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Original Article

# FORMULATION AND CHARACTERIZATION OF JACKFRUIT LEAVES EXTRACT LOADED TRANSDERMAL FILMS

**DINA PERMATA WIJAYA[1*], FITRYA[1], MELLIN VERONIKA[1]**

**[1]Departement of Pharmacy, Faculty of Mathematics and Natural Sciences, Universitas Sriwijaya, Indralaya, Ogan Hilir Regency, South Sumatra, Indonesia 30862**
**Email: dinapermatawijaya@unsri.ac.id**

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**ABSTRACT**

**Objective:** The aim of the study was the preparation and characterization of the transdermal films of jackfruit leaves extract.

**Methods:** A transdermal film loaded jackfruit leaves extract was formulated with chitosan as polymer and used variation concentration of plasticizer are combination from sorbitol and glycerol. The formulation was evaluated organoleptic, stability, folding resistance, uniformity of weight and thickness, water vapor transmission rate, retention capacity, FTIR spectrum, and drug release test.

**Results:** The results of the organoleptic test showed that the film was flexible, greenish-yellow in color, and had stable physical stability in the preparation. The increase in the concentration of plasticizer also had a significant effect ($p<0.05$) on the tensile strength test, uniformity of weight and film thickness, water vapor transmission rate, and retention capacity. The results of the FTIR test showed that there was a cross-linking interaction marked by the presence of a new peak at the wavenumber of 1556.31 $cm^{-1}$. The best penetration test results are found in formula 2 with % penetration of 31.95% and J of 18.08 g $cm^{-2}$ $h^{-1}$.

**Conclusion:** All three formulas of transdermal films of jackfruit leaves extract have met the requirements and F2 showed best *in vitro* release than F1 and F3.

**Keywords:** Jackfruit leaves, Extract, Transdermal film, Glycerol, Sorbitol


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## INTRODUCTION

The skin is the largest multilayer organ that functions as protection and can be used for systemic and topical drug delivery because of its easy accessibility [1]. There are several conventional topical dosage forms such as creams, gels, and ointments that are commonly used. However, these preparations have several drawbacks, including an unattractive appearance and do not guarantee prolonged drug contact with the skin, thus requiring a repeated application, and the ointment also has an oily nature so that it can affect patient comfort [2]. Apart from that, because the skin is composed of a hydrophobic layer with the outermost layer, namely the stratum corneum in the form of keratin and dead cells that are difficult to penetrate, the delivery and penetration of drugs in conventional topical preparations have major obstacles related to their delivery and penetration. So it is necessary to develop a dosage formulation to improve aesthetic properties, compliance, patient outcomes, and improve the penetration process. One of the developments of these innovative preparations is transdermal films [3].

The transdermal film itself must have appropriate characteristics and high stability. Transdermal films must have durable, flexible, pliable, and elastic properties [4]. And easy to use without causing any trauma during replacement. Efforts to improve the mechanical properties of the transdermal film can be achieved by adding plasticizers to the transdermal film formulation [5]. The plasticizer is one of the important excipients in film formulations, which, when added to other materials, can change the physical properties of the material. The addition of plasticizers can reduce intermolecular hydrogen bonds between polymers or intermolecular strength (overcome the brittle nature of the film), increase film flexibility, play a role in reducing the transition glass temperature (Tg) of the polymer film formed and play a role in increasing the drug release profile [2]. One of the commonly used plasticizers in the polyol group, namely sorbitol and glycerol. The use of a combination of sorbitol and glycerol can produce films with medium mechanical, viscoelastic, and water vapor permeability properties compared to the use of either one alone [6]. The combination of glycerol and sorbitol (1:1) at a concentration of 60-80% showed good film characteristics [7]. The combination of sorbitol and glycerol in a ratio of 1:1 also showed films with greater stability at nine months of storage [8]. The transdermal film itself has been widely applied in drug delivery systems with various biological activities, one of which is wound healing therapy [9]. The use of transdermal films can be aimed at second-degree healing wounds, where the wound has damaged the epidermis and has reached the upper part of the dermis. The open wound has ranked the 3rd highest proportion of types of injury in Indonesia [10]. So it is necessary to do wound care management to improve healing and reduce the risk of infection in open wounds [11].

