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OPTIMIZATION OF DICLOFENAC POTASSIUM TRANSDERMAL PATCH FORMULA USING A COMBINATION OF POLYVYNIL PYRROLIDONE K 30, ETHYL CELLULOSE AND MENTHOL WITH SIMPLEX LATTICE DESIGN METHOD

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ABSTRACT

Diclofenac potassium is one of the NSAID drugs which can cause gastrointestinal irritation and damage to the small intestinal mucosa including erosion and ulceration. The purpose of this study was to determine the effect of the combination of PVP K 30, ethyl cellulose and menthol on organoleptic, thickness, weight uniformity, moisture and folding resistance of diclofenac potassium transdermal patch.This research is an experimental study that includes an experiment to optimize the formulation of a transdermal patch preparation with the active ingredient potassium diclofenac and a combination of PVP K 30, ethyl cellulose and menthol. The optimization method uses the simplex lattice design method. There are 13 formula designs consisting of a combination of PVP K 30, ethyl cellulose and menthol. Each formula was tested for organoleptic, thickness, weight uniformity, moisture and folding resistance. Then the optimum formula was determined and analyzed using the simplex lattice design method. The combination of PVP K 30, ethyl cellulose and menthol with a simplex lattice design has an effect on the transdermal patch of diclofenac potassium which increases the consistency of the patch surface, reduces the thickness directly proportional to the weight of the patch and increases folding resistance. The proportion of PVP K 30, ethyl cellulose and menthol that can produce the optimum formula for diclofenac potassium transdermal patches with the simplex lattice design on the critical parameters of thickness, moisture, folding resistance and penetration tests, namely PVP K 30 of 14.87%, ethyl cellulose of 10.00% and 5.13% menthol.

Keywords: Diclofenac potassium; Transdermal patch; Simplex lattice design (SLD)

1. INTRODUCTION

Diclofenac is one of the well-known Non-Steroid Anti-Inflammatory Drugs (NSAIDs) with anti-inflammatory, analgesic, and antipyretic properties, comparable to or superior to other NSAIDs. Potassium diclofenac is claimed to be soluble and absorbed faster than sodium salt and is recommended for treatments requiring a short onset of action, particularly for its analgesic properties (Barros et al., 2015). Primary dysmenorrhea and mild to moderate pain can also be treated with potassium diclofenac. Two pathophysiological pathways contribute to gastrointestinal pain caused by potassium diclofenac. In addition, current clinical research has shown that NSAIDs can harm the mucosa of the small intestine. This is because endoscopic findings indicate that NSAIDs can result in mucosal damage such as erosion and ulceration (Matsui et al., 2011).

Therefore, different administration routes have been developed to minimize the digestive system side effects associated with oral potassium diclofenac administration. The transdermal

drug administration route involves delivering the drug through the skin until it reaches the bloodstream. This route has several advantages compared to oral and injection methods (Putri, 2018). The transdermal delivery system has many advantages, including easy use, reducing the frequency of drug administration, eliminating first-pass metabolism, ensuring more uniform plasma levels, and reducing side effects such as gastric irritation and patient compliance (Puspitasari *et al*., 2016).

Purnamasari et al., 2019 have formulated and evaluated potassium diclofenac transdermal patches, and the results of the study showed that patches with PVP polymer were good both physically and homogeneously, as well as in in-vitro penetration tests. However, to determine the composition of the patch preparation that produces optimum physical characteristics, optimization is needed, including the simplex lattice design (SLD) method (Suryani et al., 2015). PVP and ethyl cellulose affect delivering the active ingredient contained in the patch preparation. The use of ethyl cellulose causes the formation of a barrier, trapping the active ingredient in the preparation, resulting in the active ingredient not easily released from its base, while PVP causes the formation of pores, so it is necessary to combine PVP and ethyl cellulose (Nurmesa et al., 2019). Maulina's research on the effect of menthol on the characteristics of sodium diclofenac gel preparations found that the addition of menthol can reduce the viscosity of the preparation.

Based on the above considerations, the researchers will formulate a transdermal patch using the solvent evaporation method which has the active ingredient of potassium diclofenac by combining PVP and ethyl cellulose as polymers and menthol as an enhancer.

2. METHODS

2.1. Material

The tools used are dropper pipettes, volume pipettes (Iwaki), glass tools (Pyrex), analytical balances (OHAUS PA323), UV-Vis's spectrophotometer (Shimadzu), pH meter (OHAUS ST3100M), Digital caliper (Mitutoyo), Magnetic stirrer (Yellow-MAG HS7), Desiccator (NORMAX), Sonicator (Elma), Software Design-Expert® version 11.0 and software SPSS Version 25.

