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Formulation and characterization transdermal patches with chitosan-alginate of mangosteen peel (*garcinia mangostana l.*)

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ABSTRACT

Mangosteen peel extract contains xanthones have an anti-inflammatory effect and accelerated the process of fibroblast proliferation. The xanthones would trigger the formation of collagen which plays an important role in the wound healing process. The preparation of mangosteen peel extract into the trans-dermal patch aims to deliver the active substances through the skin and to the systemic system painlessly. The aims of this research were to formulate and characterize patch trans-dermal mangosteen peel extract. The formulation was characterized by organoleptic, uniformity of thickness and weight, folding resistance, pH, moisture content, drug content, swelling, in vitro drug release test, FTIR spectrum, and morphology by SEM. The patch trans-dermal was prepared using chitosan and sodium alginate by layer by layer using 0,2%, 0,4%, and 0,6% calcium chloride as crosslinker. The enhancement in the concentration of calcium chloride had a significant effect ($p<0,05$) on uniformity of thickness and weight, moisture content, drug content, swelling test, and in vitro drug release. The best formula was found in 0,2% calcium chloride concentration. The result of the organoleptic test showed that the film was a smooth surface, flexible, and brownish-colored. In addition, the resulting patch also had a uniform weight, qualified thickness of >300 folds, pH of 5, moisture content of 1,84%, swelling degree value of 3,41%, and penetration test results were found with a percent penetration of 38,87%. The results of the morphological obtained a pore size of 5,88 µm. The results of the FTIR spectrum showed that there was interaction by the presence of a new peak at the wave number of 1622,23 cm-1. It can be concluded that calcium chloride in patch trans-dermal affected physical properties and in vitro drug release of mangosteen peel extract.

Keywords: Mangosteen peel extract, Patch, Transdermal, calcium chloride, Chitosan, Na alginate

INTRODUCTION

Transdermal is a drug delivery system in that the drug will penetrate into the skin and enter the blood circulation to obtain a systemic therapeutic effect painlessly. The transdermal system can be formulated in the form of creams, patches, gels, emulsions, and ointments[1-3]. A transdermal patch is an adhesive patch formulation that contains drugs to be able to deliver drugs directly to blood vessels in a controlled system. The matrix system of patch transdermal consists of polymers, enhancers, active substances, and other excipients. The polymer in the matrix system will control the rate of drug release from the patch matrix[4]. The polymer to be used is chitosan which is a natural polymer that is biocompatible and biodegradable. Its solubility in low pH can cause most of the amino groups in chitosan to be protonated so that it has polycationic properties[5,6]. According to the patches made of only chitosan cannot be used directly because they are fragile and have low elasticity, so a suitable material is needed to improve the characteristics of the patch[7].

The polymer to be combined is Na alginate because can bind cations in the presence of an anionic carboxyl group in its structure. So, it's dissolved under certain conditions with chitosan which has an amino group, a polyelectrolyte complex can be formed and a combination of chitosan-Na alginate can reduce the degree of swelling and the addition of chitosan can also cover the hydrophobic properties of Na alginate[7,8]. Calcium chloride has a structure that is easily soluble in water it has a function as a source of calcium ions. The calcium chloride as a crosslinking agent is capable of strengthening the intermolecular bond of the patch and Na alginate due to the presence of a chelate complex between calcium ions and carboxylate anions. This process improves patch properties, barrier properties, and strength and prevents the patch dissolves in water. Hence the addition of calcium chloride in the patch can produce patches stronger and affect the characterization in fold resistance which identifies the elasticity and fragility of the transdermat patch and decreases the degree of swelling[9].

One of the applications of the development of transdermal patch preparation is for wound healing. The prevalence of injuries is very high in the world and in Indonesia where every year this can reach millions of cases. The common (conventional) wound treatment method using gauze has a drawback when changing the gauze, the gauze will stick to the new skin tissue and cause pain. Modern wound care methods that have been widely applied are to keep the wound area moist to facilitate the formation of new tissue and prevent cell death[10]. This has become the main reason for developing patch preparations for wound healing.

Mangosteen peel waste was counted as 59-67 tons wasted in 2010 even though the mangosteen peel has many benefits. Mangosteen peel contains xanthones, mangosteen, garsion, flavonoids, and tannins are compounds that contribute to the benefits of mangosteen peel[11]. The antioxidant activity of mangosteen peel showed that can accelerate cell recovery by enhancing the fibroblast proliferation process. In addition, xanthones can trigger the formation of collagen which plays an important role in the maintenance of the structure and wound healing[12]. Mangosteen peel extract 15% could improve wound healing percentage of 88%[13] and also mangosteen peel extract contains alpha-mangosteen compounds derived from xanthones that can heal wounds with a healing percentage of 52.57% on the 15th day[14]. This study aimed to formulate transdermal patches containing mangosteen peel extract (*Garcinia mangostana*) and characterize transdermal patches.

