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Patch Film from Celullose Derivative Incorporating with Virgin Coconut Oil and its Physical and Antibacterial Properties

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Abstract. Preparation of mucoadhesive patch film containing Virgin Coconut Oil (VCO) has been made as a medium to inhibit the growth of *Streptococcus mutans*. This research was conducted to make patch film which meets the standard physical characteristic of patch mucoadhesive film. The physical characteristic is weight uniformity, thickness, folding endurance resistance, swelling index and pH of the patch solution. The presence of fatty acids which trapped in patch was analyzed with Gas Chromatography Mass Spectrometry (GC-MS). The result showed that the patch film has uniformity value of weights ranging from 0.04 to 0.17 g. The thickness of patch was 0.53 to 0.61 mm and have folding endurance resistance more than 300 times. Swelling index for each patch increase in the 5th minutes and decrease in the 10th minutes. The surface pH of the patch almost close to pH 7. GC-MS chromatogram showed that lauric acid (C8), meristic acid (C14), palmitic acid (C16) and linoleic acid (C18) were trapped in the patch. The patch film containing VCO can inhibit the growth of *Streptococcus mutans* with inhibition zone of 157.30 ±1.088 mm^2.

Introduction

Nowadays, synthesis drug still often uses to cure inflammation in organs. Diclofenac is one of the NSAID (Nonsteroidal Anti-inflammatory Drug) that is used to cure pain and gum inflammation (gingiva). However, this synthetic drug also has a side effect such as inhibition of prostagladin production which can affect bone loss of teeth buffer bones in gum inflammation disease [1]. According to several studies, bacteria are one of the causes of gum inflammation or severe periodontitis such as *Streptococcus*, *Streptococcus β*, type A of hemolytic, type A of *Streptococcus* and *Staphylococcus* bacteria [2].

The problem that often arises in the treatment of infectious diseases is the occurrence of resistance. Bacterial resistance to antibiotics brings its problems that can frustrate therapy. In developing countries, the emergence of bacterial strains that are resistant to antibiotics causes the death rate to increase. In addition, the method of treatment using a combination of various antibiotics can also cause problems, such as the emergence of bacteria that are multiresistant to antibiotics. Widespread microbial resistance to existing drug encourages the importance of extracting new antimicrobials from natural ingredients [3].

Virgin Coconut Oil (VCO) contains a lot of MCFA (Medium Chain Fatty Acid) such as lauric acid and short-chain saturated fatty acid, so VCO has a positive role for human health, among others, as antibacterial, antifungal, antiprotozoal, maintaining heart and blood vessels healthy [4]. Some bacteria that are reported to die due to medium-chain fatty acids, including *Streptococcus*, *Staphylococcus*, *Neisseria*, *Chlamydia*, *Helicobacter pylori*. Previous research showed that VCO was able to inhibit the *Streptococcus mutans* with the best inhibition zone of 7 mm.

Recently, there are many different forms of healing inflammatory substances widespread in the market such as solution, tablet, capsule, gel, cream, and patch. The mucoadhesive patch is one of the drug delivery systems. Mucoadhesive patch usually contains polymer, drug, and filler (such as plasticizer). The patch matrix for gingivitis treatment can be made in small sizes of 1-3 cm^2 or the form of an ellipsoid so that drug transfer is better and makes the treatment more effective, comfortable

and safe because it can deliver the drug directly to the center of the gum mucosa. The mucoadhesive patch is more beneficial because it can easily attach to the gum cavity. Mucoadhesive is more flexible and much more durable for gum treatment than table and gels [5]. Patch effectiveness is influenced by the manufacturing technique that will give a difference to drug release which has an impact on the bioavailability of the drug. In addition, to manufacturing technique, the effectiveness of patch is also determined by the amount and type of additional materials used. Additional material will affect the physical properties of the patch and it affects drug stability, release, and penetration. The medicinal ingredients contained in the matrix must be able to be released from the preparation and penetrate through the biological membrane until it enters the systemic circulation.

