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Original Article

MODIFICATION AND CHARACTERIZATION OF AMPROTAB WITH HYDROXYPROPYL METHYLCELLULOSE USING CITRIC ACID AS CROSSLINKING AGENT

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ABSTRACT

Objective: This study aimed to characterize Amprotab that has been modified chemically, physically, and mechanically using HPMC and citric acid.

Methods: The study is divided into two parts: three control formulas and three treatment formulas. Control Formula 1 (without HPMC and citric acid), Control 2 (HPMC 1.5 g without citric acids), Control 3 (citric acid 1.5 g without HPMC), Formula 1 (HPMC 4.5 g and citric acid 4.5 g). By analyzing Fourier Transform Infrared (FTIR), scanning electron microscopy (SEM), swelling, tensile strength, stability (freeze-thaw cycles), X-ray Diffraction (XRD), and Thermogravimetric Analysis (TGA), copolymers modified by Amprotab were characterized.

Results: An FTIR analysis revealed that crosslinking of Amprotab was formed in formulas 1, 2, and 3 with prominent C=O ester bonds at peaks of 1730.22 cm^{-1}, 1733.12 cm^{-1}, and 1736.01 cm^{-1}. The surface morphology of the modified cassava amylum CROSSLINKED COPOLYMER (CCA) was coarser. CCA's expanding power is less than that of natural Amprotab, whereas CCA's tensile strength is greater.

Conclusion: CCA has a high value for syneresis. XRD analysis revealed that CCA has a crystal diffraction pattern of type B, and TGA analysis revealed that CCA is stable at high temperatures.

Keywords: Crosslinking, Citric acid, Amprotab, HPMC

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INTRODUCTION

Cassava (*Manihot utilissima* Pohl. or *Manihot esculenta* Crantz.) is a plant that is widespread in Indonesia and extensively cultivated worldwide [1, 2]. Amprotab is a specialized starch used exclusively for the production of tablets. It is derived from Amylum manihot starch. Amprotab can be used as a diluent, binder, and disintegrant in tablet and capsule formulations [3]. In the pharmaceutical industry, natural starch is rarely employed. This is because starch has weak flowability, is incompressible, and cannot form solid matrices [4]. Controlling the release of drugs from their dose form, sustained-release tablets are an extended-release drug delivery system employing polymers. This dosage form has the benefit to produce constant drug concentrations in the blood without the need for repeated administration of unit doses [5]. Excipients are not only utilized in conventional tablet formulations but also in tablets with extended release of active constituents, such as sustained release and controlled release tablets [5, 6]. Both formulations require excipients with sufficient gel strength to prevent drug release [8]. The functional properties of an excipient that are also required in solid preparations include the capacity to form a film that can be used as a coating material, such as film coating and sugar coating [9]. Extinction and tensile strength are the mechanical properties of the film that must be determined. The tensile strength of a film is the required force to rupture the film or induce a permanent change. Numerous scientists have physically and chemically modified tapioca starch to generate modified tapioca starch with a variety of uses [10]. The chemical and functional properties of modified starch are influenced by the distribution of substituents as well as reaction conditions, substituent type, and molar substitution [11]. Crosslinking is one of the most widespread starch modification methods. Crosslinking of starch takes place when bifunctional or multifunctional crosslinking agents form intermolecular linkages with primary hydroxyl groups (C6-OH) or secondary hydroxyl groups (C2-OH and C3-OH), thereby strengthening the intermolecular interactions between starch chains and binding molecules. Crosslinking is the formation of bond bridges between adjacent molecules via the use of various crosslinking agents [12]. Due to its carboxylic group, citric acid is one of the most promising candidates for use as a crosslinking agent, as it forms a network with cellulose chains or derivatives. Non-toxic citric acid will facilitate the synthesis of biodegradable and environmentally friendly hydrogels. Crosslinked starch has advantages over native starch due to its stronger structure, which includes high mechanical and thermal properties, high water stability, resistance to high temperatures, and a low pH [13, 14]. Shaking a mixture of granules consisting of hydrophilic polymers and drug compounds yields the monolithic hydrophilic matrix system. If this matrix system is introduced into an aqueous medium, the matrix remains intact and creates a high-viscosity inhibitory layer that regulates drug release and liquid penetration into the hydrophilic matrix system's core. Hydrophilic matrix components include methylcellulose, sodium alginate, hydroxyethyl cellulose, hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, xanthan gum, and starch. Hydroxypropyl methylcellulose is a semisynthetic polymer derived from cellulose that is stable between pH 3 and 11. Non-toxic and non-irritating properties are inherent to HPMC. The absence of HPMC, which has cathartic effects when consumed in excess [12, 13]. Tablet manufacturing can utilize HPMC as a modified-release agent, release-modifying agent, controlled-release agent, sustained-release agent, and viscosity-increasing agent. Sustained release is defined as the gradual discharge of a drug over time [17]. Polymer-based sustained-release tablets are an extended-release drug delivery system that regulates the discharge of drugs from their dosage form. This dosage form has the benefit of producing constant drug concentrations in the blood without the need of unit dose-giving repetition [5]. Crosslinking Amprotab with citric acid modifies the functional properties of starch, such as expandability, solubility, and viscosity, and serves as a guide for the formation of starch citrate bonds [18]. With the addition of 30% citric acid, the optimal digestibility of citric starch is achieved, as its digestibility has significantly decreased [19]. The swelling degree value of starch modification in xanthan gum without crosslinking agents is greater than starch modification in xanthan gum with crosslinking agents. Based on the results of this research, it is hoped that the modification of Amprotab with HPMC using citric acid as a cross-linking agent will produce modified starch, which can be used as an excipient in sustained-release tablet formulations [20].

This research aims to examine the formation of Amprotab copolymers with HPMC using citric acid as the crosslinking agent. This investigation also aims to determine chemical properties based on functional groups by means of Fourier Transform Infrared (FTIR) analysis, physical properties based on surface morphology and shape by means of scanning electron microscopy (SEM) analysis, and crystallin structure by means of X-ray Diffraction (XRD) analysis, thermal properties of starch by Thermogravimetric Analysis (TGA), expandability by swelling, and stability analysis by freeze-thaw cycles analysis, as well as mechanical properties as determined by maximal resistance using tension to analyze the tensile strength of modified cassava flour.

MATERIALS AND METHODS

Materials

Amprotab (Bratachem, Solo), HPMC (Colorcon, pharmaceutical grade), citric acid (Mitra Medica, technical), buffer K2HPO4 pro analysis (p.a) (Merck, Bratachem Solo), buffer HCl/KCl p.a (Merck, Bratachem Solo) and aquadest (Mitra Medika, Solo).

Examining amprotab organoleptic

The form, hue, flavor, and odor of Amprotab are evaluated.

Crosslinking modification of amprotab

The design of the formula for amprotab modification used is based on the research of Kawijia *et al.* (2017), with some modifications to the constituents and concentrations used so that the results of the formula are as shown in table 1 [21].

30 g of Amprotab were suspended in 100 milliliters of aquadest, along with citric acid dissolved in 50 milliliters of aquadest (0 g; 1.5 g; 3 g; 4.5 g). In a 500 ml beaker glass, a solution of Amprotab is combined with a solution of citric acid and heated to 90 °C while agitating until gelatinization. At 30 °C, 0 g, 1.5 g, 3 g, and 4.5 g of HPMC were suspended in 150 ml of aqueous solution until the solution thickened. The HPMC solution is added to a gelatinization mixture of Amprotab and citric acid, which is then heated for up to 30 min while being stirred continuously. The gelatinating results are poured into a tray and desiccated at 60 °C in a drying cabinet for 24 h to produce a starch film from Amprotab modified with HPMC and citric acid. Blending the starch film for 30 seconds and then passing it through a sieve with a 60-mesh opening partially powders it.

