Chempublish Journal
Journal Homepage: online-journal.unja.ac.id/chp
Department of Chemistry
Faculty of Science and Technology
Universitas Jambi
ISSN (Online): ISSN 2503-4588
No. 23/E/KPT/2019

Article

Characterization and In Vivo Evaluation of Durian Peel Extract in Nanoliposome Transdermal Patch for Wound Healing

Nindita Clourisa Amaris Susanto[1*], Milkazia Elda Putri[1], Dayinta Tyas Utami[1], Dian Eka Ermawati[1], Heru Sasongko[1], Sholichah Rohmani[1] Anif Nur Artanti[1], Diyah Tri Utami[1], M. Fiqri Zulpadly Mh[1], Ulfa Afrinurfadhilah Darojati[1], Annisa Diyan Meitasari[1], Meta Kartika Untari[1], Alifina Izza[2]

[1]Department of Pharmacy, Vocational School, Sebelas Maret University, Indonesia
[2]Master of Public Health, Faculty of Health, Medicine and Behavioural Science (HMBS), The University of Queensland, QLD, Australia

Abstract

Wounds are a form of continuous damage due to loss of tissue, structure and anatomical function of the skin caused by heat trauma or sharp object scratches. The prevalence of wound injury patients in Indonesia is 9.2%. One of the natural ingredients that is effective inhibiting the growth of infectious organisms is durian, especially in its peel. In this study, durian peel was formulated in liposome dosage form and applied to patch preparations. The purpose of this study was to assess the effectiveness of durian skin extract liposomes (*Durio zibethinus* Murr.) for wound healing in white rats. Durian peel (Durio zibethinus) extract was prepared by maceration using 70% ethanol and analyzed for phytochemical content and total flavonoids. The extract was formulated into liposomes using the thin-film hydration method and optimized by simplex lattice design. Liposomes were characterized and incorporated into a transdermal patch, followed by physicochemical evaluation. Wound healing activity was tested in male Wistar rats with incision wounds and observed for seven days, and the data were statistically analyzed. The results of this study are that the patches produced can provide a therapeutic effect on the healing of incision wounds in wistar strain male white rats (*Rattus norvegicus* L.) with a healing percentage on day 7th of 72.5% which is characterized by the absence of edema, bleeding, growth of fur in mice, the appearance of scabs and wound closure.

Keywords: *Antioxidant activity; Durio zibethinus; drug delivery system; flavonoid; skin regeneration.*

* Corresponding author
Email addresses: nindita_clourisa@staff.uns.ac.id (NCA Susanto)

DOI: https://doi.org/10.22437/chp.v10i1.48779
Received Octobe 05th 2025; **Accepted** May 17th 2026; **Available online** June 30th 2026
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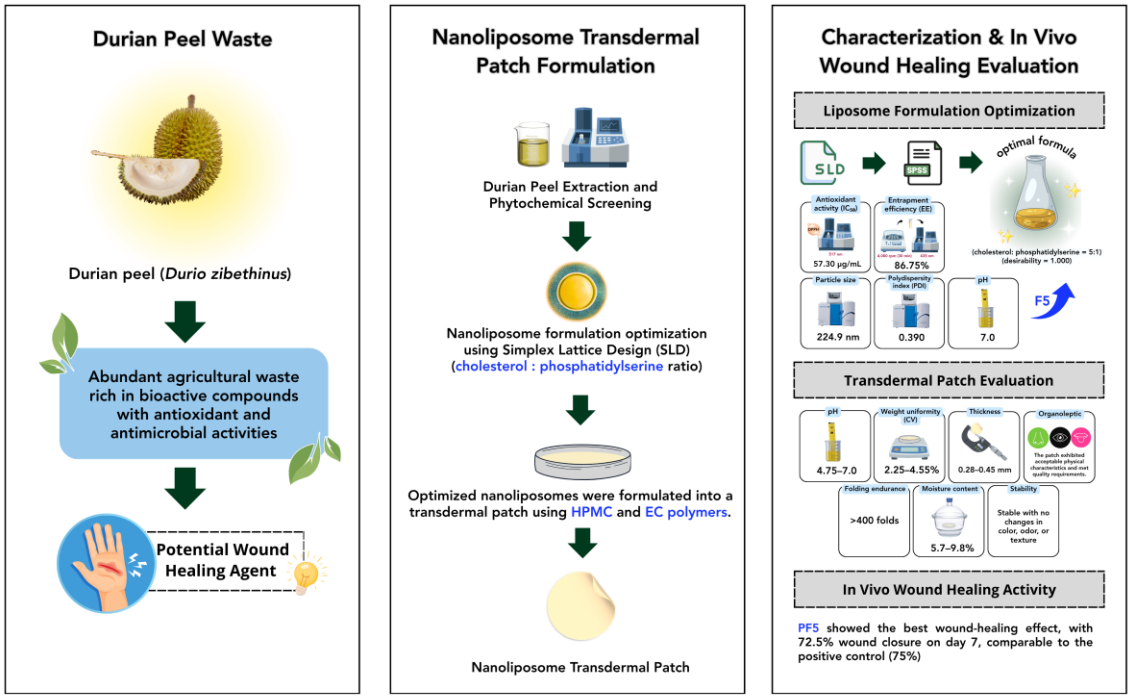
Graphical Abstract



