

FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES FROM *ELEUTHERINE BULBOSA* URB. BULB EXTRACT WITH PLASTICIZER VARIATIONS

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ABSTRACT

Objective: This research aimed to develop a transdermal drug delivery system from *Eleutherine bulbosa* Urb. bulbs as an alternative treatment with minimum side effects compared to other pain medications and increased drug penetration by determining the optimum formula(s) for transdermal patches prepared with varying plasticizer concentrations.

Methods: *Eleutherine bulbosa* Urb. bulbs were extracted by maceration using 96% ethanol. The extract was formed into transdermal patches using the solvent casting method with six formulations (F1-F6) and different types and concentrations of the plasticizer: polyethylene glycol (PEG) 400 or dibutyl phthalate. The derived patches were then evaluated for their organoleptic properties, homogeneity, weight uniformity, thickness, folding endurance, pH level, moisture content, and acceptability (hedonic scale).

Results: The evaluation of the physical properties found that all patches were dark brown, opaque, smooth-textured, and had a typical odor of the bulb's ethanol extract and uniform weight and thickness. Other characteristics included pH ranging from 5.0±0.00 to 5.86±0.04 and a moisture content between 1.04±0.04% and 4.13±0.08%. In addition, the folding endurance was 267 times for F1 and >300 times for F2-F6. The acceptability test using the five-point hedonic scale showed different preferences for these formulas.

Conclusion: F6 is the optimum formula for producing transdermal patches with excellent physical properties.

Keywords: Transdermal patches, Ethanol extract, *Eleutherine bulbosa*

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INTRODUCTION

Eleutherine bulbosa Urb., locally known as *bawang dayak* in Indonesia, is a medicinal herb commonly sought to relieve pain. The bulb part contains alkaloids, glycosides, phenolics, saponins, triterpenoids, tannins, steroids, flavonoids, and naphthoquinones and their derivatives like elecanacin, eleutherin, eleutherol, and eleutherinon [1-3]. In addition, the 96% ethanol extract of the bulb has been reported to exhibit analgesic activity in mice at a dose of 100 mg/kg BW [4].

Transdermal preparations are an alternative route of drug administration that has been extensively developed for the delivery of numerous active substances. Transdermal use can prevent the first-pass effect, resulting in minimum side effects compared to oral preparations. Transdermal preparations deliver drugs into the body through the skin to be able to exert systemic effects. A transdermal drug delivery system is a formulation used to overcome problems potentially arising from plant extract-based treatment. Formulating plant extracts into some preparations involves complex procedures. Moreover, most of their active substances have low penetration, are unstable in very acidic environments, and are metabolized in the liver [5]. An example of a transdermal drug delivery system is a transdermal patch that is prepared with polymers. Polymers are the most essential materials in making patch matrices that determine the speed of drug release as an indicator of the success of therapy. A transdermal patch is a medicated adhesive patch pasted on the skin to deliver drugs at a specific dose percutaneously into the bloodstream [6].

One of the patch components that affect its stability and elasticity is plasticizers [7]. Plasticizers are resins or liquids of low molecular weight, thus decreasing secondary bonds in polymer chains and forming ones with polymer chains instead [8]. Adding plasticizers to polymer materials can extend the resting time and increase

toughness and flexibility. On the other hand, tensile strength and hardness are expected to decrease. Incorporating plasticizers in transdermal drug delivery systems can improve the properties and appearance of patch formulation, reduce the transition temperature of polymer glass, prevent cracks, increase flexibility, and obtain the mechanical properties desired from transdermal patches [9]. Polyethylene glycol (PEG) 400 is a plasticizer with several advantages such as producing elastic, strong patches with increased tensile strength; the percent water content of patch preparations increases with the concentration of PEG 400 used [10]. In addition to PEG, dibutyl phthalate, especially at 30%, can be used as a plasticizer to create medicated patches with improved homogeneity, tensile strength, and percent elongation [11].

Considering the above description, it is necessary to study the formulation of transdermal patches from the 96% ethanol extract of *Eleutherine bulbosa* Urb. bulbs using PEG 400 or dibutyl phthalate as the plasticizer. This is intended to identify the effect of various plasticizers on the physical properties of transdermal patches.

MATERIALS AND METHODS

Eleutherine bulbosa Urb. bulbs were obtained from a farmer in Banjarbaru, Indonesia. The collected plant parts were identified at the Herbarium Bogoriense, Research Center for Biology, Indonesian Institute of Sciences (LIPI), Bogor (No. 2242/IPH.1.01/If.07/XII/2019). They were then extracted by maceration using 96% ethanol following the procedure described in Muthia *et al.* [12]. Technical grade chemicals and ingredients used to create the transdermal patches from this extract were ethyl cellulose and hydroxypropyl methylcellulose (HPMC) as polymers, PEG 400 and dibutyl phthalate as plasticizers (to enhance elasticity), propylene glycol as humectant and penetration enhancer, methylparaben as a preservative, and ethanol and aquadest as solvents. All the chemicals were purchased from Eralika (Indonesia).