MATERIALS AND METHODS

The plant material used for the study was mangosteen peel (*Garcinia mangostana*) obtained from Timbangan Village, Indralaya, Ogan Ilir, South Sumatra, Indonesia. Ethanol 70% (Dira Sonita Group, Indonesia), ethanol p.a. (Merck, Germany), alpha mangostin (Sigma Aldrich, Germany), chitosan (CV. ChiMultiguna®), sodium alginate (Nusae), calcium chloride (Sigma Aldrich, Germany), oleate acid (Bratacem, Indonesia), propylene glycol (Bratacem, Indonesia), methanol p.a (Merck, Germany).

Instrumentation

The tools used in this study included glassware (Pyrex®), Petri dishes, an analytical balance (Ohaus®), rotary evaporator (Yamato®RE 301), spin bar (Scienceware®), magnetic stirrer (IKA® C-MAG HS 4), UV-Vis spectrophotometer (UV-1700 Shimadzu®), pH meter (Lutron® pH Electrode PE-03), oven (Memmert®), digimatic micrometer (Mitutoyo Corporation, Japan).

Plant Identification

The mangosteen peel was determined at the Purwodadi Botanical Gardens Plant Conservation Center, LIPI, East Java with No: B-360/IPH.6/Ks.02/X/2020.

The extraction of mangosteen peel (*Garcinia mangostana*)

The mangosteen peel was obtained by using the maceration method with 70% ethanol solvent in a ratio of 1:10. The plant was then soaked with 70% ethanol stirred with a macerator for 3 hours and allowed to stand for 24 hours. The filtrate was filtered the remacerated 2 times. The entire filtrate obtained was then concentrated with a rotary evaporator at 60^{o}C to obtain a thick extract. The extracted mass obtained was calculated as the percent yield using Equation 1.

The material was weighed as much as 800 g and put into a maceration container, then added 6 L of 96% ethanol solvent. The obtained macerate was filtered with Whatman paper so that the residue and filtrate were obtained. The residue was macerated for 2 x 48 hours with 6 L of 96% ethanol solvent and filtered again to obtain the filtrate. The entire filtrate obtained was then concentrated with a rotary

evaporator at 60°C to obtain a thick extract. The extracted mass obtained was calculated as the percent yield using equation 1[15].

$$\%\text{Yield} = \frac{Ex}{M} \times 100\% \quad (1)$$

Noted:
Ex : obtained extract weight
M : mangosteen peel simplicial powder weight

Determination of Total Xanthon Content

The 10 mg alpha mangostin was weighed and dissolved in 100 ml of methanol p.a to form a stock solution with a concentration of 100 µg/ml. This solution was diluted to obtain solutions with concentrations of 2, 4, 6, 8, and 10 g/ml. Measurement of the maximum wavelength was carried out at a wavelength range from 200 to 400 nm using the resulting solution of alpha mangostin. All standard solutions were measured to obtain absorbance at the maximum wavelength and a linear regression equation could be obtained. The mangosteen peel extract was weighed as much as 50 mg and dissolved in methanol p.a. The solution was taken as much as 1 ml to dissolve to 10 ml methanol to obtain 10 g/ml. The absorbance of the solution was measured and calculated using the standard curve linear regression equation to obtain total xanthon[16].

Preparation of Transdermal Patches

Formulation of transdermal patches of mangosteen peel extract in Table 1. In the formula, it was 315.8 mg of chitosan and 84.2 mf of sodium alginate with variations of calcium chloride of 0.2%, 0.4%, and 0.6%. The mangosteen peel extract was used as much as 15% in the transdermal patches. The use of propylene glycol was 0.17 ml and oleic acid was 0.13 ml. The alginate solution was added with propylene glycol and oleic acid the mixed using a magnetic stirrer, the the mangosteen peel extract was added and stirred using a magnetic stirrer until homogeneous. After the solution was homogeneous, the solution was poured into a petri dish and dried in an oven at 40°C for 5 hours. Then 2% chitosan solution was added with calcium chloride. Then the chitosan solution was poured into a petri dish containing sodium alginate which had been dried, then dried again at 50°C for 24 hours. Patches without mangosteen peel extract were made as blanks.

Table 1: Formulation of transdermal patches containing mangosteen peel extract

Material	Formula		
	F1	F2	F3
Mangosteen peel extract (%)	15	15	15
Chitosan (mg)	315.8	315.8	315.8
Sodium alginate (mg)	84.2	84.2	84.2
Oleic acid (ml)	0.13	0.13	0.13
Propylene glycol (ml)	0.17	0.17	0.17
Calcium chloride	0.2%	0.4%	0.6%

Characterization of formulation Transdermal Patches
Organoleptic

The transdermal patches organoleptic test was carried out by physical observation of the transdermal patches such as shape, color, and smell[17, 18].

