Kinetics of drug release profile from maleic anhydride-grafted-chitosan film

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Abstract

A modified functional group of chitosan film was successfully prepared. Maleic anhydride (MA) was used to introduce carboxylic functional groups into chitosan film to enhance the drug loading capacity of the film and also control the drug release. The experiment was carried out by adding various amounts of MA into a chitosan solution, followed by loading the drug into the mixed solution. The drug release study was conducted by immersing the chitosan film in phosphate-buffered saline (PBS) solution (pH 7.4) as a body fluid model. This study was carried out in purpose to study the release kinetics of a drug from the modified chitosan film. Hence, the drug release data obtained were correlated with three mathematical models of drug release kinetics: Higuchi’s model, Peppas’ Model, and First-order model. Finally, the results revealed that the modified chitosan film exhibited a controlled release profile. Among the three mathematical models, the drug release profile from the modified chitosan film was best fitted with the First-order model.

Nomenclature

- \( C_A \): Concentration of drug in the film, mg/cm³
- \( C_{AL} \): Concentration of drug in liquid, mg/mL
- \( D_e \): Effective diffusion coefficient, cm²/minute
- \( H_A \): Distribution coefficient
- \( M_\infty \): Maximum drug release, mg/cm³
- \( M_t \): Accumulative drug release, mg/cm³
- \( k_h \): Higuchi’s model constant, 1/minute
- \( k_p \): Peppas’ model constant, 1/minute
- \( k_f \): First-order model constant, 1/minute
- \( n \): Diffusion characteristic of Peppas’ model
- \( L \): Half thickness of film, cm
- \( S \): Surface area of film, cm²
- \( t \): Drug release time, minute
- \( V \): Volume of liquid, cm³
1. Introduction

Chitosan, a well-known natural polycationic polymer, is gaining a lot of interest in the last decade. This substance is commonly used as a biomaterial, including in pharmaceutical application as a controlled release drug delivery system due to its properties such as film-forming abilities, biodegradability, non-toxicity, and biocompatibility. [1–4]. Chitosan has various functional groups, such as primary amine, primary hydroxyl, and secondary hydroxyl, which linked in C-2, C-3, and C-6 backbones, thus making this substance convenient to be modified [5].

In the application of the drug delivery system, one of the important properties of the system is a large capacity of the drug loading [6]. One effort that can be done to improve the properties is modification through the crosslinking method. The crosslink method has been reported to increase the ability to load drugs in the system, as well as increase the mechanical strength of the matrix and also control the release rate of the drug [7]. To enhance the ability of chitosan in attracting more positively charged drugs and controlling the drug release rate from the film, maleic anhydride (MA) was used in this study. The physical crosslinking between deprotonated carboxylic functional groups of grafted MA and protonated amine groups of chitosan are planned to promote an ionic bond, as can be seen in figure 1. The first step of the reaction mechanism is the attack of carbon atom of the carbonyl group from maleic anhydride by free electron pairs of chitosan resulted in tetrahedral as transition product. Then, the following step is the ring-opening of maleic anhydride, attacking of water molecules on hydrogen and resulted in hydronium ions [8].

As the drug model, curcumin, which is already known to have many bioactive compounds such as antioxidants, anticancer, and anti-inflammatory properties, was used in this study. The substance has a great potential to be developed and used as a medicine for various diseases. However, studies show that curcumin has a drawback that must be considered, namely, very low bioavailability. This deficiency is often associated with degradation of curcumin and poor solubility in aqueous solution. Hence, it is necessary to control the release rate of this particular substance [9–11].

The study about the modification of chitosan film by the addition of MA has been discussed by some researchers [12–14]. However, to the best of the authors’ knowledge, there is no study examining the kinetic sector for the drug release profile. Therefore, this paper addresses a kinetic study on the release rate of the drug from MA grafted-chitosan film to know the mechanism of the release and optimize the release rate.

2. Materials and methods

2.1. Materials

Low molecular weight chitosan (75%–85% DD) was purchased from Sigma Aldrich, USA. Acetic acid 100% was purchased from Merck, Germany. As a crosslinker agent, maleic anhydride (>99% of purity) was obtained from Nacalai Tesque Inc., Japan. Curcumin powder (>95% of purity), as a drug model, was supplied by Bio Basic Inc., Canada. Tween80 and acetone (99,75%) were used as a surfactant and a solvent for maleic anhydride. Phosphate buffer saline (PBS) was also used for the drug release test.

