Numerical Analysis of Temperature-Sensitive Hydrogels for Controlled Drug Release

Kiana Pourabdollah¹, Hamid Rashedi¹*, Hossein Golzar¹, Morteza Garshasbi²

Abstract

Today hydrogels are considered as the materials that are able to play important role in drug delivery systems. To design an effective hydrogel applicable network, mathematical modeling has a critical role. A successful drug delivery device relies not only on intelligent network design but also on accurate prior mathematical modeling of drug release profiles. In this study, the modeling of the inflation behavior of temperature-sensitive hydrogel has been done by providing a mathematical model according to the thermodynamics and kinetics of the temperature-sensitive gel and also considering the heat transfer into the hydrogels during the inflation. The proposed model has been investigated numerically. The comparison between numerical and experimental results shows perfectly success in integrating equations of inflation thermodynamics and kinetics for modeling the inflation behavior of temperature-sensitive hydrogels that provide a new step in the modeling of such systems.

Keywords: Hydrogel, Mathematical Modeling, Drug Delivery, Temperature-Sensitive

Introduction

Hydrogels are hydrophilic homopolymer or copolymer networks that are swollen with water intrusion into their networks and can absorb large amounts of water (up to a thousand times the dry weight). They have three-dimensional construction which cross-links between the chains that prevent network from being dissolved in solvents and just swelling phenomenon occurs through solvent entry [1, 2].

In recent years, many studies have been done on hydrogels and they are highly regarded due to its hydrophilic, biocompatible and their application in the medical field [1, 3]. Gel properties can be evaluated in terms of absorption capacity, kinetics of swelling, permeability, surface properties, mechanical and optical properties but the most important parameter that affects other properties is the degree of swelling of the gel [1, 4]. Material, which its properties such as inflation volume changes in response to environmental changes, including: temperature, PH, electric field, light intensity, ionic strength or certain chemicals such as glucose, is called Smart hydrogel [5, 6]. Temperature-sensitive hydrogels have the ability to change the size proportional to the temperature change, by the ability of inflation and backlog in response to changes in temperature, have attracted much attention in the pharmaceutical field [7–9]. The main use of smart polymers including temperature-sensitive hydrogels is controlled drug release. In this system, drugs to be put at the disposal of the body based on biological needs and it is an ideal delivery method for the treatment of cancer, diabetes and long-term fever [9].

Another application of temperature-sensitive hydrogel can be noted in its application in the field of separation [5], as the substrate for efficiency of immobilized enzyme [10, 11]. The main mechanism of controlled release systems is modeled by Fick's second law of diffusion, which leads to problems in the initial values of the border [12, 13]. The drug release system is a problem with moving boundaries [14]. Higuchi [15] introduced approximate solution for drug release system with movable boundary conditions under which a flat geometry of quasi-steady approximation regardless of boundary layers. Higuchi [16] also used the quasi-steady approximation to achieve a similar solution for spherical granules. By applying these methods rely on the initial drug loading is much greater than the solubility of the drug in the matrix, ideally, when the initial drug load at least three times the solubility of the drug in a polymeric matrix. Paul and McSpadden using a combination of variables to achieve exact answer of drug release from flat system in complete dissolution. Lee did not adopt quasi-steady approximation method but used heat treatment integral balance method instead. This method does not limit the initial loading, such as Higuchi equations [17].

AbdeKhodaie and Cheng by using a combination of variables, tried to develop the exact solution of spherical drug release from polymer network in both limited and unlimited external environment, although this solution is effective only by assuming steady state in the unlimited external environment [18].

Several models were proposed to describe the main mechanism of mass transport of swelling-controlled release systems [19–21], although only a small number of models had been suggested in mechanistic form for physicochemical phenomena during drug release. Tu and Ouano assumed Fick diffusivity for penetrating solvent in a polymer network and concentration dependence of the diffusion coefficient of solvent that has two moving boundaries, equal in
their model [22]. They presented a fuzzy model of Stephen and use of the concept of separation rates for illustrating the concept of polymer [23], the weakness of this approach is that the separation rate is used as a parameter of the model.

