https://doi.org/10.48047/AFJBS.6.6.2024.9478-9501

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

A Comparative Kinetic Study of Diclofenac Drug Release from Chitosan-Acrylic Acid and Chitosan-Acrylic Acid-co-2-Methacryloyloxyethyl Trimethylammonium Chloride Hydrogels

Mojtaba Ghadimi Yari[1*], Iman Taghi poor[2]

[1]Department of Chemistry, Faculty of chemistry application , Karaj Islamic Azad University, Karaj, Iran

[2]Department of Chemistry, Bu Ali Sina University Hamedan, Iran

*Corresponding Author

Article History

Volume 6, Issue 6, 2024
Received: 03 Feb 2024
Accepted: 06 Apr 2024
doi: 10.48047/AFJBS.6.6.2024.9478-9501

Abstract

A comparative study of the isothermal kinetic release of diclofenac drug from chitosan-acrylic acid and chitosan-acrylic acid-co-2-methacryloyloxyethyl trimethylammonium chloride hydrogels was conducted. The kinetic release curves of diclofenac from the hydrogels in distilled water at various temperatures (20-42 degrees Celsius) were determined. The ranges of drug release reactions were identified using initial amounts, saturation levels, and the empirical equation designed by Peppas and colleagues. The widely-used proportional model was employed to determine the kinetic models for both drug release and the swelling of an external solvent into the hydrogel. It was found that the kinetics of diclofenac release from both chitosan-acrylic acid hydrogels and chitosan-acrylic acid-co-2-methacryloyloxyethyl trimethylammonium chloride hydrogels could be better described by the first-order chemical reaction pattern. The drug release process was analyzed to determine the kinetic parameters, which uncovered noteworthy variations in the values between chitosan-acrylic acid and chitosan-acrylic acid-co-2-methacryloyloxyethyl trimethylammonium chloride hydrogels. The kinetic impact on the drug density was described using a first-order chemical reaction model for chitosan-acrylic acid-co-2-methacryloyloxyethyl trimethylammonium chloride hydrogel, while the chitosan-acrylic acid hydrogel was better characterized by a diffusional pattern, indicative of a diffusion-controlled process in a phase-controlled environment. The performance of a novel molecular transfer process for drug release was investigated based on the consistent correlation of kinetic parameters (lnA, Ea) with the released diclofenac amount (α), incorporating a compensatory effect. According to this mechanism, drug release is seen as the disengagement of the drug from active separation centers within the sub gel/hydrogel with varying energies. A process was designed to determine the performance of the activation energy distribution. The performance of different activation energy distributions for chitosan-acrylic acid and chitosan-acrylic acid-co-2-methacryloyloxyethyl trimethylammonium chloride hydrogels was determined.

Keywords: Drug delivery systems, Isothermal, Kinetics, Hydrogels, Drug release

Introduction

Hydrogel serves as a versatile system for loading and controlling the release of solutions with specific therapeutic properties. To further enhance the utilization of hydrogels for drug loading and controlled release, it is essential to identify the key parameters and the mechanism that governs the kinetics of drug release from hydrogels. Various mathematical models have been devised to characterize drug release profiles from polymer networks. It is widely acknowledged that drug release is significantly influenced by factors such as polymer composition, hydrogel geometry, degree of swelling, and solute distribution within the hydrogel. Three recognized kinetic patterns for drug release have been refined based on the rate-limiting step for controlled release. Distinctive controlled, controlled swelling, and chemically controlled models have been developed, and in such cases, the kinetics of drug release from hydrogels have been better described by the Peppas-Fick law, Stefan-Maxwell equations, or the empirical equation designed by Peppas and colleagues [4,5].

When drug partitioning outpaces hydrogel swelling, it allows for the utilization of a controlled swelling release pattern. This model is tailored for situations in which drug release takes place by engaging with the elastic and glassy surfaces of swollen hydrogels. The kinetic pattern for chemically controlled drug release is relevant to hydrogel transport systems where chain degradation occurs through hydrolytic degradation or the reverse reaction between the polymer network and the freely-released drug. Mathematical models for drug release kinetics have been reported in recent sources, which only predict about 60% of the initially released solution. Dittgen and colleagues presented a mathematical model that assumes drug release from the hydrogel involves both drug degradation and transport through the hydrogel, partitioning solvents between the solvent and hydrogel phases. This model is designed to predict the release of B12, methyl blue, and methyl orange from semi-permeable hydrogel networks PNIPAAm and PAAm. In recent years, various types of hydrogels such as those based on polyacrylic acid, polymethacrylic acid, chitosan-acrylic acid, and chitosan-acrylic acid-co-2-methacryloyloxyethyl trimethylammonium chloride (copolymers), as well as interpenetrating networks (IPNs) or their specific combinations, have been used as carriers in drug release systems. For this particular study, diclofenac, an analgesic and anti-inflammatory drug, was employed for drug delivery purposes.

Experimental Section

In this study, chitosan (Shanghai, China), acrylic acid (AA), 2-acryloyloxyethyl trimethylammonium chloride (MOTA), ammonium persulfate (APS), iron (II) chloride tetrahydrate ($FeCl_2 \cdot 4H_2O$), and iron (III) chloride hexahydrate ($FeCl_3 \cdot 6H_2O$) were obtained. The ammonia solution was sourced from Merck, and 96% ethanol was acquired from Jahan Alcohol Tebb-e Arak.

Synthesis of Superabsorbent Hydrogel

The polymerization reaction of chitosan (CTS) with acrylic acid (AA) and 2-(acryloyloxyethyl) trimethylammonium chloride (MOTA) using ammonium persulfate as a radical initiator and a mixture of iron II and III as a cross-linker was carried out as follows:

The procedure began with dissolving 1 gram of chitosan in 40 mL of 1% (v/v) acetic acid in a three-necked reactor heated to 85 degrees Celsius. Then, a solution containing 0.1 grams of ammonium persulfate dissolved in 5 mL of distilled water was introduced. Following a 5-minute interval, a precise quantity of acrylic acid and (2-acryloyloxyethyl trimethylammonium chloride) monomers was added to the mixture. After an hour of stirring, a mixture of FeCl2 and FeCl3 was included as a cross-linking agent. Subsequently, an ammonia solution was added after a specified duration to induce the formation of iron oxide nanoparticles, leading to the gel formation within the medium. The obtained gel was placed in ethanol for 24 hours and then in a greenhouse to dry at a specific temperature. The measurement of the properties of the synthesized hydrogel, including swelling capacity, swelling rate determination, pH effect on swelling capacity, measurement of swelling in saline solutions, and the effect of pressure on the hydrogel's swelling capacity, was conducted for characterization.

Measurement of Hydrogel Swelling Capacity

grams of the superabsorbent polymer with a particle size of 60-40 mesh were added to 250 milliliters of distilled water. The mixture was left to swell for 2 hours at room temperature. Afterward, the swollen sample was transferred to a sieve, and the excess unabsorbed water was drained after 15 minutes. The swollen hydrogel sample was then weighed to determine the equilibrium swelling capacity (Se) using equation 1.

(1)

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

In the given equation, Ws denotes the weight of the swollen hydrogel, while Wd denotes the weight of the dry hydrogel . The maximum swelling and swelling capacities of the hydrogel can be found in the table below.

Table 1 - Swelling Capacity of Two Hydrogels in Distilled Water

Hydrogel name	Iron II, grams	Iron III, grams	Acrylic acid, grams	Duplicate 2	Initiator	Swelling ratio, grams/gram
Chitosan-acrylic acid	0.23	0.8	5	-	0.12	460
Chitosan-acrylic acid-2-acryloyloxytetramethylammonium chloride	0.0662	0.1662	3	1	0.12	320.6

Determination of Polymer Densities by Immersion Method

In utilizing a polymeric material, knowing the density is usually essential. Whenever the type of polymer is specified, its density can be extracted from the tables available in Polymer Encyclopedia. Otherwise, density can be determined through a simple and quick experiment. Note that even for a known polymer, density is a function of crystallinity

percentage, presence of plasticizer, filler, etc. The method of density measurement is based on two principles:

1. If a solid object is immersed in an incompatible fluid with it (insoluble in the fluid) that has equal density, it will become buoyant and appear weightless.

2. When two miscible fluids with different densities are mixed such that the total volume of the mixture equals the sum of individual volumes (mixing does not decrease or increase the total volume), then the density of mixture is calculated using equation (1):

(1)

$$d_m = \phi_1 d_1 + \phi_2 d_2$$

In the above equation, φ and d2 respectively represent the volume fraction of component 1 and density of component 2. The density and some fluids which are mostly used in this test are presented in the table below.

