Isothermal Kinetics of (*E*)-4-(4-Metoxyphenyl)-4-oxo-2-butenoic Acid Release from a Poly(acrylic acid-*co*-methacrylic acid) Hydrogel

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ABSTRACT: A kinetic study of the release of the drug (*E*)-4-(4-metoxyphenyl)-4-oxo-2-butenoic acid (MEPBA) from a poly(acrylic acid-*co*-methacrylic acid) (PAA-*co*-MA) hydrogel was performed. The isothermal kinetic curves of MEPBA release from the PAA-*co*-MA hydrogel in bidistilled water at different temperatures ranging from 20 to 40°C were determined. The reaction rate constants of the investigated process were determined with the initial rate, the saturation rate, and Peppas's semiempirical equation. Also, a model-fitting method for the determination of the kinetics model of drug release was applied. The influence of α at the values of the kinetic parameters and the presence of a compensation effect was established. A procedure for the determination of the distribution function of the activation energies was developed. This procedure was based on the experimentally determined relationship between the activation energy and α. The mechanism of active compound release is discussed. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 107: 2768–2775, 2008

Key words: activation energy; biomaterials; drug delivery systems; hydrogels; modeling

INTRODUCTION

Hydrogels may be used as biomaterials because of the similarity of their physical properties to those of living tissues. One of the most powerful applications of hydrogels is that of controlled release systems for the targeted delivery of drugs to specific areas of the body. The swelling ability of hydrogels allows them to absorb and release high quantities of drugs.[1] In recent years, poly(acrylic acid) and its copolymers have often been used as carriers in drug-release systems.[2]

The antiproliferative activity of (*E*)-4-aryl-4-oxo-2-butenoic acids toward human cervix carcinoma HeLa cells has been reported.[3] For this study, (*E*)-4-(4-metoxyphenyl)-4-oxo-2-butenoic acid (MEPBA) was chosen because of its similar structure to Cytembena (NSC 104801), which has been commercially used as an anticancer drug.

Although there are many studies in the field of hydrogel drug-delivery systems, according to the best of our knowledge, there is not sufficient data concerning the kinetics of drug release from various types of hydrogels. Furthermore, the investigations of kinetics are restricted the description of Fickian or non-Fickian diffusion.[4] Peppas[5] gave a semiempirical equation that predicted the exponential correlation data of fractional drug release and the release time. This equation can be used to analyze the data of the controlled release of water-soluble drugs from polymers under perfect sink conditions and may be used only for systems where the drug diffusion coefficient is clearly independent from the concentration. Also, there is a lack of data concerning the determination of the kinetic parameters [the activation energy (E_a) and pre-exponential factor (ln A)] of the investigated drug-release processes. Furthermore, there are no discussions concerning the influences of the degree of drug released (α) on the kinetics and mechanism of the investigated processes.

With this in mind, in this study, we critically checked the possibility of applying Peppas's model to kinetically describe MEPBA release from a poly (acrylic acid-*co*-methacrylic acid) hydrogel. Also, the influence of α on the values of the kinetic parameters was examined. The model-fitting method as a method for the rapid and easy determination of the model of drug release was applied. On the basis of our results, a possible mechanism of the active compound release is discussed.

EXPERIMENTAL

Materials

The materials for hydrogel synthesis included acrylic acid (AA; 99.5%) and methacrylic acid (MA), which

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were supplied by Merck K Ga A, Daramsatdt. G. (Germany). *N,N*-Methylene bisacrylamide (p.a.) was purchased from Aldrich Chemical Co. (Milwaukee, WI). The initiator 2,2-azobis-[2-(2-imidazolin-2-il)-propan dihidrohlorid (VA044, 99.8%) was supplied by Wako Pure Chemicals Industries, Osaka, Japan.

