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ORIGINAL ARTICLE

Simulation of Drug Release in Expanding Hydrogels Containing Chitosan and Gelatin

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ABSTRACT: Utilizing mathematical modeling of drug release is one method for accelerating the rate of drug diffusion and penetration in hydrogel-based systems. This method facilitates a greater comprehension of drug control mechanisms and their release. Hydrogels are expanding biomaterials that necessitate regulation for use in drug release. The current study's objective is to model drug release in swelling hydrogels containing combinations of chitosan and gelatin polymers; with the aid of this simulation, the release time and concentration of the drug can be predicted. This modeling examined changes in the concentration of drugs in various hydrogels. For this simulation, the governing equations of the drug release system in Python and the numerical solution method were utilized to determine the drug release mechanism in the hydrogel. Then, the graphs of the changes in drug concentration in each hydrogel were examined to evaluate the performance of hydrogels in drug release. Observations revealed that the swelling rate of the hydrogel increases as the concentration of chitosan relative to gelatin in the hydrogel composition rises and that the drug release rate in hydrogels with more significant swelling was also accelerated. Compared to Cs-Gel (1:4) hydrogel, the drug release time in Cs-Gel (4:1), Cs-Gel (3:2), Cs-Gel (2.5:2.5) and Cs-Gel (2:3) hydrogels decreased by 52, 44, 37, and 18%, respectively. In hydrogels with a high swelling rate, the drug concentration decreased rapidly, whereas in hydrogels with a low swelling rate, the duration of drug release increased. This is due to the significance of mass transfer via mass movement and inflation rate.

INTRODUCTION

Considering the rise of sensitive protein and peptide drugs, developing new drug delivery systems to regulate drug concentrations within the body appears indispensable [1]. In addition, traditional drug delivery systems lack practical control over drug release timing, location, and rate [2]. In addition, the drug concentration in the blood fluctuates frequently and may exceed the therapeutic range, causing additional side effects [3]. With modern drug delivery systems, the speed, location,

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and timing of drug release can be precisely controlled [4-8].

Hydrogels have garnered much attention among the polymer systems used as drug containers or barriers to control the release rate [9]. Hydrogel is a three-dimensional network with transverse connections that can absorb and retain water several times in , and the kinetic performance of hydrogels with different compounds was compared [10, 11].

Due to their ability to form edible films and coatings, chitosan and gelatin have garnered a great deal of attention among biopolymers. Chitin is deacetylated to create the polycationic polysaccharide chitosan biopolymer [12]. Chitosan is the second most abundant polymer in nature, second only to cellulose, a linear biopolymer composed of multiple units [13]. Chitosan is non-toxic, compatible, free of antigenic effects, and biodegradable. It includes, from a technical standpoint, the antimicrobial properties of forming protective tissue films and coatings, the bonding properties and bonding with other biopolymers, and the antioxidant activity [14]. Chitosan is typically combined with other hydrophilic biopolymers due to its poor mechanical properties and vapor permeability [15].

Gelatin is water-soluble collagen and a linear polymer with excellent film-forming properties. It has a water-like consistency, and its gel resistance is essentially concentration-dependent. The ability of gelatin coatings to effectively inhibit oxygen makes them useful as lipid anti-oxidation agents and for delaying the growth of molds [16]. The mechanical and barrier properties of gelatin films and coatings can be improved by producing composite films of different biopolymers, such as proteins, lipids, and polysaccharides [17]. Chitosan-gelatin films are reportedly fabricated to improve the physicochemical properties of chitosan and plain gelatin coatings. Electrostatic and hydrogen bonds mediate the interaction between chitosan and gelatin, resulting in the emergence of new physical properties and new applications for these compounds [18].