In order to facilitate modeling, in most models that have been provided for temperature-sensitive hydrogels, inflation process is intended to be isotherm at the final temperature and has not been investigated heat transfer phenomena into the gel. In this study, a mathematical model will be considered which predicts changes in the amount of inflation of an intelligent temperature-sensitive hydrogel, proportion to time in response to the step changes in the surrounding temperature. The temperature-sensitive gel swelling kinetics can be achieved by considering the heat transfer within the hydrogel. In fact, the modeling the behavior of inflation temperature-sensitive hydrogels is performed by providing a new mathematical model according to the Thermodynamics and Kinetics of the temperature-sensitive gel and also taking heat transfer into the hydrogel during the process of inflation and deflation. The outline of this paper is as follows:

In section 2, the temperature-sensitive hydrogel inflation thermodynamic model and dynamic modeling of temperature-sensitive hydrogel swelling are introduced. Section 3 concerns with the numerical solution of the equations derived in section 2. Section 4 contains some discussion regards to the numerical and experimental results.

Material and Methods

Model formulation

It’s clear that hydrogel perching at an initial temperature T1, in an environment with temperature T2, creates a temperature profile in a hydrogel that functions as space and time. On the other hand, the hydrogels are so sensitive to temperature change, therefore the amount of inflation will vary with temperature change at any time or location and gel volume increases in response to the temperature change. The relationship between the amount of hydrogel inflation and temperature is described by using thermodynamics inflation. Thus, a suitable thermodynamic equation should be chosen for desired system to determine the amount of inflation due to the temperature profile at any time or location within the hydrogel.

Here to present our interest mathematical model, following assumptions are considered:

- The physical properties (density of pure polymer and water, thermal conductivity, specific heat capacity, the solvent diffusion coefficient) are assumed to be constant.
- In all parts of the gel corresponding to each temperature, solvent diffusion coefficient) are assumed to be constant.
- The physical properties (density of pure polymer and water, thermal conductivity, specific heat capacity, the solvent diffusion coefficient) are assumed to be constant.

Temperature-sensitive hydrogel inflation thermodynamic model

One of the most comprehensive choices for describing the inflation thermodynamic is use of extended Flory-Huggins model for the free energy of mixing. This model considers the affiliation to temperature and properties of hydrogels and is suitable for temperature-sensitive hydrogel system. One may right this model as [24]:

\[(\Delta \mu)_{\text{swel}} = \varphi_v + \ln(1 - \varphi_v) + \frac{d_1}{d_0} \left[ \frac{\varphi_v^2}{M_c} \left( \varphi_v \varphi_v - \varphi_v \right) \right] = 0.\]

where \(\varphi_v\), \(\varphi_v\), \(\rho\), \(v_1\), \(M_c\) and \(\varphi_0\) and represent the polymer volume fraction in the swollen hydrogel network, solvent volume fraction in the swollen hydrogel network, hydrogel density, the molar volume of solvent, average molecular weight (between chain) and the volume fraction of polymer in the synthesis conditions. \(b\), \(d_1\) and \(d_0\) and are adjustable parameters.

The parameters, \(\rho\), \(v_1\), \(M_c\), \(b\), \(d_1\) and \(d_0\) should be determined by experimental data. For this purpose, in this project, we use the experimental data related to the temperature-sensitive hydrogel poly (vinyl methyl ether) studied by Huang et al. (1987) [25].

The advantage of hydrogels used in this study is that the temperature of sudden volume change (inflation / deflation) PVMEG hydrogel system is about 310°k (37°c). Therefore, no copolymer with different comonomer, transition temperature of inflation to shrinkage is close to body temperature and the system is suitable for using in the field of drug delivery. The hydrogels used in this article are cross linked by radiation of radiochemical, so the experimental data of tension-strain elastic behavior is not available. For this reason unlike gels that are chemically networked, \(M_c\) parameter must also be considered along with \(b\), \(d_1\) and \(d_0\) as adjustable parameters.

