

Formulation and Antipyretic Activity Test Of Transdermal Patch Preparation Containing 96% Ethanol Extract Of Shallot (*Allium cepa* var. *ascalonicum*) As a Fever-Reducing Agent

Dessy Erliani Mugita Sari^{1*}, Lilis Sugiarti, Endra Pudjiastuti, Elena Rahmawati

Institut Teknologi Kesehatan Cendekia Utama Kudus, Indonesia

*Corresponding Author: dessyerlyani3@mail.com

Abstract. Fever is characterized by an increase in body temperature, namely 36.5°C–37.5°C. Antipyretic drugs consumed orally can undergo first-pass metabolism (first-pass metabolism). To avoid the occurrence of first-pass metabolism can be given a transdermal patch. Previous research suggested that shallots contain flavonoids, these compounds have antipyretic or fever-reducing potential. Shallot extract is formulated in the form of transdermal patches with different concentrations of K-base, F1 5%, F2 10% and F3 15%. Transdermal patch preparation of 96% ethanol extract of shallot (red onion) was evaluated for its physical properties and antipyretic effect test. The results showed that the concentration variations of shallot extract transdermal patch preparations did not affect the results of the patch preparation, namely the pH test, weight uniformity test and patch thickness test, while the tests that affected the results of the patch preparation were the moisture absorption test and the antipyretic effect test. The results of the antipyretic effect test showed that K+ was comparable to F3 showing the best results compared to the other groups.

Keywords: shallot, red onion, extract, transdermal patch, physical properties test.

INTRODUCTION

Fever is a condition in which body temperature becomes elevated. Body temperature is considered normal when it ranges between 36.5–37.5°C (Lazdia et al., 2022). Fever can usually be treated using antipyretic drugs or traditional remedies (Nurdin & Destiani, 2023). A traditional remedy commonly used to treat fever is shallot (red onion) (Faridah et al., 2018). Modern antipyretic drugs such as paracetamol and ibuprofen are also frequently used (Carlson & Kurnia, 2020). These antipyretic drugs are administered orally, which may lead to first-pass metabolism. In addition, long-term use or administration in excessive doses may cause side effects such as hepatotoxicity, fatal hyper necrosis, and renal tubular necrosis (Sukarno, 2021).

Shallot (*Allium cepa* var. *ascalonicum*) contains secondary metabolite compounds, particularly flavonoids, which possess antipyretic activity (Fahajh & hasanah, 2024). When crushed, shallots release the enzyme alliinase, which acts as a catalyst for alliin to react with other compounds—such as those present in the skin—to help break down blood clots (Arifin & Susanti, 2022).

A transdermal patch is a drug delivery system that administers medication through the skin at a controlled rate to achieve systemic effects (Assyfa et al., 2022). The advantages of transdermal patches include avoiding absorption problems in the gastrointestinal tract, enzyme activity, and interactions between drugs and food, beverages, or other orally administered medications. They also prevent the first-pass effect, eliminate discomfort associated with parenteral routes, and can be easily discontinued by removing the patch from the skin (Solikhah et al., 2021).

Based on the aforementioned background, to avoid first-pass metabolism and the potential harmful effects of orally administered drugs, a transdermal patch dosage form was developed. This study focuses on the antipyretic properties of shallot (*Allium cepa* var. *ascalonicum*) in reducing fever temperature. The transdermal patch formulation undergoes various evaluations, including phytochemical screening (alkaloids, flavonoids, and others), organoleptic testing, pH testing, patch weight uniformity testing, folding endurance testing, patch thickness testing, moisture absorption testing, and antipyretic activity testing using male white mice induced with 5% peptone.

METHODS

Materials

Shallots (*Allium cepa* var. *ascalonicum*), male white mice (*Mus musculus*), HPMC (Brataco), PEG 400 (Brataco), propylene glycol (Brataco), methyl paraben (Brataco), distilled water, 70% ethanol, 96% ethanol, peptone, Mg powder, concentrated HCl, ammonia, sulfuric acid, Dragendorff reagent, acetic anhydride, cotton, and feed and drinking water for mice.

