Release of Ibuprofen from Poly(ε-caprolactone-*co*-D,L-lactide) and Simulation of the Release

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ABSTRACT: A study was made of the effects of the initial ibuprofen load and of the specimen shape on the release of ibuprofen from poly(ε-caprolactone-*co*-D,L-lactide). The mol ratio of the comonomers in the copolymer was 96/4 (caprolactone to lactide) and the experiments were conducted at 37°C *in vitro*. The results showed that release of ibuprofen is fast and that the rate and profile of the release vary with both the initial load of ibuprofen and the shape of the specimen. The rate of ibuprofen release increases with the initial load and with the surface area-to-volume ratio of the specimen, obeying Fickian diffusion. The experimental findings were compared with the results of a mathematical simulation model based on the finite-difference method. Diffusion parameters needed for the simulation were determined from a separately conducted set of experiments using various methods. For the most part, the results of the simulations and the experiments were in good agreement. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 88: 1279–1288, 2003

Key words: biodegradable; diffusion; drug delivery systems; modeling; simulations

INTRODUCTION

One of the challenges in the development of biomaterials is the design of materials that enable the delivery of drugs to the human body.[1] Constant release rates are required, especially for drugs with a narrow therapeutic index. In the development of these dosage forms, mathematical models offer valuable tools that enable efficient systematic study and reduce the amount of expensive and time-consuming experimental work. Mathematical models that are developed for the study of controlled active agent release have to take into account the characteristics of the polymer, the geometry of the system, and the mechanism of mass transfer.[2]

In the case of monolithic formulations of a polymer and an active agent, the parameters that describe the process of mass transfer are the diffusion coefficient and the mass-transfer coefficient. These coefficients are dependent on the properties of the drug and the polymer. The release of the active agent proceeds first by diffusion through the copolymer matrix, where the diffusion coefficient describes the diffusion resistance in the matrix. After that, the release proceeds through an unstirred boundary layer on the surface of the specimen before entering the well-stirred region of the release medium.[3] The mass-transfer coefficient describes the mass-transfer resistance in the boundary layer.

Factors that control the release of active agents may change over the course of the release, and in this case, one model may not be sufficient to predict the whole release. Typical problems encountered in testing controlled-release devices include a nonconstant diffusion coefficient due to large solute loading or solvent incorporation into the polymer carrier, the analysis of three-dimensional geometric shapes with one-dimensional methods, an increase or decrease in the carrier size due to solvent transport, and multicomponent transport rather than single-solute diffusion.[4] These problems create substantial challenges for those developing mathematical models.

Higuchi,[5] in the 1960s, was the first mathematically to investigate the release of active agents from polymers. In the last few years, Narasimhan and Peppas,[2] Collins,[6] and Masaro and Zhu[7] reviewed the mathematical modeling of controlled active agent release and the modeling of diffusion in polymers. Fick's second law is the starting point for many models of diffusion in polymers. It is also the starting point for the numerical simulation carried out in this work. The simulation is carried out utilizing the finite-difference method, a method often applied in problems concerning heat conduction.[8] The analogy between diffusion and heat conduction also allows this method to be applied to diffusion problems.[9–11] Simulations are performed in the MATLAB environment, in three di-

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mensions, and rectangular geometries are used. The active agent is assumed to be completely dissolved in the polymer. Polymer degradation and swelling are assumed to be negligible.

The copolymer used in this work consisted of ε-caprolactone and D,L-lactide in the mol ratio of 96/4. These aliphatic polyesters are biocompatible and have been extensively studied for various applications in controlled-release formulations.[12–21] It could thus be of interest to be able to replace some of the experimental work with adequate simulations. Ibuprofen [*S*(+)-2-(4 isobutylphenyl)propionic acid)] was used as the model compound in the study because it is a small molecule, widely used, and readily available. Ibuprofen also is not destroyed in the processing of the test specimens, which includes elevated temperatures and high shear forces. The focus was on the effects that the initial load of ibuprofen and the specimen geometry have on the release. It has been reported that the release profiles of active agents can be changed by varying the geometry and dimensions of the system.[3,22] The effects of the load and specimen geometry in the form of slabs and films were simulated with the simulation model and compared with the experimental data.

