

Mass Transfer of Paracetamol from the Crosslinked Carrageenan-Polyvinyl Alcohol Film

Sperisa Distantina, Rieke Ulfha Noviyanti, Sri Sutriyani, Fadilah Fadilah, Mujtahid Kaavessina

Abstract—In this research, carrageenan extracted from seaweed *Eucheuma cottonii* was mixed with polyvinyl alcohol (PVA) and then crosslinked using glutaraldehyde (GA). The obtained hydrogel films were applied to control the drug release rate of paracetamol. The aim of this research was to develop a mathematical model that can be used to describe the mass transfer rate of paracetamol from the hydrogel film into buffer solution. The effect of weight ratio carrageenan-PVA (5: 0, 1: 0.5, 1: 1, 1: 2, 0: 5) on the parameters of the mathematical model was investigated also. Based on the experimental data, the proposed mathematical model could describe the mass transfer rate of paracetamol. The weight ratio of carrageenan-PVA greatly affected the amount of paracetamol absorbed in the hydrogel film and the mass transfer rate of paracetamol.

Keywords—Carrageenan-PVA, crosslinking, hydrogel, glutaraldehyde, paracetamol, mass transfer.

I. INTRODUCTION

OUR research is related to the development of applicability of hydrogels based on natural polysaccharides. Hydrogel is a hydrophilic polymer that has the ability of swelling in water, but not soluble in water, while maintaining the original shape. Hydrogels have a high water permeability so that it can be used as a matrix to control drug release. Raw material for making hydrogels that can be applied as a control drug release can be derived from natural polymers such as starch [1], calcium alginate-carboxymethyl cellulose [2], k-carrageenan-sodium carboxymethyl cellulose [3], and can also be derived from synthetic polymers such as PVA [4], polyvinylpyrrolidone, and polyethylene glycol [5].

Kappa carrageenan, which shows the ability to form a thermo-reversible gel, is also widely used as gelling agent, thickener and stabilizer in various industries such as food, pharmaceuticals, cosmetics, printing, and textile [6], [7]. Kappa carrageenan has a structure of D-galactose and some 2-sulfate ester groups on the 3,6 anhydro-D-galactose. PVA is a hydrophilic synthetic polymer that has biodegradable properties and excellent biocompatibility [4]. This research mixed kappa carrageenan extracted from seaweed Indonesia (*Eucheuma cottonii*) with PVA to prepare a film that can be applied as a hydrogel for drug delivery system.

To obtain the structure of the hydrogel, carrageenan-PVA

mixture needs to be modified with crosslinking. Crosslinking is the method of merging two or more molecules by a covalent bond resulting in the molecule structure becoming more rigid. A crosslinker agent is molecule that contains two or more chemically reactive substances and able to attract specific functional groups. GA is one of crosslinking agents that widely used in preparing hydrogel for controlled-release of small molecules. In the present work, GA was used as the crosslinking agent for preparing crosslinked carrageenan-PVA film.

Paracetamol drug is widely used and applied in various treatments such as medication for fever and pain relief. Paracetamol was selected as a model drug. There is no previous study on GA crosslinked carrageenan-PVA as hydrogel matrices for controlled drug delivery of paracetamol. Hezafteh [8] studied a mixture of carrageenan-PVA which crosslinking with genipin used as a matrix controller drug release β -carotene; however, drug mass transfer has not been studied. The understanding of drug mass transfer is essential to predict the drug performance. Many mathematical models of drug mass transfer have been developed by previous researchers [9]. Unfortunately, these models did not consider the equilibrium concept in interphase mass transfer [10], [11]. The purpose of this study was to develop the mathematical model that can be used to describe the phenomena of paracetamol mass transfer, as well as determine the effect of the weight ratio of PVA-carrageenan and loading time of paracetamol to the parameters of the paracetamol release rate of the film to a buffer solution.

