Journal of Physical and Theoretical Chemistry
of Islamic Azad University of Iran, 16 (1, 2) 37-47: Spring & Summer 2019
(J. Phys. Theor. Chem. IAU Iran)
ISSN 1735-2126

A deductive kinetic study of diclofenac release from chitosan-based magnetic nanocomposite hydrogels

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Received October 2019; Accepted January 2020

ABSTRACT

A descriptive study of isothermal kinetics of diclofenac release from chitosan-*g*-acrylic acid (Chit-AA) hydrogel and chitosan-*g*-(acrylic acid-*co*-[2-(acryloyloxy)ethyl]trimethylammonium chloride) (Chit-AA-AETM) hydrogel was carried out. Isothermal kinetic curves for diclofenac release from both hydrogels in distilled water at various temperatures of 20-42°C were studied. The fit method of the famous model was used to determine the kinetic models of both the drug release process and the external solvent absorption onto the hydrogel. Based on the fixed dependencies of kinetic parameters (LnA, E_a) on the amount of abandoned diclofenac (α) in the presence of compensatory effect, the function of the new molecular mechanism of a drug transfer process was investigated. According to that mechanism, drug release is considered as an isolation of the drug from the active separation centers of various hydrogels with different energies.

Keywords: drug delivery systems; isothermal kinetics; hydrogel; drug release

INTRODUCTION

Hydrogel is a mobile system that can be used both for loading and for release of solutions with specific therapeutic properties. To further develop the use of hydrogel as a means of drug loading and drug release, and to optimize the function of a drug, we must know both the key parameters and the mechanism that controls the kinetics of drug release from the hydrogels. There are several mathematical models that have been developed to describe drug release profiles. Most reports indicate that drug release is highly dependent on a variety of factors, such as a polymer composition, hydrogel geometry, infiltration, decomposition and dissolution in hydrogel. Based on the control phase for controlled release, there are three known kinetic patterns for drug release in an updated source. In such a case, the kinetics of drug release were analyzed by the Fick equation or empirical equation [1-5].

This model is specially designed for systems where the release of the drug is performed through the exposure of the elastic and glass surfaces of the swollen hydrogels. Drug release kinetic pattern for hydrogel transfer systems is chemically controlled and is mainly mathematical and semi-experimental [6]. The process of drug release from the hydrogel can be thought of as a combination of the process of drug decomposition and its transfer through hydrogel and the separation of solvents between the solvent and hydrogel phase.

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The proposed mathematical model predicts the total release rate of drug from the networks of hydrogels. For this study, diclofenac, as an anti-inflammatory drug, has been used for investigating of this model by using two chitosan-based nanocomposite hydrogels.

EXPERIMENTAL

Materials

In this paper, chitosan (shanghai china), acrylic acid (AA) and [2-(acryloyloxy)ethyl]trimethylammonium chloride (AETM), Ammonium persulfate (APS), $FeCl_2.4H_2O$, $FeCl_3.5H_2O$, ammonium hydroxide from Merck, were analytical grades and were used without additional purification. Double distilled water was used for hydrogel preparation and swelling measurements.

Preparation of hydrogel

Ammonium persulfate was used as a radical initiator and a mixture of iron II and III as a crosslinking agent as follows:

First, 1 g of chitosan was dissolved in 40 ml acetic acid 1% v/v in a reactor equipped with a mechanical stirrer and heated to 85°C. Then, 0.12 g of ammonium persulfate in 5 ml of distilled water was added to the above solution. After 5 minutes, a certain amount of AA alone or with AETM are added to the mixture. After one hour, a mixture of $FeCl_2$ and $FeCl_3$ as a crosslinking agent were added to the solution. After a certain period of time, the ammonia solution is added to form a solution of iron oxide nanoparticles. The prepared gel is first placed in ethanol and then in the oven for 24 hours to dry (at 50 °C). After grinding, the obtained powder was stored in the absence of moisture, heat, and light for further experiments. The amounts of the starting materials used for two different hydrogels are summarized in Table 1.

Measurement of the hydrogel swelling rate

0.05 g of superabsorbent hydrogel with mesh (40-60) was immersed in 250 ml of distilled water. Soak for 2 hours at ambient temperature and then the swollen sample is poured into the filter and after 15 minutes (minutes) weighs. The swelling equilibrium (S_e) of sample was determined from the following equation:

$$s_e = \left(\frac{w_s - w_d}{w_d}\right) \quad (1)$$

In the above equation, W_s is the weight of swollen hydrogel, W_d is the weight of dry hydrogel.