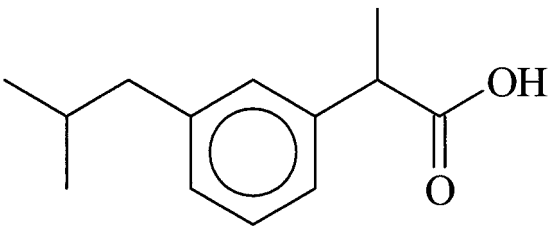
EXPERIMENTAL

Materials

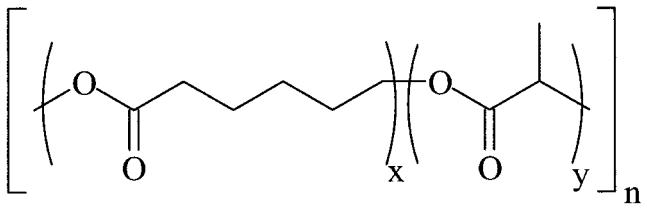
ε-Caprolactone (Fluka, Buchs, Switzerland) was dried over molecular sieves. D,L-Lactide (Purac, Gorinchem, Netherlands) was recrystallized from toluene and dried for 24 h at 40°C under reduced pressure before the polymerization. Sn(II)octoate (stannous 2-ethylhexanoate) (Sigma-Aldrich, Steinheim, Germany), glycerol (Rhône-Poulenc, France), ibuprofen [*S*(+)-2-(4 isobutylphenyl)propionic acid] (Fluka), and a buffer solution of pH 7.0 ± 0.01 (Reagecon, Clare, Ireland) were used as received.

Polymerization

The polymerization was carried out in bulk under a nitrogen atmosphere with Sn(II)octoate as the initiator. The amount of the initiator was 0.02 mol %. Glycerol was used as the coinitiator, in the amount of 0.25 mol %. The mol ratio of the comonomers in the feed was 96/4 (caprolactone to lactide). The ring-opening polymerization was carried out in a batch reactor at a temperature of 160°C for 4 h. The copolymer was stored in dry conditions and used without further purification.



Scheme 1 Structure of ibuprofen.



Scheme 2 Structure of poly(ε-caprolactone-*co*-lactide).

Preparation of the test specimens

Ibuprofen (Scheme 1) was blended with the copolymer (Scheme 2) in a corotating twin-screw midiextruder (DSM, capacity 16 cm^3, screw length 150 mm). The midiextruder has a backflow channel and was operated as a batch mixer. Ibuprofen loads of 5, 10, 20, and 30 wt % were used. The blends were mixed at 80°C for 3 min (75 rpm). Two kinds of test specimens were made from the blend: films and slabs. Slabs were injection-molded with a mini-injection molder, and film specimens were compression-molded at 80°C and cut into squares. The dimensions of the slabs were 4 × 8 × 1.6 mm^3 and the dimensions of the films were 10 × 10 × 0.25 mm^3.

Characterization of the copolymer–ibuprofen blends

The glass transition and melting temperatures were measured by a differential scanning calorimeter (DSC, Mettler). Nitrogen was used as a sweeping gas. The blends were characterized by heating them twice to ensure that their thermal histories were similar. The glass transition temperatures were determined from the second heating scan. Heating and cooling rates were 10°C/min and the temperature range was −100 to 100°C.

Molecular weights were determined by room-temperature size-exclusion chromatography (SEC, Waters System Interface module, Waters 510 HPLC pump, Waters 410 differential refractometer, Water 700 Satellite Wisp, and four linear PL gel columns: 10^{-6} m, 10^{-5} m, 10^{-7} m, and 10^{-8} m connected in series). Chloroform was used as a solvent and an eluent. The samples were filtered through a 0.5-μm Millex SR filter. The injected volume was 200 μL and the flow rate was 1 mL/min. Monodisperse polystyrene standards were used for primary calibration.

In vitro release tests

The release tests were conducted at 37°C *in vitro*. Test specimens were placed individually in Erlenmeyer bottles (30 mL) with a cap, along with 20 mL of the buffer solution. All tests were conducted in triplicate. The bottles were placed in a shaking bath at 37°C. At predetermined time intervals, the bottles were carefully shaken and 10 mL of the solution was withdrawn from the bottle and replaced with a fresh buffer solution. The amount of the released ibuprofen was determined from the buffer solution using a Unicam UV/VIS spectrometer at a maximum absorption wavelength of 265 nm.

Determination of diffusion coefficients and mass-transfer coefficients

For determination of the diffusion and mass-transfer coefficients of ibuprofen in the copolymer, release tests were conducted with thin copolymer films (30 $\times$ 30 $\times$ 0.25 mm^3). The size of the specimens in these tests was larger than in the release tests described above, as we wanted to minimize the effect of the edges on the ibuprofen release. The films were prepared and the release tests were carried out as described above, using the same ibuprofen loads (5, 10, 20, and 30 wt %). The thicknesses of the test specimens were measured at least at three points to confirm the uniform thickness of the samples. The volume of the buffer solution used was 30 mL, and 5 mL of the buffer was changed to a fresh buffer at each predetermined time point. There were 12 time points in the first 2 h of the release to provide a sufficient number of measurements for the calculations. The diffusion parameters were calculated from the results.