Studies conducted on swelling hydrogels revealed that in different polymer ratios, hydrogels have a structure with open and interconnected pores. The swelling rate of the hydrogel and the size of the holes increase as the concentration of chitosan in the polymer composition increases. While, the cavity wall's thickness decreases as the ratio of chitosan to gelatin increases, and the cavity's surface area increases [19-21]. According to some studies, chitosan hydrogel has lower porosity and pore size than chitosan-gelatin hydrogel. Furthermore, chitosan hydrogel has a higher swelling rate and lower degradability than chitosan-gelatin hydrogel [22, 23]. Various chitosan and gelatin compounds have been used to create porous hydrogels through various methods in the studies conducted [24]. Most of these studies have investigated the degree of swelling, porosity, flexibility, and degradability of hydrogels. In contrast, drug release in different environments has been considered in a small number of studies.

Inside the hydrogel, there are various types of drug release systems that are either concentrated (reservoir) or distributed in the polymer network (matrix). Also, there are multiple methods for controlling the release of drugs from hydrogel, including the permeation-controlled system, the swelling-controlled system, and the environment-sensitive system [25]. In the current study, an inflation-controlled system is desired.

Modern medicine necessitates the development of drug delivery systems to regulate the concentration and rate of drug release within the body. In light of the paucity of research on drug release, this study must be conducted. The current study's purpose is to numerically simulate drug release from swelling hydrogel. The present study's novelty is examining models containing various chitosan-to-gelatin ratios. Consequently, the drug release rate at various times has been modeled using the swelling rate of hydrogels, Python engineering software, and numerical equations that govern the hydrogel system. Then, the obtained results are used to compare the rate of drug release in hydrogels.

MATERIALS AND METHODS

The current study aimed to develop a numerical drug release model from swelling hydrogel. After t=0, the hydrogel was brought into contact with the simulated liquid. The hydrogel boundary expanded as time progressed. Using the presented model, the drug release profile for various models of hydrogel boundary swelling was analyzed using Python simulation software and other researchers' laboratory findings.

Inflation-controlled release systems are examined in the current study. Drug release in these systems is possible through penetration and swelling. Like the matrix network, the drug is dispersed within the polymer. The density of these systems, influenced by the surrounding environmental conditions, allows the drug to permeate from the system to the environment. Due to the increase in mass transfer distance in these types of systems, it is impossible to release the drug with a constant intensity, and the intensity of the drug transfer decreases over time. When these systems come into contact with a fluid, they begin to swell, and the drug is then transferred from these systems via permeation. The drug penetrates the surrounding environment in the swollen layer of the system, as shown in Figure 1. In this system, drug transfer facilitated by swelling can also increase drug transfer intensity.

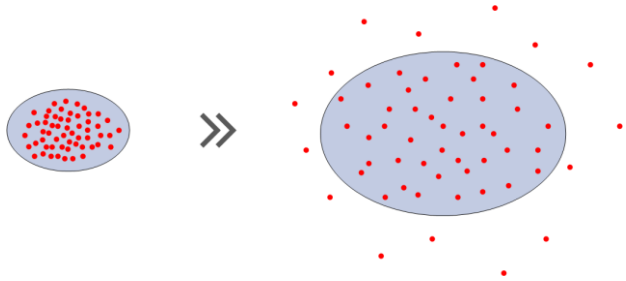

Figure 1. Schematic form of drug permeation mechanism in a swelling hydrogel to time.

Changes in drug concentration were modeled as a one-dimensional function of location (x) and time to describe drug penetration in a swelling hydrogel (t). In addition, the drug penetrates the system boundary and enters the surrounding environment. Equation 1 is the general motion-permeation equation for all mass transfer systems:

$$\frac{\partial c}{\partial t} = D\nabla^2 c - \nabla(cu) \quad (1)$$

where, c represents the drug's concentration, and u represents its penetration rate. Given that penetration is considered in only one dimension in the current study, equation 1 is written as equation 2:

$$\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2} - c\frac{\partial u}{\partial x} - \frac{\partial c}{\partial x}u \quad (2)$$

