Chem. Pharm. Bull. **46**(12) 1918—1923 (1998) Vol. 46, No. 12

Mechanochemical Solid-State Polymerization. IX. Theoretical Analysis of Rate of Drug Release from Powdered Polymeric Prodrugs in a Heterogeneous System

Shin-ichi KONDO, Shouichi HOSAKA, Isao HATAKEYAMA, Masayuki KUZUYA*

Laboratory of Pharmaceutical Physical Chemistry, Gifu Pharmaceutical University, 5–6–1, Mitahora-Higashi, Gifu 502–8585, Japan. Received July 9, 1998; accepted September 7

We theoretically derived the rate equation of drug release from a simple model in a heterogeneous system. Four assumptions were used to simplify the model. Two kinds of rate equations for drug release derived from two possible limiting cases, that the rate-determining step is a diffusion or hydrolysis controlled process, can predict the experimental results up to 50% hydrolysis. However, the predictions at the later stage by these equations are insufficient. These results suggest that the process of drug release from powdered polymeric prodrugs in a heterogeneous system must be described by both diffusion and hydrolysis. The rate equation derived from a model considering both the diffusion and hydrolysis processes can successfully predict the experimental results for several kinds of polymeric prodrugs. It is also shown that the diffusion coefficient and rate constant for hydrolysis calculated from this equation thoroughly express the character of the comonomer. The rate equation derived from the model that considers both diffusion and hydrolysis is very useful to analyze drug release from various kinds of polymeric prodrugs in a heterogeneous system.

Key words polymeric prodrug; rate equation; drug release; heterogeneous system; mechanochemical polymerization

Development of sustained- and controlled-release systems for drug delivery is one of the most active areas today in the entire field of drug research. Polymeric prodrugs, in which a drug is attached covalently to a polymer backbone and slowly released under appropriate conditions, possess unique properties distinct from those of the corresponding lower molecular weight prodrugs and can be utilized as a sustained-release delivery system. Thus, the chemotherapeutic utility of polymeric prodrugs has been the focus of intense research.[1] A large number of water-soluble and -insoluble polymeric prodrugs have already been synthesized and the nature of drug release from them has been investigated.[1,2] The kinetics of hydrolysis of side chains in water-soluble polymers (homogeneous system) have been studied extensively. Theoretical analysis of drug release has been performed on the basis that the mechanism of hydrolysis of water-soluble polymers is reversible or irreversible, intermolecular or intramolecular, and kinetically dependent or independent on the reaction state of neighboring groups.[3] There are also many papers on drug release from water-insoluble polymeric prodrugs (heterogeneous system). Nevertheless, relatively little work has been done on theoretical analysis of drug release in heterogeneous systems to our knowledge. It has been reported in several papers that drug release apparently obeyed first-order reaction kinetics.[3—5] The reason why there are few papers on theoretical analysis of drug release from water-insoluble polymeric prodrugs is that polymer hydrolysis in a heterogeneous system possesses may more problems than in a homogeneous system. The problems are as follows: the diffusion of water and catalyst into the polymer and of hydrolysis products into the water phase, the destruction of the solid dosage form, swelling of the polymer with hydrolysis, and so on.

We have reported the syntheses and nature of drug release from novel polymeric prodrugs prepared by mechanochemical solid-state polymerization.[2,5—12] Several important conclusions were reached from this series of studies. Monomers prepared based on structural criteria derived from quantum chemical considerations underwent facile mechanochemical solid-state polymerization to give the corresponding polymeric prodrugs essentially quantitatively.[6,7,9] Thus, this method eliminates the need for any work-up of the reaction mixture. One of the most striking properties observed in such polymers is that the resulting polymeric prodrugs are of very low heterogeneity (narrow molecular weight distribution) represented by M_w/M_n, which is of great value in pharmaceuticals for highly functionalized polymeric prodrugs.[7] Therefore, the present reactions seem applicable to a wide variety of vinyl monomers of an important class of bioactive compounds with different physicochemical properties, and provide a novel and simple methodology for syntheses of polymeric prodrugs through a totally dry process. It has also been reported that the rate of drug release of polymeric prodrugs in a heterogeneous system, prepared by the present method, largely depends on the content of the hydrophilic group as the side chain, the bonding type between the drug and polymer, and the structure of the spacer group.[8,11] In addition, we have synthesized hybrid polymeric prodrugs containing anticancer agents and contrast medium for chemoembolization, or anticancer agents and vitamins.[2,5,12]

