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Application of Glyoxal Acrylamide Modified K-Carrageenan as A Superabsorbent Polymer in Drug Delivery System

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Abstract

The hydrogel is superabsorbent polymers (SAP) that are biodegradable and can be obtained from polysaccharides, lipids, and proteins. Polysaccharides include cellulose, starch and their derivatives, seaweed extracts such as carrageenan, alginate, pectin, and chitosan. Carrageenan is the result of the extraction of red seaweed sap with an alkaline solution. The main objective of this study was to simultaneously increase the strength and properties of κ-carrageenan SAP film with the addition of glyoxal and acrylamide as crosslinkers. The addition of acrylamide (variated from 1 to 7 % b/v) into the κ-Carrageenan based SAP hydrogel compound and the presence of glyoxal as crosslink agent (variated from 0 to 1,0 % v/v). The physical properties of the SAP films were analyze using swelling degree and tensile strength. The structural and morphological properties of composite films were analyzed using Fourier Transform Infrared (FTIR) and Scanning Electron Microscopy (SEM). In addition, the effect of pHs on the releasing drug Poly(vinylpyrrolidone)-Iodine was investigated. This research shows that the addition of acrylamide and glyoxal can improve the physical properties of the modified κ-carrageenan film. Characterization using SEM shows that the addition of glyoxal causes the formation of tissue fibers in SAP. FTIR spectra indicated the formation of cross bonds in modified SAP film at 3294.42 cm^{-1} (carboxylic acid). The treatment under alkaline conditions will increase drug release ability.

Keywords: *κ-carrageenan; hydrogels; acrylamide; glyoxal; drug delivery*

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INTRODUCTION

The modification of polysaccharide as a biopolymer is a new method for the production of biomaterials. Superabsorbent polymer (SAP) has a three-dimensional polymer network that has a lot of water and usually used as carriers for therapeutic agents in drug administration and as scaffolds for tissue modification. Various natural and synthetic polymer developments have used hydrogels as tissue breakers. (Calo, *et al*. 2014; Ni, *et al*. 2017; Graulus, et al. 2015). Several previous studies reported the use of natural polysaccharides such as carrageenan as an

ingredient for the manufacture of superabsorbent hydrogels (Pande, P. P. 2017; Stegemann and Wang, 2011).

Carrageenans are naturally sulfated polysaccharide, consists of a linear chain of β-(1,3) sulfated ɒ-galactose and α-(1,4)-3,6-anhydrous-ɒ-galactose. Carrageenan is extracted from various species of red seaweed. There are 3 types of carrageenan that are commonly used for industrial purposes, such as *kappa*, *iota*, and *lamda* carrageenan. *Kappa*-carrageenan (KC) is an attractive biopolymer and extracted from red seaweed (*Kappaphycus alvarezii*). KC is widely used in food, cosmetic and pharmaceutical industries as a thickening, gelling, stabilizing, and emulsifying properties (Campo *et al.* 2009). Low molecular of carrageenans have biological activity, such as antioxidant, anticoagulant, antitumor, and immunomodulatory activities (De Araujo *et al.* 2003; Campo *et al.* 2009; Wijesekara *et al.* 2011; Barahona *et al.* 2011; Prajapati *et al.* 2014). The unique physical and chemical properties of KC makes it potentially suitable to be used as a drug carrier. For the pharmaceutical industry, KC is developed as a Superabsorbent Polymer (SAP), which commonly used in drug delivery materials. On the other hand, SAP of KC are formed the three-dimensional networks which can be broken under covalent bonds or certain environments (Arias, 2015). The KC polymer chains are usually physically or chemically cross-linked in order to keep the spatial structure of hydrogel (Covis, *et al.* 2016).