Uniformity of transdermal patch's thickness and weight

The thickness of transdermal patches was measured by taking 10 sheets of the resulting patches using a digimatic micrometer at nine points on each patch and the weight of transdermal patches taken one by one was measured with an analytical balance. The average value and standard deviation of the thickness and weight of the transdermal patches were calculated[19,20,21,22].

Transdermal patches folding resistance

The folding resistance test on transdermal patches is carried out by folding the patch repeatedly in the same place until it breaks or 300 times to obtain the best patch properties.

Measurement pH of transdermal patches

The transdermal patches were put into a container containing water and allowed to the swollen patch matrix surface for 1 minute. The pH of the patch was measured using a pH meter.

Moisture content test of transdermal patches

Each transdermal patch was weighed and stored in a desicator containing calcium chloride at room temperature for 24 hours. Then the patch was weighed again to get the final weight. Moisture content can be calculated from the following Equation 2[23,24,25]:

$$\%\ \text{Moisture content} = \frac{initial\ weight - final\ weight}{final\ weight} \times 100\% \quad (2)$$

Uniformity of drug content transdermal patches

The transdermal patch with a size of 2x2 cm was cut then put into phosphate buffer (pH 7.4) and dissolved using a magnetic stirred for 36 hours and then filtered. The transdermal patches without mangosteen peel extract (placebo) were prepared in the same way to be used as the blank. Then, drug content was determined using a spectrophotometer with the maximum absorption wavelength, and the absorbance was obtained.

Sweeling test

The swelling test was 2x2 cm then weighed and placed in a petri dish containing 10 ml of distilled water at 37oC for 2 hours. After that, the surface of the swollen patch was wiped with a tissue and the weight was weighed again and then observed and the degree of swelling was calculated from the following Equation 3:

$$\%\ \text{Degree of swelling} = \frac{patch\ weight\ whne\ wet - patch\ weight\ when\ dry}{patch\ weight\ when\ dry} \times 100\% \quad (3)$$

***In-vitro* release of transdermal patches containing mangosteen peel extract**

In-vitro release testing of transdermal patches of mangosteen peel extract using the Franz diffusion cell. The preparation of testing placed 50 ml pH 7.4 PBS into the receptor chamber and the spinbar was inserted. The cellophane membrane was placed in the center of the chamber. The patch to be used was cut 2x2 cm according to the cellophane membrane and placed on the top cellophane membrane facing the donor chamber. The diffusion cell that had been prepared was placed on a magnetic stirrer which was at 37±0,5oC with the speed

of 600 rpm. Samples were taken as much as 3 ml at the of 0, 5, 10, 15, 30, 45, 60, 90, 120, and 180 minutes. Each sample taken was replaced with of pH 7.4±0.5 PBS with the same volume to maintain the sink condition. The absorbance of the sample was measured by UV-Vis spectrophotometry at the maximum wavelength that had been obtained and by using a blank phosphate buffer pH 7.4. The content levels were calculated at each sampling time and the release profile[26].

The measurement of the level made can be calculated with the Wurster formula following equation 4:

$$Q = \frac{CnV + \sum_{i=1}^{n-1} Ci.S}{A} \quad (4)$$

Note:
Q: cumulative amount of mangosteen peel extract per diffusion area (µg/cm^2)
Cn: concentration of mangosteen peel extract (µg/cm^2) at the n-minute sampling
V: franz diffusion cell volume (ml)
$\sum_{i=1}^{n-1} Ci$: total concentration of mangosteen peel extract in the first sampling (minutes to (n-q)
until before the minutes to n
S: sampling volume, A: the area of the membrane (cm^2)

SEM analysis

Scanning electron microscopy was used to determine of morphology of the patch. The SEM for the chitosan-sodium alginate polyelectrolyte complex patch was studied using the membrane coating method on gold-palladium to determine the surface morphology of the membrane.

FTIR analysis

FTIR analysis was determined by taking a transdermal patch formulation that was then placed in an infrared spectrophotometry sample holder and scanned from a wave number of 4000-500 cm^{-1}. The FTIR absorption of all samples was measured using the KBr pellet method at a compression pressure of 2500 Ib/m^2.

RESULTS AND DISCUSSION

Extraction

Mangosteen peel extract using the maceration method produced a thick extract of 25.18 g with a percent yield of 2.8%. The extraction is used by the maceration method because it could avoid damage to flavonoid compounds that are no heat resistant or easily oxidized at high temperatures. This method is included as the cold extraction method through the penetration of the solvent into the cell wall so the active substances present will be dissolved. These substances will be pushed out of the cell due to differences in the concentration of the solvent outside the cell and inside the cell. The ethanol 70% solvent used in the maceration process based on its ability to dissolve almost all low molecular weight compounds such as xanthone. Determination of the total xanthone content of mangosteen peel extract using α-mangosteen as a marked compound. The total xanthone produced by mangosteen peel extract was 360 mg in 1 g of extract with a percentage of 36%.