Characteristics of Zerogel Combinations

Zerogel samples were characterized by the following structural features: The density of zerogel (ρ_{xg}), the total density (ρ_c) and the distance between macromolecular chains (d) was determined according to the methods proposed by Goodman and Peppas (equations 2 and 3). The apparent density of the composite sample was determined by pycnometric method using non-solvent n-hexane [7]:

$$\rho_c = \frac{\rho_{xg}}{M_c} \quad (2)$$

$$d = 0.154 v_2^{1/3} [0.19 M_c]^{1/2} \quad (3)$$

Table 1. Amount of reaction contents used in different sample preparations.

Hydrogel name	Fe^{2+}, g	Fe^{3+}, g	AA, g	AETM, g	APS, g	Swelling, g/g
Chit-AA	0.23	0.8	5	-	0.12	460
Chit-AA-ATEM	0.0662	0.1662	3	1	0.12	320.6

where M_c is the molar conglomeration between the global network connections and the relative value of the first combination:

$$M_c = \frac{36}{X_C} \quad (4)$$

where X_c is a relative nominal global connection (transverse connector moles and monomer molecules in the reaction composition)(Table 2).

Loading diclofenac

Diclofenac is loaded on zerogel in a solution of drug (50 ml, 25%) at various temperatures 5°C, 35°C and 40°C. The released material was detected using uv-visible spectroscopy at 298 nm and an effective amount of released drugs (Ce%) using Equation 2 as follows [8]:

$$C = \frac{pV}{m_x X} * 100 \quad (5)$$

where p is the concentration of diclofenac in solution at time t (g/ml), V is volume of solution (ml), m_x is the weight of the zerogel (g) and X is a special drug loaded in g/g of hydrogel .The amount of released diclofenac drug(α) is calculated as the effective ratio of drug concentration at time t and the amount of released diclofenac drug C_{max} [9]:

$$\alpha = \frac{C}{C_{max}} \quad (6)$$

The isothermal adsorption rate (AD) as the difference between the weight of the hydrogel sample at time t (m_t) and the weight of the zerogel (m_0) is:

$$AD(\%) = \frac{m_t - m_0}{m_0} * 100 \quad (7)$$

The absorption rate (AD_{eq}) of the hydrogel absorption is in a balanced state [10,11]. Normal adsorption (α_A) rate was determined and measured as the ratio of AD absorption at time t and the AD_{eq} absorbance amount for a given temperature:

$$\alpha_A = \frac{AD}{AD_{eq}} \quad (8)$$

Methods used to evaluate kinetic parameters

The experimental equation proposed by Peppas was used to determine the kinetic parameters of diclofenac release from Chit-AA and Chit-AA-ATEM hydrogels. The results were analyzed using the Pepps first order equation [13]:

$$-\mathrm{Ln}(1-\alpha) = k_M t \quad (9)$$

where α is the amount of diclofenac released at time t, k_M is the coefficient of apparent release and t is the time of interaction.

Isoconversion Friedman Method

The kinetic data motion analysis is based on the following equation:

$$(\frac{d\alpha}{dt})_{\alpha=const} = Af(\alpha)e^{-Ea/RT} \quad (10)$$

in which T is temperature, A is pre-factor exponential Arrhenius, E_a is the apparent activation energy, $f(\alpha)$ is the general symbol of the kinetic model and R is the gas constant.

Table 2. Loading of dilcofenac drug (X_c) in Chit-AA and Chit-AA-ATEM hydrogels.

Chit-AA		***Chit-AA-ATEM***	
X [g/g]	***T [°C]***	***X [g/g]***	***T [°C]***
0.610472973	25	0.706841216	25
0.795692568	35	0.834037162	35
0.867652027	40	0.844341216	40

RESULTS AND DISCUSSION

Isothermal dependencies of specific amount of drug release versus time (kinetic curves) for various temperatures are shown in Fig. 1. Three different range (linear, nonlinear, and saturated) of specific variations of the diclofenac release considering the release time, can be clearly seen on the kinetic curves provided for the Chit-AA and Chit-AA-ATEM hydrogels. In order to determine the effect of temperature on the shape of kinetic curves, the following parameters were used:

Linear regime time (t_l), initial release rate (r_{in}), saturation time (t_f) and final release rate of diclofenac drug (r_f) is linear, in which the release of diclofenac is in parallel with the reaction time. The initial release of diclofenac as the amount of diclofenac release during this linear curve is determined by Equation 11 [14]:

$$r_{in} = \frac{C_1}{t_1} \qquad (11)$$

where C_l is a certain amount of the drug released at the final point of the linear region of the kinetic curve. Saturation time (t_f) is the interaction time to achieve the maximum concentration of diclofenac in the C_{max} solution at a given temperature. The release rate of the diclofenac drug can be obtained from the equation:

$$r_f = \frac{C_{max}}{t_f} \qquad (12)$$

The kinetic curve parameters at various temperatures can be determined for the initial phase and saturation shown in Table 3. According to the results, it is easy to see that the values of t_l and t_f are decreased while the values of r_{in} and r_f increased in case of temperature rise for the both hydrogels. Since the increase of r_{in} and r_f are obviously due to the rising of temperature, primary and saturated kinetic parameters of dilcofenac release include LnA_f, $E_{a,f}$, LnA_{in} and $E_{a,in}$, in hydrogels can be determined using the Arrhenius equation [15].

As can be seen from the results, activation energy for the first stage of diclofenac release of Chit-AA ($E_{a,in}$ = 24.942Kj) is much higher than that for the saturation phase of the same process ($E_{a,f}$=16.628Kj). The same pattern was observed in activation energy for the release of diclofenac from Chit-AA-ATEM. However, the values of the LnA for the release of the diclofenac from Chit-AA hydrogel are contrary to the LnA, for Chit-AA-ATEM hydrogel [16].

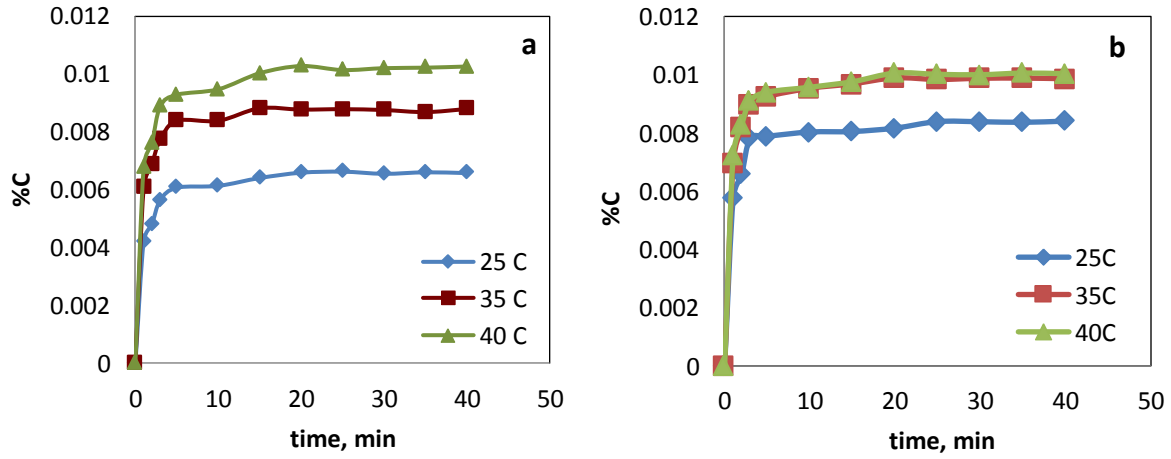

Fig. 1. Isothermal kinetic curves of the diclofenac drug released from a) Chit-AA hydrogel and b) Chit-AA-ATEM hydrogel at three temperatures of 25, 35 and 40°C.

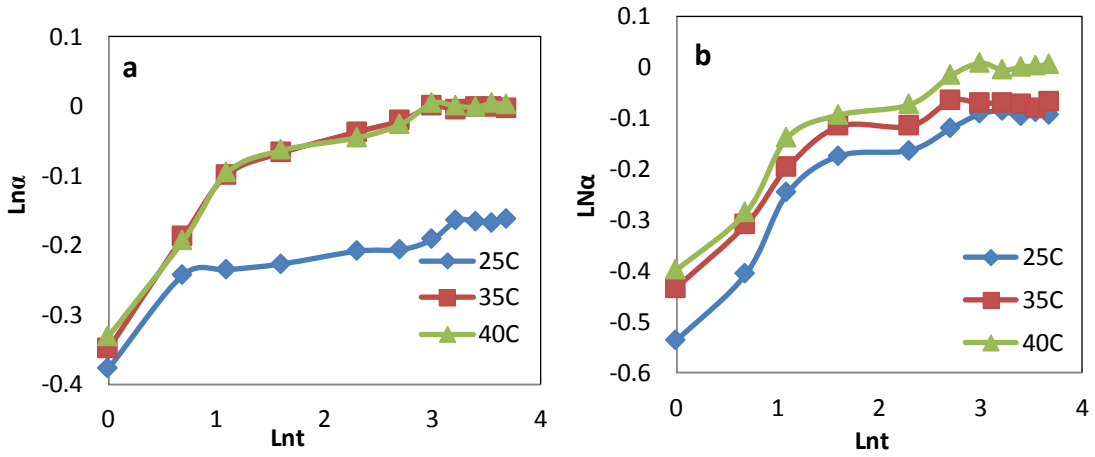

Fig. 2. *Lnα* plot against *Lnt* for diclofenac at different temperatures for a) Chit-AA and b) Chit-AA-ATEM.