Table 1- Density and molecular weight of some common liquids

Molecular weight (g/mol)	Density (g/cm)	liquid
100	0.68	Normal heptane
32	0.79	Methanol
18	1.00	Water
46	1.20	Formic acid
85	1.32	Methylene chloride
154	1.60	Crane tetrachloride
188	2.17	Ethylene rises
119	1.47	chloroform
58	0.79	Austen

Buffer Testing at pH 2 and 8:

1. Initially, a specific amount of sodium phosphate monobasic is taken. Using this, a 0.1 molar solution is prepared. Next, 4.85 grams of sodium chloride are added to the solution, and the pH is adjusted to 8.04 using a single-capacity pH meter. This is done to achieve a pH of 8. Overall, the solution is prepared in a volume of one thousand liters.

2. Subsequently, for pH 2, a certain amount of phosphoric acid is takengrams of sodium chloride are then added to the solution, which is subsequently adjusted to a volume of 900 cc. Then, using a one-capacity acid such as hydrochloric acid, the pH is adjusted to 1.94. Afterward, the volume is brought up to one thousand cc.

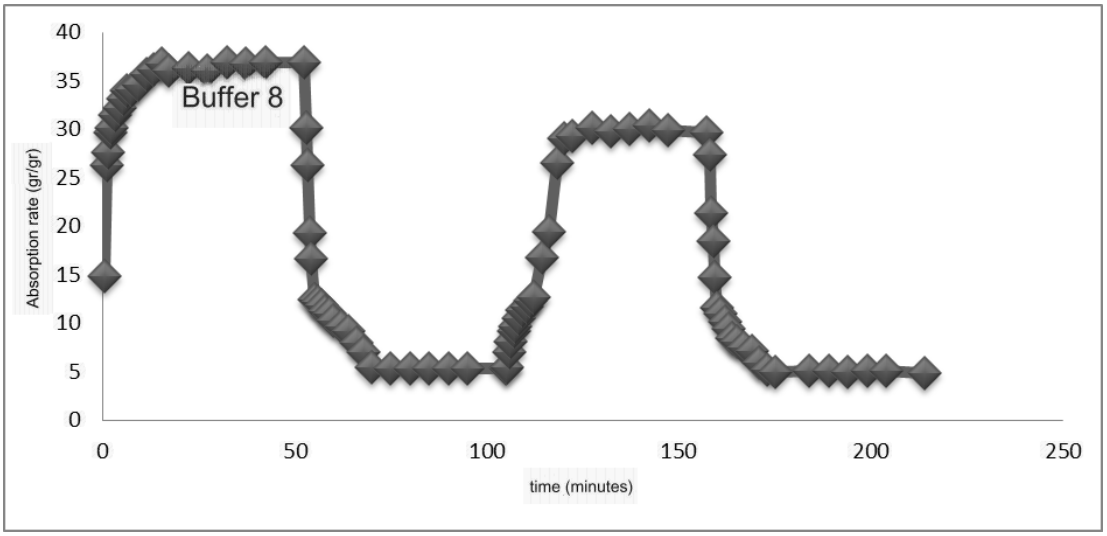


Figure 1. Investigation of Swelling and Desorption of Hydrogel in Two Environments with pH 2 and 8.

Characteristics of Composite Hydrogels:

Hydrogel samples with the following structural characteristics were identified: apparent density (ρ_{xg}), The apparent density (ρxg) was determined by measuring the composite sample's apparent density using the pycnometer method with n-hexane as the non-solvent. The overall density (ρc) and the distance between macromolecular chains (d) were then calculated using the following equations based on these measurements [7]:

(2)

$$\rho_c = \frac{\rho_{xg}}{M_c}$$

(3)

$$d = 0.154.\nu_2^{1/3}[0.19.M_c]^{1/2}$$

The molar concentration (Mc) refers to the concentration between the network junctions and provides an estimated relative value of the original composition:

(4)

$$M_c = \frac{72}{2X_c}$$

In which X_c is a relative nominal network junction (moles of crosslinker and moles of monomers in the reaction composition).

Diclofenac drug loading

Diclofenac drug loading was performed by compressing the weight of a known hydrogel sample in an additional 50 ml solvent (0.25% drug) at different temperatures of 25, 35, and 40 degrees Celsius. The released material was quantified by UV-visible spectrometry, using the absorbance at 298 nm wavelength, and the effective amount of released drug (Ce%) was calculated using equation 4 as follows [8]:

(5)

$$C = \frac{p.V}{m_x.X} * 100$$

he diclofenac drug concentration, denoted as "p," in the solution at time "t" is calculated using the formula p = (mx) / V, where "V" represents the solution volume in milliliters, "mx" denotes the weight of diclofenac drug loaded hydrogel sample in grams, and "x" signifies the specific drug loaded in the hydrogel g/g. The fraction of diclofenac drug released, denoted as "α," is determined by calculating the ratio of the amount released at time "t" to the maximum amount of diclofenac drug released, denoted as "Cmax[9].

(6)

$$\alpha = \frac{C}{C_{\max}}$$

The swelling of an external substance (Diclofenac drug solution) into hydrogels/gels

The swelling of an external solution by chitosan-acrylic acid and chitosan-acrylic acid co-2-methacryloyloxyethyl trimethylammonium chloride hydrogels with an average weight (±5%) of 0.1 g for the swelling of a specified concentration of Diclofenac solution released from the Diclofenac drug at maximum temperatures of (26)25, (36)35, and (41)40 degrees Celsius is investigated. At the beginning of each experiment, a hydrogel sample is weighed, and then it is immersed in another solution. At predetermined time intervals, the gel is weighed with the absorbed solution from the external solution until the hydrogel reaches a constant density, for example, equilibrium. [10]

Determination of Swelling Level

The isothermal swelling amount (AD) is determined by subtracting the initial weight of the hydrogel sample (m0) from its weight at time (t), and then dividing this difference by the initial weight (m0), as per Equation 6 and the subsequent formula:

(7)

$$AD[\%] = \frac{m_t - m_0}{m_0} * 100$$

For each sample, at least three swelling measurement criteria are determined, and the average values are used. The equilibrium swelling level (AD_{eq}) represents the hydrogel swelling in the equilibrium state. [11]

Normal Swelling Level

The degree of swelling a_A was measured and determined as the ratio of the swelling at time t (AD) to the equilibrium swelling (AD_{eq}) at a given temperature:

(8)

$$\alpha_A = \frac{A}{A_\infty}$$

Methods used for evaluation of kinetic parameters

Empirical equation proposed by Peppas

To determine the kinetic parameters of diclofenac drug release from chitosan-acrylic acid and chitosan-acrylic acid-graft-poly (2-methacryloxyethyl trimethyl ammonium chloride) hydrogels, the results were analyzed using the well-known Peppas semi-empirical equation [13]:

(9)

$$-\ln(1-\alpha) = k_M .t$$

Where α is the fraction of diclofenac drug released at time *t*, n_p is an external index for the process mechanism (separation exponent), k_p is the apparent release rate coefficient and *t* is the interaction time.

Friedman isoconversional method

The analysis of kinetic data is based on the following rate equation:

(10)

$$\left(\frac{d\alpha}{dt}\right)_{\alpha=const} = Af\ (\alpha)\exp\left(-\frac{Ea,\alpha}{RT}\right)$$

Where T is temperature, A is external factor, $E_{a,\alpha}$ is apparent activation energy, f(α) is general kinetic pattern symbol and *R* is gas constant.

The logarithmic form of equation 10 leads to:

(11)

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

Where $(v)_{\alpha=const}$ is a reaction extent defined for α.

For cons α-cons plotting ($\frac{1}{T}$) against V_f resulted in a convergent curve which should be a straight line whose slope enables evaluating apparent activation energy.

Results and Discussion

The determined basic structural properties of chitosan-acrylic acid and chitosan-acrylic acid-graft-poly (2-methacryloxyethyl trimethyl ammonium chloride) composite hydrogels are presented in Table 2.

Table 2 - Specific properties of CTs+AA and Cts+AA+Mota hydrogels

	x_g[kg/m^3]ρ	M_c[g/mol]	$_c$[*10^{4}mol/cm^3]ρ	d[nm]
CTs+AA	1253.8	596458	19.9678	42.08
Cts+AA+Mota	1147.8	256913	17.0351	12.6

As observed from the presented results, the structural characteristics of chitosan-acrylic acid and chitosan-acrylic acid co-2-methacryloyloxyethyl trimethylammonium chloride hydrogels show slight differences.