Formulation of a transdermal patch containing mangosteen peel extract

Mangosteen peel extract of transdermal patches was prepared using the layer-by-layer method. The layer-by-layer method was chosen because the method produced good characteristics patches and homogeneous patches. Sodium alginate produced a negatively charged carboxylic acid group which would bind with the positive amine group of chitosan. The crosslinking process of $CaCl_2$ will occur when calcium ions replace the sodium ions in the three-dimensional structure formed in the sodium alginate and establish a complex. The interaction of chitosan and sodium alginate and the addition of calcium chloride will form a polyelectrolyte complex. The formation of this crosslinking complex strengthens the calcium alginate-chitosan bond thus producing a patch that is not easily torn. In addition, the presence of this interaction increases the stability of the active substances in the polymer[27].

The characteristics of transdermal patches

The characterization of transdermal patches is presented in Table 2.

Table 2: The characterize of transdermal patches of mangosteen peel extract

Characterize	F1	F2	F3
Organoleptic	Brownish-colored, smooth surface, and flexible	Brownish-colored, smooth surface, and flexible	Brownish-colored, smooth surface, and flexible
Weight uniformity (mg±SD)	127.9±0.458	131.8±0.814	142.1±0.794
Thickness uniformity (mm±SD)	0.138±0.002	0.149±0.002	0.159±0.001
Folding endurance	>300	>300	>300
pH	5.033±0.021	5.036±0.006	5.033±0.015
Moisture content (%±SD)	1.389±0.481	1.487±0.056	1.180±0.511
Swelling(degree of swelling±SD)	6.231±0.082	3.407±0.162	2.674±0.134

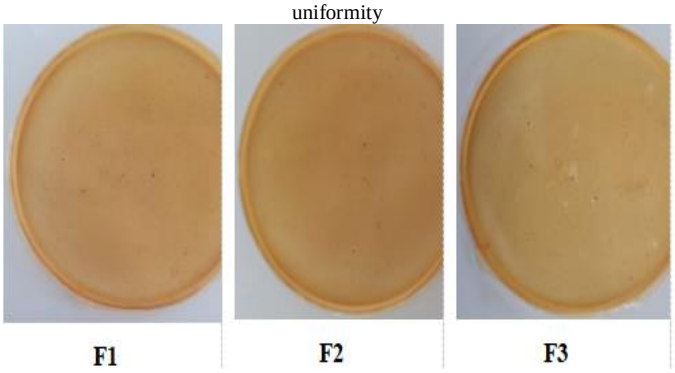
Organoleptic

The organoleptic test was to see the visual of the transdermal patches preparation that had been made. The transdermal patches of F1 had a more transparent surface than F2 and F3 due to the concentration of calcium chloride in F2 and F3 being higher than F1. The all of formula transdermal patches had a flexible, thin texture with a smooth surface. The flexibility of transdermal patches was gained from the addition of a plasticizer in the formula. The interaction between the polymer and plasticizer results from the reduction in the structural strength of the polymer and increased the elasticity of transdermal patches. The presence of plasticizers accounted for the decrease of intermolecular and intramolecular hydrogen bonds and the intermolecular attraction of adjacent polymer chains due to the produced patch avoided cracking and increased the elasticity of the transdermal patch. The organoleptic of transdermal patches can be seen in Figure 1.

The weight uniformity test was to evaluate the process of preparation of transdermal patches. The thickness of the transdermal

patch was able to identify that the active substances were evenly distributed on the patch therefore it was more easily accepted for usage and did not interfere with the physical appearance of a transdermal patch.

Figure 1: The Transdermal patches of mangosteen peel extract weight uniformity



The weight uniformity test obtained of F3 had a weight higher than F1 and F2. The F3 weight is higher than F1 and F2 because the concentration of calcium chloride is high and caused an increase in the preparation weight. The evaporation process on the solvent during the transdermal patches preparation with drying process caused the weight of the patch .The weight of transdermal patches were identified to uniform if the %CV was ≤5%. The formula of transdermal patches had uniformity due to the %CV value ≤5%. The data obtained were further tested for DMRT and showed a significant difference between the formula.