Synthesis

Poly(acrylic acid-*co*-methacrylic acid) (PAA-*co*-MA) hydrogel

PAA-*co*-MA was synthesized with a procedure based on the simultaneous radical polymerization of AA and MA (1 : 1 mol) and crosslinking of the formed PAA-*co*-MA; the application of the procedure was based on a modified general procedure described in our previous works.[6,7] This procedure differed from the previously described one as follows: the solution of AA and MA (1/1 mol/mol) in the form of a 20 wt % solution was prepared and mixed with a solution of *N,N*-methylene bisacrylamide (0.1 wt %). After these mixtures were stirred well to ensure homogeneity and nitrogen bubbling throughout the mixture for 0.5 h, the initiator solution (0.06 mol % of the monomer) was added, and the mixture was once again rapidly homogenized by stirring. The prepared solution was placed in a Petri dish and stored in a dry oven for 5 h at 80°C. After the polymerization was finished, the obtained gel-type product was transformed into the Na^+ form (60%) by neutralization with a 3% solution of Na_2CO_3. The resulting hydrogel was cut into approximately equal discs and placed in excess distilled water. The water was changed seven times every 5 h (or 12 h during the night) to remove the unreacted monomers and the sol fraction of the polymer. In addition, the obtained hydrogel was dried in an air oven in a temperature regime of 80°C for 2 h, 90°C for 3 h, and 105°C to constant mass. The obtained product was stored in a vacuum exicator before use. For this investigation, the obtained hydrogel was again ground and used in the form of powder.

MEPBA

MEPBA was synthesized according to a previously described procedure.[3] The sodium-salt-form solution was used for this investigation (we prepared it as follows: 0.514 g of anhydrous Na_2CO_3 was added to 1 g of MEPBA and dissolved in 25 mL of water).

MEPBA loading

MEPBA loading was carried out by the immersion of a known weight of the xerogel sample (0.1 g) in an excess of MEPBA solution (50 mL of 0.25% solution) at ambient temperature; this was left swelling for 24 h. The swollen hydrogel was removed from the solution and dried in a thermal oven at 105°C for 4 h.

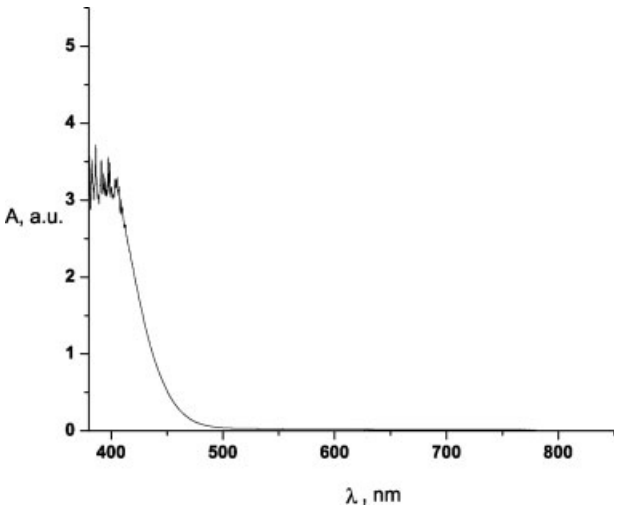

Figure 1 UV spectra of the water solution of MEPBA in Na^+ salt form.

MEPBA release

MEPBA release was carried out by the immersion of the hydrogel–MEPBA loaded sample in bidistilled water at temperatures of 20, 32, and 40°C. The concentration of the released substance was monitored spectrometrically on a Cintra 10e UV–visible spectrometer (serial number V 3163, Dandenong Australia) with an absorption value of $\lambda = 410$ nm.

α was calculated as a ratio of the MEPBA concentration at a time to the equilibrium released concentration:

$$\alpha = \frac{C}{C_{max}} \quad (1)$$

where C is the MEPBA concentration in solution at time t and C_{max} is the maximum MEPBA concentration in solution at a certain temperature.

RESULTS AND DISCUSSION

The UV spectra of MEPBA in sodium salt form is shown in Figure 1. The measurements of absorbances at $\lambda = 410$ nm were used for the kinetic investigation of MEPBA release.

The isothermal dependences of a specific amount of MEPBA released from the PAA-*co*-MA hydrogel versus the reaction time (kinetic curve) for different temperatures are shown in Figure 2.