Introduction

Wounds are a form of tissue damage characterized by the loss of skin structure and anatomical function caused by trauma such as heat exposure, mechanical injury, or sharp object scratches [1]. The prevalence of wound injuries in Indonesia is reported to be approximately 9.2%, indicating that wound management remains an important health concern. One of the most common types of wounds is incision wounds, which occur due to trauma caused by sharp objects. Proper wound management is essential to prevent infection and accelerate tissue repair. In this context, antimicrobial agents are commonly used to reduce the risk of infection, while antioxidant agents play an important role in accelerating the healing process by reducing oxidative stress and preventing further cellular damage [2].

In recent years, the use of traditional medicine has gained increasing attention as an alternative therapeutic approach. Traditional medicinal plants are widely considered safer than synthetic drugs because they generally produce fewer side effects when used appropriately [3]. In addition, many medicinal plants contain various bioactive compounds that exhibit antimicrobial, anti-inflammatory, and antioxidant activities, which are beneficial for wound healing [4], [5].

One plant that has potential as a natural therapeutic agent is durian peel (*Durio zibethinus*). Durian is widely consumed in many tropical countries, and its peel is often considered agricultural waste. However, several studies have reported that durian peel contains various bioactive compounds such as flavonoids, alkaloids, and saponins that possess antibacterial and antioxidant activities. These bioactive compounds contribute to the biological properties of durian peel and support its potential

utilization in pharmaceutical and biomedical applications [6].

Among these compounds, flavonoids play an important role as natural antioxidants. Flavonoids can neutralize free radicals and reduce oxidative stress by inhibiting the formation of reactive oxygen species (ROS), which are responsible for cellular damage and delayed wound healing. By reducing oxidative stress and inflammation, flavonoids can promote tissue regeneration and accelerate the wound healing process [7].

Although durian peel contains promising bioactive compounds, the stability of these compounds is often limited because they are sensitive to environmental factors such as light, temperature, and oxidation. These limitations may reduce the effectiveness of the active compounds during application. Therefore, an appropriate drug delivery system is required to protect the active compounds and enhance their therapeutic effectiveness.

Liposomes have been widely studied as drug delivery systems due to their ability to encapsulate bioactive compounds and improve their stability, biocompatibility, and bioavailability [8]. Liposomes are vesicular structures composed of phospholipid bilayers that can carry both hydrophilic and lipophilic compounds. Previous studies have reported that liposome formulations provide higher entrapment efficiency compared to other vesicular systems such as niosomes. For example, liposome formulations have shown an entrapment efficiency of approximately 67%, which is higher than that of niosome preparations that demonstrate around 24% entrapment efficiency [9]. In addition, liposomes can improve therapeutic effectiveness by enhancing compound stability, facilitating tissue penetration, and improving biodistribution to target sites [10].

Therefore, this study aimed to formulate durian peel (*Durio zibethinus*) extract into a liposome-based system and incorporate it into a transdermal patch preparation. The liposome formulation was characterized and evaluated for its antioxidant activity and physicochemical properties. Furthermore, the effectiveness of the liposome-based transdermal patch containing durian peel extract was evaluated in vivo for incision wound healing in white rats.

Materials and Methods

Materials

Durian peel (*Durio zibethinus*) was obtained from Karanganyar, Central Java, Indonesia. Experimental animals used in this study were male Wistar rats weighing 150–200 g obtained from Karanganyar, Central Java, Indonesia. The materials used included cholesterol (Sigma, Missouri, USA), phosphatidylserine (Nutricost, Vineyard, Utah, USA), polyvinylpyrrolidone (PVP K-30) (Nitra Kimia, Indonesia), hydroxypropyl methylcellulose (HPMC) (Sigma-Aldrich, Missouri, USA), ethyl cellulose (EC) (Sigma-Aldrich, Missouri, USA), propylene glycol (Dow Chemical Pacific, Singapore), ethanol 96%, and quercetin (Sigma, Missouri, USA).