The materials used are Diclofenac potassium (PT. Zenith Pharmaceutical), PVP K 30 (PT. Zenith Pharmaceutical), Ethylcellulose (PT. Zenith Pharmaceutical), Menthol (PT. Zenith Pharmaceutical), Dibutyl phthalate (PT. Zenith Pharmaceutical), Methylparaben (PT. Zenith Pharmaceutical), Ethanol 96% (PT. Brataco Indonesia), KH2PO4 (Merck), NaOH (Merck), Aquadest (PT. Brataco Indonesia).

2.2. Determination of Formula Using Simplex Lattice Design (SLD)

The formula of Diclofenac potassium patch was selected using SLD program to get the most optimum Diclofenac potassium patch formula containing combination of PVP K 30, ethyl cellulose and methol will be made up of 30% of the formula. The formula will be made with a weight of 5.0 grams. Response or parameters used are thickness, moisture and folding resistance.

2.3. Formulation of Film Patch Diclofenac Potassium

A matrix-type transdermal patch containing potassium diclofenac was prepared using various concentrations of PVP K 30 and ethyl cellulose polymers, as well as menthol enhancer, obtained from the SLD method. Potassium diclofenac and the polymer (PVP K 30: ethyl cellulose) were first dissolved using ethanol as a solvent in separate glass containers. Then, they were mixed together with menthol, dibutyl phthalate, and methyl paraben and homogenized using a sonicator for 20 minutes to form a thick mass. The resulting solution was poured into patch molds made of glass measuring 5 x 5 cm. The solvent was allowed to evaporate at room temperature for 24 hours (Mita et al., 2018). The variations in the concentrations of PVP K 30, ethyl cellulose, and menthol can be seen in **Table 1**.

Table 1. The Formula of Diclofenac Potassium Patch Based on SLD Method

Formula	Material (%)						
	DPO	X_1*	X_2*	X_3*	DPT**	MP**	Ethanol 95%
1	2	14	14	2	30	0.3	Add 100
2	2	10	10	10	30	0.3	Add 100
3	2	11.34	15.33	3.33	30	0.3	Add 100
4	2	10	14	6	30	0.3	Add 100
5	2	10	18	2	30	0.3	Add 100
6	2	12.66	12.67	4.67	30	0.3	Add 100
7	2	10	18	2	30	0.3	Add 100
8	2	11.34	11.33	7.33	30	0.3	Add 100
9	2	14	10	6	30	0,3	Add 100
10	2	18	10	2	30	0,3	Add 100
11	2	15.33	11.34	3.33	30	0,3	Add 100
12	2	18	10	2	30	0,3	Add 100
13	2	10	10	10	30	0,3	Add 100

DPO= Diclofenac Potassium, X_1= Polivinyl Pyrrolidon K 30, X_2= Ethyl Cellulose, X_3= Menthol, DPT= Dibuthyl Phthalat, MP= Methylparaben(*) based on result of SLD method. (**) percentage was based on dry weight of the polymer

2.4. Characteristics of Diclofenac Potassium Film Patch

2.4.1. Organoleptic Test

The characteristics of the film, including color, odor, and surface consistency, are observed (Suryani et al., 2015).

2.4.2. Thickness Test

The thickness of the film is measured using a digital caliper at three different points, and the average thickness is calculated (Suryani et al., 2015).

2.4.3. Weight Uniformity Test

The weight variation of the film in each formula is determined by weighing each patch individually, and the average weight is calculated (Suryani et al., 2015).

2.4.4. Moisture Content test

Each finished patch is weighed (initial weight) and then stored in a desiccator containing silica gel at room temperature for 24 hours. The patch is then weighed again (final weight) (Suryani et al., 2015).

$$\%\ Moisture\ Content = \frac{(initial\ weight - final\ weight)}{initial\ weight} \times 100\% \quad (1)$$

2.4.5. Folding Endurance Test

Folding endurance is the number of folds required to break the film. This test not only describes the strength of the film composed using polymers but also checks how efficient polymers and plasticizers provide flexibility. This test involves a simple phenomenon, which is repeatedly folding the film in the same place until it breaks. Thus, the number of times the film can be folded in the same place without cracking or breaking can be determined. The film is considered to meet the criteria if it can withstand folding more than 200 times (Setyawan et al., 2015).