Methods

Shallot Processing

The sample used in this study was shallots obtained from Dusun Brumbung, Tahunan Village, Gabus District, Grobogan Regency. The shallots selected were fresh, reddish-purple in color, not perforated, and free from pest infestation. The samples were cleaned of dirt, washed under running water, drained, and then cut into small pieces. Subsequently, they were dried in a drying cabinet at $\pm 40^{\circ}\text{C}$ until dry (indicated by being brittle when crushed). The dried samples were then ground using a blender and sieved using a no. 40 mesh sieve.

Extraction Process

Shallots were extracted using the maceration method. A total of 450 grams of simplicia powder was placed into a jar lined with aluminum foil, then poured with 30 parts of 96% ethanol (3 liters), covered, and left for 5 days protected from light while being stirred frequently. The residue was re-macerated with 15 parts of 96% ethanol (1.5 liters) in the jar, left for 2 days protected from light while being stirred. The extract was then concentrated using a rotary evaporator at 40°C until no liquid dripped, and further concentrated on a water bath until a thick extract was obtained (Sinaga et al., 2020).

Preparation of Pepton-Inducing Solution

A total of 5 grams of peptone was weighed, then distilled water was added little by little until dissolved and transferred into a 100 mL volumetric flask. The volume was then adjusted to 100 mL by adding distilled water (Herdaningsih et al., 2019).

Preparation of Transdermal Patch Dosage Form

The formulation of the transdermal patch dosage form containing 96% ethanol extract of shallots (*Allium cepa* var. *ascalonicum*) as an antipyretic was based on the study by Sukarno (2021), as shown in Table 1 below:

Ingredient Name	Control (-) (%)	Control (+) (%)	(+) F1 (%)	F2 (%)	F3 (%)	Function
Bye-bye fever	–	–	–	–	–	Antipyretic
Shallot Extract	–	–	5	10	15	Active Ingredient
HPMC	6	–	6	6	6	Polymer
PEG 400	10	–	10	10	10	Plasticizer
Methyl Paraben	0.1	–	0.1	0.1	0.1	Preservative
Propylene Glycol	5	–	5	5	5	Enhancer
70% Ethanol	30	–	30	30	30	Cosolvent
Distilled Water	Ad 100	–	Ad 100	Ad 100	Ad 100	Solvent

Notes:

K–: Base (transdermal patch without extract)

K+: Bye-bye fever

F1: Patch formulation with 5% shallot ethanol extract

F2: Patch formulation with 10% shallot ethanol extract

F3: Patch formulation with 15% shallot ethanol extract

The preparation of the patch began by weighing all materials according to the formula in Table 1. In the first container, the extract was dissolved with ethanol. In the second container, HPMC was dispersed with part of the distilled water and stirred until it swelled. In the third container, methyl paraben was dissolved in propylene glycol, followed by the addition of PEG 400 and gently stirred until homogeneous to avoid aeration and maintain patch clarity. Next, the mixtures from the second and third containers were combined and stirred until homogeneous, then mixed with the first container and stirred again until homogeneous. The remaining distilled water was then added. If bubbles appeared during mixing, the preparation was allowed to stand for ± 24 hours to remove the bubbles. After the desired patch mass was formed, the preparation was poured into a dish, measured to 2 cm $\times$ 2 cm, and placed into an oven at 50°C for 5 hours. After the film layer formed, patch characteristic testing could be performed.

Uji Parameter Fisik Sediaan Patch Transdermal

a. Organoleptic Test

The organoleptic test was carried out by observing the shape, color, and odor of the transdermal patch preparation.

b. pH Test

The pH test was performed by adding 10 mL of CO₂-free distilled water into the patch and allowing it to stand for 1 hour. The surface pH was measured using a pH meter. The acceptable pH range to avoid skin irritation is 4.5–6.5 (Bharkatiya et al., 2010).

c. Patch Weight Uniformity Test

The weight uniformity test was conducted by weighing the transdermal patch preparation using an analytical balance, where three patches were each weighed. The average weight and standard deviation were then determined. The requirement for weight uniformity is that the patches must be uniform and must not deviate by more than 5% (Nurmesa et al., 2019).

d. Folding Endurance Test

The folding endurance test was measured by repeatedly folding the patch at the same position until the patch tore. The number of folds was considered the folding endurance value. The folding endurance meets the standard if it is more than 200 folds (Rajesh & Sujith, 2013).

