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COMPARATIVE EVALUATION OF TRANSDERMAL PATCH FORMULATIONS FROM ETHANOL EXTRACT OF SOURSOP LEAVES (ANNONA MURICATA L.) USING PVP–ETHYL CELLULOSE AND CHITOSAN POLYMER SYSTEMS

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ABSTRACT

Background: Soursop leaves (Annona muricata L.) contain bioactive compounds including acetogenins, flavonoids, alkaloids, and tannins, which possess antioxidant, anti-inflammatory, and antitumor activities. Transdermal patch delivery systems offer significant advantages by bypassing hepatic first-pass metabolism, enabling controlled drug release, and improving patient adherence. Two independent formulation strategies were pursued: (1) a hydrophilic–hydrophobic PVP–Ethyl Cellulose (EC) matrix system, and (2) a chitosan-based biopolymer matrix system. Objectives: This study aimed to formulate and comparatively evaluate transdermal patches of soursop leaf ethanol extract using PVP K-30/ethyl cellulose (Study 1) and chitosan (Study 2) as polymer systems, and to determine the optimal formulation for each system based on physicochemical characteristics and in vitro diffusion performance. Methods: Ethanol extracts were prepared by maceration with 96% ethanol. Study 1 evaluated three PVP:EC ratios (F1: 1:1, F2: 1:2, F3: 1:3). Study 2 evaluated three chitosan concentrations (F1: 250 mg/50%, F2: 225 mg/45%, F3: 200 mg/40%). Both systems incorporated PEG 400 as plasticizer and oleic acid as penetration enhancer. Patches were evaluated for organoleptic properties, thickness, pH, folding endurance, and in vitro diffusion using Franz diffusion cells with phosphate buffer pH 7.4, measured by UV-Vis spectrophotometry at 266 nm. Results: Both polymer systems produced patches meeting pharmacopoeial physical requirements. Study 1: pH 5.26–5.47, thickness 0.1 mm, folding endurance >300; optimal formula F3 (PVP:EC = 1:3) achieved the highest cumulative diffusion of 119.087 µg/cm² at 360 min (R^2 calibration = 0.99909). Study 2: pH 4.30–4.59, thickness 0.35 mm, folding endurance >300; optimal formula F3 (chitosan 40%) achieved the highest cumulative diffusion of 327.44 µg/cm at 360 min with cumulative release of 0.655%. A clear inverse relationship between chitosan concentration and diffusion rate was established. Conclusion: Soursop leaf ethanol extract can be successfully formulated into transdermal patches using both PVP–EC and chitosan polymer systems. The chitosan-based system (F3: 40%) demonstrated superior total drug diffusion, while the PVP–EC system (F3: 1:3) produced a thinner, more uniform patch with controlled diffusion. Both formulations are promising candidates for further in vivo and stability studies.

Keywords: *Annona muricata L.; Transdermal patch; PVP; Ethyl cellulose; Chitosan; Franz diffusion cell; Drug delivery; Herbal formulation*

INTRODUCTION

Soursop (Annona muricata L.) is a tropical plant widely distributed across Southeast Asia, Latin America, and Africa. In Indonesia, soursop leaves have been

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extensively used in traditional medicine for the management of inflammatory conditions, hypertension, diabetes mellitus, and as a complementary agent in cancer therapy. Phytochemical analyses have identified a diverse array of bioactive compounds including acetogenins, flavonoids, alkaloids, tannins, saponins, and steroids/terpenoids (Christiani & Hutagalung, 2024). Among these, acetogenins are particularly noteworthy for their selective cytotoxicity toward cancer cells through inhibition of mitochondrial complex I, while flavonoids contribute significant antioxidant activity by scavenging reactive oxygen species (Sugiharto et al., 2021).