In the previous research, mucoadhesive patch was made with hydroxypropyl methylcellulose (HPMC) polymer material, PEG as a plasticizer, and the active ingredient was Flurbiprofen. Mucoadhesive patch formulations were made using Zidovudine active ingredients with a combination of 100 mg of cow gelatin and 150 mg of hydroxypropyl methylcellulose (HPMC) along with PEG 400 as plasticizers showing as the best composition of mucoadhesive patch production [5]. In this research, mucoadhesive patches were made using active ingredients of Virgin Coconut Oil (VCO) incorporating in patch film based on hydroxypropyl methylcellulose polymers and arabic gum. VCO is capable of killing various kinds of bacteria, it is expected that mucoadhesive patch containing active VCO substances can also inhibit *S. mutans* that causing inflammation of the gingiva.

Experimental Section

Material. The ingredients used were VCO, HPMC, arabic gum, PEG 400, phosphate buffer saline (PBS) pH 6.8, ethanol, distilled water, KOH, NaCl, hexane, BF_3 NA (Nutrient Agar), Nutrient Broth (NB), and *Streptococcus mutans* bacteria.

Patch production. The mucoadhesive patch was arranged using a solvent casting method. The amount of polymer used was 250 mg with the composition of 100 mg arabic gum and 150 mg HPMC. PEG 400 as a plasticizer was used at 10% (b/v). The HPMC polymer was dissolved in 4 mL PBS pH 6.8 which was used as a solvent in the casting method and gum arabic was dissolved into VCO (variation in concentration of 0.5, 1.0, 1.5, and 2.0 MIC in the patch) then PEG 400 was added. Both solutions were stirred with a magnetic stirrer for 30 minutes to ensure constant distribution was achieved. Polymer solutions containing VCO are poured into a petri dish, then heated at 45 °C for 5 h to form a dry and flexible film. The dried patch was moved carefully. Patches were packaged using aluminum foil and stored in a desiccator to maintain patch integrity and elasticity until further usage [5].

Physical characterization of the patch. (a) Patch thickness: Three patches of each formula were measured at 3 different points, namely the right, middle, and left edges using micrometer coupler with an accuracy of 0.001 mm. The thickness value obtained was from the average value of the three places. Patches that are both in the 0.5-20 mm thickness range with %CV, no more than 5%. (b) The uniformity of patch weight: Three patches of each formula were cut by 2 cm^2, then weighed individually using an analytical balance. The uniformity of weights was calculated for each patch formula [5]. (c) Folding durability: The patch was cut 4 cm^2 and randomly taken as many as 10 sheets for each formula and folded repeatedly in the same place so that the patch was cracked. The number of folds that do not cause crack patch was calculated as the value of folding resistance. Patch already meet the criteria if the number of the fold is carried out more than 300 folds [6]. (d) The pH of patch surface solution: Three patches of each formula were put into a cup of glass containing 5 mL of calibrated distilled water (pH 6) for 1 h in room temperature. Then the patch surface pH was measured using a pH meter [5]. (e) Patch swelling index of patch film: Swelling Index test was carried out by taking three patches for each formula and then weighing (W1) then inserting each into a petri dish containing 20 ml of phosphate buffer solution of pH of 6.8. The patch was then lifted at a predetermined interval time (5^{th}, 10^{th}, 15^{th}, 20^{th}, 25^{th}, 30^{th}). The liquid left on the patch surface was absorbed with filter paper and then weighed again (W2). (f) The characterization of the patch by Gas Chromatography-Mass Spectrometry (GC-MS): Before being analyzed by GC-MS, the patch

containing VCO must be esterified first. The patch was weighed as much as 2 grams and then crushed and dissolved with ethanol solvent. The patch solution was added with 5 mL KOH, then heated at 80 °C for 20 minutes. The resulting solution was added 5 mL BF_3 and then heated at 80 °C for 20 minutes, then cooled. Then, a solution of 2 mL of NaCl was added and then shaken. Then, the solution was added 5 mL of hexane and then was shaken. The solution will form 3 layers and it took the middle layer which was an esterified fatty acid. This solution will be analyzed using the GC-MS tool to check what fatty acids are still trapped in the patch.

