PENGARUH KOMBINASI POLIMER HIDROKSIPROPIL METILSELULOSA DAN NATRIUM KARBOKSIMETILSELULOSA TERHADAP SIFAT FISIK SEDIAAN PATCH EKSTRAK ETANOL HERBA SELEDRI (Apium graveolens L.)

by Galuh Kartikasari

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Pengaruh Kombinasi Polimer Hidroksipropilmetilselulosa dan Natrium karboksimetilselulosa terhadap Sifat Fisik Sediaan *patch* Ekstrak Etanol Herba Seledri (*Apium graveolens* L.)

The Effect of Combination of Hydroxypropylmethylcellulose and Carboxymethylcellulose Sodium Polymers to The Physical Properties of Celery (*Apium graveolens* L.) Ethanolic Extract Patch

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ABSTRACT

Celery herbs (*Apium graveolens* L.) contain apigenin compounds (flavonoids) that are effective as antihypertensiv. Celery herbs used in the form of decoction and oral preparations have a deficiency that is voluminous and can cause gastric irritation. Patches were chosen because it can prevent gastric irritation and reduce the frequency of drug administration because the drug is delivered over the skin with a long duration. This study aimed to know the effect of variations in the ratio of the concentrations of hydroxypropyl methylcellulose (HPMC) and carboxymethylcellulose sodium (CMC sodium) polymers to the physical properties of celery herbs ethanol extract patch.

This study was conducted with maceration of celery herbs using 96% ethanol and then dispersed in patch made with variations in the concentrations ratio of HPMC and CMC sodium polymers of 3:1, 1:1, and 1:3. Patches were tested for physical properties including organoleptic, pH, thickness, weight, folding endurance, and moisture content. Statistical analysis of test data used One Way ANOVA and Paired Samples T Test.

The results of statistical analysis showed that the increase concentrations ratio of CMC sodium polymer in the combination of HPMC and CMC sodium polymers could increase the thickness, weight, and moisture content of celery herbs ethanol extract patch. The best patch was formula 2 with the same concentration ratio of HPMC and CMC sodium polymers because it showed the best results with a pH 6,12-6,29, thickness 1,37-1,53 mm, weighting 2,24-2,52 gram, folding endurance more than 300 times, and the moisture content was quite stable.

Keywords: celery herbs, patch, HPMC, CMC sodium

1. Introduction

Celery is one of the herbal that used by people to decrease blood presure in hypertension. Celery contains of active compounds such as flavonoids, saponins, tannins 1%, essential oils 0.033%, flavo-glucosides (apiin), apigenin, phytosterols, choline, lipases, phthalids, asparagines, bitter substances, vitamins (A, B and C), and alkaloids (Saputra and Fitria, 2016). One of the main components of flavonoids in celery is apigenin (Al-Snafi, 2014). Apigenin is vasorelaksator that is dilating blood vessels with mechanisms such as calcium antagonists so that it can function as an antihypertensive agent (Palmer, 2007). Ethanol extract of celery that given orally at a dose of 550 mg B.W for 7 days can reduce systolic blood pressure by 6.62 mmHg and diastole by 4.59 mmHg (Dewi et al., 2010).

Celery plants are usually used for treatment by infused into water, but the dosage of the infused water celery is less precise and still contains many components that are not needed for treatment and voluminous, especially amount of drugs taken in a day. The formulation of celery herbal medicines in oral preparations such as liquid, infused and capsules has also begun to be developed, but oral preparations still have side effects such as stomach irritation and require higher doses to get therapeutical effect (Patel et al., 2012). Celery patch is one of drugs delivery system that delivered topically are the choices that are expected to resolve deficiencies in oral preparations and to increase the effectiveness of treatment.

