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Isothermal kinetics of (*E*)-4-(4-metoxyphenyl)-4-oxo-2-butenoic acid release from poly(acrylic acid) hydrogel

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Abstract

The isothermal kinetics of the release of the drug (*E*)-4-(4-metoxyphenyl)-4-oxo-2-butenoic acid (MEPBA) from poly(acrylic acid) hydrogel were studied. The isothermal kinetic curves of MEPBA release from the poly(acrylic acid) hydrogel in bidistilled water at different temperatures ranging from 22 °C to 42 °C were determined. The reaction rate constants of the investigated process were determined using the initial rate, saturation rate and power law. Also, to quickly determine the kinetic model of drug release, the so-called method of reduced time was applied. The influence of the degree of the MEPBA released (α) at the values of the kinetic parameters as well as the presence of a compensation effect was established. The procedure for determining the distribution function of activation energies was developed. This procedure was based on the experimentally determined relationship between the activation energy and the degree of drug released. The process of MEPBA release from PAA hydrogel, almost in entire range, can be described with the model of the drug desorption from the active centers with different specific energies.

Keywords: Kinetics; Isothermal; Models; PAA hydrogel; MEPBA release

1. Introduction

Hydrogels are three-dimensional crosslinked polymeric structures that are able to swell in an aqueous environment. Due to its characteristic properties such as swellability in water, hydrophilicity, biocompatibility and intoxicity, hydrogels have been used in a wide range of biological, medical, pharmaceutical and environmental applications [1]. Hydrogels are used extensively in medicine and pharmaceutics as drug delivery systems, contact lenses, catheters, wound dressing and biosensors [2]. Hydrogels may be used as biomaterials, thanks to the similarity of their physical properties to those of living tissues. One of the most powerful applications of hydrogels is to act as controlled release systems for targeted delivery of drugs to specific areas of the body. More specifically, due to the intimacy and extended duration of contact, ionic hydrogels are used to immobilize a drug delivery device on a specific site for targeted release and optimal drug delivery [3]. After intimate contact is established, the rate and duration of drug release depends on the swelling behavior of the hydrogel [4]. The swelling ability of hydrogels allows them to absorb and release high quantities of drugs [1].

Poly(acrylic acid) (PAA) and its copolymers have often been used as carriers in drug release systems in recent years [5]. The possibility of applying PAA-based hydrogels crosslinked by macrodiisocynates for retarded drug release was investigated [6]. The work presented by Changez et al. lead to the conclusion that it is possible to deliver gentamicin sulphate using IPNs based on PAA and gelatin in a controlled manner. The authors recommended that these devices may have good therapeutic potential for the treatment of local infections like osteomyelitis [7].

A mucoadhesive polymer complex composed of chitosan and PAA loaded with triamcinolone acetonide (TAA) was prepared. It was found that the TAA was released from the chitosan/PAA complex by non-Fickian diffusion [8].

Antiproliferative activity of (*E*)-4-aryl-4-oxo-2-butenoic acids towards *human cervix carcinoma* HeLa cells has been reported [9]. For this study the (*E*)-4-(4-metoxyphenyl)-4-oxo-2-butenoic acid (MEPBA) was chosen due to its similar structure to Cytembena (NSC 104801), which has been commercially used as an anticancer drug. The compound exerted medial *in*

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vitro activity. In spite of this, because of the presence of sparingly polar 4-MeO-substituent on phenyl moiety is convenient for preliminary examination of entrapping with chosen carrier polymer bearing a number of polar or ionized functional groups.

Although there are many researches in the field of hydrogel drug delivery systems, according to the best of our knowledge there is no sufficient data concerning the kinetics of drug release from various types of hydrogels. Furthermore, the kinetics investigations are restricted to describe the process as being Fickian or non-Fickian diffusion [8]. The semi-empirical equation, which predicted that the fractional release was exponentially related to release time, was applied by Peppas for drug release [10]. This equation could be used to analyze data of 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 concentration.

The majority of up-to-date reports reveal that the release of drugs is strongly dependant on a variety of factors, such as polymer composition, hydrogel geometry, degree of swelling and dissolution and diffusion of solute in the hydrogel [11–18]. In those reports it is suggested that the release occurs mainly by diffusion without studying in detail the factors that could affect the drug release which are the results of interactions or physical–chemical affinities of the solute between the hydrogel and the solvent. Recently, Reis et al. [19] gave mathematical model that describes 100% of released solute by considering the release process as a diffusion transport process and as a partition phenomenon on which the partitioning of solutes occurs between the solvent phase and the hydrogel.

Despite of this, there is a lack of data concerning the determination of the kinetic parameters (activation energy (E_a) and pre-exponential factor ($\ln A$)) of the investigated drug release processes. Moreover, there are no discussions regarding the influence of the drug release degree on the kinetics and mechanism of the investigated process.

Bearing in mind the discussion above, in the present study, (*E*)-4-(4-metoxyphenyl)-4-oxo-2-butenoic acid (MEPBA) was used as a model of an active compound and the isothermal kinetics of its release from poly(acrylic acid) hydrogel, sodium salt form (60%) were investigated. The kinetics' models and kinetic parameters of the MEPEBA release (E_a, $\ln A$) were determined. Correlation between the kinetics' parameters of the investigated process and the degree of drug release was examined.

2. Materials and methods

2.1. Materials

Materials for hydrogel synthesis: acrylic acid (99.5%) (AA) was supplied by Merck A.G., Germany. *N*,*N*-Methylene bisacrylamide (p.a.) (MBA) was purchased from Aldrich Chemical Co., Milwaukee, USA. The initiator, 2,2-azobis-[2-(2-imidazolin-2-il)-propan dihidrohlorid (VA044), (99.8%) was supplied by Wako Pure Chemicals Industries, Ltd., USA. Bidistilled water was used in the polymerizations, swelling and active substance release studies.

