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Optimization of chitosan – tapioca starch composite as polymer in the formulation of gingival mucoadhesive patch film for delivery of gambier (*Uncaria gambir* Roxb) leaf extract

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Abstract

The present study was intended to prepare and optimize the mucoadhesive buccal patch of gambier leaf extract using chitosan (CH) and tapioca starch (TS) composite as the polymer complexes. The patch formulation was designed based on 2^2 factorial design in order to optimize the composition of CH and TS. The physical and chemical characteristics of the prepared patches, including mass and thickness uniformity, folding endurance, surface pH, swelling index, percent of elongation, and mucoadhesive time were successfully evaluated. Based on statistical analysis, the optimum concentration of CH and TS was 900 mg and 300 mg, respectively, with desirability percent of 0.968. The characterization of the optimum patch showed that the variability coefficient of the mass and thickness uniformity was 0.4805 ± 0.1887% and 0.9716 ± 1.2026%, surface pH of the patch was 6, folding endurance more than 300 times, elongation percent was 53.333 ± 0.1082%, and mucoadhesive time was 320 ± 1.1547 min. The catechin content, as the active agent of the gambier leaf extract, was 92.1667 ± 0.3626%, and the FT-IR characterization indicated that there are no chemical interactions between each patch component.

Keywords: Mucoadhesive patch, gambier leaf extract, chitosan, tapioca starch.

1. Introduction

Oral health is directly related to general health as well as the typical life quality of patients [1]. Unfortunately, oral diseases such as gingivitis and other periodontal disease exist as a severe dental and mouth problem, almost around 98% of the adult population. As reported by Eke, Dye, Wei, Thornton-Evans and Genco [2], the prevalence of gingivitis in Southeast Asia reached 95% of adults. Particularly in Indonesia, gingivitis has considered the

second largest dental and mouth disease after dental cavities with a high prevalence of 96.58% [3]. Gingivitis is an inflammatory lesion or inflammation that occurs in soft tissue in the area around the teeth or gingival tissue [4]. Although it is considered as a harmless disease, untreated gingivitis and with a certain severity can progress into other worse periodontitis diseases which cause further and systemic tissue damage through the blood vessels. Hence, the treatment of gingivitis has gained considerable attention globally.

In the last decade, the treatment of gingivitis was focused mainly on the mechanical cleaning of the mouth components, particularly on tooth surfaces. Unfortunately, this approach cannot comprehensively overcome gingivitis since this disease is also affected by a particular bacterial infection [5]. Consequently, various antimicrobial agents have widely applied for a treatment adjunct of gingivitis, particularly in the refractory problem [6]. For instance, English, Pack and Molan [7] have investigated that manuka honey has superior antimicrobial properties which can significantly reduce gingival bleeding within 21 days test.

One of the natural products that have antimicrobial activity and showed high potency for treating gingivitis is gambier (*Uncaria gambir* Roxb). As reported by Aditya and Ariyanti [8], gambier plants containing a polyphenol compound named catechin that has the potential as an anti-inflammatory, antioxidant, and antibacterial. Moreover, it also reported that catechin from gambier contains up to 73.3% and exhibited the ability to inhibit gram-positive bacteria such as *Enterococcus faecalis* [9, 10]. Hence, it has the potential to be utilized as an adjunction on gingivitis treatment. However, it needs an extraordinary attempt for delivering the drug into the gingival target.

Recently, several novel drug delivery approaches have been developed for treating gingivitis diseases, such as mouthwash and oral gel. However, the established method suffers from its long-term disadvantage. For example, the use of chlorhexidine mouthwash for more than 4 months has reported as the cause of mucosa membrane peeling and even increasing the risk of mouth cancer [11]. Therefore, it has become a necessity to develop another pharmaceutical formula that can get rid of the established gingivitis drug. The mucoadhesive patch has gained much attention and considered as the most potential alternative treatment of gingivitis due to its high flexibility, effectiveness, and easy preparation [12].