The diffusion coefficients were calculated from the experimental results using four different equations, in order to compare these equations. The first two equations were the early-time (eq. (1)) and late-time (eq. (2)) approximations.[23] The equations are approximations of the complete equations presented by Crank.[24] The early-time approximation is valid for the first part of the release (0–60%), and the late-time approximation, for the release after 40% of the active agent has been released:

$$\frac{M_t}{M_0} = 4\left(\frac{Dt}{\pi l^2}\right)^{1/2} \qquad 0 \le \frac{M_t}{M_0} \le 0.6 \tag{1}$$

$$\frac{M_t}{M_0} = 1 - \frac{8}{\pi^2}\exp\left(\frac{-\pi^2 Dt}{l^2}\right) \qquad 0.4 \le \frac{M_t}{M_0} \le 1.0 \tag{2}$$

where M_t is the amount of the active agent released in time t; M_0, the amount of the total active agent in the specimen; D, the diffusion coefficient; and l, the thickness of the specimen.

The third equation used for the determination of the diffusion coefficient was derived from eq. (3), which is an equation that describes the active agent release from rectangular slabs[3,25]:

$$\frac{M_t}{M_0} = 1 - \frac{512}{\pi^6}\sum_{m=0}^{\infty}\frac{1}{(2m+1)^2}\exp\left(-\frac{(2m+1)^2\pi^2}{a_p^2}Dt\right) \times \sum_{n=0}^{\infty}\frac{1}{(2n+1)^2}\exp\left(-\frac{(2n+1)^2\pi^2}{b_p^2}Dt\right) \times \sum_{p=0}^{\infty}\frac{1}{(2p+1)^2}\exp\left(-\frac{(2p+1)^2\pi^2}{c_p^2}Dt\right) \tag{3}$$

where a_p, b_p, and c_p are the dimensions of the rectangular test specimen. An approximation of the first term (when $m = 0$, $n = 0$, and $p = 0$) was made, and because of the form that the equation takes, we call it the three-dimensional late-time approximation:

$$\frac{M_t}{M_0} = 1 - \frac{512}{\pi^6}\exp\left[-\pi^2 Dt\left(\frac{1}{a_p^2} + \frac{1}{b_p^2} + \frac{1}{c_p^2}\right)\right] \tag{4}$$

The fourth method used was the method of Siepmann et al.[3] This method was used to determine the diffusion and mass-transfer coefficient simultaneously. The coefficients were obtained from eq. (5), which was fitted to the experimental results:

$$\frac{M_t}{M_0} = 1 - \sum_{n=1}^{\infty}\frac{2G^2}{\beta_n^2(\beta_n^2 + G^2 + G)}\exp\left(-\frac{\beta_n^2}{l^2}Dt\right) \tag{5}$$

where the β_n's are the positive roots of

$$\beta_n \tan \beta_n = G \tag{6}$$

and

$$G = \frac{lh}{2D} \tag{7}$$

where G is a dimensionless constant and h is the mass-transfer coefficient. In this work, the first seven positive roots of eq. (6) were used.

Modeling

The starting point of the modeling is Fick's second law in three dimensions when the diffusion coefficient is constant[24]:

$$\frac{\partial C}{\partial t} = D\left(\frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2} + \frac{\partial^2 C}{\partial z^2}\right) \tag{8}$$

where C is the concentration of the active agent; t, the time; and x, y, and z, the coordinates of the system. In the finite-difference method, the rectangular device to be simulated is divided into small cells; at the center of each is a point called a node. The finite-difference method restricts the determination of the concentration to discrete points in space (the nodes) and time. Accurate results are obtained by choosing sufficiently small spatial and time steps.

For the problem of this work, the following equation was obtained[8]:

$$\frac{C^{p+1}_{m,n,o} + C^{p}_{m,n,o}}{\Delta t} = D\left(\frac{C^{p}_{m+1,n,o} + C^{p}_{m-1,n,o} - 2C^{p}_{m,n,o}}{\Delta x^2} + \frac{C^{p}_{m,n+1,o} + C^{p}_{m,n-1,o} - 2C^{p}_{m,n,o}}{\Delta y^2} + \frac{C^{p}_{m,n,o+1} + C^{p}_{m,n,o-1} - 2C^{p}_{m,n,o}}{\Delta z^2}\right) \quad (9)$$

where the superscript p denotes the previous time point, and the superscript $p + 1$, the new time point. Subscripts denote the coordinates of the lattice cells into which the specimen is divided. Subscript m denotes the coordinates along the x-axis; n, along the y-axis; and o, along the z-axis.

Using a network in which $\Delta x = \Delta y = \Delta z$ and rearranging,

$$C^{p+1}_{m,n,o} = A(C^{p}_{m+1,n,o} + C^{p}_{m-1,n,o} + C^{p}_{m,n+1,o} + C^{p}_{m,n-1,o} + C^{p}_{m,n,o+1} + C^{p}_{m,n,o-1}) + (1 - 6A)C^{p}_{m,n,o} \quad (10)$$

where

$$A = \frac{D\Delta t}{\Delta x^2} \quad (11)$$

Equation (10) is the finite difference equation on which the simulation is based. In this equation, unknown nodal concentrations for the new time point ($p + 1$) are determined exclusively by the known nodal concentrations at the previous time point (p).

