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Skin Penetration of Corn Silk (*Zea mays* L.) Transdermal Patch on Wistar Mice Skin Using Franz Diffusion Cell

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Abstract

***Background**: Corn silk (Zea mays L.) contains many active compounds, especially the flavonoid quercetin which has pharmacological activity as an antihyperlipidemic agent by reducing cholesterol and triglyceride levels in the body. Antihyperlipidemic treatment by oral route, such as statin drugs, has the disadvantage of experiencing a first-pass effect in the liver, which reduces the bioavailability of the drug. In addition to avoiding the first-pass effect, transdermal patches can improve patient compliance because they are easy to use. **Objective**: This study aims to optimize the transdermal patch formula of corn silk extract and test the penetration of the optimum formula by in vitro. **Method**: Optimization of the formula using the Regular Two-Level Factorial Design method on Design Expert®. This study used 2 factors, namely HPMC with a concentration of 3%-4% and PVP with a concentration of 1%-2%. The optimum formula obtained was subjected to in vitro penetration test using Franz diffusion cell. **Results**: Based on the results of factorial design analysis, the optimum formula of transdermal patches is at HPMC and PVP concentrations of 3.49% and 1% with moisture content, moisture uptake, percentage of elongation, and folding endurance respectively of 7.79%, 4.19%, 13.26% and 470.58 fold. The optimum formula of corn silk extract transdermal patch preparation also had an optimum percent cumulative amount of penetrated flavonoids of 96.06% and flux of 6.17 µg/cm^2.hour at 3 hours. **Conclusion**: Transdermal patch dosage of corn silk extract with HPMC and PVP concentrations of 3.49% and 1% proved to have good characteristics and penetration rate.*

***Keywords**: franz diffusion, optimization, transdermal patch, Zea mays L.*

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INTRODUCTION

Due to abnormal fat metabolism or function, hyperlipidemia is characterized by elevated levels of total cholesterol, triglycerides, low-density lipoprotein (LDL), and decreased levels of high-density lipoprotein (HDL) (Mala *et al*., 2019). Eating disorders, obesity, the genetic disease familial hypercholesterolemia (FH), and diabetes are the causes of hyperlipidemia (Yao *et al*., 2020). Corn silk (*Zea mays* L.) is a natural constituent with antihyperlipidemic properties that can be used to treat this disease.

Corn silk contains secondary metabolites such as alkaloids, steroids, carotenoids, saponins, anthocyanins, phenolics, and flavonoids (Al-Oqail *et al*., 2019; Kim *et al*., 2019; Yucharoen *et al*., 2023). The pharmacological activities of corn silk include anti-inflammatory, anti-diabetic, antioxidant, anti-bacterial, anti-fatigue, anti-depressant, and antihyperlipidemic (Hasanudin *et al*., 2012; Linard De Carvalho *et al.*, 2019; Wang & Zhao, 2019; Limmatvapirat *et al.*, 2020; Lapčík *et al.*, 2023). Research conducted by Wang *et al.* (2017) proved that corn silk thick extract at 400 and 800 mg/kgBW could significantly reduce total cholesterol, triglyceride, and LDL levels in rat test animals. This activity relates to the flavonoid compound in corn silk, namely quercetin. Research conducted by Yucharoen *et al.* (2023) proved that ethanol thick extract of corn silk contains 4.71 ± 0.79 mg quercetin equivalent/g extract. By inhibiting intestinal cholesterol absorption by reducing the expression of the epithelial cholesterol transporter, quercetin can function as an antihyperlipidemic. Niemann-Pick C1-like 1 (NPC1L1) inhibits the formation of lipid oxidative stress, enhances PPAR expression, and inhibits macrophage-modified LDL oxidation by decreasing the content. LDL particles contain -tocopherol (Agung, 2021; Fukaya *et al*., 2021; Yi *et al*., 2021).

Oral antihyperlipidemic drugs, such as statins, can be well absorbed, but they may undergo a first-pass effect in the liver, thereby decreasing drug bioavailability (Korani *et al*., 2019). Therefore, a transdermal patch was devised using corn silk extract. Transdermal delivery has advantages such as preventing the first-pass effect, increasing bioavailability, and increasing patient compliance due to its ease of use (Tijani *et al*., 2021). The active substance is released on the surface of the epidermis by diffusion through the corneal layer into the dermis, allowing it to enter the systemic circulation and be delivered to the target organ (Arum *et al*., 2022). A polymer is an essential component in the production of transdermal patches. This study utilized Hydroxy Propyl Methyl Cellulose (HPMC) and Polyvinyl Pyrrolidone (PVP) as polymers. The concentrations of HPMC and PVP used were 3% to 4% and 1% to 2%, respectively. The polymer was optimized using the Regular Two-Level Factorial Design method on Design Expert® software because this method is simple and easy to analyze the influence of independent variables, as in the research of Pratiwi *et al*. (2020). Polymers can affect drug discharge from the matrix of a transdermal patch. The medication release capability of the matrix of a transdermal patch can be evaluated in vitro using the Franz Diffusion Cell method.