The gel density and the overall network density of the chitosan-acrylic acid hydrogel are higher than those of the chitosan-acrylic acid co-2-methacryloyloxyethyl trimethylammonium chloride hydrogel, and the molar network density (Mc) for the chitosan-acrylic acid hydrogel is higher than that for the chitosan-acrylic acid co-2-methacryloyloxyethyl trimethylammonium chloride hydrogel, with a greater distance between micro-molecular chain (d). Table 2 illustrates the loading of diclofenac drug into two hydrogels at different temperatures. The results clearly indicate that the loading of diclofenac drug increases with temperature for both hydrogels, with the chitosan-acrylic acid hydrogel exhibiting higher loading at all applicable temperatures. Isothermal dependencies of a specific released drug (C) over time (release kinetics curves) for different temperatures are presented in Figure 1a for the Cts+AA hydrogel and in Figure 1b for the mota+Cts+AA hydrogel. In investigating the impact of temperature on the shape of release kinetics curves, the study employed specific parameters: linear domain time (t1), initial drug release amount (Vin), saturation time (tf), and saturated release of diclofenac drug (Vf). The linear domain time (t1) denotes the duration during which the release of diclofenac drug increases consistently with reaction time, serving as a gauge for assessing the temperature's influence on the shape of the release kinetics curves. The initial release amount of diclofenac drug (Vin) within this linear phase is determined by Equation 11 [14]

(12)

$$v_{in} = \frac{c_1}{t_1}$$

C1 represents the specific quantity of drug released at the conclusion of the linear phase of the diclofenac release kinetic curve, with t1 denoting the corresponding time interval.

The saturation time (tf) is the duration required to achieve the maximum concentration (cmax) of released diclofenac in a solution at a set temperature. Furthermore, the fraction of diclofenac drug released is calculable using the subsequent equation:

(13)

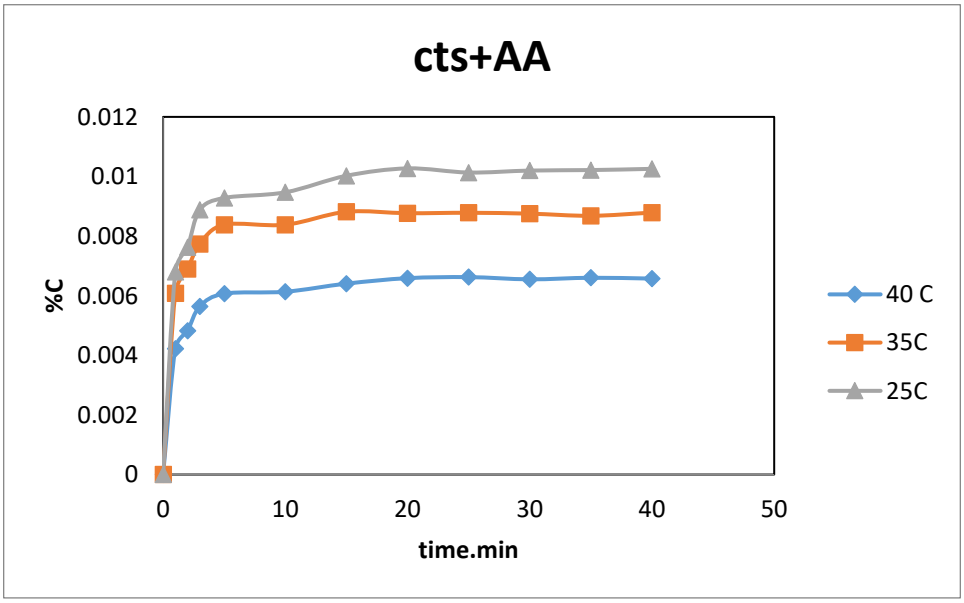
$$v_f = \frac{c_{max}}{t_f}$$

The rheological parameters for the curve at different temperatures can be determined, akin to those presented in Table 3, for the initial and saturation phases. The results in Table 3 show a clear trend: as the values of vin and vf increase with rising temperature, the values of t1 and tf decrease for both hydrogels. Given the evident correlation between the increase in vin and vf and the temperature, the rheological parameters for the initial and saturation phases of diclofenac drug release from the hydrogels (lnAf, Ea, f, lnAin, Ea, in) can be established using the Arrhenius equation [15]

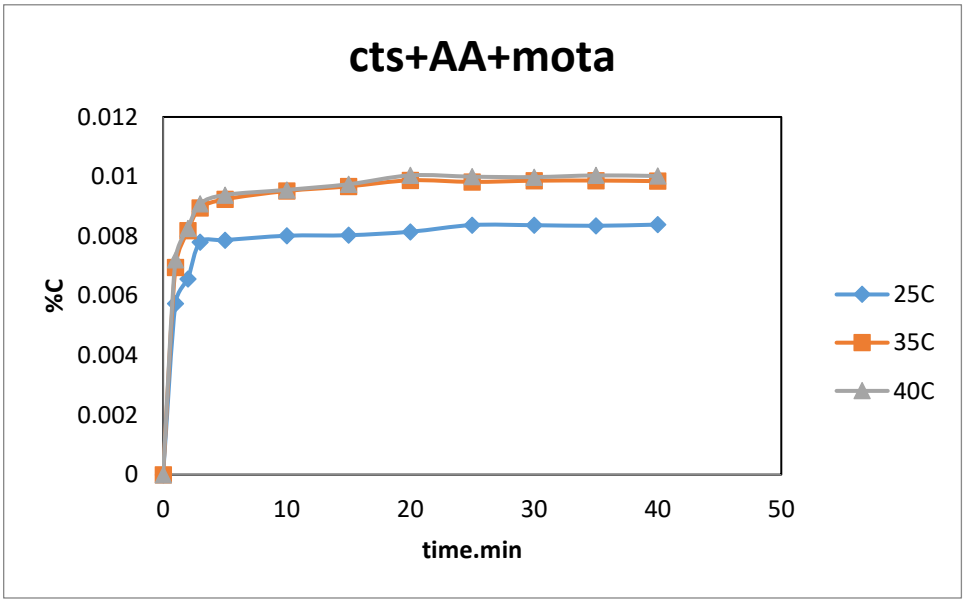
Table 3 - Loading of a specific drug (X_t) Loading of diclofenac drug in Cts+AA and Cts+AA+Mota hydrogels.

CTs+AA		Cts+AA+Mota	
T [◦C]	*X* [g/g]	T [◦C]	X [g/g]
25(26)	0.610472973	25(26)	0.706841216
35(36)	0.795692568	35(36)	0.834037162
40(41)	0.867652027	40(41)	0.844341216

The obtained results are also presented in Table 3.