In order to develop polymeric prodrugs possessing a suitable rate of drug release, we need to establish the relationship between polymer structure and the rate. Thus, it is essential to study theoretically the rate of drug release from water-insoluble polymeric prodrugs. In this paper the rate equations for drug release from water-insoluble polymeric prodrugs, in which the vinyl monomer of drug is contained at more than 50 mol%, have been derived from a simple model based on several assumptions. The validity of these equations has been examined by comparison with experimental results for several kinds of polymeric prodrugs prepared by mechanochemical solid-state polymerization.

Experimental

Materials Acrylamide supplied by Tokyo Kasei Co., Ltd. (Japan) is

* To whom correspondence should be addressed.

commercially available, and was purified by recrystallization from benzene and dried *in vacuo*. Methacryloyl derivatives, 1-(2-methacryloyloxy)ethylcarbamoyl-5-fluorouracil and *N*-(4-pyridyl)methacrylamide, were prepared according to the literature.[11,12]

Mechanochemical Solid-State Polymerization Mechanochemical polymerization was performed by ball milling of solid monomer in a stainless steel twin-shell blender at room temperature for 2 h in vacuum glove box (Sanplatec Corp.) according to the method previously reported.[7] Air in the vacuum glove box was replaced by purified nitrogen gas and the remaining oxygen in this system removed with a High Capacity Gas Purifier (Supelco, Inc.). The oxygen concentration was monitored with an Oxygen analyzer (LC 750/PC-120, Toray Engineering Co., Ltd.) and kept below 20 ppm.

Method of Hydrolysis The hydrolysis of powdered polymeric prodrugs (5.0—6.0 mg) was conducted in pH 7.4 phosphate buffer solution at 37± 0.2 °C in a heterogeneous system with a flow-through-cell apparatus, according to the previous paper.[12] Released 5-fluorouracil was periodically assayed by the UV absorption spectrum (Recording Spectrophotometer UV-2200 (P/N 206-17000), Shimadzu Co.) at a wavelength of 266 nm.

Particle Diameter and Density The particle diameter of each polymeric prodrug was measured with a Coulter Counter Multisizer II (Coulter Electronics) using 100 and 70-μm aperture tubes. The results are the average of 3 analyses. The particle density was determined by the pycnometer method.

Results and Discussion

Assumptions First of all, the mechanism of drug release from powdered polymeric prodrug in a heterogeneous system is considered. The hydrolysis of polymeric prodrug is initiated by contact with water. In the case of a polymer possessing highly hydrophilicity water can easily enter the powdered polymeric prodrug, so that hydrolysis would occur throughout the powder. On the other hand, in the case of a hydrophobic polymer the hydrolysis will occur only at the interface of the prodrug core and the drug-depleted region, since it is difficult for water to enter the polymeric prodrug core. The content of water in powdered polymeric prodrug increases with the progress of hydrolysis to produce hydrophilic groups, such as amino or hydroxyl groups, as the hydrolyzate. Consequently, the polymer may swell and the particle diameter may change. It is also considered that the diffusivity of free drug changes with the position in the powdered polymeric prodrug due to the difference in the degree of swelling. Many parameters, as described above, make the precise description of a rate equation for heterogeneous systems difficult.