2.5. Determination of Diclofenac Potassium Content in Film Patch

The film is cut into small pieces, weighed, and dissolved in 50 ml phosphate buffer 7.4, then sonicated for 50 minutes. The resulting solution is filtered and 1 ml of it is pipetted and diluted to 10 ml, then sonicated again for 10 minutes and filtered. To determine the drug content in each formulation, the maximum wavelength is 276 nm. The obtained absorbance is compared with the calibration curve to determine the concentration of potassium diclofenac in the patch preparation (Purnamasari et al., 2019).

2.6. Determination of The Optimum Formula

The determination of the optimum formula is done by examining the results of physical characterization tests of the patch matrix in each formula. In the physical characterization test of the patch matrix, thickness, moisture content, and folding endurance are measured. The results of each formula's response are then processed using the simplex lattice design method in Design Expert software version 11. The optimum formula is determined based on the highest desirability value obtained from the method's results.

2.7. Verification of The Optimum Formula

Verification is conducted by creating a matrix of the optimal formula predicted by the simplex lattice design in Design Expert software version 11. The production of the matrix patch is replicated three times. The observed results of the matrix are then compared with the predicted response of the optimal formula from the simplex lattice design. Verification is then carried out using the One Sample T-test in SPSS 25 software.

2.8. Data Analysis

The data for the testing of characteristics and penetration rate of potassium diclofenac transdermal patch will yield values for each response and the equation model. The simplex lattice design model will generate an optimum formula obtained after inputing the thickness, moisture, and fold resistance test values using Analysis of Variance (ANOVA) in Design Expert software version 11. The optimal formula is obtained based on the respective parameter values obtained, and contour plots are created for each parameter. The contour plots for the moisture, thickness, and folding endurance test parameters are superimposed to determine the optimal region. The testing results from the optimal formula are then compared to the predicted results obtained from Design Expert using SPSS 25 with a One Sample T-test at a confidence level of 95%.

3. RESULT AND DISCUSSION

3.1. Characteristics of Diclofenac Potassium Film Patch

The evaluation of characteristics is to determine the physical characteristics of potassium diclofenac transdermal patch, including organoleptic properties, thickness, weight uniformity, moisture content, and folding endurance. The results of the film patch characteristics can be seen in **Table 2**.

Table 2. The Result of Characteristics Diclofenac Potassium Film Patch

Formula	Thickness ± SD(mm)	Weight Uniformity ± SD(gram)	Moisture Content ± SD(%)	Folding Endurance ±SD
F1	0.71 ± 0.005	1.972 ± 0.0008	1.268 ± 0.047	226±3.559
F2	0.66 ± 0.017	1.633 ± 0.0008	1.349 ± 0.074	207±2.828
F3	0.73 ± 0.005	1.914 ± 0.0017	1.459 ± 0.064	178±4.243
F4	0.69 ± 0.009	1.785 ± 0.0022	1.544 ± 0.195	169±3.559
F5	0.75 ± 0.005	1.989 ± 0.0025	1.242 ± 0.121	158±2.828
F6	0.70 ± 0.009	1.858 ± 0.0009	1.345 ± 0.090	223±4.243
F7	0.74 ± 0.005	1.989 ± 0.0021	1.242 ± 0.081	160±3.559
F8	0.68 ± 0.009	1.764 ± 0.0005	1.379 ± 0.026	218±2.828
F9	0.68 ± 0.021	1.771 ± 0.0016	1.648 ± 0.246	226±4.243
F10	0.72 ± 0,005	1.969 ± 0.0012	1.763 ± 0.200	232±3.559
F11	0.70 ± 0.008	1.929 ± 0.0012	1.732 ± 0.109	228±4.243
F12	0.71 ± 0.005	1.971 ± 0.0021	1.778 ± 0.236	238±3.559
F13	0.66 ± 0.012	1.632 ± 0.0008	1.489 ± 0.057	218±2.828

3.1.1. Organoleptic Test

Organoleptic testing was conducted by observing the color, odor, and consistency of the surface of the potassium diclofenac film patch. Based on observations, the film patch is generally white to yellowish in color, wet, and has a distinctive menthol smell. However, there are

differences in the surface consistency of each film patch. F3, F4, F5, F7, F9, F10, F11, and F12 have non-smooth (cracked) film conditions, unlike F1, F2, F6, F8, and F13 which have smooth film conditions. This is due to the difference in polymer concentration in each formula. Formulas with non-smooth and cracked film conditions were found more in F5 and F7, which had a higher concentration of ethyl cellulose polymer. Purnamasari et al., (2019) stated in their research that a polymer combination of PVP:ethyl cellulose (1:3) produces a white, clear, and non-smooth patch. The results of the organoleptic test for diclofenac potassium film patches can be seen in the **Table 3**.