Table 3: The weight uniformity of transdermal patches

Formula	Average (mg)±SD	%CV
F1	127.9^{a}±0.458	0.374
F2	131.8^{b}±0.814	0.665
F3	142.1^{c}±0.794	0.648

Note: the numbers followed by different lowercase letters were significantly different based on the DMRT (α=0.05)

The thickness results

The transdermal patch thickness uniformity was expected to have a uniform thickness. Thickness uniformity could identify that the patch which had been made was uniform, and was able to distribute the active substances into the skin evenly. The thickness of patches can affect the usage convenience and also its physical appearance. The thickness of the transdermal patch will also affect the release of the active substances in it, the thicker the transdermal patch the more difficult it will be to penetrate the active substances[28]. The result of measurement thickness uniformity showed that the all of formulas had met the transdermal patches thickness requirement of <1mm[18]. Based on the results, it showed that the increase in transdermal patch thickness was directly proportional to the increase in calcium chloride concentration. This was due to an increase in the concentration of calcium chloride causing an increase in the percentage of gel content because of the formation of cross-links between Ca^{2+} ions and the carboxylate group that occurred in sodium alginate, thereby making the transdermal patch thick. In addition, the thickness of the patch can be affected by the volume of the used solution and the width of the used impression, the wider the mold used the thinner the transdermal patch produced. The thickness uniformity of all of the formulas represented that had %CV value was ≤5%. The data obtained by the DMRT indicated a significant difference between the formula on the uniformity of the thickness of the transdermal patch preparation.

Table 4: The thickness uniformity of transdermal patches

Formula	Average (mm)±SD	%CV
F1	0.138^{a}±0.002	0.002
F2	0.149^{b}±0.002	0.002
F3	0.159^{c}±0.002	0.002

Note: the numbers followed by different lowercase letters were significantly different based on the DMRT (α=0.05)

The folding resistance of transdermal patch

The folding resistance test showed that the F1, F2, and F3 had good folding resistance requirements is >300 folds. The folding resistance of the transdermal patch can be affected by a plasticizer in the formula. The plasticizer that used in this research is propylene glycol. The plasticizer will form hydrogen bonds with the polymer causing the patch to become elastic and not break easily[29]. In addition to the presence of plasticizer, cross-linking interactions between calcium alginate and chitosan form cross-links strengthened the calcium alginate-chitosan bonds hence the patches not easily torn.

The pH of the transdermal patch

The pH measurement was to determine the safety of the preparation when used on the skin. The requirement for pH in topical preparations is 4-8, if the pH of topical preparations is too acidic it will cause skin irritation while if the pH is too alkaline it can cause scaly and dry skin[30]. The range pH of all of the formulas is 5.033-5.036 indicating that transdermal patches come to the requirement of pH topical preparations. The results that were obtained were then further analyzed by Kruskal-Wallis, the result showed that all of the formulas had no influence on the concentration of calcium chloride variations on pH as indicated by a significant value of 0.996 (sig >0.05).

The moisture content of the transdermal patch

Measurement of moisture content in transdermal patches aimed to determine the quality of the patch preparation. The moisture content affects the physical appearance of the patch. Low moisture content can keep the patch more stable, flexible, and less brittle[31]. While the moisture content in the patch is too high, it will be easy for the patch to have bacteria contamination and affect the elasticity of the patch itself so that it is easily torn or brittle[32]. Moisture content can also affect the penetration of the active substances in transdermal patches.

Table 5: The moisture content of the transdermal patch

Formula	Average (%)±SD	%CV
F1	1.389^{a}±0.481	0.393
F2	1.487^{b}±0.056	0.045
F3	1.180^{c}±0.511	0.417

Note: the numbers followed by different lowercase letters were significantly different based on the DMRT (α=0.05)

The results showed that the moisture content met the

requirement of <10% with the largest moisture content found in F2[33]. The water content in the patch that binds to the polymer causes the expansion (swelling) of the patch has different characteristics from the water that is adopted thus during the drying process in the oven this water is not lost. Moisture content can also be influenced by the addition of plasticizer because it has hydrophilic properties and can reduce intermolecular bonds between polymer chains so is able to increase the moisture content of the preparation[34]. The data obtained by DMRT showed that there was no significant difference between the formula on the moisture content of the transdermal patches.

Uniformity of drug content transdermal patches

The uniformity of drug content aimed to determine the level of mangosteen peel extract in the transdermal patch preparations. It also could identify that the preparation process had been conducted properly. The results showed the average recovery percent of F1 was 89.37%, F2 was 95.73%, and F3 was 99.1%. The all of formulas could be identified as good because they met the requirement with a range of 85-110%. The uniformity of transdermal patch levels is influenced by the homogeneity of the solution used to make the transdermal patch. The homogeneity of this solution will affect the active substances contained in the extract because if it is not homogeny the active substances content will be unequal. The data obtained by the DMRT showed a significant difference between the formula on the transdermal patches.

Swelling test

The aim of the swelling test was to determine the level of water absorption of the transdermal patch. Patch resistance to moisture where the path absorbs a lot of moisture will affect the quality of the patch in the form of patch elasticity making it easy to tear. In addition, the extensibility of a patch can affect the release of the active substances from the transdermal patch so it can penetrate into the skin membrane. The results showed that the biggest swelling test was in F1 than in F2 and F3. Swelling of the patch caused by the presence of COO^- ions form hydrophilic alginate, causing the patch to absorb water and expand. F1 had a higher expansion power because there were still a lot of COO- ions, while in F3 it was lower due to the addition of calcium chloride concentration. The higher the concentration of calcium chloride in the transdermal patch of formula, the greater of strength of the ionic bond formed. The stronger the bond, the more stable the network or bond formed[35].