The higher $E_{a,in}$ is higher than $E_{a,f}$ and a non-basic characteristic of the diclofenac release process of these hydrogels, for example, due to its complexity, shows both kinetic models and mechanisms. It can also be easily seen the values of $E_{a,in}$ for Chit-AA hydrogel are somewhat less than that for Chit-AA-ATEM hydrogel. While $E_{a,f}$ for the release of diclofenac drug from Chit-AA hydrogel, is much higher than that for Chit-AA-ATEM hydrogel.

To determine the release parameters of diclofenac drug from Chit-AA hydrogel and Chit-AA-ATEM hydrogel, the results were analyzed using the linear form of the experimental equation designed by Peppas (Equation 8). When the *Lnα* gives a straight line to *Ln (t)*, one can design the kinetics of the process under consideration with the proposed model from the slopes and sections of these straight lines.

Figure 2a, b show the *Lnα* pattern against *Ln(t)* at various temperatures for the release of diclofenac drug from Chit-AA hydrogels and Chit-AA-ATEM, respectively.

Table 3. Reverse curve parameters for release of diclofenac drug from Chit-AA and Chit-AA-ATEM hydrogels at different temperatures.

	t_l, min	T, ◦C	$r_{in,\%/min}$	$r_{f,\%/min}$	t_f, min	$C_{max,\%}$	Initial stage	Saturation stage
Chit-AA	4	25	0.00151751	0.00036605	18	0.022213	$E_{a,in}$=24.942 Kj R^2=0.9889	$E_{a,f}$=16.628 Kj R^2= 0.999
	3.5	35	0.00239508	0.00062972	14	0.029692		
	2.8	40	0.00331475	0.00078918	12	0.034654		
Chit-AA-ATEM	3	25	0.002189	0.00036407	23	0.028343	$E_{a,in}$=41.57 Kj R^2=0.9526	$E_{a,f}$=33.256 Kj R^2=0.9598
	2.5	35	0.002728	0.00049376	20	0.033268		
	2	40	0.002753	0.00057311	17	0.033849		

Table 4. Kinetic parameters (k_m) and application range l at different temperatures for release of diclofenac from Chit-AA and Chit-AA-ATEM hydrogels.

	T, ˚C	Lnk_m	k_m, min^{-1}	Kinetic parameters
Chit-AA	25	- 0.3147	0.729	E_a=12.259 Kj
	35	-0.2441	0.78258	
	40	-0.2491	0.77866	
Chit-AA-ATEM	25	-0.4435	0.6405	E_a=28.689 Kj
	35	-0.3447	0.7073	
	40	-0.3215	0.72405	

Table 5. Collection of kinetic models used to determine the best model for diclofenac release process from Chit-AA and Chit-AA-ATEM hydrogels

Model	Reaction mechanism	General expression of the kinetics model, f(α)	Integral form of the kinetics model, g(α)
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	$2/3\,\alpha^{-1/2}$	$\alpha^{3/2}$
P5	Zero-order (Polany-Winger equation)	1	α
P6	Phase-boundary controlled reaction (contracting area, i.e. bidimensional shape)	$2(1-\alpha)^{1/2}$	$[1-(1-\alpha)^{1/2}]$
P7	Phase-boundary controlled reaction (contracting volume, i.e. tridimensional shape)	$3(1-\alpha)^{2/3}$	$[1-(1-\alpha)^{1/3}]$
P8	First order (Mampel)	$(1-\alpha)$	$-\ln(1-\alpha)$
P9	Second order	$(1-\alpha)^{2}$	$(1-\alpha)^{-1}-1$
P10	Third order	$(1-\alpha)^{3}$	$0.5[(1-\alpha)^{-2}-1]$
P11	Avrami-Erofe'ev	$2(1-\alpha)[-\ln(1-\alpha)]^{1/2}$	$[-\ln(1-\alpha)]^{1/2}$
P12	Avrami-Erofe'ev	$3(1-\alpha)[-\ln(1-\alpha)]^{2/3}$	$[-\ln(1-\alpha)]^{1/3}$
P13	Avrami-Erofe'ev	$4(1-\alpha)[-\ln(1-\alpha)]^{3/4}$	$[-\ln(1-\alpha)]^{1/4}$
P14	One-dimensional diffusion	$1/2\,\alpha$	α^{2}
P15	Two-dimensional diffusion (bidimensional particle shape)	$1/[-\ln(1-\alpha)]$	$(1-\alpha)\ln(1-\alpha)+\alpha$
P16	Three-dimensional diffusion (tridimensional particle shape) Jander equation	$3(1-\alpha)^{2/3}/2[1-(1-\alpha)^{1/3}]$	$[1-(1-\alpha)^{1/3}]2$
P17	Three-dimensional diffusion (tridimensional particle shape) Ginstling-Brounshtein	$3/2[(1-\alpha^{)-1/3}-1]$	$(1-2\,\alpha/3)-(1-\alpha)^{2/3}$