e. Patch Thickness Test

The patch thickness test was performed by measuring the thickness of three patches individually. Thickness was measured using a micrometer at three different points. If the patch is too thin, it tends to be fragile, and if too thick, it may interfere with drug penetration into the body. The patch thickness requirement is not more than 1 mm (Shirsand et al., 2012).

f. Moisture Absorption Test

According to Hermanto et al. (2019), the moisture absorption test was carried out by weighing the patch, then storing it in a desiccator for 24 hours. After that, the patch was placed in an oven at 40°C for 24 hours and weighed again. The percentage of moisture absorption was calculated using the following formula:

$$\% \text{Moisture Absorption} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100\%$$

g. Antipyretic Effect Test

The antipyretic effect test was conducted by adapting the test animals for 1 week, after which the mice were fasted for 8 hours before treatment. The fur on the abdominal and dorsal areas of the mice was shaved, then allowed to rest for 1 day to avoid inflammation caused by shaving. Before induction, the mice's body temperature was checked, then induced with 5% peptone via intramuscular injection. After induction, the temperature was checked again using a thermometer. The transdermal patch was applied to each mouse's body. The body temperature of each mouse was observed at 15, 30, 45, and 60 minutes.

Data Analysis

pH test, Weight Uniformity Test, Folding Endurance Test, Moisture Absorption, Antipyretic Effect Test were tested using two-way ANOVA (Analysis of Variance) test analysis and further analysis using Duncan's test, performed with SAS Software (Statistical Analysis System)

RESULTS AND DISCUSSION

In this study, physical parameter tests of the transdermal patch preparation containing 96% ethanol extract of shallots and antipyretic tests were carried out.

Physical Property Testing of Transdermal Patch Preparations

a. Organoleptic Test

The results of the organoleptic test of the transdermal patch preparation containing 96% ethanol extract of shallots can be seen in Table 2.

Table 2. Organoleptic Test Results

Formula	Color	Odor	Form
K-	Off-white	Odorless	Solid gel
F1	Cream	Characteristic odor of shallots	Solid gel
F2	Light brown	Characteristic odor of shallots	Solid gel
F3	Dark brown	Characteristic odor of shallots	Solid gel

Based on the results in Table 2, the transdermal patch preparation showed differences in the physical characteristics among K-, F1, F2, and F3 in terms of aroma and color. The difference in aroma is caused by the variation in the extract concentration added to the preparation; the higher the amount of extract added, the stronger the aroma produced in the transdermal patch. Meanwhile, the difference in color is also due to the varying concentrations in the transdermal patch formulation; the more 96% ethanol extract of shallots added, the darker the color produced in the patch preparation.

b. pH Test

The required pH range for transdermal patch preparations is 4.5–6.5, which corresponds to the pH of human skin so that it does not cause irritation when applied to the skin surface (Zakaria et al., 2021). The results of the pH test on the transdermal patch preparation containing 96% ethanol extract of shallots are shown in Table 3.

Table 3. pH Test Results

Formula	Mean $\pm$ SD	Standard	Description
K-	5.23 $\pm$ 0.07 ^b	4.5–6.5	Acceptable
F1	5.27 $\pm$ 0.11 ^b	4.5–6.5	Acceptable
F2	5.31 $\pm$ 0.00 ^b	4.5–6.5	Acceptable
F3	5.22 $\pm$ 0.04 ^b	4.5–6.5	Acceptable

Note: Superscripts indicate no significant difference compared to K– ($p > 0.05$).

Based on the results in Table 3, all formulations fall within the acceptable pH range of 5.00–5.31. These values ensure the patches are safe for skin application and do not cause irritation. A pH below this range may potentially cause itching.

c. Weight Uniformity Test

Patch weight uniformity can be analyzed from the average patch weight value. A small standard deviation (SD) value indicates uniformity in the weight of the patch produced. According to Hermanto et al., (2019), standard deviation is a measure used to quantify the deviation of data. The results of the transdermal patch preparation weight uniformity test can be seen in Table 4.