One of the most studied mucoadhesive patches is a hydrogel film-based patch that can be prepared by combining two polymers. Kaur and Kaur [13] have successfully prepared a mucoadhesive patch for carvedilol delivery using chitosan and pectin as interpolymer complex and reported that the obtained patch demonstrated good *in vitro* and *in vivo* results. Recently, Ren, Clancy, Tamer, Schaller, Walker and Collins [14] also successfully employed

chitosan as a potential excipient in pharmaceutical formulation for drug delivery. In this work, we have developed a novel mucoadhesive buccal patch for the delivery of gambier leaf extract using chitosan (CH) and tapioca starch (TS) composite polymer. The obtained patch was expected to be a potential drug for gingivitis treatment since the gambier leaf extract has reported containing a high amount of catechin which has good anti-bacterial activities. Moreover, it was also reported that chitosan has positively charged polycation which is able to inhibit the growth of bacteria and mold [13]. In addition, chitosan can also increase the strength of the patch attachment in the buccal mucosa by binding to mucin and making it suitable to be used as a polymer in the patch preparations for the treatment of gingivitis [11, 15].

2. Experimental section

2.1. Materials

The chemical used in this work, including tapioca starch (PT. Budi Starch Sweetener, Tbk), glycerin (Sigma Aldrich) , toluene (Merck), hydrochloric acid (HCl), methanol (Sigma Aldrich), acetic acid (Merck), sodium hydroxide (NaOH) (Merck), phosphate buffer (KH_2PO_4) (Sigma Aldrich), sodium tripolyphosphate (STPP) (Sigma Aldrich) and ethyl acetate (Sigma Aldrich) were in reagent grade and used as received without further purification. The chitosan with the degree of acetylation > 80% and maximum granule size of 0.2 mm was purchased from CV. Chi Multiguna, Indonesia, and the catechin were obtained from Andalas Sitawa Fotolab, Indonesia.

2.2. Modification of tapioca starch

Prior to further utilization, the tapioca starch sample was subjected to modification using STTP in order to increase its physicochemical properties [16]. Briefly, 15 g of TS and 0.22 g of STTP were dissolved into 37.5 mL of distilled water followed by vigorous stirring until a homogenous mixture was formed. The pH of the solution was adjusted as 10.5 by addition of 5% NaOH solution then followed by vigorous stirring at ± 45 °C for 1 h. After then, the pH was adjusted to 5.5 by the addition of 0.1 N HCl solution in order to stop the reaction process. The obtained solid was filtered, rinsed, and dried 40 °C and the final product was stored in a tightly closed vessel and ready for further utilization.

2.3. Preparation of Mucoadhesive Patch

In this work, the mucoadhesive patches were prepared by the solvent casting method. In all experiments, except CH and TS as the polymer, the amount of glycerin and acetic acid as plasticizer and solvent were fixed as previously reported by Nafee, Boraie, Ismail and Mortada [17]. In brief, CH was dissolved in 15 mL of 1.5%(v/v) acetic acid solution under vigorous stirring for 30 min. Next, the prepared TS was added and followed by the addition of 10 mL of an acetic acid solution under further vigorous stirring for 30 min. On the other plate, the gambier leaf extract was mixed with 5% (v/v) of glycerin and 1.5% acetic acid solution under vigorous stirring until a homogenous solution was obtained.

The gambier leaf extract was then added into the CH and TS mixture followed by further vigorous stirring until the homogenous mixture was obtained. The result of the viscous solution was poured in a petri dish (9 cm in diameter) and was dried in an oven at 40 °C for 8 h. The obtained dried film was then cut into a 1x1 cm square shape. Finally, the mucoadhesive buccal patch film was stored in tightly closed storage in order to maintain the patch elasticity. The used gambier extract amount (5.06 mg/cm^2) was determined based on the human equivalent dose (HED). Since the used petri dish was 9 cm in diameter (63,585 cm^2), thus the total amount of gambier leaf extract that used in the formulation was 321.74 mg.

2.4. Optimization of mucoadhesive patch

The formulation of the patch was optimized according to the factorial design approach. The effect of CH and TS composition on the physicochemical properties of the produced patches, including folding endurance, thickness and mass uniformity, surface pH, elongation percent, swelling index, and mucoadhesive time, was evaluated by means of 2^2 factorial design. The lower and higher value of the lower and upper levels of each factor was represented as (+1) and (-1). The patch's formulation was then determined based on that the simulated design as can be seen in Table 1. The obtained data were analyzed using Design Expert Version 12 software by Stat-Ease, Inc.