By using the least square curve fitting package in MATLAB software, from compliance thermodynamic equation of inflation and inflation experimental data in terms of temperature [25] parameters were calculated with great precision and the final equation derived as follows:

\[\varphi_v + \ln(1 - \varphi_v) + \left( 1 - \frac{19946}{T} \right) \left( \frac{\varphi_v^2}{1 - 0.8 \varphi_v} \right) \left( \frac{1}{1542.1} \right) \left( \varphi_v \varphi_v - \varphi_v \right) = 0.\]

Dynamic modeling of temperature-sensitive hydrogel swelling

The total mass balance and the balance of the cylindrical temperature-sensitive polymer hydrogel system can be derived as the following equations, respectively:

\[
D \frac{\partial^2 \varphi_v}{\partial r^2} + \frac{2 \varphi_v \sin \theta \cos \theta}{\partial z} + \frac{\partial \varphi_v}{\partial z} + \frac{2 \varphi_v \sin \theta \cos \theta}{\partial r} = \frac{2 \varphi_v \sin \theta \cos \theta}{\partial r} + \frac{\partial \varphi_v}{\partial z} \]

\[
D \frac{\partial^2 \varphi_v}{\partial r^2} + \frac{2 \varphi_v \sin \theta \cos \theta}{\partial z} + \frac{\partial \varphi_v}{\partial z} + \frac{2 \varphi_v \sin \theta \cos \theta}{\partial r} = \frac{2 \varphi_v \sin \theta \cos \theta}{\partial r} + \frac{\partial \varphi_v}{\partial z} \]

\[
D \frac{\partial^2 \varphi_v}{\partial r^2} + \frac{2 \varphi_v \sin \theta \cos \theta}{\partial z} + \frac{\partial \varphi_v}{\partial z} + \frac{2 \varphi_v \sin \theta \cos \theta}{\partial r} = \frac{2 \varphi_v \sin \theta \cos \theta}{\partial r} + \frac{\partial \varphi_v}{\partial z} \]

\[
D \frac{\partial^2 \varphi_v}{\partial r^2} + \frac{2 \varphi_v \sin \theta \cos \theta}{\partial z} + \frac{\partial \varphi_v}{\partial z} + \frac{2 \varphi_v \sin \theta \cos \theta}{\partial r} = \frac{2 \varphi_v \sin \theta \cos \theta}{\partial r} + \frac{\partial \varphi_v}{\partial z} \]

Where \( D \) and \( K \) show the diffusion coefficient of water in the hydrogel and the proportion of dry hydrogel density to water density.

After deciding the criteria, the balance of thermal energy for temperature-sensitive hydrogel in cylindrical coordinates can be derived as follows:

\[
\frac{\partial T}{\partial t} = \left[ \frac{D}{K + \varphi(1-K)} \right] \left[ \frac{\partial^2 T}{\partial \rho^2} \sin \theta + \frac{\partial^2 T}{\partial z^2} \cos \theta - V \right] \left[ \frac{\partial T}{\partial \rho^2} \sin \theta + \frac{\partial T}{\partial z^2} \cos \theta \right] + \frac{K_z}{\rho_s + \varphi(1-\rho_s)} \left[ \frac{2}{\sqrt{\rho_s^2 + z^2}} \frac{\partial T}{\partial \rho} \sin \theta + \frac{\partial T}{\partial z} \cos \theta \right].
\]

Due to the swell of the hydrogel, the following equation is considered for the moveable level that is located on the common border of hydrogel and fluid surroundings.

\[
\frac{dR}{dt} = V \mid R(t).
\]

Initial conditions are described by Eq. (7), (8):

\[
t = 0: \quad T = T_{\text{initial}}
\]
\[
t = 0: \quad R_{0i} = R_i.
\]

And boundary conditions can be written as:

\[
\left\{ \frac{\partial T}{\partial \rho^2} \sin \theta + \frac{\partial T}{\partial z^2} \cos \theta \right\} = 0
\]
\[
\left\{ \frac{\partial V}{\partial \rho^2} \sin \theta + \frac{\partial V}{\partial z^2} \cos \theta \right\} = 0
\]

Symmetry condition in the center of a cylindrical

\[
r = 0
\]
\[
R_0 = R(t) \quad T = T_{\text{final}}.
\]