One of the plants that can be used for this activity is jackfruit. Almost all parts of the jackfruit plant can be used as traditional medicine [12]. One of them is jackfruit leaves (*Artocarpus heterophyllus* Lamk.) which can be used to treat fever, ulcers, wounds, and several types of skin diseases, especially *Staphylococcus aureus* as a natural pathogenic bacteria [13]. Based on the description above, in this study, jackfruit leaf extract will be used as an active substance in the formulation of transdermal preparations using sorbitol and glycerol plasticizers in a 1:1 ratio with 3 different concentrations.

## MATERIALS AND METHODS

### Plant material

The plant material used for the study was leaves of the jackfruit (*Artocarpus heterophyllus* Lamk.) obtained from Timbangan Village, Indralaya, Ogan Ilir, South Sumatera, Indonesia. The jackfruit leaves were determined at the Purwodadi Botanical Gardens Plant Conservation Center, LIPI, East Java.

### Chemical and reagent

Chitosan with a deacetylation degree>85% was purchased from CV. Chi Multiguna, Indonesia, sodium tripolyphosphate (STPP) (Sigma Aldrich, Germany), quercetin (Sigma Aldrich, Germany), sodium hydroxide (NaOH) (Merck, Germany), lactic acid (Merck, Germany), glycerol (Sigma Aldrich, Germany), sorbitol (Sigma Aldrich, Germany), ethanol 96% (PT. Bratachem, Indonesia), aqua dest (PT. Bratacem, Indonesia), cellophane membrane.

**The extraction of jackfruit leaves (*Artocarpus heterophyllus* Lamk.)**

The material was weighed as much as 640 g and put into a maceration container, then added 3 L of 96 % ethanol solvent. The maceration container was closed and stored for 2 x 24 h in a place protected from direct sunlight while stirring occasionally. Then filtered and separated between the dregs and the filtrate. Perform remaceration by adding 2 L of 96 % ethanol into the container containing the dregs. Close and re-store 2 x 24 h. Perform remaceration again with 2 L of ethanol. Furthermore, the ethanol filtrate obtained was collected and the liquid filter was evaporated using a rotary evaporator at a temperature of 55 ˚C to obtain a thick ethanol extract [14].

**Preparation of transdermal film**

Formulation of transdermal film of jackfruit leaves extracts in table 1. The 25 ml of 1% chitosan solution was put into a beaker, then stirred using a magnetic stirrer and this stirring was carried out continuously during the filmmaking process. After that, 0.1% NaTPP solution was added to the chitosan solution using a 30 ml burette, then 0.1 N NaOH was added to the mixture and the pH was checked with the help of a pH meter repeatedly until pH 5. Then 8.6 grams were added. Extract that has been dissolved with a little 70% ethanol into the mixture, then stirred until homogeneous. Then added, plasticizer glycerol and sorbitol in a ratio of 1:1 according to the variation of concentration of F1 (60%) F2 (80%) and F3 (100%) v/w of the dry weight of chitosan. Then, 1 ml of propylene glycol was added as a penetration enhancer. Then the mixture was poured into a petri dish with a diameter of 5.5 cm (after the bubbles were removed) and put in an oven at 60 °C for 40 h. Then the film preparations were stored in an airtight container containing silica for 4 d (constant weight was achieved).

**Table 1: Formulation of transdermal films contain jackfruit leaves extract**

| Ingredients | Amount of ingredients in the formula (ml) | | |
|---|---|---|---|
| | F1 | F2 | F3 |
| Chitosan solution 1% | 25 | 25 | 25 |
| NaTTP solution 0,1% | 30 | 30 | 30 |
| Propylene glycol | 1 | 1 | 1 |
| Glycerol | 0.4 | 0.6 | 0.8 |
| Sorbitol | 0.4 | 0.6 | 0.8 |
| Jackfruit Extract | 37.5 mg | 37.5 mg | 37.5 mg |

**Characterization of formulation transdermal films**

**Organoleptic**

The organoleptic examination was carried out by physical observation on the film, including testing the shape, color, and smell of the film [15].

**Physical stability**

All film samples were stored in sealed containers with silica for 3 w. Evaluation of the physical stability test on this transdermal film was observed how the visual condition of the film during storage for 3 w [7].

**Film folding resistance**

The folding resistance test on the film is carried out by repeatedly folding the film in the same place until the film breaks. Film folding is done up to 300 times. The number of times the film can be folded in the same place without stopping is the value of the folding resistance of the film [16].