Table 1. Formulation of the mucoadhesive patch based on 2^2 factorial design

Formula	Coded Level		Actual Level		Gambier Extract (mg)	Glycerin (%)	Acetic acid (mL)
	CH	TS	CH (mg)	TS (mg)			
F1	-1	-1	600	150	321.74	5	30
F2	+1	-1	900	150	321.74	5	30

F3	-1	+1	600	300	321.74	5	30
F4	+1	+1	900	300	321.74	5	30

CH: Chitosan, TS: Tapioca starch

2.5. Mucoadhesive patch evaluation

2.5.1. Thickness and mass uniformity

The mass and thickness uniformity were evaluated by choosing 10 patches randomly then weighed on an analytical scale, and the thickness was measured using vernier caliper. All the measurements were conducted in triplicate, and the standard deviation of each measurement was calculated.

2.5.2. Surface pH and folding endurance

The surface pH of the patches was measured as conducted by Kaur and Kaur [13]. The patch samples were soaked in phosphate buffer until swelled within 30 min then the surface pH was measured. The folding endurance of the patch was tested by folding the patch repeatedly in the same place until broke.

2.5.3. Elongation and swelling index

The elongation of the patches was tested by measuring the initial length of the patch. The patch was stretched until its maximum flexibility length, and the final length of the patch after stretched was measured. The degree of swelling of the prepared patches was measured by weighing the initial patch (W_1) then was soaked in phosphate buffer solution pH 6.8 at time intervals of 5, 15, 30, and 60 min. The remaining solution was carefully removed using filter paper then the absorbed patch was reweighed (W_2). The swelling index was evaluated by the following formula:

$$Swelling\ index = \frac{W_2 - W_1}{W_1}$$

2.5.4. Mucoadhesive time

The mucoadhesive time was studied in *ex vivo* using the goat mucosal membrane. The mucosal membrane was attached to a glass slab using cyanoacrylate glue. The patch was hydrated with phosphate buffer pH 6.8 then attached to the prepared mucosal membrane. The prepared glass slab was then immersed vertically into a glass beaker containing 500 mL of phosphate buffer 6.8 at 37 °C ± 1 °C followed by stirring at 50 rpm in order to represent the buccal condition. After then, the time needed by the patch to release from the mucosal

surface was observed and recorded as the mucoadhesive time. The above experiment was conducted in triplicate [18].

2.5.5. Drug content analysis

The drug content in the patches was analyzed using catechin as the standard. In this work, it was formulated that each patch contained 5.06 mg of gambier leaf extract. The patch that has the best formulation was soaked into 5 mL of 1.5% acetic acid solution for 15 min followed by the addition of 5 mL ethyl acetate solution under vigorous stirring for 30 min. After then, the ethyl acetate part was separated and analyzed using a UV-Vis spectrophotometer at wavelength 279 nm.

2.5.6. Diffusion and stability

The diffusion test was conducted using Franz diffusion cell at 37 ^{o}C ± 0.2 ^{o}C. The mucosa membrane was placed between the donor and the acceptor compartment. The patch was directed into the mucosa membrane then the donor compartment was filled by 1 mL of phosphate buffer pH 6.8 under vigorous stirring. The buffer phosphate (5 mL) on the acceptor compartment was taken at time interval 0, 15, 30, 45, 60, 90, 120, 180, 240, 300, dan 360 min. The taken solution was diluted and analyzed using a UV-Vis spectrophotometer.

The stability test of the mucoadhesive patch was carried out by the heating-cooling cycle method. The patches were stored at 4 °C for 24 h then was placed in the compartment with temperature 40 ± 2 °C for 24 h. The test was conducted in 3 cycles or 6 days. The stability of the patches was evaluated by measuring the contents before and after the test.

2.5.7. Molecular interaction analysis

The molecular interaction between each patch compositions was analyzed using the FT-IR instrument. The FT-IR spectra of the patch were recorded using a Shimadzu Prestige-21 instrument using KBr disc with a wavenumber 400–4000 cm^{-1}.