Patch is a dosage form that aims to deliver drugs through the skin membrane into the blood circulation (Valenta and Auner, 2004). Patch preparations have the advantage of being easy to use, reducing the frequency of drug administration, eliminating first-pass metabolism, reducing side effects such as stomach irritation, and increasing patient compliance (Madhulata and Naga, 2013). Polymers are the main components of the patch matrix and play an important role because the polymers are in charge of controlling drug release from the patch matrix (Sharma et al., 2011). Hydroxylmethylcelulose (HPMC) polymers and Carboxylmethylcellulose (CMC-Na) are hydrophilic polymers. Research conducted by Prabhu et al. (2011) that formulated patch preparations with various polymer combinations, it was produced that the formulation with the combination of hydrophilic polymer HPMC and CMC -Na was the best formulation because it provided faster drug release. Formulated patch formula is expected to know the effect of a combination of HPMC polymers and CMC-Na on the physical properties patch of celery herb ethanolic extract and fullfil patch that have good physical properties.

2. Material and Methods

2.1. Material

Celery leaves herb (*Apium graveolens* L.) C.V Herbadream Palur, Karanganyar, Central Java, ethanol 96% technis grade (Brataco), silica GF254, n-butanol (Merck), acetate acid (Merck), aquadest (Agung Jaya), quercetin standard (Sigma), HPMC (Hercules Tianpu), CMC-Na (Changshu Wealthy), nipagin (Agung Jaya), PEG 400 (DOW), propylene glycole (DOW).

2.2. Celery Herbs Ethanolic Extraction

Fresh green celery herbs with dark colour are wet sorted, then washed and drained under sun with a black cloth covered. Dry celery herbs then dry sorted and blended into powder. Amount of 500 gram celery herbal powder was put into maceration jar, macetaed with 2.5 liters of 96% ethanol until the surface of the powder was completely submerged. Maceration jars are tightly closed, left for 3 days in a light-protected place while occasionally stirring. The maceration results are filtered, then the filtrate is evaporated at temperature of 45-50°C with a rotary evaporator, then concentrated with a waterbath until a thick extract is obtained.

2.3. Physical Caracteristics of *Celery Herbs Ethanolic Extract*

2.3.1. Calculation of extract yield

The extract yield is calculated by means of the weight of the extract obtained (grams) divided by the total weight of the initial simplicia (grams), the results expressed in percent (%).

2.3.2. Organoleptic examination of extracts

Organoleptic examination of the extract includes the shape, color, and odor carried out with the senses and aims for a simple and subjective initial introduction.

2.3.3. Water content testing

Amount of 1.0 gram extract was placed on an empty aluminum pan of the moisture analyzer, then the extract was leveled. The instrument cover is closed and set at a temperature of 105° C, the moisture analyzer will heat the extract until it shows the value of the sample water content that is read constantly.

2.3.4. Identify flavonoid content

Flavonoid identification was carried out using Thin Layer Chromatography (TLC) with the stationary phase of the TLC silica gel plate and the mobile phase of n-butanol: acetic acid: water (4: 1: 5). The standard used is quercetin which is included in the flavonoid total group. The TLC plate was preoven for 3 minutes at 45° C. Mobile phase n-butanol: acetic acid: water (4: 1: 5) is put into the chamber and saturated. The TLC plate that had been dosed with the sample was eluted in the chamber, then the TLC plate was aerated and then spot appearance on the TLC plate under UV light of 254 nm and 366 nm (Kusnadi and Devi, 2017).

3.4. Formulation of Celery Herbs Ethanol Extract Patch

Celery herb (*Apium graveolens* L.) ethanol extract patch preparations were prepared in 3 formulas with varying ratio of HPMC and Na CMC polymer concentrations.