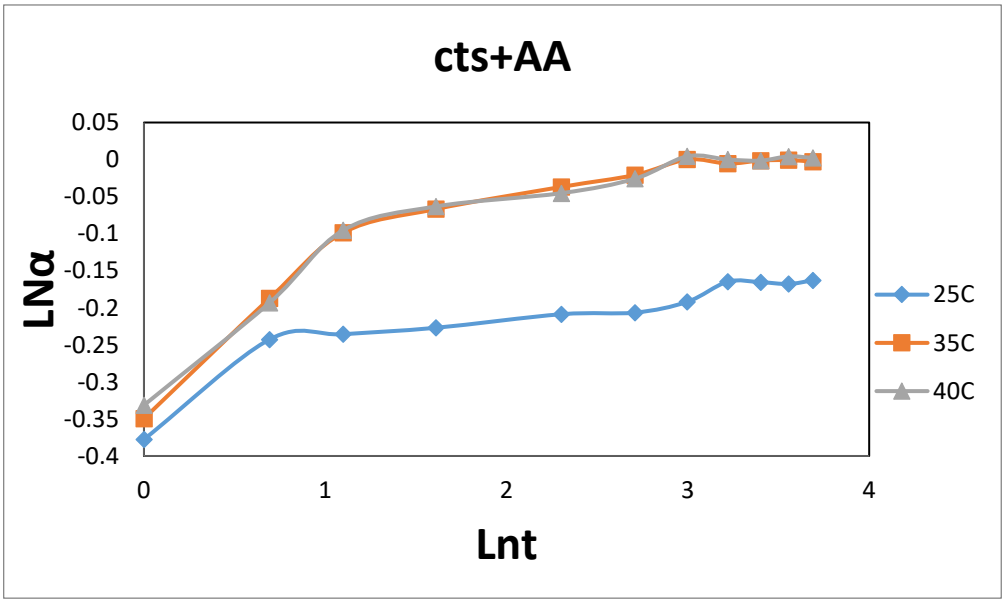


2a

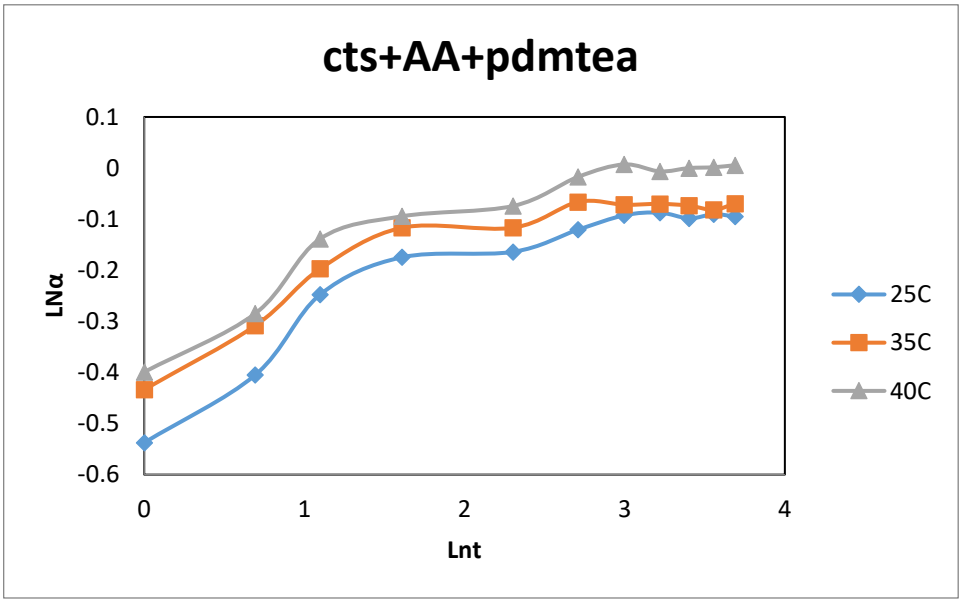


2b

Figure 1: Isothermal release kinetics curves of diclofenac drug released from a) chitosan-acrylic acid hydrogel and b) chitosan-acrylic acid-2-acryloyloxyethyl trimethyl ammonium chloride hydrogel at three temperatures of 25, 35 and 40 degrees Celsius.



3a



3b

Figure 3a,b- lnX versus lnt plot for diclofenac drug released at different temperatures from a) chitosan-acrylic acid hydrogel and b) chitosan-acrylic acid-2-acryloyloxyethyl trimethyl ammonium chloride hydrogel.

Based on the results obtained, it is evident that the activation energy for the initial stage of diclofenac drug release from chitosan-acrylic acid hydrogel (Ea,in=24.942 kJ) significantly exceeds the activation energy for the saturation phase of the same process (Ea,f=16.628 kJ). A similar trend is observed in the activation energy values for the release of diclofenac drug from chitosan-acrylic acid-2-acryloyloxyethyl trimethyl ammonium chloride hydrogel, albeit with differing magnitudes. Additionally, the lnA values for the release of diclofenac drug from chitosan-acrylic acid hydrogel contradict those for chitosan-acrylic acid-2-acryloyloxyethyl trimethyl ammonium chloride hydrogel. [16]

Table 4- Inverse curve parameters for the release of diclofenac drug from Cts+AA and Cts+AA+Mota hydrogels at different temperatures (correlation coefficient-R, standard deviation-SD).

	T, ◦C	tl, min	$v_{in,\ \%/min}$	t_f, min	$v_{f,\ \%/min}$	$c_{max,\ \%}$	Kinetic parameters	
							Initial stage	Saturation stage
Cts+AA	25 C	4	0.00151751	18	0.00036605	0.022213	$E_{a,in}$= 24.942 kj	$E_{a,f}$ = 16.628kj

	35 C	3.5	0.00239508	14	0.00062972	0.029692	R=0.9889	R= 0.999
	40 C	2.8	0.00331475	12	0.00078918	0.034654		
Cts+AA+ Mota	25 C	3	0.002189	23	0.00036407	0.028343	$E_{a,in}$= 41.57kj	$E_{a,f}$ = 33.256kj
	35 C	2.5	0.002728	20	0.00049376	0.033268	R=0.9526	R= 0.9598
	40 C	2	0.002753	17	0.00057311	0.033849		

The higher value of $E_{a,in}$ compared to $E_{a,f}$ is a non-trivial characteristic of the release process of diclofenac drug from these hydrogels, indicating complexity from both kinetic and mechanistic perspectives. Moreover, from both kinetic and mechanistic models, it is evident that the values of $E_{a,in}$ for the chitosan-acrylic acid hydrogel are somewhat lower than those for the diclofenac drug from the chitosan-acrylic acid 2-acryloyloxyethyl trimethylammonium chloride hydrogel, while the values of $E_{a,f}$ for the release of diclofenac drug from the chitosan-acrylic acid hydrogel are significantly higher than those from the chitosan-acrylic acid 2-acryloyloxyethyl trimethylammonium chloride hydrogel. To determine the release parameters of the diclofenac drug from chitosan-acrylic acid and chitosan-acrylic acid 2-acryloyloxyethyl trimethylammonium chloride hydrogels, the results underwent analysis using Peppas' empirical equation (Equation 8) in its linearized form. A straight line obtained from plotting lnα against ln(t) indicates that the kinetics of the process can be modeled with the proposed model. From the slopes and intercepts of these straight lines, the individual values (np) and the apparent release rate constant (kp) can be derived. Figures 2a and 2b depict the lnα versus ln(t) plots for the release of diclofenac drug from chitosan-acrylic acid and chitosan-acrylic acid 2-acryloyloxyethyl trimethylammonium chloride hydrogels at different temperatures.

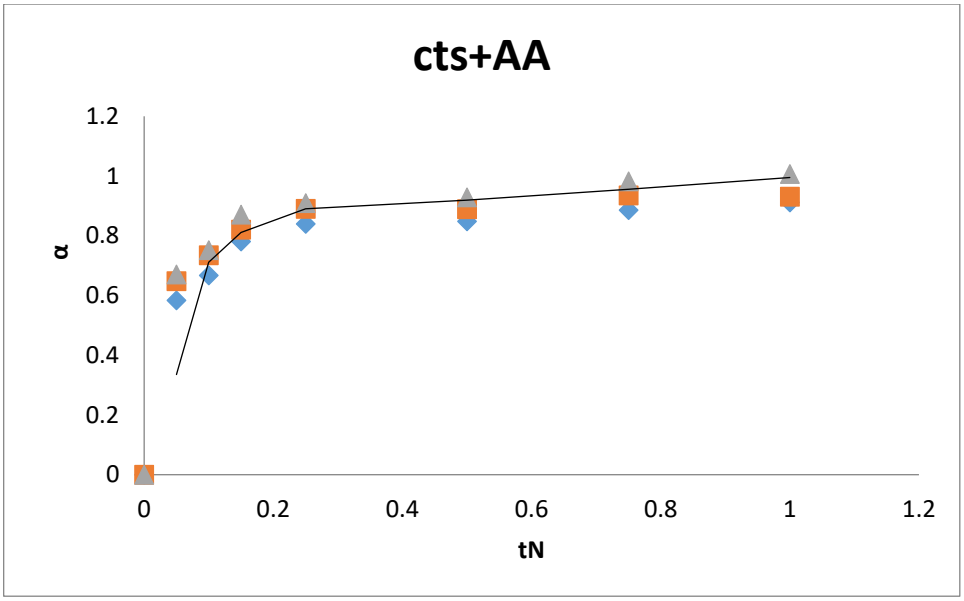
Table 5 - Kinetic parameters (k_p, n_p) and practical range (l) at different temperatures for the release of diclofenac drug from Cts+AA and Cts+AA+Mota hydrogels.

	T, ◦C	n_P	lnk_P	k_P, min^{-1}	R	Kinetic parameters
Cts+AA	25C	0.0439	- 0.3147	0.729	R=0.8066	Ea=12.259kj
	35C	0.076	- 0.2441	0.78258	R=0.8357	
	40C	0.078	- 0.2491	0.77866	R=0.8151	
Cts+AA+Mota	25C	0.0865	-0.4435	0.6405	R=0.8583	Ea=28.689kj

	35C	0.1095	-0.3447	0.7073	R=0.8189	
	40C	0.1004	0.3215-	0.72405	R=0.8787	

Table 6- The set of kinetic models used to determine the kinetic model of diclofenac drug and its release process from Cts+AA and Cts+AA+Mota hydrogels

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	$3/2[(1-\alpha)^{-1/3}-1]$	$(1-2\alpha/3)-(1-\alpha)^{2/3}$