Table 3. The Result of Organoleptic Test of Diclofenac Potassium Film Patch

Formula	Color	Odor	Consistency of The Surface
F1	Off-white to pale yellow	Mentol smell	Smooth surface, not cracked and wet
F2	Off-white to pale yellow	Mentol smell	Smooth surface, not cracked and wet
F3	Off-white to pale yellow	Mentol smell	Smooth surface, slightly cracked and wet
F4	Off-white to pale yellow	Mentol smell	Smooth surface, slightly cracked and wet
F5	Off-white to pale yellow	Mentol smell	Uneven surface, cracked and wet
F6	Off-white to pale yellow	Mentol smell	Smooth surface, not cracked and wet
F7	Off-white to pale yellow	Mentol smell	Uneven surface, cracked and wet
F8	Off-white to pale yellow	Mentol smell	Smooth surface, not cracked and wet
F9	Off-white to pale yellow	Mentol smell	Smooth surface, slightly cracked and wet
F10	Off-white to pale yellow	Mentol smell	Smooth surface, slightly cracked and wet
F11	Off-white to pale yellow	Mentol smell	Smooth surface, slightly cracked and wet
F12	Off-white to pale yellow	Mentol smell	Smooth surface, slightly cracked and wet
F13	Off-white to pale yellow	Mentol smell	Smooth surface, not cracked and wet

3.1.2. Thickness Test

The results of the thickness testing were analyzed using Design Expert with simplex lattice design method. The response results can be seen in **Figure 1**.

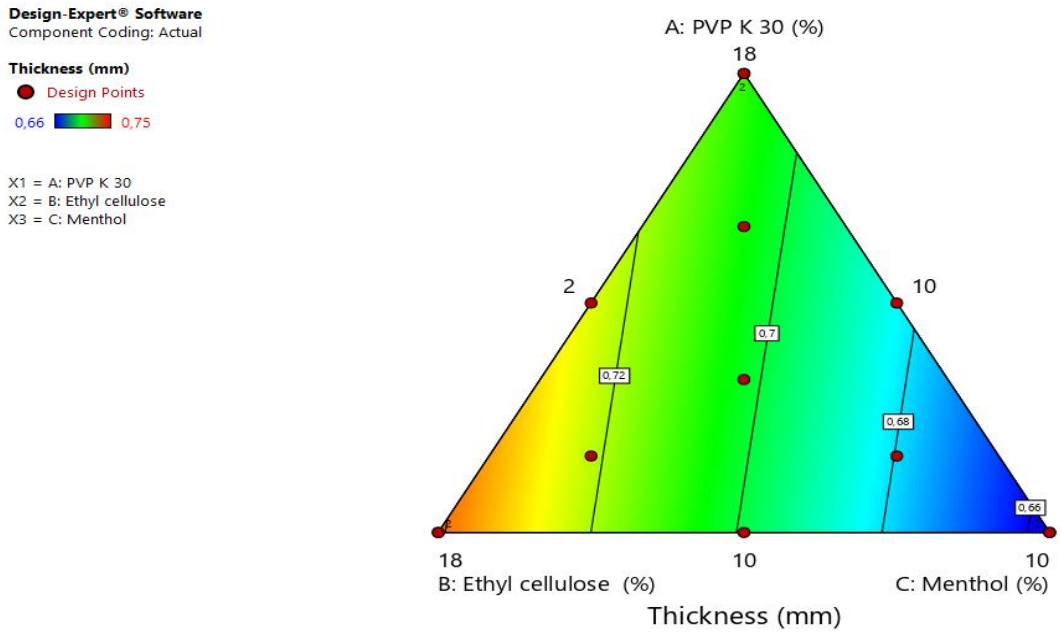

Figure 1. Contour Plot of The Thickness Response of Potassium Diclofenac Film Patch

The response of thickness based on ANOVA analysis at a 95% confidence level obtained the simplex lattice design equation for thickness as formulated in Eq (2).