**Tensile strength and elongation**

Tensile strength and elongation test were carried out on 5 samples of the film by using a Clipping test to find out how much the tensile strength and elongation results of the transdermal film preparation were obtained. Elongation testing is done by comparing the increase in length produced by the film with the length of the film before testing. Tensile strength and elongation can be calculated by the formulas of equations 1 and 2:

$$\sigma = \frac{F\ maks}{A} \ldots\ldots (1)$$

Description: Σ: Tensile strength (N/mm$^2$)

$F_{max}$: interactive tempo style (N)

A: sample cross-sectional area (m$^2$)

$$\sum = \frac{L}{L0} \text{x } 100\% \ldots\ldots (2)$$

Description: ∑: elongation (%)

L: (L− $L_0$) increase in length (mm)

$L_0$: original length (mm)

**Uniformity of film weight and thickness**

The thickness of the transdermal film was measured by taking 10 sheets of the resulting film then weighed one by one with an analytical balance and the thickness of the film was measured using a digimatic micrometer (Mitutoyo Corporation, Japan) at nine points on each film [17]. The average value and standard deviation of the weight and thickness of the film were calculated.

**Transition rate of water vapor**

The water vapor transmission rate test was carried out by following the modified procedure [18]; namely, a brown bottle containing 30 g of silica (RH 0%, water vapor pressure 0 kPa) was covered with the film under test and then placed in a desiccator containing aqua dest. The ambient temperature is set at 25±1 °C and relative humidity is 90%±5% in a desiccator. The initial weight of the bottle was calculated after all samples were in the desiccator for 24 h with the ambient temperature and relative humidity. The weight gain of bottles was measured every 3 d for 9 d (until a constant rate of weight gain was obtained by linear regression r =±0.9999) [7]. The water vapor transmission rate is calculated by equation 3 [18]:

$$\text{WVTR (g/m}^2\text{. Days)} = \frac{\Delta w}{A \times \Delta t} \ldots (3)$$

Note: w: difference in weight of water absorbed in the bottle over time

A: surface area of the film tested (m$^2$)

Δt: time of weight change (days)

**Water retention capacity**

This test was carried out by developing the film in a 7.4 phosphate buffer solution for 24 h. When the film has expanded, it will be centrifuged at 4000 rpm for 5 min to remove excess water and then weighed. This weight is considered the wet weight of the film (W1). Next, the film was dried in an oven at 105 °C until a constant weight was reached. The dry film was weighed and considered as dry weight (W0). The water retention capacity of the film is calculated by equation 4:

$$\%\text{Water Retention Capacity} = \frac{W1-W0}{Wo} x\ 100\% \ldots\ldots\ldots (4)$$

Note: W1: film weight when wet

$W_0$: film weight when dry [19].

**FTIR analysis**

FTIR analysis was performed by taking a transdermal film preparation which was then placed in an infrared spectroscopic sample holder and

scanned from a wave number of 4000–500 $cm^{-1}$. The spectrum obtained will then be analyzed using origin pro 8.5.1 [20].

***In vitro* release**

**Calibration curve**

The quercetin calibration curve was made by weighing as much as 5 mg of quercetin into a 5 ml volumetric flask, then dissolved with an ethanol solvent to the mark of 5 ml. So that obtained the mother liquor with a concentration of 1000 ppm. The 1000 ppm mother liquor was then taken as much as 2.5 ml and dissolved into ethanol solvent up to 25 ml (100 ppm) in a 25 ml volumetric flask. The standard curve solution will be made in several series of dilutions, namely 20, 30, 40, 50, and 60 ppm. A total of 1.5 ml of each solution concentration was added with 0.1 ml of 10% $AlCl_3$ and 0.1 ml of sodium acetate, then 5 ml of distilled water was added [21]. The measurement of the absorbance of the standard solution was carried out at a wavelength of 400–800 nm using a UV-Vis spectrophotometer.

***In vitro* release of transdermal films containing jackfruit leaves extract**

*In vitro* testing was carried out using the flow-through method through a modification of the Franz diffusion cell, which consisted of a diffusion cell, peristaltic pump, stirrer, beaker, receptor holding water bath, thermometer, and 4 mm diameter hose. The preparation was placed on a membrane impregnated with spangler fluid and allowed to diffuse for 3 h at 37±1 ˚C using 330 ml of receptor fluid. The membrane used was cellophane and the liquid used was phosphate buffer pH 7.4.