Table 1: Amprotab modification formula with HPMC uses citric acid as crosslinking agent

Formulation	Amprotab	HPMC	Citric acid	Aquadest
Control 1	30 g	0 g	0 g	300 ml
Control 2	30 g	1.5 g	0 g	300 ml
Control 3	30 g	0 g	1.5 g	300 ml
Formula 1	30 g	1.5 g	1.5 g	300 ml
Formula 2	30 g	3 g	3 g	300 ml
Formula 3	30 g	4.5 g	4.5 g	300 ml

Table 2: Interpretation of functional groups from the results of FTIR analysis of Amprotab modification

Formulation	Wavenumber (cm^{-1})	Functional Group Interpretation
Control 1 (30 g Amprotab)	3304.20	O-H Amprotab
Control 2 (30 g Amprotab/1.5 g HPMC)	3425.72	O-H Amprotab-HPMC
Control 3	3434.40	O-H alcohols and carboxylic acids
(30 g Amprotab/1.5 g citric acid)	1731.19	C=O ester
Formula 1	3418.01	O-H alcohols and carboxylic acids
(30 g Amprotab/1.5 g HPMC/1.5 g citric acid)	1730.22	C=O ester
Formula 2	3382.32	O-H alcohols and carboxylic acids
(30 Amprotab/3 g HPMC/3 g citric acid)	1733.12	C=O ester
Formula 3	3428.62	O-H alcohols and carboxylic acids
(30 g Amprotab/4.5 g HPMC/4.5 g citric acid)	1736.01	C=O ester

Table 3: Average size of Amprotab at 250x magnification

Formulation	Control 1	Control 2	Control 3	Formula 1	Formula 2	Formula 3
Average sizes (µm)	134.76	226.6	152.6	148.9	230.8	184.4

Table 4: Peak list analysis of X-ray diffraction (XRD)

Formula	Pos. [°2Th.]	*Height* [cts]	FWHM *Left* [°2Th.]	*d-spacing* [Å]	Rel. Int. [%]
Control 3	14.3387	69.01	0.9446	6.17726	27.34
	17.0383	252.41	0.7872	5.20410	100.00
	19.2694	75.75	0.6298	4.60629	30.01
	21.9363	97.72	0.6298	4.05196	38.72
	23.9613	61.17	0.6298	3.71391	24.23
Formula 1	17.1371	87.63	0.9446	5.17434	100.00
	21.8614	32.66	0.9446	4.06567	37.27
Formula 2	11.5811	6.32	0.6298	7.64118	3.48
	14.4766	30.75	0.9446	6.11872	16.94
	17.1077	181.54	0.7872	5.18315	100.00
	21.9621	59.00	0.7872	4.04724	32.50
	24.3068	33.66	0.9446	3.66189	18.54
	72.4600	20.32	0.9446	1.30440	11.19
Formula 3	17.0237	132.83	0.9446	5.20855	100.00
	22.0700	40.74	0.9446	4.02771	30.67
	24.0390	21.02	0.9446	3.70207	15.83

Phosphate buffer preparation

The HCl/KCl buffer solution is made by making solution A, which is 0.2 M KCl (14.9 g in 1000 ml), and solution B, which is 0.2 M HCl, by mixing 1.66 ml of HCl into 100 ml of aquadest. Solution B is added to solution A until the pH of the solution reaches 1.2 [22]. Make a phosphate buffer solution by dissolving 1 g of K_2HPO_4 using aquadest in a 1000 ml measuring flask until the limit mark. The phosphate buffer solution's pH is adjusted by adding H_3PO4 solution or KOH solution little by little until it reaches the desired pH of 4.5 and 7.4 [23].

Fourier transform infrared (FTIR) analysis

The Amprotab copolymer was analyzed with FTIR spectrophotometer with a wavenumber range of 500–4000 cm^{-1}. The higher the polymer composition, the wider the absorption intensity produced. Citric acid crosslinked starch will exhibit ester linkages, indicating the absorption of C=O esters [24].

Scanning electron microscopy (SEM) analysis

The morphological form of Amprotab copolymer was observed by *scanning electron microscopy* (Phenom pro-X desktop). The dried sample was coated with gold and observed with a voltage of 5 kV at different magnifications (250x and 800x).

Swelling index analysis

Swelling index analysis was performed by immersing 0.1 g of copolymers from each formula into 10 ml of buffer solution with pH 1.2, 4.5, and 7.4 at room temperature (28 °C). This study uses varying times of immersion, namely for 15 min, 30 min, and 60 min. The swelling index and swelling rate are calculated by the formulas equation (1) and equation (2).

$$Swelling\ index = \frac{Wt-Wo}{Wo} \text{ x } 100\% \text{ ..... (1)}$$

$$\text{S□□□□□□□ rate} = \frac{Wt-Wo}{Time} \text{ .... (2)}$$

Freeze-thaw stability test

Amprotab 5% w/v in aquadest is heated at 95 °C for 30 min with constant stirring. After that, eight centrifuge tubes were filled with 10 ml of starch gel and weighed. The starch gel in each centrifugation tube is weighed, then was frozen in the *freezer* at-20 °C for 22 h. After 22 h, the process of thawing takes place at room temperature for two hours. The cycle of freezing and thawing is carried out for 5 consecutive days (5 *cycles*). Starch gels that have reached 5 cycles of freezing and thawing are centrifuged at a speed of 8000 rpm for 10 min until the liquid phase and solid phase are formed, then the liquid phase is taken to be weighed so that air weight [25]. This stability analysis (*freeze-thaw cycles*) is expressed through the percentage of syneresis. The percentage syneresis formula is expressed in equation (3).

$$\% \text{ Syneresis} = \frac{\text{Water weight}}{\text{Initial sample weight}} \text{ x } 100\% \text{ .... (3)}$$

Tensile strength analysis

The copolymers of each formula are formed into a rectangular shape with a minimum size of 4 cm long and 1 cm wide, then attached to a tensile strength tool and measured tensile strength (s) with the equation formula (4) [26].

$$\text{Tensile strength} = \frac{\text{Force}}{\text{Film wide x Film thick}} \text{ ..... (4)}$$

X-ray diffraction (XRD) analysis

X-ray diffraction is a technique used to reveal information on the structure of a sample. XRD characterization was carried out using an X-ray diffractometer (PAN alitycal X'pert 3 powder) with a temperature of 25 °C operated at 400 kV and 300 mA. The sample is placed in an aluminum sample container and the diffraction pattern plots the intensity against the detector angle of 2θ and the scanning range is 10° to 80° in increments of 0.02°.

Thermogravimetric analysis (TGA)

Thermogravimetric analysis aims to determine the thermal properties of natural Amprotab and crosslinking modified Amprotab. The test was heated using a thermogravimetric analyzer at a temperature of 30 °C to 600 °C with a heating speed of 20 °C/min [27].

RESULTS AND DISCUSSION

Amprotab used in this study has organoleptic properties, namely in the form of clearly white, fine granules, smelling typical of starch, and tasteless, practically insoluble in cold water and ethanol.