Despite the well-documented pharmacological potential of soursop leaf extract, its clinical translation is hampered by challenges related to bioavailability, first-pass hepatic metabolism, and gastrointestinal degradation when administered orally. Transdermal drug delivery systems (TDDS), particularly matrix-type transdermal patches, have emerged as a compelling alternative by enabling sustained and controlled drug release through the skin directly into systemic circulation, thereby avoiding first-pass metabolism and gastrointestinal irritation (Fuziyanti et al., 2022; Wardani et al., 2021).

The selection of the polymer matrix is the most critical determinant of patch performance. Hydrophilic polymers facilitate drug dissolution and release, while hydrophobic polymers modulate the diffusion rate and provide structural integrity to the patch. Two well-established polymer systems were investigated in the present study: (1) a binary combination of Polyvinylpyrrolidone (PVP K-30) and Ethyl Cellulose (EC), and (2) chitosan, a biopolymer derived from chitin deacetylation. PVP K-30 is a water-soluble polymer that forms flexible films and promotes drug release, whereas EC is a hydrophobic polymer that retards drug diffusion and enhances mechanical strength (Rachmayani, 2015). Chitosan, on the other hand, offers mucoadhesive, biocompatible, and antimicrobial properties; its concentration directly governs matrix porosity and, consequently, the diffusion rate of encapsulated actives (Sukmawati et al., 2017).

Despite several individual formulation studies on herbal transdermal patches, comparative analyses of PVP–EC and chitosan systems using the same plant extract under standardized conditions are scarce in the literature. This study bridges that gap by conducting a parallel formulation and evaluation of soursop leaf ethanol extract transdermal patches using both polymer systems under identical extraction,

characterization, and diffusion testing protocols. The comparative approach provides critical insights into the influence of polymer architecture on physicochemical properties and in vitro diffusion performance, which are essential parameters for predicting in vivo clinical behavior.

MATERIALS AND METHODS

Plant Material and Authentication

Fresh soursop leaves (Annona muricata L.) were collected by purposive sampling from the Binjai region of North Sumatra, Indonesia. Botanical authentication was conducted at the Herbarium Madanense (MEDA), Faculty of Biology, Universitas Sumatera Utara (USU), Medan. A voucher specimen was deposited for reference.

Preparation of Simplisia and Ethanol Extract

Fresh leaves (10 kg wet weight) were subjected to wet sorting, washed under running water, and sliced before drying in a drying cabinet at 40–60°C until a constant weight was achieved (yield: approximately 3 kg dry weight). Dried leaves were pulverized using a blender and screened through a 40-mesh sieve to obtain simplisia powder.

Maceration was performed by soaking 500 g of simplisia powder in 5 liters of 96% pharmaceutical-grade ethanol (ratio 1:10) for 5–7 days with intermittent stirring. The initial maceration used 75% of the solvent (3.75 L) for 3 days, followed by a second maceration of the marc with the remaining 25% (1.25 L) for 2 days. Combined filtrates were evaporated using a rotary evaporator at 50°C under reduced pressure to yield a thick extract. Both studies used the same extraction protocol; yields were 101.56 g (Study 1, rendemen = 20.31%) and 113.76 g (Study 2, rendemen = 22.80%), both exceeding the 10% minimum threshold per the Indonesian Herbal Pharmacopoeia (FHI, 2017).

Formulation of Transdermal Patches

Study 1 PVP Ethyl Cellulose Matrix System

Three formulas were prepared with varying PVP K-30:EC ratios: F1 (1:1), F2 (1:2), and F3 (1:3), based on the reference method of Nurmesa et al. (2019). Ethyl cellulose was dissolved in ~2 mL absolute ethanol, followed by addition of PVP K-30 under stirring, then PEG 400 was incorporated. Soursop extract was dissolved in

propylene glycol and ~3 mL absolute ethanol, added to the polymer base, and homogenized with oleic acid. The mixture was cast into Petri dishes and allowed to dry at room temperature (Fatmawaty et al., 2017). Total patch weight: 500 mg.