$$Y = +0.7090(A) +0.7410(B) +0.6570(C) \quad (2)$$

Where: Y = Thickness; A = PVP K 30; B = Ethyl cellulose; C = Menthol

The contour plot shows the relationship between the three components, namely PVP K 30, ethyl cellulose, and menthol in the diclofenac potassium film patch towards the thickness of the film patch with the formation of color gradation, where orange represents the boundary of the highest value while dark blue represents the boundary of the lowest value. Based on the contour plot (**Figure 1**), it can be seen that ethyl cellulose affects the thickness of the film patch, as evidenced by the presence of orange color on the ethyl cellulose plot, which means that an increase in the concentration of ethyl cellulose can increase the thickness value. This can also be seen from the regression coefficient values which indicate that ethyl cellulose (+0.740) has the most significant effect in increasing the thickness of the film patch compared to PVP K 30 and menthol.

The thickness of the film patch in this test ranged from 0.66-0.76 mm (**Table 2**). The factors that influenced the difference in thickness between the formulas were the physicochemical properties of the polymer used. The test results for each formula showed that F5 and F7 had a higher average thickness compared to the other formulas. This was because F5 and F7 had the highest concentration of ethyl cellulose. According to Suryani et al., (2015), if ethyl cellulose polymer is used excessively, it will form thick and uneven fibers that can affect the thickness of the film patch. Other variables that can affect the thickness of the film patch are the size of the mold, the volume of the solution, and the total amount of solids in the solution.

3.1.3. Weight Uniformity Test

The weight uniformity test was analyzed based on the average weight of the film patch and its standard deviation. Standard deviation is a measure used to assess the variation or dispersion of a data set. According to the literature, a good standard deviation value is ≤ 0.05 (Hermanto & Nurviana, 2019). The results of the potassium diclofenac film patch weight testing can be seen in **Table 2**.

The results of each formula were considered to meet the requirements. However, the weight of each formula's film patch is different due to the different amounts of additional materials in each formula. Weight uniformity is affected by the polymer component which has a more hydrophilic property, which during the process of making the film patch and the aging process, water will easily be retained in the film patch, which will affect the resulting weight (Ermawati & Prilantari, 2019). In the potassium diclofenac patch formula, the polymer that has a hydrophilic property is PVP K 30. The weight of the film patch can also be influenced by the manufacturing method itself because it can allow the patch solution to remain partially in the container (Arifin et al., 2019). However, in this study, the highest patch weight was obtained in formulas F5 and F7, where F5 and F7 also have a higher thickness than other formulas, so it can be said that the weight of the patch formula is directly proportional to its thickness.

3.1.4. Moisture Content Test

The result of the moisture content testing was analyzed using Design Expert with a simplex lattice design method. The response can be seen in **Figure 2**. The moisture content response was analyzed using Design Expert with the simplex lattice design method. The ANOVA test results at a 95% confidence level obtained the equation for moisture content response as formulated in Eq (3).

$$Y = +1.74\ (A) +1.25\ (B) +1.45\ (C) \quad (3)$$

Where: Y = Moisture content; A = PVP K 30; B = Ethyl cellulose; C = Menthol

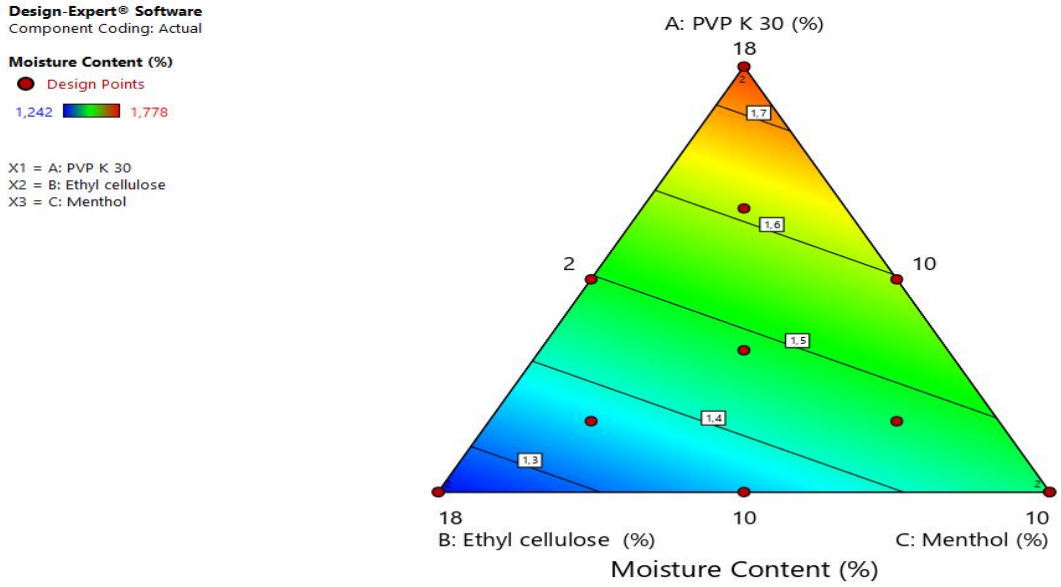

Figure 2. Contour Plot of The Moisture Content Response of Potassium Diclofenac Film Patch