Preparation of extract durian peel (Durio zibethinus)

The Durian peel (*Durio zibethinus*) was dried using an oven at 60℃ for 1 day, cut into small pieces and ground using a blender. Extraction was carried out by maceration method with 70% ethanol to obtain paste extract of durian peel in a ratio (1:10) in glass jar protected from direct sunlight. Maceration was done by soaking the simplisia powder in 70% ethanol solvent for

3x24 hours. The filtrate was concentrated with a waterbath at 40 ℃ to get a good yield. The paste extract was obtained by drying in an oven at 105 ℃ for 30 minutes until a constant weight was obtained [11].

Phytochemical screening

Phytochemical screening of Durian peel (*Durio zibethinus*) extract using standard procedures to reveal the presence of chemical constituents such as alkaloids, flavonoids, tannins, saponins, and triterpenoids [12].

Determination of total flavonoids content

10 mg Quercetin standard was dissolved in ethanol, to make stock solution 1000 ppm. The stock solution was diluted to 100 ppm and diluted into concentration series of 2 ppm, 4 ppm, 6 ppm, 8 ppm, and 10 ppm. Furthermore, 10 mg of extract was weighed and dissolved in ethanol using 10 mL volumetric flask. Serial solution and 1 mL of extract solution were taken, added 0.2 mL $AlCl_3$, 0.2 mL potassium acetate, 3 mL ethanol, and aquadest 10 mL. The mixture was incubated for 30 minutes at room temperature and the absorbance value was analyzed using UV-Vis spectrophotometry at a wavelength of 435 nm [13].

Preparation of liposome

The optimal formula determination in this study was used the simplex lattice design method with Design Expert software version 13. Optimization was carried out to determine which cholesterol and phosphatidylserine components produced the optimal formula. The responses measured were antioxidant activity and adsorption efficiency. Liposomes were prepared by dissolving the basic ingredients: cholesterol and phosphatidylserine dissolved with chloroform in a rotary evaporator. The phosphate solution was added for hydrating the liposome thin film at the same time as the extract was added. The resulting liposomes were homogenized into vesicles using an ultrasonic cell disruptor for 30 min [13]. The formulas used are listed in Table 1.

Evaluation and characterization of liposome

Organoleptic. The organoleptic examination was done by visual observation based on shape, color, and odour compared to the other journal studies that have been conducted.

pH test. The test was carried out by inserting the pH meter into the liposome preparation for 5 seconds. Then observe the number shown on the pH meter screen. The obtained results were compared with the pH value of topical skin preparations [14].

Antioxidant activity test

The antioxidant activity was evaluated using the DPPH free radical scavenging assay. A 1000 ppm stock solution of the extract was prepared by dissolving 10 mg of the extract in 10 mL of 96% ethanol. The stock solution was subsequently diluted to obtain working concentrations of 20, 40, 60, 80, and 100 ppm. Similarly, a 500 ppm liposome stock solution was prepared by diluting 5 mL of the liposomal formulation with 96% ethanol to the required volume, followed by serial dilution to the same concentration range (20–100 ppm). For the assay, 1 mL of each sample solution was mixed with 2 mL of 0.1 mM DPPH solution, vortexed, and incubated in the dark at room temperature for 30 min to allow the radical scavenging reaction to reach equilibrium. The absorbance was then measured at 517 nm using a UV–Vis spectrophotometer, with 96% ethanol as the blank. The percentage of DPPH radical scavenging activity was

calculated, and the IC_{50} value was determined from the linear regression of inhibition percentage against sample concentration. All measurements were performed in triplicate [15].

Characterization of particle size

Particle measurement of liposome preparation was done by taking 3 mL of liposome preparation and putting it into a cuvette. The preparation was added with aqua pro injection. The cuvette containing the sample was inserted into the PSA tool holder [16].

Entrapment efficiency (EE) test

The entrapment efficiency (EE) of the liposome preparation was carried out by separating the unabsorbed durian fruit peel extract using a centrifugator at 4,000 rpm for 30 min. The results of the separation formed supernatant and sediment. Then 1mL supernatant was diluted in 10 mL volumetric flask, and added distilled water until the limit mark. The absorbance value of the supernatant was analyzed using UV-Vis spectrophotometry at a wavelength of 435 nm [14].

Characterization of FTIR

Observation of functional groups using an infrared spectrophotometer was carried out on samples of durian peel extract, cholesterol powder, phosphatidylserine, and liposome base by inserting the sample into the FTIR instrument tube. The functional groups were identified based on the wavelength and intensity of the absorption peaks.