Three distinct ranges of the changes in α with time were clearly observed from the presented kinetics

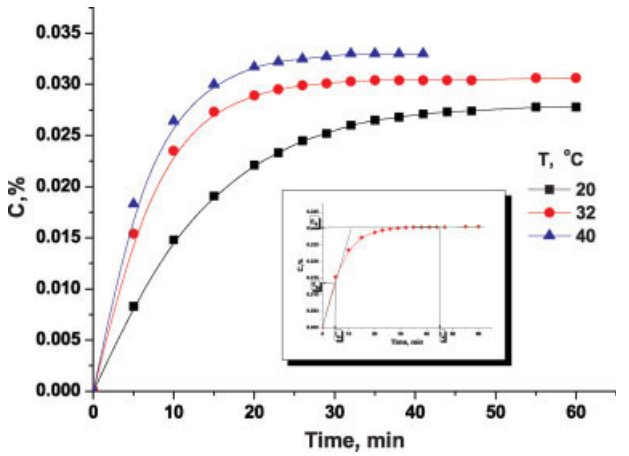

Figure 2 Isothermal kinetic curves of released MEPBA from the PAA-*co*-MA hydrogel at different temperatures. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

curves for the PAA-*co*-MA hydrogel, that is, linear, nonlinear, and saturation ranges. To determine the influence of temperature on the shape of the kinetics curves, the following parameters were defined: the time range of linearity (t_L), the initial MEPBA release rate (v_{in}), the saturation time (t_s), and the saturation MEPBA release rate (v_s).[7]

t_L is the time interval within which the concentration of MEPBA release increased linearly with the release time. v_{in} is expressed with eq. (2):

$$v_{in} = \frac{C_L}{t_L} \tag{2}$$

where C_L is the concentration of MEPBA released in the final point of the linear part of the kinetic curve of MEPBA release and t_L is time that corresponds to this linear part of the kinetic curve.

t_s represents the time required to achieve C_{max} at a certain temperature, whereas v_s can be calculated from the following equation:

$$v_s = \frac{C_{max}}{t_s} \tag{3}$$

The values of the parameters of the shape of the kinetics curve at different temperatures are given in Table I. According to the results given in Table I, the values t_L and t_s decreased, whereas those of v_{in} and v_s increased with increasing temperature. Because the increase of v_{in} and v_s with temperature was exponential, the kinetic parameters (the activation energies and pre-exponential factors) of the initial and saturation phases of MEPBA release from the PAA-*co*-MA hydrogel ($E_{a,in}$, ln A_{in}, $E_{a,s}$, and ln A_s, respectively) were determined by the application of the Arrhenius equation. The obtained results are given in column 7 of Table I. As shown by the obtained results, the value of $E_{a,in}$ (35.1 kJ/mol) was higher than the value of $E_{a,s}$ (26.6 kJ/mol), contrary to the values of ln A. The significantly higher value of $E_{a,in}$ than $E_{a,s}$ implied a nonelementary character of the process of MEPBA release from this hydrogel, that is, its complexity from the point of view of both the mechanism and the kinetics model.

To ensure the possibility of kinetically modeling the MEPBA release process, Peppas's semiempirical equation was expressed:[5]

$$\alpha = k_P t^{n_P} \tag{4}$$

It was used in linearized form:

$$\ln \alpha = \ln k_P + n_P \ln t \tag{4a}$$

where α is the degree of MEPBA released at time t, n_P is a diffusion exponent, and k_P is the apparent release rate. In the ranges of α within which the plot of ln α versus ln t gave a straight line, it was possible to determine the values of n_P and k_P from the slopes and intercepts of these straight lines.

Figure 3 presents the plot of ln α versus ln t. As shown in Figure 3, a plot of ln α versus ln t gave straight lines in limited ranges of the investigated release process. The obtained results for the determined parameters (n_P and k_P) and a range of applicability (L) for the determined parameters are presented in Table II..

As shown by the results presented in Table II, it was possible to determine the kinetic parameters n_P and k_P for MEPBA release from the PAA-*co*-MA hydrogel for narow L [α = (30–55)–(68–80)%]. As shown in Table II, the constant k_P increased as the temperature increased; meanwhile, the release exponent (n_P) decreased from 0.77, which was characteristic of a non-Fickian type of diffusion, to 0.54, which

TABLE I
Values of the Parameters of the Shape of Kinetics Curves for MEPBA Release from the PAA-*co*-MA Hydrogel at Different Temperatures and the Kinetic Parameters (E_a and ln A) Calculated on Their Basis