As the initial condition of the equation, it was assumed that the concentration of the drug at the hydrogel's boundary and environs was equal to zero. The boundary condition for the desired one-dimensional system assumed that the drug concentration in all the hydrogel was constant and equal to one at zero time. After zero time and the beginning of hydrogel swelling, it was assumed that the right side boundary of the system was swollen with the swelling function ($x=x_{(t)}=L.g_{(t)}$; where, L was the initial length of the hydrogel, and $g_{(t)}$ was the swelling function in terms of time). Therefore, at time t=0, the right boundary of the hydrogel began to move with velocity $u_{(x,t)}$. This system's left boundary was permanently fixed and motionless. As a result, the speed of the growing boundary is determined by the length of the boundary's edge, and the system's growth can be considered in terms of the $x_{(t)}$ function. The boundary conditions of the investigated system are shown in Figure 2.

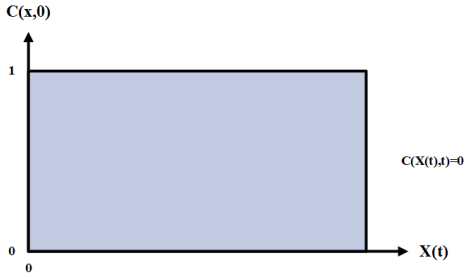

Figure 2. Schematic form of the boundary conditions of the desired system.

The current study examined five models of swelling hydrogels containing different ratios of chitosan to gelatin. The models listed are Cs-Gel (4:1), Cs-Gel (3:2), Cs-Gel (2.5:2.5), Cs-Gel (2:3) and Cs-Gel (1:4) hydrogels. The amount of changes in each model's boundary was computed as a function of time using Python software. Hydrogels' swelling behavior was accurately predicted by the models mentioned. In the equations of drug concentration changes, the rate of growth of the hydrogel boundary must be included. The growth rate of the hydrogel boundary can be compared by measuring the swelling rate of two hydrogels. In the present study, the effect of the growth of the system boundary on the drug concentration in the hydrogel has been compared based on the assumption that the growth of the boundary of each hydrogel can be predicted over time using the functions of swelling changes.

RESULTS AND DISCUSSION

In the current section, concentration changes in three hours for various hydrogels are depicted graphically. These graphs were generated with Python software and depicted the concentration of a drug over time. Initially, the alterations, as mentioned above, are more pronounced; however, as the drug concentration in the hydrogel decreases, the alterations diminish over time. The changes in swelling and drug concentration over time are depicted in Figures 3 and 4, respectively. Figures 3 and 4 show that the highest swelling of the hydrogel boundary and drug concentration occurred in the early times, and this swelling and concentration gradually decreased over time.

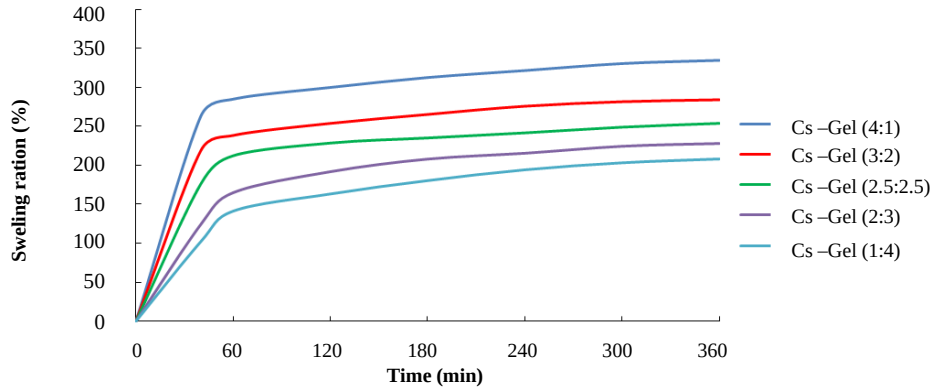

Figure 3. Swelling ratio of different hydrogels relative to time.