Amprotab copolymer-HPMC-citric acid

Based on fig. 1 show that the starch film layer in control 1 was made up of smaller cracked sheets, while formula 1, 2, and 3 copolymers modified with HPMC and crosslinked using citric acid as a crosslinking agent, produce a starch film that is stronger and more elastic. The addition of citric acid produces a stronger and more elastic copolymer and the greater the concentration of HPMC, the stronger the starch copolymer and the less breaks easily [28].

Fourier transform infrared (FTIR) analysis

The esterification reaction that occurs during the modification of Amprotab with HPMC and citric acid will produce a new molecule, identified by FTIR as C = O ester. This reaction binds 1 mole of Amprotab and 1 mole of HPMC to 1 mole of citric acid as a crosslinking agent, allowing it to be crosslinked. Crosslinking Amprotab with HPMC and citric acid yields a new C=O ester group formed by the binding between the carboxyl group of citric acid and the hydroxyl groups of starch and HPMC.

The O-H bond of the acid will absorb in an area between 2500 and 3300 cm-1, while the alcohol will absorb between 3230 and 3550 cm-1. If these absorptions appear together, it will give a very wide absorption in an area from 2500 to 3550 cm-1. The absence of boundaries between these two types of O-H may be caused the absorption of C-H. C=O absorption appears at 1730 cm-1. Alcohols O-H bonds absorb at the greater wavenumbers of acids, which are between 3230 and 3550 cm-1. The absorption of C=O ester groups appears at wavenumbers around 1722-1737 cm-1, C-O esters in the area around 1218–1238 cm-1, and C-H stretching in the area around 2893–2945 cm-1.

The results of FTIR analysis showed the presence of an O-H group from Amprotab (Control 1) at wavenumber 3304.20 cm-1 and an O-H group from Amprotab-HPMC modification (Control 2) at wavenumber 3425.72 cm-1. The presence of O-H groups of alcohols and carboxylic acids at wavenumber 3434.40 cm-1 and C=O ester groups appeared at wavenumber 1731.19 cm-1 of cassava-citric acid starch modification (Control formula 3). The presence of O-H groups of alcohol and carboxylic acids from cassava-HPMC-citric acid starch modifications, namely formulas 1, 2, and 3, respectively, at wavenumbers 3418.01 cm-1, 3382.32 cm-1, and 3428.62 cm-1 and C=O ester groups appear at wavenumbers 1730.22 cm-1, 1733.12 cm-1, and 1736.01 cm-1, respectively.

Scanning electron microscopy (SEM) analysis

SEM analysis is carried out with the aim of determining the morphological differences of starch granules. The results of SEM analysis can be seen in fig. 1, fig. 3, and fig. 4. Control formulas 1 and 2 have irregular granule shapes with a fairly flat surface. Control formulas 1, 2, and 3 have irregular starch granule shapes with uneven or rough surfaces. As a result of control formula 3, formulas 1, 2, and 3 underwent a modification of the crosslinking (addition of citric acid), thus causing the surface morphology to be rough. Sago starch has a surface shape that is not too dense or sharp, while sago starch that undergoes crosslinking modification has a rough surface shape. Crosslinking sago starch will form a rougher, coarser, and denser surface [29, 30].

The calculation of the average size of Amprotab granules (table 3) shows that HPMC-modified Amprotab and citric acid (formulas 1, 2, and 3) have a larger average starch granule size compared to starch without the addition of HPMC and citric acid (control formula 1). This is likely because the crosslinking modified Amprotab granules are stronger, so even if mashed in the same way, it produces starch powder with granules that are larger (starch film is hard to disintegrate) compared to starch without the addition of HPMC and

citric acid. The results of Amprotab-HPMC (control 2) have an average size of granules almost as large as Amprotab-HPMC-citric acid modified granules (formula 2). The starch film has high structural integrity, good compatibility between mixed components, and decreased roughness in the presence of HPMC, thus affecting the mechanical and optical properties of the film. Crosslinking causes changes in starch properties, such as increasing viscosity, increasing gel strength, making starch granules stronger, not being easy to expand or swelling, being acid-resistant (low pH), shearing, and being resistant to high-temperature cooking [31].

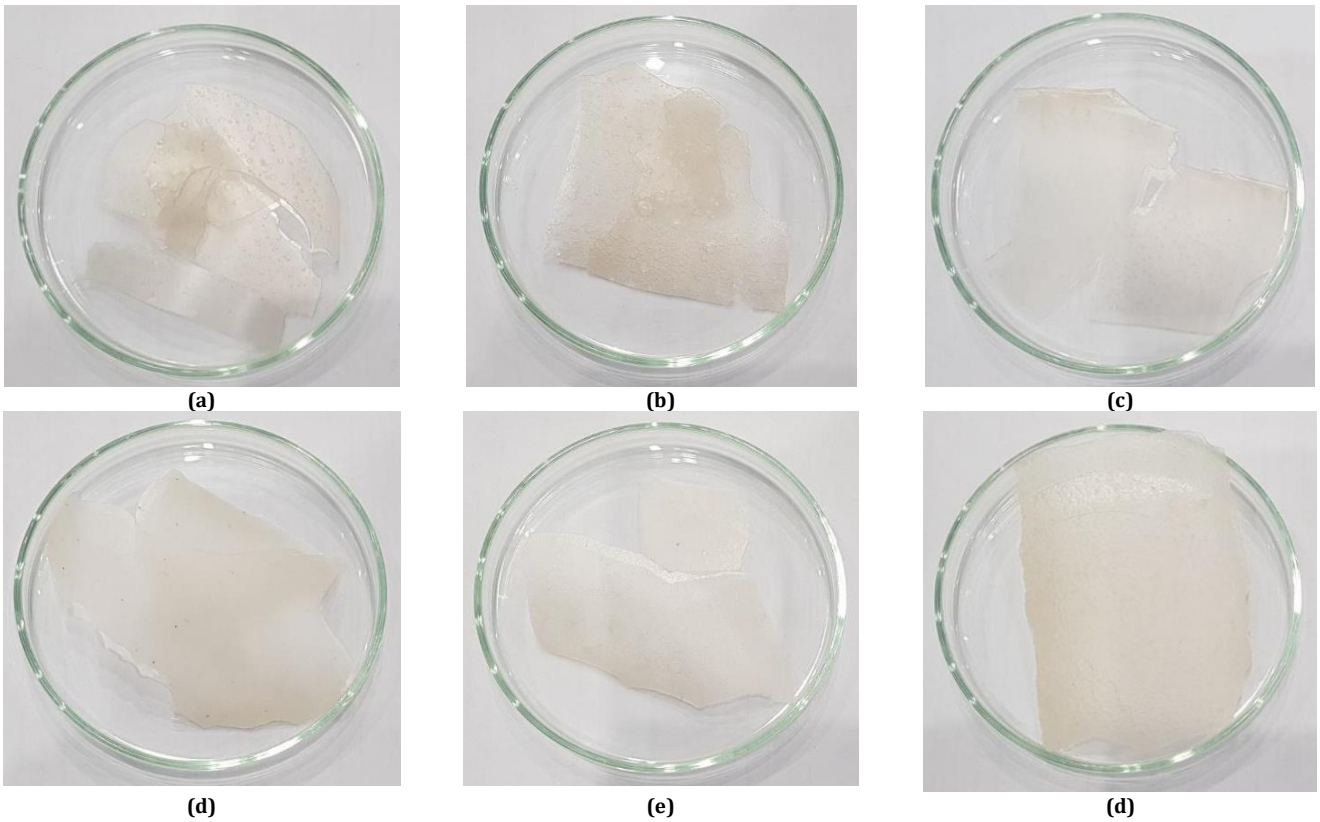

Fig. 1: The photograph of copolymer: (a) Control 1 (30 g Amprotab/0 g HPMC/0 g citric acid). (b) Control 2 (30 g Amprotab/1.5 g HPMC/0 g citric acid), (c) Control 3 (30 g Amprotab/0 g HPMC/1.5 g citric acid), (d) Formula 1 (30 g Amprotab/1.5 g HPMC/1.5 g citric acid), (e) Formula 2 (30 g Amprotab/3 g HPMC/3 g citric acid), and (f) Formula 3 (30 g Amprotab/4.5 g HPMC/ 4.5 g citric acid)