**Numerical solution**

In order to solve Eq. (2), (3), (5), first, Eq. (2) is used to obtain temperature dependency based on the volume fraction of the water. From the integration of the Eq. (2) and (5), after performing some mathematical operations and sequential differentiation, the following equation can be derived

\[
\frac{\partial \varphi}{\partial t} = \frac{K_z}{k + \varphi(1-k)} \left[ \frac{\partial^3 \varphi}{\partial \rho^3} \sin \theta + 2 \frac{\partial^3 \varphi}{\partial \rho^2 \partial z} \sin \theta \cos \theta + \frac{\partial^3 \varphi}{\partial z^3} \cos \theta \right] + \left[ \frac{D}{k + \varphi(1-k)} \right] \left[ \frac{\partial \varphi}{\partial \rho} \sin \theta + \frac{\partial \varphi}{\partial z} \cos \theta \right]^2,
\]

where \( F(\varphi) = T \). Now using following new variables

\[
z = \frac{\sqrt{\rho^2 + z^2}}{R_0},
\]
\[
Z = \frac{R(z)}{R_0},
\]

where \( z \) and \( Z \) represent the location within the hydrogel (dimensionless number between zero and one) and the location of a moveable interface (dimensionless), one can derive following equation

\[
\frac{\partial \varphi}{\partial t} = \frac{2k_z}{(k + \varphi(1-k))} \left[ \frac{\partial \varphi}{\partial z} \right]^2 + \frac{1}{Z} \left[ \frac{\partial \varphi}{\partial t} \right] \left[ \frac{D}{k + \varphi(1-k)} \right] \left[ \frac{\partial^2 \varphi}{\partial \rho \partial z} \sin \theta + \frac{\partial \varphi}{\partial z} \cos \theta \right] + \frac{1}{Z^2} \left[ \frac{\partial^2 \varphi}{\partial \rho^2} \sin \theta + \frac{\partial \varphi}{\partial z} \cos \theta \right] + \frac{1}{Z^2} \left[ \frac{\partial^2 \varphi}{\partial z^2} \cos \theta \right],
\]
\[
\frac{z}{Z} \frac{dV}{dz} + z+Z = D \left[ z \frac{\partial \varphi}{\partial z^2} + 2z \frac{\partial \varphi}{\partial z} \right]
\]
\[
\frac{dZ}{dt} = V \mid z = 1.
\]

So the initial and boundary conditions can be rearranged as follows

\[
\begin{aligned}
\text{Initial conditions:} & \quad t = 0 \quad \text{and} \quad 0 \leq z \leq 1 \\
\varphi = \varphi_o \\
Z = 1 \\
V = 0
\end{aligned}
\]
\[
\begin{aligned}
\text{Boundary conditions:} & \quad Z = 0 \quad \frac{\partial \varphi}{\partial z} = 0 \\
Z = 0 \quad \frac{\partial V}{\partial z} = 0
\end{aligned}
\]

In this article for numerical solution of the nonlinear partial differential equations obtained in this section, the finite difference method in the implicit manner and the definition of derivatives with Crank-Nicolson method that is suitable for modeling transport phenomena [26–29].

The proposed numerical method is as follows:

By dividing the space into \( N \) equal parts:

\[
Z = N \Delta z
\]
\[
\text{for} \quad i = 1,2,3,...,N+1 \rightarrow Z = (i - 1) \Delta z.
\]

And due to boundary conditions:
The system of equations can be investigated in three modes: In the center of the hydrogel (i=1), in the middle of the hydrogel (i=2, 3, ..., N) and in the surface of the hydrogel (i=N+1). Due to boundary conditions, defined derivatives and use of the Crank-Nicolson method, the following equations are obtained:

\[
\begin{align*}
\frac{\partial \phi}{\partial t} &= 0 \rightarrow 3\phi_{i,j+1} + 4\phi_{i,j+1} - 3\phi_{i,j} - 4\phi_{i,j-1} + \phi_{i,j+2} \\
\frac{\partial \phi}{\partial z} &= 0 \rightarrow 3\phi_{i,j+1} + \phi_{i,j-1} - 3\phi_{i,j} - \phi_{i,j+2} + \phi_{i,j-2}
\end{align*}
\]