The three-dimensional network structures that characterize of SAP materials influence by cross-linking. The swelling and elasticity properties are attributed to the presence of chemical cross-links or physical properties within polymer chains. The cross-linking of hydrogel is important because the physical states of the hydrogels changed in the different cross-linking levels (Wang and Stegemann, 2011). The previous study was confirmed that adding glyoxal as a crosslinker agent could improve mechanical properties (Hoemann CD, Chenite A, Sun J, Hurtig M, Serreqi A, Lu Z, 2007). There have been examined the use of glyoxal, a dialdehyde with relatively low toxicity as a crosslinker agent, and characterized the resulting changes in matrix and cell properties. Glyoxal has a supporting factor in the formation of the oxalic acid phase in the water phase. Oxalic acid is the only water-soluble organic compound that has been identified as an abundant aerosol and processing in clouds is its dominant formation pathway (Zia, *et al.* 2017). The advantage of using glyoxal has many volatile organic precursors under atmospheric conditions (Dey, *et al.* 2014). Adding glyoxal as a crosslinker is also worked in several studies using another seaweed-based compound such chitosan to improve the mechanical properties (Giri, *et al.* 2012).

New copolymers with the properties of natural and synthetic polymers will be produced with an acrylamide (AAm) graft on polysaccharides. In several studies shown that adding AAm into chitosan or alginate-based compound for hydrogel was improved their swelling properties of hydrogel from chitosan or alginate- based compound (Zhang, *et al.* 2007; Kulkarni, *et al.* 2011; Graulus, *et al.* 2015). Aam is a chemical that is widely used in the industry, especially the pharmaceutical industry. In previous research, the AAm enhanced the swelling ratio of the hydrogel and promoted the process of wound healing due to their ability to increase the swelling degree properties (Rashidzadeh *et al.* 2014). The addition of acrylamide in several seaweed-based compounds that the swelling degree increase significantly due to higher concentration of acrylamide (Zhang, *et al.* 2011). Kulkarni et al, 2011 have synthesized hydrogel beads of poly AAm grafted κ-carrageenan and sodium alginate for ketoprofen drug delivery.

KC SAP film has limited physical properties for control the release of drugs or bioactive compounds application, because their hydrophilic properties and a higher solubility in acidic condition. Modified carrageenan hydrogels have been proven to be a potential carrier for delivery of different drug molecules with respect to size and type (Pourjavadi, *et al.* 2007; Kurkani, *et al.* 2011). However, to the best of our knowledge, no previous studies have demonstrated the effect of glyoxal and acrylamide for modified κ-carrageenan as a superabsorbent polymer (SAP) in the drug delivery system.

The main objective of this study was to simultaneously increase the strength and properties of κ-carrageenan SAP film with the addition of glyoxal and acrylamide as crosslinkers. Tensile strength and swelling degree were used to analyze the physical properties of the SAP. The structure of composite films was analyzed using Fourier Transform Infrared (FTIR), and the morphological was characterized by Scanning Electron Microscopy (SEM). In addition, the effect of pHs on the releasing drug *Poly(vinylpyrrolidone)-Iodine* was investigated.

MATERIALS AND METHODS

Materials

Semi refined κ-carrageenan with molecular weight of 275 kDa was obtained from CV. Karagen Indonesia, Semarang, Central of Java, Indonesia. κ-carrageenan contains 36.5% of 3,6-anhydrous-D-galactose and 15.1% of sulfate. Acrylamide (≥99%) that used in this research was supplied from Merck (Cat. No: 800830) and Glyoxal (40% solution in water) was obtained from Merck, (Cat. No. 820610). Poly(vinylpyrrolidone)-Iodine from Sigma Aldrich (CAS No. 25655-41-8) is used as the active ingredient trapped in the modified SAP k-carrageenan material.

Preparation of film

SAP film was created by mixing two based compounds of 1% w/v KC as a polysaccharide and acrylamide (AAm) as a monomer (variated amount from 1 to 7 % w/v) and then glyoxal (variated amount from 0 to 1 % v/v) as crosslinker was added into 100 ml of distilled water. The temperature of the solution

was adjusted using stirrer hot plate equipment at 80ºC. The process condition was maintained for 20 minutes with a stirring speed of 250 rpm. The SAP film production used manual casting methods. The assessment of SAP films has been reacted to the acrylic glass then dried at room temperature for 30 hours.