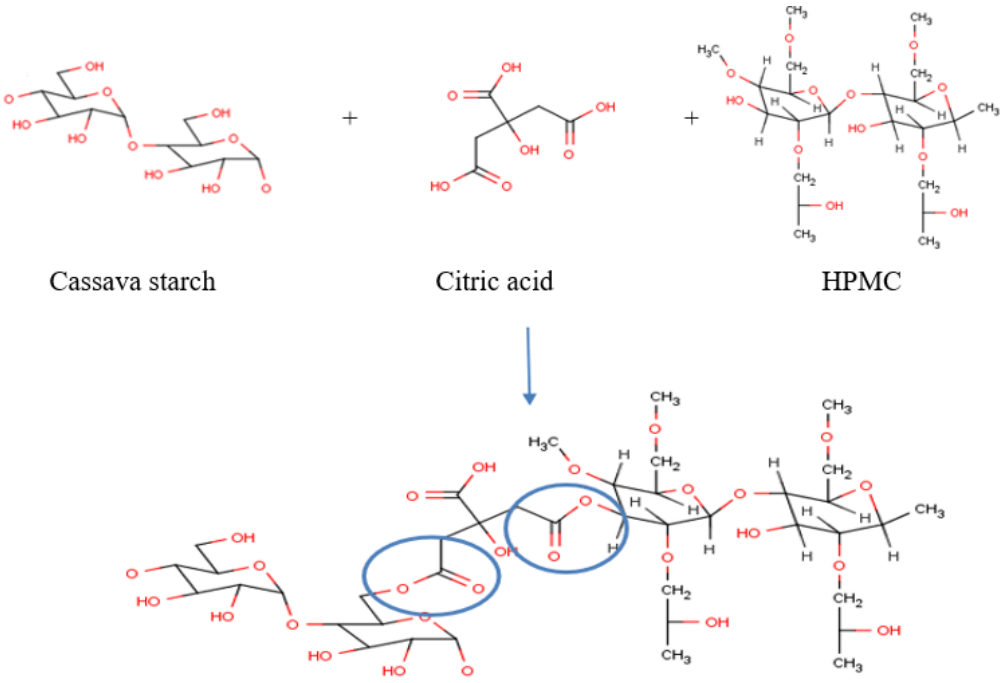

Fig. 2: Mechanism of esterification reaction between amprotab-citric acid-HPMC

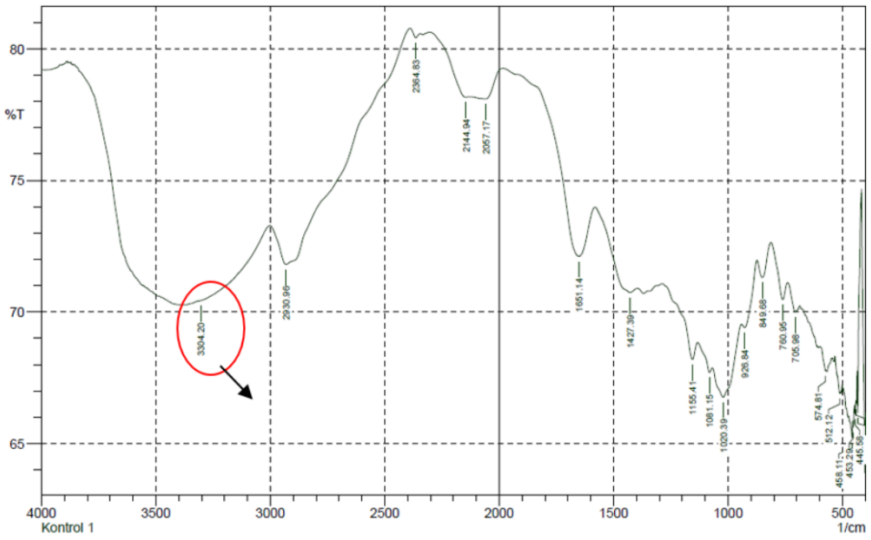

Fig. 3: FTIR analysis results from the control 1 (30 g Amprotab/0 g HPMC/0 g citric acid)

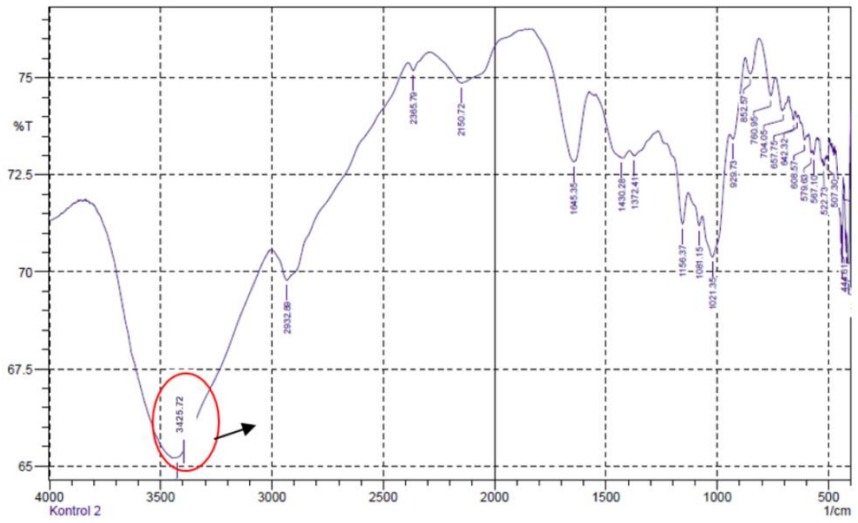

Fig. 4: FTIR analysis results from the control 2 (30 g Amprotab/1.5 g HPMC/0 g citric acid)

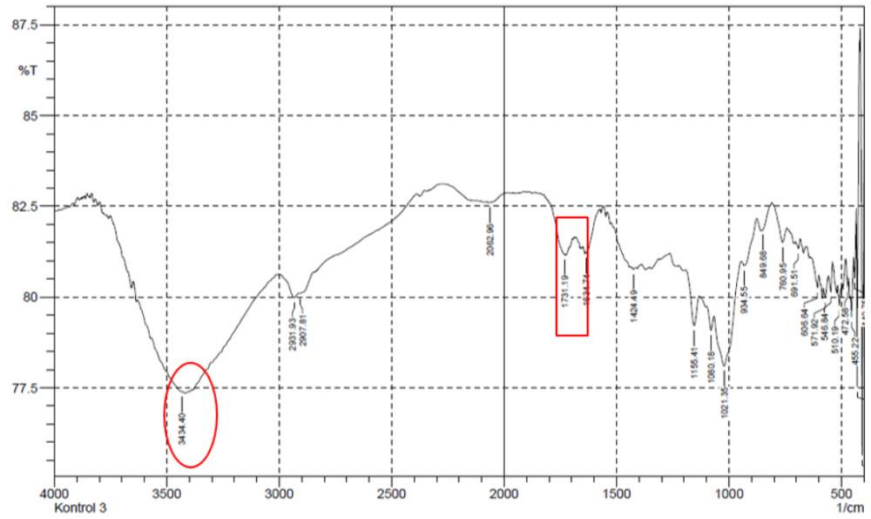

Fig. 5: FTIR analysis results from control 3 (30 g Amprotab/0 g HPMC/1.5 g citric acid)