Table 1. Liposome formulation

Materials	Formulas				
	F1	F2	F3	F4	F5
Extract	10 mg	10 mg	10 mg	10 mg	10 mg
Cholesterol	30 mg	20 mg	40 mg	10 mg	50 mg
Phosphatidylserine	30 mg	40 mg	20 mg	50 mg	10 mg
Chloroform	10 mL	10 mL	10 mL	10 mL	10 mL
Phospate buffer	20 mL	20 mL	20 mL	20 mL	20 mL

Preparation of patch transdermal

The patch formulas used are listed in Table 2. The preparation of liposomes from *Durio zibethinus* Murr. durian peel extract was carried out using the lipid layer hydration method. The first step was to dissolve cholesterol and phosphatidylserine in an organic solvent, chloroform, then add the *Durio zibethinus* Murr. durian peel extract. The solution mixture was then evaporated using a rotary evaporator at 30℃ to obtain a thin lipid layer. After that, the lipid layer was hydrated using a phosphate buffer and evaporated again using a rotary evaporator for 15 min to form a homogeneous suspension.

Evaluation of patch transdermal

Evaluation of transdermal patch preparation includes organoleptic test, pH, weight uniformity, thickness, folding resistance, moisture content, and stability test [17].

Experimental animal preparation

Male rats of 3 months Wistar strains weighing 150-200 grams were acclimatized in individual cage for one week before incision. The characteristics of the rats were white, red eyes, elongated head and tail that exceed the body's length.

Wounding of rats

Lidocaine creams were used to anesthetize of rats to create the wound. The rat's hair was shaved on the right and left sides of its back. Wounds were made with a diameter of 1-2 cm using a biopsy punch.

Table 2. Patch formulation

Materials	Formulas					
	PF0	**PF1**	**PF2**	**PF3**	**PF4**	**PF5**
Liposome	0	5 mL Liposome F1	5 mL Liposome F2	5 mL Liposome F3	5 mL Liposome F4	5 mL Liposome F5
HPMC	2 gr	2 gr	2 gr	2 gr	2 gr	2 gr
EC	1 gr	1 gr	1 gr	1 gr	1 gr	1 gr
PG	10 mL	10 mL	10 mL	10 mL	10 mL	10 mL
Ethanol	40 mL	40 mL	40 mL	40 mL	40 mL	40 mL
Aquadest	100 mL	100 mL	100 mL	100 mL	100 mL	100 mL

Experimental design

The injured rats were divided into seven groups with three rats in each group, consisting of a negative control group, a positive control group, and five treatment groups treated with liposome patch formulations PF1, PF2, PF3, PF4, and PF5. The positive group was given povidone iodine patches and the negative group was given patches without durian peel extract liposomes. The liposomal patch treatment was applied to each mouse twice a day in the morning and evening. The patch was sized 3x3cm [18].

Observation and data collection

The wound diameter of the mice (negative, positive, and treatment: patch groups with various concentrations) was measured using a caliper on four sides of the wound by looking at the average wound diameter from the development of the wound healing process on the mice's back every three days by comparing the wound healing process of the incision. Observations were conducted from day 1 to day 7 after the wound was created. Measurements using the percentage conversion formula, the wound diameter measurements were then converted into the percentage of healing (%). The percentage of wound healing was then calculated using the percentage conversion equation 1 [18].

$$Px = \frac{d1-dx}{d1} \times 100\% \quad (1)$$

Where: Px : percentage of wound healing on day x (in %); d1 : First day wound diameter (cm); dx : wound diameter x day (cm).

Data analysis

Data were analyzed using IBM SPSS Version 26.0 Shapiro wilk method to test normality, levene test was used to test homogeneity and the respective differences in wound healing in test animals using kruskal wallis [18].

Result and Discussion

Plant determination

Determination of Durian peel (*Durio zibethinus*) conducted in laboratory of Biology Study Centre, Faculty Mathematics and Natural Sciences, Universitas Sebelas Maret, Surakarta with the certificate number of 019/UN27.9.6.4/Lab/2025 showed that the plant used was the species D. *zibethinus* Murr.

Moisture content and yield

The durian peel symplisia is brown in color, smells like durian, slightly rough texture, and has a moisture content of 5.56%, while the extract obtained has a distinctive smell of durian skin, brown color, slightly thick texture, and yield of 22.54%. Durian fruit peel (*Durio zibethinus* Murr.) used in this formulation has a good moisture content, which should not be more than 10% and the extract that has been made gets a better yield compared to the yield value using 96% ethanol solvent which produces a % yield of 16.84% [11].

Phytochemical screening

Phytochemical screening showed that the durian peel extract (*Durio zibethinus*) contained several bioactive compounds, including alkaloids, flavonoids, tannins, saponins, and triterpenoids. These results are consistent with previous studies that reported similar phytochemical constituents in durian peel extracts [12]. The presence of these compounds suggests that durian peel has significant potential for pharmaceutical and biomedical applications. Flavonoids and tannins are known for their strong antioxidant activity, which can reduce oxidative stress and support tissue regeneration during the wound healing process. Meanwhile, alkaloids and saponins exhibit antimicrobial properties that may help prevent infection in wounds. Similar phytochemical compounds have also been reported in other plant species used for wound healing, indicating that these metabolites play an important role in the therapeutic effects of medicinal plants.