Antibacterial Activity of Patch Film

Media preparation. Rejuvenation of *S. mutans* bacteria using growth media in the form of NB (Nutrient Brouth) and NA (Nutrient Agar), as much as 0.8 g of NB media was dissolved into 100 mL of distilled water and stirred until it dissolves completely and as much as 2 g. NA was dissolved in 100 mL of distilled water and then heated and stirred using a magnetic stirrer until boil up. Then, it sterilized using an autoclave at 12 °C, 1 atm pressure for 1 h [7].

Antibacterial activity testing. At the end of the needle, the stock of *S. mutans* bacteria was then inoculated into Nutrient Brouth (NB) and then incubated at 37 °C for 24 h. 0.2 mL of NB media containing test bacteria was taken and mixed with soft nutrient agar (NA) into the petri dish, then stirred the tested bacteria and nutrient agar until mixed. After solidifying, then tap the patch that has been cut with a diameter of 6 mm to the surface so that it is solid. Furthermore, the petri dish was incubated at 37 °C for 24 h and clear zone measurements were formed around the holes of petri dish using a ruler, antibacterial activity test on the patch was repeated twice [7].

Results and Discussion

The patch made consists of a polymer combination in the form of HPMC, arabic gum, PEG 400 and the active ingredient is VCO. The solvent used was a solution of Phosphate Buffered Saline (PBS) pH 6.8. The method used in making this patch was the solvent casting method. Solvent casting is a technique by dissolving the polymer into its solvent first, then mixing it with active were cast a glass petry dish, and heated at a certain temperature.

The physical test result from making patch that does not contain VCO and patch containing VCO produce patch in the form of clear white sheet, soft textured, flexible, and have a distinctive odor originating from VCO except for patch that Based on the appearance, the results obtained in making patch with or without the addition of VCO do not have a significant effect. The color of them almost the same.

Characteristic of the patch physical properties. The characterization of the physical properties of patch was done to look at the patch that has the best characteristics that match the criteria. The physical test of properties carried out in the form of thickness, weight uniformity, pH of the solution, folding endurance resistance, and index of development.

The average thickness of patch film. Thickness testing was done by measuring patch at three different points using micrometer coupler. Thickness values were obtained from the average measurement result and the standard deviation was calculated to ensure the thickness of each patch was not more than 5%.

Based on Table 1, it can be seen that the patch thickness produced was quite uniformed. The five patch formulas have thicknesses ranging from 0.53 mm to 0.61 mm. The lowest patch thickness was indicated by the addition of 0.5 MIC VCO into the patch with a thickness of 0.53 mm, while the thickest patch was indicated by the addition of 2.0 MIC VCO into the patch with a thickness of 0.61 mm. Based on patch thickness data, %CV produced from all patch formulas was in the range of 0.96-2.16%. Thus, it can be concluded that all patch formulas that produced meet patch thickness criteria because %CV patch thickness criteria were less than 5%. Patch thickness was influenced by the amount of substance contained in the patch. Patch thickness increases with the increasing

concentration of VCO in the patch. The more amount of substances in the patch, the thicker the patch was produced [8].