3. Result and discussion

3.1. Characterization of Modified Tapioca Starch

The physical appearance of the pristine and modified TS is displayed in Figure 1. Compared with the pristine form, modified TS exhibited better powdered and coarser form.

Moreover, the modified TS has a brighter color, tasteless, and odorless. The average solubility of pristine and modified TS was recorded as 30.35 and 12.32%, respectively. This finding can be attributed to the linking of some hydroxyl groups of the starch with the phosphate group of TSPP that causing the decrease of the number of hydroxyl groups that can interact with water molecules. The decrease of TS solubility after modification was advantageous since the starch swelling power will be more controllable and the starch will not easily expand and swell when contacted with water. Moreover, by decreasing the TS solubility, when used as the patch polymer, the release of the drug from the patch can be more controllable.

Figure 1. The physical appearance of the pristine and modified TS

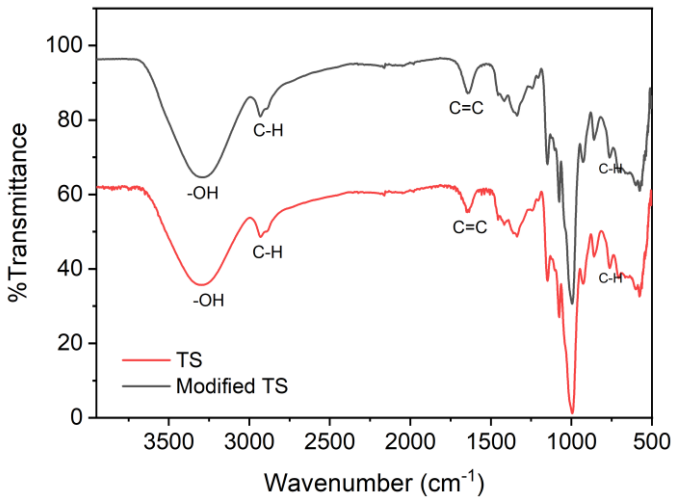

Figure 2. FT-IR spectra of tapioca starch (TS) and modified TS

Next, the FT-IR spectra of pristine and modified TS are presented in Figure 2. This characterization was aimed to investigate the formation of chemical interaction between TS and STPP. As can be observed in Figure 2, the result exhibited that there are no chemical interactions between both materials since no new vibration band was observed. Based on

these findings, the modified TS was then utilized as the polymer composite for the preparation of a mucoadhesive buccal patch of gambier leaf extract.

3.2. Mucoadhesive patch characterization

The physical appearance of the prepared mucoadhesive patch can be seen in Figure 3. The prepared patch exhibited a brown-red color, smooth texture, and uniform drug distribution. The physical characteristic of the prepared patches is presented in Table 2. The thickness of the prepared patches ranged from 0.374 ± 0.006 to 0.535 ± 0.005 mm, where the thickest was produced by the F4 formula. Moreover, the coefficient of variation (CV %) of the obtained data was less than 5%, which indicated that all formulas produce uniform patch thickness with good test reproducibility.

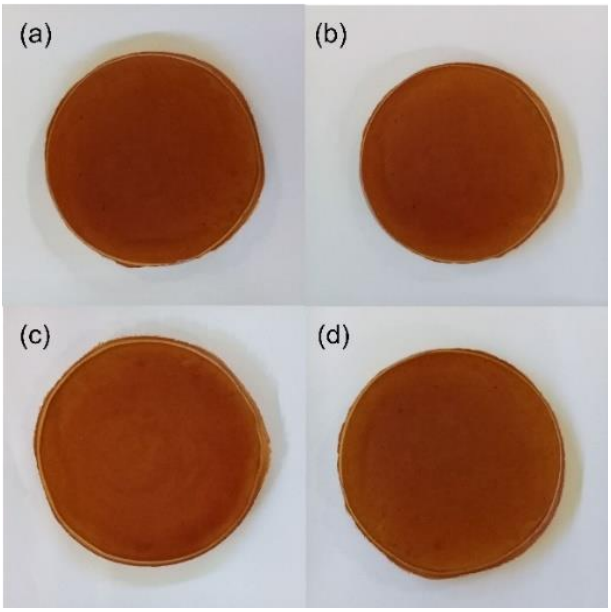

Figure 3. The physical appearance of the prepared mucoadhesive patch (a) F1, (b) F2, (c) F3, (d) F4