We have already reported the nature of hydrolysis of polymeric prodrugs prepared by mechanochemical polymerization in a heterogeneous system.[2,5,8,11,12] These polymeric prodrugs are polymethylmethacrylate derivatives or copolymers of acrylamide and methacrylate derivative of a drug and were insoluble in water. Since it would be difficult for water to enter the polymeric prodrug core, the first assumption is that the hydrolysis occurs only at the interface of the prodrug core and the drug-depleted region. The geometry of the device is thus one of the factors that determine the release profile. The second assumption is that the geometry of the model is a sphere, since powdered polymeric prodrug has been used. The hydrolyzed polymers were also insoluble in water and did not swell visually. In order to simplify the model, the third assumption is that the particle diameter and the diffusion coefficient of free drug in polymer powder are constant, regardless of reaction progress. Since it is assumed that the diffusion and hydrolysis processes are the most important in drug release from water-insoluble polymeric prodrugs, only these processes are considered in the model. Based on these assumptions, we now derive the rate equation of drug release from water-insoluble polymeric prodrugs.

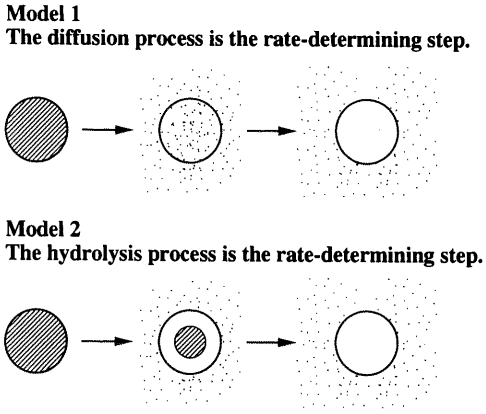

Fig. 1. Illustration of Two Limiting Cases of Drug Release from Water-Insoluble Polymeric Prodrugs

The shaded area denotes the polymeric prodrug.

Rate Equation of Drug Release for Two Limiting Cases Two limiting cases, determined by the relative rates of diffusion and hydrolysis, may be considered. Figure 1 shows a depiction of the two limiting cases.

Model 1 is the case where diffusion is relatively slow compared to the rate of hydrolysis. It can be considered that this model is essentially equal to the case in which the active agent is uniformly dissolved in the polymer matrix, the so-called monolithic solution,[13] since the polymeric prodrug is rapidly hydrolyzed compared to the desorption rate of drug from polymer particle. Desorption of monolithic solution may be expressed by two approximations as follows.[13]

At early time:

$$\frac{M_t}{M_0}=6\left(\frac{Dt}{r^2\pi}\right)^{1/2}-\frac{3Dt}{r^2} \tag{1a}$$

At late time:

$$\frac{M_t}{M_0}=1-\frac{6}{\pi^2}\exp\left(\frac{-\pi^2 Dt}{r^2}\right) \tag{1b}$$

where M_0=total amount of drug, M_t=amount of drug released after time t, r=radius of powdered polymeric prodrug and D=diffusion coefficient.

Model 2 is the case where the rate of diffusion is much faster than that of hydrolysis. Since hydrolysis in a heterogeneous system may progress at the interface between the liquid and solid phase, the area of polymeric prodrug shown by the shaded area in Fig. 1 decreases with the progress of hydrolysis. Free drug produced by hydrolysis may be immediately released from the polymer particle. Consequently, the mechanism of drug release in model 2 is similar to that of powder dissolution in many aspects. The rate of hydrolysis may be proportional to the surface area of the powdered polymeric prodrug, since hydrolysis occurs at the interface between liquid and solid phase. Assuming that the particle shown in Fig. 1 has a radius r and a surface area $4\pi r^2$, the rate equation for hydrolysis is written

$$\frac{dM}{dt}=4\pi r^2 k \tag{2}$$

where M=amount of drug released after time t and k=rate constant of hydrolysis.