Table 1. Physical properties of film patch before and after incorporated with VCO

Variation of VCO in Patch	Average Thickness (mm)	Folding Endurance Patch	The pH of Patch Surface	Weight of patch
Without VCO	0.55±0.01	352±0.577	6.98±0.02	0.0412±0.000
0.5 MIC	0.53±0.01	382±2.08	6.97±0.02	0.1132±0.000
1.0 MIC	0.57±0.01	421.±2.30	7.00±0.02	0.1228±0.001
1.5 MIC	0.57±0.01	438±1.73	7.05±0.03	0.1670±0.000
2.0 MIC	0.61±0.01	451±1.53	7.06±0.01	0.1709±0.000

Weight uniformity of patch. Testing the uniformity of patch weight was done to evaluate the consistency of the manufacturing process. A good manufacturing process will produce a relatively uniform product. The uniformity of the weight made was expected to provide uniform distribution of active substances [3]. Evaluation of patch weight test results using standard patch weight uniformity from 3 same samples, the value of %CV cannot be more than 2% [9, 10]. Based on Table 1, it can be seen that the average weight of the patch produced increases in line with the increasing of VCO concentration in the patch. Based on the measurement results, it is known that the resulting patch has an increase in weight on each addition of the VCO concentration in the patch. Patch weight ranges from 0.04-0.17 g. The lowest average weight of the patch comes from a patch that does not contain VCO which is equal to 0.04 g, while the average weight of the heaviest patch was a patch containing 2 MIC VCO in the patch. Based on patch weight uniformity test data, %CV produced from each patch formula ranged from 0.07-0.88% so it can be concluded that all patch formulas produced to meet the criteria for the uniform weight of patch because %CV criteria of uniformity of patch weight were less than 2%.

Patch solution pH test. The determination of pH of the patch solution is done to look at the possibility of side effect produced by the patch that was applied, so it will not irritate the gum mucosa. The pH of the patch solution was measured from each formula using pH meter. Based on Table 1, all patch formulas produce the patch solution which was almost close to the normal human salivary of 5.6-7 pH. Based on the data obtained, the pH of the patch solution was not significantly affected by the addition of the VCO concentration in the patch. It can be seen from the standard deviation generated on each formula that it is relatively small [11].

Folding endurance test. This folding resistance test aims to determine the folding capacity of the polymer patch. The folding endurance test was done manually by folding patch repeatedly at one point and the same point until it breaks. The patch with a folding resistance of more than 300 folds is said to fit the patch criteria [12]. Visually, all patch formulas produce the same color and surface shape, were flexible and elastic. Based on the test result, it can be concluded that the folding resistance of each patch formula exceeds 300 folds, so that the patch can be said to meet the patch criteria. The most fold produced by patches containing 2 MIC VCO is as many as 452 folds, while the lowest folding resistance was produced by the patch that does not contain VCO which has 352 folds. Based on Table 1, the increasing of VCO concentration in the patch can increase the durability of the folded patch. The fatty acid contained in VCO has plasticizing properties [13]. Therefore, the more the VCO in the patch, the more elastic the patch will be. Another factor that affects the durability of the folding patch was the presence of a polymer in the form of HPMC which was used to function as a binder. The presence of strong bonds on HPMC can produce a patch with large folding resistance. In addition, the addition of PEG 400 as plasticizer as much as 10% (b/v) was able to form patch film become more flexible.

Swelling index test. Swelling index of the patch film was a critical point in determining the bioadhesive properties of the polymer. The swelling index test was carried out to evaluate water absorption capability. The swelling index was measured by observing the change in patch weight which was left in a phosphate buffer pH of 6.8 for 30 minutes at 5th minute interval.

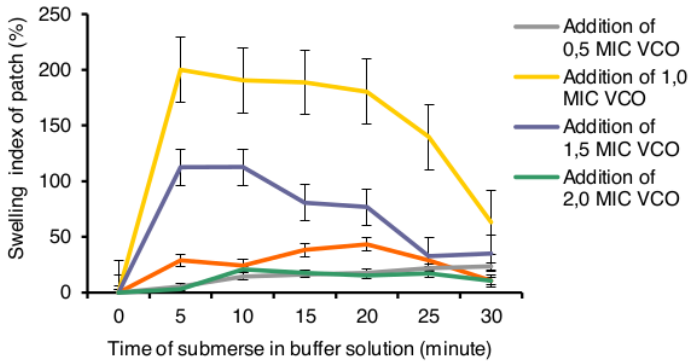


Figure 1. Swelling index of the patch that was incorporated with VCO

In Fig. 1, it is known that swelling index of patch film for each formula increased on the 1-5th minute on average and began to decline in 10-30 minutes. According to the patch development index criteria, the patch begins to expand within 1-5 minutes and will return in 10-30 minutes. Thus, it can be concluded that the patch meets the criteria. The highest swelling index indicated by patches with the addition of 0.5 MIC VCO in the patch while the lowest was patch without containing VCO.