At the surface of the specimen, the mass transfer across the boundary layer has to be considered. For lattice cells with one face exposed at the surface of the specimen, the following equation can be derived:

$$C^{p+1}_{m,n,o} = A(C^{p}_{m+1,n,o} + C^{p}_{m-1,n,o} + C^{p}_{m,n+1,o} + C^{p}_{m,n-1,o} + C^{p}_{m,n,o+1} + BC_0) + (1 - 5A - AB)C^{p}_{m,n,o} \quad (12)$$

where

$$B = \frac{h\Delta x}{D} \quad (13)$$

TABLE I
Melting Points, Glass Transition Temperatures, and Heats of Fusion of the Ibuprofen–Copolymer Blends

Ibuprofen load (wt %)	T_m (°C)	T_g (°C)	ΔH (J/g)
0	52	−58	63
5	51	−57	53
10	46	−55	54
20	46	−54	53
30	43	−52	55

where h is the mass-transfer coefficient in the boundary layer, and C_0, the concentration of the active agent in the surrounding fluid.

For cells with two faces exposed at the surface (i.e., cells at edges),

$$C^{p+1}_{m,n,o} = A(C^{p}_{m+1,n,o} + C^{p}_{m-1,n,o} + C^{p}_{m,n+1,o} + C_{m,n,o-1} + 2BC_0) + (1 - 4A - 2AB)C^{p}_{m,n,o} \quad (14)$$

For cells with three faces exposed at the surface (i.e., corner cells),

$$C^{p+1}_{m,n,o} = A(C^{p}_{m+1,n,o} + C^{p}_{m,n,o} + C^{p}_{m,n,o+1} + 3BC_0) + (1 - 3A - 3AB)C^{p}_{m,n,o} \quad (15)$$

The stability of the method requires that the coefficient associated with the cell of interest at the previous time (p) is greater than or equal to zero.[8] From that and from the equations for the different cases noted above, it follows that

$$1 - 6A \geq 0 \quad \text{for the cells inside the specimen} \quad (16)$$

$$1 - 5A - AB \geq 0 \quad \text{for cells at surfaces} \quad (17)$$

$$1 - 4A - 2AB \geq 0 \quad \text{for cells at edges} \quad (18)$$

$$1 - 3A - 3AB \geq 0 \quad \text{for corner cells} \quad (19)$$

When all these criteria are fulfilled, the simulation is stable.

The simulation assumes that the diffusion resistance is located at the interfaces of the lattice cells. Since the simulation is done in three dimensions, the effect of the surface area is not ignored. The whole three-dimensional shape of the specimen is taken into account. Different rectangular shapes can be simulated by changing the dimension parameters. Other assumptions that are made in the modeling work are that

- Polymer swelling is negligible.

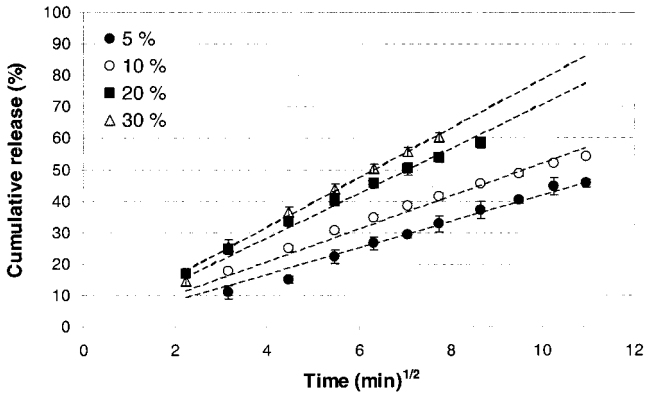


Figure 1 Results of the diffusion coefficient experiments for different loads of ibuprofen. Early-time approximation.

- Perfect sink conditions are maintained throughout the simulation.
- An active agent is released through the polymer matrix only by Fickian diffusion.
- The diffusion coefficient is constant throughout the simulation. (The active agent release is assumed to occur rapidly in comparison with the polymer degradation.)
- The polymer matrix density is constant.

The simulation requires that the diffusion coefficient of the active agent in the polymer matrix and the mass-transfer coefficient in the boundary layer are known or can be estimated. Other parameters needed for the simulation are dimensions of the specimen, simulation time, simulation time step, size of the lattice cell (spatial step), and initial load of the active agent.

RESULTS AND DISCUSSION

Characterization

The melting points (T_m) and glass transition temperatures (T_g) for the copolymer and blends of ibuprofen and the copolymer were measured by DSC. The results are presented in Table I. The melting point of pure ibuprofen was also measured and it was 53.5°C. The possible melting peak of the pure ibuprofen is not separable from the melting peak of the copolymer (52.0°C), because the melting points are so close to each other. However, it was noticed that the melting points of the blends showed a significant shift to lower temperatures with an increase in the ibuprofen load, and no separate peak was observed for pure ibuprofen around 53°C for any of the blends. The change in the melting point was linear in relation to the ibuprofen load in the blend.