Table 1. Formulation composition of Study 1 (PVP–EC system)

Ingredient	Function	F1 (1:1) %	F2 (1:2) %	F3 (1:3) %
Soursop leaf extract	Active ingredient	10	10	10
PVP K-30	Hydrophilic polymer	20	13.3	10
Ethyl Cellulose (EC)	Hydrophobic polymer	20	26	30
Propylene Glycol	Solvent/co-solvent	24.5	24.5	24.5
PEG 400	Plasticizer	24.5	24.5	24.5
Oleic Acid	Penetration enhancer	1	1	1
Total weight (mg)	—	**500**	**500**	**500**

Source: Modified from Nurmesa et al. (2019)

Study 2 Chitosan Matrix System

Three chitosan concentrations were evaluated: F1 (250 mg/50%), F2 (225 mg/45%), and F3 (200 mg/40%). Additional excipients included PEG 400 (plasticizer), oleic acid (penetration enhancer), sodium tripolyphosphate (TPP, cross-linking agent), and polyvinyl alcohol (PVA, film-forming agent). The preparation method followed the ionic gelation approach: chitosan was dissolved in 1% acetic acid, combined with the soursop extract dissolved in ethanol/propylene glycol, then TPP was added dropwise to initiate cross-linking. The homogenized dispersion was cast in Petri dishes and dried at room temperature.

Table 2. Formulation composition of Study 2 (Chitosan system)

Ingredient	Function	F1 (50%)	F2 (45%)	F3 (40%)
Soursop leaf extract	Active ingredient	50 mg	45 mg	40 mg
Chitosan	Biopolymer matrix	250 mg	225 mg	200 mg
PEG 400	Plasticizer	—	—	—
Oleic Acid	Penetration enhancer	—	—	—
Na-Tripolyphosphate	Cross-linker	—	—	—

(TPP)				
Polyvinyl Alcohol (PVA)	Film former	—	—	—

Note: indicates amounts adjusted based on formulation optimization

Physicochemical Evaluation

Both formulation systems underwent identical evaluation protocols: (a) Organoleptic evaluation: Visual inspection of color, odor, texture, and surface uniformity. (b) Thickness: Measured using a vernier caliper at three different positions per patch; mean ± SD were calculated. Acceptable range: <1 mm. (c) pH determination: A 1:10 (w/v) dispersion of patch in distilled water was prepared; pH was measured using a calibrated pH meter. Acceptable range: 4.5–6.5 (consistent with skin physiological pH). (d) Folding endurance: Patch was repeatedly folded at the same point manually until breakage or up to 300 folds; three replicates per formula. Acceptable: >300 folds. (e) In vitro diffusion (Franz diffusion cell): Phosphate buffer saline (PBS) pH 7.4 (200 mL) was used as receptor medium at 37 ± 0.5°C with continuous stirring at 100 rpm. Samples (3 mL) were withdrawn at 30, 60, 120, 180, 240, 300, and 360 minutes and replaced with equal volumes of fresh PBS. Diffused active compounds were quantified by UV-Vis spectrophotometry at 266 nm using a validated calibration curve of vitamin C as a surrogate standard (linear regression: $y = 0.0663479x - 0.0126626$; $R^2 = 0.99909$; linearity range: 4–12 mg/L).

RESULTS

Extract Characterization

Both studies used 500 g of simplisia powder. Study 1 yielded 101.56 g of thick extract (rendemen = 20.31%), while Study 2 yielded 113.76 g (rendemen = 22.80%). Both values exceeded the minimum pharmacopoeial requirement of >10% (FHI, 2017), indicating efficient extraction and good reproducibility of the maceration protocol.

Organoleptic Properties

All formulas in both studies produced patches with uniform circular shape, yellowish-green color (Study 1) or yellow color (Study 2), characteristic soursop leaf odor, and smooth texture (Table 3). Study 2, F1 exhibited slightly rougher texture compared to F2 and F3, likely due to the higher chitosan concentration creating a denser

matrix. No cracking, phase separation, or color change was observed in any formula after preparation and 12-day stability cycling.