T (°C)	t_L (min)	v_{in} (%/min)	t_s (min)	v_s (%/min)	C_{max} (%)	Kinetic parameters
20	8.45	1.49×10^{-3}	55.0	0.51×10^{-3}	0.0278	$E_{a,in}$ = 35.1 kJ/mol
32	4.99	2.95×10^{-3}	45.0	0.68×10^{-3}	0.0306	ln A_{in} = 7.9 min^{-1}
40	3.07	3.68×10^{-3}	31.9	1.04×10^{-3}	0.0328	$E_{a,s}$ = 26.6 kJ/mol
						ln A_s = 3.2 min^{-1}

was characteristic of the first law of diffusion. These changes may have indicated possible changes in the mechanism of MPEBA release from the PAA-*co*-MA hydrogel. It was possible to determine the kinetic parameters $E_{a,P}$ and ln A_P because k_P showed Arrhenius dependence on temperature changes. The obtained value for $E_{a,P}$ was 38.6 kJ, which was slightly higher than the value of $E_{a,in}$ (35.1 kJ/mol) and significantly higher than the value of $E_{a,s}$ (26.6 kJ/mol).

To determine the true values of the kinetic parameters and kinetics model, keeping in mind that Peppas's model was applicable only at certain stages of the investigated process of MEPBA release and that the drug-release process was one that took place at an interface (solvent–drug–hydrogel–solvent), we applied the model-fitting method. This method is widely used for the determination of the kinetic model for solid-state reactions.[8] According to the model-fitting method, kinetic reaction models are classified into five groups depending on their reaction mechanisms: (1) power law reactions, (2) phase-controlled reactions, (3) reaction orders, (4) reactions described by the Avrami equation, and (5) diffusion-controlled reactions.

Applying the model-fitting method, we determined the kinetic model of the MEPBA release process from the PAA-*co*-MA hydrogel by comparing (graphical and analytical) the experimentally obtained function $\alpha_e = f(t_N)$ with theoretical functions for different solid-state reaction models $\alpha = f(t_N)$,[9] where t_N is the so-called normalized time:

$$t_N = \frac{t}{t_{0.9}} \tag{5}$$

where $t_{0.9}$ is the release time at $\alpha = 0.9$ at a certain temperature.

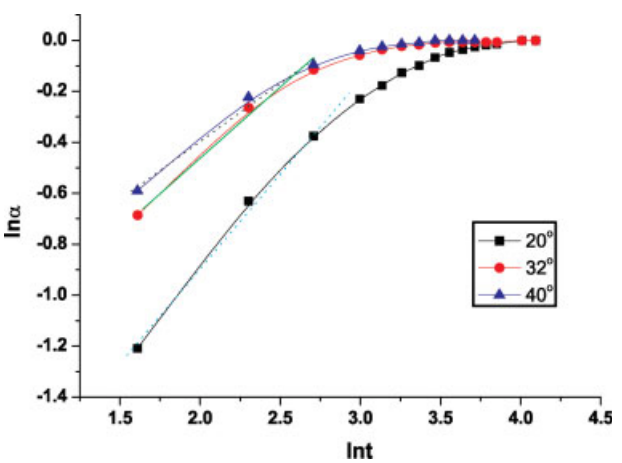

Figure 3 Isothermal dependences of $-\ln(1 - \alpha)$ versus ln t. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE II
n_P, k_P, and L from Eq. (4) and Kinetic Parameters ($E_{a,P}$ and ln A_P) for MEPBA Release from the PAA-*co*-MA Hydrogel

T (°C)	n_P	ln k_P	k_P (min)	L (%, α)	Kinetic parameters
20	0.77	−2.43	0.088	30–68	E_a = 38.6 kJ/mol
32	0.61	−1.67	0.189	50–77	ln A_P = 13.5 min^{-1}
40	0.53	−1.44	0.237	55–80	R = 0.986

R* = correlation coefficient.

A set of the kinetic reaction models used for the determination of the model of MEPBA release kinetics is shown in Table III.

Figure 4 shows plots of $\alpha = f(t_N)$ for selected theoretical reaction models from Table III (solid curves) and experimental plots of $\alpha_e = f(t_N)$ for the MEPBA release process from the PAA-*co*-MA hydrogel at the investigated temperatures.