Several studies have demonstrated that plant extracts rich in flavonoids and phenolic compounds show strong antioxidant and antibacterial activities, which contribute to their effectiveness in promoting wound healing. Therefore, the presence of these bioactive compounds in durian peel extract supports its potential use as a natural therapeutic agent in wound treatment.

Determination of total flavonoids content

Calibration curve measurements obtained absorbance at a concentration of 2 ppm of 0.02732; 4 ppm of 0.06026; 6 ppm of 0.07144; 8 ppm of 0.10358; and 10 ppm of 0.1336. These results obtained a linear regression equation $y = 0.0256x + 0.0024$ with a correlation coefficient value of R^2 = 0.9824. The determination of total flavonoid content showed that the durian peel extract at a concentration of 1000 ppm produced an absorbance value of 0.19458 with a flavonoid content of 7.5072 % w/w QE (Quercetin Equivalent). This result indicates that durian peel extract contains a moderate level of flavonoid compounds. Flavonoids are well known as important bioactive compounds that contribute to antioxidant activity, which plays a significant role in protecting cells from oxidative stress.

The presence of flavonoids in plant extracts is often associated with their ability to scavenge free radicals and enhance tissue repair processes during wound healing.

Several studies have reported that durian peel contains phenolic and flavonoid compounds that contribute to its antioxidant properties. Previous research also showed that plant extracts with higher flavonoid content generally exhibit stronger antioxidant activity and better biological activity in wound healing applications. Although the flavonoid content obtained in this study can be categorized as moderate compared to some medicinal plants with higher phenolic levels, it still indicates that durian peel has promising biological activity. Variations in flavonoid levels may occur due to differences in extraction methods, solvent type, plant maturity, and environmental conditions.

The presence of flavonoids in durian peel extract suggests its potential application as a natural antioxidant source in pharmaceutical and biomedical fields. In the context of wound healing, flavonoids can promote tissue regeneration by reducing oxidative stress, stimulating fibroblast proliferation, and enhancing collagen synthesis. Therefore, the flavonoid content detected in durian peel extract supports its potential development as an active ingredient in topical formulations such as liposome-based transdermal patches for wound treatment.

Optimization, evaluation and characterization of liposome

The running result obtained are as in the table 3. Formula optimization was performed using the simplex lattice design method. This method was chosen because it requires fewer experiments, and minimizing material usage. The simplex lattice design method can optimize the formula for various different amounts of material composition, with the total being kept the same [16]. The test results show that the two variables indicate a significant response ($P<0.5$) to the optimal antioxidant and EE values obtained in Table 4. The prediction of the optimal formula for this liposome preparation was performed using Design Expert version 13 software with Simplex Lattice Design. Based on the analysis of the software, the desirability value of the predicted optimal formula can be seen in Table 5. The desirability value indicates the achievement of a model used against the expected target, with a value ranging from 0 to 1. The closer the desirability value is to one, the more optimal the result. From the experimental results, a desirability value of 1.000 was obtained with a cholesterol to phosphatidylserine ratio of 5:1.

Table 3. Results of running the simplex lattice design method

Std	Run	Cholesterol	Phosphatidylserine
5	1	20	40
4	2	40	20
1	3	50	10
3	4	30	30
2	5	10	50

Table 4. Results of the anova *simplex lattice design* on the results of the formula experiment

The results of ANOVA			Fit statistic			
Parameter	**p-Value**	**Significance**	R^2	**Adjusted R^2**	**R^2 adjusted R^2**	**Adeq Precision**
Antioxidant	<0.0001	Significant	0.9999	0.9998	N/A	252.2996
EE	<0.0001	Significant	0.9993	0.9991	N/A	184.6367

The results of the liposome antioxidant activity test (can be seen in Table 5) show different IC_{50} values for each formula. The addition of cholesterol at a certain concentration can increase the encapsulation efficiency of active substances and reduce leakage in the liposome bilayer membrane so that the bioavailability of antioxidants also increases. In addition, formulating extracts in liposome preparations can increase their antioxidant activity because the liposome properties tend to be stable so that the encapsulated active substances can be optimally targeted [19]. Based on the cholesterol content of each formula, formula 5:1 was obtained with the strongest antioxidant at a cholesterol level of 83.33%. The comparison used was ascorbic acid solution with an IC_{50} value of 13.14 ppm and durian fruit peel extract produced an IC_{50} value of 115.57 ppm, because ascorbic acid is able to donate hydrogen atoms and react preferentially with radicals to produce ascorbyl free radicals which are relatively more stable [20].