During the diffusion process, the liquid is taken as much as 3 ml at a certain time. Each intake was replaced with 3 ml of 7.4 phosphate buffer solution. Sampling was carried out at 5, 10, 15, 30, 45, 60, 90, 120, and 180 min. After that, 0.1 ml of 10 % $AlCl_3$ and 0.1 ml of sodium acetate were added from each solution concentration. Aqua dest ad 5 ml. After that 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 [21, 22].

The measurement of levels made can be corrected by the Wurster equation [23]. The Wurster formula can be seen through equation 5 as follows:

$$Q = \frac{CnV + \sum_{i=1}^{n-1} Ci.S}{A} \quad \ldots\ldots\ldots\ldots\ldots\ldots (5)$$

Note:

Q: Cumulative amount of jackfruit leaf extract per diffusion area (µg/$cm^2$)

Cn: Concentration of jackfruit leaf extract (µg/$cm^2$) at the nth minute sampling

V: Franz diffusion cell volume (ml)

$\sum_{i=1}^{n-1} Ci$: Total concentration of ethanol extract in the first sampling (minutes to (n-q) until before the nth minute)

S: Sampling volume

A: The membrane area ($cm^2$).

**RESULTS AND DISCUSSION**

**Plant determination**

Based on determination letter No: 792/IPH.06/HM/VIII/2019, the result of the determination shows that the Latin name of the jackfruit leaf is *Artocarpus heterophyllus* Lmk. With family Moraceae. The determination jackfruit was carried out at the Purwodadi Botanical Gardens Plat Conservation Center, LIPI, East Java. Determination aims to ensure the identity of the plants used.

**Extraction**

A total of 640 grams of Simplicia sample powder that has been macerated obtained as much as 109.25 grams of an extract with a yield of 17.07%. The higher the percentage yield obtained, the better the extraction method chosen.

**Table 2: Characterization of jackfruit leaf extract on transdermal films**

| Characterization | F1 | F2 | F3 |
|---|---|---|---|
| Folding resistance | >300 | >300 | >300 |
| Tensile strength ($N/m^2$) | 6.54±0.196 | 5.74±0.269 | 4.80±0.317 |
| Elongation (%) | 112.63±0.321 | 131.27±0.383 | 137.77±0.508 |
| Thickness (mm) | 0.082±0.001 | 0.085±0.001 | 0.087±0.001 |
| Uniformity of weight (mg) | 299.44±0.882 | 349±3.333 | 399.33±1 |
| Water vapor transmission rate ($g/m^2$. day) | 718.31±4.695 | 732±4.695 | 741.78±4.695 |
| Water retention capacity (%) | 693.73±12.547 | 676.36±8.104 | 620.03±4.848 |

Data was given in mean+SD, n = 3

**Organoleptic**

The organoleptic of transdermal film preparations with jackfruit leaf extract showed the same results in all three formulas, which had a thin and flexible film shape, greenish-yellow color, and a distinctive smell. The resulting film can be thin and flexible due to the process of evaporation of water due to heating to reduce the volume of the film-forming liquid. Furthermore, the film-forming liquid will continue to evaporate, which results in a change in the shape of the particles because the polymer particles will be close to each other. Then the polymer chains diffuse to each other to form strong and stable bonds [8]. While the film can be flexible due to the use of plasticizers. That increasing the use of plasticizer concentration in the formula can reduce chain interactions between biopolymers so that the resulting film can be more elastic [7]. The organoleptic of transdermal films of jackfruit extract is shown in fig. 1.

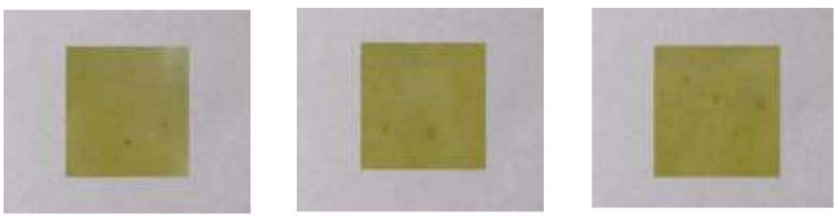


**Fig. 1: Transdermal films of jackfruit leaves extract (a) F1 (b) F2 (c) F3**

**Physical stability**

The stability film preparations aim to determine whether or not there are changes that occur in the preparation during storage. This stability test was carried out by comparing the visual film at the beginning of storage to 3 w of storage. The film produced produces a preparation with a thin and flexible shape and has a greenish-yellow color. In the transdermal film deviation time for 3 w, the film showed a stable dosage form with film properties that remained flexible and there was no color change in the film.