Based on the description above, research was conducted on "Penetration of Transdermal Patch Preparations of Corn Silk Extract (*Zea mays* L) in the Skin of Wistar Rats Using the Franz Diffusion Cell Method". Corn silk (*Zea mays* L.) was extracted using the maceration method with 96% ethanol as the solvent. Optimization of a formula utilizing the Regular Two-Level Factorial Design method in Design Expert® software. This research uses factors A (HPMC) and B (PVP). The corn silk (*Zea mays* L.) transdermal patch was evaluated to obtain the optimum formula and in vitro diffusion test to describe the ability of the drug substance to penetrate after being released from the preparation.

MATERIALS AND METHODS

Materials

The materials used in this research were corn silk (Zea mays L.), Wistar male white rats (Local, Indonesia), AlCl3 (Merck®, Indonesia), sodium acetate (Merck®, Indonesia), methanol (Merck®, Indonesia), ethanol 96 % (Merck®, Indonesia), phytochemical screening reagent, NaOH (Merck®, Indonesia), KH2PO4 (Merck®, Indonesia), HPMC (MakingCosmetic®, USA) with a viscosity of 83.92 Poise, PVP (JH Nanhang Life Sciences Co., Ltd, China), propylene glycol (DOW®, Indonesia), Dimethylol-dimethyl (DMDM) hydantoin (PA Chemical, Indonesia), distilled water (Local, Indonesia), and silica (Local, Indonesia).

Tool

The tools used in this research were an oven (IMU55L), glass jar (DLX Glass®), grinder (MKS-ML500), digital scale (NewTech Electronic Balance®), magnetic stirrer (IKA® C-MAG HS 4), Franz diffusion cell (Kalfaro), test tube (Pyrex®), beaker (Pyrex®), 100-1000 µl micro pipette (Dragon Lab®), aluminum foil (Best Fresh®), filter paper (Sumber Ilmiah Persada), micrometer screw (Tricle Brand®), stative (Trivi®), clamp (Trivi®), rotary evaporator (Dragon Lab®), and desiccator (Duran®).

Method

Preparation of corn silk extract

The maceration procedure was used to extract 1 kilogram of powdered corn silk simplicia. The samples were macerated with 96% ethanol at a 1:10 (w/v) ratio and remacerated with the same ratio. This mixture is thoroughly agitated, sealed, and left for 72 hours. Remaceration is performed for 48 hours (Widyaningrum *et al*., 2020). The filtrate was filtered using filter paper and evaporated at 50°C using a rotary evaporator until a viscous extract was obtained. Equation 1 is utilized to determine the extract's percentage yield.

$$\% \text{ Yield Extract } = \frac{\text{Weight of Extract}}{\text{Weigh of Simplicia}} \text{ x } 100\% \text{ ………….……… [1]}$$

Phytochemical screening

Phytochemical screening includes qualitative examination of flavonoids, alkaloids, terpenoids/steroids, tannins and saponins (Ministry of Health of the Republic of Indonesia, 2017).

Determination of total flavonoid content

Total flavonoid contents were determined using a modified aluminum chloride colorimetric method using quercetin as a standard solution (Limmatvapirat *et al*., 2020). Quercetin was used as a standard. The quercetin concentration used to create the calibration curve is 20-60 ppm. Then, 5 mL of quercetin and corn silk extract samples were reacted with 0.1 mL of 0.01 mol/L aluminum chloride and 0.1 mL of sodium acetate. The mixture was then left at ambient temperature for 10 minutes, and the absorbance value at 430 nm was determined using a UV-Vis spectrophotometer.

Transdermal patch formulation

The formulation of the transdermal patch is based on Yusuf's (2020) research with minor modifications. This research altered the concentration of the active substance and polymer. Utilizing a 2^2-factorial design with two factors and two levels, the polymer was optimized using HPMC and PVP as the two factors and 3-4% and 1-2% as the two levels. The formula was presented in Table 1.

Preparation of transdermal patches

As mass 1, HPMC was dispersed in a 1:1 mixture of ethanol and distilled water as the solvent. Mass 2 of PVP was dispersed in ethanol. Then, mass 1 and mass 2 are thoroughly combined until uniform. In ethanol, the extract was dissolved. While agitating, the extract solution, propylene glycol, and DMDM (Dimethylol-dimethyl) hydantoin were added to the polymer solution. The mixture was then poured into a petri dish coated with liquid paraffin and desiccated for 24 hours at 42ºC (Putri *et al*., 2019).