Swelling Measurements

The degree of swelling of SAP was calculated by weighing the dry SAP film, then the SAP film was immersed in distilled water for 3 hours at room temperature. After 3 hours, the wet SAP film is weighed, and the degree of swelling is calculated by the following equation (Mignon, et al. 2015):

$$Swelling\ Level\ \left(\frac{g}{g}\right) = \frac{weight\ of\ wet\ SAP\ Film\ (g)}{weight\ of\ dry\ SAP\ Film\ (g)} \quad (1)$$

Drug Release

The capability of drugs releasing considered by trapped the Poly(vinylpyrrolidone)-Iodine (PI) into SAP film. Furthermore, the SAP film that contains PI, immersing in a buffer solution with pH 6, pH 7.4, and pH 8. The degree of PI release was measured using a UV-VIS spectrophotometer at a wavelength of 520 nm every 5 minutes for 50 minutes (Zhang *et al.* 2011). The UV-Vis double beam spectrophotometer (Shimadzu UV-1900i). The absorbance value shown on the reading of the spectrophotometer shows the concentration of PI.

Tensile Strength

The mechanical properties (Tensile strength) of SAP film were analyzed using a Machine Type M350-10CT (Testometric Co., Ltd., Rochdale, Lancs., UK). (MPa). All samples were analyzed with the same size (5 cm x10 cm). SAP films were equilibrated at 27◦C and 53% relative humidity in desiccators with silica absorbent for 2 days prior to testing (Arias *et al*., 2016).

FTIR

The functional groups of modified κ-carrageenan SAP were analyzed using Fourier Transform Infrared Spectrometer Perkin-Elmer (PC1600, Perkin-Elmer, USA). The dried hydrogel samples were grinded, and the obtained highly dispersed powders were pressed with KBr. Then, the formed pellets were used for the measurements of FT-IR spectroscopy (Pourjavadi *et al*., 2004). FTIR test of modified κ-carrageenan SAP was carried out at wavenumbers 4000-250 cm^{-1}.

SEM

The microstructure of modified κ-carrageenan SAP was examined using Scanning electron microscopy (SEM) (JSM650 Series, JEOL, Japan). The SEM images were obtain using resolution HV mode (3.0 nm (30kV), 8nm (3kV), 15 nm (1 kV)), with the magnification of 5000x.

RESULTS AND DISCUSSION

Swelling and Tensile Strength

The polymer water absorption influenced by the addition of crosslinker. The effect of crosslinker Aam content on the swelling degree of the crosslinked KC/AAm SAP is shown in Fig. 1. This research shows that the addition of AAm has increased the degree of swelling. The maximum swelling degree (28.1738 g/g) is achieved with the addition of 4% monomer AAm. If the addition of Aam is lower than 4% by weight, the swollen SAP has a bad crosslinking, because the soluble non-crosslinked copolymer dissolved in water and copolymer cannot be produced properly. Furthermore, the increase in the number of acrylamide monomers (above 4%), causes a decrease in the degree of swelling. The swelling degree of SAP increased up to a certain level. Increasing the crosslinking density of SAP will result in a decrease in the space between the polymer chains. A rigid structure is formed which cannot hold large amounts of air (Zhang, *et al.*, 2011; Montaser, *et al*., 2019; Yu, *et al.* 2011; Kulkarni, *et al.* 2012; Arias, *et al.* 2016).

Zhang *et al.*, 2011 reported that more crosslinked networks in polymeric chains occurred, affect a higher crosslinking density and more insoluble copolymers in the water. Montaser et al 2019 reported that the swelling ratio (%) of (polyvinyl alcohol/ sodium alginate) hydrogel and (polyvinyl alcohol/sodium alginate-g-N-isopropyl acrylamide) hydrogel increase systematically with increasing the content of sodium alginate and sodium alginate-g-N-isopropyl acrylamide. Rashidzadeh, *et al.* 2014 reported that water absorption will increase with increasing AAm concentration. This could be caused by the higher of the contents made the crosslinking density lower. The swelling behavior in polyethylene glycol methyl ether methacrylate / 2-(dimethylamino) ethyl methacrylate hydrogels (Ramadan *et al.* 2014) and κ-carrageenan/methacrylamide hydrogels (Pourjavadi *et al.* 2004) is controlled by the concentration of crosslinker.