2.1.1. Synthesis

Poly(*acrylic acid*) *hydrogel* (*PAA*), which was used in this investigation was synthesized following the procedure based on the simultaneous radical polymerization of acrylic acid and crosslinking of the formed poly(acrylic acid), which was done by the procedure which was based on the modified general procedure described in our previous works [20,21]. This procedure goes as follow: a solution of acrylic acid in the form of 20 wt% was prepared and mixed with a solution of MBA (0.1 wt%). After stirring these two mixtures well for half an hour to ensure homogeneity of the reaction mixture and nitrogen bubbling throughout the mixture, the initiator solution (0.06 mol% of the monomer) was added and the reaction 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 finished, the obtained gel-type product was transformed into the Na^+ form (60%) by neutralizing with a 3% solution of Na_2CO_3. The resulting hydrogel was cut to approximately equal discs and placed in excess distilled water. The water was changed 7-times every 5 h (or every 12 h during the night), in order to remove the unreacted monomers and the sol fraction of the polymer. Next, 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 until the sample reached a constant mass. The obtained product (xerogel) was stored in a vacuum exicator before use. For this investigation, the obtained xerogel was again ground and used in the form of powder.

(*E*)-*4*-(*4-Metoxyphenyl*)-*4-oxo-2-butenoic acid* (*MEPBA*) was synthesized according to the previously described procedure [9]. The sodium salt form solution that was used for this investigation was prepared as follows: 0.514 g of anhydrous Na_2CO_3 was added to 1 g of MEPBA and dissolved in 25 ml of water).

2.2. MEPBA loading

MEPBA loading was carried out by immersing the known weight of the xerogel sample (0.1 g) in an excess of MEPBA solution (50 ml of 0.25% solution) at an ambient temperature. The mixture was left swelling for 24 h. The swollen hydrogel was removed from the solution and dried in a thermal oven at 105 °C until it reached a constant mass. Consequently, the MEPBA loaded xerogel was obtained.

2.3. MEPBA release

MEPBA release was carried out by immersing the xerogel-MEPBA loaded sample in bidistilled water at temperatures 22 °C, 31 °C and 42 °C. The concentration of the released substance was monitored spectrometrically on a Cintra 10e, UV–vis spectrometer, serial no. V 3163, UK, using the absorption at $\lambda = 410$ nm.

Degree of MEPBA released (α) is calculated as a ratio of the MEPBA concentration at time (t) and equilibrium released concentration (Eq. (1)):

$$\alpha = \frac{c}{c_{max}} \quad (1)$$

where c is MEPBA concentration in the solution at time (t), and c_{max} is the maximal (equilibrium) concentration of MEPBA in the solution at a certain temperature.

2.4. Absorption of external medium (MEPBA solution) to the xerogel/hydrogel

The absorption of external medium was determined by leaving xerogels with an average weight of 0.1 g (±5%) to absorb the MEPBA solution with a concentration that corresponds to the maximal released MEPBA at temperatures 22 °C, 31 °C and 42 °C. At the beginning of each experiment, a sample of xerogel was measured by weight and then it was immersed in excess solution. At predetermined time intervals the gel with absorbed solution was removed from the solution and weighed. This was done until the hydrogel obtained a constant mass, i.e., until reached equilibrium.

2.4.1. Determination of the absorption degree

The isothermal absorption degree (AD), defined as the difference between the weight of the hydrogel sample at time (t) (m_t) and the weight of xerogel (m_o) divided by the weight of the xerogel sample (m_o), was calculated according to Eq. (2) and determined as a function of time:

$$\mathrm{AD}\,(\%) = \frac{m_t - m_o}{m_o} \times 100 \tag{2}$$

The equilibrium absorption degree (AD_{eq}) is the absorption degree of the hydrogel at equilibrium. For each sample at least three absorption measurements were performed and the average values were reported.

2.4.2. Normalized absorption degree

The normalized absorption degree (α_A) was defined as the ratio between the absorption degree (AD) at time (t) and the equilibrium absorption degree (AD_{eq}):

$$\alpha_A = \frac{\mathrm{AD}}{\mathrm{AD_{eq}}} \tag{3}$$

3. Methods used to evaluate kinetics parameters

Power law: to determine the kinetic parameters of MEPBA release from PAA hydrogel, the results were analyzed by applying the linearized form of the well known power law equation on time [10] (Eq. (4)):

$$\alpha = kt^n \tag{4}$$

where n is an exponent indicative for the mechanism of the process, coefficient k the apparent release rate and t is interaction time.

The Friedman's differential iso-conversional method [22]: the kinetic analysis of experimental data is based on the following rate equation:

$$\left(\frac{\mathrm{d}\,\alpha}{\mathrm{d}t}\right)_{\alpha=\mathrm{const}} = Af(\alpha)\exp\left(-\frac{E_{a,\alpha}}{RT}\right) \tag{5}$$

Table 1
The characteristic properties of the hydrogel used

Property	Value
Equilibrium swelling degree in distilled water at 25 °C (SD_{eq})	11,300%
Initial swelling rate in distilled water at 25 °C (v_{in})	75% min^{-1}
Xerogel density (ρ_{xg})	994 kg/m^3
Molar mass between the network crosslinks (M_c)	7200 g/mol
Crosslink density (ρ_c)	1.4×10^4 mol/cm^3
Distance between the macromolecular chains (d)	1.02 nm

where T is the temperature, A the pre-exponential factor, $E_{a,\alpha}$ the apparent activation energy, $f(\alpha)$ the general expression of the kinetics model and R is the gas constant. The logarithm form of Eq. (5) leads to:

$$\ln(v)_{\alpha=\mathrm{const}} = \ln A + \ln f(\alpha) - \frac{E_{a,\alpha}}{RT} \tag{6}$$

where $(v)_{\alpha=\mathrm{const}}$ is the reaction rate for defined α. For α = const., the plot $\ln v_\alpha$ versus $(1/T)$, obtained from the conversional curve should be a straight line whose slope allows the evaluation of the apparent activation energy.

4. Results and discussion

The characteristic properties of the hydrogel sample used in this investigation, which have been determined by the methods described in our previous investigation [21], are summarized in Table 1.

The isothermal dependences of a specific amount of MEPBA released (c) versus interaction time from PAA hydrogel (kinetic curves) for different temperatures are shown in Fig. 1 and the dependences of MEPBA released degree (α) versus interaction time are shown in Fig. 2.