A change in the glass transition temperature was observed as well: The glass transition temperature shifted to a higher temperature as the load of ibuprofen in the polymer was increased. This indicates strong interactions between ibuprofen and the copolymer. Ibuprofen is an acidic compound and could form hydrogen bonds with the copolymer.

Heat of fusion values of the blends were compared to determine the changes in the crystallinity. The values presented in Table I are normalized to the copolymer content in the blend. The crystallinity is slightly lower for the blends with ibuprofen than for the pure copolymer. The result suggests that ibuprofen disturbs the crystallization of the copolymer.

The processing of the copolymer had only a slight effect on the molecular weight. The copolymer was blended with ibuprofen in a midiextruder, where the heat and shear forces may cause polymer degradation. During processing (3 min at 80°C), the weight-average molecular weight decreased from 137,000 to 129,000 g/mol. The molecular weights were not further affected by the release tests. At this stage, polymer degradation was not a factor when simulation and experimental data were compared, since a bioresorbable matrix, consisting of mainly polycaprolactone (PCL), is hydrolytically stable in the studied release times, that is, 1 week at most.

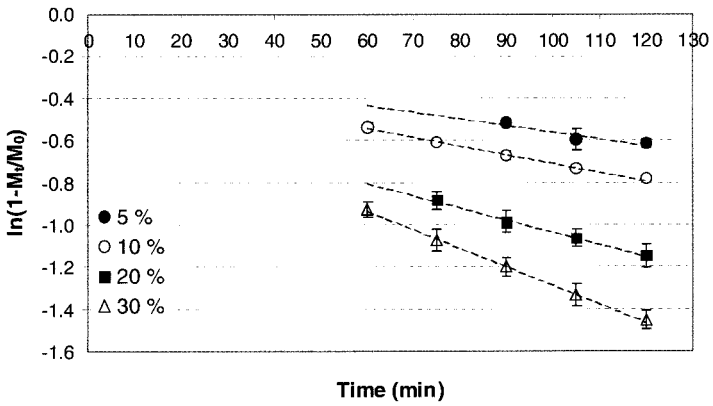


Figure 2 Results of the diffusion coefficient experiments for different loads of ibuprofen. Late-time approximation.

TABLE II
Diffusion Coefficients of Ibuprofen in the Copolymer Calculated Using Different Mathematical Approaches

Ibuprofen load (wt %)	Diffusion coefficient $\times 10^{-13}$ (m^2/s)			
	Early-time approximation	Late-time approximation	3-Dimensional late-time approximation	Siepmann's equation
5	3.6	3.4	3.1	3.9
10	5.3	4.1	4.0	5.5
20	9.9	5.9	5.6	9.7
30	13.4	9.7	8.6	13.0

Determination of the diffusion parameters

The diffusion coefficients of ibuprofen in poly(ε-caprolactone-*co*-D,L-lactide) were determined using the equations described in the Experimental section, that is, the early- and late-time approximations, the three-dimensional late-time approximation, and Siepmann's method. The early-time approximation was used for the first 60% of the release and both late-time approximations were used for the release from 40% to the end. When the results of the first 60% of the release were plotted as a function of the square root of time, linear plots were obtained (Fig. 1). This means that Fickian diffusion is obeyed. Linear plots were also obtained when the results of the last part of the release (40–100 %) were plotted as a function of $\ln(1 - M_t/M_0)$ (Fig. 2). The diffusion coefficients were calculated from the slopes of the plots and, along with the diffusion coefficients determined by Siepmann's method, are presented in Table II.

The determination of the mass-transfer coefficient using Siepmann's method resulted in very high mass-transfer coefficients. In addition, the values were similar for all ibuprofen loads, that is, around 5×10^{-7} m/s. This indicates that the composition of the blend does not affect the mass-transfer coefficient. It was noted by Siepmann et al.[3] that the mass-transfer coefficient depends essentially on the rate of stirring. In this study, the stirring conditions were similar for all the studied specimens.

Both diffusion parameters were additionally determined by fitting. The same set of experimental results was used for fitting as for the mathematical determination of the diffusion parameters. Simulation results were fitted to the experimental results by adjusting the diffusion parameters. The results are presented in Table III. The values of the coefficients obtained by fitting are smaller than are the ones determined mathematically. The order of magnitude is, however, the same. When comparing the values, it can be noted that using the three-dimensional late-time approximation resulted in values very close to the fitted values. In both these cases, the three-dimensional shape of the specimen is considered, whereas the other methods are only one-dimensional.

