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 formulated 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 5.8±0.04 and a moisture content between 1.0±0.04% and 4.2±0.00%. 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
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 [16]. 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

<table>
<thead>
<tr>
<th>No.</th>
<th>Sample</th>
<th>Species</th>
<th>Family</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Onion bulbs</td>
<td>Eleutherine bulbosa Urb.</td>
<td>Iridaceae</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Formulas</th>
<th>Physical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Color</td>
</tr>
<tr>
<td>F1</td>
<td>Dark brown</td>
</tr>
<tr>
<td>F2</td>
<td>Dark brown</td>
</tr>
<tr>
<td>F3</td>
<td>Dark brown</td>
</tr>
<tr>
<td>F4</td>
<td>Dark brown</td>
</tr>
<tr>
<td>F5</td>
<td>Dark brown</td>
</tr>
<tr>
<td>F6</td>
<td>Dark brown</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Formulas</th>
<th>Weight uniformity (gram)</th>
<th>Thickness (mm)</th>
<th>Folding endurance (times)</th>
<th>pH</th>
<th>Moisture content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>4.02±0.04</td>
<td>1.28±0.06</td>
<td>266.66±20.89</td>
<td>5.43±0.04</td>
<td>1.12±0.01</td>
</tr>
<tr>
<td>F2</td>
<td>4.12±0.07</td>
<td>1.22±0.02</td>
<td>493±10.02</td>
<td>5.5±0.00</td>
<td>1.21±0.02</td>
</tr>
<tr>
<td>F3</td>
<td>4.18±0.05</td>
<td>1.41±0.02</td>
<td>746±4.41</td>
<td>5.86±0.04</td>
<td>4.13±0.08</td>
</tr>
<tr>
<td>F4</td>
<td>4.15±0.04</td>
<td>1.30±0.04</td>
<td>989.66±123.3</td>
<td>5.36±0.04</td>
<td>1.19±0.008</td>
</tr>
<tr>
<td>F5</td>
<td>3.96±0.05</td>
<td>1.40±0.04</td>
<td>1314±177</td>
<td>5.4±0.00</td>
<td>1.50±0.004</td>
</tr>
<tr>
<td>F6</td>
<td>3.91±0.01</td>
<td>1.28±0.01</td>
<td>1594±93.35</td>
<td>5.0±0.00</td>
<td>1.04±0.04</td>
</tr>
</tbody>
</table>

*mean±Standard Deviation, n = 3 observations

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 plastic. 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 266.66–1,594 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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