According to the results shown in Figure 4, we can state with great assurance that the kinetics of MEPBA release from the PAA-*co*-MA hydrogel at all of the investigated temperatures could best be described with the kinetic model F1, which corresponds to a first-order chemical reaction:

$$-\ln(1 - \alpha) = k_M t \tag{6}$$

where k_M is a model constant for the first-order chemical reaction rate.

The isothermal dependences of $-\ln(1 - \alpha)$ versus time of MEPBA release from the PAA-*co*-MA hydrogel are shown in Figure 5. Table IV gives the values of the model's constants for the rate of MEPBA release from the PAA-*co*-MA hydrogel at different temperatures. The model's constants were calculated from the slopes of the straight lines of the dependence values of $-\ln(1 - \alpha)$ versus time (Fig. 5).

Because the increase in the model's constants with temperature was exponential, the model's kinetic parameters ($E_{a,M}$ and ln A_M) of MEPBA release were determined by the Arrhenius equation. The obtained results are given in Table IV. Accordingly, we found that the activation energy of MEPBA release for the entire process, determined on the basis of the model constant for the rate of MEPBA release, had a value of 27.5 kJ/mol, and the value of the pre-exponential factor was 8.8.

The obtained results imply some discrepancies between the values of the activation energy for the early beginning and the final part of the investigated process and the activation energy determined by the application of the model of the first-order chemical reaction (F1). To determine the effect of α at the values of the kinetic parameters of that process, the kinetic parameters at different α's from PAA-*co*-MA hydrogel were determined by application of the

TABLE III
Set of the Kinetic Models Used to Determine the Kinetics Model of the MEPBA Release Process from the PAA-*co*-MA Hydrogel

Model	Kinetics mechanism	General expression of kinetics model, $f(\alpha)$	Integral form of kinetics model, $g(\alpha)$
P1	Power law	$4\alpha^{3/4}$	$\alpha^{1/4}$
P2	Power law	1	$\alpha^{1/3}$
P3	Power law	$2\alpha^{1/2}$	$\alpha^{1/2}$
P4	Power law	$2/3\alpha^{-1/2}$	$\alpha^{3/2}$
R1	Zero order (Polany–Winger equation)	1	α
R2	Phase-boundary controlled reaction (contracting area, i.e., bidimensional shape)	$2(1-\alpha)^{1/2}$	$[1-(1-\alpha)^{1/2}]$
R3	Phase-boundary controlled reaction (contracting volume, i.e., tridimensional shape)	$3(1-\alpha)^{2/3}$	$[1-(1-\alpha)^{1/3}]$
F1	First order (Mampel)	$(1-\alpha)$	$-\ln(1-\alpha)$
F2	Second order	$(1-\alpha)^2$	$(1-\alpha)^{-1}-1$
F3	Third order	$(1-\alpha)^3$	$0.5[(1-\alpha)^{-2}-1]$
A2	Avrami–Erofeev	$2(1-\alpha)[-\ln(1-\alpha)]^{1/2}$	$[-\ln(1-\alpha)]^{1/2}$
A3	Avrami–Erofeev	$3(1-\alpha)[-\ln(1-\alpha)]^{2/3}$	$[-\ln(1-\alpha)]^{1/3}$
A4	Avrami–Erofeev	$4(1-\alpha)[-\ln(1-\alpha)]^{3/4}$	$[-\ln(1-\alpha)]^{1/4}$
D1	One-dimensional diffusion	$1/2\alpha$	α^2
D2	Two-dimensional diffusion (bidimensional particle shape)	$1/[-\ln(1-\alpha)]$	$(1-\alpha)\ln(1-\alpha)+\alpha$
D3	Three-dimensional diffusion (tridimensional particle shape) Jander equation	$3(1-\alpha)^{2/3}/2[1-(1-\alpha)^{1/3}]$	$[1-(1-\alpha)^{1/3}]^2$
D4	Three-dimensional diffusion (tridimensional particle shape) Ginstling–Brounshtein	$3/2[(1-\alpha)^{-1/3}-1]$	$(1-2\alpha/3)-(1-\alpha)^{2/3}$

isoconversion method.[10] The basic assumption of the isoconversional method is that the reaction rate is only a function of temperature for a certain conversion degree. On the basis of that premise, the general expression for the reaction rate is given by eq. (7):

$$v = A\exp\left(-\frac{E_a}{RT}\right)f(\alpha) \tag{7}$$

where $f(\alpha)$ is the reaction model. A simple rearrangement of eq. (7) leads to the following equation:

$$\ln(v)_\alpha = \ln[A_\alpha f(\alpha)] - \frac{E_{a,\alpha}}{RT} \tag{8}$$

where v is the rate of drug released, $E_{a,\alpha}$ is the activation energy at a certain value of α, and A_α is the pre-exponential factor at a given value of α.