Table 6: Swelling test of transdermal patch

Formula	Average (%)±SD	%CV
F1	6.231^a±0.082	0.067
F2	3.407^b±0.162	0.132
F3	2.674^c±0.134	0.109

Note: The numbers followed by different lowercase letters were significantly different based on the DMRT (α=0.05)

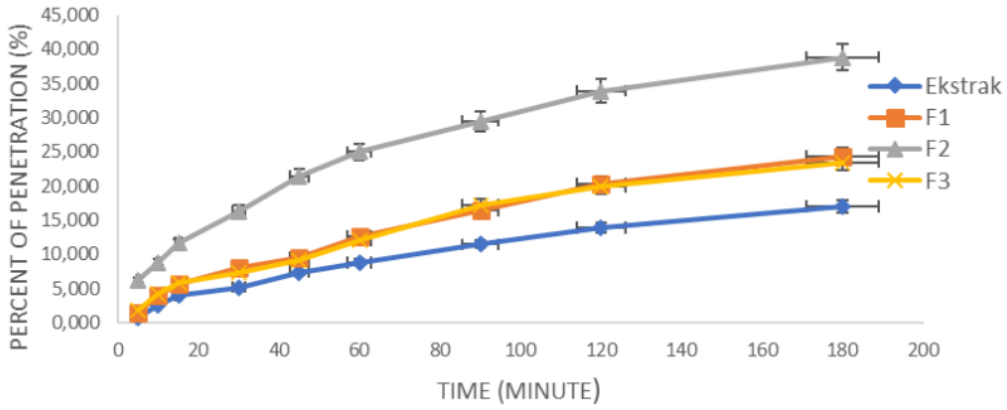
This causes a more compact structure and makes less water absorption into the patch, causing the swelling degree to decrease. The data obtained by the DMRT showed a significant difference between the formulas on the degree of swelling of the transdermal patches.

The *in-vitro* release of a transdermal patch containing mangosteen peel extract

The aim of the invitro release study was to see the effect of calcium chloride concentration in a transdermal patch on the active substance penetration ability through the membrane and also to determine the release profile of the active substances from the transdermal patch preparation. The in-vitro release study transdermal patch of mangosteen peel extract was conducted by using the Franz Diffusion Cells method and using a hydrated cellophane membrane as an artificial membrane which was analogous to the horny layer or stratum corneum of the skin.

The in-vitro release study of the mangosteen peel extract transdermal patch followed in three stages. The first stage was that the patch would experience hydration which was related to the ability of the transdermal patch to absorb water into the patch, the next stage occurred after water absorption was the swelling of the transdermal patch, and the last stage of drug transport from within the patch and across the membrane to the dissolution medium. In this study, cellophane was used as a membrane. The cellophane membrane has a porous surface so the active substances will penetrate through the gaps between cells, thus it can describe drug penetration through the paracellular route.

Figure 2: Percent of penetration mangosteen peel extract in the transdermal patch



The study was carried out on all formulas with varying concentrations of calcium chloride crosslinker and mangosteen peel extract as a comparison. Sampling was done by taking 3 ml of solution at the receptor at certain time intervals for 3 hours. The phosphate buffer solution was returned to as much as 3 ml to maintain the sink condition. The sink condition is a condition where there is excess media that will allow the drug substance to dissolve continuously, where the condition of the drug can not dissolve anymore. The obtained sampling results were then measured using UV-Vis spectrophotometry with 245 nm wavelength. To get the content level of active substances, the standard curve of α-mangosteen was obtained with the linear equation of y=0.0742x + 0.0818 with a linearity of 0.991.

Based on the graph of the penetration test that had been carried out, it was discovered that the cumulative amount of the α-mangosteen active substance that was penetrated had increased within the addition of time. The results showed that the percent of penetration F1 was 24.36%, F2 was 38.87%, F3 was 23.49%, and mangosteen peel extract was 17.02%. This interpreted that the penetration process occurred better in the transdermal patch than in the extract form which was applied to the membrane because the cumulative amount of active substances penetrated in the mangosteen peel extract had the smallest than in a transdermal patch. This was because the transdermal patch had been designed to contain penetration enhancers and plasticizers that could help the process of active substances penetration more easily into the system.

The crosslinker concentration will affect the content level of penetrated active substances, this is because the high concentration of the used causes the tigh the structure of the produced patch causing the swelling process on the patch to decrease as a result of the hydrophilicity of the transdermal patch decreasing due to the liquid medium is not easy to diffuse into the patch. On another hand, the moisture content also affects the release of the active substance because the high moisture content of the transdermal patch can release active substances is greater in the F2. This percent of penetration F2 is higher than F1 and F3.