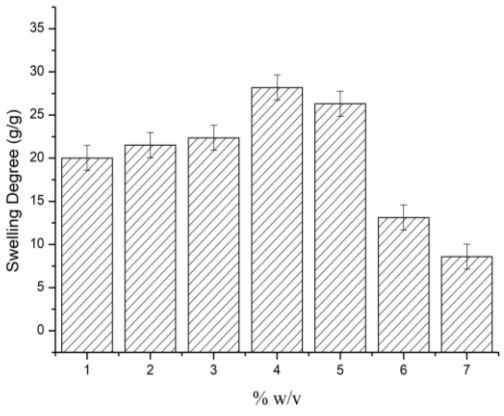


Figure 1. Effect of acrylamide concentration on swelling degree of SAP κ-carrageenan

Therefore, the swelling behavior of κC hydrogels can be controlled according to its desired application.

The degree of SAP swelling is influenced by the functional groups contained in SAP. The functional groups include the -OH, -NH_2, -COOH, -CONH, and -SO_3H groups. When SAP is immersed in water an interaction occurs between SAP and water, the hydration process, and the formation of the hydrogen bonds. The formation of hydrogen bonds occurs between the functional group -COO- in acrylamide which is hydrophilic with H^+ ions in water (Abidin *et. al*, 2012).

The increasing concentration of AAm in SAP cause the number of hydrophilic groups to increase caused the degree of swelling to increase. The addition of AAm which exceeds the optimum degree (4% by weight) will cause the density of the distance between molecules in SAP are also increased. As a result, water is difficult to penetrate into the SAP tissue, so the degree of SAP swelling decreases, as explained by (Erizal, *et al.* 2010) that increasing the concentration of acrylamide will reduce the degree of SAP swelling. Figure 2. shows variations in crosslinker levels added in SAP film making to the degree of swelling. The addition of glyoxal levels resulted in a decrease in the degree of swelling. The decrease in the degree of swelling is caused by the crosslinking bonds formed within SAP (Wang and Stegeman, 2011; Hoeman, *et al.* 2007). Crosslink bonding causes the SAP polymer bonding network to become tighter, resulting in smaller pore size and causes the empty space where the binding of water in the SAP network is reduced. SAP application requirements as a wound dressing that has a degree of swelling more than 10 g/g and has a high resistance to pull. To determine the value of resistance to SAP traction, characterization was performed by performing a tensile strength test.

The effect of different concentrations of crosslinker (glyoxal) for the degree of swelling and tensile strength of SAP shows in Figure 3. Tensile strength is the maximum stress that material when stretched or pulled before the material is broken. The addition of glyoxal levels resulted in an increase in SAP tensile strength.

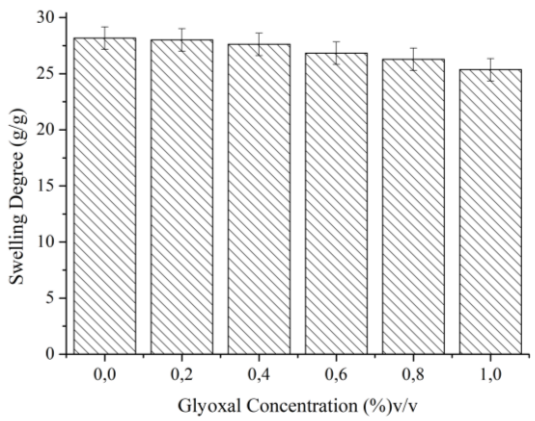


Figure 2. Effect of glyoxal concentration on swelling degree of SAP κ-carrageenan