The mass of the prepared patched was recorded in a range of 0.031 ± 0.0001 to 0.043 ± 0.0002 g where the heaviest and the lightest was produced by F4 and F1 formula, respectively. This finding was attributed to the concentration of the CH and TS polymer in which F4 has the highest concentration of CH and TS, while F1 has the lowest polymers CH and TS concentration. The surface pH assessment of the prepared patches showed that it was around 6 that close to the biological pH of the mouth (around 5.8 – 7.4). Hence, it will not

cause irritation on the buccal mucosal surface when used and safe for oral use on the buccal mucosa [19].

Table 2. Physicochemical properties of the prepared mucoadhesive buccal patches

Patches Properties	Patches Code			
	F1	F2	F3	F4
Thickness (mm)	0.374 ± 0.006	0.471 ± 0.006	0.411 ± 0.005	0.535 ± 0.005
Mass (g)	0.031 ± 0.0001	0.039 ± 0.0002	0.036 ± 0.0003	0.043 ± 0.0002
Surface pH	6	6	6	6
Elongation (%)	43.333 ± 5.773	76.666 ± 11.547	56.666 ± 11.547	53.333 ± 5.773
Folding Endurance	>300	>300	>300	>300
Swelling Index	48.19 ± 2.950	75.93 ± 0.786	44.86 ± 1.181	57.76 ± 1.205
Mucoadhesive Time	174 ± 6.557	209 ± 8.144	185 ± 4.725	320 ± 1.154

Next, the folding endurance test was conducted by repeatedly folding the prepared patch in order to investigate the ability of the patch resistance when repeatedly folded. The obtained results indicated that the folding endurance of the prepared patch was more than 300 times. As reported by Parivesh, Sumeet and Abhishek [20], a good mucoadhesive patch should have folding endurance values more than 300 times. This finding indicated that used plasticizer can increase the flexibility of patch matrices by decreasing the hydrogen bonding of the two polymers. Moreover, when the plasticizer binds to the polymer matrix, the plasticizer can increase the empty volume between the polymer chains which allows the chain segment to move freely thereby increasing the movement of the polymer; the patch becomes more flexible and elastic [21].

Percent elongation test on the prepared patches was conducted in order to investigate the degree of patch elasticity against mechanical pressure than can break the patch. Basically, this evaluation was directly related to the folding endurance test. The results of this test can be seen in Table 2. The smallest percentage of elongation was produced by formula 1, with an average value of 43% while the most significant percentage of elongation was produced by formula 2 with an average value of 76%. The addition of CH composition has caused the decreasing of the patch pore size [22]. Consequently, the value of tensile strength and elongation increases by increasing the CH content. TS also has high flexibility, but its characteristic is highly depending on the moisture condition. The higher the water content in the surrounding environment, the less tensile strength of the patch [23].

Swelling properties is one of the most critical factors affecting the bioadhesive properties of the polymer and very important to predict the drug release mechanism. In this work, the swelling index of each patch formulations was tested, and the results are presented in Table 2. The highest swelling index value was obtained by F2 of 75.93% with CH and TS concentration of 900 and 150 mg, respectively. On the other hand, the smallest swelling index value was obtained by F3 with CH and TS concentration of 600 and 300 mg, respectively. This finding related to the CH properties which are a matrix hydrogel or water-insoluble matrix that can absorb water molecules [24]. On the other hand, TS can absorb water molecule vastly due to the presence of empty volume cavity that filled by the solvent and diffused into the patch to accelerate the dissolution of the gel. The formation of a gel layer will inhibit the penetration of liquid into the patch. Consequently, by increasing the time, the increment of percent development will decrease [19].

The mucoadhesive time of the prepared patches was evaluated in order to investigate the time needed by the patch to release from the mucosa membrane. The results showed that F4 with CH and TS concentration 900 and 300 mg, respectively, exhibited the longest mucoadhesive time (320 min) while the shortest was F1 (174 min). This finding was profoundly affected by CH concentration since it has glucosamine unit and the free amino group that can interact with sialic acid form mucin glycoprotein in the mucosa [25]. The adsorption of mucin glycoprotein by CH polymer was dominated by electrostatic interaction between the positive charge of CH with the negative charge of the mucin glycoprotein. Moreover, the hydrophilic group that was owing to the TS polymer, also enhancing the patch attachment in the mucus. So then, the higher concentration of CH and TS (F4), the longer the mucoadhesive time of the patch.