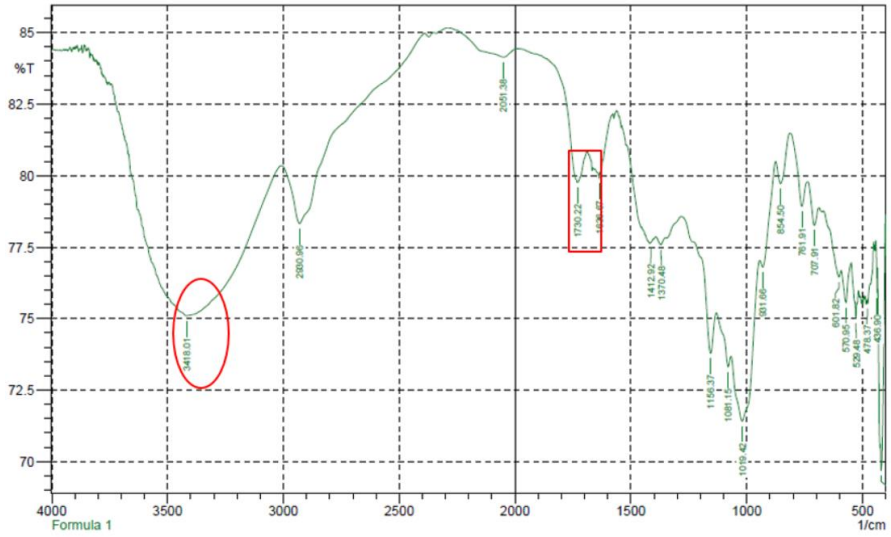

Fig. 6: FTIR analysis results from formula 1 (30 g Amprotab/1.5 g HPMC/1.5 g citric acid)

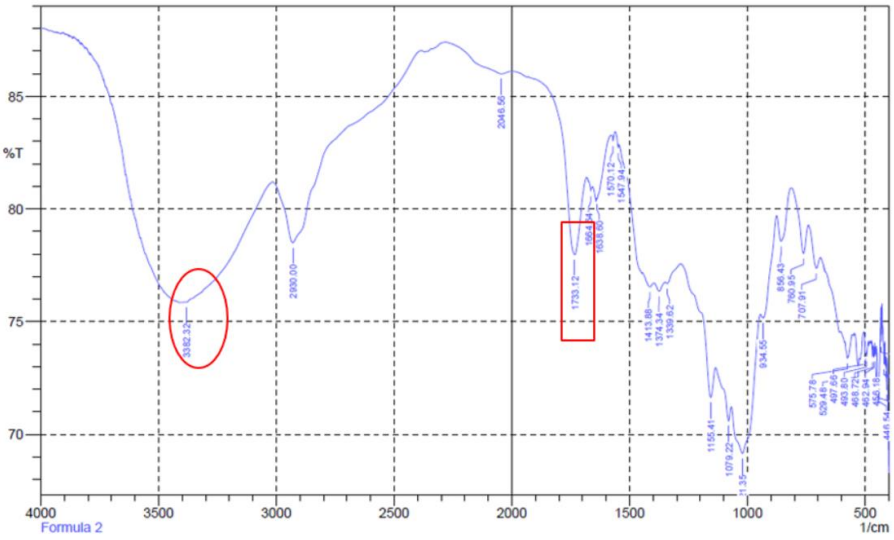

Fig. 7: FTIR analysis results from formula 2 (30 g Amprotab/3 g HPMC/3 g citric acid)

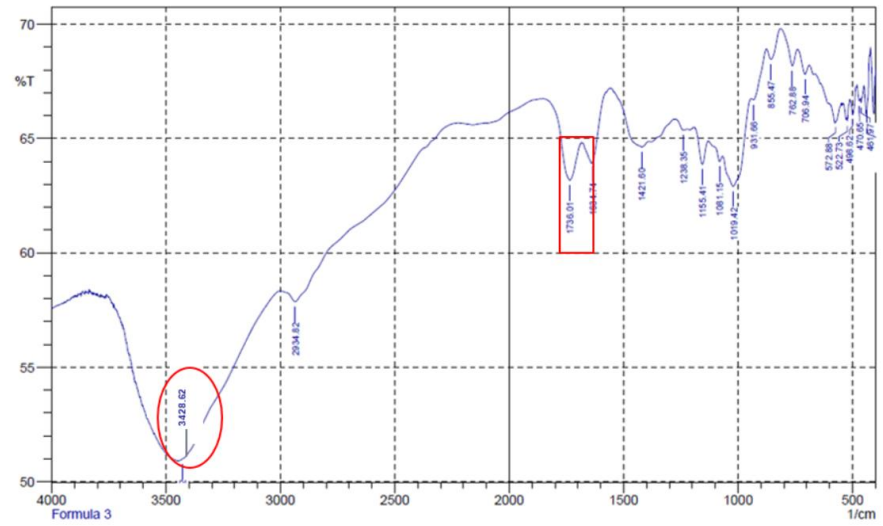

Fig. 8: FTIR analysis results from formula 3 (30 g Amprotab/4.5 g HPMC/4.5 g citric acid)

Swelling analysis

Amprotab copolymer film was immersed in a buffer solution at pH 1.2, which corresponds to the pH conditions of the stomach when it is empty; pH 4.5, which corresponds to the pH conditions of the mouth and stomach when they are full; and pH 7.4, which corresponds to the pH conditions of the intestines. In fig. 15, 16, and 17, the results of swelling analysis reveal that the swelling rate of formulations 1, 2, and 3 is less than that of the control at pH 1.2, 4.5, and 7.4. This is consistent with Norma's (2012) findings that water diffusion occurs more rapidly in copolymers without crosslinking modifications than in crosslinking-modified copolymers. Crosslinks in starch copolymers tighten the network structure of the copolymer, making it more difficult for liquid to penetrate the copolymer.

The results of swelling analysis depicted in fig. 18, 19, and 20 indicate that the degree of swelling control is superior to that of formulations 1, 2, and 3 at pH values of 1.2, 4.5, and 7.4. Due to the formation of ester bonds in crosslinking modified copolymers, which causes the network structure to become denser, water diffusion into the copolymer becomes more difficult. Formula 3 exhibits a greater degree of swelling than Formulations 1 and 2. A higher concentration of HPMC may result in a greater degree of edema in formulation 3. With increasing HPMC concentration, granule absorption, tablet hardness, and swelling index can be substantially enhanced [32]. Because starch copolymers are acidic, the average swelling rate at pH 7.4 is lower than at pH 1.2 and 4.5, and the amount of unreacted citric acid increases as more citric acid is added. If acidic copolymers are immersed in an acidic pH containing a great deal of H+, then the likelihood of minor interactions leading to swelling is also low. In contrast to alkaline pH, which contains a great deal of OH-, it readily interacts with acidic copolymers, so the degree of enlargement is greater at alkaline pH than at acidic pH. At pH 1.2, the degree of edema is greater than at pH 4.5, most likely due to the influence of HPMC stability, which decreases at very low pH. HPMC, which is a semi-synthetic polymer derived from cellulose and stable at pH 3–11, is a thermoplastic polymer.