Table 1. The 2^2-factorial design for transdermal patch formulation

Ingredients	Formula			
	F1	F2	F3	F4
Corn Silk Extract (mg)	200	200	200	200
HPMC*	3	4	3	4
PVP*	1	1	2	2
Propylene Glycol (mL)	0.11	0.11	0.11	0.11
DMDM Hydantoin (mL)	0.01	0.01	0.01	0.01
Distilled Water (mL)	15	16	12	13
Ethanol (mL)	ad 50	ad 50	ad 50	ad 50

*The ratio was calculated to a total of 400 mg polymer

Table 2. Criteria for Optimum Formula

Parameters	Goals
Thickness	Minimum
% Moisture Content	In range
% Moisture Uptake	Minimum
% Elongation	Maximum
Weight Uniformity	Minimum
Folding Endurance	Maximum

Evaluation of transdermal patches

Organoleptic

Organoleptic analysis involves observing the patch's form, odor, color, and surface condition (Indrawati *et al*., 2022).

Thickness

The thickness of a patch is measured with a screw micrometer or a vernier caliper. The data obtained was then calculated as an average value (mean ± standard deviation) (Hashmat *et al*., 2020).

Percentage of moisture content

The patch weight was measured and then placed in a desiccator for 72 hours. After 72 hours, the weight was measured again (Budhathoki *et al*., 2016). The percentage of moisture absorption capacity is calculated based on equation 2.

$$\% \text{ Moisture content} = \frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}} \text{ x } 100\%$$

………….……… [2]

Percentage of moisture uptake

The patch weight was measured and then stored in a desiccator for 24 hours. After 24 hours, the patch weight was measured again (Budhathoki *et al*., 2016). The percentage of moisture uptake is calculated based on equation 3.

$$\% \text{ Moisture uptake} = \frac{\text{Final Weight - Initial Weight}}{\text{Initial Weight}} \text{ x } 100\%$$

………….……… [3]

Percentage of elongation break test

The patch is clamped between the top and bottom material clamps by applying a load or force. The final length can be seen if the patch is torn (Panda, 2022).The elongation percentage is calculated based on equation 4.

$$\% \text{ Elongation} = \frac{\text{Final length - Initial length}}{\text{Initial length}} \text{ x } 100\%$$

….… ………………… [4]

Weight Uniformity

Patch weights were weighed using an analytical balance. For each 3 patches, the average weight, standard deviation and % CV were calculated (Panda, 2022).

Folding Endurance

The patch is folded repeatedly in the same position until it tears. The number of folds is a value of fold resistance (Budhathoki *et al*., 2016).

Irritation Test

The skin irritation test was conducted on 15 volunteers by placing a patch on the back of their hand and observing for 24 hours for indicators of redness, erythema, and edema (Wahyuni *et al*., 2023).

Determination of optimum formula

The optimum formula is determined using Design Expert® based on a desirable value close to 1. The criteria for determining the optimum formula can be seen in Table 2.

Franz diffusion penetration test

The penetration test was conducted using Franz diffusion cells and the back skin of a mice. Between the donor and receptor compartments was mice epidermis. The patch is applied directly to the epidermis. As a diffusion medium, 50 ml of phosphate buffer solution at pH 7.4 was added to the receptor compartment. At a temperature of 37 ± 0.5°C and a speed of 200 rpm, tests were conducted. At 0, 15, 30, 45, 60, 90, 120, 150, and 180 minutes, 3 mL of solution was pipetted from the receptor compartment and replaced with 3 mL of fresh medium. The sample was subsequently filtered and placed in a 10 mL vial. (Putri *et al*., 2019). Using a UV-Vis spectrophotometer, the flavonoid concentrations of the samples were determined. Based on equation 5, the cumulative quantity of flavonoids that penetrate is calculated.

$$Q = \frac{\text{Cn.V} + \sum_{i=0}^{n-1} \text{C. S}}{\text{A}}$$

………………………………… [5]

Note

Q : the cumulative amount of flavonoids penetrated ($\mu g/cm^2$)
Cn : flavonoid concentration at the nth hour
$\sum_{i=0}^{n-1} C$: total flavonoid concentration in the first sample collection until before the nth hour
V : Franz diffusion cell volume (mL)
S : sampling volume (mL)
A : membrane area (cm^2)

Next, the flavonoid penetration level (flux) was calculated using Fick's law (equation 6).

$$J = \frac{Q}{t.\ A}$$

…………………………………………….. [6]

Note

J : flux of flavonoid penetration rate ($\mu g/cm^2$.hour)
Q : the cumulative amount of flavonoids passing through the diffusion membrane ($\mu g/cm^2$)
t : time (hour)
A : membrane area (cm^2)

Data analysis

Formula design and evaluation data analysis were carried out using the Factorial Design method of Design Expert® software.

