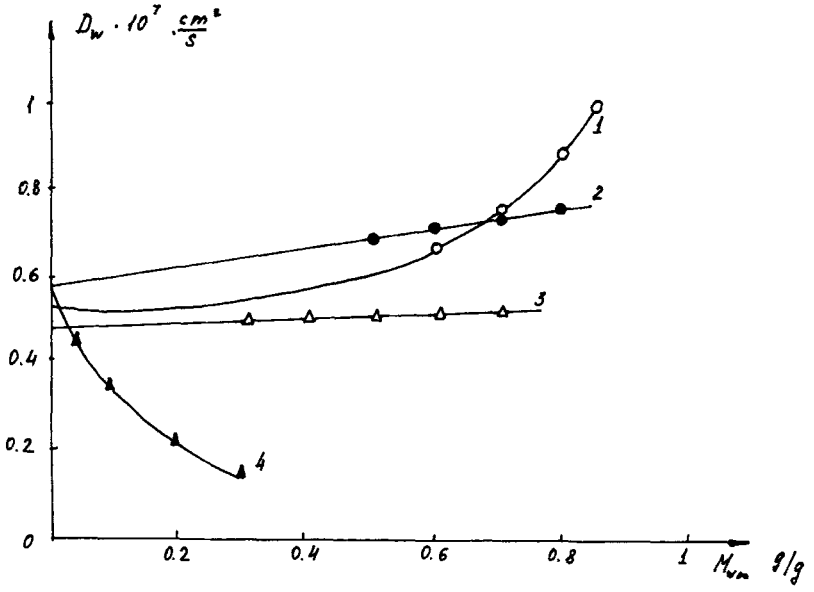


FIGURE 2 Dependence of the diffusion coefficients of water vapour on the concentration of water in MAn-VAc copolymer (1) and its residues after thermal degradation at 10 (2), 20 (3) and 30 (4) minutes.

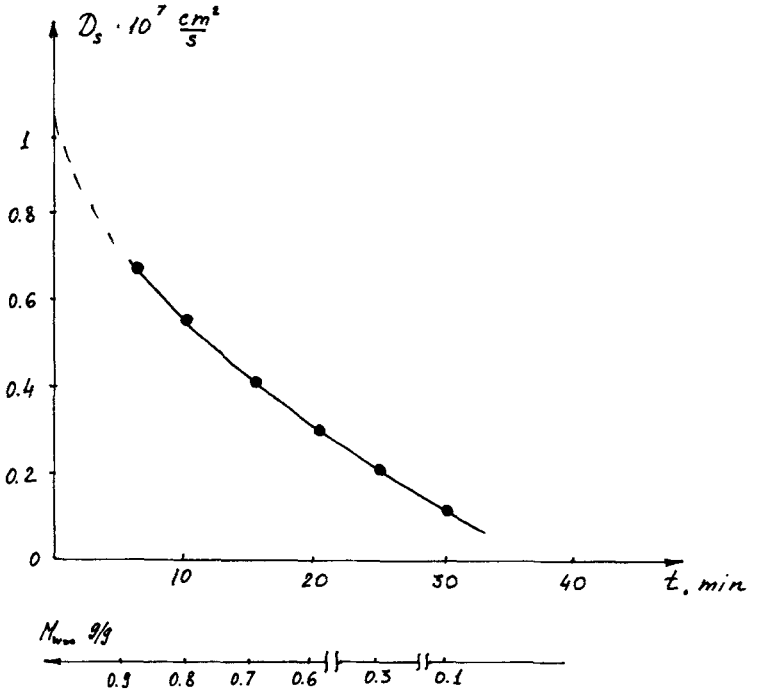


FIGURE 3 Dependence of the diffusion coefficient of drug on time of thermal degradation and the corresponding equilibrium value of overall water uptake.

described in Reference 9. Figure 3 illustrates the dependencies of D_s on the time of degradation. The intercept of the curve in Figure 4 with the Y-axis corresponds to the diffusion coefficient of the drug in pure water, and this dependence, as a whole, is the dependence of the diffusion coefficient of the drug on the concentration of water in the polymer, which should be put into the model (expression (7)).