Table-1. Celery Herb (*Apium graveolens* L.) Ethanol Extract Patch Formula

Ingredients	Function	Formula (gram)		
		F1	F2	F3
Celery ext	Active substances	0.25	0.25	0.25
HPMC	Hydrophylic polimer	0.30	0.20	0.10
Na CMC	Hydrophylic polimer	0.10	0.20	0.30
PEG 400	*Plasticizer*	0.40	0.40	0.40
Propylen glycole	*Penetration enhancer*	0.30	0.30	0.30
Nypagin	Presetvatives	0.01	0.01	0.01
Etanol 96%	Solvent	5.00	5.00	5.00
Aquadest	Solvent	ad 16	ad 16	ad 16

CMC-Na was dissolved in part of aquadest at temperature of ± 50° C. HPMC was dissolved in the remaining aquadest until inflate then put in CMC-Na mucilago. Nipagyn and celery extract were dissolved with 96% ethanol then put into the mixture, added PEG 400 and propylenglycol, then stirred until homogeneous and put in petri dish molds. The patch is dried at room temperature for 4 days, then packaged and tested. Each formula was made with 3 patches of celery herb ethanol extract.

3.5. Physical Properties of Celery Herb Ethanol Extract Patch Test

3.5.1. Organoleptic Test

Organoleptic tests were performed by observing the shape, color, odor, and surface condition of the patch (Puspitasari et al., 2016).

3.5.2. pH test

The surface pH test is carried out by means of a patch put in a container containing 10.0 mL of CO_2-free aquadest at room temperature and allowed to stand for 1 hour, then the surface pH of the patch is measured with a pH meter (Kumar et al., 2012).

3.5.3. Thickness test

Patch thickness test is done by measuring patch at 5 different points using calipers, then the average is calculated (Madhulata and Naga, 2013).

3.5.4. Weight test

Three patch preparations were weighed one by one with electric scales, then the average weight of each patch was calculated (Parivesh et al., 2010).

3.5.5. Multiplication test

Patch preparation is folded repeatedly in the same place until the patch is broken or folded up to 300 times manually (Jhawat et al., 2013). The number of folds estimates the value of patch resistance to folding (Parivesh et al., 2010).

3.5.6. Humidity test

Moisture content (MC) patch preparations were measured using a moisture analyzer with a temperature of 105°C (Kumar et al., 2012). Some patches are placed on an empty aluminum pan that has been cleaned, then the lid is closed and wait until temperature at 105°C, the measurement of moisture content begins until the tool shows the moisture content of the patch preparation.

3. Results and Discussion

3.1. Celery Herb Extraction

Dried celery herbs have been pulverized to reduce the size of the simplicia so that contact with the search fluid is wider and the extraction process is more optimal. Amount 500 gram celery herbal powder macerated with 96% ethanol solvent. The selection of the solvent used is based on the same solubility and polarity (*like dissolve like*). According to Harborne (1987), flavonoids include polar compounds so they can dissolve and find in 96% ethanol solvents which are also polar. Ethanol 96% solvent is the most optimal search fluid with phenolic and flavonoid content parameters (Agustiningsih et al., 2010).

3.2. Celery Herb Ethanol Extract

The yield of celery herb ethanol extract was 5.68%. Organoleptic examination of celery herb ethanol extract showed that the resulting extract was thick in form with a dark green color and a distinctive odor of celery. The results of the water content test of celery herb ethanol extract that is equal to 8.00% that have fullfil the requirements of the extract water content limit is less than 10% (MOH RI, 2008).

Identification of flavonoid content in celery herb ethanol extract was carried out qualitatively by thin layer chromatography (TLC). The stationary phase of TLC silica gel is polar, while the mobile phase is n-butanol: acetic acid: water (4: 1: 5) which has higher polarity so that it can separate polar flavonoid compounds. The silica gel TLC plate was roasted to reduce the water content in the TLC plate so that the absorption capacity of the TLC plate was maximum. A chamber filled with a mobile phase (*eluent*) is saturated first to fill the entire surface of the chamber with eluent vapor so that it can produce good elution (Kusnadi and Devi, 2017).

The standard used in TLC is quercetin because quercetin is a flavonoid total group compound (Azizah et al., 2014). TLC test produced standard quercetin and celery herb ethanol extract spots were almost parallel with Rf values of 0.96 and 0.94, respectively. The

Rf value of celery herb ethanol extract is close to the standard Rf value of quercetin. This shows that the ethanol extract of celery herbs contains flavonoid compounds (figure-1).