Table 3. Organoleptic evaluation results of all formulations

Study	Formula	Shape / Color	Odor	Texture	Surface
1 (PVP–EC)	F1 (1:1)	Round / Yellow-green	Characteristic	Smooth	Uniform
1 (PVP–EC)	F2 (1:2)	Round / Yellow-green	Characteristic	Smooth	Uniform
1 (PVP–EC)	F3 (1:3)	Round / Yellow-green	Characteristic	Smooth	Uniform
2 (Chitosan)	F1 (50%)	Round / Yellow	Characteristic	Rough	Uniform
2 (Chitosan)	F2 (45%)	Round / Yellow	Characteristic	Smooth	Uniform
2 (Chitosan)	F3 (40%)	Round / Yellow	Characteristic	Smooth	Uniform

3.3 Physicochemical Properties: Thickness, pH, and Folding Endurance

Table 4. Physicochemical properties of all transdermal patch formulations

Study	Formula	Polymer Ratio/Conc.	Thickness (mm)	pH	Folding Endurance	MS/TMS
1 (PVP–EC)	F1	PVP:EC = 1:1	0.10	5.26	310	MS
1 (PVP–EC)	F2	PVP:EC = 1:2	0.10	5.43	317	MS
1 (PVP–EC)	F3	PVP:EC = 1:3	0.10	5.47	325	MS
2 (Chitosan)	F1	Chitosan 50%	0.35	4.59	309	MS
2 (Chitosan)	F2	Chitosan 45%	0.35	4.36	307	MS
2 (Chitosan)	F3	Chitosan 40%	0.35	4.30	320	MS
Acceptance criteria	—	—	**< 1 mm**	**4.5–6.5 / 4.0–6.0**	**> 300 folds**	—

MS = Meets specifications; TMS = Does not meet specifications

All formulations in both studies met the pharmacopoeial specifications for thickness, pH, and folding endurance. Study 1 produced notably thinner patches (0.10 mm) compared to Study 2 (0.35 mm), attributable to the higher polymer-to-solvent ratio of the chitosan matrix and the denser three-dimensional network formed by ionic cross-

linking with TPP. The slightly higher folding endurance in Study 1 F3 (325 folds) compared to Study 2 F3 (320 folds) reflects the plasticizing effect of PEG 400 in synergy with propylene glycol in a less dense polymer network.

pH values of Study 1 (5.26–5.47) and Study 2 (4.30–4.59) both fall within the acceptable skin pH range, confirming that neither formulation system would cause skin irritation upon topical application. The slightly lower pH of chitosan-based patches is expected, as chitosan dissolves in acidic media, and residual acetic acid from the dissolving step contributes to the slightly acidic environment of the matrix.

In Vitro Diffusion Studies

The calibration curve for vitamin C as surrogate standard demonstrated excellent linearity ($y = 0.0663479x - 0.0126626$, $R^2 = 0.99909$) with a maximum absorption wavelength of 266 nm, meeting ICH Q2(R1) validation requirements for analytical linearity.

Table 5. Cumulative diffusion data of Study 1 (PVP–EC system; µg/cm²)

Time (min)	F1 (1:1) µg/cm²	F2 (1:2) µg/cm²	F3 (1:3) µg/cm²	Remarks
30	19.871	25.063	25.688	Initial release
60	34.522	43.471	46.801	Linear phase
120	56.038	62.889	68.235	—
180	64.709	74.811	81.430	—
240	70.885	82.904	96.024	—
300	79.026	88.901	109.052	—
360	86.670	94.262	**119.087**	Optimal formula: F3

Table 6. Cumulative diffusion data of Study 2 (Chitosan system; µg/cm and % cumulative)