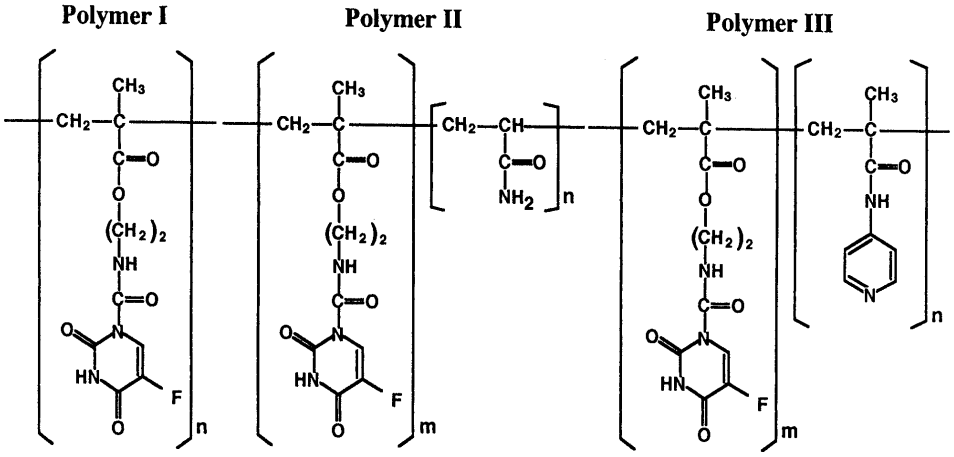

Fig. 2. Structures of Polymeric Prodrugs Containing 5-Fluorouracil as a Side Chain

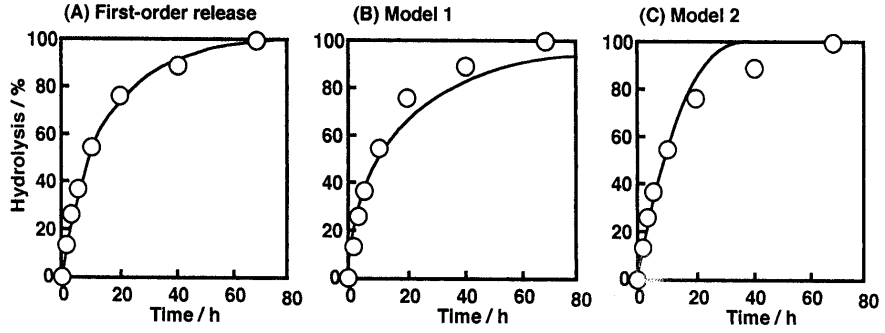

Fig. 3. Hydrolysis Profiles of Polymer I Prepared by Mechanochemical Polymerization in a Flow-Through-Cell System at pH 7.4

Through hydrolysis, the radius of polymeric prodrug is reduced by dr, and the infinitesimal volume of this lost section is

$$dV=-4\pi r^2 dr$$

The amount of drug contained in the powdered polymeric prodrug per unit volume, ρ, is written

$$\rho=\frac{3M_0}{4\pi r_0^3} \tag{3}$$

where M_0=total amount of drug in the polymeric prodrug and r_0=initial radius of polymeric prodrug. Thus, ρdV may be set equal to dM

$$dM=-4\pi r^2 \rho dr \tag{4}$$

Equations (2) and (4) give

$$k dt=-\rho dr$$

Integration with $r=r_0$ at $t=0$ produces the expression

$$r=r_0-\frac{k}{\rho}t \tag{5}$$

The amount of drug released after time t, M_t, is written

$$M_t=M_0-\frac{4}{3}\pi r^3\rho$$

Equations 3 and 5 are substituted into the above equation to yield

$$M_t=M_0-M_0\left(1-\frac{k}{\rho r_0}t\right)^3$$

$$=M_0-M_0(1-at)^3 \quad a=\frac{k}{\rho r_0}$$

The fractional release, M_t/M_0, is given by

$$\frac{M_t}{M_0}=1-(1-at)^3$$

$$=3at-3a^2t^2+a^3t^3 \tag{6}$$

Comparison of Experimental Results with the Predictions of Model 1 and 2 Experimental verification of the rate equations derived from models 1 and 2 was attempted with several systems. Figure 2 shows the structure of polymeric prodrugs containing 5-fluorouracil as a side chain. Drug release from these polymeric prodrugs was performed in a flow-through-cell system at 37 °C in pH 7.4 phosphate buffer solution. Data for drug release from polymer I are plotted as a function of the release time in Fig. 3, as a representative example. Figure 3 also shows the predictions of drug release obtained by Eqs. 1, 6, and an apparent first-order release equation.