The results of this stability test following the results of the study reported where the combination of plasticizers of glycerol and sorbitol 1:1 in the manufacture of films can increase the stability of the film compared to using plasticizers of sorbitol and glycerol separately [8]. However, in the third formula, with a concentration of 100% plasticizer, the film preparation became wetter during 3 w of storage when compared to the other two formulas. The use of larger glycerol in the formula can result in a transfer from the glycerol plasticizer to the surface of the film preparation so that the preparation can become wetter [8].

The stability of transdermal film preparations is strongly influenced by the moisture conditions of the film itself. The moister the film preparation, the worse the stability of the preparation. Film conditions that are too moist can increase the risk of microorganism contamination [24]. So that if the preparation is stored for a long time, the stability of the film preparation can decrease.

**Film folding resistance**

The film folding resistance test is defined as the number of folds of film that are successfully folded on the film in the same place until the film breaks. This test was conducted to determine the maximum strength of the film in overcoming the applied pressure. The results of the folding resistance of the film are strongly influenced by the type of plasticizer used in the transdermal film formulation. Plasticizer serves to reduce hydrogen bonds in the polymer structure to create a film that is flexible and not easily broken.

The use of a 1:1 combination of glycerol and sorbitol plasticizers into the preparation of transdermal films of jackfruit leaf extract (*Artocarpus heterophyllus* Lamk) resulted in films with good folding resistance in each formula. Whereat each concentration of plasticizer in F1, F2, and F3 the film folding resistance exceeds the specified requirements, which is more than 300 times shown in table 2. This can be seen during the film folding test; the number of film folds reached more than 300 times, with the film still in good condition or not damaged.

The results of testing the folding resistance of the jackfruit leaf extract (*Artocarpus heterophyllus* Lamk) where the folding resistance of the film using the active substance asiaticoside with the plasticizer of sorbitol and glycerol at a ratio of 1:1 also resulted in folding>300 folds [25].

**Tensile strength and elongation**

Tensile strength is defined as the maximum tensile force that the film can achieve per unit surface area of the film to be able to stretch or elongate until the film is torn or broken. While elongation (elongation at break) is defined as the percentage change between the initial length and the final length of the film when the film is pulled to break. Tensile strength is a value that can determine the strength of the transdermal film, where the greater the tensile strength value, the better the film will withstand mechanical stress. While elongation is a value that determines the level of elasticity of the film, where the greater the value of elongation at break, the film has good elasticity.

Testing the tensile strength and elongation of this film is very important because the film that will be used as a wound dressing must have flexible, elastic, or flexible properties. It is intended that the transdermal film as a wound cover can follow body movements that have different contours, especially around joints such as the knee. So that in its use, the film does not cause new trauma or damage to the area where the wound occurred. Testing the tensile strength and elongation of the transdermal film preparation of jackfruit leaf extract resulted in different strengths in each formula.

The results of the one-way ANOVA analysis showed that the tensile strength of the jackfruit leaf ethanol extract film yielded a significant value<0.05, and the elongation at break also resulted in a significant value>0.05. This shows that there is a significant effect on increasing the concentration of plasticizers used in the formula.

The increase in the concentration of plasticizer can cause the tensile strength of the film to be lower, but the elongation (elongation at break) will be higher. The highest tensile strength value was found in the transdermal film with a concentration of 60%, namely 6.54 Mpa±0.196, while the highest elongation value was found in the film with a concentration of 100%, which was 137.77%±0.508. Meanwhile, the lowest tensile strength value was found in the transdermal film with a concentration of 100%, which was 4.80 Mpa±0.317, while the lowest elongation value was found in the film with a concentration of 60%, which was 112.63%±0.285. This is because the plasticizer can reduce the energy in a molecular movement so that it reduces the stiffness and the tensile strength value also decreases, but the elongation value can increase at the break.

Increasing the concentration of plasticizers can result in reduced intermolecular attractive forces during the evaporation of water. This can cause the resistance to mechanical treatment of the film to decrease [26]. The flexibility of the film will increase, but the tensile strength will decrease as the concentration of the plasticizer increases; this is because the plasticizer can hydrogen bond with the polymer in the film preparation [26]. The higher the use of plasticizers will cause the bond to become more tenuous. Based on this, the resulting film will be softer, pliable, and flexible with the tensile strength value that tends to decrease.