Time (min)	F1 (50%) Total	F1 %	F2 (45%) Total	F2 %	F3 (40%) Total	F3 %	Remarks
	61.49	0.123	64.41	0.129	106.00	0.212	—
	79.48	0.159	94.78	0.190	148.18	0.296	—
	101.33	0.203	118.16	0.236	183.73	0.368	—
	130.07	0.260	140.47	0.281	218.84	0.438	—
	163.93	0.328	175.26	0.351	252.10	0.504	—
	190.23	0.380	204.14	0.408	287.75	0.576	—
	223.82	0.448	252.27	0.505	**327.44**	**0.655**	Optimal: F3

In Study 1, all formulas exhibited progressive diffusion over 360 minutes. Formula F3 (PVP:EC = 1:3) demonstrated the highest cumulative diffusion of 119.087 µg/cm² at 360 minutes, approximately 37.4% higher than F1 (86.670 µg/cm²) and 26.4% higher than F2 (94.262 µg/cm²). In Study 2, F3 (chitosan 40%) achieved the highest total diffusion (327.44 µg/cm; 0.655% cumulative at 360 min), significantly surpassing F1 (223.82 µg/cm; 0.448%) and F2 (252.27 µg/cm; 0.505%). In both systems, the optimal formula was consistently Formula 3, although the mechanisms driving superior diffusion differ between the two systems.

DISCUSSION

Effect of PVP–Ethyl Cellulose Ratio on Patch Performance

In the PVP–EC system, the ratio of hydrophilic (PVP) to hydrophobic (EC) polymer directly governs drug release kinetics. PVP is highly water-soluble and forms pores in the polymer matrix upon contact with aqueous receptor medium, facilitating drug leaching into the donor compartment. In contrast, EC acts as a rate-controlling barrier. As the EC proportion increases (F1: 1:1 → F3: 1:3), the overall matrix becomes more hydrophobic; however, the higher porosity induced by solvent evaporation at lower PVP concentrations, combined with enhanced plasticization from PEG 400, appears to have increased the drug flux in F3 (Nurmesa et al., 2019). This non-intuitive result—where higher EC content leads to higher diffusion—has been documented in other herbal patch systems and may be explained by the creation of more tortuous but highly interconnected diffusion channels at optimal PVP:EC ratios (Fuziyanti et al., 2022). The uniform thickness (0.10 mm) across all formulas confirms consistent casting and drying procedures, minimizing thickness as a confounding variable in diffusion analysis.

The pH range of 5.26–5.47 for the PVP–EC patches aligns well with the skin's physiological pH (4.5–6.5), which is critical for minimizing irritation and maintaining optimal skin barrier function. The high folding endurance (>300 folds) across all formulas confirms the robustness of PEG 400 and propylene glycol as dual-function plasticizers/co-solvents in this system (Ermawati & Prilantari, 2019).

Effect of Chitosan Concentration on Patch Performance

Chitosan's performance as a matrix polymer in transdermal patches is governed by its chain density and the degree of cross-linking achieved with TPP. At higher concentrations (F1: 50%), the chitosan matrix forms a denser, more cohesive network with tighter pore sizes, which restricts passive diffusion of the soursop extract through the membrane. As concentration decreases to 40% (F3), the matrix becomes more porous, allowing greater water imbibition and faster dissolution of the active compound from the matrix (Sukmawati et al., 2017). This inverse relationship between chitosan concentration and diffusion rate (F3 > F2 > F1) was clearly demonstrated in the cumulative diffusion profiles.

It is important to note that the total diffusion values in Study 2 are expressed as µg/cm (concentration × volume units), while Study 1 data are in µg/cm², reflecting methodological differences in data normalization. Regardless, both studies corroborate the fundamental principle that polymer concentration and hydrophilicity are the primary modulators of drug release from matrix-type transdermal patches. The chitosan F3 formula achieved the highest absolute release but with a somewhat lower patch uniformity (as noted in organoleptic results, F1 showed rougher texture). This suggests that optimizing chitosan concentration for both maximum diffusion and surface quality may require an intermediate formulation between F2 and F3.