The drug release of polymer I appeared to be best fit by a first-order release equation. Although models 1 and 2 successfully predict the experimental results up to 50% hydrolysis, the predictions at the later stage are insufficient. Model 1 underestimates the degree of drug release at the later stage,

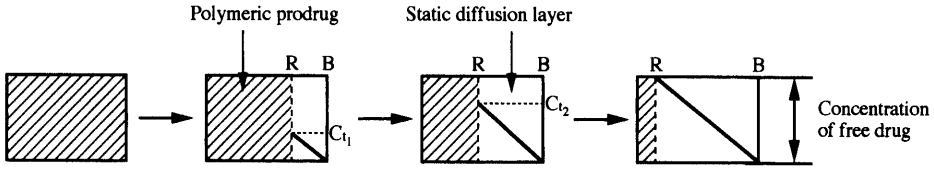

Fig. 4. Schematic Representation of Progressive Changes of Drug Release from Polymeric Prodrug of the Slab Type

B denotes the interface between the surrounding aqueous layer (perfect sink) and water-insoluble polymer (solid dosage form). R denotes the receding boundary between the region of polymeric prodrug and the region containing free drug. C_{t_1} and C_{t_2} are the concentrations of free drug at time t_1 and t_2, respectively.

and model 2 overestimates. Similar results were obtained for other polymeric prodrugs. These results suggest that the rate equations for drug release from polymeric prodrugs in heterogeneous systems must take account of both diffusion and hydrolysis.

A Model Possessing Both Diffusion and Hydrolysis Processes (Model 3) Figure 4 schematically shows a model possessing both diffusion and hydrolysis processes. The region of shading is a polymeric prodrug. The solid line in the diagram would essentially represent the concentration gradient existing after time, t. This model assumes that polymeric prodrug in the surface layer is hydrolyzed and that free drug in the polymer diffuses away at the first step. When polymeric prodrug in the surface layer is completely hydrolyzed, the next layer begins to be depleted. The interface between the region of polymeric prodrug and the region containing free drug thus moves in to the interior as a front.[14] Since hydrolysis in a heterogeneous system may be proportional to the area of the interface, the rate of hydrolysis is constant for a slab. As the distance for diffusion becomes greater with reaction progress, due to the receding boundary, the rate of diffusion at the interface becomes slower. Consequently, the concentration of drug at the boundary rises with hydrolysis. Based on this scheme, the rate equation was derived for a sphere (Fig. 5).

As the rate of hydrolysis is proportional to the area of the boundary, the following equation is derived.

$$\frac{dM}{dt}=4\pi r^2 k \tag{7}$$

where k=rate constant of hydrolysis, M=amount of drug released after t and r=radius of polymeric prodrug at t. Integration with $r=r_0$ at $t=0$ produces the following expression in a similar manner as model 2.

$$r=r_0-\frac{k}{\rho}t \tag{8}$$

where ρ=amount of drug contained in the powdered polymeric prodrug per unit volume (see Eq. 3).

As free drug is released from polymer powder by diffusion, the following equation is produced according to Fick's law.

$$\frac{dM}{Sdt}=-D\frac{dC}{dr}$$
$$\frac{dM}{dt}=-4\pi r^2 D\frac{dC}{dr} \tag{9}$$

where S=diffusional area, D=diffusion coefficient and C=concentration at r. Integrating this we obtain[15]

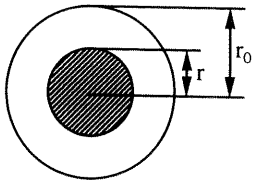

Fig. 5. Schematic Diagram of Partly Hydrolyzed Polymeric Prodrug Particles

The shaded area denotes the polymeric prodrug.

