



## Formulation Optimization Peel-Off Gel Mask Base of Red Rice Ethanol Extract in Combination of HPMC and PVA using Factorial Design Method

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### ABSTRACT

In earlier research, red rice extract was shown to possess anti-oxidant, anti-inflammatory, anti-cancer, and anti-photoaging qualities. It was also shown to inhibit the degradation of collagen and hyaluronic acid (HA) in cutaneous fibroblast cells caused by sunlight. Red rice has been used for cosmetics for centuries, and its benefits have been applied to modern skin care products. It can be made as a peel-off gel mask to increase its practicality. The peel-off gel mask has the main ingredients of PVA as a film layer and HPMC as a gelling agent. This research is experimental research with extraction stages, DPPH assay, and gel formulations. Formula optimization was carried out through a Factorial Design method approach with a total of 12 formulas. The results of the evaluation of the physical properties of the red rice ethanol extract peel-off gel mask were processed using *Design Expert* software ver 13. The results of this study obtained an optimum formula with HPMC and PVA concentrate levels of 15.37% and 4.99%, respectively. The results of the physical evaluation of the red rice ethanol extract peel-off gel mask with the optimum formula obtained a pH of 5.89, a spread of 5.19 cm, and a drying time of 14.71 minutes.

**Keywords:** Peel-Off Gel Mask; Factorial Design; HPMC; PVA

### INTRODUCTION

For centuries, rice has been used in cosmetics. Now, its benefits are used in contemporary skincare products. Rice has many dermatological benefits, including anti-aging, anti-inflammatory, brightening, sun protection, and moisturizing. According to research, ingredients extracted from rice are generally harmless, non-irritating, and hypoallergenic <sup>1</sup>. One type of rice that can be widely used for anti-aging treatments is red rice. Previous studies discovered that red rice extract has anti-oxidant, anti-inflammatory, anti-cancer, and anti-photo-aging properties. Previous research found that red rice extract prevented sunlight-induced

collagen degradation and hyaluronic acid (HA) in dermal fibroblast cells <sup>2</sup>.

One practical cosmetic product is the peel-off gel mask, which can be removed immediately after drying without rinse. It removes dirt and dead skin cells, leaving the skin clean and refreshed and restoring its freshness and softness. Regular use of this mask can reduce fine wrinkles <sup>3</sup>. The main ingredient of a peel-off gel mask is *Polyvinyl Alcohol* (PVA), which can improve the film's transparency, elasticity, and clarity. In addition, gelling agents such as *Hydroxypropyl Methylcellulose* (HPMC) play an essential role as emulsifying agents, suspending agents, and stabilizing

agents in topical preparations such as gels and ointments <sup>4,5</sup>.

Until now, no formulation of peel-off gel mask from red rice extract using a factorial design method with variations of PVA and HPMC has been reported. In previous research <sup>5</sup>, optimization of peel-off gel mask formulations was carried out using the factorial design method with a combination of banana peel flour, PVA, and gelatin (5:12:5). Whereas in the study <sup>6</sup>, the red rice extract peel-off gel mask using PVA and HPMC base ingredients was formulated using simplex lattice design with a variety of preservatives *methylparaben* 0.119%, *propylparaben* 0.151%, and *tea tree oil* 0.13%. The optimum formula of the peel-off gel face mask reported using PVA, HPMC, and *ethanol* (9.08%: 0.95%: 18.77%) with a predicted viscosity value of 8512.14 cPs, spreadability of 6.88 cm, and dry time of 10.98 minutes <sup>7</sup>.

PVA affects the viscosity and drying time of the preparation, while HPMC affects the viscosity and spreadability of the preparation <sup>4,8,9</sup>. Previous research shows that variations in the PVA and HPMC concentrate levels can increase the viscosity and spreadability of peel-off mask preparations <sup>10,11</sup>. The choice of a combination of PVA and HPMC gels aims to reduce the formation of films that tend to be stiff due to PVA, while HPMC aims to produce a more elastic base gel <sup>12</sup>.

The researcher wants to optimize the formula using the factorial design method to obtain the optimal formula. Optimization with the factorial design method is the application of regression equations to model the relationship between the response variable and one or more independent variables. Factorial is the most common type of design for process improvement. In research, factorial is used to find the effects of various conditions on the study's results and to see the interactions within them <sup>13</sup>. The advantage of factorial design over experiments one factor at a time is that it is more efficient and allows interactions to be detected <sup>14</sup>.