The values of the diffusion coefficients calculated from the late-time approximation are lower than the coefficients calculated from the early-time approximation. Late in the release (after 40% of ibuprofen is released), the ibuprofen load is already significantly lower than the initial load and this probably has an effect on the value of the diffusion coefficient. The calculated diffusion coefficients show a linear relationship as a function of active agent concentration. In conclusion, these results indicate that the ibuprofen load has a strong effect on the diffusion properties and that the diffusion coefficient changes as ibuprofen is depleted from the specimens.

Comparison of the experimental release tests and simulation

There were three sets of simulations done in this study. The first set of simulations was carried out using the average values of the diffusion coefficients determined from one-dimensional mathematical equations (early- and late-time approximations and Siepmann's equation) and the mass-transfer coefficient determined using Siepmann's equation. The second set of simulations was carried out using diffusion coefficients from the three-dimensional late-time approximation and the mass-transfer coefficient from Siepmann's equation. The third set of simulations was carried out using the diffusion and mass-transfer coefficients determined by the fitting.

The results of the first set of simulations are presented in Figures 3 and 4 along with the experimental results. The results for slabs are shown in Figure 3 and for films in Figure 4. In addition to the experimental results of the films of the size $10 \times 10 \times 0.25$ mm^3 in Figure 4, the results of the diffusion coefficient exper-

TABLE III
Diffusion and Mass-Transfer Coefficients Determined by Fitting Simulations to the Experimental Results

Ibuprofen load (wt %)	Mass-transfer coefficient $\times 10^{-7}$ (m/s)	Diffusion coefficient $\times 10^{-13}$ (m^2/s)
5	0.3	2.5
10	0.4	4.0
20	2.0	6.5
30	3.0	9.0

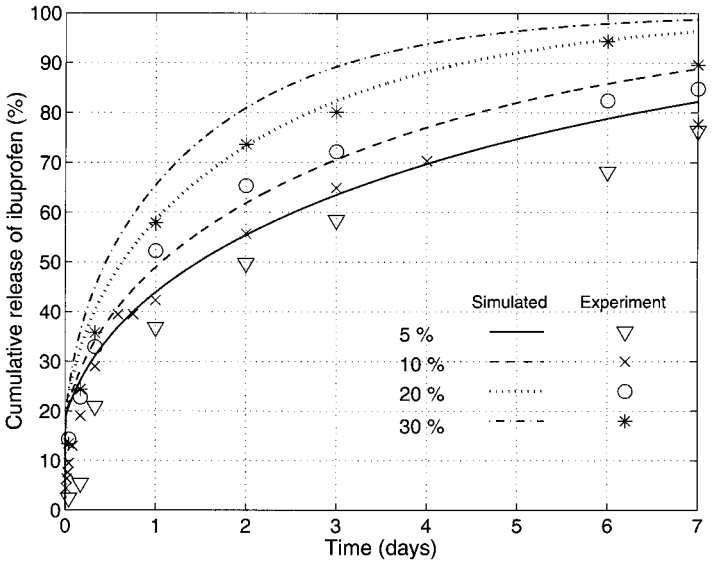


Figure 3 Cumulative release profile of ibuprofen from slabs. Experimental and simulated results for different loads of ibuprofen. Simulations were carried out using diffusion parameters determined from experimental results using one-dimensional equations.

iments (films of 30 × 30 × 0.25 mm^3) are plotted as well for comparison. The larger films are marked with smaller symbols. Note that the time scale of Figures 3 and 4 is different. It can be seen from the experimental results that ibuprofen release is significantly faster from the films than from the slabs. The release is also accelerated at higher ibuprofen loads. These kinds of results for different polymers and different model compounds were also observed earlier.[3,26,27] The area-to-volume ratio of the films is 8.7, and for the slabs, 2.0. Apparently, the diffusion path is shorter, on average, for the ibuprofen molecules in the films than for the molecules in the slabs, and release occurs faster from the films. The results imply that the ibuprofen release varies and can be controlled by changing the geometry and ibuprofen load of the specimen.

The match between the simulated and the experimental results in Figures 3 and 4 is quite poor. In the beginning of the simulated release curves, a burst is observed. The rest of the simulations are on the right path but the burst deviates a lot from the experimental release. The burst is due to the high mass-transfer coefficient used in the simulations. Since the mass-transfer coefficient is very large in comparison with

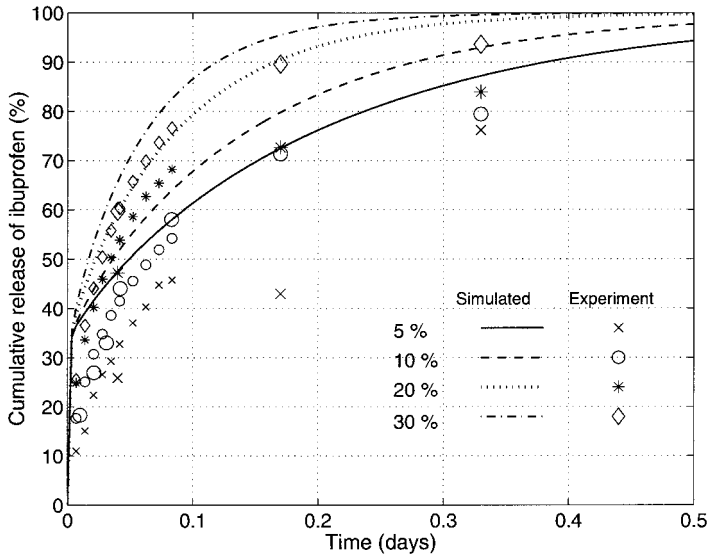


Figure 4 Cumulative release profile of ibuprofen from films. Experimental and simulated results for different loads of ibuprofen. Simulations were carried out using diffusion parameters determined from experimental results using one-dimensional equations.