In the center of the hydrogel:

\[
\begin{align*}
\frac{\partial \phi}{\partial t} &= 0 \rightarrow 3\phi_{i,j+1} + 4\phi_{i,j+1} - 3\phi_{i,j} - 4\phi_{i,j-1} + \phi_{i,j+2} \\
\frac{\partial \phi}{\partial z} &= 0 \rightarrow 3\phi_{i,j+1} + \phi_{i,j-1} - 3\phi_{i,j} - \phi_{i,j+2} + \phi_{i,j-2}
\end{align*}
\]

Discretizing the Eq. (13) yields:

\[
\begin{align*}
\frac{\phi_{i,j+1} - \phi_{i,j}}{\Delta t} &= \frac{4}{\Delta z^2} \left[ \phi_{i,j+1} - 2\phi_{i,j+1} + \phi_{i,j-1} \right] \\
\frac{\partial \phi}{\partial z} &= 0 \rightarrow 3\phi_{i,j+1} + \phi_{i,j-1} - 3\phi_{i,j} - \phi_{i,j+2} + \phi_{i,j-2}
\end{align*}
\]

In the middle of the hydrogel, Eq. (14) can be written as:

\[
\begin{align*}
\frac{\phi_{i,j+1} - \phi_{i,j}}{\Delta t} &= \frac{4}{\Delta z^2} \left[ \phi_{i,j+1} - 2\phi_{i,j+1} + \phi_{i,j-1} \right] \\
\frac{\partial \phi}{\partial z} &= 0 \rightarrow 3\phi_{i,j+1} + \phi_{i,j-1} - 3\phi_{i,j} - \phi_{i,j+2} + \phi_{i,j-2}
\end{align*}
\]

In the surface of the hydrogel, Eq. (15) can be written as:

\[
\frac{\phi_{i,j+1} - \phi_{i,j}}{\Delta t} = \frac{4}{\Delta z^2} \left[ \phi_{i,j+1} - 2\phi_{i,j+1} + \phi_{i,j-1} \right]
\]

Now, two sets of non-linear algebraic equations are created, one of them is related to the speed (V) and the other is related to the volume fraction of water (φ). In written algorithm that was considered in an array with 2N + 2 members, named xnew, that the elements 1 to N + 1 are related to φ values at the time of j + 1 and elements N + 2 to 2N + 2 are related to the velocity at the time of j + 1.

Also an array was considered with 2N + 2 members and with name of xold that the elements 1 to N + 1 are related to φ at the time of j + 1 and elements N + 2 to 2N + 2 are related to the velocity at the time of j.

Thus, at any given time a series of equations is assumed with N (The number of divisions), delz (intervals place), delt (intervals time), xold and an initial guess for xnew that z = zfinal (achieving the final equilibrium volume).

To solve the foregoing equations, programming is done in Matlab software. The series of equations can be solved if experimental data of inflation kinetics of hydrogel that we determined its thermodynamic state with the Eq. (2) is available. Therefore, inflation dynamics of poly (vinyl methyl ether) hydrogels are examined accordance with reported synthesis conditions in Huang et al. [25].

In addition, to solve a system of equations, it is necessary to specify the following values: hydrogel radius at the initial balance of temperature (\(R_0\)), hydrogel radius at the final balance of temperature (\(R_{final}\)), ratio of \(\frac{V_{final}}{V_{final}}\) (k), D (Diffusion coefficient) and the proportion of thermal conductivity coefficient of hydrogel to specific heat capacity of hydrogel (KgCp). In relation to the first three parameters, Experimental data is available in [25]. The value of the diffusion coefficient of the same type of hydrogel has been reported in another article by Gehrke et al., [30].

The advantages of the reported diffusion coefficient are that the average diffusion coefficient during the process of inflation and contraction of hydrogels has been reported, and that plays the important role of many errors caused by not getting diffusion coefficient variable. (KgCp) is an adjustable parameter in the equation, which has been obtained from compliance modeling results with experimental results of kinetics inflation.
Results and Discussion

Values of the parameters used in the simulations are presented in Table 1.