Three distinct ranges of the changes of the degree of MEPBA release with time can be clearly observed from the presented kinetics curves for the PAA hydrogel, i.e., a linear, non-linear and saturation range. In order to determine the influence of temperature on the shape of the kinetics curves the following

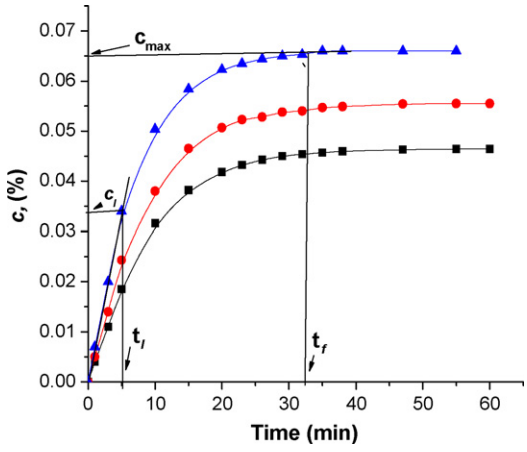

Fig. 1. The isothermal kinetic curves of released MEPBA from PAA hydrogel at (■) 22 °C, (●) 31 °C and (▲) 42 °C.

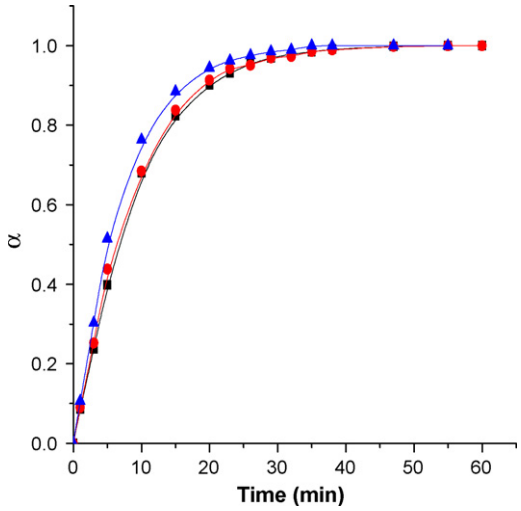

Fig. 2. A plot of α vs. time for (■) 22 °C, (●) 31 °C and (▲) 42 °C.

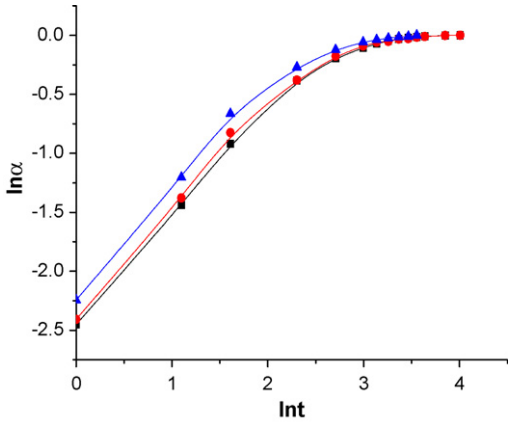

Fig. 3. The plot of $\ln\alpha$ vs. $\ln(t)$ for MEPBA release from PAA hydrogel at (■) 22 °C, (●) 31 °C and (▲) 42 °C.

parameters were defined: the time of range of linearity (t_l), the initial MEPBA release rate (v_{in}), the saturation time (t_f) and the saturation MEPBA release rate (v_f). The time of range of linearity (t_l) is the time interval within which the MEPBA release increases linearly with the interaction time. The initial MEPBA release rate is defined as the MEPBA release rate during this linear region of the conversion curve by the following equation:

$$v_{in} = \frac{c_l}{t_l} \tag{7}$$

where c_l is the concentration of MEPBA released at the final point of the linear region of the kinetic curve of MEPBA release and t_l is time that corresponds to this linear region of the kinetic curve.

The saturation time (t_f) represents the interaction time required to achieve the maximal concentration of released MEPBA in the solution (c_{max}) at a certain temperature, while the saturation MEPBA release rate can be calculated from the following equation:

$$v_f = \frac{c_{max}}{t_f} \tag{8}$$

The parameters of the shape of the kinetics curve parameters at different temperatures are given in Table 2, as well as the kinetic parameters calculated for the initial and saturation phase.

According to the results given in Table 2 it can easily be seen that the values of t_l and t_f decrease while those of v_{in} and v_f increase as temperature increases. Since the increase of v_{in} and v_f with temperature is exponential, the kinetic parameters of the initial and saturation phase of the MEPBA release from PAA hydrogel ($E_{a,in}$, $\ln A_{in}$, $E_{a,f}$, $\ln A_f$) can be determined by applying the Arrhenius equation. The obtained results are also given in Table 2. As it can be seen from the obtained results, the activation energy for the initial stage of the MEPBA release ($E_{a,in}$ = 26.6 kJ/mol) is dramatically higher than the activation energy for the saturation phase of the same process ($E_{a,f}$ = 5.4 kJ/mol). The same pattern is followed by the values of the preexponential factor ($\ln A$) but with a smaller difference in magnitudes between the stages.

In order to determine the kinetics' parameters of MEPBA release from PAA hydrogel, the results were analyzed by applying the linearized form of the so-called power law equation (4) (Eq. (9)):

$$\ln\alpha = \ln k + \ln t \tag{9}$$

When the plot of $\ln\alpha$ versus $\ln(t)$ gives a straight line, it is possible to determine the values of the diffusion exponent (n) and the apparent release rate (k) from the slopes and intercepts of these straight lines. Fig. 3 presents the plot of $\ln\alpha$ versus $\ln(t)$ for MEPBA release from PAA hydrogel at different temperatures.

As can be seen from Fig. 3, a plot of $\ln\alpha$ versus $\ln(t)$ did not give a straight line throughout the entire range of the investigated release process. From the plot of $\ln\alpha$ versus $\ln(t)$ (Fig. 3) the kinetic parameters, n and k, were calculated for the range within which the data is linear, i.e., for corresponding range of applicability (L). The obtained results of the determined parameters (n and k) and the range of applicability for the determined parameters are presented in Table 3.