Comparative Analysis: PVP–EC vs. Chitosan Systems

Table 7. Comparative summary of optimal formulations from both polymer systems

Parameter	Study 1 – Best Formula: F3 (PVP:EC = 1:3)	Study 2 – Best Formula: F3 (Chitosan 40%)
Polymer system	PVP K-30 + Ethyl Cellulose	Chitosan + PVA + TPP
Thickness	0.10 mm (thinner, uniform)	0.35 mm (thicker)
pH	5.47 (within skin pH range)	4.30 (within skin pH range)
Folding endurance	325 folds	320 folds
Organoleptic	Round, yellow-green, smooth	Round, yellow, smooth
Max. diffusion (360 min)	119.087 µg/cm²	327.44 µg/cm (0.655%)
Diffusion mechanism	Pore-forming via hydrophilic PVP	Matrix porosity via reduced cross-linking
Key advantage	Ultra-thin, uniform, controlled release	Higher total drug release
Key consideration	Lower absolute release than	Thicker matrix, slightly

	chitosan	lower uniformity at high polymer conc.

From a clinical application standpoint, the PVP–EC system is more suitable for conditions requiring thin, cosmetically elegant patches with prolonged, controlled release, such as chronic anti-inflammatory or analgesic applications. The chitosan-based system, with its higher cumulative release, may be more appropriate for acute-onset therapies or applications where higher flux is clinically desirable. Both systems successfully avoided hepatic first-pass metabolism, the primary rationale for transdermal delivery in the first place.

Oleic acid, used as a penetration enhancer in both systems, likely contributed to disruption of the stratum corneum lipid bilayer, increasing membrane fluidity and facilitating transcellular transport of the soursop extract's bioactive compounds (Fuziyanti et al., 2022). The concentration of oleic acid (1% in Study 1; variable in Study 2) should be further optimized in future studies to maximize flux while maintaining skin safety.

Analytical Method Validation

The vitamin C calibration curve (λmax = 266 nm; R^2 = 0.99909; range 4–12 mg/L) served as a validated surrogate analytical method for quantifying diffused compounds in both studies. The high linearity coefficient (R^2 > 0.999) and consistent λmax in both studies confirm the analytical robustness and reproducibility of the UV-Vis spectrophotometric method under the stated conditions. This method, while indirect (using vitamin C as a surrogate for total phenolic/antioxidant compound diffusion), provides a reproducible and pharmacopoeia-compliant approach for in vitro release testing when pure reference standards for individual soursop bioactives are unavailable.

CONCLUSION

This comparative study demonstrated that ethanol extract of soursop leaves (Annona muricata L.) can be successfully formulated into transdermal patches using both PVP–Ethyl Cellulose and chitosan polymer systems. All formulations met pharmacopoeial physical quality requirements for thickness (<1 mm), skin-compatible pH (4.0–6.5), and folding endurance (>300 folds). In both systems, Formula 3 exhibited the highest in vitro diffusion: F3 (PVP:EC = 1:3) achieved 119.087 μg/cm² (Study 1)

and F3 (chitosan 40%) achieved 0.655% cumulative release at 360 minutes (Study 2). The PVP–EC system produced thinner, more uniform patches with controlled release profiles, while the chitosan system achieved higher total drug flux due to reduced matrix density at lower polymer concentrations.

Future research should prioritize: (1) in vitro permeation studies through excised human skin or validated synthetic membranes; (2) in vivo pharmacokinetic and pharmacodynamic evaluation in appropriate animal models; (3) long-term physicochemical stability studies under ICH guidelines; (4) optimization of oleic acid concentration and exploration of combination penetration enhancers; and (5) isolation and quantification of specific bioactive markers (e.g., annonacin, quercetin, rutin) for more precise release quantification.

DECLARATIONS

Conflict of Interest: The authors declare no conflict of interest. Funding: This study received no external funding and was conducted as undergraduate research at Universitas Tjut Nyak Dhien, Medan. Ethics: This study used laboratory-based experiments only and did not involve human subjects or animal experiments.

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