RESULTS AND DISCUSSION

Corn silk extract

The corn silk extract produced in this study was brownish green, had a distinctive odor, and was thick, yielding 9.79%. Figure 1 depicts the organoleptic results of corn silk extract. The percentage yield results acquired differ from previous research conducted by Fajrina *et al.* (2021), which found a 23.65% yield. Various factors, including the extraction process and the vicariance of secondary metabolite compounds due to disparities in growing locations, contributed to the differences in yields. The solvent employed can influence the efficacy of an extraction procedure. This study utilized a 96% ethanol solvent. Flavonoids are compounds with limited water solubility and greater solubility in organic solvents such as methanol and ethanol (Mubarokah *et al*., 2023). A 96% ethanol has a water content with a small concentration of 4%. The extraction process in this study is similar to that of Fajrina *et al*. (2021), who used ethanol as a solvent and the maceration method, so the differences in results are likely due to the distinct growing locations. This statement is proven by research conducted by Utomo *et al*. (2020), which demonstrates that differences in the height of the same plant will provide significant differences in the content of secondary metabolites. However, the yield obtained in this study still satisfies the requirements of the Indonesian Herbal Pharmacopoeia for extract yield percentage, which is at least 7.2% (Ministry of Health of the Republic of Indonesia, 2017).

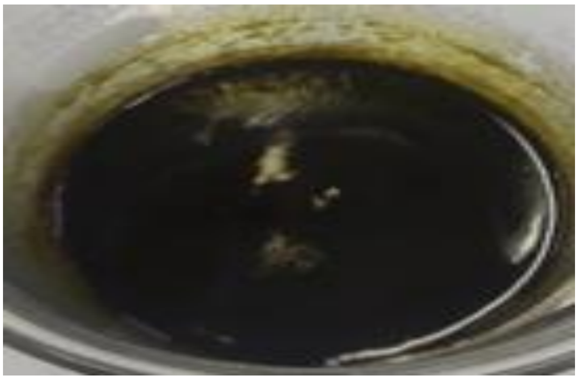

Figure 1. Corn silk extract

Phytochemical screening

The objective of phytochemical screening is to identify the phytochemical class of compounds present in corn silk extract. Various chemical reagents are utilized in the analysis technique for phytochemical screening. Table 3 displays the results of the phytochemical screening of corn silk extract.

Table 3. Phytochemical screening result

Compound	Observation result	Conclusion
Alkaloids	White precipitate	Positive (+)
Flavonoids	Yellowish-red color	Positive (+)
Tannins	Greenish-black color	Positive (+)
Terpenoids	Bluish-green color	Negative (-)
Steroids	Bluish-green color	Positive (+)
Saponins	Permanent foam	Positive (+)

Table 3 demonstrates that corn silk extract contains phytochemical compounds including alkaloids, flavonoids, tannins, steroids, and saponins. According to research conducted by Limmatvapirat *et al.* (2020), corn silk extract includes alkaloids, flavonoids, tannins, steroids, and saponins. Corn silk extract's potential as an antihyperlipidemic agent will be determined by the phytochemical compounds it contains.

Many studies have proven the effect of phytochemical compounds on antihyperlipidemic activity. Research conducted by Islam *et al.* (2021) found that *Rhizoma coptidis*, containing a combination of five main alkaloids, could reduce the accumulation of lipids and cholesterol in HepG2 cells and control the levels of total cholesterol, triglycerides, LDL-c, and HDL-c in hamsters experiencing hypercholesterolemia. Flavonoids have been studied extensively for their ability to act as antihyperlipidemia by inhibiting intestinal cholesterol absorption by reducing the expression of the epithelial cholesterol transporter Niemann-Pick C1-like 1 (NPC1L1), inhibiting the formation of lipid oxidative stress, increasing PPAR expression, and inhibiting the oxidation of macrophage-modified LDL by reducing the α-tocopherol content of LDL particles (Agung, 2021; Fukaya *et al*., 2021; Mulyani, 2020; Yi *et al*., 2021). Research conducted by Issac *et al.* (2018) proved that giving tannins of 25 and 50 mg/kg BW p.o. for 35 days was able to reduce LDL and VLDL levels and increase HDL levels in mice that had been induced by streptozotocin-nicotinamide. Saponin compounds have also been proven to be able to act as antihyperlipidemia. Research conducted by Elekofehinti *et al.* (2013) demonstrated that the use of 20-100 mg/kgBW of saponin for 21 days was able to reduce glucose, TC, TG, and LDL levels and increase HDL levels in rats induced by alloxan. Research conducted by Wang *et al.* (2017) also proved that corn silk extract at 400 and 800 mg/kgBW could significantly reduce total cholesterol, triglyceride, and LDL levels in rat test animals.

Total flavonoid content (TFC)

Using the regression equation of the quercetin standard calibration curve, namely y = 0.0114x – 0.0024 with a correlation coefficient of 0.9994, the total flavonoid content in the extract was determined. According to Table 4, corn silk extract contained 36.6 ± 0.003 mg RE per gram of extract. This very high total flavonoid content is consistent with the findings of Singh *et al.* (2022), who reported that corn silk extract contained multiple flavonoid compounds in the form of maysin, apigmaysin, 3-methoxymaysine, ax-4-OH maysin, and isoorientin-2''-O-a-L-rhamnoside.