**Uniformity of weight and thickness**

The uniformity test of film weight and thickness serves to determine variations in weight and thickness of the resulting film preparation. It is important to test the weight uniformity to evaluate the preparation process. The process of making a good preparation will produce a relatively uniform preparation so that the dosage of the active substance will also be uniform in the preparation. Uniformity of the dose of the active substance in preparation is very important to achieve a therapeutic effect. While testing the thickness of the film is important because the thickness of the film can affect the diffusion process on the penetration of the active substance in the transdermal film preparation.

The results of the weight uniformity test on each formula showed films with uniform weights. This is indicated by the small CV value on weight uniformity, which is<5% (attachment 8.5). For the films with CV values <5% in the weight uniformity test, then the process carried out to produce the film is appropriate, and the film has met good weight uniformity.

Thickness tests were also carried out on films of the same size (2x2 cm) and measured at nine different points on the film. The increase in the concentration of plasticizer used, it will produce thicker preparations. This is because the higher the concentration of plasticizer, the total solids in the solution will increase. The highest value of film thickness is found in formula 3 with a plasticizer concentration of 100%, which is 0.087 mm±0.001, while the lowest film thickness value is found at 60% plasticizer concentration, which is 0.082 mm±0.001.

**Water vapor transmission rate**

The water vapor transmission rate is defined as the amount of moisture lost per unit time divided by the surface area of the test film. The rate of water vapor transmission is one of the important evaluations that must be carried out on wound healing films. Where the ideal wound healing film should be able to control the moisture lost from the wound optimally. Water vapor lost from the skin normally ranges from 700-1220 g/m$^2$ per day and for injured skin, the moisture loss ranges from 800-1300 g/m$^2$ per day, while for third-degree burns, the water vapor lost can reach 10000 g/m$^2$ per day in granulation wounds [7]. The normal temperature of 35℃ the rate of water loss for normal skin is 204±12 g/m$^2$ per day; for skin with wounds, it is 279±26 g/m$^2$ per day, and for skin with deep burns. one was 5138±202 g/m$^2$ per day in granulation wounds [27].

The results of the test showed that the increase in the concentration of the plasticizer used, the water vapor transmission rate also

increased. This is because the amount of plasticizer concentration can cause mobility and flexibility in the polymer structure of the film, which makes the polymer structure modified to a loose structure. As a result, the matrix of the film will decrease, causing the value of the water vapor transmission rate to increase. Meanwhile, at a lower concentration of plasticizer, the polymer structure produced from the film becomes denser and more compact, so the value of the water vapor transmission rate will be lower. There is no ideal water vapor transmission rate value [7]. However, the value of the water vapor transmission rate should not be too low because it can cause a buildup of wound exudate so that it can slow down the wound healing process and increase the risk of bacterial growth in the wound area. However, the water vapor transmission value should also not be too high, which can cause the wound to become dehydrated. The results of the one-way Anova test obtained a significant value <0.05. This shows that there is a significant effect on increasing the concentration of plasticizers used in the formula.

**Water retention capacity**

Water retention capacity is defined as the maximum amount of liquid that can be absorbed and retained by the film as a percentage [7]. There is an increase in the percentage of the amount of liquid that can be absorbed by the film with an increase in the concentration of plasticizer. This is because the increase in the use of plasticizers (sorbitol: glycerol) can increase the presence of OH groups in the film preparation, which makes the film hydrophilic so that the film with a higher concentration of plasticizer can bind water better in the transdermal film preparation. The highest absorption value of the amount of liquid is found in formula 3 with a plasticizer concentration of 100%, which is 693.74±12.55, while the lowest liquid absorption value is found in formula 1 with a plasticizer concentration of 60%, which is 620.03±4.45. However, for the three formulas, it has been shown that the film can absorb large amounts of exudate.

The liquid absorption process carried out by this film preparation aims to be able to absorb exudate, especially in wet wounds. This is intended to prevent the accumulation of exudate in the wound, which can cause bacterial proliferation so that it can cause a foul odor in the infected wound. The value of water retention capacity in wound dressing films is not specific. Where everything is adjusted for the function and purpose of the use of the wound cover film [7].