3.3. Optimization of mucoadhesive buccal patch

The patch formulation that produced the optimum patch properties was evaluated by 2^2 factorial design, and the obtained data were analyzed using Design Expert 12 software. The effect of CH concentration (x_1) and TS concentration (x_2) on the patch folding endurance (y_1), mass uniformity (y_2), thickness uniformity (y_3), surface pH (y_4), elongation percent (y_5), swelling index (y_6), and mucoadhesive time (y_7) was assessed based on the following mathematical equation.

$$y = b_0 + b_1x_1 + b_2x_2 + b_{12}x_1x_2$$

Where y is the dependent variable, b is the regression coefficient, and x is the independent variable.

The statistical models were fitted to each dependent variable by determining the predicted and adjusted R-square value of the produced model equation. The obtained model was further evaluated by analysis of variance (ANOVA) for determining the model significance. The regression and ANOVA analysis of each dependent variable are presented in Table 3. It can be observed that the concentration of CH and TS was significantly affecting the mass uniformity, elongation percent, swelling index, and mucoadhesive time. Meanwhile, it was not significantly affecting the folding endurance, patch thickness, and surface pH.

Table 3. Regression and ANOVA analysis of each response

Response	Regression			ANOVA		
	R^2	Adjusted R^2	Predicted R^2	p-value	F value	Significance
y_1	0.00	-0.375	-4.90625	1.00	0.00	not significant
y_2	0.9999	0.9999	0.9999	< 0.0001	65043	Significant
y_3	0.5638	0.4002	0.0186	0.07175	3.4473	not significant
y_4	0.00	-0.375	-9.500	1.00	0.00	not significant
y_5	0.7250	0.6219	0.3814	0.0124	7.0333	Significant
y_6	0.9862	0.9811	0.9691	< 0.0001	191.73	Significant
y_7	0.9934	0.9910	0.9852	< 0.0001	405.35	significant

Next, the desirability approach was employed in order to analyze the optimized formula. According to the analysis result, as displayed in Figure 4, it can be obtained that F4 with the concentration of CH and TS of 900 mg and 300 mg, respectively, was the best formulation with the highest desirability percent of 0.968. The prediction value of the optimized formula according to the obtained model and the experimental result of the patch characteristic is presented in Table 4. The Residual Standard Error (RSE) showed that the obtained prediction value has high accuracy. The lower RSE value indicated that the prediction value approaching the experimental value. Thus, the optimized formula (F4) was subjected to further characterization and analysis.

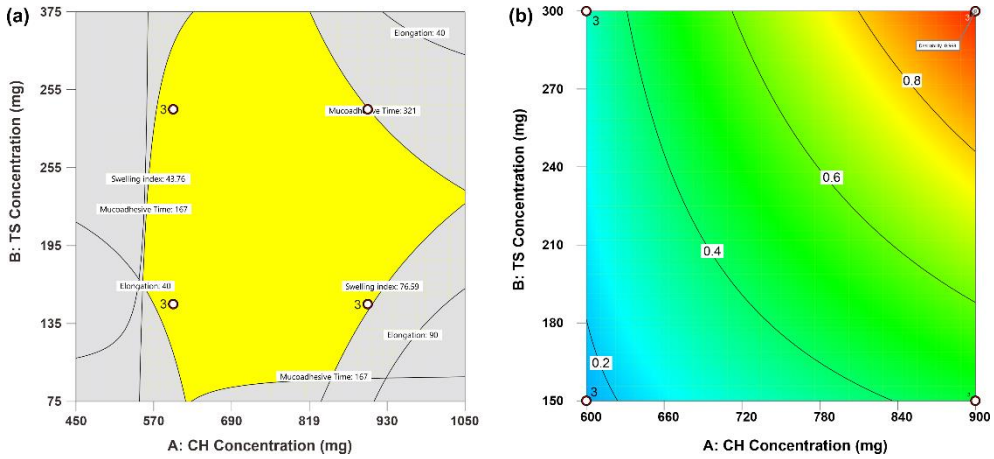

Figure 4. The overlay plot (a) and desirability plot (b) of the optimization result