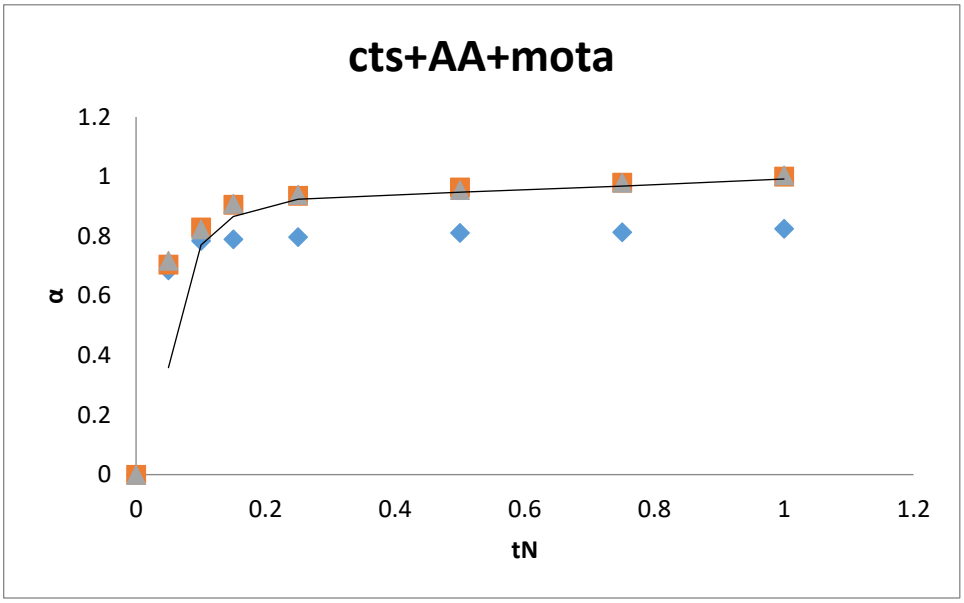
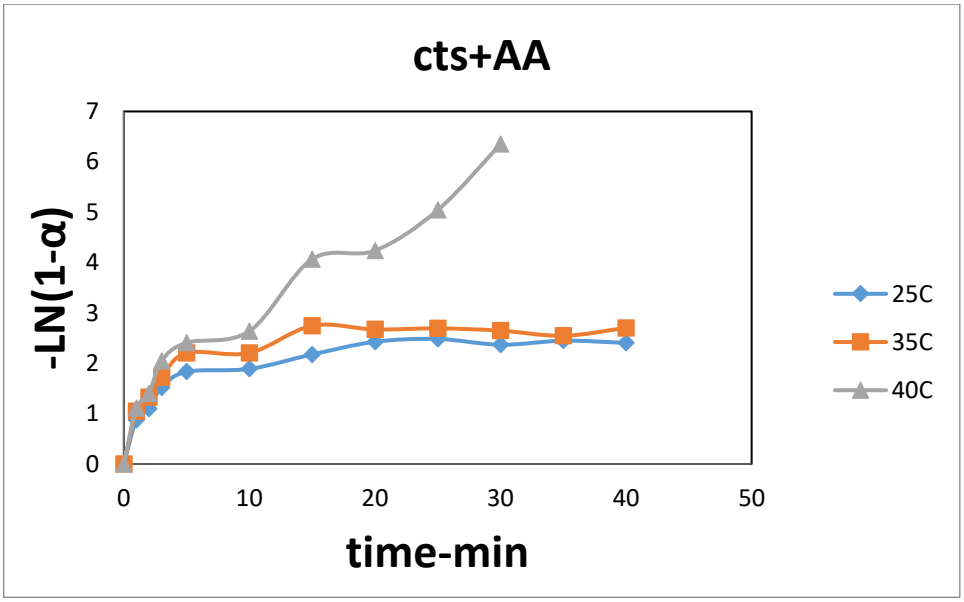
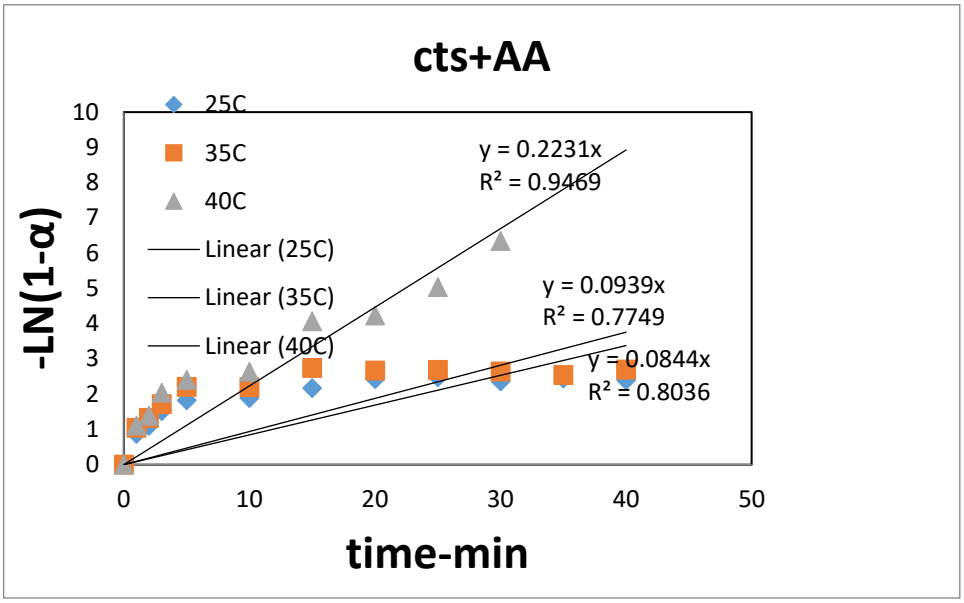
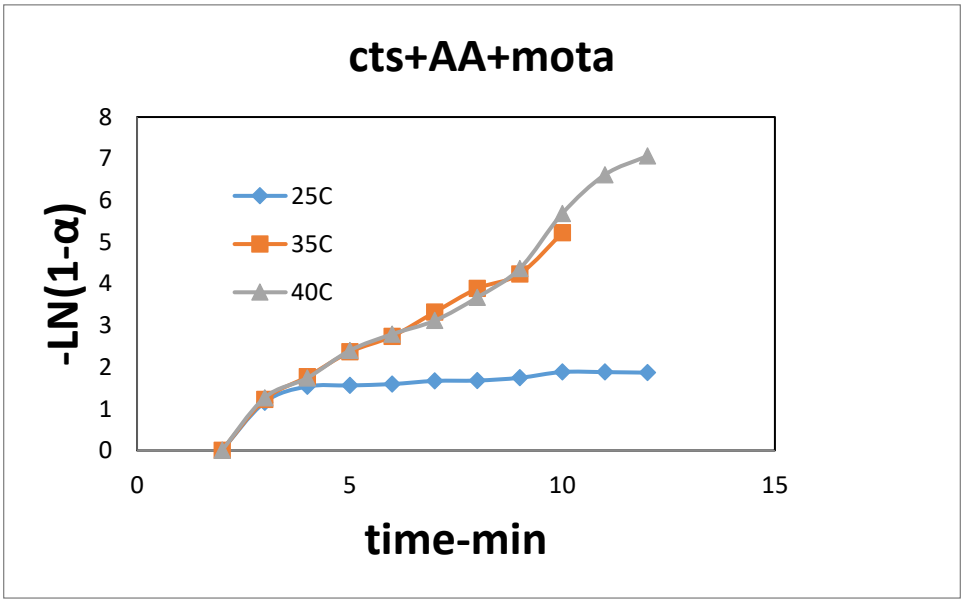


Figure 4- $\alpha=f(t_N)$ plot for theoretical kinetic motion patterns:

F1 (linear curve....) and Rs (dotted curve and....) and experimental $\alpha=f(t_N)$ plots for a) cts+AA hydrogel at temperatures 25, 35, 40 b) cts+AA+mota hydrogel at 25, 35, 40




cts+AA
25C
35C
40C
Linear (25C)
Linear (35C)
Linear (40C)
y = 0.2231x
R² = 0.9469
y = 0.0939x
R² = 0.7749
y = 0.0844x
R² = 0.8036
-LN(1-α)
time-min