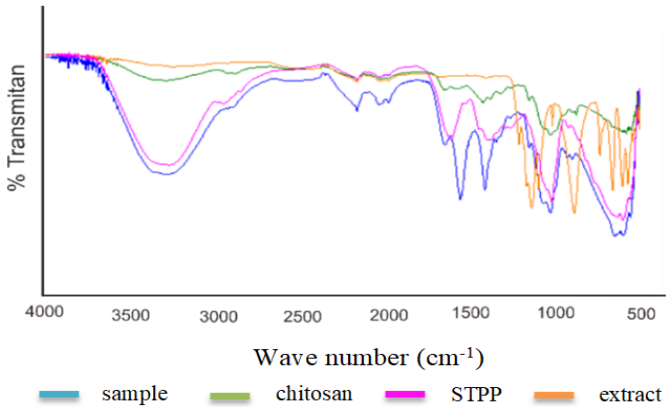


**Fig. 2: FTIR spectrum analysis**

Based on the analysis carried out with FTIR spectrum results (fig. 2) were obtained wherein each formula it was seen that there was a cross-linkage between chitosan-tripolyphosphate which was indicated by the presence of a peak in the wavenumber area of 1550-1640 $cm^{-1}$. This indicates the presence of an N-H group for the primary amine obtained from chitosan. In addition, in the chitosan-tripolyphosphate cross-linking of each sample, there is a peak indicating the presence of a phosphate group obtained from sodium tripolyphosphate. In the comparison of pure sodium tripolyphosphate, the possibility of a phosphate group is present, which is indicated by the presence of a peak at a wavenumber of 1135.87 $cm^{-1}$. However, in the IR spectrum of each formula, this phosphate group produces a non-sharp peak. This is because the phosphate group only acts as an impurity that does not interact in the chitosan-tripolyphosphate cross-link.

The results of the IR spectrum measurement on pure chitosan showed the presence of an OH group which was marked by the presence of a peak at a wavenumber of 3287.76 $cm^{-1}$. This is because, chitosan is a poly (N-amino-2 deoxy-D-glucopyranose) compound characterized by the presence of OH groups, $NH_2$ groups, C=O amide groups, and $CH_3$ groups. The transdermal film preparation is also known to have a hydroxide (OH) group, which is indicated by the presence of a peak at a wavenumber of 3284.09 $cm^{-1}$. The presence of a hydroxy group (OH) in the spectrum of this transdermal film preparation is thought to be obtained from the flavonoid compounds contained in jackfruit leaf extract, where flavonoids are phenolic compounds. This can be seen in the comparative spectrum of the jackfruit leaf ethanol extract, where the IR spectrum results indicate the presence of the OH group of the alcohol bound to the aliphatic and aromatic groups. This is evidenced by the presence of a peak at wave number 3271.08 $cm^{-1}$ in the IR spectrum.

The presence of the OH functional group band in the transdermal film preparation is known to be very wide, so it is suspected that the $NH_2$ group of chitosan in the preparation after the film is formed can be covered. The IR spectrum band of the OH functional group between pure chitosan and transdermal film samples is also known to experience a wavenumber shift. In pure chitosan, the peak of OH was present at a wavenumber of 3287.76 $cm^{-1}$ while in the transdermal film sample, the peak was present at a wavenumber of 3277.37 $cm^{-1}$. This could be due to the addition of plasticizers, namely sorbitol and glycerol. Based on this, it can be identified that in the matrix system of transdermal film preparations, there has been the formation of new bonds between chitosan and the plasticizers of sorbitol and glycerol so that the OH bonds in the chitosan polymer chain become weak. From the results of the FTIR analysis, it was found that in the process of making transdermal film preparations, a physical mixing process occurred, marked by the presence of hydrogen interactions between chains.

***In vitro* release**

Based on the test results, the cumulative amount of penetrated jackfruit leaf ethanol extract reached >20% after 3 h for formulas F1, F2, and F3. While the ethanol extract as a comparison after penetration testing, the cumulative percent value was only 12.89% after 3 h. This indicates that the penetration process of the active substance is better in the dosage form compared to the direct extract, which is applied to the membrane. The *in vitro* release study of transdermal films of jackfruit extract showed in table 3.