The mechanism of solute mass transfer from solid to liquid consists of a series of steps. The steps are the diffusion mass transfer of solute in the solid to the surface of solid and the interphase mass transfer from surface of solid to liquid bulk. In this research, the experimental setup and procedure used to drug release test was conducted in a batch system by placing the hydrogel film in a glass beaker containing buffer solution. The proposed mathematical model of paracetamol release took some following assumptions:

1. The hydrogel film was a thin slab solid (less than 0.1 cm), so that paracetamol diffusion in film was very fast than interphase mass transfer,
2. Volume of the solution was constant, and
3. Weight of film was constant.

The process of paracetamol mass transfer is shown in Fig.

1.

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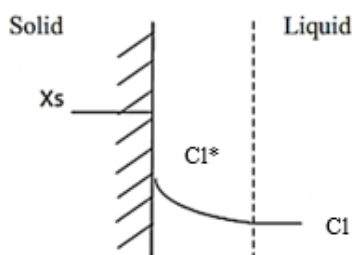


Fig. 1 Process of Paracetamol Mass Transfer from solid to buffer solution

Mass transfer rates of paracetamol from the surface of the solid to the liquid are calculated as in (1):

$$NA = kCa (Cl^* - Cl) \quad (1)$$

In the interphase, the equilibrium relationship between concentration of paracetamol in liquid (Cl^*) and concentration of paracetamol in solid surface (Xs) followed Henry's Law, as shown in (2):

$$Cl^* = H \cdot Xs \quad (2)$$

The concentration of paracetamol in solids was determined using a mass balance of paracetamol in the beaker for every time, as shown in (3):

$$Xs = \frac{Xo \cdot M - Cl \cdot V}{M} \quad (3)$$

The relationship of concentration of paracetamol in liquid as function of release time was derived by evaluating the mass balance of paracetamol in solution for every time. This relationship (4):

$$Cl = \frac{b}{a} - \frac{b}{a} \exp(-a \cdot t) \quad (4)$$

In this case:

$$a = kCa \cdot H \cdot (V/M) + kCa \quad (5)$$

$$b = kCa \cdot H \cdot Xo \quad (6)$$

where, NA = mass transfer rate ($\text{g paracetamol}/\text{cm}^2/\text{hr}$), kCa = volumetric mass transfer coefficient ($1/\text{hr}$), Cl = concentration of paracetamol in liquid ($\text{g paracetamol}/\text{mL}$), Cl^* = concentration of paracetamol in liquid that equilibrium with concentration of paracetamol on the surface solids ($\text{g paracetamol}/\text{mL}$), H = equilibrium constant ($\text{g solids}/\text{mL}$), Xo = initial concentration of paracetamol in a solid ($\text{g paracetamol}/\text{g film}$), Xs = concentration of paracetamol in a solid after being soaked in a buffer solution for a specific time ($\text{g paracetamol}/\text{g film}$), Cl = concentration of paracetamol in the solvent (buffer) for release ($\text{g paracetamol}/\text{mL solvent}$), V = Volume of solvent (buffer) (mL), M = weight of solids (film) (g), t = time of release (hr).

II. MATERIALS AND METHODS

A. Material

Materials used were red seaweed (*Eucheuma cottonii*, Indonesia), PVA, GA 25%w, KOH, paracetamol, ethanol, distilled water, NaOH, and KH_2PO_4 .

B. Preparation of Carrageenan from Seaweed

Ten grams of dried seaweed was soaked in 0.3 N KOH overnight, and then heated at 60°C for 30 minutes. The seaweed was washed with tap water until pH neutral. Washing was done five times and stirred for 5 minutes. As a solvent, 100 ml of distilled water is heated in a glass beaker to a temperature of 80°C , the seaweed was added and the extraction time started to be counted. The weight ratio of seaweed and the volume of solvent was kept constant ($1/50 \text{ g/mL}$) by adding hot water. After 1 hour of extraction, the filtrate was separated from the residue and immediately poured into a glass beaker containing ethanol (90% by weight) at a temperature of $\pm 5^\circ\text{C}$. Carrageenan fibrous was collected and dried in an oven at 60°C for 24 hours (to a constant weight).

C. Preparation of Carrageenan-PVA film

The carrageenan-PVA film was prepared by mixing carrageenan and PVA with a total weight of polymer was 5 grams. Variations in the weight ratio of carrageenan: PVA were presented in Table I.