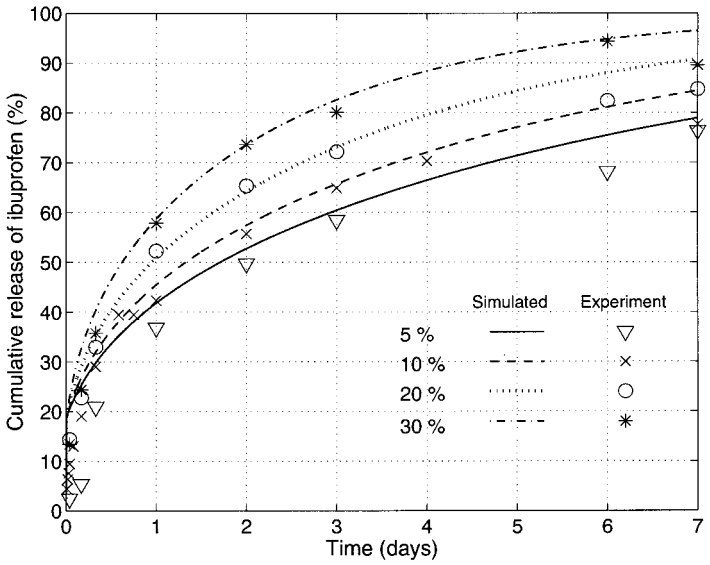


Figure 5 Cumulative release profile of ibuprofen from slabs. Experimental and simulated results for different loads of ibuprofen. Simulations were carried out using diffusion coefficients determined from experimental results using three-dimensional late-time approximation and mass-transfer coefficient determined from Siepmann's equation.

the diffusion coefficient, it has importance only at the beginning of the release. The active agent molecules that are located very near the surface in the specimen are released first, and since they are close to the surface, the only resistance that they will encounter is the mass-transfer resistance on the boundary layer. Later in the release, molecules have to travel to the surface layer by diffusion. When the diffusion resistance is much larger than is the mass-transfer resistance at the surface layer, the diffusion resistance becomes the factor that controls the ibuprofen release.

The results of the second set of simulations for slabs and films are presented in Figures 5 and 6, respectively. Experimental results are presented as well. The match between the simulations and experimental results is better than in Figures 3 and 4. However, there is still a burst in the beginning of the simulated release curves due to the high mass-transfer coefficient used in the simulations. For the second set of simulations, diffusion coefficients were determined from the three-dimensional late-time approximation where the whole shape of the spec-

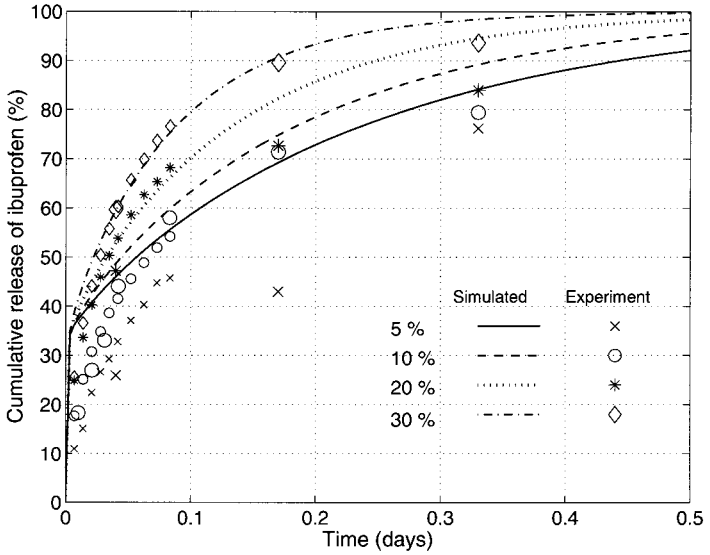


Figure 6 Cumulative release profile of ibuprofen from films. Experimental and simulated results for different loads of ibuprofen. Simulations were carried out using diffusion coefficients determined from experimental results using three-dimensional late-time approximation and mass-transfer coefficient determined from Siepmann's equation.

