Effect of Na_2SO_3 concentration to drug loading and drug release of ascorbic acid in chitosan edible film as drug delivery system membrane

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Abstract. Chitosan is a type of carbohydrate compounds produced from waste marine products, in particular the class of shrimp, crabs and clams. Chitosan is often process into edible films and utilized for food packaging also has potential as a membrane for drug delivery system. Drug loading and drug release can be controlled by improve the characteristics of the membrane by adding crosslinker. The purpose of this research is to study the effect of addition of crosslinker to the rate of loading and release of ascorbic acid in the chitosan edible film. $\text{Na}_2\text{S}_2\text{O}_3$ was used as crosslinker. Two grams of chitosan was dissolved into 100 ml of distilled water. Acetic acid and plasticizer were added in the solution then heated at 50°C . $\text{Na}_2\text{S}_2\text{O}_3$ solution with mass various of $\text{Na}_2\text{S}_2\text{O}_3$ dissolved, 0.15; 0.3; and 0.5 grams were added about 30 mL to make edible film. The analysis include of drug loading, drug release and tensile strength. The result showed that the loading of edible film with crosslinker 0.15 g; 0.3 g; and 0.5 g respectively were 60.98 ppm; 52.53 ppm; and 40.88 ppm, meanwhile for the release with crosslinker 0.15 g; 0.3 g; and 0.5 g respectively were 3.78 ppm; 5.72 ppm; and 5.97 ppm.

Keywords : Na_2SO_3 , drug loading, drug release, chitosan, edible film

1 Introduction

Drug Delivery System is a system that can deliver drugs as early as possible, provide pharmacological effects for as long as possible, and deliver the drug directly to the target. Therefore, the preparation of the drug is designed in such way that it has the characteristic that we want. There are several advantages of new drug delivery systems versus conventional preparations such as they can reduce the use of drug, optimize total amount of drugs needed to obtain the desired therapeutic response, and minimize undesirable effects (Indrawati, 2009).

(Skurtys et al., 2009) defines edible film as a thin film that can be consumed and used as a coating or barrier between food and the environment. Edible films are classified into three categories based on the component properties of hydrocolloids (proteins, polysaccharides), fat (fatty acids, acylglycerols), and composites (mixtures of hydrocolloids and fats). The main mechanism of film formation in the polysaccharides is the separation of the polymer segments and the reshaping of the polymer chain into the layer or gel matrix usually achieved by solvent evaporation thereby creating hydrophilic hydrogen bonds as well as electrolyte and ionic crosslinking (Butler et al., 1996).

Chitosan can be chemically modified to manipulate the properties needed in its application. Chitosan has some weakness they are less stable, not

elastic, and hard. According to drug delivery applications, the desired properties are their solubility and release of controlled drugs. One of the chitosan modifications is the addition of cross-linker. The cross-linker will be bind to the chitosan amine group to form a network that will allow the drug to be trapped inside and the release of the drug can be controlled (Anitha, 2012).

2 Materials and Methods

2.1 Materials

The materials which used in this research were chitosan, glycerol, $\text{Na}_2\text{S}_2\text{O}_3$, aquadest, ascorbic acid, and buffer solution.

2.2 Methods

2.2.1 Film Preparation

The process of making edible film from chitosan begins with 2 gram of chitosan dissolved in 100 mL 1% acetic acid solution. Then, 1.2 gram of glycerol (as plasticizer) were added and heated at 60°C while stirred using magnetic stirrer for 60 minutes. After 60 minutes, $\text{Na}_2\text{S}_2\text{O}_3$ solution (as crosslinker) were added with mass variation of 0.15, 0.3, and 0.5 gram in 30 mL of aquadest while heated. The heating was

continued for 30 minutes and then poured into the petridish plate for film casting and entered into the oven at 60°C for $\pm$ 24 hours. The dried film was inserted into the desiccator for $\pm$ 1 day to ensure the film was completely dry and ready to be released from the mold.

2.2.2 Drug Loading Analysis

Ascorbic acid was entered into edible film by diffusion. Edible film dipped in ascorbic acid solution with concentration 80 ppm for 2 hours. Edible film that already contained drug was dried in ambient temperature. The drug loading test was performed by spectrophotometer uv-vis method using 2 cuvet pieces. The ascorbic acid solution of residual film-immersion was incorporated into the cuvet and analyzed using a uv-vis spectrophotometer with a wavelength (λ) of ascorbic acid at 256.6 nm.

2.2.3 Drug Release Analysis

Edible film from drug loading analysis containing ascorbic acid with various concentrations was fed into 20 mL of buffer solution with pH 7.4 for 2 hours. Concentration of ascorbic acid detached from the film to buffer solution was measured with a uv-vis spectrophotometer with a wavelength (λ) of ascorbic acid at 265 nm.

3 Result and discussion

3.1 Drug Loading

The aim of crosslinker addition in chitosan was to get the properties that we need. The cross-linker would be bind to the amine group present in the chitosan and form a network, so that the drug could be loaded and the release of the drug could be controlled (Anitha, 2012). The profile of ascorbic acid loading in various concentration of crosslinker were shown in figure 1.