Table 5. Formula recommendations based on *Design Expert* software

No	**Cholesterol**	**Phosphatidylserine**	**Antioxidant**	**EE**	***Desirability***
1	50	10	57,3	86.8897	1,000

Table 6. Evaluation of organoleptic, pH, IC_{50}, particle size analyzer, polydispersity index, and entrapment efficiency

Formulas	**Evaluation Test**					
	Organoleptic	**pH**	**IC_{50} (µg/mL)**	**Size (nm)**	**PDI**	**EE (%)**
F1	Liquid, yellowish-white color, characteristic odor of phosphatidylserine	7.49	59.59	218.7	0.381	68.624
F2	Liquid, yellowish-white color, characteristic odor of	7.15	108.89	216.1	0.178	58.469

Formulas	Evaluation Test					
	Organoleptic	pH	IC_{50} (µg/mL)	Size (nm)	PDI	EE (%)
	phosphatidylserine					
F3	Liquid, yellowish-white color, characteristic odor of phosphatidylserine	7.10	58.52	223.9	0.389	76.082
F4	Liquid, yellowish-white color, characteristic odor of phosphatidylserine	7.24	112.49	217.6	0.165	30.206
F5	Liquid, yellowish-white color, characteristic odor of phosphatidylserine	7.41	57.30	224.9	0.390	86.754

The prepared liposomes exhibited a milky-white appearance with a slight yellowish tint, a liquid consistency, and a characteristic odor of phosphatidylserine powder, consistent with previous reports [14]. As presented in Table 6, the particle size of all formulations ranged within the Large Unilamellar Vesicles (LUVs) category (100–1000 nm). Liposomes with particle sizes between 100 and 300 nm are considered particularly suitable for cosmetic applications and topical drug delivery systems because they facilitate enhanced skin penetration while maintaining formulation stability. Among the formulations, Formula 3 exhibited the lowest polydispersity index (PDI), indicating the most homogeneous particle size distribution. A PDI value approaching 0 reflects a narrow and uniform particle size distribution, whereas values greater than 0.7 indicate a highly heterogeneous population of vesicles [16]. A low PDI is desirable because it contributes to improved physical stability, reproducibility, and predictable drug release behavior. The entrapment efficiency (EE) of the liposomal formulations ranged from 30.206% to 86.754%, with Formula 5 exhibiting the highest EE. The increased entrapment efficiency observed in Formula 5 is attributed to its higher cholesterol content. Cholesterol enhances the rigidity and stability of the phospholipid bilayer by reducing membrane fluidity and permeability, thereby minimizing encapsulated compound leakage and improving drug retention within the liposomal vesicles [7]. These findings demonstrate that cholesterol concentration plays a critical role in determining the encapsulation performance and stability of liposomal formulations.

Evaluation of patch transdermal

Evaluation of patch transdermal showed solid texture, colorless, and odorless (PF0) and solid texture, brown color, and distinctive smell of ethanol (PF1, PF2, PF3, PF4, PF5). The test results in the pH test obtained a pH ranging from 4.75-7 so that it still meets the safe pH for topical use because the range is between 4-7. Dose uniformity is very important in this preparation, where the patch weight must

be and the Coefficient of Variation (CV) value must meet the requirements <5%. Based on table 7. shows that the CV value produced has met the requirements. The thickness of the patch should not be more than 1 mm, if the patch is too thick it will be difficult to release the active substance from the patch and the results obtained have met the requirements. The folding resistance of the patch is found that the number of folding resistance has met the requirements, which is >300. The humidity of the patch preparation has a requirement of <10% and generally 2-10%. Based on table 7. shows that humidity ranges from 5,7-10%. The stability of the patch formula is obtained with a preparation with a shape, texture and color that does not change during treatment so that the formulation exhibited good stability test [17].

Table 7. Organoleptic test, pH, weight uniformity, thickness, folding resistance, moisture content, stability test

Formula	Evaluation Test						
	Organoleptic	**pH**	**Weight uniformity (%)**	**Thickness (mm)**	**Folding resistance**	**Moisture content (%)**	**Stability**
PF0	Solid, colorless, and odorless	4.75	4.55	0.45	>400	5.7	No change in color, odor, and consistency
PF1	Solid, brown color, characteristic odor of ethanol	5.9	3.54	0.36	>400	6	No change in color, odor, and consistency
PF2	Solid, brown color, characteristic odor of ethanol	6.1	3.15	0.35	>400	6,9	No change in color, odor, and consistency
PF3	Solid, brown color, characteristic odor of ethanol	6.71	2.25	0.28	>600	8,2	No change in color, odor, and consistency
PF4	Solid, brown color, characteristic odor of ethanol	6.4	2.85	0.32	>600	7,1	No change in color, odor, and consistency
PF5	Solid, brown color,	7.0	2.44	0.31	>600	9.8	No change in color, odor, and