TABLE I
VARIATION OF SAMPLE

Code of sample	weight ratio of carrageenan- PVA	weight of carrageenan (gram)	weight of PVA (gram)
Film 1	5 : 0	5	0
Film 2	1 : 0,5	3,3	1,7
Film 3	1 : 1	2,5	2,5
Film 4	1 : 2	1,7	3,3
Film 5	0 : 5	0	5

Thirty milliliters of distilled water was heated to 80°C , the mixture of carrageenan-PVA was then added and stirred with a stirrer until a homogeneous solution was produced. The solution were poured into molds and dried at room temperature to a constant weight. The obtained film was cut to $1.5 \text{ cm} \times 1.5 \text{ cm}$, each piece weighing 0.03 to 0.04 grams.

D. Preparation of Crosslinked Carrageenan-PVA

While the oven was turned on until a stable temperature of 110°C was obtained, the carrageenan-PVA films were soaked in a solution of GA 4% for 2 minutes. Then the films were drained and wiped with a paper napkin. The carrageenan-PVA films were placed in porcelain dish then put in the oven at a temperature 110°C and the crosslinking time started to be counted. After 25 minutes, all the films were washed in 50 ml of distilled water with stirring for 1 minute. All films were drained and soaked in 50 ml of ethanol for 4 hours. Then the films were drained and wiped with a paper napkin and dried at room temperature to a constant weight.

E. FTIR Characterization

FTIR test were done using a Fourier Transform Infra Red (FTIR) Shimadzu Prestige-21. FTIR spectra were used to determine the structure of the obtained film.

F. Preparation of Buffer Solutions

NaOH 0.8 grams were dissolved in 100 mL of distilled water and 3.4 g KH_2PO_4 dissolved in 250 mL of distilled water. Then the solution of NaOH 73 ml and 250 ml KH_2PO_4 were mixed in a flask and distilled water was added until 500 mL solution. The obtained solution with pH 7.4 was stored.

G. The Release Test of Paracetamol

The standard absorbance curve that shows the relationship between the absorbance and the concentration of paracetamol in the buffer (Cl) was made. This calibration curve was used to determine the Cl data collected from the paracetamol release test. To measure the paracetamol mass transfer, a paracetamol loaded film was soaked in 30 ml of buffer solution. Every 1 hour, a 3 ml sample was taken and its absorbance values were measured using UV-Vis spectrophotometry (Genesys 20) with a wavelength of 328 nm.

H. Determination of Henry's Constant (H) and kCa

Henry's constant was determined based on the concentration of paracetamol in a buffer solution when equilibrium state was attained. The maximum constant Cl value as a function of time was taken as the value of the Cl at equilibrium state, which then referred to as Cl^* . The Xs value can be determined by (3) and the value H was evaluated by (2). The kCa value in (4) was determined by guessing the value of the kCa which gives value of Cl calc not far from Cl data. The optimization of this value was calculated by determining the minimum value of the sum of square error (SSE). This trial and error was done using Solver program on Excel. The SSE value Equation follows (7).

$$\text{SSE} = \sum_i^{\text{data}} (\text{Cl data} - \text{Cl calc})^2 \quad (7)$$

where Cl data was Cl value collected from experiment data and Cl calc was the Cl value evaluated by (4) with a certain kCa value.

III. RESULT AND DISCUSSION

A. FTIR Analysis Film

Carrageenan-PVA film sample control and crosslink was analyzed by Fourier Transform Infra-Red (FTIR) to determine the changes of structure after crosslinking. Fig. 2 shows the FTIR spectra of control film and crosslinked film. The x-axis shows the wavelength (cm^{-1}) and the y-axis shows the light transmittance through the sample. Fig. 2 shows that there are new peaks at a wavelength of 1712 cm^{-1} on film 4 crosslink and 1735 cm^{-1} in the film 2 crosslink. This is indicated by the arrow (\uparrow) on the graph. According to Mansur et al. [12], crosslinking PVA with GA formed acetal group ($\text{CH}_3\text{CO}-$)

indicated by peak of $1710\text{-}1716 \text{ cm}^{-1}$ and at a wavelength of $1750 \text{ to } 1735 \text{ cm}^{-1}$. Therefore, crosslinking carrageenan-PVA mixture with GA in this research also forms the acetal group.