The effect of the deceleration of drug release by controlled degradation of the copolymer in question is shown in Figure 5, where the kinetics of release from a polyamide coating by an undegraded and a partially degraded blend is represented through both calulations and experimental data.

The modelling of drug release in osmotic systems. Among different reservoir systems, we consider here those which have a hole (the so-called "osmotic systems") for drug release. Generally, the release of the drug core is described by the following equations

$$C_d = \exp(-\sigma \int j_w \, d\tau/\rho V_0) \int \exp(\sigma \int j_w \, d\tau/\rho V_0) v_s(\tau) \, d\tau$$

$$j_d = j_w C_d/\rho,$$

$$v_d = j_d \sigma$$

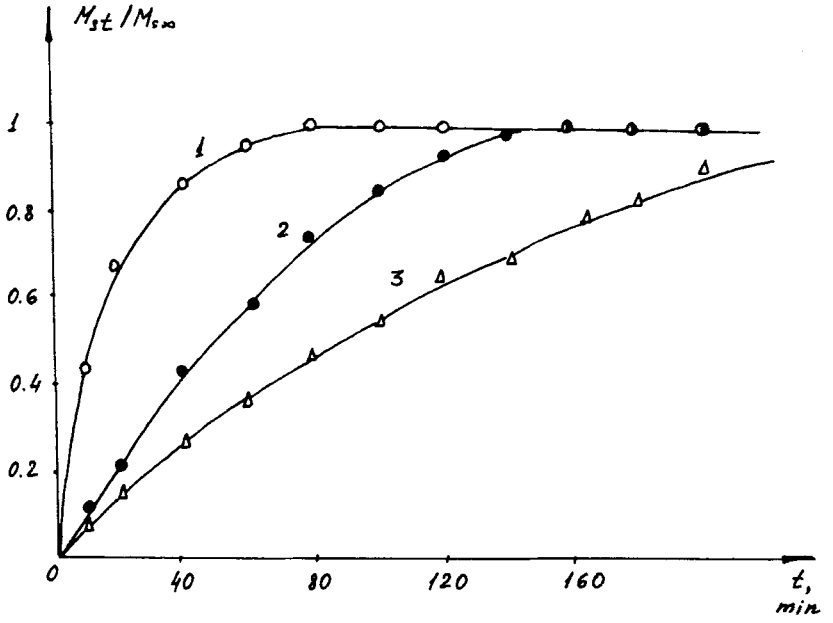


FIGURE 4 Computed and experimental kinetics of drug release from a polyamide textile bandage through a MAn-VAc film (1) and its residues after thermal degradation at 10 (2) and 20 (3) minutes. $M_{st}/M_{s\infty}$ is the relative value of total amount of drug released.

$$M_{st}/M_{s\infty} = 1 - \left(\int_0^1 C_s(x, t) \, dx/(C_{s0} \cdot 1) \right) \text{(in theory)}.$$

Experimental data are labeled by points.

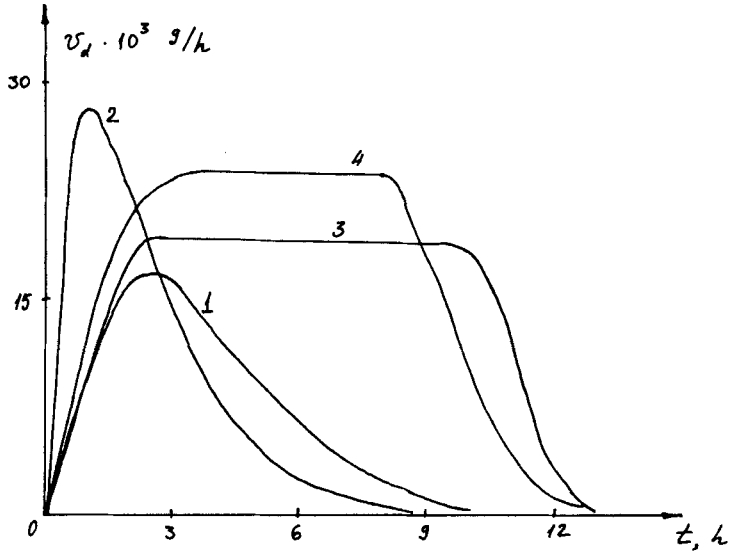


FIGURE 5 Computed kinetics for the controlled release of drugs from a reservoir system. D_{w0} [cm²/s] = 10^{-8}. C_{w0} = 0.01 g/g.