Transdermal patch of corn silk extract

The transdermal patch containing corn silk extract was manufactured using solvent casting. The solvent casting method was selected because it is straightforward and uncomplicated to implement (Borbolla-Jiménez *et al*., 2023). The evaluation results of the four transdermal patch formulations are presented in Table 5.

According to Table 5, both F1 and F2 satisfy the patch thickness requirements of 0.15 to 0.2 mm. The thickness of the transdermal patch impacts the drug's release, permeation, retention, and diffusivity through the epidermis (Latif *et al*., 2022). All formulations satisfy the moisture absorption test requirements of 3.52–9.79% and the drying shrinkage test requirements of 10%. When the percentage of moisture absorption and drying shrinkage is low, the patch is more stable and microbial contamination is minimized (Fuziyanti *dkk*., 2022). All formulations pass the test requirements for percentage of elongation > 5% and folding endurance > 200 times. The research by Omar *et al*, (2019) and Pal *et al*, (2023) found that a high percentage of elongation and folding resistance indicates that the patch has excellent mechanical properties and elasticity so that it does not tear easily when applied to the skin. Using Design Expert, the influence of the HPMC and PVP factors on the observed response will be determined based on the measured characteristics of the transdermal patch preparation.

Design expert analysis

Optimization of model fitting

Model fitting analysis is the first stage in the optimization procedure. Model fitting analysis is carried out to determine which parameters can be continued for the optimization process. With parameters such as R^2, adjusted R^2, predicted R^2, adequate precision, and p-value, the DoE method of model fitting can yield accurate prediction results. Each response model satisfies the criteria. If R^2 is greater than 0.70, the difference between adjusted R^2 and predicted R^2 should not exceed 0.2, the adequate precision value should be greater than 4, and the p-value should be less than 0.05 (Apriani *et al*., 2023). Table 6 displays the results of the six measured responses' model-fitting analysis.

Table 4. Total flavonoid content in corn silk extract

Replication	Absorbance	Mean Absorbance ± SD	CV%	TFC/g (mg) ± SD
1	0.441	0.415 ± 0.003	0.008	36.6 ± 0.003
2	0.416			
3	0.418			

Table 5. Transdermal patch evaluation results

Parameter	Formula			
	F1	F2	F3	F4
Organoleptic	Smooth, thin, pale yellow, slightly sticky, typical smell of corn silk extract	Smooth, thin, pale yellow, slightly sticky, typical smell of corn silk extract	Smooth, thin, pale yellow, slightly sticky, typical smell of corn silk extract	Smooth, thin, pale yellow, slightly sticky, typical smell of corn silk extract
Thickness (mm)	0.158 ± 0.019	0.158 ± 0.004	0.133 ± 0.004	0.148 ± 0.025
Moisture Content (%)	8.422 ± 0.366	7.118 ± 1.369	11.503 ± 1.097	5.826 ± 0.097
Moisture Uptake (%)	5.614 ± 0.244	2.681 ± 0.108	7.200 ± 1.297	2.913 ± 0.048
Elongation (%)	16.049 ± 1.008	10.309 ± 0.948	11.592 ± 0.5394	11.969 ± 0.375
Weight Uniformity (%)	0.041 ± 0.009	0.004 ± 0.037	0.004 ± 0.03	0.042 ± 0.001
Folding Endurance	431 ± 4.899	512.333 ± 5.558	311 ± 3.742	384.333 ± 5.437
Irritation Test	No irritation	No irritation	No irritation	No irritation

Table 6. Model Fitting Result

Responses	Parameter				
	R^2	*Adjusted* R^2	*Predicted* R^2	*Adequate Precision*	*p-value*
Thickness	0.2906	0.0246	-0.5961	2.2116	0.4065
% Moisture Content	0.7572	0.8516	0.7572	10.9547	0.0003
% Moisture Uptake	0.9244	0.8961	0.8299	11.8126	<0.0001
% Elongation	0.8844	0.8410	0.7399	2.2116	0.0004
Weight Uniformity	0.4127	0.1924	-0.3215	3.1183	0.2124
Folding Endurance	0.9954	0.9937	0.9897	57.3938	<0.0001

*The result indicates that there is a significant influence on the response ($p < 0.05$)

Based on Table 6, the parameters of thickness and weight uniformity do not meet the requirements for a good model, in contrast, the parameters of moisture content, moisture uptake, percentage of elongation and folding endurance which show good model results. These four parameters have R^2 values greater than 0.7, ranging from 0.7572 to 0.9954, indicating that between 75.72 and 99.54 percent of the data obtained is influenced by the factors used, namely HPMC (A), PVP (B), and the interaction between the two factors (AB). While the remainder is an estimate of error for each parameter. The difference between the adjusted R^2 and predicted R^2 of the four parameters is also less than 0.2, indicating that the data analyzed and the data predicted by the Design Expert system are comparable. The adequate precision value of the four parameters is greater than 4, indicating that the model is resistant to arising disturbances. The p-values of the four parameters also indicate that the factors used have a significant effect on the observed parameters ($p<0.05$). Based on the result, these four parameters can be utilized for response analysis and formula optimization.