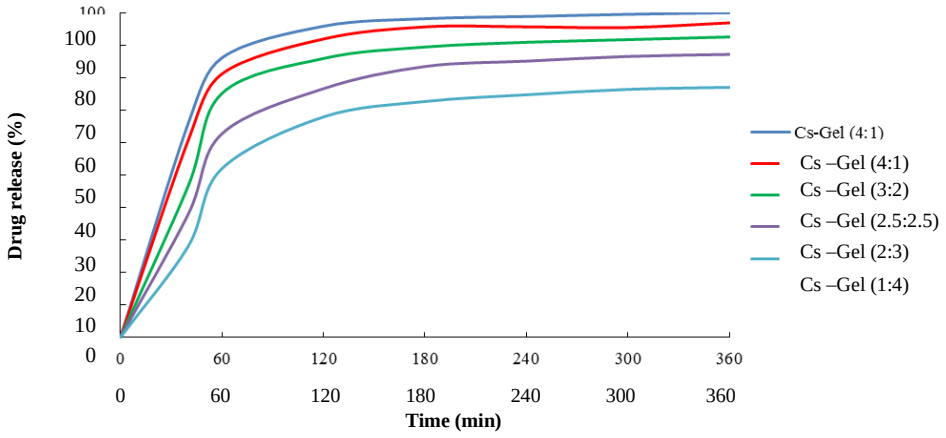

Figure 4. Drug release of different hydrogels relative to time.

Figure 4 shows that after 34 minutes, the drug concentration in Cs-Gel (4:1) hydrogel decreases by 50%; however, due to a decrease in the mass transfer driving force, the drug release rate decreases with time. After 130 minutes, the concentration of the drug in this hydrogel reached almost zero, indicating that the drug was released entirely. According to Figure 3, the hydrogel edge has grown by nearly 300%, from 1 centimeter to 4 centimeters.

The phase transitions of Cs-Gel (3:2) hydrogel in 170 minutes, CS-Gel demonstrated that the hydrogel boundary expanded to 3.5 cm. At this point, the drug concentration in the hydrogel had reached about 10%, and 90% of the drug had been extracted from the hydrogel. The drug release time has been lengthened by increasing the growth rate of Cs-Gel (3:2) hydrogel relative to Cs-Gel (4:1) hydrogel.

The growth trend of the Cs-Gel (2.5:2.5) hydrogel boundary, in which chitosan and gelatin are combined in equal proportions, revealed that the drug concentration in this hydrogel reached 10% after 240 minutes; and compared to Cs-Gel (4:1) and Cs-Gel (3:2) hydrogels; it requires more time to release the drug completely. According to Figure 3, the slower speed of this hydrogel results in a lower rate of drug release than Cs-Gel (4:1) and Cs-Gel (3:2) hydrogels. In 360 minutes, the boundary of this hydrogel expanded to 2.5 times its initial size, which is less than the Cs-Gel (4:1) and Cs-Gel (3:2) hydrogels.

According to Figure 4, the changes in drug concentration in Cs-Gel (4:1) and Cs-Gel (3:2) hydrogels, which had the highest swelling rate, revealed that the limit of Cs-Gel (4:1) hydrogel in 36 minutes increased by 2.5-fold and that more than 50% of the drug was released. While the Cs-Gel (3:2) hydrogel, which has less border growth, has reduced the drug concentration to 50% in less time, it has done so in a shorter period (40 minutes). In the first 180 minutes, the growth rates of Cs-Gel (4:1) and Cs-Gel (3:2) hydrogels differed slightly; as a result, the drug release rates in these two types of hydrogels were highly similar. Compared to Cs-Gel (1:4) hydrogel, Cs-Gel (4:1) and Cs-Gel (3:2) hydrogels reduced drug release time by 52 and 44%, respectively. This time was significantly longer for hydrogels with less boundary growth. In Table 1, the reduction in drug release time relative to Cs-Gel (1:4) hydrogel, which had the shortest total drug release time, is calculated.