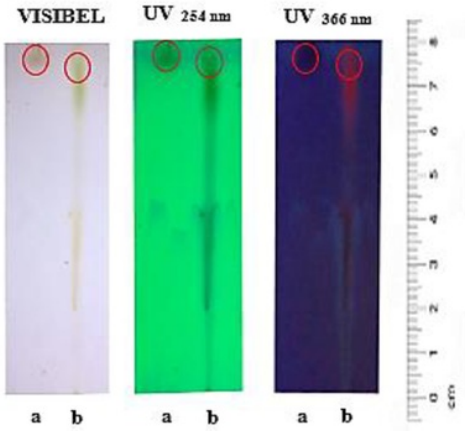


Figure-1. Results of TLC of standard quercetin and celery herb ethanol extract spots were almost parallel with Rf values of 0.96 (a) and 0.94 (b) at UV 254 and UV 366

3.3. Result of Physical Properties of Celery Herb Ethanol Extract Patch

Organoleptic test of patch preparations aims to determine whether there are differences and organoleptic changes in preparations during storage. Organoleptic test results showed the preparation of patch formulas 1,2, and 3 there was no difference, which was typical of the smell of celery and had a patch-shaped appearance with a brownish green color and smooth surface conditions. Organoleptic test at week 0 and week 4 also did not change. This shows that variations in the ratio of polymer concentrations of HPMC and CMC-Na have no effect on organoleptic patch preparations and the resulting patch preparations remain stable during storage at room temperature.

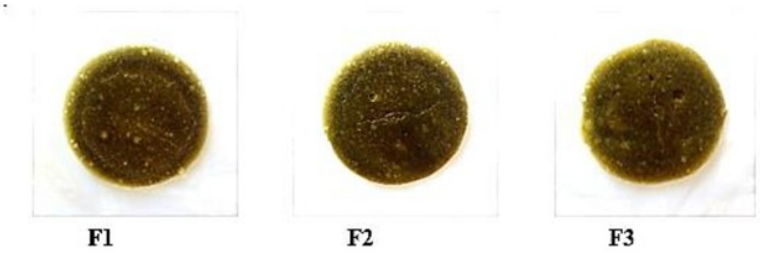


Figure-2. Results of Organoleptics of Celery Herb Ethanol Extract Patch

3.3.1. pH value

The pH test results in Figure-3 show that the three formulas before and after storage have met the pH requirements for preparations that do not irritate the skin, namely 5-9 (Kumar et al., 2012). The pH value of the three patch formulas decreases during storage, but is still in the pH range that is safe for the skin so it does not cause skin irritation. Paired

samples T-Test results, the pH of each patch formula during storage obtained sig F1, F2, and F3 respectively 0.017; 0.031; and 0.021, indicating that the pH of each formula during storage contained a significant difference (sig <0.05). One Way Anova test results between the patch formula obtained sig value 0.114 which indicates that the pH of the three formulas did not have a significant difference because sig>0.05. The results of the analysis showed that the variation in the ratio of polymer concentrations of HPMC and CMC-Na on the ethanol extract of the celery herb extract patch did not significantly influence the pH value of the preparation.

3.3.2. Thickness Test

Patch matrix that is thinner will be preferred because it is more comfortable to use and better patch appearance (Setyawan et al., 2014). Graphic Figure-3 shows the thickness of each patch formula decreases during storage. Formula 3 has the highest thickness value compared to formulas 1 and 2 (F3> F2> F1). The high concentration of CMC-Na will produce a thicker patch matrix because CMC-Na is hygroscopic, whereas HPMC polymers will produces a thinner patch matrix (Kurniawati, 2016). Paired Samples T-Test showed that thickness of each patch formula during storage resulted in sig F1, F2, and F3 values respectively are 0.004; 0,001; and 0.006. The results of the analysis show the thickness of each formula during storage there was a significant difference (sig <0.05). One Way Anova test between patch formulas obtained sig value of 0,000 which indicates the thickness of the three formulas there is a significant difference because sig <0.05. Post Hoc test results are known to the group that gives an average difference in thickness value is formula. The analysis results show that the variation of the ratio of HPMC and CMC-Na polymers on the ethanol extract of celery herb patches affects the thickness of the patch, which is increasingly the concentration of CMC-Na polymers compared to HPMC polymers will increase thicker of patch.