Table 1: Formulations of transdermal patches from *Eleutherine bulbosa* Urb. bulb extract

Ingredients		F1	F2	F3	F4	F5	F6
Bulb extract	(gram)	1.21	1.21	1.21	1.21	1.21	1.21
Ethyl cellulose	(%b/b)	2	2	2	2	2	2
HPMC	(%b/b)	1	1	1	1	1	1
PEG 400	(%b/v)*	40	50	60	-	-	-
Dibutyl phthalate	(%b/v)*	-	-	-	40	50	60
Propylene glycol	(%b/v)	15	15	15	15	15	15
Methylparaben	(%b/b)	0.2	0,2	0,2	0,2	0,2	0,2
96% ethanol	(%b/v)	20	20	20	20	20	20
Distilled water	(gram)	ad 15	ad 15	ad 15	ad 15	ad 15	ad 15

*Percentage of the polymer weight

Preparation of transdermal patches

The transdermal patch was prepared with solvent casting using six formulas (table 1). This method involves dissolving polymers and other components in a solvent, pouring the resulting solution into the mold, and evaporating the solvent, leaving only the active drug in the patch [13]. In this research, the bulb extract was first dissolved in propylene glycol. Then, HPMC and ethyl cellulose were dispersed in distilled water and 96% ethanol, respectively, and then mixed and stirred for 15 min. The mixture was added to the dissolved bulb extract and PEG 400 and stirred for 20 min. Next, methylparaben was dissolved in 96% ethanol and then added to the mixture. The resulting mixture was then poured into the mold and oven-dried at 60 °C for 20 h until a dry patch was formed. Afterward, it was cut into smaller round-shaped patches with a diameter of 3 cm and then stored in a desiccator [14, 15]. The same procedure was repeated for the other plasticizer, dibutyl phthalate.

Physical appearance evaluation

Transdermal patches were evaluated visually based on their physical characteristics: color, transparency, and surface texture [16].

Weight uniformity test

In this test, three patches were weighed. Their weight variations were observed and then averaged for each formula [17].

Patch thickness measurement

For each formula, the patch thickness was measured on several different sides using a caliper. The thickness of the patch matrix is the average of measurements on three sides [7].

Folding endurance test

The folding endurance was determined by repeatedly folding the patch at the same point until it broke [18]. A patch has excellent folding endurance if it can be folded >300 times [19].

pH measurement

This test aimed to measure the pH of the patch surface. First, the patch was submerged in 10 ml of CO₂-free aquadest. Then, after one hour, the surface pH was read using a pH meter [19].

Moisture content test

The patch was weighed to determine its initial weight and then stored in a desiccator containing silica at room temperature for 24 h. afterward, the patch was weighed again to obtain its constant weight [17].

Acceptability test using the hedonic scale

Twenty respondents selected for the acceptability test were asked to use the transdermal patches made with different formulations. Then, their responses to the patch application were recorded using a questionnaire, including color, elasticity, aroma, surface condition, surface adhesiveness, and skin sensation [20]. Their acceptability was assessed with a five-point hedonic scale: like extremely (5), like very much (4), like (3), dislike slightly (2), and dislike very much (1) [21].

RESULTS AND DISCUSSION

The test sample used in this study was the bulb of *Eleutherine bulbosa* Urb., which has proved efficacious as an analgesic in rats when administered at a dose of 100 mg/kg BW [4]. The sample has been standardized for specific and non-specific parameters [12] and tested for safety using the OECD 425 toxicity test [22]. Based on the organoleptic test results, the transdermal patches were round (shaped as the mold used), slightly blackish-brown (fig. 1), opaque, smooth-textured, and had a typical odor of the bulb's ethanol extract. These results indicate that the drying process at 60 °C is the optimum condition for making transdermal patches. In addition, the weight uniformity test found that the transdermal patches weighed 3.91–4.18 g, suggesting heterogeneity or variation across the formulas [23].

Table 2: Plant determination results

No.	Sample	Species	Family
1	Onion bulbs	<i>Eleutherine bulbosa</i> Urb.	<i>Iridaceae</i>

Table 3: Physical characteristics of transdermal patches prepared from *Eleutherine bulbosa* Urb. bulb extract with different formulas

Formulas	Physical characteristics		
	Color	Transparency	Surface texture
F1	Dark brown	Opaque	Smooth
F2	Dark brown	Opaque	Smooth
F3	Dark brown	Opaque	Smooth
F4	Dark brown	Opaque	Smooth
F5	Dark brown	Opaque	Smooth
F6	Dark brown	Opaque	Smooth

Table 4: Weight uniformity, thickness, folding endurance, pH level, and moisture content of transdermal patches prepared from *Eleutherine bulbosa* Urb. bulb extract with different formulas