Table 2
The parameters of the conversion curve for MEPBA release from PAA hydrogel at different temperatures

Temperature (°C)	t_l (min)	v_{in} (min^{-1})	t_f (min)	v_f (% min^{-1})	c_{max} (%)	Kinetic parameters	
						Initail stage	Saturation stage
22	8.00	3.25×10^{-3}	37	0.027	0.046	$E_{a,in}$ = 26.6 kJ/mol,	$E_{a,f,}$ = 5.4 kJ/mol,
31	6.70	4.33×10^{-3}	35	0.028	0.055	$\ln A_{in}$ = 5.11 min^{-1},	$\ln A_f$ = 1.42 min^{-1},
42	5.44	6.43×10^{-3}	32	0.031	0.066	R = 0.998	R = 0.973

Table 3
The kinetic parameters and range of applicability (L) for MEPBA release from PAA hydrogel

Temperature (°C)	n	$\ln k$	k (min^{-1})	L (%α)	Kinetic parameters
22	0.907	−2.435	0.088	8.6–68.1	E_a = 9.42 kJ/mol,
31	0.898	−2.372	0.93	9.0–68.5	$\ln A$ = 1.38 min^{-1},
42	0.877	−2.194	0.111	10.6–76.3	R = 0.974

As it may be seen from the results presented in Table 3, it was possible to determine the kinetic parameters, n and k, for MEPBA release from PAA hydrogel for the range of applicability of α = 10–70%. As could also be easily seen, the rate constant k increases with temperature increase, meanwhile the release exponent (n), whose value is about 0.9, slightly decreases. These changes might indicate the possible changes of the mechanism with temperature increase of MPEBA release from PAA hydrogel. It was possible to determine the kinetic parameters (E_a and $\ln A$) because the rate constant "k" shows Arrhenius dependence on temperature changes. The obtained value for activation energy was E_a = 9.42 kJ/mol, which is significantly lower than the activation energy for the initial stage of the MEPBA release ($E_{a,in}$ = 26.6 kJ/mol) and higher than the value of the activation energy for saturation stage of the same process ($E_{a,f}$ = 5.4 kJ/mol).

Because the obtained values of the kinetic parameters for the different stages of the investigated process of MEPBA release kinetics are somewhat different, another method, the so-called "model of reduced time" [23] was applied. In accordance with that procedure, the experimentally determined conversion curve $\alpha_{exp} = f(t)_T$ was transformed into the so-called universal conversion curve $\alpha_{exp} = f(t_N)_T$. The reduced time, t_N, was introduced to normalize the time interval of the monitored process. The t_N was defined by the following equation:

$$t_N = \frac{t}{t_{0.9}} \quad (10)$$

where $t_{0.9}$ is the moment in time at which α = 0.9. By applying the reduced time, it was possible to calculate the universal conversional curves for the different kinetics models [24]. The kinetics model of the investigated process was determined by comparing (graphically and analytically, using the sum of sqauares of the residual) the experimentally determined curves with the theoretical curves. The chosen kinetics model is the one for which the sum of sqauares of the residual is minimal.

A set of the reaction kinetics models used to determine the model which best describes the kinetics of the MEPBA release process from PAMA hydrogel is shown in Table 4.

Fig. 4 shows the plot $\alpha = f(t_N)$ for the selected theoretical kinetics model (F1 and R3) presented in Table 4 and the exper-

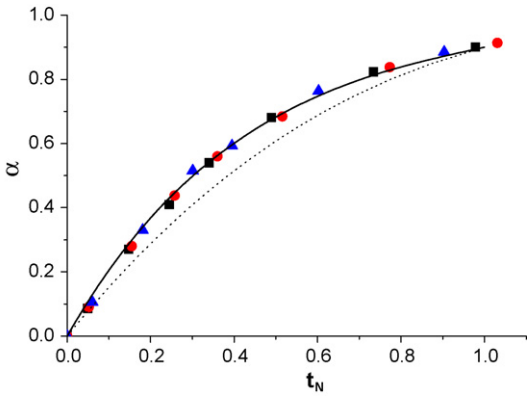

Fig. 4. The plot of $\alpha = f(t_N)$ for the theoretical kinetics reaction models: F1 (solid curve, –) and R3 (dot curve, . . .) and the experimental plots of $\alpha = f(t_N)$ at: (■) 22 °C, (●) 31 °C and (▲) 42 °C.

Table 4
The set of the kinetics models used to determine the kinetics model of MEPBA release process from PAA hydrogel [25]

Model	Reaction mechanism	General expression of the kinetics model, $f(\alpha)$	Integral form of the kinetics model, $g(\alpha)$
P1	Power law	$4\alpha^{3/4}$	$\alpha^{1/4}$
P2	Power law	$3\alpha^{2/3}$	$\alpha^{1/3}$
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–Erofe'ev	$2(1-\alpha)[-\ln(1-\alpha)]^{1/2}$	$[-\ln(1-\alpha)]^{1/2}$
A3	Avrami–Erofe'ev	$3(1-\alpha)[-\ln(1-\alpha)]^{2/3}$	$[-\ln(1-\alpha)]^{1/3}$
A4	Avrami-Erofe'ev	$4(1-\alpha)[-\ln(1-\alpha)]^{3/4}$	$[-\ln(1-\alpha)]^{1/4}$
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	$3/2[(1-\alpha)^{-1/3}-1]$	$(1-2\alpha/3)-(1-\alpha)^{2/3}$

Table 5
The values of the model's constant for the rate of MEPBA release (k_M) at different temperatures from PAA hydrogel

Temperature (°C)	k_M min^{-1}	L (%α)	Kinetic parameters
22	0.1169	0–99	$E_{a,M} = 7.81 \pm 0.1$ kJ/mol,
31	0.1265	0–99	$\ln A_M = 1.03$ min^{-1},
42	0.1428	0–99	$R = 0.991$

imental plots of $\alpha = f(t_N)$ for the MEPBA release process from PAA hydrogel at the investigated temperatures.

According to the results shown in Fig. 4, it can be stated with great assurance that the kinetics of MEPBA release from PAA hydrogel at all of the investigated temperatures can best be described with the kinetic model F1 ($\sigma = 10^{-4}$), which corresponds to the first-order chemical reaction:

$$-\ln(1-\alpha) = k_M t \tag{11}$$

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

The isothermal dependences of a $-\ln(1-\alpha)$ versus interaction time for MEPBA release from PAA hydrogel are shown in Fig. 5.

Table 5 shows the values of the model's constant for the rate of MEPBA release from PAA hydrogel at different temperatures which was obtained from the slopes of the isothermal dependences $-\ln(1-\alpha)$ on the time of the drug release (Fig. 5).

Since the increase of the model's constant with temperature is exponential, the model's kinetics parameters (activation energy ($E_{a,M}$) and pre-exponent factor ($\ln A_M$)) of MEPEBA release from PAA hydrogel are determined by applying the Arrhenius equation. The obtained results are also given in Table 5. According to that, it was found that the activation energy of the MEPBA release for the entire process which was determined on the basis of the model constant for the rate of MEPBA release (k_M) had a value of 7.81 kJ/mol, as well as, the pre-exponential factor ($\ln A$) was 1.03. Although these values for the kinetic parameters are the closest to those calculated from the initial MEPBA release rate and the power law equation, they are significantly dissimilar from the values obtained on the basis of the saturation MEPBA release rate.