Table 4. Results of Weight Uniformity Test

Formula	Mean $\pm$ SD	Standard
K–	0.740 $\pm$ 0.01 ^b	Within 5% deviation
F1	0.718 $\pm$ 0.02 ^b	Within 5% deviation
F2	0.752 $\pm$ 0.07 ^b	Within 5% deviation

F3	0.750 ± 0.03 ^b	Within 5% deviation
Formula	Mean ± SD	Standard

Note: Superscripts in the column indicate no significant difference between the K-groups ($p > 0.05$).

Based on the results in Table 4, The average patch weights ranged from 0.718–0.752 g. Variations may have resulted from residues sticking to equipment such as beakers or mortar and pestle.

d. Folding Endurance Test

According to Hermanto et al., (2019), the folding resistance test for patch preparations aims to determine the fold resistance of a patch preparation. Increased folding resistance of a patch indicates that the patch has a good film so it is not easily torn during use and storage. The results of the folding resistance test for transdermal patch preparations can be seen in Table 5.

Table 5. Folding Strength Test Results

Formula	Mean ± SD	Standard	Description
K–	250 ± 4.04 ^a	≥ 200	Acceptable
F1	309 ± 0.57 ^a	≥ 200	Acceptable
F2	244 ± 5.29 ^a	≥ 200	Acceptable
F3	222 ± 3.46 ^a	≥ 200	Acceptable

Note: Superscripts in the columns indicate a significant difference between the K- groups ($p < 0.05$).

Based on the results in Table 5, All formulas exceeded the minimum standard of 200 folds, showing good flexibility. F1 exhibited the highest folding endurance. Increasing extract concentration generally reduces flexibility. Differences may also arise from variability in pressure during manual folding or incomplete HPMC hydration during preparation.

e. Patch Thickness Test

Patch thickness significantly influences the penetration of active ingredients into the skin (Latifah & Rahman, 2024). The thinner the patch, the better the penetration of active ingredients into the skin because there is less space for the active ingredients to move, resulting in a longer lasting effect (Hermanto et al., 2019). The results of the transdermal patch thickness test can be seen in Table 6.

Table 6. Patch Thickness Results

Formula	Thickness	Standard	Description
K–	1 mm	Not more than 1 mm	Acceptable
F1	1 mm	Not more than 1 mm	Acceptable
F2	1 mm	Not more than 1 mm	Acceptable
F3	1 mm	Not more than 1 mm	Acceptable

Based on the results in Table 6, the thickness of all transdermal patch formulations—K–, F1, F2, and F3—meets the required specifications, as each patch exhibited a thickness not exceeding 1 mm. Patch thickness may be influenced by differences or variations in ingredient concentration, as well as other factors such as mixing technique, transfer of materials into the mold, mold surface area, solution volume, and drying conditions.

f. Moisture Absorption Test

Moisture absorption is a response parameter used to evaluate the ability of a patch to absorb moisture (Fatmawaty et al., 2017). The percentage of moisture absorption is related to the hydrophilicity of the polymer or plasticizer. The higher the hydrophilicity of the polymer or plasticizer used, the greater the moisture absorption value will be (Hermanto et al., 2019). The results of the moisture absorption test are presented in Table 7.

Table 7. Moisture Absorption Test Results

Formula	Mean $\pm$ SD	Standard	Description
K–	23.733 $\pm$ 7.29 ^b	< 10%	Not acceptable
F1	24.436 $\pm$ 4.41 ^b	< 10%	Not acceptable
F2	23.233 $\pm$ 1.37 ^b	< 10%	Not acceptable
F3	24.823 $\pm$ 1.48 ^b	< 10%	Not acceptable

Note: The superscript in the table indicates no significant difference compared to the K– group ($p > 0.05$).

Based on the results in Table 7, the moisture absorption percentage was relatively high, reaching approximately 24.83%. This may be influenced by the hygroscopic nature of the extract or by factors related to equipment use during the experiment, which could affect moisture absorption values.