The contour plot shows the relationship between the three components, namely PVP K 30, ethyl cellulose, and menthol. The color gradient is formed in shades of orange, green, and blue, where orange represents the highest value and dark blue represents the lowest value. Based on the contour plot results, it can be seen that PVP K 30 can influence the moisture content of the film patch, as indicated by the presence of orange color in the PVP K 30 plot, which means that increasing the concentration of PVP K 30 can increase the moisture content value. This is also supported by the regression coefficient values which show that PVP K 30 (+1.74) has the most significant effect on increasing the moisture content of the film patch compared to ethyl cellulose and menthol.

In general, the percentage of moisture capacity of the film will increase if the hydrophilicity of the polymer or plasticizer used also increases (Fuziyanti et al., 2022). A good film patch is said to contain little water, so the stability of the patch will be good. The required range of water content is 1-10% (Kumar et al., 2013). The results of the moisture content percentage test show that the film patch in each formula has values that meet the required range. The formula with the highest percentage of moisture content is obtained in formulas F10 and F12 because they contain a higher concentration of PVP K 30 than other formulas. This is in line with the study conducted by Fatmawaty et al., (2017), which found that the combination of PVP:EC with a higher concentration of PVP resulted in a moisture content percentage of 29%, which did not meet the required range.

The factors that can affect the humidity are the physicochemical properties of the materials used, namely the polymer and plasticizer. Dibutyl phthalate as a plasticizer is hydrophilic, similar to the polymer PVP K 30 which can increase the percentage of humidity (Fuziyanti et al., 2022). Therefore, a combination with a hydrophobic polymer is needed, otherwise there will be a high increase in humidity percentage (Puspitasari et al., 2016).

3.1.5. Folding Endurance Test

The result of the folding endurance testing was analyzed using Design Expert with simplex lattice design method. The response can be seen in **Figure 3**. The response of foldability based on ANOVA test at 95% confidence level obtained the simplex lattice design equation for foldability as formulated in Eq (4).

$$Y = +233.90(A) +157.09(B) + 213.76(C) +118.55(AB) +30.55(AC) -50.31(BC) \quad (4)$$

Where: Y = Foldability; A = PVP K 30; B = Ethyl Cellulose; C = Menthol

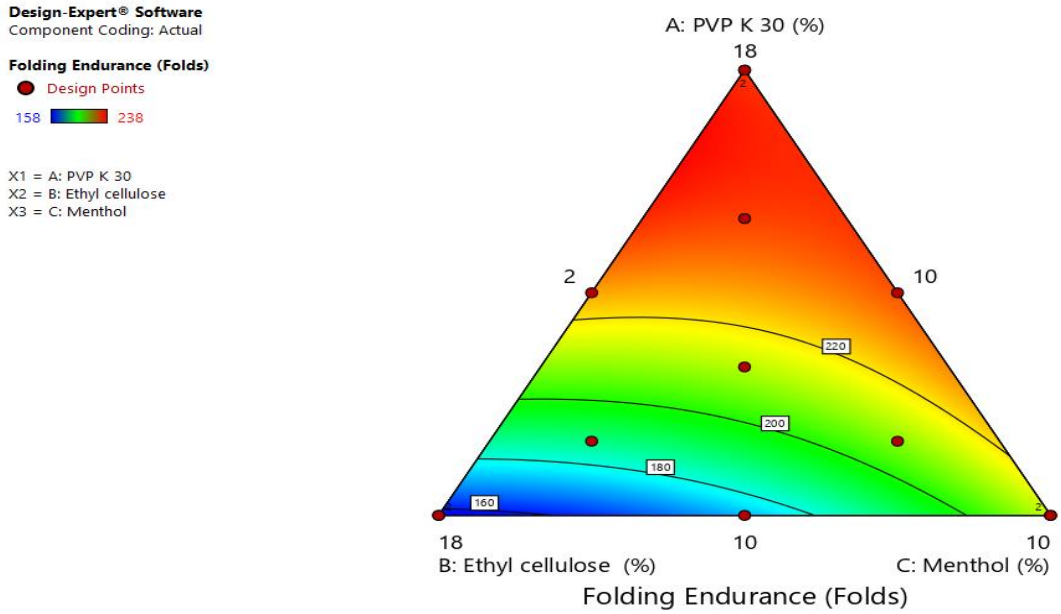

Figure 3. Contour Plot of The Fold Endurance Response of Potassium Diclofenac Film Patch