The factor influence the height of the patch development index is the concentration of VCO in the patch. The nature of VCO that can resist water (nonpolar) causes water to be difficult to enter into the patch matrix so that the absorption of the patch against water is reduced. If water absorption was reduced, the patch development index value will decrease. However, if the absorption of water was too high or too fast it can cause damage to the preparation so that all patches break or dissolve before the expected time [3, 14]. Therefore, the higher the concentration of VCO in the patch, the lower the degree of swelling index. However, a patch that contains VCO produces a lower degree of swelling index compared to a patch that did not contain VCO. This is thought to be the effect of the fatty acid contained in VCO which has plasticizing properties.

In drug preparation, the process of absorption of water in a polymer mass is the initial stage for the release of drug from the preparation to the action place. If the active substance remains trapped in the preparation and was not released, then the healing action cannot be achieved. Patch development index is very important to predict the release of active substances. The release of active substances was faster when the polymer is rapidly hydrated and undergoing development [13, 15]. Thus, it can be predicted that patch containing 0.5 MIC VCO has a faster release time of active substances compared to another patch formula.

VCO molecular content analysis in patch. Chemical content analysis is carried out to identify the compound trapped in the patch. For comparison, pure VCO sample is used. This analysis was carried out using the GC-MS (Gas Chromatographic Mass Spectrometry) method.

In Fig. 2, there are 10 peaks while in Fig. 3, there are 8 peaks. However, both chromatograms have 4 main compounds that have the highest peak. To find out the type of fatty acid and its retention time, it can be seen in Table 2.

Antibacterial activity of patch mucoadhesif film toward *S. mutans bacteria*. The bacterial inhibitory test was carried out to determine the ability of the patch containing VCO to inhibit the *Streptococcus mutans* bacteria which causes gingival inflammation. The inhibition test is done by using the disc method. The clear zone formed can be seen in Fig. 4. Fig. 4 shows that VCO has an antibacterial effect on *S. mutans*. This is indicated by the formation of the clear zone around the patch.

The clear zone was calculated to get the inhibitory zone of the patch against *S. mutans*. The patch placed on the surface of agar media was no longer visible after the incubation for 24 h. The patch which has the largest area of inhibition zone was the patch with an addition of 2.0 mL VCO which was 157.3 mm^2. The patch that has the smallest inhibitory zone was the patch without VCO (0.47 mm^2).