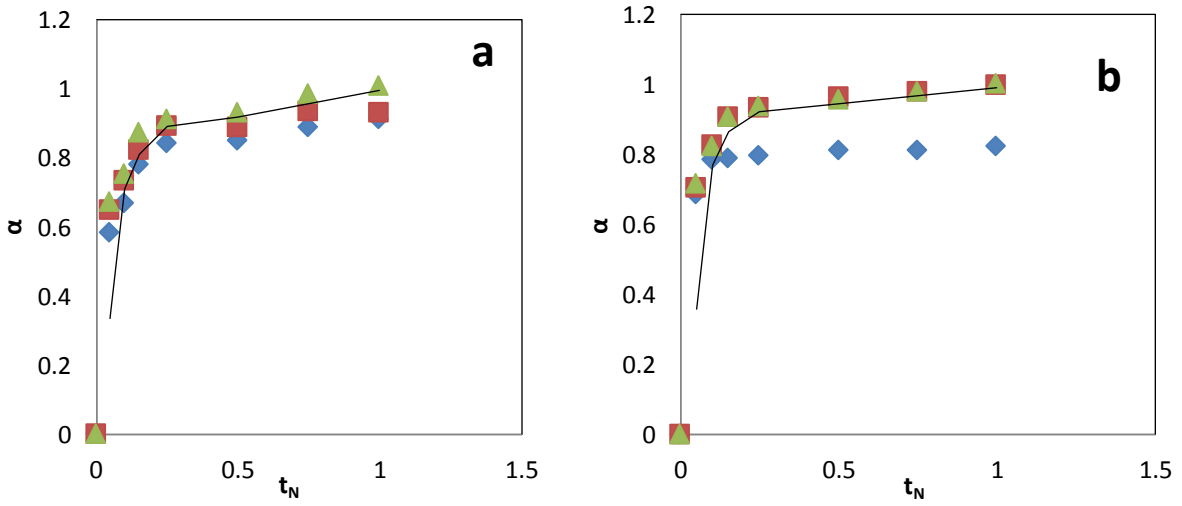

Fig. 4. Plan $\alpha = f(t_N)$ for theoretical kinetic motion patterns: F1 (Linear curve) and Rs (point curve) and experimental plot $\alpha = f(t_N)$ for a) Chit-AA hydrogel and b) Chit-AA-ATEM hydrogel at three temperatures of 25, 35, 40 °C.