Figure 1. Drug Loading vs Crosslinker

From the results of the data obtained, the more cross-linker added to the edible film caused the ascorbic acid loading was reduced because of the formation of crosslinks or network minimized the pores that

existed in the edible film so that ascorbic acid was entangled less slightly. According to the existing theory, the more crosslinkers were added, more crosslinks were formed so the smaller the pores caused the film was difficult to absorb the liquid.

3.2 Drug Release

Drug release was done by inserting a drug-filled film into the assumed buffer solution according to the liquid condition in the body. The concentration of the released drug into the liquid was observed until the concentration of the drug was constant (the drug concentration in the film was depleted) at a given time. The profile of ascorbic acid release in various concentration of crosslinker were shown in figure 2.

Figure 2. Drug Release Profile in Various Concentration of Crosslinker

Chitosan which dissolved in a solution with an acidic pH, converted an amine group ($-NH_2$) becomes ionized positively ($-NH_3^+$). This positive ionized group was further capable of forming ionic interactions with negatively charged drugs (Bhumkar and Pokharkar, 2006). Overall, the formed system tended to leave free ammonium groups that would reject each other, thus weakening the complex nanoparticles that had been formed. Therefore, it was necessary to add a crosslinker for stabilizing the remaining positive charge.

The more the addition of crosslinkers caused fewer ascorbic acid released of the film because of the small pores. But the results showed more ascorbic acid released. This happened because the non-bonding crosslinker molecule would interfere with the bonds that have formed in the edible film so that it could be weaken the strength of the bond that caused the ascorbic acid separated from the edible film easily.

By using ascorbic acid in the form of small grains, it could be assumed that the solute diffusion in solids to the surface was very rapid, so the extraction rate was determined by the speed of the solute transfer from the liquid to the surface of solid.

The solute mass transfer process from the liquid to the surface of solid were shown in the figure 3 :

Figure 3. Mass Transfer between liquid to solids phase

The mass transfer rate of ascorbic acid from the liquid into the solid followed the equation:

$$Na = kc (Cl^* - Cl) \quad (1)$$

With:

Cl = Ascorbic acid concentration in solution, gram of ascorbic acid / mL of the sample solution

Cl* = The concentration of ascorbic acid in a solution that was equal to the concentration of ascorbic acid on the surface of the solid, gram of ascorbic acid / mL of the sample solution

kc = Mass transfer coefficient, cm / min

Na = The mass flux of ascorbic acid, gram of ascorbic acid / cm².min

Since the surface area was difficult to evaluate, we used a factor which showed the mass transfer surface area, so the equation becomes:

$$Na = kca (Cl^* - Cl) \quad (2)$$

kca = volumetric mass transfer coefficient, 1/ hour (Welty, 2008)

The equilibrium relationship between ascorbic acid concentration in solid and solution was approached to follow Henry's Law,

$$Cl^* = H Cs \quad (3)$$

H = Henry constant, gram ascorbic acid / gram sample solution

Cs = Ascorbic acid concentration in solid, gram ascorbic acid/gram film

The solubility of ascorbic acid into the solvent was approximated by the mathematical model as followed:

The equations below take the assumption:

- Diffusion through the membrane edge was ignored
- The volume in the system was constant
- Isothermal Process
- Drug concentration in the membranes were uniform
- Mass transfer rates from the surface to the membrane were considered fast

- The carrier medium (membrane) did not had significant swelling or erosion during drug release

The mathematical model proposed to represent release process of ascorbic acid with buffer solvents were:

$$kca = \frac{[Cl' \cdot M]}{2[Cl' \cdot V \cdot H + Cl' \cdot M + H \cdot Cs \cdot M]} \quad (4)$$

Where,

kca = Volumetric mass transfer coefficient, 1/ hour

Cl' = Ascorbic acid concentration in solution, gram of ascorbic acid / mL of the sample solution

M = Weight of solid, gram

V = Volume of buffer solution, mL

H = Henry constant, gram ascorbic acid/gram sample solution

Cs = Ascorbic acid concentration in solid, gram of ascorbic acid/gram solid

Based on the equation (4), the mass transfer coefficient of ascorbic acid (kCa) in various concentrations of crosslinker could be calculated and gave the results in Table 1 :

Table 1. Values of H and kca in Drug Release Process

Crosslinker (gram)	H (gram ascorbic acid / gram sample solution)	
	Kca (1/hour)	
0,15	0,0959	0,1965
0,3	0,1113	0,2474
0,5	0,1430	0,2526

4 Conclusion

Crosslinker addition in edible film decreased drug loading but increased drug release. The effect of crosslinker concentration to the ascorbic acid mass transfer in drug release were increased mass transfer coefficient with a range of 0,1965 – 0,2526 hour⁻¹ and Henry's law constants with a range of 0,0959 – 0,1430. Based on the edible film result, the recommended treatment is the addition 0.5 gram of crosslinker.

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