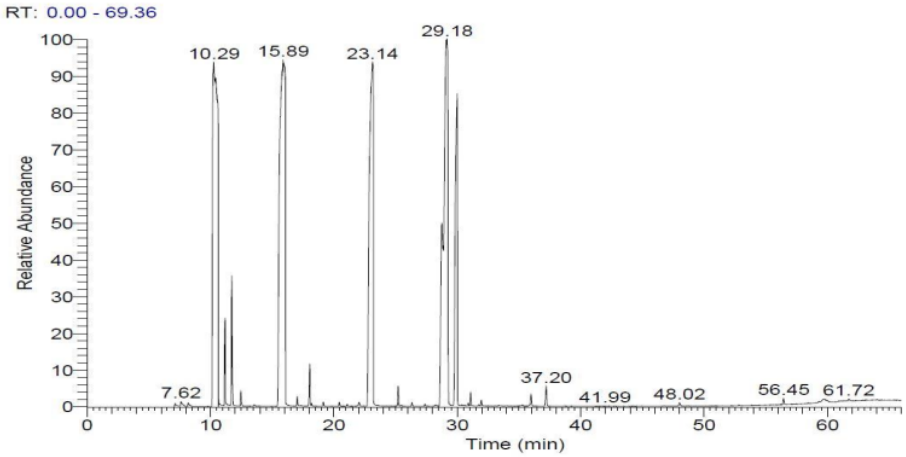


Figure 2. VCO chromatogram before incorporating into the patch

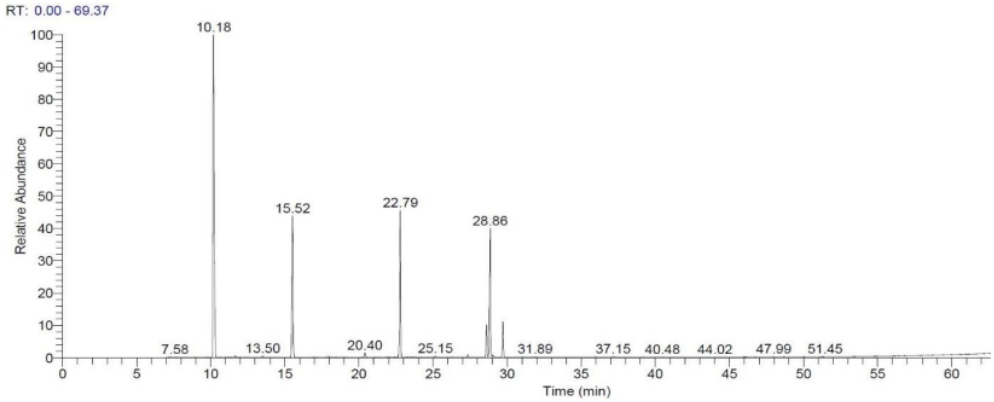
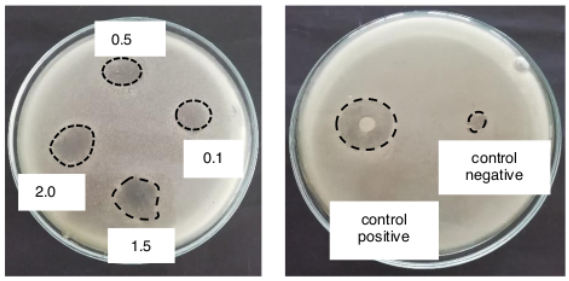


Figure 3. Chromatogram patch film containing VCO

Table 2. The compound in the patch by GC-MS

Molecular name	VCO formula	VCO	Molecular		Patch containing	
		Weight (g/mol)	Retention time (minute)	Peak area (%)	Retention time (minute)	Peak area (%)
Dodecanoic acid, methyl ester	$C_{13}H_{26}O_2$	214	10.27	11.10	10.18	34.94
Methyl Tertradecanoate	$C_{15}H_{30}O_2$	242	15.89	18.19	15.52	18.55
Hexadecanoic acid, methyl ester	$C_{17}H_{34}O_2$	270	23.14	17.33	22.80	17.72
9-octadecanoic acid (Z), methyl ester	$C_{19}H_{36}O_2$	296	29.18	4.61	28.86	16.73

Based on Table 3, the higher the concentration of VCO in the patch, the greater of inhibition zone. It was shown that the patch inhibition zone containing 2.0 MIC VCO (15.38 mL/g) was greater than the diameter of the inhibitory zone of the patch containing another volume of VCO. It is caused by the number of fatty acids contained in the VCO. The higher the concentration of VCO in the patch, the faster the diffusion process into the media containing bacteria and inhibited the growth of bacteria [8].