$$\left(\frac{dM}{dt}\right)_t=\frac{4\pi DC_s}{\left(\frac{1}{r}-\frac{1}{r_0}\right)}$$
$$=\frac{4\pi DC_x}{\left(\frac{1}{x}-\frac{1}{r_0}\right)} \tag{10}$$

where x=radius between r_0 and r, C_s=concentration of drug at r, and C_x=concentration of drug at x. The following equation is obtained

$$C_x=C_s\frac{r(r_0-x)}{x(r_0-r)} \tag{11}$$

It is assumed that the rate of hydrolysis is equal to that of disappearance by diffusion at the boundary. Equations 7 and 10 give

$$4\pi r^2 k=\frac{4\pi DC_s}{\left(\frac{1}{r}-\frac{1}{r_0}\right)}$$
$$C_s=\frac{kr(r_0-r)}{Dr_0} \tag{12}$$

It is apparent that the total amount of the drug contained in the powder at time t is the sum of the amount of polymeric prodrug shown by the shaded area in Fig. 5 and that in the region no longer saturated with the drug ($r<x<r_0$). The total residual amount of drug, M_r, equals

$$M_r=\frac{4}{3}\pi r^3\rho+\int_r^{r_0}4\pi x^2 C_x dx$$

Equation 11 is substituted into the above equation and integration produces the expression

$$M_r=4\pi\left[\frac{r^3\rho}{3}+\frac{C_s}{3}r(r_0^2+r_0 r-2r^2)\right]$$

Equations 8 and 12 are substituted into the above equation

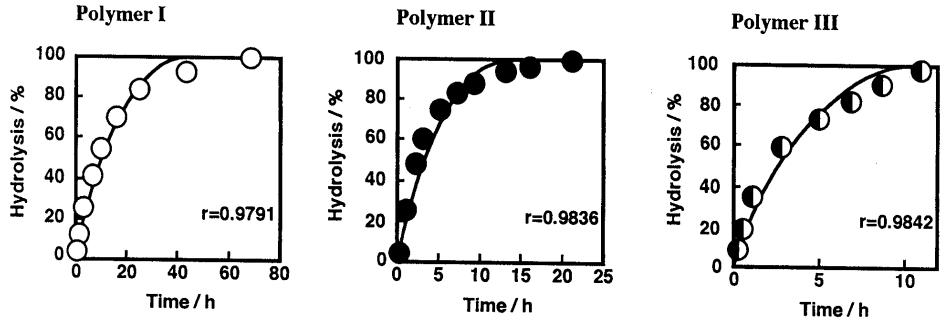

Fig. 6. Hydrolysis Profiles of Polymeric Prodrugs Prepared by Mechanochemical Polymerization in a Flow-Through-Cell System at pH 7.4

Table 1. Geometric Mean Diameter on a Number Basis and Particle Density of Polymeric Prodrugs

	Geometric mean diameter (μm)	Particle density (g/cm^3)
Polymer I	2.85	1.26
Polymer II	2.75	1.27
Polymer III	2.93	1.35

Table 2. Hydrolysis Rate Constant (k) and Diffusion Coefficients (D) Calculated by the Equation of Model 3

	k ($\times 10^{-4}$ mol/m^2/h)	D ($\times 10^{-13}$ m^2/h)
Polymer I	2.67	3.64
Polymer II	6.42	26.4
Polymer III	11.3	5.09

$$M_r=\frac{4\pi}{3}\left[r_0^3\rho-3r_0^2kt+\frac{3r_0k^2}{\rho}\left(1+\frac{r_0k}{2D\rho}\right)t^2-\frac{k^3}{\rho^2}\left(1+\frac{4r_0k}{D\rho}\right)t^3+\frac{7k^5}{2Dr^4}t^4-\frac{k^6}{Dr_0r^5}t^5\right] \quad (13)$$