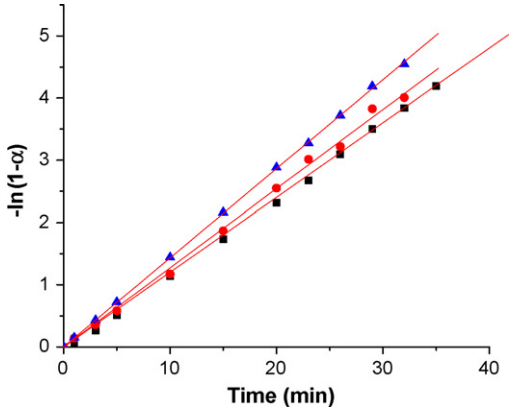

Fig. 5. The plots of $-\ln(1-\alpha)$ vs. interaction time at: (■) 22 °C, (●) 31 °C and (▲) 42 °C.

The isothermal kinetic of the drug (MEPBA) release from PAA hydrogel is assumed to be predetermined with the kinetic of the MEPBA transfer from its solution to the xerogel/hydrogel and with the kinetic of absorption of the external medium to the hydrogel.

The established existence of limited quantity of the equilibrium concentration of MEPBA in the external medium, the increase of the equilibrium concentration of the MEPBA in the external medium with temperature increase, and also the possibility to describe the kinetic of the investigated process with the kinetic model of the first-order chemical reaction, indicate that the kinetic of the MEPBA release from hydrogel can be considered as reversible first-order chemical reaction. Accordingly to that, it can be described with the following scheme (12):

$$A^* \underset{k_{ab}}{\overset{k_t}{\Leftrightarrow}} A \tag{12}$$

where A^* is MEPBA concentration in its solution in the hydrogel; A the MEPBA concentration in the external medium; k_t the constant of the MEPBA transfer rate from its solution in the hydrogel to the external medium and k_{ab} is constant of the MEPBA absorption rate from its external medium to the hydrogel.

Lets denote with A_0^* and A_∞^* the concentrations of the MEPBA in its solution in the hydrogel in time $t = 0$ and $t = \infty$, respectively, and with A_0 and A_∞ the concentrations of the MEPBA in the external medium in time $t = 0$ and $t = \infty$. According to the law of conservation of matter, the following is valid:

$$A_0^* + A_0 = A^* + A = A_\infty^* \tag{13}$$

i.e.:

$$A^* = A_\infty^* + A_\infty - A \tag{14}$$

Because:

$$v = \frac{dA}{dt} = k_t A^* - k_{ab} A \tag{15}$$

The introduction of Eq. (14) in Eq. (15) gives the following equation:

$$v = \frac{dA}{dt} = k_t(A_\infty^* - A_\infty - A) - k_{ab} A \tag{16}$$

Bearing in mind that:

$$k_t A_\infty^* = k_{ab} A_\infty \quad \text{i.e.} \quad A_\infty^* = \frac{k_{ab} A}{k_t} \tag{17}$$

We can get the expression for the rate of the reversible first-order chemical reaction:

$$v = \frac{dA}{dt} = (k_t + k_{ab})(A_\infty - A) \tag{18}$$

If we denote with $\alpha = A/A_\infty$, expression (18) is transformed to the following equation:

$$v = \frac{dA}{dt} = (k_t + k_{ab})(1 - \alpha) \tag{19}$$

Accordingly, to that, model's constant of the rate of the reaction of the MEPBA release (k_m) is equal to the sum of constants k_t and k_{ab}, i.e.:

$$k_m = k_t + k_{ab} \tag{20}$$

Bearing in mind that:

$$E_a = RT^2 \left(\frac{d\, v/dT}{v} \right) \tag{21}$$

by using the expression (19), it is easy to obtain the expression for effective activation energy of MEPBA release for the reversible first-order chemical reaction ($E_{a,R}$) which is kinetically predetermined with the reversible first-order chemical reaction (22):

$$E_{a,R} = \frac{k_t E_{a,t} + k_{ap} E_{a,ab}}{k_t + k_{ab}} \tag{22}$$

where $E_{a,t}$ is activation energy of the MEPBA transfer from its solution in the hydrogel to the external medium, $E_{a,ab}$ the activation energy of the MEPBA absorption from the external medium to the hydrogel and $E_{a,R}$, is effective activation energy which is independent on the degree of released drug but is predetermined with the kinetic parameters of the MEPBA transfer from its solution in the hydrogel to the external medium and with the MEPBA absorption from the external medium to the hydrogel.

Experimentally determination of A_0^*, A^* and A_∞^*, and consequently determination of the constant of the MEPBA transfer rate from its solution in the hydrogel to the external medium (k_t) is an especially complex procedure. Thus, we try to determine the constant of the MEPBA absorption rate from its external medium to the hydrogel (k_{ab}) in order to approve the previously given kinetic model.

Fig. 6 presents kinetic curves of isothermal absorption of the external MEPBA solution in the hydrogel. The MEPBA concentration corresponds to the maximal experimentally found concentration of MEPBA released and experiments were undertaken at same temperatures as MEPBA release experiments.

Assuming that kinetic of absorption of the external solution of the MEPBA in the hydrogel can be modeled with the kinetic of first-order chemical reaction, dependence $\ln AD/AD_{eq} - AD$

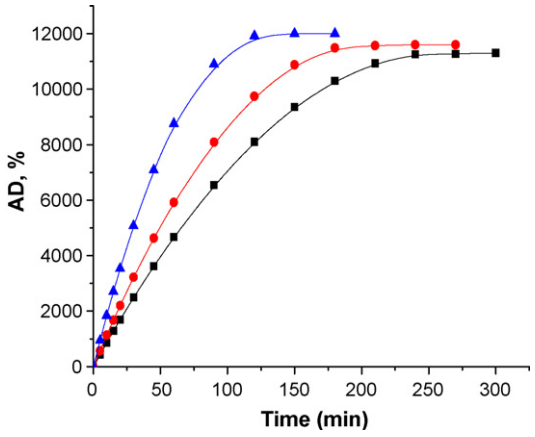

Fig. 6. Absorption of external solution in the hydrogel at: (■) 22 °C, (●) 31 °C and ▲ 42 °C.