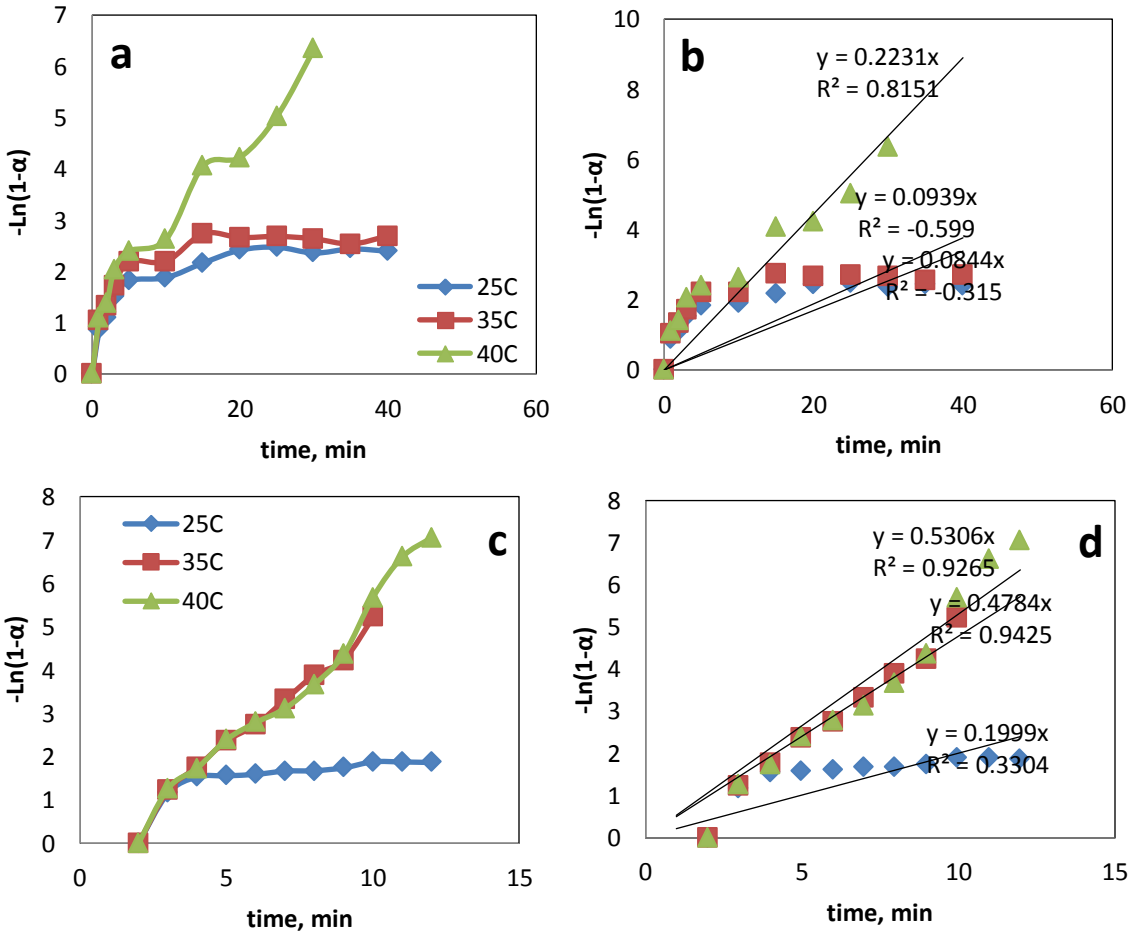

Fig. 5. -Ln (1-α) designs against the release time of diclofenac for a, b) Chit-AA hydrogel and c, d) Chit-AA-ATEM hydrogel at three temperatures of 25, 35, 40 °C.

As shown in Figures 2a and 2b, *Lnα* versus *Ln(t)* produced straight lines in the limited domains of the release process in both hydrogels. The kinetic parameters E_a and k_m were calculated for those internal domains from the slopes and sections of these straight lines. The results was shown in Table 4. As can be seen, determination of k_m parameter for release of diclofenac from Chit-AA hydrogel is in application range of 25-60% α and for Chit-AA-ATEM hydrogel is 15-55% α. Also, diclofenac release from Chit-AA hydrogel was reached to the steady state, k_m value rises with increasing temperature.

These changes may indicate alteration in the mechanism by increasing the temperature in the release of diclofenac from both hydrogels. It can even determine the kinetic parameters of *LnA*, E_a. The amount of activation energy for Chit-AA hydrogel was equivalent to E_a=12.259Kj, which is much lower than the activation energy for the initial release stage ($E_{a,in}$= 24.942Kj) and the activation energy of the saturation stage ($E_{a,f}$ = 16.628Kj). The same observation are obtained for diclofenac release from Chit-AA-ATEM hydrogel (E_a= 28.689Kj, $E_{a,f}$=33.256Kj and $E_{a,in}$=41.57Kj). Since the obtained values of the kinetic parameters for the various stages are varied, the kinetics of diclofenac release is different.

The kinetic response pattern is classified into five groups according to the reaction mechanism:

1-Reaction of the power mechanism
2-Controlled reaction phase
3-Sequential response
4-The reaction described by the deformation equation
5-.Controllable reactions of isolation

In fitness model $\alpha = f(t_N)$, which became the world-famous inverse model, t_N was known at the time. The t_N was chosen to normalize the interval of monitoring process and was chosen by:

$$t_N = \frac{t}{t_{0.9}} \quad (13)$$

where $t_{0.9}$ is time to reach the α =0.9. By applying the time of reduction, it was possible to apply global inverse curves for different kinetic models. The chosen kinetic pattern is a pattern in which the sum of the remaining squares is minimal [18]. A set of kinetic models is used to determine the model which best performs the diclofenac release process. As shown in Table 5, Figures 3a and 3b, designs for the selected theoretical kinetic pattern (F1 and R3) and experimental designs $\alpha = f(t_N)$ for the diclofenac release process of a) Chit-AA Hydrogel And b) Chit-AA-ATEM hydrogel are used at the examined temperatures. According to the results, with great assurance, the kinetics of the release of diclofenac from both hydrogels at all studied temperatures can be described by the kinetic model F1 (deviation squared root ($\sigma=10^{-4}$) which is related to the first chemical reaction.