The contour plot shows the relationship between the three components, namely PVP K 30, ethyl cellulose, and menthol in the potassium diclofenac film patch against the film patch humidity, with the formation of color gradations, where the orange color is the limit of the highest value while the dark blue is the limit of the lowest value. Based on the contour plot results, it can be seen that PVP K 30 can affect the folding endurance of the film patch, as evidenced by the presence of orange color on the PVP K 30 plot, which means that an increase in PVP K 30 concentration can increase the folding endurance value. From the regression coefficient values, it is known that PVP K 30 (+233.90) has the most significant influence in increasing the film patch thickness compared to PVP K 30 and menthol. It is also known that the interactions that occur between PVP K 30: ethyl cellulose and PVP K 30: menthol provide positive values, namely (+118.55) and (+30.55), which means that these interactions can increase the folding endurance value, unlike the interaction between ethyl cellulose and menthol, which provides a negative value, namely (-50.31), which means that the interaction between the two can decrease the folding endurance value of the potassium diclofenac film patch.

The use of polymer and plasticizer combination can be seen from the good folding endurance (> 200) in F10 and F12, which are formulas that use a higher concentration of dibutyl phthalate (0.42 g) and a combination of PVP K 30 polymer compared to ethyl cellulose, while for F5 and F7, the folding endurance is < 200 times, indicating poor performance. F5 and F7 are formulas that use the same concentration of dibutyl phthalate as F10 and F12, but the polymer combination in F5 and F7 uses a higher concentration of ethyl cellulose than PVP K 30. According to the research conducted by Fatmawaty et al., (2017), the proper concentration of polymer combination has a significant effect on the folding endurance of film patches, not only plasticizers, where PVP is hydrophilic and can increase elasticity, making it less prone to breakage, and ethyl cellulose is a hydrophobic polymer that can increase the strength of the film patch, making it less prone to tearing. This indicates the importance of using PVP K 30 as a polymer and dibutyl phthalate as a plasticizer to increase the flexibility/elasticity and folding endurance of the film patch.

3.2. Determination of Diclofenac Potassium Content in Film Patch

Determination of the content (concentration) of diclofenac potassium in the film patch was carried out to measure the active ingredient in each formula. The film patch was dissolved using phosphate buffer pH 7.4 with the help of a sonicator for approximately 60 minutes, then analyzed by UV-Vis spectrophotometry at a wavelength of 276 nm. This test was carried out in triplicate

for each formula, and the average concentration and standard deviation (SD) were calculated. The results showed that the average concentration of diclofenac potassium in each formula ranged from 98.33% ± 0.036 to 101.45% ± 0.028. The results of the test for diclofenac potassium concentration in the film patch for each formula can be seen in **Table 4**.

Table 4. Diclofenac Potassium Concentration in The Film Patch

Formula	Diclofenac Potassium Concentration ± SD (%)
F1	98.56 ± 0.036
F2	99.78 ± 0.028
F3	99.18 ± 0.042
F4	101.32 ± 0.036
F5	98.79 ± 0.036
F6	99.45 ± 0.036
F7	98.86 ± 0.042
F8	99.34 ± 0.036
F9	101.45 ± 0.028
F10	99.87 ± 0.036
F11	99.65 ± 0.036
F12	98.33 ± 0.036
F13	99.67 ± 0.036

3.3. Determination of The Optimum Formula

The determination of the optimum area of potassium diclofenac patch was carried out using Design Expert 11 software in this study, which used a numerical approach to determine the optimum formula. The data input as parameters were the characteristics of the patch, including thickness, moisture content, and folding endurance. The result of the desirability contour plot obtained a value of 0.862, where the desirability value that approaches 1 indicates the more perfect the result. Desirability represents the magnitude of the value that matches the desired value (Raissi & Farsani, 2009). The achievement of the maximum value in desirability indicates that the selection of goals in the four test parameters is correct. The result of the desirability contour plot can be seen in **Figure 4**.