Optimization of Responses Analysis

Response analysis was carried out to see the effect of HPMC concentration (A), PVP (B), and the interaction of the two factors (AB) on the parameters of moisture content, moisture uptake, elongation, and folding endurance. The results of the response analysis can be seen in Table 7 and Figure 2.

According to Table 7, HPMC concentration (A) has a significant effect on moisture content, moisture uptake, percentage of elongation, and folding endurance, whereas PVP concentration (B) has a significant effect on moisture uptake, percent elongation, and folding endurance, and the interaction of the two factors (AB) has a significant effect on moisture content and percentage of elongation ($p<0.05$). Figure 2, a depiction of the normal plot of residuals, also supports these findings. The factor points outside the straight line indicate that the factor has both positive and negative influences. This positive and negative influence can be observed by locating the point within the positive or negative region. In addition, it can be determined from the coefficient notation whether or not there is a negative indication. Positive influence indicates that the higher the concentration of the factor employed, the greater the resulting response value. Conversely, negative influence means that the observed response value decreases as the concentration of the factor used increases.

Tabel 7. Results of responses analysis

Parameter		*Intercept*	A (HPMC)	B (PVP)	AB (*Interaction*)
% Moisture Content	*Coefficient*	8.21736	-1.74488	0.447208	-1.09339
	p-value		0.0001*	0.1226	0.0029*
	% contribution		61.1718	4.0183	24.0201
% Moisture Uptake	*Coefficient*	4.6023	-1.80495	0.454317	-0.3385
	p-value		< 0.0001*	0.0449*	0.1147
	% contribution		84.15	5.3314	2.95966
% Elongation	*Coefficient*	12.4087	-1.41228	-0.770592	1.45784
	p-value		0.0009*	0.0241*	0.0008*
	% contribution		37.4216	11.1412	39.8754
Folding Endurance	Coefficient	409.667	38.6667	-62.00	-2.00
	p-value		< 0.0001*	< 0.0001*	0.2872
	% contribution		27.8537	71.6132	0.0745195

*The result indicates that there is a significant influence on the response ($p<0.05$)