Freeze-thaw cycles analysis

Based on the stability analysis (freeze-thaw cycles), modified Amprotab exhibited an increase in syneresis. Syneresis values obtained from formulations 1, 2, and 3 (HPMC-modified Amprotab and citric acid) were 64.81 %, 56.68 %, and 62.22%, respectively, which was 18.80% higher than control 1 (Amprotab without HPMC and citric acid). This contradicts the statement by Larasati *et al.* (2017) that citrate starch (modified starch) exhibits a decrease in syneresis. Due to the high value of the degree of crosslinking, the percentage of modified starch syneresis decreases, allowing the starch paste to remain stable during chilling. The increased syneresis in crosslinking modified Amprotab is likely a result of the starch solution's high acidity [33]. Acid can impair the hydrogen bonds in starch, making it more difficult for water to bind to starch granules. The reaction between citric acid and starch can lead to hydrolysis. The pH has an effect on the frequency of starch chain fractures. Acidity, pH, and water binding can influence syneresis [34]. Increased syneresis indicates poor freeze-thaw stability. With a high syneresis value, the results of Amprotab modification with HPMC and citric acid as crosslinking agents are unstable at low temperatures [35].

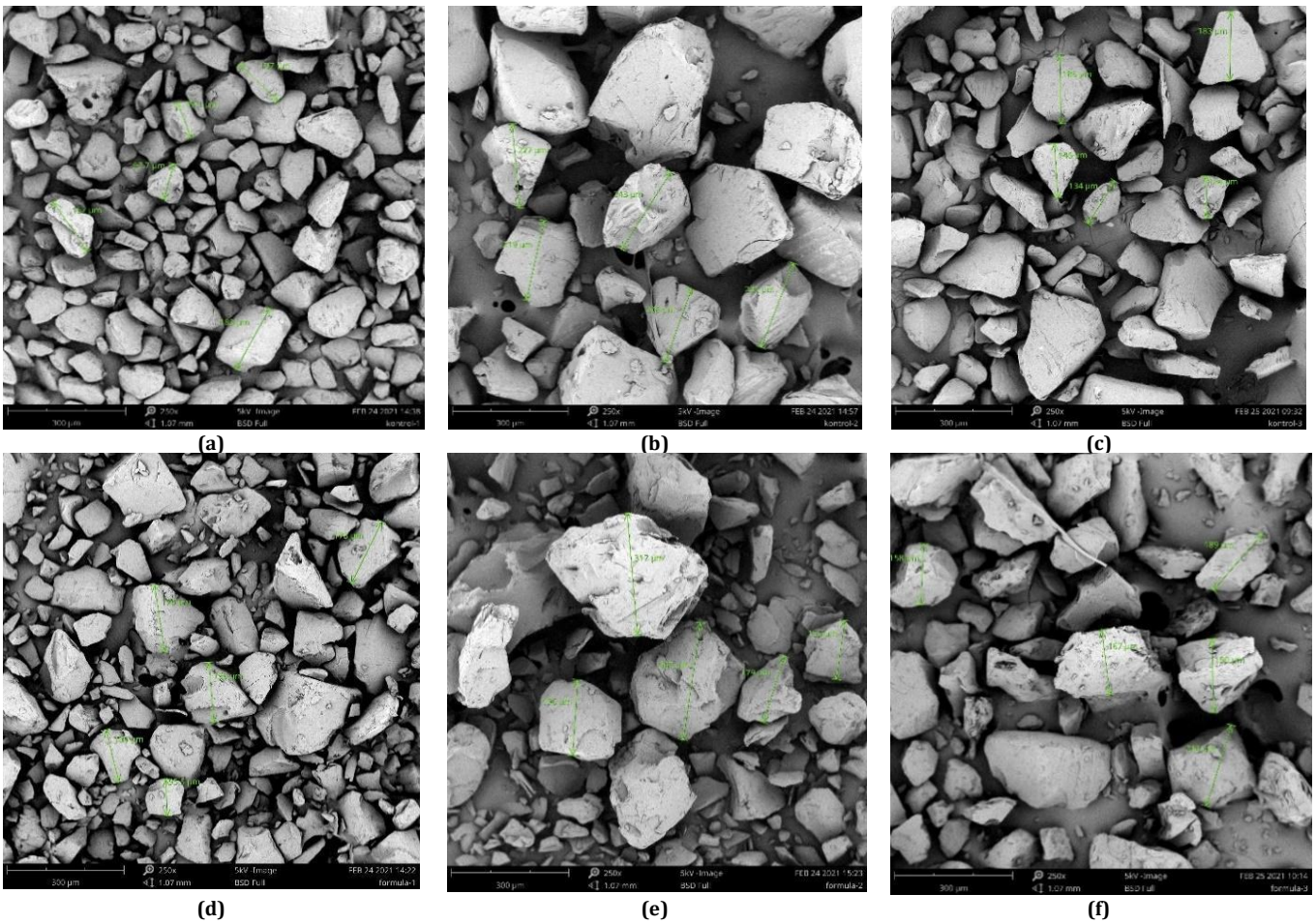

Fig. 9: SEM analysis results: (a) Control 1 (30 g Amprotab/0 g HPMC/0 g citric acid). (b) Control 2 (30 g Amprotab/1.5 g HPMC/0 g citric acid) and (c) Control 3 (30 g Amprotab/0 g HPMC/1.5 g citric acid), (d) Formula 1 (30 g Amprotab/1.5 g HPMC/1.5 g citric acid). (e) Formula 2 (30 g Amprotab/3 g HPMC/3 g citric acid) and (f) Formula 3 (30 g Amprotab/4.5 g HPMC/4. 5 g citric acid)