cts+AA+mota
25C
35C
40C
-LN(1-α)
time-min

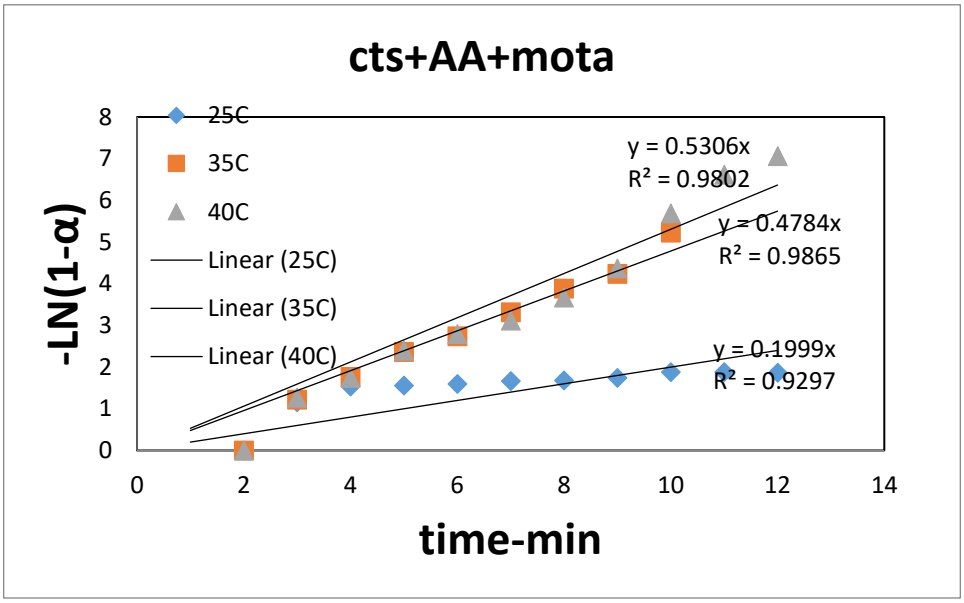


Figure 5 - Plots of **-LN(1-α)** against release time for a) chitosan-acrylic acid hydrogel at 25, 35, 40 b) chitosan-acrylic acid 2-acryloyloxyethyl trimethylammonium chloride hydrogel at 25, 35, 40.

In Figures 2a and 2b, straight-line lnα versus ln(t) plots are observed within specific ranges of the release process for both hydrogels. By analyzing the ln(t) versus ln(α) plot, the rheological parameters np and kp were computed within the linear data ranges, such as the practical application range (l). These straight-line segments allow for the determination of valuable information regarding the external separation values np and the apparent release rate kp from the slopes and intercepts.

The obtained results present the determined parameters (np, kp) and the practical range (l) for the specified parameters in Table 4. Analysis of the results in Table 4 reveals the determination of kinetic parameters np and kp for diclofenac drug release from the chitosan-acrylic acid hydrogel within the practical range of l 25~60% α. Similarly, for the chitosan-acrylic acid 2-acryloyloxyethyl trimethylammonium chloride hydrogel, the parameters are evaluated within the range of 15~55% α.

Furthermore, it is evident that the constant value kp increases with temperature for the release of diclofenac drug from the chitosan-acrylic acid hydrogel, while the release factor np, approximately 0.9, experiences a slight decrease. Conversely, for the release of diclofenac drug from the chitosan-acrylic acid 2-acryloyloxyethyl trimethylammonium chloride hydrogel, np exhibits a slight increase, reaching a value of 1.

These variations may suggest potential changes in the temperature-dependent mechanism of diclofenac drug release from the hydrogels. They allow for the determination of kinetic parameters lnA and Ea, as the constants kp and the Arrhenius dependence on temperature changes become apparent. The activation energy for diclofenac drug release from the chitosan-acrylic acid hydrogel is approximately 12.259 kJ, notably lower than the

activation energy for the initial release stage (Ea,in = 24.942 kJ) and higher than the activation energy for the saturation stage (Ea,f = 16.628 kJ) of the same process. For the release of diclofenac drug from the chitosan-acrylic acid 2-acryloyloxyethyl trimethylammonium chloride hydrogel, the activation energy is roughly 28.689 kJ, which is lower than both the activation energies for the initial and saturation stages of diclofenac drug release (Ea,f = 33.256 kJ and Ea,in = 41.57 kJ). As there are some differences in the obtained rheological parameters for various stages of the investigated kinetic release process, another method known as the well-established proportionality model was utilized.

Based on the proportional model method, the kinetic reaction pattern has been categorized into 5 groups according to the reaction mechanism:

1. Electrochemical reactions
2. Phase-controlled reactions
3. Sequential reactions
4. Reactions described by the Avrami equation
5. Separation-controlled reactions using the inverse curve fitting process, which has been established experimentally. The expression αexp=f(t) was converted into the widely recognized global inverse curve, where tN denotes the normal time. The time constant tN was selected to normalize the time gap in the monitoring process, and was defined as follow :

(14)

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

In this context, $t_{0.9}$ represents the moment when α equals 0.9. By employing the reduced time, the use of global inverse curves $\alpha = f\,(t_N)$ for various kinetic models was made possible. The determination of the goodness of fit assessed through the sum of squared residuals was used to evaluate the performance of theoretical experimental curves $\alpha = f\,(t_N)$. The selected kinetic pattern is one that minimizes the sum of squared residuals.[18]

A range of kinetic models has been employed to identify the most effective model for the diclofenac drug release processes, as detailed in Table 5. The plots in Figures 3a and 3b depict the selected theoretical kinetic pattern (F1 and R3) from Table 5, alongside experimental plots for the release process of diclofenac drug from a) chitosan-acrylic acid hydrogel and b) chitosan-acrylic acid 2-acryloyloxyethyl trimethylammonium chloride hydrogel at the temperatures under investigation. Based on the findings in Figures 3a and 3b, it can be confidently affirmed that the kinetics of diclofenac drug release from both hydrogels at all temperatures under scrutiny can be characterized by the kinetic model F1 (root mean square deviation (σ=10-4), which corresponds to a first-order chemical reaction

(15)

$$-ln(1-\alpha) = k_M.t$$

The model constant "kM" represents the first-order chemical reaction rate. Figures 4a and 4b display the isothermal dependencies of "a−ln(1−α)" versus reaction time for the

release of diclofenac from both chitosan-acrylic acid hydrogel and chitosan-acrylic acid 2-acryloyloxyethyl trimethylammonium chloride hydrogel, respectively.[19]

In Table 6, the model constant values for the release of diclofenac from chitosan-acrylic acid hydrogel at different temperatures are presented. These values were obtained from the slopes of the isothermal dependencies −ln(1−α) versus release time (Figures 4a and 4b). As the increase in the model constant is temperature-equilibrated, the kinetic model parameters including the activation energy (Ea,M) and pre-exponential factor (lnAM) for the release of diclofenac from both chitosan-acrylic acid hydrogel and chitosan-acrylic acid 2-acryloyloxyethyl trimethylammonium chloride hydrogel were determined using the Arrhenius equation. The results in Table 6 also reveal that the activation energy for the diclofenac release process from the chitosan-acrylic acid hydrogel, based on the model constants for kM, was Ea = 12.259 kJ with an external factor lnA equal to 1. Although these values are closer to the calculated values from the saturation release of diclofenac and the empirical equation designed by Pepas (Ea = 24.942 kJ), they differ significantly from the values obtained based on the initial release of diclofenac (Ea,in = 24.942 kJ). Furthermore, it was determined that the activation energy for the release of diclofenac from chitosan-acrylic acid 2-acryloyloxyethyl trimethylammonium chloride hydrogel was Ea,f = 33.256 kJ, with an external factor of Ea = 28.689 kJ. These results indicate differences in activation energy values for the initial and final stages of the examined diclofenac release process from chitosan-acrylic acid 2-acryloyloxyethyl trimethylammonium chloride hydrogel, similar to the determined activation energy using the first-order chemical reaction model (F1). Additionally, based on the ability to describe the kinetics of the examined process with the first-order chemical reaction pattern, it suggests that the kinetics of diclofenac release from the hydrogel can be considered a chemical reaction according to the work of Reis and colleagues. This can be expressed according to the following pattern

(16)

$$A^* \overset{K_f K_{ab}}{\rightleftarrows} A$$

The concentration of diclofenac in its own solution within the hydrogel is represented by A*, while A represents the concentration of diclofenac in the external medium. The transfer rate constant of diclofenac from its solution in the hydrogel to the external medium is denoted as Kt, and Kab is the constant for the amount of diclofenac from the external medium to the hydrogel. The concentrations of diclofenac in its own solution within the hydrogel at times t=0 and t=∞ are denoted as A0* and A∞* respectively, while A0 and A∞ represent the concentrations of diclofenac in the external medium at times t=0 and t=∞. The equations, based on the law of conservation of mass, are given by

(17)

$$A^*{}_0 + A_0 = A^* + A = A *_\infty$$

And

(18)

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

is valid because:

(19)

$$V = \frac{dA}{dT} = K_t.A * -K_{ab}.A$$

is obtained and by adding equation 18 into equation 19 we get to equation 20: the following equation:

(20)

$$V = \frac{dA}{dT} = K_t(A^*_\infty - A_\infty - A) - K_{ab}.A$$

And by remembering the equation:

(21,22)

$K_t A^*_\infty = K_{ab}.A_\infty$ and $A^*_\infty = \frac{K_{ab}.A_\infty}{K_t}$

we can get to the increase of the first order reverse chemical reaction rate:

(23)

$$V = \frac{dA}{dT} = (K_t + K_{ab})(A_\infty - A)$$

If we add $\alpha_A = \frac{A}{A\infty}$, then the above equation transforms into the below equation:

(24)

$$V = \frac{dA}{dT} = (K_t + K_{ab})(1 - \alpha)$$

Thus, the constant rate of diclofenac drug release k_m equals the sum of constants k_t and k_{ab}:

(25)

$$K_m = K_t + K_{ab}$$

that we should remember that:

(26)

$$E_a = RT^2 \frac{\left(\frac{dv}{dT}\right)}{v}$$

By utilizing equation 22, we can readily derive the formula for the effective activation energy of the diclofenac drug release process for the first-order reverse chemical reaction, denoted as Ea,R. This value is determined by the first-order reverse chemical reaction:

(27)

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

The activation energy for the release of diclofenac from its solution in the hydrogel to the external medium (Ea,t), the activation energy for the absorption of diclofenac from the external medium to the hydrogel (Ea,ab), and the effective activation energy dependent on the released amount of diclofenac (Ea,R) are crucial parameters in this study. Determining these parameters, along with A0*, A*, and A∞* to ultimately establish the transfer rate constant of diclofenac from its solution in the hydrogel to the external medium (kt), involves a specialized combination process, considering the predetermined kinetic parameters for the transfer and absorption of diclofenac.

To validate the previous kinetic pattern, we aimed to determine the adsorption constant (Kab) representing the amount of diclofenac adsorbed from the external medium to the hydrogel. This involved using a concentration of diclofenac solution dependent on the obtained concentration of released diclofenac in the experimental test. The experiments were conducted similarly to the diclofenac release experiments at constant temperatures. Figures 5a and 5b illustrate the isothermal adsorption degrees of diclofenac solution against reaction time for acrylic acid-chitosan hydrogel and acrylic acid-chitosan hydrogel with 2-acryloyloxyethyl trimethyl ammonium chloride, and Table 7 displays the adsorption degrees parallel to the hydrogels at different temperatures in the external solution of diclofenac.

Analysis of the results indicates that an increase in temperature leads to a slight decrease in ADeq for the acrylic acid-chitosan hydrogel. However, both hydrogels (ADeq) show a greater increase overall. Furthermore, employing the proportionality model method revealed that the absorption kinetics of the external solution of diclofenac in the acrylic acid-chitosan hydrogel can be fully described by the R2 model, which is specific to the controlled phase region reaction (Table 3). This indicates that a specific equation must be valid, as per the aforementioned model:

(28)

$$-Ln(1-\alpha) = K_{m,ab}t$$

Where $K_{m,ab}$ is the constant rate model. [20]

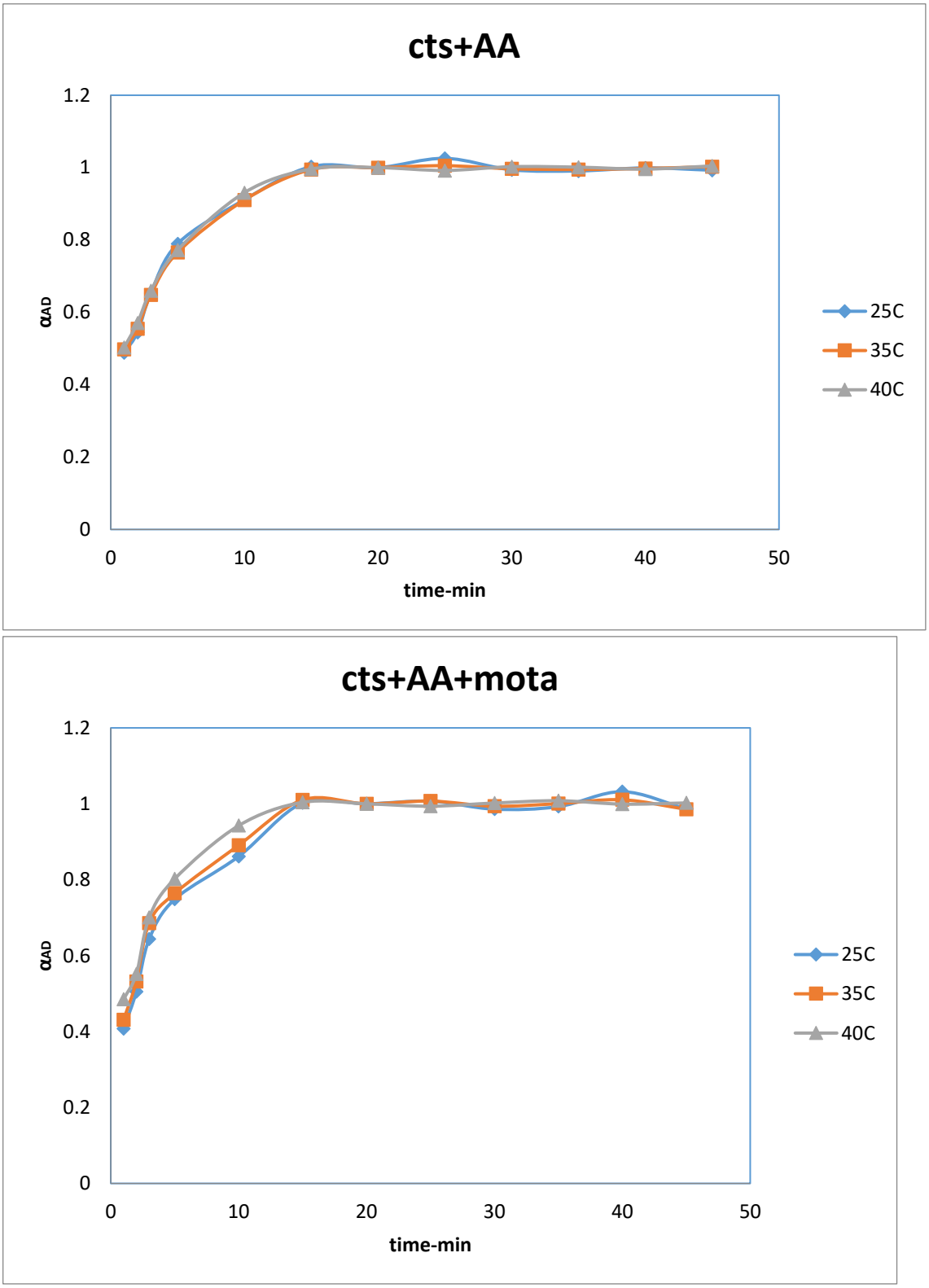


Figure 6- Absorption of external solution in hydrogels a) chitosan-acrylic acid hydrogel at temperatures of 25, 35, 40 b) chitosan-acrylic acid-2-acryloyloxyethyl trimethyl ammonium chloride hydrogel at temperatures of 25, 35, 40