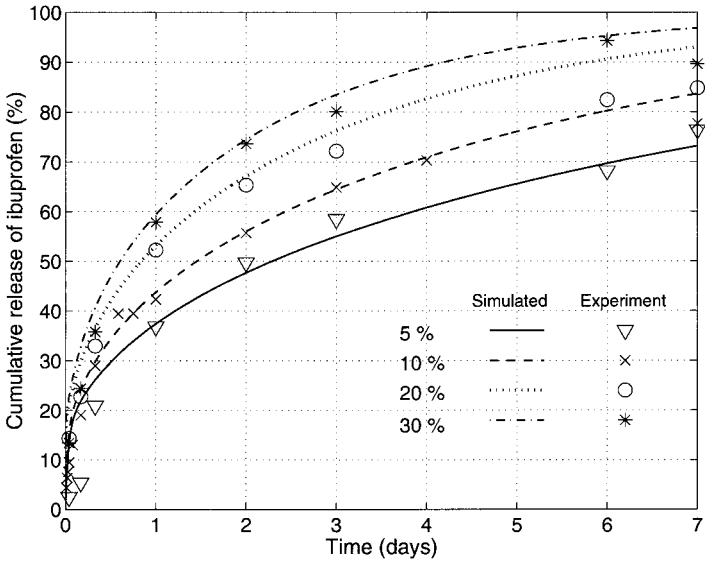


Figure 7 Cumulative release profile of ibuprofen from slabs. Experimental and simulation results for different loads of ibuprofen. Simulations were carried out using diffusion parameters determined by fitting.

imen is taken into account. This probably gives a better approximation of the diffusion coefficient than do the one-dimensional equations.

The third set of simulations was carried out using diffusion and mass-transfer coefficients determined by fitting. The results are presented in Figures 7 (for slabs) and 8 (for films) along with the experimental results. In both cases, simulations agree very well with the experimental results. There is no burst observed in the beginning of the simulated results and that is partly the reason why simulations agree so well with the experimental results. The mass-transfer coefficients obtained by fitting were much smaller than was the coefficient obtained using Siepmann's equation.

The calculation routines were built in a MATLAB environment, and the simulations could be run in a reasonable time. Of course, the time required for the simulation depends on how the time and spatial steps are chosen. More accurate simulations might be achieved if the change of the diffusion coefficient over the course of the ibuprofen release were taken into account, especially with high loads. Nevertheless, the simulation with the finite difference method proved to be efficient and could be developed into a useful tool.

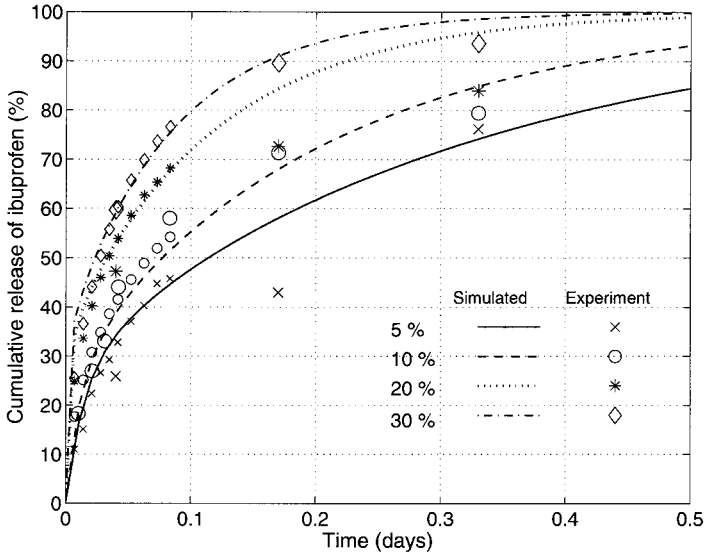


Figure 8 Cumulative release profile of ibuprofen from films. Experimental and simulated results for different loads of ibuprofen. Simulations were carried out using diffusion parameters determined by fitting.

CONCLUSIONS

The release of ibuprofen from poly(ε-caprolactone-*co*-D,L-lactide) with a comonomer ratio of 96/4 was studied with two different test geometries and four initial loads of ibuprofen (5, 10, 20, and 30 wt %). Numerical simulations based on the finite-difference method were carried out with diffusion parameters determined using various methods.

The DSC analysis suggests that the ibuprofen was dissolved in all the blends. The DSC results, together with the diffusion and mass-transfer coefficients obtained from the experimental results, show that the ibuprofen load has a marked effect on the properties of the blend.

The shape of the specimen and the initial concentration of ibuprofen in the blend have a significant effect on the ibuprofen release. The release rate can be tailored over a wide range by adjusting these two factors.

Numerical simulations based on the finite-difference method are useful in predicting the release of a completely dissolved active agent. The effect of the shape on the release can be studied using this kind of simulation model. However, the change in the diffusion coefficient over the course of the release affects the release rate. If this change was incorporated into the simulation, the convergence between simulation and experimental results would probably be improved.

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