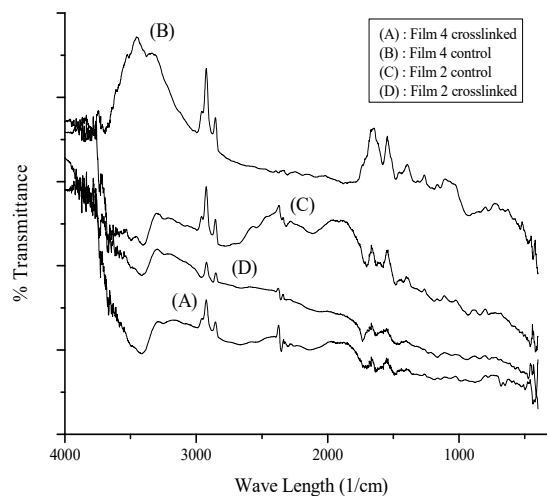


Fig. 2 FTIR Spectra of Carrageenan -PVA Control and Crosslinked Film

The possibility crosslinking reaction carrageenan and PVA films with GA are shown in Figs. 3 and 4.

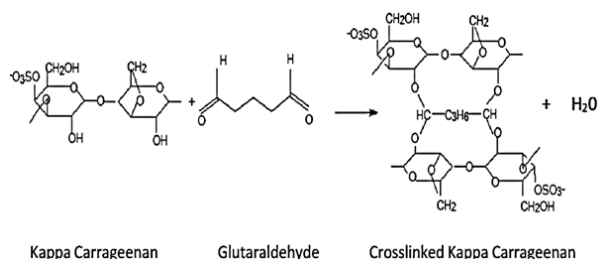


Fig. 3 Structure of Crosslinked Carrageenan

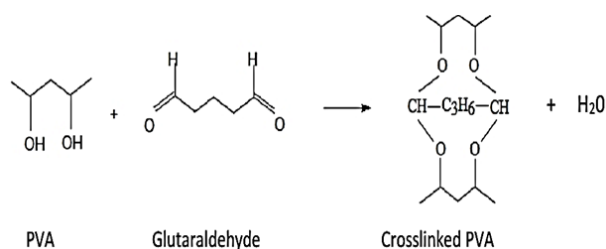


Fig. 4 Structure of PVA Crosslinked

B. Relationship between Cl data and Cl Calc

The concentrations of paracetamol in solution as a function of time with various films are presented in Fig. 5.

The result of the calculation parameters of paracetamol release rates on the various films can be seen in Table II.