**Table 3: *In vitro* release study**

| Formula | The cumulative amount (µg/ml) | % Cumulative |
|---|---|---|
| Extract | 77.79±0.492 | 12.89±0.082 |
| FI | 155.27±0.565 | 25.72±0.094 |
| FII | 192.88±0.881 | 31.95±0.146 |
| FIII | 182.24±1.485 | 30.21±0.246 |

Data was given in mean+SD, n = 3

The factor that determines the success of the penetration of the active substance is very dependent on the ability of the active substance to be separated from the polymer. The mechanism of the penetration process of the film preparation itself is related to the ability of the film preparation to be able to bind water to the environment around the skin so that the film can swell and cause the active substances contained in the film to penetrate through the skin to the target to produce a therapeutic effect. In this study, a polymer, namely chitosan, was used, which is a hydrophilic polymer, and the plasticizers used, namely sorbitol and glycerol, are also hydrophilic. The use of these hydrophilic materials will lead to better water binding in the environment around the skin so that the film preparation can be maximized in the swelling and release process.

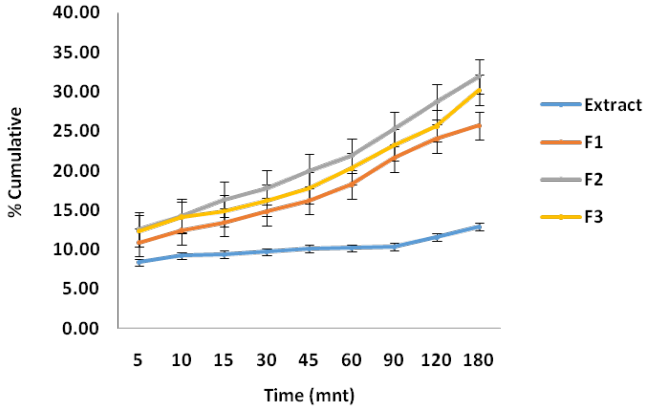


**Fig. 3: %cumulative of jackfruit leaves extract to a penetration**

The penetration process of this film preparation is also assisted by the penetration enhancer, namely propylene glycol. The use of this penetration enhancer can increase the hydration effect on the skin, which causes the outermost layer of skin, namely the stratum corneum, which consists of keratin cells and dead skin, to soften so that the active substances in the preparation can penetrate the skin. Based on the data from the penetration test results that have been carried out, the cumulative percentage of jackfruit leaf extract that penetrated the highest was found in formula 2 with a plasticizer concentration of 80% (cumulative percentage 31.95% within 3 h). This is because the process of releasing the active substance can be influenced by the use of plasticizers, where an increase in the concentration of plasticizers will be directly proportional to the percentage of the cumulative amount of extract that can be penetrated. Plasticizers can bond with polymers through hydrogen bonds, which will cause the polymer structure to become looser. This makes the penetration process easier. Accumulative percent graph of transdermal films of jackfruit extract shown in fig. 3.

However, in formula 3, with a concentration of 100% plasticizer, the percentage of active substances penetrated is smaller than that of formula 2, which is a cumulative percentage of 30.21% within 3 h. This is due to the thickness of the film. Where the thicker the film, the more difficult the penetration process. It is known that formula 3 has a higher film thickness value than formula 2. While the cumulative percentage value of the lowest penetrated jackfruit leaf extract is found in formula 1 with a plasticizer concentration of 60% (25.72% cumulative percentage within 3 h). This is influenced by the density of the polymer structure and the concentration of the plasticizer used. The tighter the structural bonds of the polymer, the more difficult it is for the active substance to penetrate the membrane. The cumulative percentage of each formula still shows a graph that continues to increase, where the cumulative percentage released will also continue to increase.

The penetration process on the cellophane membrane will go through the transcellular penetration route, namely by hydrating the outermost layer of the skin very high so that the environment will be very watery. This will cause the keratin cells to be disrupted in their structure. So that the hydrophilic drugs will be able to pass through this penetration pathway. The penetration mechanism that occurs in this film preparation occurs when the film experiences swelling due to the use of hydrophilic polymers. So that the film will expand, then the active substance will be released from the preparation and will penetrate through the pores of this cellophane membrane. Statistical test results showed that the value of drug release flux in each formula was not significant ($p>0.05$).

## CONCLUSION

All three formulas of transdermal films of jackfruit leaves extract have met the requirements and F2 showed the best *in vitro* release than F1 and F3.

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## AUTHORS CONTRIBUTIONS

All the authors have contributes equally.

## CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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