Table 4. The comparison of prediction and experimental value of the patch evaluation

Patch evaluation	Prediction value	Experimental value	%RSE
Mass uniformity	0.480567	0.4816	0.2149
Thickness uniformity	0.971667	0.9716	-0.0689
Elongation percent	53.3333	53.3333	0
Swelling index	57.7667	57.7666	-0.0017
Mucoadhesive time	320.333	320	-0.1039

3.4. Analysis and characterization of the optimized patch formula

The content of the gambier leaf extract in the optimum patch formula was determined by UV-Vis method using catechin as a standard. The F4 patch was diluted with 1.5% of acetic acid and ethyl acetate solution with a ratio of 1:1, and the catechin content was measured by the standard curve method. The obtained results indicated that the catechin content in the optimum patch formula was 92.1667%. This finding was in accordance with the limit of the catechin content of 90 – 110% [26].

Next, the patch diffusion test was conducted in order to investigate the capability of gambier leaf extract content to be penetrated through the mucosa membrane. The result of this analysis is presented in Figure 5. It can be observed that between the gambier leaf extract from the patch and pristine gambier leaf extract from eluent exhibited different diffusion profiles. The pristine gambier leaf extract showed a higher diffusion percent compared with the gambier leaf extract from the patch. This phenomenon probably due to the pristine gambier leaf extract can be directly diluted in the carrier medium, then the catechin content

can be directly diffused into the acceptor whereas the catechin content in the patch was hindered or trapped by the matrix polymer.

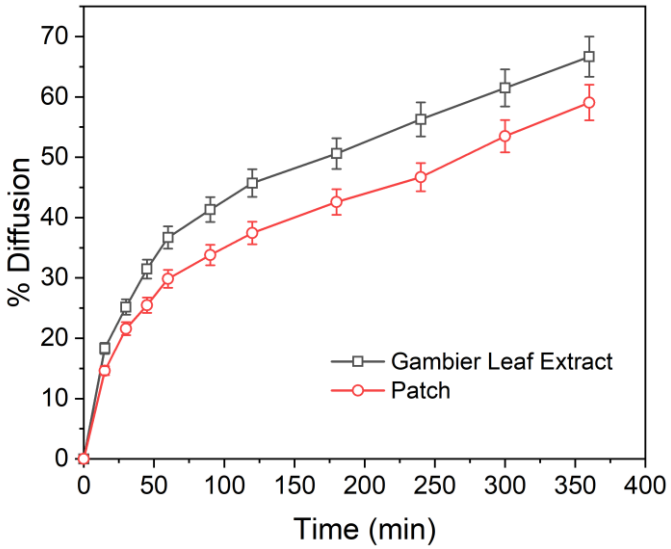

Figure 5. Correlation of contact time with the diffusion percent of the gambier leaf extract and standard catechin from the optimum patch formula

In average, the number of catechin compound that was diffused from pristine gambier leaf extract was 3372.97 µg while the number of catechins that was diffused from the patch was 2988.32 µg. However, the initial content of catechin in the pure gambier leaf extract and F4 patch was 5060 µg. This finding indicated that the catechin content couldn't be diffused totally due to lag time and detention from hydrogen bonding between CH and TS polymer, thus blocking the entry of solvents into the matrix. Furthermore, due to both CH and TS were able to absorb water and form a hydrogel, the cavity of the polymer was narrowed then the release of the drug was prevented [27]. Moreover, due to the solubility of catechin in water is only 0.9445 ± 0.11 mg/mL, it will tend to be released slowly into the acceptor medium [28].

The stability test on the optimum patch was conducted by the heating/cooling cycle in order to investigate the patch stability and consistency in a particular environmental condition. The result of the stability analysis is displayed in Figure 6. The obtained result showed that the patch was more stable than the pure gambier leaf extract after tested for 6 days. The reduction of catechin content in the patch was only 1.05%, while the pure gambier leaf extract was 1.99%. The stability of the patch was affected by the presence of hydrogen bonding between the catechin molecule with the patch polymer complexes that can protect

the active compound of the catechin like polyphenol from the significant temperature change also the degradation process due to oxidation during the test period [29].