Table 1. Values of the parameters used in the simulations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\bar{M}_e$</td>
<td>1542.1 gr/mol</td>
</tr>
<tr>
<td>$D$</td>
<td>$2.7 \times 10^{-7}$ m$^2$/s</td>
</tr>
<tr>
<td>$K$</td>
<td>1.34 water density</td>
</tr>
<tr>
<td>$d_1$</td>
<td>-1994.6 Adjustable parameters</td>
</tr>
<tr>
<td>$d_2$</td>
<td>7 Adjustable parameters</td>
</tr>
<tr>
<td>$k_s/c_s$</td>
<td>$6.4 \times 10^3$</td>
</tr>
<tr>
<td>$\rho$</td>
<td>1.34 Hydrogel density gr/cm$^3$</td>
</tr>
<tr>
<td>$V_i$</td>
<td>18 Solvent molar volume cm$^3$/mol</td>
</tr>
<tr>
<td>$\varphi_0$</td>
<td>0.96 Volume fraction of polymer in synthesis conditions</td>
</tr>
</tbody>
</table>

The results of thermodynamic equation of inflation

Comparison of the results obtained from the thermodynamic model was selected in section 2.1 and experimental results on equilibrium inflation of temperature-sensitive poly (vinyl methyl ether) hydrogel that is made by Huang et al [25] are provided in Fig. 1, 2, and 3.

Figure 1. Equilibrium volume fraction of water in the hydrogel in terms of temperature.

The simulated and measured values of the volume fraction of water in the equilibrium inflation of hydrogel, in terms of the corresponding temperature, are depicted in Fig. 1. The values of hydrogel volume in the state of equilibrium inflation, in terms of the corresponding temperature, are shown in Fig. 2.

Figure 2. Equilibrium inflation of hydrogel volume in terms of temperature.

In the same way, semi-logarithmic graph of temperature according to equilibrium inflation volume ratio at a corresponding temperature to the initial volume of non-swollen hydrogel is shown in Fig. 3.

Figure 3. Semi-logarithmic graph of temperature according to inflation volumes ratio.

As can be seen in the graph with increasing temperature, the hydrogel swelling is reduced and at the experimental temperature, 310 K, hydrogel reaches the steady volume which is the non-swollen volume of hydrogel in synthesis conditions. It can be stated that according to the chemical structure of the poly (vinyl methyl ether) hydrogel, it is predicted that at low temperatures, between water molecules and hydrogel, hydrogel bonds are established and by increasing the temperature the hydrogen bonds get weakened and destroyed so the hydrogel contracts. According to the concordance of the results of selected thermodynamic models, experimental results of equilibrium swelling and according to the selected equation, predicts temperature of sudden volume change of gel (310 k) with good accuracy (310,895 k), it can be stated that the selection of Eq. (2) on the base of Flory-Rehner and Extended Flory-Huggins models for the hydrogel systems which was
studied, was an appropriate choice and also adjustable parameters of model $M_c = 1542.1$ gr/mol and $b = 0.8$, $d_0 = 7$, $d_1 = -1994.6$ k are well-settled. So, selected thermodynamic equation can be used in the kinetic modeling of inflation. 

The results of kinetic equations of inflation for poly (vinyl methyl Ether) hydrogel

Change of Inflammatory properties of poly (vinyl methyl ether) hydrogel in response to changes in ambient temperature has been shown in Fig. 4. In the other words, kinetics inflation (volume change over time) of temperature-sensitive poly (vinyl methyl ether) hydrogels, based on the results of the model, in response to temperature changes are shown in these charts and compared with experimental results. In the charts provided in Fig. 4, non-swollen hydrogel with an initial radius, $R_0 = 0.81$cm, and initial temperature, $T_0 = 321K$, is placed in the vicinity of pure water with different temperatures 298K, 295K, 303K. Results of the model and also experimental results are shown that the volume of hydrogels increased in response to this temperature changes and after a certain time, the volume reaches the final balance.

Comparison between the charts shows that by reducing the temperature of the surrounding, volume changes are getting faster and in the other words, the speed of hydrogel response become faster.

Kinetics of changes in volume and contraction of the gel in response to increasing ambient temperature is also shown in Fig. 5. The results of the numerical model and also experimental results of the gels contraction phenomena are shown in the charts of Fig. 5.