Formula	Evaluation Test						
	Organoleptic	pH	Weight uniformity (%)	Thickness (mm)	Folding resistance	Moisture content (%)	Stability
	characteristic odor of ethanol						consistency

The FTIR characterization results (Figure 1) showed a shift in the O–H functional group between the cholesterol and extract samples after the formation of the liposome preparation. The O–H stretching vibration was observed at approximately 3200–3600 cm^{-1}, and the absorption band became broader, indicating hydrogen bonding interactions between the components in the liposome system. This phenomenon may occur due to interactions between molecules containing polar functional groups, such as hydroxyl (–OH) groups from phenolic compounds in the extract and polar groups present in phospholipids, which can form hydrogen bonding interactions.

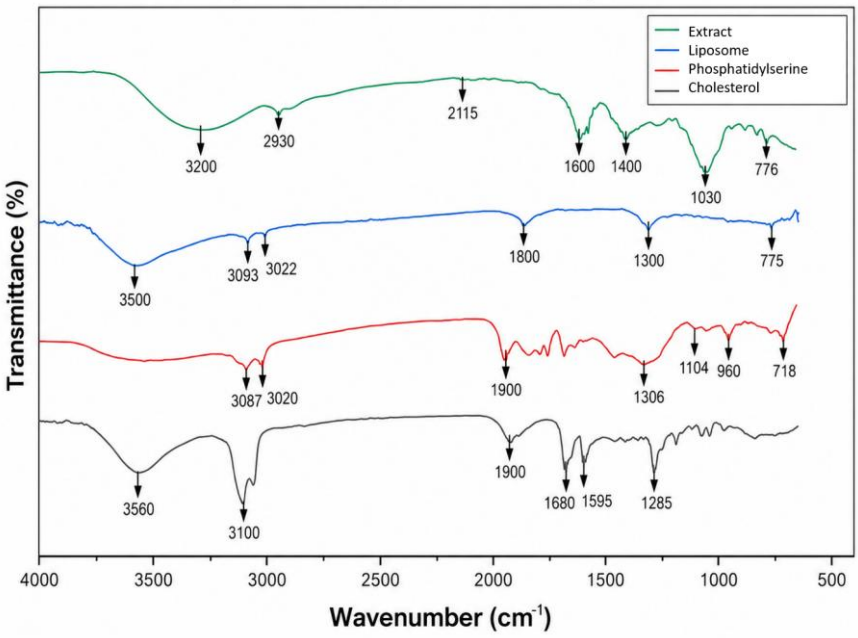


Figure 1. FTIR characterization results of liposomes

The FTIR characterization showed several shifts in functional groups after the formation of the liposome system. The N–H stretching vibration was observed in the region of approximately 3300–3500 cm^{-1}, which may originate from the interaction between polar groups present in the extract and the phospholipid components. These shifts may occur due to hydrogen bonding interactions among cholesterol, phosphatidylserine, and the bioactive compounds contained in the extract.

Furthermore, the C–H stretching vibration observed at approximately 2850–2950 cm^{-1} showed changes after the formation of the

liposome system. These changes may occur due to interactions with other functional groups present in the extract, such as hydroxyl (–OH) groups from phenolic compounds and flavonoids, which can affect intermolecular interactions and binding strength within the liposome structure [21].

Wound healing activity of liposome patch

All experimental procedures involving rats were approved by the Research Ethics Committee of RSUD Dr. Moewardi (No. 1.475/VI/HREC/2024). Male Wistar rats were anesthetized with lidocaine to reduce pain caused by the incision, as it may induce muscle relaxation. Wound diameter measurements were taken every three days until the wound diameter approached zero. The wound drying process was characterized by the absence of edema and bleeding, the formation of scabs on the skin as an indicator of the healing process, and the gradual reduction of wound size. The statistical test results showed a significant difference ($p < 0.05$) between the treatment groups in the observation of wound healing days (Table 8).

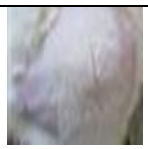
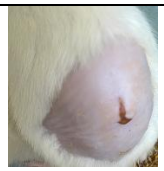
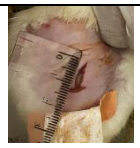
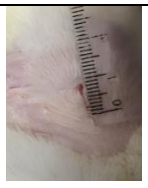
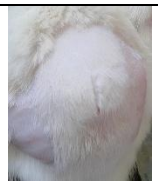
Table 8. Wound diameter result in rats.