Formulas	Weight uniformity* (gram)	Thickness* (mm)	Folding endurance* (times)	pH*	Moisture content* (%)
F1	4.02±0.04	1.28±0.06	266.66±20.89	5.43±0.04	1.21±0.01
F2	4.12±0.07	1.22±0.02	493±102.01	5.5±0.00	1.21±0.02
F3	4.18±0.05	1.41±0.01	746±44.1	5.86±0.04	4.13±0.08
F4	4.15±0.04	1.30±0.04	989.66±123.3	5.36±0.04	1.19±0.008
F5	3.96±0.05	1.40±0.04	1314±177	5.4±0.00	1.50±0.004
F6	3.91±0.01	1.28±0.01	1594±93.35	5.0±0.00	1.04±0.04

*mean±Standard Deviation, n = 3 observations

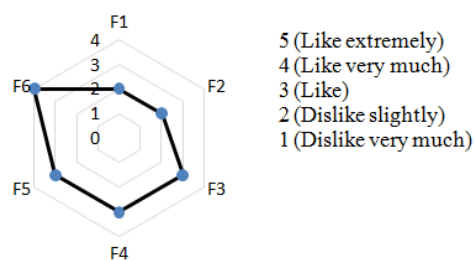


Fig. 1: Diagram of the acceptability test of the transdermal patches made from *Eleutherine bulbosa* Urb. bulb extract using the five-point hedonic scale

Likewise, the transdermal patches also had different thicknesses, ranging from 1.22 mm to 1.41 mm. Patch thickness varies proportionally with the amount of the added polymer. More polymers in the formulation thicken the patch, increase water absorption into the matrix, and prolong the drying time [24]. Moreover, using large doses of extracts and other components (ingredients) also thickens the resulting patches. As for the folding endurance, F1 (40% PEG 400) produced patches with poor durability when repeatedly folded, whereas F2 (50% PEG 400) and F3 (60% PEG 400) exhibited good endurance to folding. In contrast, all formulas with dibutyl phthalate as the plasticizer, namely F4 (40% dibutyl phthalate), F5 (50%), and F6 (60%), produced patches that could be folded >300 times without breaking. On average, F4 patches could be folded about 989 times, F5 1,314 times, and F6 1,594 times. Therefore, it can be concluded that the higher the plasticizer concentration used in the formula, the more durable the resulting transdermal patch to folding.

In Ameliana *et al.* [19], PEG 400 produced elastic patches with a folding endurance of >300 folds. PEG 400 increases permeability and wetting, thus creating patches with improved hydrophilicity. At the same time, it lowers polymer crystals, resulting in favorable elasticity and flexibility. Using dibutyl phthalate as a plasticizer, Singh and Vijaykumar [9] produced a strong and elastic patch. Because dibutyl phthalate has a low molecular weight, it can enter the polymer chain to form a patch film and interact with specific groups in the polymer [25]. The interaction of the plasticizer molecules is responsible for the high percentage of patch elongation.

The formulas produced varying pH levels, from 5.0 to 5.86. This pH range is between 4.5 and 6.5, which meets the requirement for transdermal patches, i.e., that the preparation is safe to use as it can be tolerated by or does not irritate the skin. Furthermore, the resulting transdermal patches had 1.04–4.13% moisture content, meaning that all formulas produced medicated patches that comply with the specified requirements, 1–10%. A relatively low moisture content creates a stable patch and impedes microbial contamination. In contrast, high moisture content reduces patch stability and increases the possibility of contamination by microbes present in the air and water. In addition, microbes proliferate rapidly in humid temperatures [26]. Moisture content also contributes to the percutaneous penetration of active substances, which occurs by skin hydration [27].

Adopting the procedures and provisions in SNI 01-2346-2006, the acceptability test revealed different levels of public preference for the

preparations, ranging from 2 (dislike slightly) to 4 (like very much). The five-point hedonic scale is a relative measurement for color, elasticity, aroma, surface condition, surface adhesiveness, and skin sensation. F6 (60% dibutyl phthalate) was the most preferred formula (fig. 1), particularly because it produced highly elastic patches.

CONCLUSION

The study created transdermal patches from the 96% ethanol extract of *Eleutherine bulbosa* Urb. bulbs with various types and concentrations of plasticizers: PEG 400 (40, 50, 60% of the polymer weight) and dibutyl phthalate (40, 50, 60% of the polymer weight). Their organoleptic characteristics are, among others, blackish-brown to dark brown, opaque, and smooth-textured, with a typical odor of the bulb's ethanol extract. Other characteristics include weight in the range of 3.91–4.18 g, thickness 1.22–1.41 mm, folding endurance 266.66–1594 times, pH level at 5.0–5.86, and 1.04–4.13% moisture content. In addition, based on the acceptability test results using the five-point hedonic scale, the patches receive different responses, from 2 (dislike slightly) to 4 (like very much). It has been found that compared with other formulas, F6 (60% dibutyl phthalate) is optimum for producing patches with high folding endurance and acceptability.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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