$$k_{w1} = 0,\ k_{w2} = 10\ (1),$$

$$k_{w1} = -30,\ k_{w2} = 10\ (2),$$

$$k_{w1} = 60,\ k_{w2} = 10\ (3),$$

$$k_{w1} = 30,\ k_{w2} = 1\ (4).$$

The equation for water transport should be modified depending on the geometry of the pill. For a first approximation we consider the pill to be a sphere of radius R, and the corresponding equation is:

$$\partial C_w/\partial t = r^{-2}(\partial/\partial r)(D_w \cdot r^2 \partial C_w/\partial r) R < r < R + 1 \qquad (1)$$

The mathematical model for controlled drug release takes into account different dependencies of the diffusion coefficient of water. The constant diffusion coefficient was the initial point for the modelling of transport processes in the system as a whole.

For a reservoir system we neglect the effect of the drug on water uptake. Except for this, the main regularities of water transport remain unchanged in comparison with a matrix system.

The results of modelling the drug release itself are presented in Figure 5. The kinetic curve for the release are obtained for a case of constant D_w, showing the general laws of drug release, of which the main are:

1. Increase of drug concentation in the solution of the pill followed by acceleration of release.

2. Steady-state or maximum of release due to completion of the processes of relaxation and the formation of a saturated solution.
3. Decrease of the velocity of release followed by a tendency for the activity of water in the liquid phase and the saturated solution to be the same, which is caused by dissolution of the core of the pill.

Curve 2 (Figure 5) characterizes the case of an exponential decrease of the diffusion coefficient ($k_{w1} < 0$) as the concentration of water in the polymer increases. For this case the deceleration of the flux of solvent follows an increase in the activity of water in the saturated solution. Because of the equality of the fluxes of water and the dissolved drug, the velocity of drug release will be lower as time goes by. For this reason a polymer coating which is characterized by such a concentration dependence of the diffusion coefficient does not provide steady-state release. This can be seen in Figure 5 (curve 2).

On the other hand it is obvious that a steady-state flux of the solution of the drug could be reached when the effect of dissolution of the pill is compensated for by an increase in the diffusion coefficient of water based on the positive $D_w(C_w)$ dependence. Curves 3 and 4 in Figure 5 show the modelling of such a system for which we used reasonable values of k_{w1} corresponding to experimental $D_w(C_w)$ dependencies reported in Reference 10. It is shown that the time interval for the steady-state part of drug release is defined by constants involved in the expression for D_w. Figure 5 (curves 3 and 4) illustrates that the positive dependence $D_w(C_w)$ provides a steady-state release and the longer the k_{w1} the higher. At the same time the rate of steady-state release depends on the contribution of swelling stresses and becomes higher as k_{w2} decreases.

As a whole, the proposed model enables the prediction of the behavior of system of the reservoir type for the controlled release of drugs with various polymer coatings, and to give recommendations for providing the mechanism and the rate of release which are required.

The Nomenclature

C_w = water concentration in polymer;
C_s = drug content in polymer;
C_{s0} = initial content of drug in polymer;
S = solubility of drug in polymer;
a_s = activity of drug in polymer;
D_w = diffusion coefficient of water in polymer;
D_{w0} = diffusion coefficient of water in dry and unstressed polymer;
D_s = diffusion coefficient of drug in polymer;
D_{s0} = diffusion coefficient of drug in pure water;
f = mechanical stress;
s = swelling strain;
G_0, G_∞ = initial and final elastic moduli;
β = frequency of stress relaxation;
M_{wt} = overall water uptake;
$M_{w\infty}$ = equilibrium value of overall water uptake;

C_d = concentration of saturated solution of drug;
j_d = drug flux;
v_s = velocity of crug core dissolution;
ρ_w = solvent density;
σ = area of hole;
v_d = velocity of drug release.

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