k_M from Eq. 9 is obtained when *-Ln(1-α)* versus time for diclofenac release from both hydrogels are drawn (Figures 4a, b) [19]. Table 6 shows the steady-state model for the release of diclofenac from Chit-AA hydrogel at various temperatures which is obtained from the isothermal-slope of *-Ln (1-α)* versus time when the drug is released (4a, b). Since the increase in the rate constant is balanced with temperature, the kinetic parameters (activation energy ($E_{a,M}$) and the previous agent (LnA_M) for the release of diclofenac from Chit-AA hydrogels were determined using the Arrhenius equation. It was found that activation energy of the diclofenac release process for the whole process was determined based on the model constants for k_M (the rate constant).

It has a value of E_a=12.259Kj and the external factor *LnA* is 1. They are very different from the values obtained based on the initial release of the diclofenac drug ($E_{a,in}$=24.942Kj). It was also revealed the activation energy of dislocation of diclofenac for the whole process based on the fixed model from Chit-AA-ATEM hydrogel. The $E_{a,f}$ value was 33.256Kj and its external value was E_a=28.689Kj. The results show differences between the activation energy values for the start and the final part of the process. Release of diclofenac from Chit-AA-ATEM hydrogel are consistent with chemical-reactive model (F1) as well as activation energy. An increase in the concentration of diclofenac in the external composition is occurred by increasing the temperature, may be explained the possibility of describing the kinetics of the examined process. With the kinetic pattern, the chemical reaction of the first order, shows the kinetics of diclofenac release from hydrogel can be considered as a chemical reaction consistent with the work of Reese et.al. According to that, it can be stated in the following way:

$$A^* \underset{K_{ab}}{\overset{K_f}{\rightleftarrows}} A \quad (14)$$

where *A** and *A* are the concentration of diclofenac in hydrogel and in external solution, and K_f and K_{ab} are drug delivery rate constant from hydrogel to external solution and from external solution into hydrogel, respectively. According to the law of conservation of matter of equations:

$$A^*_0 + A_0 = A^* + A = A^*_\infty \quad (15)$$

Let A^*_0 and A^*_∞ denote the concentration of diclofenac in hydrogel, at time, $t=0$ and $t=\infty$ and A_0 and A_∞ are the concentrations of diclofenac drug in the external solution at time $t=0$ and $t=\infty$.

$$A^* = A^*_\infty + A_\infty - A \quad (16)$$

It is due because:

$$r = \frac{dA}{dt} = k_t A^* - k_{ab} A \quad (17)$$

It is obtained by adding 16 in 17:

$$r = \frac{dA}{dt} = k_t(A^*_\infty - A_\infty - A) - k_{ab} A \quad (18)$$

When V=0 in equilibrium time:

$$A^*_\infty = \frac{k_{ab} A_\infty}{k_t} \quad (19)$$

By substitute the Eq. 19 in Eq. 18, we have:

$$r = \frac{dA}{dt} = (k_t + k_{ab})(A_\infty - A) \quad (20)$$

If we add $\alpha_A = \frac{A}{A\infty}$, then equation 22 is converted to the following equation:

$$r = \frac{dA}{dt} = (k_t + k_{ab})(1 - \alpha) \quad (21)$$

Thus, the steady-state dose of diclofenac release is equal to the sum of the constants k_t and k_{ab}:

$$k_m = k_t + k_{ab} \quad (22)$$

We must remember that:

$$E_a = RT^2\left(\frac{dk}{kdT}\right) \quad (23)$$

Using Eq. 21, we can easily obtain the effective activation energy formula for the diclofenac release process for the first reverse order $E_{a,R}$ reaction which is predetermined by the first reverse order chemical reaction:

$$E_{a,R} = \frac{k_t E_{a,t} + k_{ab} E_{a,ab}}{k_t - k_{ab}} \quad (24)$$

In which $E_{a,t}$ is the activation energy of the diclofenac release from hydrogel to the external solution, $E_{a,ab}$ is the activation energy of the absorption of diclofenac from the external solution by hydrogel and $E_{a,R}$ is an effective activation energy that depends on the amount of drug released. However, due to the kinetic parameters of the transfer of diclofenac drug from hydrogel to the external solution and with the absorption of diclofenac drug from the external solution by hydrogel is preset .The determination of A^*_0, A^* and A^*_∞ and, therefore, the determination of the fixed rate of transfer of the diclofenac drug from hydrogel to the external solution k_t is a specialized complex process. So we are trying to determine the steady state of absorption of diclofenac from external solution to the k_{ab} hydrogel to confirm the previous kinetic pattern. For this purpose, we used diclofenac solution with concentration as high as which that found in the market. Dependences of degrees of isothermal absorption of diclofenac solution versus reaction time can be seen in Figures 6a and b, respectively, for Chit-AA hydrogel and Chit-AA hydrogel. Table 6 shows the degrees of parallel absorption of Chit-AA hydrogel and Chit-AA-ATEM hydrogel at different temperatures in the external solution of diclofenac. As described, it is obvious that for both hydrogels if AD_{eq} are exposed to temperature rise, AD_{eq} for Chit-AA hydrogel is slightly lower. Using the proportional model method described above, it has been found that the kinetics of the external solution of diclofenac in Chit-AA hydrogel can be fully described as R_2 which is specific to the controlled phase (Table 3).This shows that the following equation should be valid:

$$-\mathrm{Ln}(1 - \alpha) = k_{m,ab} t \quad (25)$$

where $k_{m,ab}$ is the fixed model rate [20].

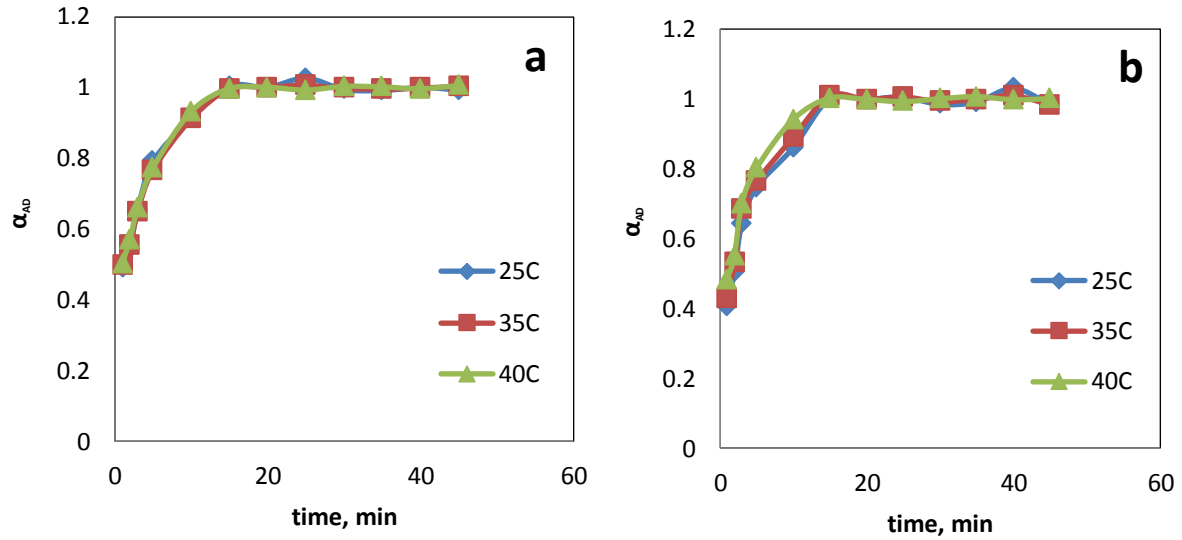

Fig. 6. External soluble adsorption in hydrogels a) Chit-AA hydrogel and b) Chit-AA-ATEM hydrogel at three temperatures of 25,35,40 °C.

Table 6. Parallel absorption of diclofenac for Chit-AA hydrogel and Chit-AA-ATEM hydrogel at different temperatures.

	ADeq[%]		
T, °C	25	35	40
Chit-AA-ATEM	518.6	536.85	537.47
Chit-AA	465.56	464.23	469.17

CONCLUSIONS

According to the calculations, the activation energy for Chit-AA hydrogel is lower than activation energy for Chit-AA-ATEM hydrogel. Thus, the amount of drug release in the Chit-AA hydrogel is much higher than the second hydrogel which according to empirical and theoretical calculations are consistent with these results. The diclofenac emission process from both Chit-AA hydrogel and Chit-AA-ATEM hydrogel to a water solution is a complex heterogeneous process that can be modeled kinetically with a total number of first-order depletion reactions that are heterogeneous in energy.

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