Figure 6 presents the dependences $\ln v_{\alpha,Ti} = f(1/T)$, where T is the temperature in [K], for different α's.

As shown by the obtained results presented in Figure 6, there was a linear relationship between $\ln v_{\alpha,Ti}$ and the inverse temperature $(1/T_i)$ for all α's

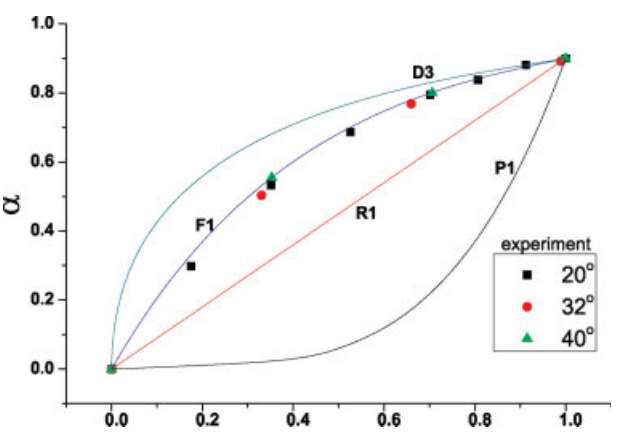

Figure 4 A Plot of $\alpha = f(t_N)$ for the selected theoretical kinetics models D3, F1, R1, and P1 (solid lines) and experimental points for MEPBA release from PAA-*co*-MA hydrogel. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

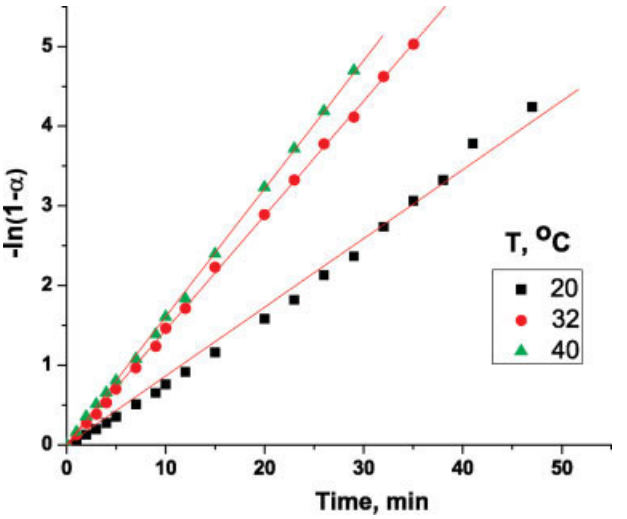

Figure 5 Isothermal dependences of $-\ln(1-\alpha)$ versus release time. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE IV
Values of the Models' Constants for the Rate of MEPBA Release (k_M) at Different Temperatures and Kinetic Parameters ($E_{a,M}$ and ln A_M)

T (°C)	k_M (min^{-1})	Kinetic parameters
20	0.080	
32	0.142	$E_{a,M}$ = 27.5 kJ/mol
40	0.163	ln A_M = 1.80 min^{-1}

from the PAA-*co*-MA hydrogel. From the slopes and intercepts of these straight lines, the values of the kinetic parameters were obtained.

Figure 7 presents the variation of ln A_α with $E_{a,\alpha}$ with changes in α.

By comparing the values of $E_{a,\alpha}$ and ln A_α, one may conclude that the increase in ln A also coincided with the increase in E_a, and this was the so-called compensation effect.[11] The existence of the compensation effect confirmed the previously exposed hypothesis about the complexity of the investigated process of MEPBA release from the PAA-*co*-MA hydrogel. A linear relationship between ln A_α and $E_{a,\alpha}$ was obtained. The changes in ln A_α with $E_{a,\alpha}$ at various α's could be expressed as

$$\ln A_\alpha = -8.8 + 0.62E_{a,\alpha} \quad (9)$$

As shown, the kinetic parameters of the MEPBA release kinetics were significantly dependent on α; meanwhile, the mechanism of drug release was not influenced by the changes in temperature within the investigated temperature region.