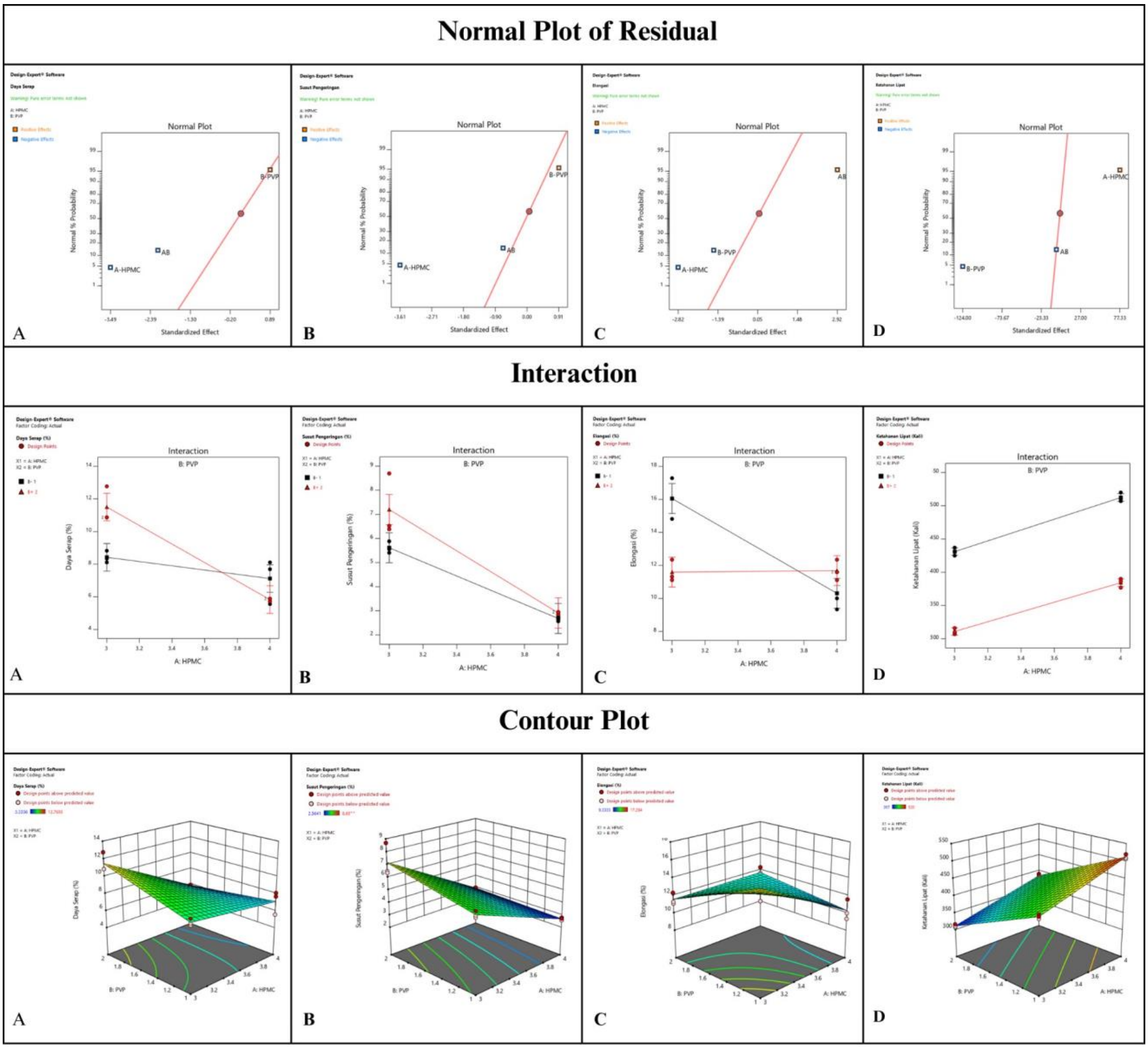

Figure 2. Normal graph plot of residual, interaction, and contour plot of moisture content (A), moisture uptake (B), elongation (C), and folding endurance (D)

Table 8. Optimum formula result

HPMC	PVP	Moisture Content	Moisture Uptake	Elongation	Folding Edurance	*Desirability*
3.487	1	7.788	4.187	13.256	470.582	0.913

The interaction between HPMC and PVP (AB) only affected moisture content and percentage of elongation significantly. This is evident in the % contribution of the AB factor to the moisture content parameter and the percentage of elongation that contributes more than 20%. The moisture uptake and folding endurance parameters are not substantially affected by the AB factor because the % contribution of the AB factor is much less than the estimated % error for these parameters, which are 7.5589% and 0.4585% respectively. Figure 2 also illustrates the interaction between the two variables (AB). Interaction graph in which the intersections of lines represent the interaction between factors A and B at both low and high concentrations. Figure 2's Contour Plot graph also depicts the predicted response area based on the used HPMC and PVP concentrations.

Based on the % contribution value in Table 7, the HPMC (A) factor has the greatest influence on moisture content and moisture uptake with a % contribution value of 61.1718% and 84.15%, respectively. The PVP (B) factor has the greatest influence on folding endurance with a % contribution value of 71.6132%, and the interaction between the two factors (AB) had the

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greatest effect on % elongation at 39.8754%. Figure 3 demonstrates that HPMC has a negative influence on the moisture content and moisture uptake parameters, as depicted by the normal plot of residual graph. This is possible because, unlike PVP, HPMC is not hygroscopic (Rowe *et al*., 2009). The higher the concentration of HPMC, the lower the resultant patch's moisture content and moisture uptake. PVP has a positive effect on the absorption capacity and drying shrinkage parameters due to the hygroscopic properties (Abdul *et al*., 2021). Contour Plot graph in Figure 3 corroborates this. According to the evaluation results in Table 5, PVP has a substantial effect on the parameters describing the resistance to folding. The hygroscopic nature of PVP has a negative effect on folding endurance because the resulting patch is still moist. During testing, wet patches will tear and break more readily. Nonetheless, according to the results of this study's folding endurance evaluation, all formulations met the evaluation criteria of > 300 folding cycles (Simaremare *et al*., 2022). The percentage of elongation is influenced not only by a single factor, but also by the interaction between the two factors, as depicted in Figure 2's interaction graph. The slope angle of the two lines indicates that the strong interaction between HPMC and PVP has a considerable impact, which is corroborated by the % contribution data from the interaction between the two factors (AB), which can be found in Table 7. This interaction exerts a positive influence, such that the greater the interaction between the two parameters, the greater the percentage elongation of the preparation. The interaction between PVP polymer and HPMC can increase the preparation's percentage elongation (Jayaprakash et *al*., 2010; Magfirah & Utami, 2022).

Optimum formula

Determining the optimum formula using Design Expert® software with response criteria according to the target in Table 2 by removing the parameters of patch thickness and weight uniformity due to having model fitting results that do not meet the requirements. Determining the optimum formula is done by looking at the desirability value, which is close to 1, which indicates that the formula is most comparable to the desired criteria. The optimum formula for corn silk extract transdermal patch preparation is at the HPMC : PVP concentration, 3.49 : 1, with a desirability value of 0.913. The characteristic results of the transdermal patch preparation in the optimum formula can be seen in Table 8.

Franz diffusion penetration of transdermal patch

Using a Franz diffusion cell device, the optimal formula penetration test was conducted to ascertain the amount of flavonoid compounds that penetrated through the skin during a specific time interval from the corn silk extract transdermal patch. Mice skin from the Wistar strain is used as the membrane because its permeability value is comparable to that of human skin, at 103.08 cm/hour x 10^{-5} and 92.27 cm/hour x 10^{-5}, respectively (Chandra, 2019). The skin membrane of the Wistar strain mice used was 1.76 cm^2. Before using animals for experimentation, a code of ethics with the number 022307099 must be obtained from the Ahmad Dahlan University Research Ethics Committee. Table 9 and Figure 3 display the penetration test results of the optimum transdermal patch formulation.