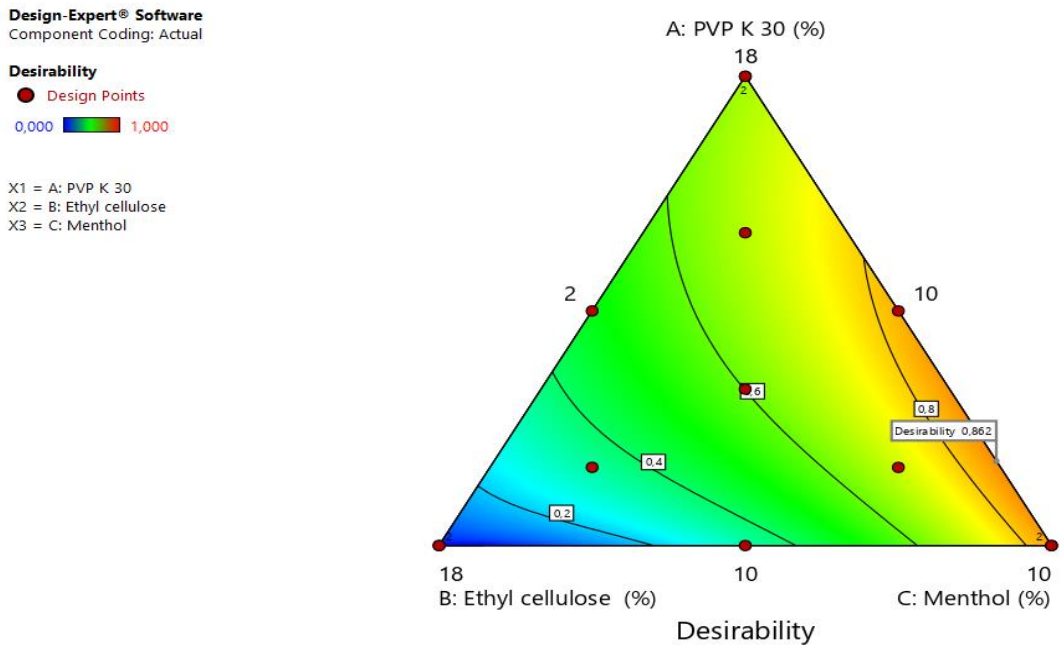

Figure 4. Contour Plot Desirability

The optimum formula for the potassium diclofenac patch components was predicted using simplex lattice design, consisting of PVP K 30 (14.87%), ethyl cellulose (10.00%), and menthol (5.13%). Three replications of the optimum formula were made and tested to obtain the thickness, moisture content, and folding endurance values of the optimum formula, which will then be verified by comparing them to the predicted values obtained from each test parameter.

3.4. Verification of The Optimum Formula

The results of the predicted values compared to the testing values of the optimum patch formula of potassium diclofenac can be seen in **Table 5**.

Table 5. Comparison of The Predicted Value with The Optimum Formula Testing Value

Parameter	Predicted Value	Test Value	*Sig.*	Explanation
Thickness (mm)	0.69	0.71	0.588	No Different
Moisture Content (%)	1.628	1.640	0.825	No Different
Folding Endurance	233	235	0.464	No Different

The comparison between the predicted values and the test values of the optimum formula was analyzed using SPSS 25 with a One Sample T-test at a 95% confidence level to determine whether there was a significant difference or not between the predicted and test values. The results of the One Sample T-test showed a sig value > 0.05 for all parameters, indicating that there was no significant difference between the predicted and test values of the optimum formula.

4. CONCLUSION

The combination of PVP K 30, ethyl cellulose, and menthol using the simplex lattice design had an effect on the transdermal patch of potassium diclofenac, where it improved the surface consistency of the patch, reduced the thickness proportionally to the weight of the patch, and increased the fold endurance. The optimum formula of the transdermal patch of potassium diclofenac was achieved by using proportions of PVP K 30 at 14.87%, ethyl cellulose at 10.00%, and menthol at 5.13% based on the critical parameters of thickness, moisture content, and folding. The data for the testing of characteristics and penetration rate of potassium diclofenac transdermal patch will yield values for each response and the equation model. endurance using the simplex lattice design.

5. ACKNOWLEDGMENT

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6. CONFLICT OF INTEREST

All authors declare no conflict of interest.

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