According to Hermanto et al. (2019), previous studies conducted moisture absorption testing using a climatic chamber at 40°C for 24 hours, and the results met the required criteria. This difference in testing conditions may have significantly influenced the outcome of the moisture absorption test in this study.

g. Antipyretic Effect Test

The antipyretic effect test was conducted to evaluate the antipyretic activity of the transdermal patch containing 96% ethanol extract of shallots in male white mice induced with 5% peptone. Body temperature was measured before induction (T0), and after induction with 5% peptone, body temperature was measured again (T1) to confirm whether an increase in temperature occurred following induction.

The febrile mice were then randomly divided into five treatment groups. After treatment, body temperature was measured at 15, 30, 45, and 60 minutes (T15–T60). The results of the antipyretic effect test can be seen in Table 8.

Table 8. Average Body Temperature of Mice After Induction with 5% Peptone Followed by Administration of Bye-bye Fever and Transdermal Patch Containing 96% Ethanol Extract of Shallots

Time (minutes)	Mice Body Temperature (C°)				
	K–	K+	F1	F2	F3
T0	36.46 $\pm$ 0.16 ^b	36.38 $\pm$ 0.13 ^b	36.38 $\pm$ 0.30 ^b	36.24 $\pm$ 0.15 ^b	36.26 $\pm$ 0.05 ^b
T1	38.58 $\pm$ 0.41 ^b	38.36 $\pm$ 0.18 ^b	38.46 $\pm$ 0.42 ^b	38.84 $\pm$ 0.47 ^b	38.74 $\pm$ 0.60 ^b
T15	37.76 $\pm$ 0.76 ^b	36.80 $\pm$ 0.14 ^b	37.42 $\pm$ 0.68 ^b	37.10 $\pm$ 0.68 ^b	36.42 $\pm$ 0.22 ^b
T30	37.50 $\pm$ 0.83 ^b	36.58 $\pm$ 0.17 ^{ab}	36.58 $\pm$ 0.14 ^a	36.54 $\pm$ 0.29 ^b	36.10 $\pm$ 0.10 ^b
T45	37.10 $\pm$ 0.66 ^b	36.36 $\pm$ 0.19 ^{ab}	36.22 $\pm$ 0.08 ^b	36.24 $\pm$ 0.21 ^b	35.90 $\pm$ 0.07 ^b
T60	36.86 $\pm$ 0.60 ^a	36.20 $\pm$ 0.18 ^{ab}	35.96 $\pm$ 0.05 ^a	35.96 $\pm$ 0.15 ^a	35.46 $\pm$ 0.21 ^b

Note: The superscript indicates no significant differences compared to the K+ group ($p > 0.05$).

Based on the results in Table 7, the results show that all treatment groups experienced an increase in temperature from T0 (36.26–36.51°C) to T1 (38.36–38.76°C), confirming successful induction of fever using 5% peptone. At the 60-minute mark, the greatest temperature reduction occurred in the positive control group (K+) and formulation F3, decreasing from T1 (38.36–38.84°C) to T60 (35.2–36.86°C).

Based on the temperature reduction shown in Figure 1, the K– group receiving the patch exhibited a temperature decrease, although it did not return to normal levels. At 30 minutes, temperature reduction occurred in groups K+, F2, and F3, while F1 reached normal body temperature at 45 minutes.

Statistical analysis shown in Table 8 indicates a significant difference at the 60-minute mark between the K+ group and F3. This suggests that both the positive control (Bye-bye Fever) and formulation F3 were able to reduce body temperature significantly. Therefore, it can be concluded

that the positive control (K+) is comparable with formulation F3, indicating that the transdermal patch containing 96% ethanol extract of shallots (*Allium cepa* var. *ascalonicum*) exhibits antipyretic activity.

CONCLUSION

Based on the results of the study, it can be concluded that:

1. The transdermal patch preparation containing 96% ethanol extract of shallots (*Allium cepa* var. *ascalonicum*) meets the required criteria for transdermal patch evaluation parameters, including pH test, folding endurance test, patch thickness test, and antipyretic test. However, it does not meet the requirements for the weight uniformity test and moisture absorption test.
2. The transdermal patch preparation containing 96% ethanol extract of shallots (*Allium cepa* var. *ascalonicum*) exhibits antipyretic activity in mice induced with 5% peptone.
3. The best formulation of the transdermal patch as an antipyretic is F3, as it is able to reduce the mice's body temperature more rapidly and return it to normal compared to the other treatment groups.

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