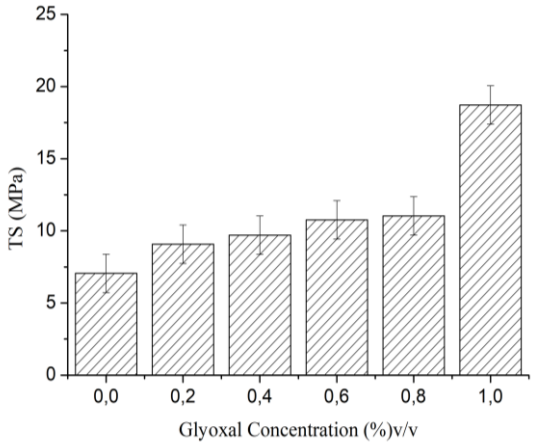


Figure 3. Effect of glyoxal on tensile strength

Crosslink ties connect bonds between networks that are in SAP so that the molecular bonds in SAP become stronger. SAP requirements as a wound dressing have a degree of swelling of more than 10 g/g and high tensile strength. So that SAP is used with the characteristic swelling degree of 26 (g/g) and tensile strength of 12,750 (N/mm^2) which is achieved in the addition of glyoxal as much as 0.825% (w/w).

In recent studies shown that hydrogel from polysaccharide is low strength due to their hydrophobic properties. Modified carrageenan has been a future study to improve its mechanical properties. In the previous study showed that the used of crosslinker could potentially improve the tensile strength properties of hydrogel due to their hydrophobic associated properties and can rebuild a good chemical bond, it also decreases the swelling degree due to higher concentration of crosslinker could increase the solution density and decrease the swelling properties (Zhang, *et al.* 2017; Pettineli, *et al.* 2019; Karimi, *et al.* 2018). Crosslinking of the swelling properties analysis with glyoxal in this research also was shown to modulate swelling degree to decrease.

Herris, *et al.* 2015 reported the investigation of chitosan-glycol/glyoxal as an injectable biomaterial for vocal fold tissue engineering. This research indicated that a combination of chitosan-glycol/glyoxal hydrogels could be potential candidates for use in human vocal fold tissue repair and regeneration. Hoemann *et al.* 2007 reported the hypothesis that glyoxal was responsible for the modification of chitosan gelation. Wang, *et. al.* 2011 investigated the glyoxal crosslinking of cell-seeded chitosan/collagen hydrogels for bone regeneration. This research examined the use of glyoxal to crosslink of materials and characterized the resulting changes in matrix and cell properties.

FTIR Results

Figure 4. shows that SAP k-carrageenan-acrylamide without glyoxal and SAP k-carrageenan-acrylamide with glyoxal. The FTIR spectra show a