The possibility of describing the drug release from a hydrogel with a first-order chemical reaction model reinforces the statement that the investigated process of drug release presented a kinetically controlled reaction and that the kinetics of drug release were restricted by the rate of drug release, in which

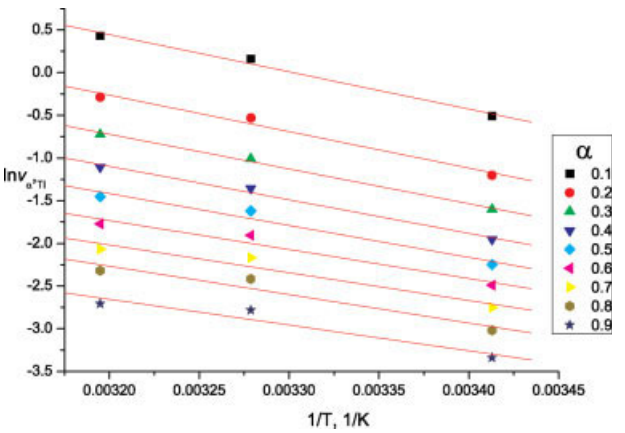

Figure 6 Dependences ln $v_{\alpha,Ti} = f(1/T)$ for different α's. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

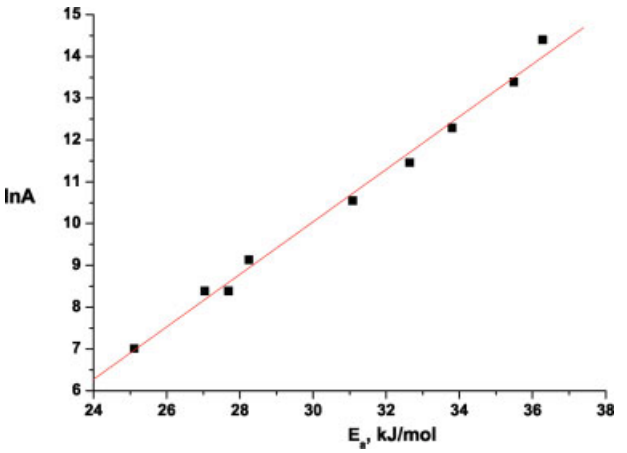

Figure 7 Changes of ln A_α with $E_{a,\alpha}$ with various α values from the PAA-*co*-MA hydrogel. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

the drug was bonded to the hydrogels' differently energetically distributed active centers. The drug-release kinetics were determined by the rate of the drug released from the active center. Thus, the experimentally determined dependences of the kinetics parameters from α, the presence of the compensation effect, and the accomplishment of the maximum drug-release rate for low α (i.e., the high values of E_a) could be explained with the following:

1. In the hydrogel structure, there were active centers with different specific energies and energetic distributions.
2. The degree of the efficiency of the active center in a specific interaction was proportional to its specific energy.
3. The value of E_a for the release process was inversely proportional to the value of the specific energy of the active center.

With that in mind, at low α's and relatively low values of E_a, the active centers with specific low energies must have participated in this process of release. The active centers with their low specific energies were more abundant than those with high energies due to thermodynamics and statistic requirements. The ln A value was, therefore, high as it was proportional to the mass concentration of the active centers; this explained the compensation effect and the maximum rate of drug delivery at low α's.

However, at high α's, when the E_a value was low, the active centers with high specific energies must have participated in the drug-release process. Because of their low distribution, the value for ln A was also low, and thus, the rate of the process was minimal.