2.2. Methods

2.2.1. Film preparation

Chitosan film was prepared based on the previous experiment with slight modification by dissolving 0.6 g of chitosan in 20 ml acetic acid solution 1% v/v using a constant speed of stirring for 2 h [8, 15]. Parallel with that, MA (50; 100; 200% weight MA/weight chitosan) was dissolved in 10 ml of acetone 25% v/v. The obtained MA solution was then poured into the chitosan solution and stirred for 4 h. After that, the drug model, curcumin (20% weight curcumin/weight chitosan), and Tween 80 (70% weight Tween 80/weight chitosan) were added into the mixed solution, and then the solution was stirred for an hour. The final solution was cast on a petri dish (5 ml for each Petri dish) and dried at room temperature for 48 h. To remove the excess of MA, the dried film was washed using 25% v/v acetone solution. The code names for each sample are presented in table 1. For Fourier Transform Infrared (FTIR) Spectroscopy, the obtained film was scanned by SHIMADZU IR Prestige-21 in the range of 400–4000 cm\(^{-1}\). The samples were scanned in solid state using KBr Pellets with a resolution of 4 cm\(^{-1}\) and 10 number of scans.

2.2.2. Kinetic study

The film was cut into small circles with a diameter of 1.25 cm and then immersed in 20 ml of PBS solution. At a particular time, the drug concentration in the PBS solution was measured using a visible spectrophotometer (Genesys-20). Three kinetic models were employed to study the drug release mechanism from the film: Higuchi’s model, Peppas’ model, and the First-order model, respectively [16–18].
Higuchi Model:

\[
\frac{M_t}{M_\infty} = k_h t^{0.5}
\]  

Peppas Model:

\[
\frac{M_t}{M_\infty} = k_p t^n
\]

First-order Model:

\[
\frac{M_t}{M_\infty} = 100(1 - e^{-k_1t})
\]

Other than the previous three models, a mathematical model was proposed using a diffusion mechanism based on the volume element of thin film, as seen in figure 2.

\[
\frac{\partial^2 C_A}{\partial x^2} = \frac{1}{D_e} \frac{\partial C_A}{\partial t}
\]  

\( C_A \) is the concentration of the drug in the film (mg/cm\(^3\)), \( D_e \) is the drug diffusivity coefficient in the film (cm\(^2\)/s), \( x \) is the position of the center of the film (cm), and \( t \) is drug release time (min). The boundary conditions of the differential equation (4) are as follows:

\[
C_A(x, 0) = C_{A0}
\]

\[
C_A(L, t) = H_A \times C_{AL}
\]

\[
\frac{dC_A}{dx}(0, t) = 0
\]

\( C_{AL} \) is the concentration of the drug in the liquid (mg/cm\(^3\)) and \( H_A \) is the distribution coefficient. The value of \( C_{AL} \) was derived from the following equation, where \( S \) and \( V \) are surface area and membrane volume:

\[
C_{AL} = C_{AL0} + \frac{2S}{V} \left( L \cdot C_{A0} - \int_0^L C_A \, dx \right)
\]
3. Results and discussion

3.1. FTIR analysis
In order to confirm the successful of grafting, FTIR spectroscopy needs to be performed. Figure 3 shows both spectra of the sample of C and C50. The appearance of broadband around 3448.72 cm\(^{-1}\) represents the hydrogen bonding of amine groups. The amide I and II stretching appear around 1651 and 1558.48 cm\(^{-1}\), respectively. While the C–O–C stretching appears at 1095.57 cm\(^{-1}\). The appearance of a new band at 1712.79 cm\(^{-1}\) is occurred due to the stretching of C=O band from carboxyl groups of grafted maleic in chitosan backbone. Nadia et al (2020) also observed the new peak at 1705.07 cm\(^{-1}\), which represents to C=O band [19].

The shifting of the amide group and C–O–C band in C50 spectra occur because the grafting follows amidation and esterification reaction. These results confirm that the reaction is successfully conducted.