The penetration process of the transdermal patch was also assisted by a penetration enhancer and plasticizer. Propylene glycol as a plasticizer could modify the properties of the patch by reducing the intermolecular bonds in the polymer so the permeability of the transdermal patch increased and the active substances were easily penetrated. Oleic acid as a penetration enhancer worked to form a new lipid layer with the lipid layer of the stratum corneum to reduce the capacity of skin barrier function [19].

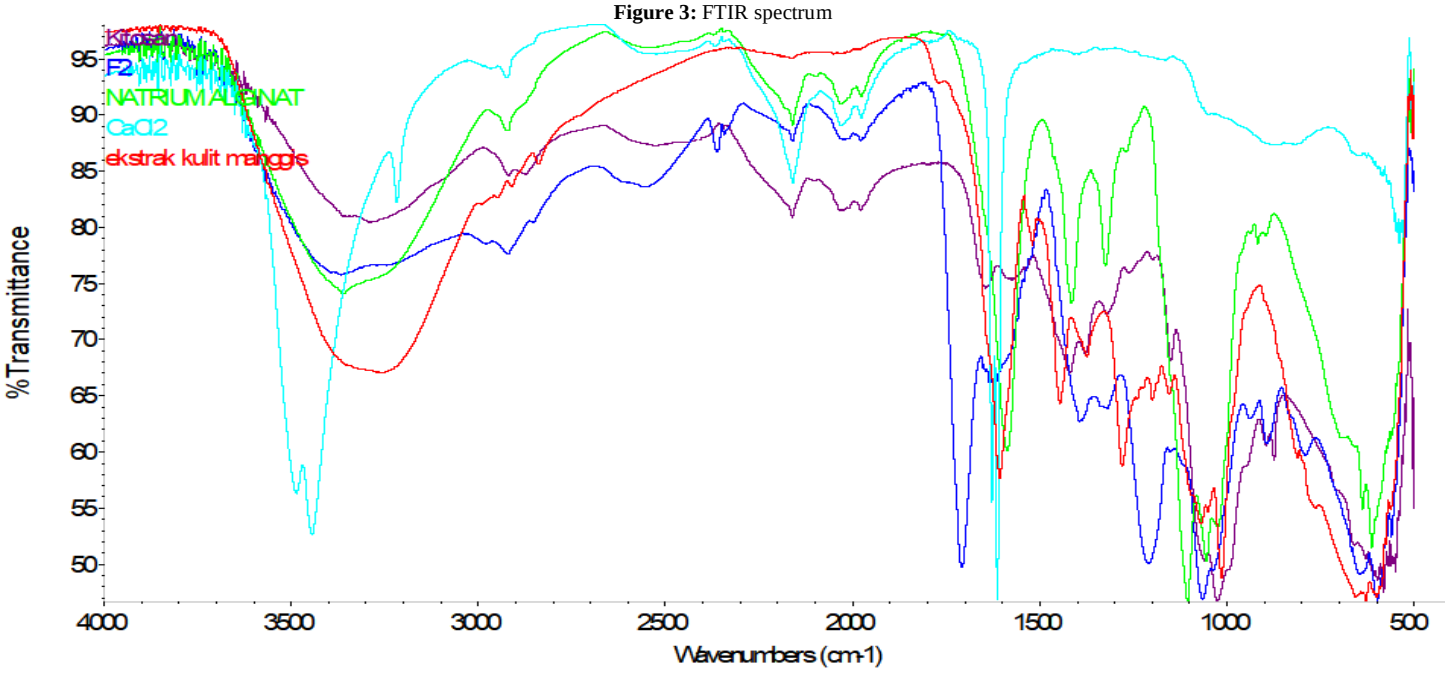
Table 7: Percent of cumulative (%) penetration of mangosteen peel extract in a transdermal patch

Formula	Flux (μg/cm^2.h)
Extract	1.51^a±0.514
F1	2.29^a±0.802
F2	5.25^b±2.891
F3	2.35^a±0.919

Note: the numbers followed by different lowercase letters were significantly different based on the DMRT (α=0.05)

The percent cumulative showed that the release rate of active substances per unit minute. Based on results in the Table 7, the highest penetration of active substances was F2. This showed that the F2 has the best release rate of active substances. This is because the release of mangosteen peel extract in F2 can be influenced by concentration calcium chloride. The data obtained by DMRT identified a significant difference in F2 to the percent of cumulative or flux of the transdermal patch.

Figure 3: FTIR spectrum



FTIR analysis

The spectrum of FTIR showed the absorption band of chitosan which was used as a comparison at a wave number of 3287.76 cm^{-1}, which showed bending vibrations of the OH and NH groups. The absorption width and the shift in the OH number were due to the overlap with the NH group of the amine. There was an absorption at wave number 2918.52 cm^{-1} which indicated the presence of the CH functional group. In addition, there was an absorption at a wavelength of 1644.47 cm^{-1} which indicated the presence of a secondary amine group. There was also an absorption at wave number 1149.19 cm^{-1} which was the amino characteristic band.