In the charts of Fig. 5 hydrogel with an initial radius, $R_0 = 1.56$, cm is in the equilibrium inflation with ambient temperature, $T_0 = 293.5K$. The kinetics of the hydrogels contraction, are shown in these charts, after exposure to environments with different temperatures (308K, 303K, 313K). As Fig. 5 illustrates, at higher final temperature, the speed of accountability of hydrogel increased and contraction occurred faster which was in conformity with experimental observation.

Reversibility of volume change process of poly (vinyl methyl ether) hydrogels that had been confirmed by experimental results was confirmed by modeling results. Comparison between the graphs of inflation (or swelling) and contraction of hydrogel in Fig. 6 shows that contraction phenomenon occurs in a shorter time than inflation.

Justifying this action can be mentioned to reduce the thickness of the hydrogel in the process of contraction and its impact on accelerating the heat transition. Also, according to the theory that has been proposed by Gehrke [5], friction between the hydrogel and the surrounding fluid is proportional to $\eta V^2 \xi^2$. Where $\eta$, $V$ and $\xi$ represent the fluid viscosity, speed of progressive limit of gel and mesh size in the hydrogel network.

Therefore, at the beginning of the process of contraction that meshes have maximum dimensions, friction gets lower in comparison with starting of inflation process and it can be expected that the contraction process occurs faster than inflation.
Conclusion
According to the results, presented mathematical model for studying kinetics of inflation of temperature-sensitive hydrogel in this study, can be used very well to estimate the rate of absorption of water and predict the response time of hydrogels to changing in the surrounding temperature, which is important in the field of hydrogel application in biological separation phenomena. Due to the ability of proposed model in the field of modeling the inflation behavior of temperature-sensitive hydrogels, in the next steps the influence of the drug diffusion equations can be considered and the drug release from such hydrogels can also be evaluated by simultaneously solving the system of equations.

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References
## Supplements

### Nomenclature

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>Molar volume ((cm^3/mol))</td>
</tr>
<tr>
<td>D</td>
<td>Diffusion coefficient ((m^2/s))</td>
</tr>
<tr>
<td>S</td>
<td>Surface area ((m^2))</td>
</tr>
<tr>
<td>T</td>
<td>Absolute temperature (°k)</td>
</tr>
<tr>
<td>(\rho)</td>
<td>Density of hydrogel system ((gr/cm^3))</td>
</tr>
<tr>
<td>(\rho_W)</td>
<td>Water density ((gr/cm^3))</td>
</tr>
<tr>
<td>(\rho_p)</td>
<td>Density of dry hydrogel ((gr/cm^3))</td>
</tr>
<tr>
<td>(\varphi_p)</td>
<td>The volume fraction of polymer in the inflated hydrogel</td>
</tr>
<tr>
<td>(\varphi)</td>
<td>The volume fraction of water in the inflated hydrogel</td>
</tr>
<tr>
<td>(\varphi_{initial})</td>
<td>The equilibrium volume fraction of water in the hydrogel (in the initial temperature)</td>
</tr>
<tr>
<td>(\varphi_{final})</td>
<td>The equilibrium volume fraction of water in the hydrogel (in the final temperature)</td>
</tr>
<tr>
<td>C</td>
<td>Mass concentration of water in the inflated hydrogel ((mol/cm^3))</td>
</tr>
<tr>
<td>(K_g)</td>
<td>Hydrogel thermal conductivity coefficient ((r/mol.°k))</td>
</tr>
<tr>
<td>(C_p)</td>
<td>Hydrogel specific heat capacity ((r/mol.°k))</td>
</tr>
<tr>
<td>(V)</td>
<td>Hydrogel bulk speed ((cm/s))</td>
</tr>
<tr>
<td>T</td>
<td>Time ((s))</td>
</tr>
<tr>
<td>(R(t))</td>
<td>Inflated hydrogel radius at time (t) ((cm))</td>
</tr>
<tr>
<td>(R_0)</td>
<td>Initial hydrogel radius ((cm))</td>
</tr>
<tr>
<td>(R_f)</td>
<td>Final hydrogel radius ((cm))</td>
</tr>
<tr>
<td>Z</td>
<td>Dimensionless distance</td>
</tr>
<tr>
<td>(Z)</td>
<td>position of dimensionless intersection</td>
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</tbody>
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