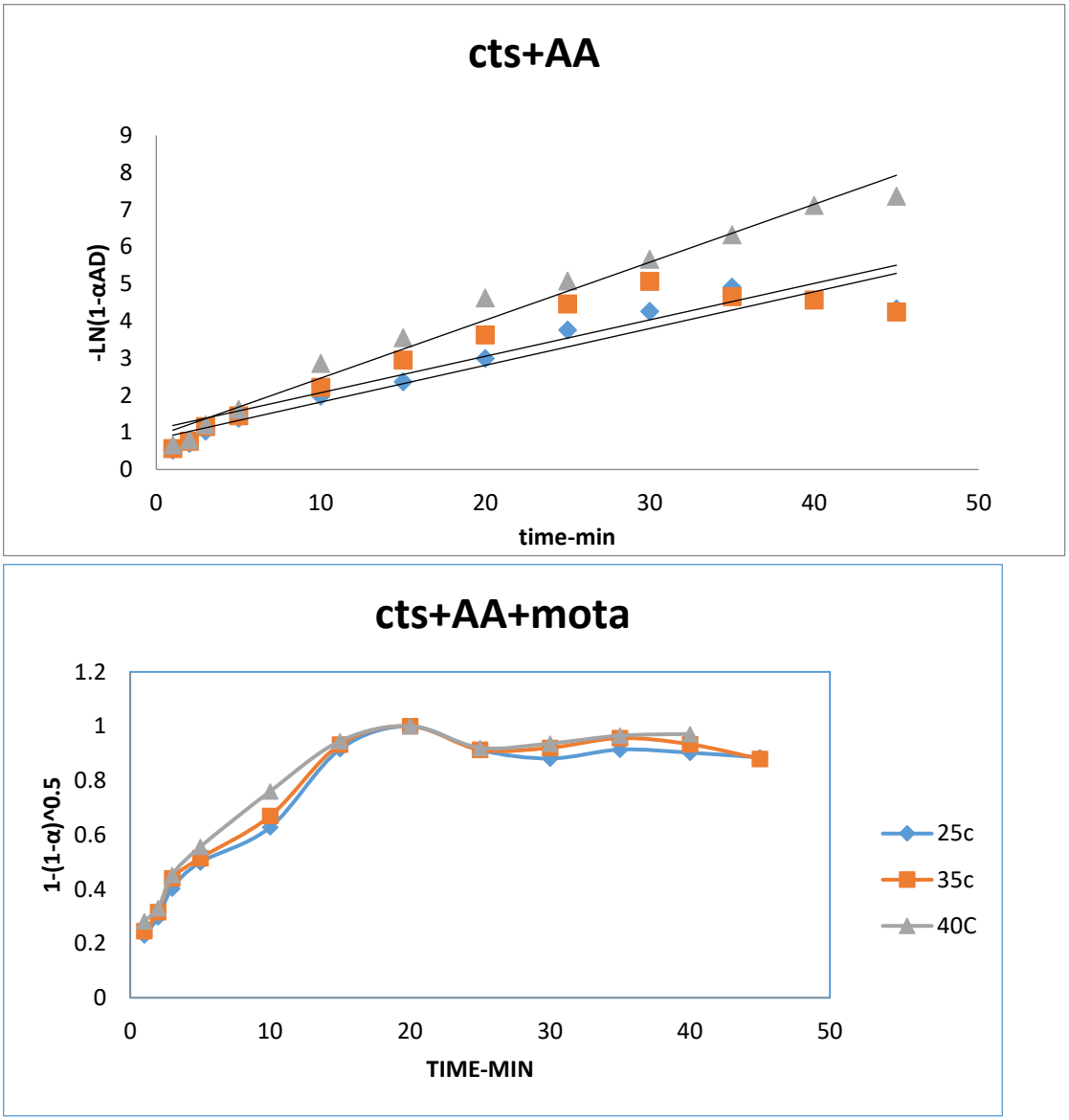


Figure 7- Plot of **1-(1-α)^0.5** versus time at temperatures of 25, 35, 40 for **cts+AA** and **cts+AA+mota** hydrogels

Table 7- Absorption capacity of CTs+AA and Cts+AA+Mota hydrogels for diclofenac drug in external solution

CTs+AA	ADeq[%]	Cts+AA+Mota	ADeq[%]
25C	518.6	25C	465.56
35C	536.85	35C	464.23
40C	537.47	40C	469.17

Conclusion

Considering that hydrogels are three-dimensional networks with significant porosity, they act as water absorbers. Due to hydrogen bonding in water molecules, a considerable amount of water molecules is physically accommodated within the hydrogel. In the hydrogel (acrylic acid-chitosan with 2-acryloyloxyethyl trimethyl ammonium chloride), strong van der Waals interactions between the hydrogel and polar ion-type water molecules result in a stronger bond between them. Consequently, it exhibits higher activation energy compared to the acrylic acid-chitosan hydrogel. With an increase in temperature, molecular movements intensify, leading to longer intermolecular bonds. As a result, molecules find greater separation, allowing more water to enter the hydrogel network. Due to the increased activity of water molecules at higher temperatures, water molecules inside the hydrogel exert higher pressure, causing reversed osmosis. Therefore, water molecules tend to exit the hydrogel network. Our studies indicate that with an increase in temperature, molecular movements increase, weakening the bonds and reducing activation energy. This makes water molecules easily exit the hydrogel.

As temperature rises, the bonds between water molecules and the hydrogel weaken, increasing pressure within the hydrogel network at higher temperatures, facilitating reverse osmosis. The obtained activation energy from kinetic equations indicates that these interactions are of a physicochemical nature. As the temperature increases, these bonds weaken, resulting in a reduced activation energy, as confirmed by experimental results aligning well with the theoretical equations. The theoretical conversion curves for water removal at different temperatures for both hydrogels, using Flory-Rehner formula and Peppas equations, have proportionally represented the conversion rate (α) against reaction times as random variables. According to the calculations, the activation energy for the acrylic acid-chitosan hydrogel is lower than that for the acrylic acid-chitosan hydrogel with 2-acryloyloxyethyl trimethyl ammonium chloride. Consequently, the drug release in the acrylic acid-chitosan hydrogel is slightly higher, consistent with both experimental and theoretical calculations.

References

[1] N.A. Peppas, A.G. Mikos, Preparation methods and structure of hydrogels, in: N.A. Peppas (Ed.), Hydrogels in Medicine and Pharmacy, vol.1, CRC Press, Boca Raton, Florida, 1986, pp. 2–23.
[2] L. Masaro, X.X. Zhu, Prog. Polym. Sci. 24 (1999) 731–775.
[3] P.L. Ritger, N.A. Peppas, J. Control. Rel. 5 (1987) 23–36.
[4] P.L. Ritger, N.A. Peppas, J. Control. Rel. 5 (1987) 37–42.
[5] S.W. Kim, Y.H.T. Bae, Pharm. Res. 9 (1992) 283–290.
[6] C.S. Brazel, N.A. Peppas, Biomaterials 20 (1999) 721–732.
[7] C.S. Brazel, N.A. Peppas, Polymer 40 (1999) 3383–3398.
[8] C.S. Brazel, N.A. Peppas, Eur. J. Pharm. Biopharm. 49 (2000) 47–58.
[9] C.C. Lin, A.T. Metters, Adv. Drug Deliver. Rev. 58 (2006) 1379–1408.
[10] N.A. Peppas, Y. Huang, M. Torres-Lugo, J.H. Ward, J. Zhang, Ann. Rev. Biomed.

Eng. 2 (2000) 9–29.

[11] N.A. Peppas, P. Bures,W. Leobandung, H. Ichikawa, Eur. J. Pharm. Biopharm. 50 (2000) 27–46.

[12] J. Siepmann, N.A. Peppas, Adv. Drug. Deliver. Rev. 48 (2001) 139–157.

[13] B. Amsden, Macromolecules 31 (1998) 8382–8395.

[14] D.G. Kanjickal, S.T. Lopina, Crit. Rev. Ther. Drug Carrier Syst. 21 (2004) 345–386.

[15] S.E. Sakiyama-Elbert, J.A. Hubbell, J. Control. Rel. 98 (2004) 389–402.

[16] R.B. Greenwald, Y.H. Choe, J. McGuire, C.D. Conover, Adv. Drug. Deliver. Rev. 55

(2003) 217–250.

[17] L. Serra, J. Doménech, N.A. Peppas, Biomaterials 27 (2006) 5440–5451.

[18] A.V. Reis, M.R. Guilherme, A.F. Rubira, E.C. Muniz, J. Coll. Inter. Sci. 310 (2007)

128–135.

[19] M. Dittgen, M. Durrani, M.K. Lehman, Pharma. Sci. Pharma Sci 7 (1997) 403–437.

[20] A. Besheer, K.M.Wood, N.A. Peppas, K. Mäder, J. Control. Rel. 111 (2006) 73–80.

[21] Z. Jurani´ c, Lj. Stevovi ´ c, B. Drakuli ´ c, T. Stanojkovi ´ c, S. Radulovi ´ c, I. Jurani´ c, J. Serb.

Chem. Soc. 64 (9) (1999) 505–512.

[22] B. Adnadjevic, J. Jovanovic, B. Drakulic, Thermochim. Acta 466 (2007) 38–48.

[23] B. Adnadjevic, J. Jovanovic, I. Krkljus, J. Appl. Polym. Sci. 107 (5) (2008)

2768–2775.

[24] J.Jovanovic, B.Adnadjevic, V.Randjelovic, D.Uskokovic, 7th International Conference

on Fundamental and Applied Aspects of Physical Chemistry, September

21-23, 2004, Belgrade, Proceedings, vol2, I-16-P, p.623-624.

[25] L. Gudman, N.A. Peppas, J. App. Pol. Sci. 55 (1995) 919.

[26] N. Peppas, Pharm. Acta Helv. 60 (4) (1985) 110–111.

[27] H. Friedman, J. Polym. Sci. 6C (1963) 183–195.

[28] M.E. Brown, D. Dollimore, A.K. Galway, Reaction in the Solid State Comprehensive

Chemical Kinetics, vol. 22, Elsevier, Amsterdam, Oxford, New York, 1980,

pp. 87–91.

[29] S. Vyazovkin, C.A.Wight, Thermochim. Acta 340/341 (1999) 53–68.

[30] A.V. Reis, M.R. Guilherme, A.F. Rubira, E.C. Muniz, J. Coll. Interf. Sci. 310 (2007)

128–135.

[31] S. Vyazovkin,W. Linert, Int. Rev. Phys. Chem. 142 (2) (1995) 355–369.