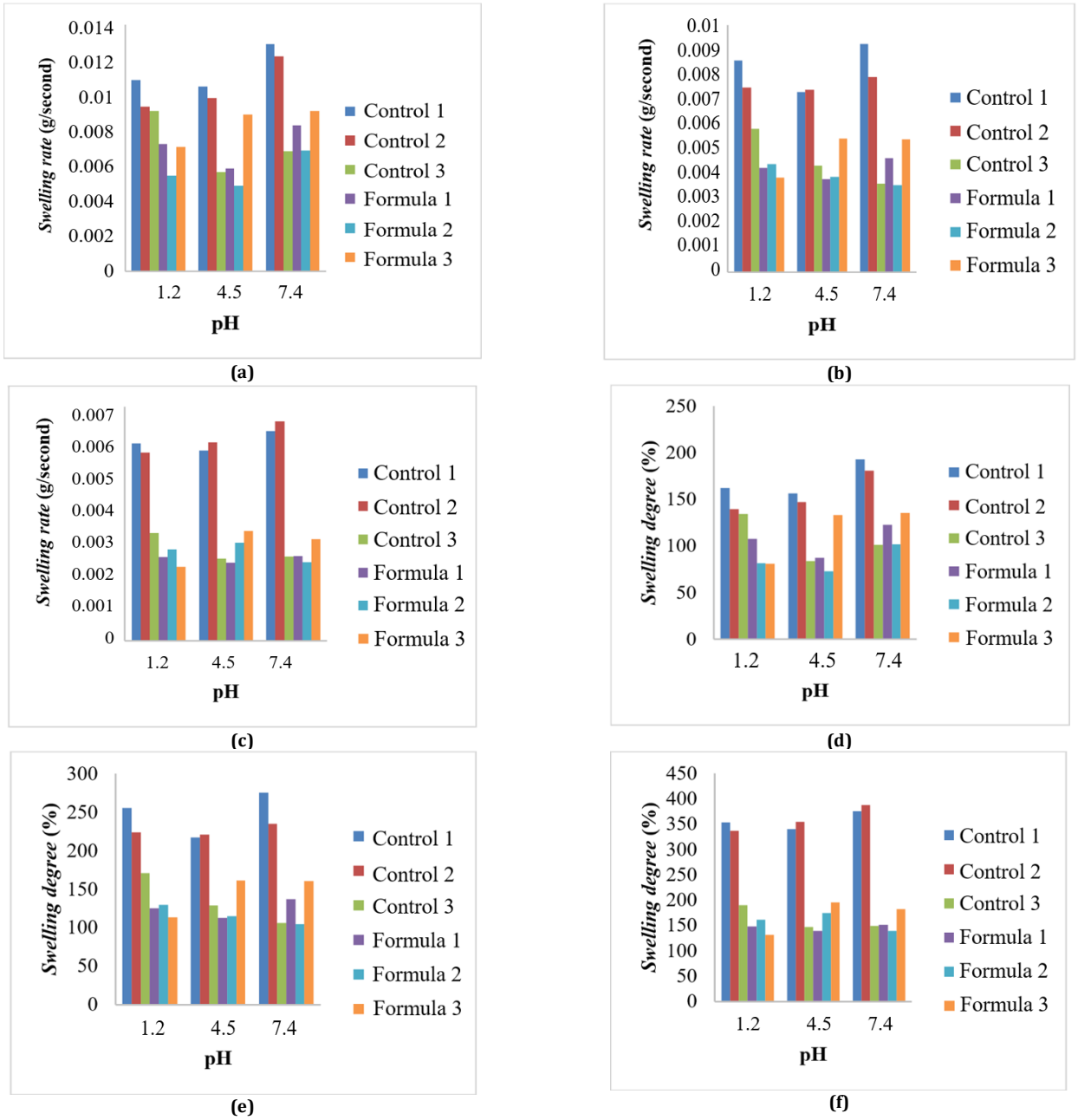

Fig. 10: The graphs of swelling speed at (a) 15 min, (b) 30 min, (c) 60 min and degree of swelling at (d) 15 min, (e) 30 min, (f) 60 min

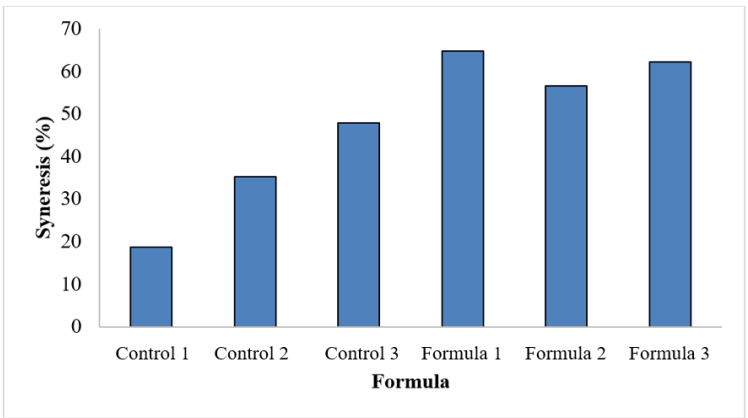

Fig. 10: Stability analysis result graph (freeze-thaw cycles)

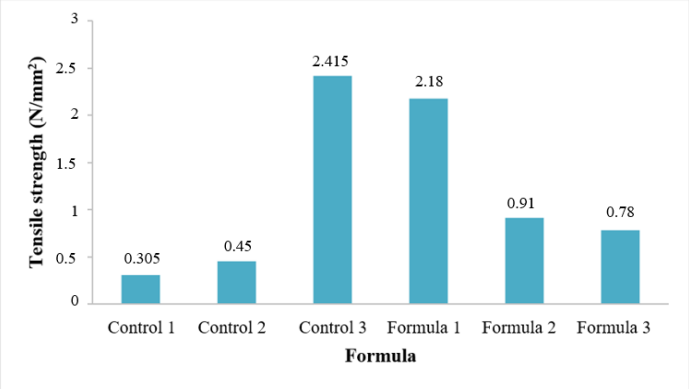

Fig. 11: Result of tensile strength analysis

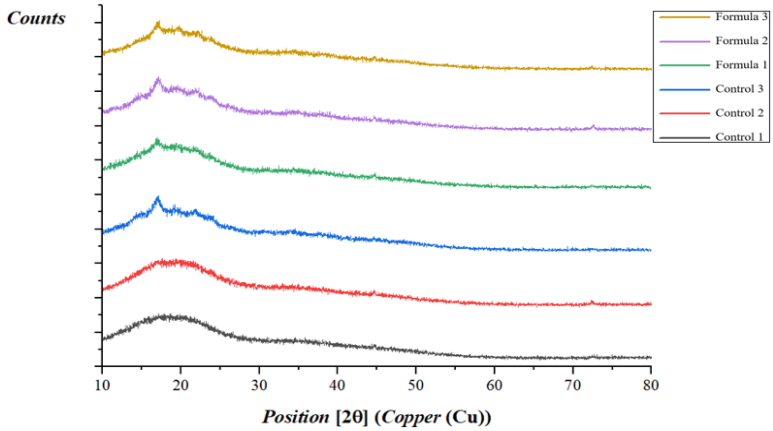

Fig. 12: Analysis results of X-ray diffraction (XRD)