Table 1. The percentage of drug release time reduction in different hydrogels compared to Cs-Gel (1:4) hydrogel.

Hydrogel type	Drug release time reduction (%)
Cs-Gel (4:1)	52
Cs-Gel (3:2)	44
Cs-Gel (2.5:2.5)	37
Cs-Gel (2:3)	18

According to Table 1, less chitosan was present in hydrogels with a slower swelling rate. Mass movement in the hydrogel polymer network reduced the drug release rate and had a lower mass flux for drug release. The findings from the modeling are consistent with those from previous studies; in the research conducted by Islam et al. [26] hydrogels at pH=6.8 exhibited the greatest swelling and release rates of progesterone drugs, dexamethasone, and aspirin. The drug release rate was the lowest at pH=1.2, which had the lowest swelling rate.

According to Figures 3 and 4, it can be seen that the growth process of the hydrogel has a significant impact on the changes in drug concentration. As the hydrogel boundary expanded, the drug concentration decreased. The Cs-Gel (1:4) hydrogel, which had the lowest boundary growth relative to the other hydrogels, resulted in the longest drug release time. In other hydrogels, the discharge time of the drug decreased as the boundary growth process increased, indicating the effect of the growth rate of the drug-carrying hydrogel. By increasing the ratio of chitosan to gelatin in the hydrogel formulation, the growth rate of the hydrogel increased, and the time required to release the drug from the hydrogel decreased. The Cs-Gel (4:1) hydrogel, which has the highest growth rate, had an approximate drug release time of 130 minutes.

According to research in this field, drug release systems (hydrogels) improve the treatment process and reduce adverse effects [27, 28]. Changes in the composition of the drug-carrying hydrogel and its synthesis method allowed the researchers to demonstrate that the amount and location of drug release can be controlled [29-31]. In a study, Islam and Yasin [32] analyzed the rate of dexamethasone release from a hydrogel composed of chitosan and polyvinyl alcohol (PVA). Their findings revealed that the swelling rate of the hydrogel decreases as the PVA concentration rises. Additionally, they discovered that during the first two hours, less than 10% of dexamethasone is removed from the hydrogel, whereas after six hours, this amount reaches over 80%. In their research, Patel et al. [33] prepared and optimized chitosan-gelatin films. According to their findings, increasing the concentration of chitosan in the composition of the hydrogel film increased its swelling and water absorption. In addition, they discovered that hydrogel films composed of chitosan and gelatin could be helpful for drug release in wounds.

As one of the limitations of the current study, we can mention the mathematical simulation simplifications. These simplifications include the constant consideration of the mass transfer coefficient in the equations and the restriction of swelling ability to the hydrogel boundary. In addition, considering 360 minutes and examining specific chitosan-to-gelatin ratios are additional limitations. For future research, evaluating a greater variety of ratios using laboratory methods and comparing the results to those of numerical methods is suggested. Checking the results of numerical methods with more complex rates and boundaries is also possible. Finally, additional parameters influencing drug release (such as the effect of temperature and pH of the environment) should be investigated.

CONCLUSIONS

The current study's objective was to examine various chitosan-to-gelatin ratios in swelling hydrogels; Python software was used to perform a mathematical simulation of drug release. The results demonstrated that high ratios of chitosan to gelatin produced the greatest border growth and the quickest drug release. In contrast, low ratios produced the least border growth and the slowest drug release. Consequently, regulating drug release and achieving optimal conditions based on various objectives is possible. Hydrogels with a slower growth rate can be used for drugs that need to be released in the body at a low flow rate, and fluctuations in drug concentration can cause patient complications. Also, drugs requiring a high concentration in the body can be administered using hydrogel with a higher swelling rate.

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Conflict of interests

The authors declare no conflict of interest.

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