Groups	Percentage of wound diameter in rats (%)		
	1	4	7
Positive Control	25.00 ± 0.00	50.00 ± 0.00	75.00 ± 0.00
Negative Control	22.50 ± 0.00	27.50 ± 0.00	32.50 ± 0.00
Liposome patch 1	22.50 ± 0.00	30.00 ± 0.00	65.00 ± 0.00
Liposome patch 2	22.50 ± 0.00	30.00 ± 0.00	60.00 ± 0.00
Liposome patch 3	22.50 ± 0.00	32.50 ± 0.00	70.00 ± 0.00
Liposome patch 4	22.50 ± 0.00	27.50 ± 0.00	52.50 ± 0.00
Liposome patch 5	22.50 ± 0.00	32.50 ± 0.00	72.50 ± 0.00

The in vivo evaluation of the patch preparations demonstrated gradual wound closure in the rat test animals (Table 9). On day 1, all groups showed similar incision wounds characterized by redness and slight swelling around the wound area. By day 4, scab formation began to appear in most treatment groups, indicating the initiation of the wound healing process. The healing process was characterized by the absence of edema and bleeding, the formation of scabs on the wound surface, and the gradual reduction of wound diameter. By day 7, the wound area in several treatment groups had significantly decreased, indicating progressive tissue regeneration. Among the treatment groups, the PF5 liposome patch group showed the highest

percentage of wound healing (72.5%) on day 7, indicating better healing activity compared to the other liposome formulations. The order of wound healing effectiveness from the fastest to the slowest was povidone iodine plaster (positive control), PF1, PF2, PF3, PF4, and the negative control group. These results suggest that liposome-based patch formulations contributed to accelerating the wound healing process

Table 9. Visualize of wound diameter result in rats.

Formula	Day 0	Day 3	Day 7
+			
-			
Liposom patch 1			
Liposom patch 2			
Liposom patch 3			
Liposom patch 4			
Liposom patch 5			

The accelerated wound healing effect may be associated with the presence of bioactive compounds in durian peel extract, particularly flavonoids, which exhibit strong antioxidant activity. Flavonoids play an important role in reducing oxidative stress by inhibiting the formation of reactive oxygen species (ROS), scavenging existing ROS, and enhancing the activity of endogenous antioxidant defense systems. The reduction of ROS levels is important in promoting effective wound healing because excessive oxidative stress can delay tissue regeneration.

In addition, the incorporation of durian peel extract into a liposome delivery system may further enhance the therapeutic effect. Liposomes can stabilize therapeutic compounds, facilitate penetration through biological membranes, and improve tissue uptake and biodistribution of bioactive compounds in vivo. The presence of other active compounds in durian peel, such as alkaloids and saponins, may also contribute synergistically to antimicrobial and tissue repair activities. Overall, the wound healing process observed in this study was characterized by the absence of edema and bleeding, the appearance of scabs on day 4, and significant wound closure by day 7 [22]. Faster wound closure is beneficial because it reduces the risk of infection and promotes more efficient tissue regeneration. These findings are supported by the antioxidant activity test of the liposome preparations, which showed moderate to strong antioxidant activity, further supporting their role in accelerating the wound healing process [22].

Conclusions

Based on the results of the study it can be concluded that, durian fruit peel extract liposomes (Durio zibethinus Murr.) can be formulated as a patch using a combination of HPMC and EC as the polymer. The resulting liposome preparation underwent several physical evaluation tests and showed results that met the required standards, particularly in the stability test, as no changes in shape, color, or odor were observed. In addition, the patch preparation also underwent several physical evaluation tests, including weight uniformity, thickness, folding resistance, pH, moisture content, and cycling tests to determine patch stability. The results of these evaluations indicated that the patch formulations met the required criteria. Furthermore, the prepared patches demonstrated therapeutic effects in the healing of incision wounds in male Wistar rats (Rattus norvegicus L.), with a wound healing percentage of 72.5% on day 7. The healing process was characterized by the absence of edema and bleeding, the formation of scabs, hair regrowth around the wound area, and gradual wound closure.

Acknowledgement

This research supported by RKAT PTNBH Universitas Sebelas Maret for the 2025 Fiscal Year through he Research Grant Scheme HGR-UNS with Agreement Letter Number: 371/UN27.22/PT.01.03/2025.

Author Contributions

Conceptualization, NCAS; Methodology, NCAS; Formal Analysis, NCAS; MEP; Investigation, MEP; Resources, DTU; Data Curation, NCAS; MEP and DTU; Writing – Original Draft Preparation, NCAS; MEP and DTU; Writing – Review & Editing, NCAS; MEP and DTU; Visualization, NCAS; MEP and DTU. All authors have read and agreed to the published version of the manuscript

Conflict of Interest

The authors declare no conflict of interest.

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