The fractional release, M_t/M_0, is given by

$$\frac{M_t}{M_0}=1-\frac{M_r}{M_0} \quad (14)$$

where M_t=amount of drug released after time t. Equations 13 and 14 give

$$\frac{M_t}{M_0}=3at-3a^2\left(1+\frac{b}{2}\right)t^2+a^3(1+4b)t^3-\frac{7}{2}a^4bt^4-a^5bt^5$$

$$a=\frac{k}{\rho r_0} \quad b=\frac{r_0k}{D\rho} \quad (15)$$

Experimental Verification of Model 3 Experimental verification of drug release for model 3 was also attempted with the three kinds of polymeric prodrugs shown in Fig. 2. These polymeric prodrugs were selected to investigate the effect of comonomer on the rate of drug release. Figure 6 shows the profiles of drug release of these polymeric prodrugs with the prediction of drug release obtained by Eq. 15. The correlation coefficient is also shown in Fig. 6. Model 3 can give accurate predictions of the experimental data for these polymeric prodrugs. It must be noted that this is an independent prediction of the data and not a fitting, as was the case of an apparent first-order rate equation (*vide supra*).

The particle diameter and density of the polymeric prodrugs are needed to calculate the hydrolysis rate constant and diffusion coefficient from Eq. 15. This data is shown in Table 1. The geometric mean diameter on a number basis, and the particle density resemble each other. Although the powdered polymeric prodrugs possess a wide particle size distribution, the distributions were similar to one another.[16] These results should be responsible for the observation that particles are not fractured due to a long duration of vibratory milling.

Table 2 shows the hydrolysis rate constants and diffusion coefficients calculated from Eq. 15 using the mean diameter and particle density shown in Table 1. Separately, the hydrolysis of 1-(2-methacryloyloxy)ethylcarbamoyl-5-fluorouracil, which is composed of polymer I, was performed in the flow-through-cell system at 37 °C in pH 7.4 phosphate buffer solution. Although the powdered monomer is insoluble in water, it has completely disappeared at the end of reaction to decompose to 5-fluorouracil and 2-aminoethyl methacrylate. The rate constant for hydrolysis of monomer was calculated from Eq. 6, based on model 2. The mean diameter and particle density of monomer were 2.54 μm and 1.26 g/cm^3, respectively. The rate constant for hydrolysis of monomer was 1.51×10^{-3} mol/m^2/h and about 6 times that of polymer I, as shown in Table 2. This result suggests that the slower rate of hydrolysis of polymer I is attributed to a polymer effect. The diffusion coefficient of polymer II, which contains the hydrophilic monomer, is about 7 times that of polymer I. It is suggested that diffusion of free drug in polymer II progresses readily. It is also shown that the rate constant for hydrolysis of polymer II is 2.4 times that of polymer I. The bigger rate constant for hydrolysis of polymer II should be responsible for the wettability of polymeric prodrug. The rate constant for hydrolysis of polymer III is 4.2 times that of polymer I, although the diffusion coefficients are approximately the same. This result suggests that the basic side chain promotes hydrolysis by inter- and/or intramolecular catalytic reaction. These results show that diffusion coefficients and rate constants for hydrolysis calculated from this equation exactly express the character of the comonomer.

Conclusion

The conclusions drawn from the present study can be summarized as follows. We derived the rate equation for drug release from a simple model based on several assumptions in a heterogeneous system. Four assumptions were used to simplify the model. Rate equations for drug release derived from

the two limiting cases, determined by the relative rates of diffusion and hydrolysis, predict the experimental results up to 50% hydrolysis. The predictions at greater conversion, however, are insufficient. These results suggest that the process of drug release from polymeric prodrugs in a heterogeneous system must be described by both diffusion and hydrolysis. The rate equation was then derived from a model considering both diffusion and hydrolysis processes (model 3). The rate equation derived from model 3 successfully predicts the experimental results. It was also shown that the diffusion coefficient and rate constant for hydrolysis calculated from this equation exactly express the character of the comonomer. The rate equation derived from model 3 is useful for analysis of drug release from various kinds of polymeric prodrugs in heterogeneous systems.

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