According to Table 9 and Figure 3, the cumulative value of flavonoids that penetrated that can penetrate rat skin is 32.59 $\mu g/cm^2$ at 3 hours. After 3 hours, a controlled release occurred. Probably due to the matrix-type formulation of the patch, in which the HPMC and PVP polymers bind to the active ingredient of the corn silk extract and regulate the rate of drug release (Das *et al*., 2022). According to Sivasankarapillai *et al.* (2021), the matrix-type patch has an intracellular penetration pathway that progressively traverses the stratum corneum, hair follicles, and sweat glands. These two routes will ultimately lead to the blood vessels. HPMC with a predominating hydrophilic composition absorbs water upon contact with phosphate buffer liquid at pH 7.4 and swells to form a gel with pores capable of releasing active substances. In contrast to PVP, which has the property of being readily wetted and thus can increase the release of active substances, HPMC has properties that limit the release of active substances (Aung *et al*., 2020). In addition, as an enhancer, propylene glycol can increase the rate of flavonoid penetration in corn silk extract (Carrer *et al*., 2020). By increasing the mobility of lipid molecules, propylene glycol increases the solubility of the active substance and the permeability of the stratum corneum, thereby increasing the penetration of the active substance into the epidermis layers (Haque & Talukder, 2018; Kis *et al*., 2022).

Table 9. Cumulative amount and flux penetration of extract corn silk transdermal patch

Time (hour)	Cumulative Amounts of Flavonoids (µg/cm^2)	Flux (µg/cm^2.hour)
0	3.50	0
0.25	18.56	42.18
0.5	18.77	21.33
0.75	21.32	16.15
1	23.72	13.48
1.5	24.03	9.10
2	25.69	7.30
2.5	27.84	6.33
3	32.59	6.17

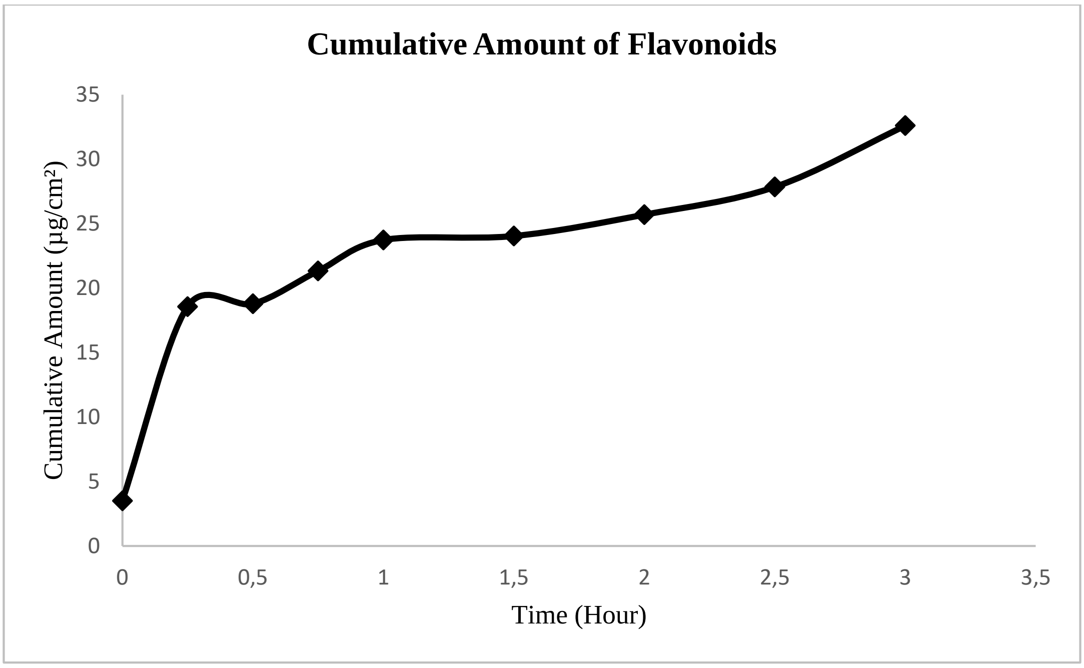

Figure 3. Cumulative amounts of flavonoids graph

CONCLUSION

The concentration of HPMC and PVP affects the evaluation of patch formulations, specifically the moisture content, moisture uptake, elongation percentage, and folding endurance. The HPMC:PVP ratio of 3.487 : 1 yielded the optimum formula based on the optimization of the factorial design analysis of the preparation evaluation response. The optimal formulation for the transdermal patch containing corn silk extract had a high cumulative rate of penetration and flux.

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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