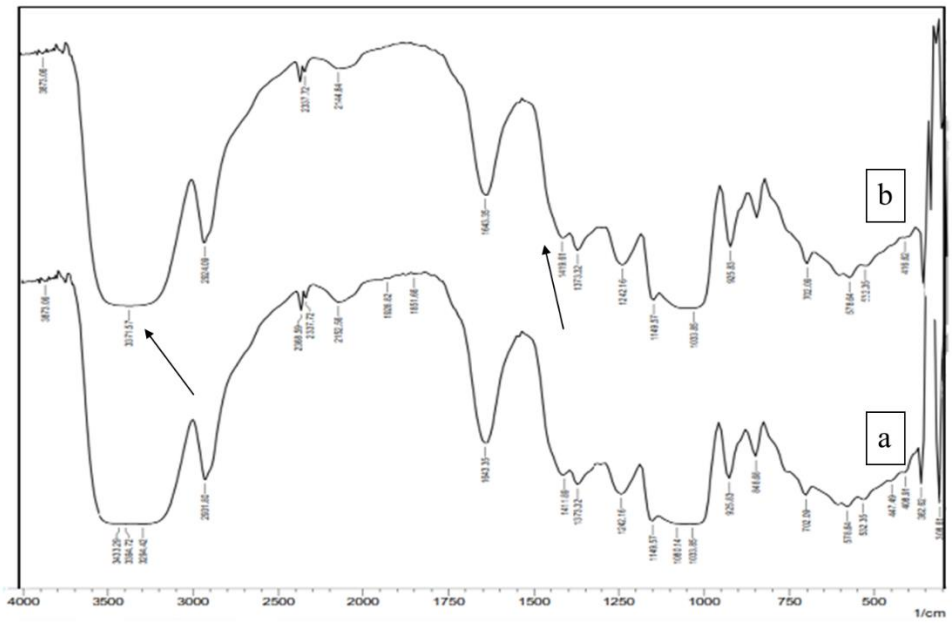
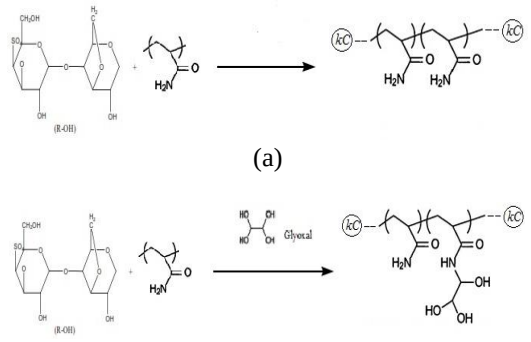


Figure 4. FTIR spectra of modified κ-carrageenan (a) without glyoxal (b) with glyoxal

Table 1 FTIR spectra of SAP κ-carrageenan

Area (1/cm)	Group Function	Name of The Group Function	Adsorb Area (%)	
			Without Glyoxal	With Glyoxal
2850-2960	C-H	Alkane	2924.09	2931.8
1350-1470			1373.32 1419.61	1411.89
675-870	C-H	Alkene	702.09	702.09 848.68
675-870	C-H	Aromatic	702.09	702.09 848.68
1640-1680	C=C	Alkene	1643.35	1643.35
1080-1300	C-O	Alcohol Eter Carboxylate Acid Ester	1149.57 1242.16	1242.16 1149.57 1080.14
2000-3600	O-H	Alcohol Phenol (Hydrogen Bound)	2144.84 2924.09	3433.29 3394.72 3294.42 293.,8 2368.59 2337.72 2152.56
3000-3600	O-H	Carboxylate Acid		3433.29 3394.72 3294.42
3310-3500	N-H	Amine		3433.29 3394.72
1180-1360	C-N	Amine	1242.16	1242.16
1345-1385	NO2	Nitro	1373.32	1373.32

slightly different absorption area. The addition of glyoxal causes OH absorption at 3294.42 cm^{-1}, 3394.72 cm^{-1}, and 3433.29 cm^{-1}, and the emergence of NH absorption at 3394.72 cm^{-1}. O-H and N-H groups in the absorption region show the functional groups of carboxylic acids and amines formed in SAP k-carrageenan-acrylamide with glyoxal. The difference in FTIR spectra also occurs at 1640-1680 cm^{-1} which shows the change of C=C functional group.



(a)

(b)

Figure 5. Reaction mechanism of modified SAP *k*-carrageenan (a) without glyoxal (b) with glyoxal

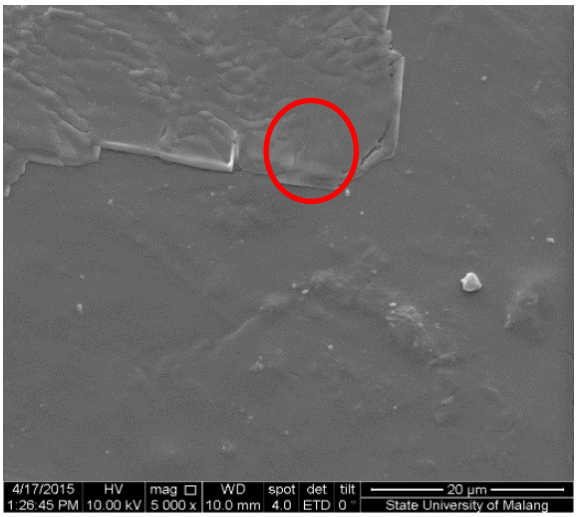
The difference in the absorption area between SAP k-carrageenan-acrylamide without glyoxal and SAP k-carrageenan-acrylamide with glyoxal can be seen in Table 1. Hydroxyl group (-OH) from carbocycle acid was found in SAP hydrogel with the presence of glyoxal as the crosslinking agent. Previous research has been reported that the reaction between glyoxal and amine groups could occur in the hydroxyl group (-OH) of carbocycle acid (Dey, *et al.* 2014; Pettineli, *et al.* 2019; Karimi, *et al.* 2018).