(a) (b)

Figure 4. Antibacterial activity of patch against *Streptococcus mutans* bacteria; control (+): VCO, control (-): patch without VCO

Table 3. Effect of VCO on inhibition zone of film patch

	Clear zone (mm)	Inhibition zone (mm^2)	Antibacterial activity
VCO Control	19.38	266.42	Strong
Without VCO	6.05	0.47 ±0.80	Weak
0.5 MIC VCO	12.50	94.39 ±1.16	Strong
1.0 MIC VCO	13.50	144.80 ±1.13	Strong
1.5 MIC VCO	15.25	154.30 ±1.23	Strong
2.0 MIC VCO	15.38	157.30 ±1.09	Strong

The antibacterial power based on the diameter of the inhibition zone is divided into 4 very strong categories (inhibition zone more than 314 mm^2), strong (inhibition zone 78.5-314 mm^2), moderate (inhibition zone 19.63-78.5 mm^2), and weak (zone inhibition of less than 19.63 mm^2). Based on the data of inhibition zone diameter obtained, it is known that the mucoadhesive patch containing VCO has an inhibition range of 94.39-157.3 mm^2. Thus, it can be concluded that the mucoadhesive patch inhibitory activity against *S. mutans* was a strong category. While the patch without VCO has inhibitory zone diameters of 0.47 mm^2, which was a weak category.

Virgin Coconut Oil (VCO) has antibacterial properties. This is due to the moderate fatty acid content of the VCO. The medium-chain fatty acid can inhibit the growth of gram-negative bacteria and gram-positive bacteria such as *S. mutans* . In the results of the GC-MS analysis of pure VCO and patch containing VCO (Table 4), medium-chain fatty acid compounds were obtained. These fatty acids include lauric acid (C12), meristic acid (C14), palmitic acid (C16) and linoleic acid (C18). The target of action of fatty acid in cell membranes. Fatty acid will interfere with the electron transport chain and oxidative phosphorylation. In addition, to disrupting cellular energy production, fatty acid can also cause the failure of nutrient to absorb, the formation of peroxidation, and degradation of product oxidation or direct lysis of bacterial cell [4, 16].

Medium-chain fatty acid and the derivative such as lauric acid in the human body are converted into a monosaccharide compound, namely monolaurin. Monolaurin is an antibacterial compound. In its mechanism, monolaurin can destroy bacteria that have lipid sheath by the effect the integrity of

the lipid membrane (a layer of bacterial wrapping). This is what causes *S. mutans* bacterial cell membranes to be easily disintegrated by antibacterial compounds from VCO [16].

Patch loss during incubation for 24 h due to cellulose found in HPMC. Cellulose is a structural polysaccharide, which will be hydrolyzed by an enzyme from pathogenic bacteria to be glucose. This glucose will be used by *S. mutans* in its metabolic process. *S. mutans* bacteria can hydrolyze patch containing VCO. However, medium-chain fatty acids such as lauric acid and other fatty acid contained in the patch can disrupt the stability and permeability of *S. mutans* membrane and disseminating their lipid membrane. This effect will disrupt all metabolic process that occurs in the cell membrane bacteria and inhibits the growth of bacteria [4, 16].

Summary

Mucoadhesive patch film incorporated with VCO has been successfully made and obtained the physical characteristic of mucoadhesive patch film in term of a thin white sheet, soft, flexible, and have an acceptable odor comes from VCO. The mucoadhesive patch film has all physical properties that meet patch requirement with weight uniformity of the average patch ranging from 0.04-0.17 g, thickness of the average patch ranges from 0.53 mm to 0.61 mm, folding endurance resistance of patch was more than 300 folds. The degree of the swelling index of each formula increases on the 5^{th} minutes and decreases in the 10^{th} minutes. The pH of the patch surface solution was close to neutral pH (pH 7). Based on GC-MS analysis there were fatty acids trapped in mucoadhesive patches films such as lauric acid (C10), myristic acid (C14), palmitic acid (C16), and linoleic acid (C18) originated from VCO. Mucoadhesive patch film containing VCO was able to inhibit *S. mutans* bacteria. The mucoadhesive patch which has the greatest inhibitory zone was containing 2.0 MIC VCO with inhibition zone of 157.30 mm^2 and the activity of the inhibitory power was fairly strong.

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