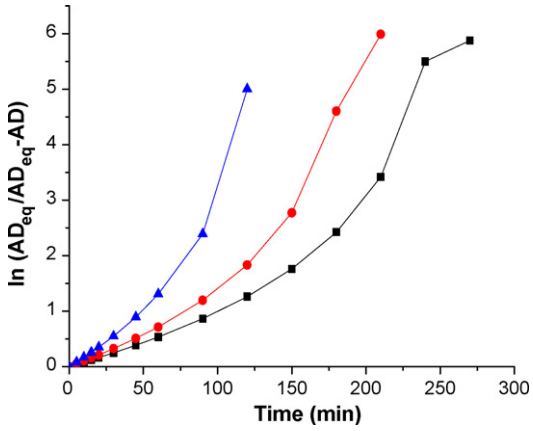

Fig. 7. A plot of $\ln AD_{eq}/AD_{eq} - AD$ vs. time at: (■) 22 °C, (●) 31 °C and (▲) 42 °C.

from time was assessed. In that case, a plot of $\ln AD/AD_{eq} - AD$ versus time should give straight lines with slopes giving the values of the constant of the MEPBA absorption rate from its external medium to the hydrogel (k_{ab}).

Fig. 7 presents dependence of $\ln AD_{eq}/AD_{eq} - AD$ from time for the absorption of external MEPBA solution at investigated temperatures.

As can be seen from Fig. 7, the plots of $\ln AD_{eq}/AD_{eq} - AD$ as a function of time give straight lines only a limited range of the degree of absorption (that are the range of applicability (L). Only for these parts of the investigated absorption process, from the slopes of the straight lines it was possible to determine the constant of the MEPBA absorption rate from its external medium to the hydrogel ($k_{ab,1}$).

Table 6 presents the influence of temperature on the range of applicability (L) and the absorption rate constants ($k_{ab,1}$). As absorption temperature increases absorption rate constants also increase while their ranges of applicability decrease.

The kinetic parameters (activation energy ($E_{a,ab}$) and pre-exponent factor ($\ln A_{ab}$)) for the MEPBA absorption from its external medium to the hydrogel were determined by applying the Arrhenius equation, since the increase of the absorptions rate constants with temperature was exponential. The obtained results are also given in Table 6.

By applying the previously described method of "model of reduced time" it was established that kinetic of absorption of the external solution of MEPBA in the hydrogel, can be described in entire with the model "R2" which is characteristically for the "phase boundary controlled reaction" (see Table 4). That would

Table 6
The influence of temperature on the absorptions rate constants ($k_{ab,1}$) and their ranges of applicability (L) and correlation coefficients (R)

Temperature (°C)	L (%)	R	$k_{ab,1}$ (min^{-1})	Kinetic parameters
22	0–71.7	0.996	0.01031	$E_{a,ab,l} = 32.07$ kJ/mol,
31	0–69.8	0.996	0.01308	$\ln A_{ab,l} = 8.38$ min^{-1},
40	0–59.0	0.998	0.01979	$R = 0.997$

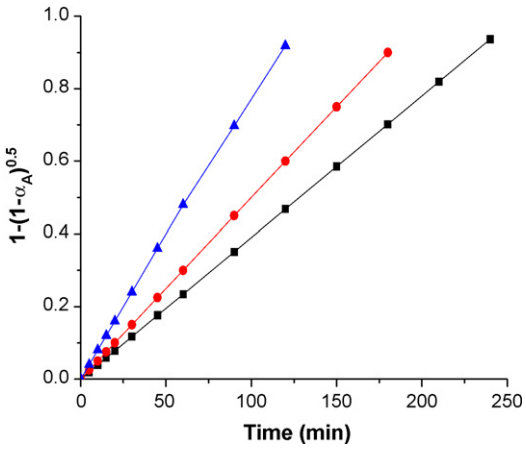

Fig. 8. A plot of $1-(1-\alpha_A)^{1/2}$ vs. time at: (■) 22 °C, (●) 31 °C and (▲) 42 °C.

imply that the following expression should be valid:

$$1-(1-\alpha_A)^{1/2} = k_{m,ab}t \quad (23)$$

where $k_{m,ab}$ is the model's constant rate.

Fig. 8 presents the dependence $(1-(1-\alpha)^{1/2})$ on time at different investigated temperatures, for absorption of the external solution of MEPBA in the hydrogel.

The dependence $(1-(1-\alpha_A)^{1/2})$ on time, at all of the investigated temperatures for almost whole range of the process absorption of external MEPBA solution (range of applicability $L \geq 94\%$) gave straight lines. The true value of the model's absorptions rates constants ($k_{m,ab}$) were determined based on these slopes. Table 7 shows the influence of temperature on the changes of degree of applicability of applied model and the model's absorptions rates constants ($k_{m,ab}$).

Based on the obtained results that are presented in Table 7, it is easy to observe that as the temperature of absorption increases the model's absorptions rates constants ($k_{m,ab}$) increase as well.

Based on Eq. (20) and on the known values of constants k_m and k_{ab}, the constant k_t was determined and presented in Table 8, column 2. Since the increase of the constants of the MEPBA transfer rate from its solution in hydrogel to the external medium (k_t) with temperature was exponential, the kinetics parameters of the MEPBA transfer from its solution in hydrogel to the external medium were determined by applying the Arrhenius equation and the obtained results are given in Table 8. Also, the values for effective activation energy of MEPBA release for the reversible first-order chemical reaction ($E_{a,R}$) calculated by using Eq. (22) are presented in Table 8.

The established data that the MEPBA absorption from the external solution can describe only in limited range of the absorption degree with the kinetic's model of the first-order chemical reaction, in significant part makes suspicion to the state that the kinetic of the MEPBA release from the hydrogel can be described with the model of the reversible first-order chemical reaction.

Also, according to the kinetic model of reversible first-order reaction the MEPBA release process from hydrogel, described with Eq. (22) is independent on the degree of MEPBA released. In order to examine the dependence of the activation energy of the investigated drug release process from PAA hydrogel on the degree of released MEPBA, the Friedman's iso-conversional method was applied. By using that method, activation energies for different degree of released MEPBA were determined. Fig. 9 presents the dependences $\ln v_{\alpha,T_i} = f(1/T)$ for different degrees of released MEPBA from PAA hydrogel.