3.2. Drug release kinetics
The comparisons approach of the drug concentration between the experimental results and the calculated results based on parameter estimation for different mathematical models such as Higuchi’s model, Peppas’
model, and the first-order model are presented in figures 4, 5, 6, respectively. In addition, another proposed mathematical modeling, which included a diffusion mechanism based on the volume element of a thin film is presented in figure 7.

The results from the experiments showed that the addition of MA into chitosan decreased the release rate of the drug and led to more effective as a potential drug carrier. The result of plotting experimental data with Higuchi’s model in figure 4 showed that this model is only accurate for C100 and C200, which have lower amounts of drug release from the film. For C and C50, Higuchi’s models will fit only at the beginning of release while the constant rate occurred. While the system reached equilibrium, the existing model did not take the equilibrium parameter into account.

For the Peppas’s model, the model will fit for C100 and C200. Based on the previous study, the value of constant n in Peppas’ model indicates whether the drug release from the film followed Fickian diffusion ($n < 0.5$) or non-Fickian diffusion mechanism ($0.5 < n < 1$) [17, 20]. The calculated diffusion characteristic of Peppas’ model ($n$) for drug release rate from chitosan-MA film as shown in table 2 for all samples are less than 0.5, which means that this model followed the Fickian diffusion mechanism.

The results revealed that the modified chitosan film exhibited a controlled release profile and among the three mathematical models, the drug release profile from the film was best fitted with the First-order model (highest R-squared ($R^2$)) among the linear regression models (Higuchi’s model, Peppas’s model, and First-order model).

Further observation of the mechanism is carried out with the proposed mathematical modeling using equations (4)–(8). The profile of drug release fitted with experimental data can be seen in figure 7 and the obtained parameters are presented in table 3. From the results, it can be seen that the effective diffusion constant,

![Figure 4. Higuchi’s model for the release rate of the drug from chitosan-MA film and its regression.](image-url)
was decreased along with the addition of MA. Consequently, the less drug release on medium, the lower its diffusivity through the membrane film. This phenomenon might be occurred due to a stronger ionic bonding within the film due to the presence of carboxylic acid from MA.
Although the First-order model and our proposed model were fitted with the experimental data, the film swelling characteristics and degradation rate that might be influenced on the drug release should be considered for further improvement in mathematical modeling.

### 4. Conclusion

The modification of chitosan film using maleic anhydride as a crosslinker agent was successfully carried out. The introduction of carboxylic acid from MA was proven to lower the release rate of the drug. In this study, the best-suited model for the release of curcumin from chitosan-MA film is the First-order model in which the release of chitosan was slightly rapid in the beginning and gradually became stagnant. Although the First-order model and our proposed model were fitted with the experimental data, the film swelling characteristics and degradation rate that might be influenced on the drug release should be considered for further improvement in mathematical modeling.

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**Figure 7.** Proposed model for the release rate of drug from chitosan-MA film.

**Table 2.** Parameters of Higuchi, Peppas, and First-order Model of drug release rate from chitosan-MA film.

| Sample | Higuchi | Peppas | First-order |
|--------|---------|--------|-------------|
|        | $k_h$   | $R^2$  | $k_p$   | $n$   | $R^2$  | $k_f$ | $R^2$ |
| C      | 0.0944  | 0.5392 | 0.6058  | 0.11  | 0.7404 | 0.1020 | 0.996 |
| C50    | 0.0851  | 0.2965 | 0.5770  | 0.12  | 0.6823 | 0.0934 | 0.9865 |
| C100   | 0.0826  | 0.7491 | 0.4334  | 0.16  | 0.9011 | 0.0435 | 0.987 |
| C200   | 0.0674  | 0.9861 | 0.0934  | 0.43  | 0.9543 | 0.0110 | 0.867 |

**Table 3.** Parameters of drug release rate from chitosan-MA film.

| Sample | $D_h$   | $H_d$     |
|--------|---------|-----------|
| C      | 1.67E-05| 2.84E+03  |
| C50    | 4.55E-05| 3.82E+03  |
| C100   | 4.38E-06| 2.81E+03  |
| C200   | 3.07E-07| 2.80E+03  |
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