If we assumed that the distribution of the active centers existed, the function of the distribution of the

probability values of the activation energies [$f(E_a)$] could be defined. Because the model of first-order reaction kinetics can describe the kinetics of drug release, the following equation is valid:

$$\alpha = 1 - \int_0^\infty \Phi(E_a, T) f(E_a) dE \tag{10}$$

where E_a is the activation energy and $\Phi(E_a,T)$ is equated to

$$\Phi(E, T) = \exp[-A_o \int_0^T \exp(-\frac{E}{RT}) dT] \tag{11}$$

With the variable $x = E_a/RT$, eq. (11) is rewritten as follows:

$$\Phi(E_a, T) = \exp\left\{-\frac{A_o E_a}{R}\left(\frac{e^{-x}}{x} - \int_x^\infty \frac{e^{-x}}{x} dx\right)\right\}$$
$$= \exp\left\{-\frac{A_o E_a}{R} p(x)\right\} \tag{12}$$

where $p(x)$ is the so-called p function, which is well known in the field of thermal analysis. By employing the approximation $p(x) = e^{-x}/x^2$, we can write

$$\Phi(E, T) = \exp\left[-\frac{A_o RT^2}{E_a} \exp\left(-\frac{E_a}{RT}\right)\right] \tag{13}$$

To estimate the $f(E_a)$ curve from the experimental data of α versus time, the possibility of an approximate representation for eq. (13) was examined. Since the $\Phi(E_a,T)$ function changed rather steeply with E_a at a given temperature, it seemed reasonable to assume $\Phi(E_a,T)$ by the step function U at an activation energy $E_a = E_{a,s}$ as

$$\Phi(E_a, T) = U(E_a - E_{a,s}) \tag{14}$$

This approximation corresponds to the assumption of only a single reaction whose activation energy is $E_{a,s}$ at a given temperature T. Therefore, eq. (13) was simplified to

$$\alpha = 1 - \int_{E_s}^\infty f(E_a) dt \tag{15}$$

According to eq. (14) we can write

$$\alpha = 1 - \int_0^{E_s} f(E_a) dE_a \tag{16}$$

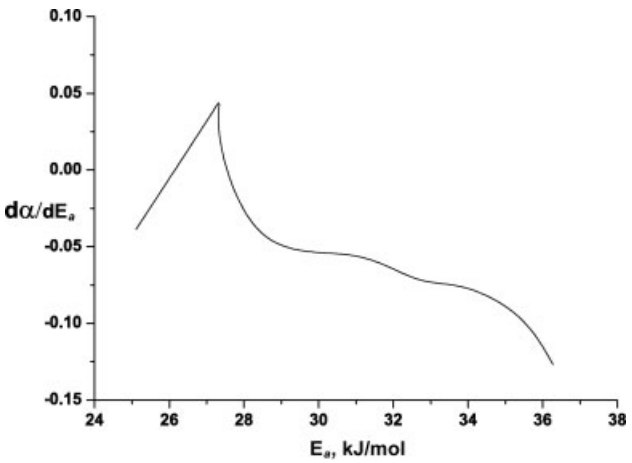

Figure 8 Distribution function of the activation energies.

Thus, $f(E_a)$ is given by differentiating eq. (14) by $E_{a,s}$ as

$$f(E_a) = \frac{d\alpha}{dE_{a,s}} \tag{17}$$

Therefore, we could directly obtain the density distribution function of activation energies by differentiating the experimentally determined relationship α versus E_a, that is, $f(E_a) = d\alpha/dE_a$. The density distribution function $f(E_a)$ is presented in Figure 8. As clearly shown, the dependence curve $f(E_a)$ versus E showed a well-designed maximum at $\overline{E_a} = 27$ kJ/mol.

The complex character of the MEPBA release process from the PAA-*co*-MA hydrogel was a consequence of energetically heterogeneous desorption complexes in the MEPBA–hydrogel, whereas the values of the activation energy determined on the basis of the suggested kinetics model corresponded to the most probable value from the curve of the activation energies' distribution.

CONCLUSIONS

The process of MEPBA release from the PAA-*co*-MA hydrogel to a water solution was a complex heterogeneous process that could be kinetically described with a model of first-order reaction kinetics. The kinetic parameters (E_a and ln A) varied with α. The dependence of the activation energy and pre-exponential factor from α presented the consequence of the presence of the energetic heterogeneity of the desorption complexes of the MEPBA–hydrogel. The density distribution function of the activation energies showed a well-designed maximum at $\overline{E_a}$ = 27 kJ/mol. This value of $\overline{E_a}$ was in good agreement with value of activation energy for the entire process of the MEPBA release ($E_{a,M}$ = 27.5 kJ/mol) determined on the basis of the model constants for the rate of MEPBA release from the PAA-*co*-MA hydrogel.

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