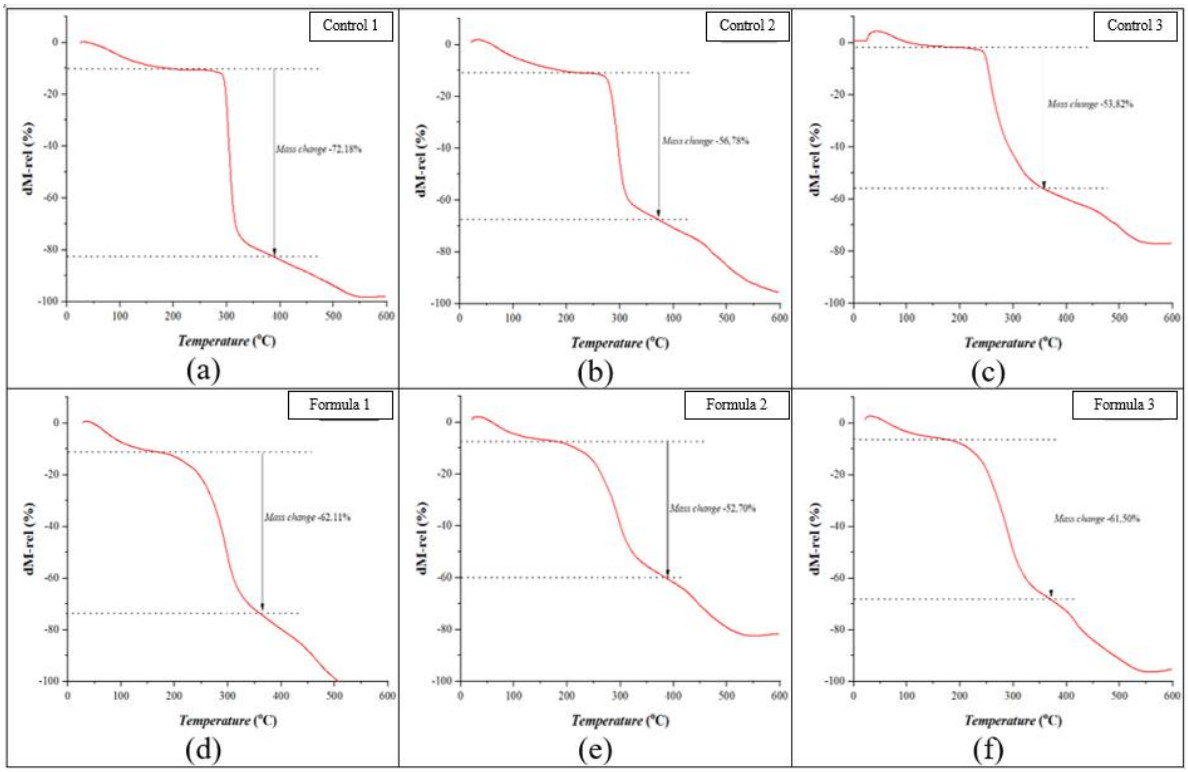

Fig. 13: Results of thermogravimetric analysis (TGA): (a) Control 1 (30 g Amprotab/0 g HPMC/0 g citric acid), (b) Control 2 (30 g Amprotab/1.5 g HPMC/0 g citric acid), (c) Control 3 (30 g Amprotab/0 g HPMC/1.5 g citric acid), (d) Formula 1 (30 g Amprotab/1.5 g HPMC/1.5 g citric acid), (e) Formula 2 (30 g Amprotab/3 g HPMC/3 g citric acid) and (f) Formula 3 (30 g Amprotab/4.5 g HPMC/4.5 g citric acid)

Tensile strength analysis

Fig. 11's analysis of tensile strength demonstrates that the tensile strength of HPMC-modified Amprotab and citric acid (formulas 1, 2, and 3) is higher than that of starch without the addition of HPMC and citric acid (control 1). Formula 1 has a tensile strength of 2.18 N/mm², which is greater than Formula 2's 0.91 N/mm² and Formula 3's 0.78 N/mm² values. Amprotab and citric acid modification (control 3) resulted in the highest tensile strength value, followed by Amprotab modification with HPM and citric acid (formulas 1, 2, and 3) and an increase in the amount of HPMC and citric acid added. The incorporation of HPMC into the matrix enhances mechanical strength. HPMC can increase the interaction forces between starch molecules, thereby promoting the formation of a matrix that is more cohesive and resistant. The effect of increasing the concentration of HPMC in a film is reversed, as the film's tensile strength and modulus of elasticity decrease significantly while elongation is unaffected. Increased HPMC in formulations also increases phase separation between macromolecules, resulting in a decrease in intermolecular forces on starch and a corresponding decrease in the mechanical resistance of k-films [36]. Citric acid can hydrolyze the branched chains of starch molecules, resulting in the formation of a highly linear structure. This permits the formation of more hydrogen bonds between the starch chains, thereby enhancing the tensile strength of the resultant film. As the percentage of citric acid in a mixture increases, the residual citric acid acts as a plasticizer and reduces the interaction between macromolecules, resulting in a reduction in ultimate tensile strength and an increase in strain at break.

X-Ray diffraction (XRD) analysis

The purpose of X-ray diffraction spectral pattern testing is to determine the variety of starch crystallinity. Starch is a semicrystalline material with crystalline and amorphous regions in its granules. This crystalline region is predominantly composed of amylopectin polymers, whose outer branches form crystallites that decompose during gelatinization. Fig. 23 demonstrates that unmodified crosslinking starch (Controls 1 and 2) formed an amorphous diffraction pattern, which can occur when starch is injured during the heating or gelatinating process. The higher the temperature used during heating procedures, the more starch will be damaged as the starch changes into gelatinized starch [37]. Crosslinking modified Amprotab (control 3, formulas 1, 2, and 3) resulted in a diffraction pattern exhibiting criticality. Due to its stronger structure, crosslinked starch has advantages over native starch, including high mechanical and thermal properties, high water stability, resistance to high temperatures, and a low pH [38]. Table 4 demonstrates that modified Amprotab yields have type B crystal characteristics characterized by the strongest or highest peaks of formulas 1, 2, and 3, namely 17.1371°, 17.1077°, and 17.0237°, as well as several other minor peaks ranging from 11° to 24°. Starch has multiple X-ray diffraction patterns. Patterns of type A XRD have prominent diffraction peaks at approximately 15° and 23° and imprecise peaks at approximately 17° and 18°. Type B starch's XRD pattern exhibits the strongest diffraction peaks at approximately 17°, along with smaller peaks at 15°, 20°, 22°, and 24°, and characteristic peaks at 5.6°. The typical XRD type C pattern combines characteristics of types A and B. The greatest peaks of the typical XRD type C pattern are located at 17° and 23°, with smaller peaks at 5.6° and 15° [39].

Thermogravimetric (TGA) analysis

TGA revealed that crosslinking-modified Amprotab had a mass loss that was approximately 10 to 20% less than natural Amprotab. At temperatures below 100 °C, natural Amprotab and crosslinking-modified Amprotab began to experience a modest mass loss, most likely due to the presence of moisture in the starch. At temperatures between 200 °C and 390 °C, formulations 1, 2, and 3 (modified Amprotab) lost approximately 62.11, 52.70, and 61.51% of their mass, respectively. With a temperature range of 250 °C to 390 °C, natural Amprotab (control 1) lost approximately 72.18 percent of its mass. At temperatures between 390 °C and 600 °C, the mass loss of crosslinking-modified Amprotab is less than that of natural Amprotab, with the exception of formula 1. The mass loss of crosslinked starch films of citric acid and adipic acid is slightly greater than that of the control film. This may be the result of residue-free citric acid and adipic acid decomposing. The six crosslinking agents enhance the starch/PHA composite film's thermal stability to some extent [40].

Citric acid effectively binds starch, increases strength, and greatly reduces film mass loss in water and formic acid. Crosslinked starch films show wide melting peaks and have much higher thermal stability (lower mass loss) compared to uncrosslinked starches at temperatures between 320ºC and 600ºC, showing much better resistance to thermal degradation due to crosslinking. Crosslinked films have much higher thermal stability than non-crosslinked films above 320 °C [40, 41]. The temperature of films with citric acid and adipic acid is higher compared to other types of films. The crosslinked films of citric acid and adipic acid have better thermal stability due to lower weight reduction [40].

CONCLUSION

Amprotab is modified with HPMC and citric acid as crosslinking agents, and the crosslinking procedure yields starch with superior properties compared to natural Amprotab, namely a lower swelling value and a higher tensile strength value. This demonstrates that the modified starch in this study is capable of resisting or controlling the drug's release, allowing it to be used as a matrix or film in sustained-release tablet formulations.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

All authors declare no conflict of interest, Suprapto Suprapto acts as data collection, data processing and data analysis, Teuku Nanda Saifullah Sulaiman acted as a supervisor helped in data analysis and article correction, Abdul Rohman as supervisor, correction of FTIR data, Akhmad Kharis Nugroho as supervisor and article correction.

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