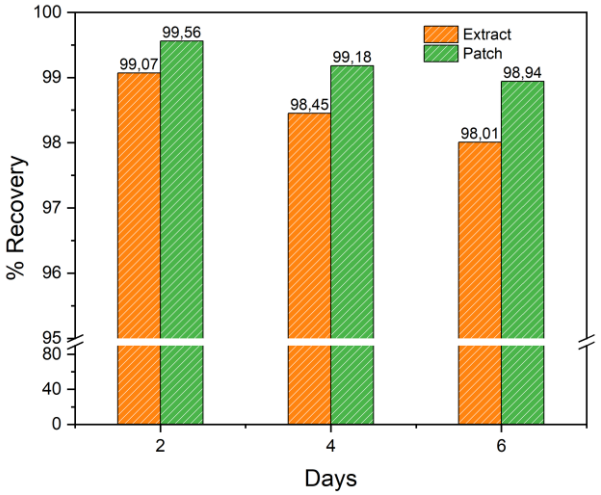

Figure 6. Reduction of the %recovery of gambier leaf extract and patch

In order to investigate the probability of a new chemical bonding formation between the polymer and the gambier leaf extract as the active compound, FT-IR analysis was carried out to the optimum mucoadhesive patch. The FT-IR spectra of the optimum patch, placebo, and the pure gambier leaf extract are presented in Figure 7. It can be observed that there is no new vibration peak was observed. This finding indicated that there are no chemical interactions between the patch components. The above characterization indicated that the gambier leaf extract could be formulated into the mucoadhesive patch as a potential patch for gingivitis treatment.

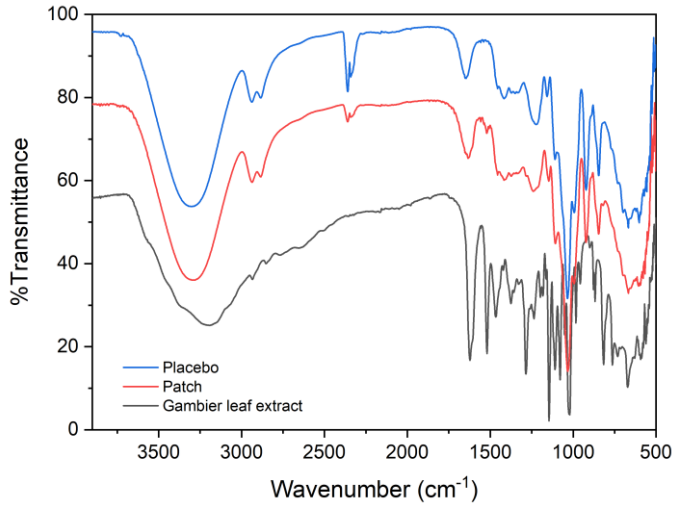

Figure 7. FT-IR spectra of the optimum patch, gambier leaf extract, and plasticizer

4. Conclusion

In this study, a new composite of CH and TS was successfully formulated as a potential interpolymer complex of a mucoadhesive patch of gambier leaf extract. The composition of the CH and TS composite was optimized by 2^2 factorial design. The obtained results indicated that the used composite exhibited a good characteristic as a mucoadhesive patch polymer. The optimum composition of CH and TS was 900 mg and 300 mg, respectively. The characterization of the optimum mucoadhesive patch indicated that the prepared patch has high stability and has no chemical interaction between each patch component.

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AUTHORSHIP STATEMENT

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All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the *International Journal of Biological Macromolecule*.

Authorship contributions:

Miksusanti: Conceptualization, Methodology, and Software. **Annuria Najma Fithri**: Data curation, Writing- Original draft preparation. **Herlina**: Visualization, Investigation. **Dina Permata Wijaya**: Supervision. **Tarmizi Taher**: Conceptualization, Validation, Writing- Reviewing and Editing.

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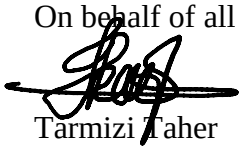
On behalf of all author.



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