A recent study also reported that the addition of glyoxal will have no significantly changed to their reaction caused by there has not been interaction between glyoxal and hydrogel film (Dey, *et al.* 2014; Pettineli, *et al.* 2019; Karimi, *et al.* 2018). The possible reactions to the synthesis of SAP k-carrageenan-acrylamide without glyoxal and the synthesis of SAP k-carrageenan-acrylamide with glyoxal in the sequence are shown in Figure 5.

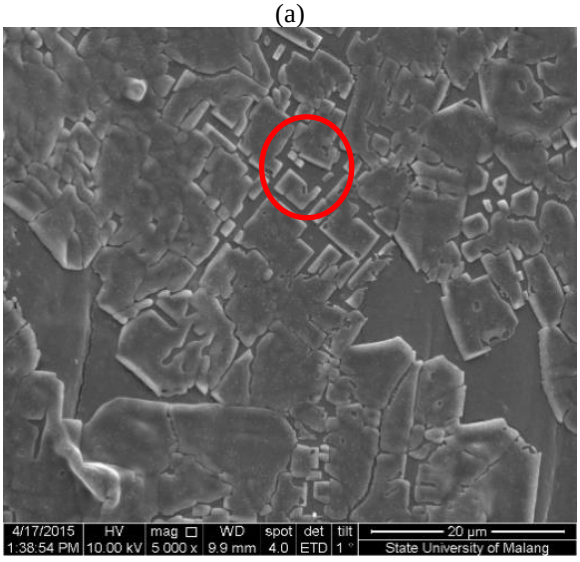
The reaction mechanism can be described according to the following steps. First, glyoxal dissolves in water, forming non-volatile hydrates HO-HO-C-C-OH-OH, then the hydroxyl group -OH very reacted to amine NH- in the presence of acrylamide in the based solution compounds. Once the hydroxyl glyoxal was reacted into the film formula the next reaction takes place with 2 molecules of the polyacrylamide, a biopolymer is formed by an intermediate bridge (Zaitoun and Kohler, 1996).

SEM Analysis

Figure 6a. shows the SEM results from SAP k-carrageenan-acrylamide without glyoxal with magnification 5000x. The SEM results appear to have a flatter surface (uniform) and have a wider free space for water absorption, so the degree of swelling is large, which is 28.1738 g/g. Whereas Figure 6.b shows SEM results from SAP k-carrageenan-acrylamide with glyoxal which shows the presence of tissue fibers in the SAP surface. According to (Hezaveh and Muhamad, 2013) tissue fibers show that new bonds (cross bonds) are formed. As explained in the phenomenon of decreasing the degree of swelling with the addition of glyoxal before, the addition of glyoxal levels will reduce the degree of swelling of SAP because the empty space for water absorption is



(a)



(b)

Figure 6. SEM results of modified SAP *k*-carrageenan (a) without glyoxal, (b) with glyoxal

narrower compared to SAP k-carrageenan-acrylamide without glyoxal, so the degree of swelling is smaller, which is 25.3607 g / g. The similar results showed that the change of the surface area of hydrogel film due to the addition of crosslinker. It is possible that the surface area becomes coarse (Wang and Stegeman, 2011; Pettineli, *et al.* 2019; Karimi, *et al.* 2018).