As can be seen from the obtained results presented in Fig. 9, there was a linear relationship between the $\ln v_{\alpha,T_i}$ and the inverse temperature $(1/T_i)$ for all of the degrees of released MEPBA from PAA hydrogel. From the slopes and intercepts of these straight lines the values of the kinetics parameters ($E_{a,\alpha}$ and $\ln A_\alpha$) for each value of the degree of MEPBA released (α) have been obtained. The dependences of $E_{a,\alpha}$ versus α, and $\ln A_\alpha$ versus α are shown in Fig. 7.

As can be seen from the results presented in Fig. 10, both $E_{a,\alpha}$ and $\ln A_\alpha$ decreased almost linearly with an increase of the degree of MEPBA release from PAA hydrogel for $\alpha \leq 0.6$, while for $\alpha > 0.6$ $E_{a,\alpha}$ is about 8 kJ/mol and $\ln A_\alpha$ is about 2. By comparing these values of activation energies ($E_{a,\alpha}$) and pre-exponential factors ($\ln A_\alpha$), it may be concluded that the increase of $\ln A_\alpha$ also coincides with the increase of $E_{a,\alpha}$ and this is the so-called

Table 7
The changes of ranges of applicability (L), model rates constants ($k_{m,ab}$) and correlation coefficients (R) with temperature

Temperature (°C)	L (%)	R	$k_{m,ab}$ (min^{-1})	Kinetic parameters
25	0–94	1	0.0039	$E_{a,m,ab}$ = 26.6 kJ/mol,
30	0.94	1	0.005	$\ln A_{m,ab}$ = 5.28 min^{-1},
40	0–94	0.9997	0.00781	R = 0.993

Table 8
The values of constants k_t at different temperatures and the kinetic parameters of the investigated MEPBA transfer-absorption process

Temperature (°C)	k_t (min^{-1})	Kinetic parameters	
22	0.1130	$E_{a,t}$ = 6.82 kJ/mol,	$E_{a,R}$ = 7.48 kJ/mol,
31	0.1215	$\ln A_t$ = 0.60 min^{-1},	$E_{a,R}$ = 7.60 kJ/mol,
42	0.1350	R = 0.997	$E_{a,R}$ = 7.89 kJ/mol

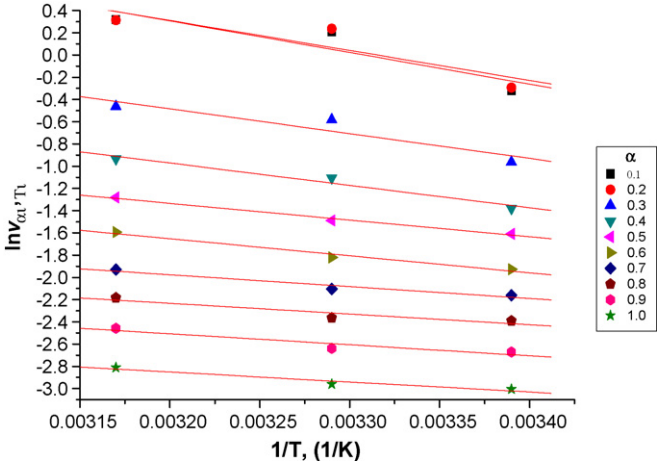

Fig. 9. The dependences of $\ln v_\alpha T_i$ on inverse temperature ($1/T$) for different degrees of MEPBA released.

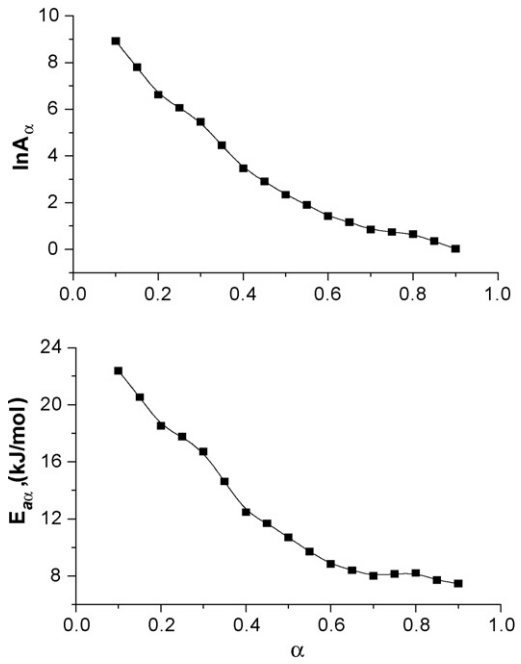

Fig. 10. The dependences of $E_{a,\alpha}$ and $\ln A_\alpha$ vs. degree of released MEPBA.

compensation effect [24,25]. Fig. 8 presents the changes of $\ln A_\alpha$ with $E_{a,\alpha}$ with changes of the degrees of MEPBA release.

As can be seen from the results presented in Fig. 11, the linear relationship between $\ln A_\alpha$ and $E_{a,\alpha}$ is obtained. The changes of the pre-exponential factor $\ln A_\alpha$ with activation energy at varying degrees of MEPBA release (α), can be expressed as

$$\ln A_\alpha = -3.9 + 0.57\, E_{a,\alpha} \tag{24}$$

The established dependence of activation energy on the degree of released MEPBA as well as the presence of compensation effect obscured the possible description of the MEPBA release kinetic with the model of reversible first-order chemical reaction. The linear decrease of the activation energy with the degree of released MEPBA in the range of $0 < \alpha < 0.6$, clearly imply that the MEPBA absorption, which is in connection the MEPBA desorption, has the dominant influence on the kinetics of MEPBA release.

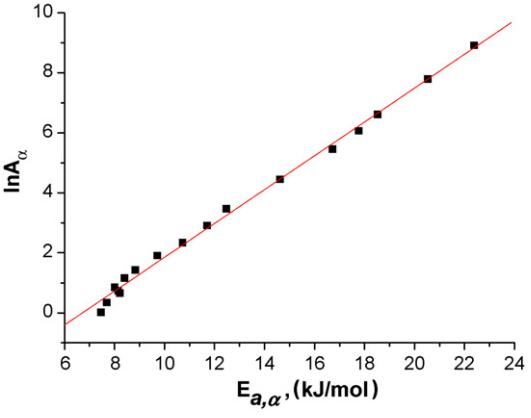

Fig. 11. A plot of $\ln A_\alpha$ dependence on $E_{a,\alpha}$ with changes of α.