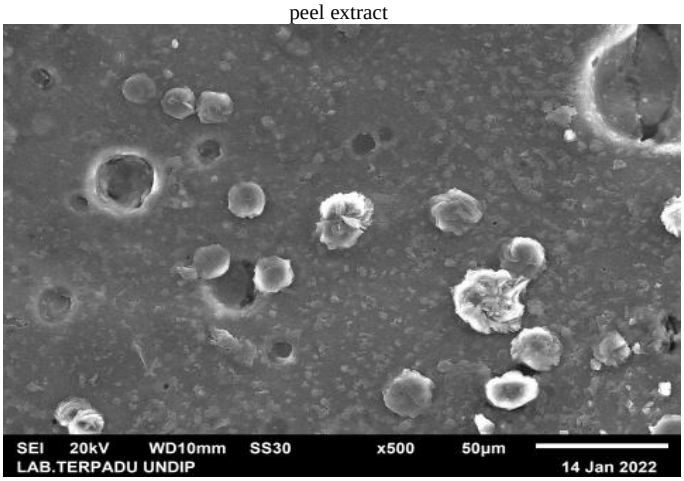
Sodium alginate showed that there was an absorption at 3361.13 cm^{-1} which indicated the presence of a hydroxyl group OH bonded to hydrogen. Wave number of 1586.06 cm^{-1} indicated the presence of a carbonyl group (C=O) as an aromatic group, the number of 1053.61 cm^{-1} identified the presence of a carboxylic group (C-O). The absorption peak of 917.60 cm-1 represented a typical of guluronic fingerprints, while 612.59 cm-1 showed a typical region of guluronate fingerprints, these two areas indicated the specific markers for sodium alginate compounds. The spectrum results on the extract discovered there were several spectra that indicated that the extract contained xanthone flavonoids including the C-O group at 1279.24 cm^{-1}, O-H at 3251.58 cm^{-1}, and C-O at 1279.24 cm^{-1}.

In the transdermal patch spectrum, it can be seen that there was an absorption at 3366.72 cm^{-1} which indicated the presence of a hydroxide group. This hydroxide group could be derived from mangosteen peel extract, where the extract contained xanthone which produced O-H absorption at a wave number of 3366.72 cm^{-1}. In addition to the hydroxide group, there was a spectrum that appeared at the wave number 1393.40 cm^{-1} which showed the presence of a C=O group of carboxylate in sodium alginate. An absorption also appeared at the wave number 1708.16 cm^{-1} which identified the presence of a C=O group. The loss of the absorption band in the 1149.19 cm^{-1} region which characterized the amine group interpreted that the amine group of chitosan had been protonated and interacted with the group. This was reinforced by the presence of another absorption also formed at wave number 1622.23 cm^{-1}, which was the N-C=O group, which was a newly emerged group of sodium alginate and N-H of chitosan. The ionic bond formed from COO^- in sodium alginate and NH^{3+}in chitosan was strong enough to cause the appearance of the functional group N-C=O. The presence of absorption at wave numbers 1740-1630cm^{-1} (C=O) and 1630-1510 cm^{-1} (N-C=O) showed a reaction between the carboxylate group of alginate and the amine group of chitosan[7].

SEM analysis

The SEM analysis aimed to see the surface morphology of the transdermal patch containing mangosteen peel extract. The F2 was chosen because it had the best characteristics seen from the invitro penetration and physical properties.

Figure 4: The SEM analysis of the transdermal patch containing mangosteen peel extract



Morphological observation of the transdermal patch containing mangosteen peel extract was carried out at 500 times magnification. Based on the observation of the patch could be seen that the surface was slightly rough with small pores and some particles, this was because the solution made was less homogeneous. The pores sizes in the patch were at least in the range between 3.35-13.36 µm. The observation result and SEM measurement showed that the average surface pore on the transdermal patch was 5.88 µm. The pores and cavities on the surface of the patch will accelerate drug release from the matrix.

CONCLUSION

The transdermal patch of mangosteen peel extract was successfully formulated with a layer-by-layer method using chitosan-sodium alginate with variation concentration of calcium chloride in 0.2%, 0,4%, and 0.6%. The transdermal patches of mangosteen peel extract showed well physical properties and an in vitro penetration study. The FTIR analysis of transdermal patches indicates that there is an interaction with chitosan-sodium alginate. The in-vitro release studies showed that mangosteen peel extract was more enhanced than mangosteen peel extract. Based on comparing physical properties and in vitro release studies, F2 was selected as the best formulation. The SEM analysis showed that there are pores the indicated mangosteen peel extract will release from transdermal patches.

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CONFLICT OF INTEREST

The author declares that there are no conflicts of interest regarding the publication of this paper.

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