Effect of pH Soaking Buffer on Drug Release

Figure 7 shows that PI concentration of drug release is increased every 5 minutes period until 50 minutes. The increase in drug release is due to the longer immersion of SAP in the buffer, the more drugs are released. Drug release at pH 8 reached 0.04%, pH 7.4 reached 0.03% and at pH 6 it reached levels of 0.03%. The highest release of the drug occurs in the release of drugs from SAP in a buffered pH of 8, followed by a pH of 7.4 and pH 6. In this research reported that increasing the alkaline compound could increase the drug release ability.

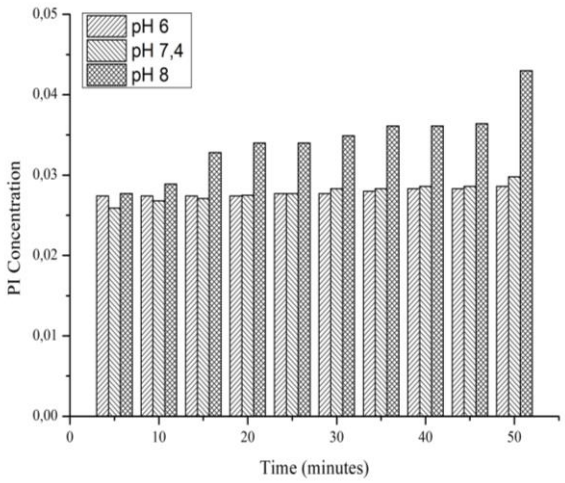


Figure 7. Drug release of PI at different pH

This research shows that pH conditions affect PI release in edible films. Figure 8 shows the SAP film layer containing PI at various pH. In acidic conditions, PI release tends to be slow. Furthermore, the liquid around the SAP remains clear if the SAP is immersed in water.

The previous study explained that in the hydrogel tissue an electrostatic repulsion of the carboxylic acid group occurred. At low pH, the electrostatic repulsion of carboxylic acids in the tissues is low, so the amount of drug released is small. At an alkaline pH, the presence of OH will increase the electrostatic pressure between the carboxyli c acid groups, so that the amount of drug released will be greater (Hossein Hosseinzadeh, *et al*. 2010; Sariyer, *et al.* 2020; Montaser, *et al.* 2019; Mignon, *et al.* 2015; Kulkarni, *et al.* 2012; Pourjavadi, *et al*. 2009; Gupta, *et al.* 2002).

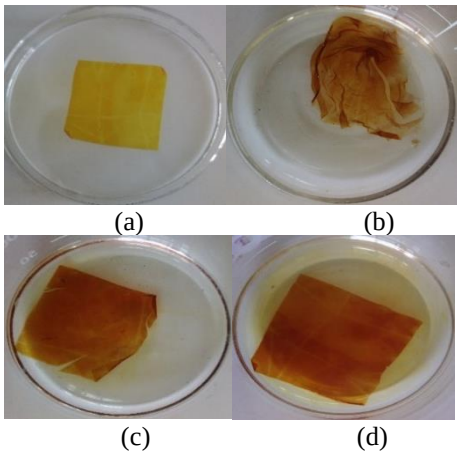


Figure 8. Modified κ-carrageenan SAP containing PI (a) dry condition (b) pH 6 (c) pH 7.4 (d) pH 8

CONCLUSION

The addition of acrylamide monomer increases the swelling degree of SAP in water. The maximum degree of swelling of 28.1738 (g / g) was achieved with the addition of 4% (w / v) acrylamide. The addition of glyoxal content resulted in an increase in the tensile strength of κ-carrageenan SAP. FTIR analysis showed that the addition of glyoxal would not significantly change the functional group of the κ-carrageeenan SAP film, because there was no interaction between the glyoxal layer and the hydrogel. SEM results from SAP k-carrageenan-acrylamide with glyoxal showed the presence of tissue fibers on the SAP surface. Treatment under alkaline conditions can increase the drug release ability of Poly(vinylpyrrolidone)-Iodine.

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