Describing the MEPBA release from a hydrogel with a first-order chemical reaction model strongly supports that the investigated process of MEPBA release is a kinetically controlled reaction and that its kinetics depend highly on the rate of the MEPBA release of the MEPBA bonded to the hydrogels' active centers that are energetically distributed through the hydrogel. Because the kinetics of the MEPBA released are determined by the rate of MEPBA release from the active center, the experimentally determined dependence of the kinetic parameters from the degree of MEPBA release (α), the compensation effect and achievement of the maximal MEPBA release rate for low degrees of MEPBA release (i.e., the high values of E_a) could be explained with following proposal:

- On the hydrogel structure, there are active centers with different specific energy and energetic distributions.
- The degree of efficiency of the active center in the specific interaction is proportional to its own energy.
- The value of E_a for the release process is inversely proportional to the value of the specific energy of the active center.

Bearing that in mind, during the release process at low degrees of release and relatively low values of activation energy, active centers with low specific energies must participate. Active centers with low energies are more abundant than those with high energies due to their thermodynamics and the statistics of their requirements. Consequently, the $\ln A$ value is high as it is proportional to the mass concentration of the active centers and this explains the presence of the compensation effect, as well as the maximal rate of MEPBA delivery at the low degrees of the MEPBA release.

On the contrary, however, the active centers with high specific energies must participate when the degrees of the MEPBA release are high and E_a is low. Due to their sparse distribution, the $\ln A$ value is low and the rate of the process is minimal.

If it was assumed that the distribution of the active centers existed, then the function of distribution of the probable values of activation energies $f(E_a)$ could be defined. Because the model of first-order reaction kinetics can describe the kinetics of MEPBA release, the following equation is valid:

$$\alpha = 1 - \int_0^\infty \Phi(E_a,\ T) f(E_a)\, \mathrm{d}\, E_a \tag{25}$$

where $\Phi(E_a, T)$ is equated to

$$\Phi(E_a,\ T) = \exp\left(-A_0 \int_0^T \exp\left(-\frac{E_a}{RT}\right)\, \mathrm{d}T\right) \tag{26}$$

By using a variable $x = E_a/RT$, Eq. (26) is rewritten as follows:

$$\Phi(E_a,\ T) = \exp\left\{-\frac{A_0 E_a}{R}\frac{\mathrm{e}^{-x}}{x} - \int_x^\infty \frac{\mathrm{e}^{-x}}{x}\mathrm{d}\,x\right\}$$

$$= \exp\left\{-\frac{A_0 E_a}{R} p(x)\right\} \tag{27}$$

where $p(x)$ is the so-called "p-function" that is well known in the field of thermal analysis. By employing an approximation

$p(x) = e^{-x}/x^2$, we can write that

$$\Phi(E_a,\ T) = \exp\left[-\frac{A_0 RT^2}{E}\exp\left(-\frac{E_a}{RT}\right)\right] \quad (28)$$

To estimate the $f(E_a)$ curve from the experimental data of α versus time, the possibility of an approximate representation for Eq. (28) was examined. Since the $\Phi(E_a, T)$ function changes rather steeply with activation energy at a given temperature, it seems to be reasonable to assume $\Phi(E_a, T)$ that by the step function U at an activation energy $E_a = E_{a,s}$ as

$$\Phi(E_a,\ T) = U(E_a - E_{a,s}) \quad (29)$$

This approximation assumes that it is only single reactions whose activation energy is E_s at a given temperature T. Then Eq. (25) is simplified to:

$$\alpha = 1 - \int_{E_{a,s}}^{\infty} f(E_a)\,dt \quad (30)$$

According to Eq. (29) we can write that:

$$\alpha = 1 - \int_{0}^{E_s} f(E_a)\,dE_a \quad (31)$$

therefore, $f(E_a)$ is given by differentiating Eq. (29) by $E_{a,s}$ as

$$f(E_s) = \frac{d\alpha}{dE_s} \quad (32)$$

Thus, the density distribution function of activation energies could be directly obtained by differentiating the experimentally determined relationship: α versus E, i.e., $f(E_a) = d\alpha/dE_a$. Fig. 12 shows the density distribution function of activation energies $f(E)$ for MEPBA release from PAA hydrogel.

The density distribution function of activation energies shows a well-designed maximum at $\bar{E}_a = 8.14$ kJ/mol. That E_a value is in good correspondence with the E_a value obtained from the model constant of MEPBA release from PAA hydrogel and the $E_{a,\alpha}$ value that was determined by applying Friedman's iso-conversion method for $\alpha > 0.6$.

Accordingly to that, the established kinetic of MEPBA release cannot be described with the model of reversible first-order chemical reaction. With great degree of assurance, we can state that the MEPBA release process from PAA hydrogel, almost in entire range can be described with the model of the drug (MEPBA) desorption from the active centers with different specific energies.

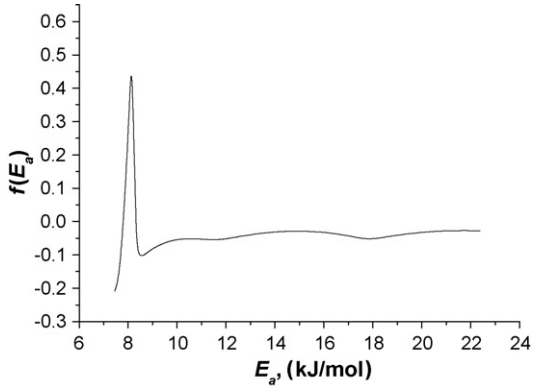

Fig. 12. The function of the density distribution $f(E_a)$ for MEPBA release from PAA hydrogel.

5. Conclusions

The process of MEPBA release from the PAA hydrogel into a water solution is a complex heterogeneous process that can be kinetically described with the model of first-order reactions kinetics. The kinetic parameters (E_a, $\ln A$) vary with the degree of MEPBA release (α). The distribution of activation energies is a consequence of the energetic heterogeneity of the active centers. The function of density distribution of the probability of activation energies shows a well-signed maximum for $E_a = 8.14$ kJ/mol. That E_a value is in good correspondence with the E_a value obtained from the model constant of MEPBA release from PAA hydrogel and the $E_{a,F}$ value which was determined by applying Friedman's iso-conversion method for $\alpha > 0.6$.

The established kinetic of MEPBA release cannot be described with the model of reversible first-order chemical reaction. With great degree of assurance, we can state that the MEPBA release process from PAA hydrogel, almost in entire range can be described with the model of the drug (MEPBA) desorption from the active centers with different specific energies.

Acknowledgement

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