3.3.3. Weight Test

The lighter of patch is more comfortable to use (Kurniawati, 2016). The graph in Figure-3 shows the weight of each patch formula decreases during storage. Formula 3 has the greatest weight compared to formulas 1 and 2 (F3> F2> F1). CMC-Napolymer can absorb and retain water in the patch so that the weight of the patch increases. CMC-Na polymer can significantly increase patch weight compared to HPMC polymers (Kurniawati, 2016). Paired Samples Test T-Test for weight of each patch formula during storage resulted in sig values F1, F2, and F3 respectively 0.010; 0,000; and 0.007. The results showed the weight of each formula during storage there was a significant difference (sig <0.05). One Way Anova test between formulas obtained sig value of 0.018. This shows the weight of the three formulas there is a significant difference (sig <0.05). Post Hoc test results are known to the group that gives a difference is formula 1 to formulas 2 and 3. The analysis results show variations in the ratio of HPMC and CMC-Na polymers in celery herb ethanol extract patche influence the patch weight, where the greater concentration of CMC-Na polymers will increase weight of patch.

3.3.4. Moisture Content Test

Low moisture content of patches will cause patch brittle, but the high moisture content of the patch will cause patch to be easily overgrown with bacteria (Mukherjee et al, 2005). The graph in Figure-3 shows the humidity value of each patch formula decreases during storage. Formula 3 has the highest moisture content compared to formulas 1 and 2 (F3> F2>

F1). CMC-Na polymers have hygroscopic properties so that they can absorb and retain water (Rowe et al., 2009). HPMC polymers can increase the permeability of the patch matrix so that water will more easily come out of the preparation during drying (Kurniawati, 2016). Propylenglycol also plays a role in increasing patch humidity because it is hygroscopic (Rowe et al., 2009). The moisture value of patch preparations on the market with the brand "Kool Fever" is 52.46%. The moisture content of the formula 1 week 0 approaches the "Kool Fever" patch, but the 4th week is significantly different. The moisture content of formula 2 at weeks 0 and 4 approaches the "Kool Fever" patch. The moisture content of the formula 3 weeks to 0 and 4 is higher than the "Kool Fever" patch and the difference is quite significant.

Paired Samples T-Test Moisture test of each formula during storage resulted in sig F1, F2, and F3 values respectively 0.043; 0.094; and 0.060. These results indicate the humidity of formula 1 during storage there is a significant difference (sig <0.05). Moisture formula 2 and 3 during storage there is no significant difference (sig>0.05). One Way Anova test results obtained between the formula sig value of 0.000, which means the humidity patch of the three formulas is significantly different (sig <0.05). The Post Hoc Test found that formulas 1, 2, and 3 each gave significant differences. The results of the analysis showed variations in the polymer concentration of HPMC and CMC-Na on the ethanol extract of the celery herb extract patch affected the moisture patch, where the greater the concentration of the CMC-Na polymer compared to HPMC, the higher the moisture patch produced.