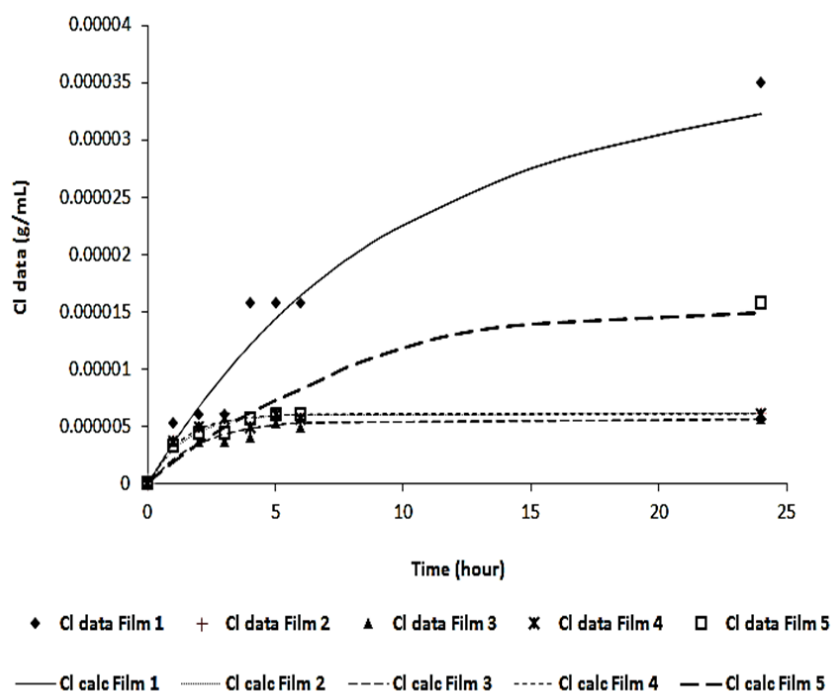


Fig. 5 Comparison between Cl data and Cl Calculate with Loading Time 12 hours

TABLE II
PARAMETER X_o , H , AND kCa ON LOADING TIME 12 HOURS TO VARIETY OF FILMS CARRAGEENAN-PVA OF SAMPLE

Film	X_o	Cl^*	X_s	H	kCa
1	0.03092	0.000035	0.03090	0.00113	0.10545
2	0.03167	0.000005	0.03167	0.00019	0.67312
3	0.00615	0.000006	0.00614	0.00092	0.48799
4	0.01664	0.000006	0.01663	0.00036	0.74221
5	0.01684	0.000016	0.01683	0.00093	0.12309

Fig. 5 shows the concentration of paracetamol in a buffer solution as a function of time at various weight ratios of carrageenan-PVA with a loading time of 12 hours. Table I shows the results of the calculation parameters of paracetamol release rates on the various films with loading time of 12 hours.

Based on Fig. 5, it is shown that the Cl_{calc} values are close to Cl_{data} ; thus, the mathematical model proposed in this study can be used to calculate the rate of paracetamol release from the film to buffer solution. The mathematical model of paracetamol release took the following assumptions. The thin film has a thickness of less than 0.1 cm; then it is assumed that paracetamol diffusion in the solid is very fast compared to interphase mass transfer. The preparation of the carrageenan-PVA hydrogel also kept the volume of solution and the size and weight of solids were constant.

From Fig. 6 it can be seen that the highest concentration of paracetamol which diffuses into the buffer solution was attained from Film 1 with a 5:0 carrageenan-PVA ratio. That may be caused by the structure of the carrageenan which is more hydrophilic than the PVA, and so the carrageenan films absorbed water more easily and release the paracetamol.

The lower concentration of paracetamol which diffuses into a buffer solution occurred on Film 2 and Film 4 with 1:0.5 and 1:2 carrageenan-PVA ratios, respectively. These data indicate that the composition of polymer influences the rate of paracetamol release. Hezafteh [8] also found the similar results. Hydrogel based on genipin crosslinked carrageenan-PVA films was used to minimize drug release of β -carotene and the release of β -carotene was controlled by the carrageenan-PVA polymer proportion.

C. Effect of Carrageenan-PVA Ratio of the Release of Parameter Paracetamol (X_o , H , and kCa)

From Table II, it can be seen that the Film 1 (pure Carrageenan) with a loading time of 12 hours has X_o value that is higher than Film 5 (pure PVA). The X_o value may indicate how much paracetamol can be stored in the film. Carrageenan films absorb more pure paracetamol due to the OH groups and sulfate groups on the polymer. The X_o value on a combination of carrageenan-PVA films shows a clear trend, namely Film 3 < Film 4 < Film 2.

From Table II it can be seen that the Film 5 (pure PVA) has a Henry's constant value which is lower than the balance of Film 1 (pure carrageenan). However, for Henry's constant value of carrageenan-PVA films has a tendency that is Film 2 < Film 4 < Film 3.

From Table II, it can be seen that Film 5 (pure PVA) has a kCa value higher than Film 1 (pure carrageenan). The pure carrageenan film absorbed more paracetamol resulting in reaching the saturated condition faster. These conditions caused the release of paracetamol to be slow. The kCa value on a combination of carrageenan-PVA films has the same

tendency; that is, $k_{Ca} \text{ Film 3} < k_{Ca} \text{ Film 2} < k_{Ca} \text{ Film 4}$.

IV. CONCLUSION

Based on the results of the experiment the following conclusions can be drawn:

1. From the experimental results, the proposed mathematical models can be used to describe the paracetamol mass transfer.
2. Differences in carrageenan-PVA film composition lead to differences in the rate mass transfer of paracetamol from film to buffer solution.

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