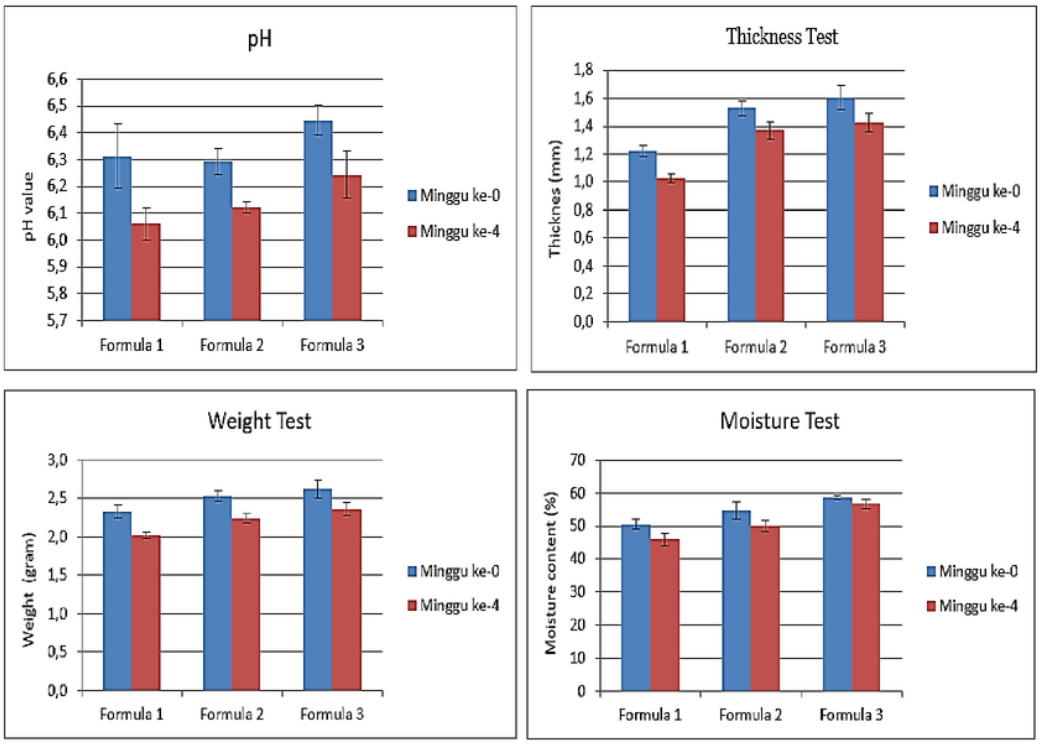


Figure-3. Results of pH value, Thickness, Weight and Moisture content of each patch formula during storage for 4 weeks obtained F1, F2, and F3 have significant difference (sig <0.05). Results show that the variation of the ratio of HPMC and CMC-Na polymers on the

ethanol extract of celery herb patches affects to the physical caracteristics, which is increasingly the concentration of CMC-Na polymers compared to HPMC polymers.

3.3.5. Folding Endurence of Patch

The greater of folding endurance of patch means that met good quality patch, because the patch is not easily damaged or broken. The results that showed at table-2,it is means that number of folds of the three formulas are > 300 times. This shows that the three patch formulas have met the requirements of good folding endurance > 300 folds (Jhawat et al., 2013). Variation concentration of HPMC polymer and CMC-Na in each formula did not affect the folding endurance of celery herb ethanol extract patches. The folding endurance of patch is caused by the influence of the use of plasticizer of PEG 400 so that it can produce a flexible patch that are not easily damaged or broken.

Table-2. Results of folding endurance test of celery herb sthanolis extract patch during 4 weeks

Formula [HPMC : CMC-Na]	Replication	Weeks	
		0	4
F1 [3 :1]	I	> 300	> 300
	II	> 300	> 300
	III	> 300	> 300
F2 [1:1]	I	> 300	> 300
	II	> 300	> 300
	III	> 300	> 300
F3 [1:3]	I	> 300	> 300
	II	> 300	> 300
	III	> 300	> 300

Conclutions

Increasing the concentration of CMC-Na polymers in a combination with HPMC polymers in celery herb (*Apium graveolens* L.) ethanol extract patches can increase the thickness, weight, and moisture of the patch. The best ethanol extract of celery herb patch is formula 2 because it shows the best results with pH 6.12-6.29; thickness 1.37 -1.53 mm; weighing 2.24-2.52 grams; folding endurance > 300 times, and moist patch.

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