## MATERIALS AND METHODS

### Equipment

The types of equipment used in this research are a rotary evaporator (BOECO - RVO 400 SD), pH meter (Ohaus), Uv-Vis spectrophotometer (Shimadzu 2700), spreadability test kit, and Brookfield viscometer.

### Materials

The materials used in this research were red rice, 96% ethanol, HPMC (local supplier), propylene glycol (local supplier), PVA (local supplier), propylparaben (local supplier), methylparaben (local supplier), aquadest local supplier, tea tree oil (Intan Chemical), 96% ethanol (analytic grade), and DPPH (2,2-diphenyl-1-picrylhydrazyl) (analytic grade, Sigma-Aldrich).

### Extraction

Red rice comes from Pekalongan, Central Java, Indonesia. Red rice was ground, sieved, and macerated with 96% ethanol solvent. Three hundred grams of red rice fine powder was then put into a glass with 750 mL of 96% ethanol, soaked for two days with stirring, and filtered with filter paper to produce filtrate. The remaining pulp was then macerated with 750 mL of 96% ethanol and, soaked for two days, filtered again. After that, the filtrates that have been made are combined and thickened with a rotary evaporator until a thick extract is produced <sup>15</sup>. The resulting extract was weighed in a container, then the weight was compared to the initial weight of the powder and then was clicked 100% with the formula:

$$Yield (\%) = \frac{B1}{B2} \times 100\%$$

B1 = Weight of the final extract

B2 = Weight of initial raw material

The water content of red rice extract was measured using a Moisture Balance tool to determine the water content in the extract.

### DPPH radical scavenging activity test

The method has been modified Ten milligram of DPPH powder was weighed, and 10 mL of ethanol p.a solvent was

added to a volumetric flask. Then, 2.5 mL was taken, and 25 mL of ethanol p.a solvent was added, which showed a concentrate level of 100 µg/mL, and this solution was used as a comparison. Then, a sample solution with a concentrate level of 1000 µg/mL was made by weighing 10 mg into 10 mL of ethanol pro analysis in a measuring flask. Then, a sample concentrate level of 5 µg/mL, 10 µg/mL, 15 µg/mL, and 20 µg/mL were made. The maximum reading of the sample in ethanol pro analysis was 516 nm<sup>16</sup>.

## Formulation

The formulas used were derived from a 2<sup>3</sup>-factorial design of two levels and two factors. HPMC and PVA are generally used as the base for gel masks with a range of PVA 10-16%, HPMC 2-5<sup>17</sup>. The two levels and factors used in the factorial design were PVA concentrate levels (10% and 16%) and HPMC (2% and 5%). Based on the 2<sup>3</sup>-factorial design, eight peel-off gel mask formulas were obtained (Table 1).

**Table 1.** Materials of Red rice Extract Peel-Off Gel Mask Formula according to *Design Expert ver 13*

Materials	Concentration (%)											
	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8	Run 9	Run 10	Run 11	Run 12
Red rice Extract	1	1	1	1	1	1	1	1	1	1	1	1
PVA	10	16	10	10	10	16	10	16	16	10	16	16
HPMC	2	5	5	5	2	2	2	5	2	5	2	5
Propylene Glycol	15	15	15	15	15	15	15	15	15	15	15	15
Methylparaben	0.058	0.058	0.058	0.058	0.058	0.058	0.058	0.058	0.058	0.058	0.058	0.058
Propylparaben	0.221	0.221	0.221	0.221	0.221	0.221	0.221	0.221	0.221	0.221	0.221	0.221
Tea Tree Oil	0.121	0.121	0.121	0.121	0.121	0.121	0.121	0.121	0.121	0.121	0.121	0.121
Ethanol	15	15	15	15	15	15	15	15	15	15	15	15
Aquadeast	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad
	100	100	100	100	100	100	100	100	100	100	100	100

PVA was added to distilled water that had been heated until fully expanded (container A) and stirred until homogeneous. Then, HPMC was added to distilled water, and stirring was carried out until it expanded (container B). Propylene glycol was dissolved with propylparaben and methylparaben (container B). After that, containers B and C were put into container A in order and mixed until homogeneous. After incorporating the rice extract, stir until homogeneous. Then, add distilled water up to 100 and stir until homogeneous<sup>5</sup>.

## Evaluation of peel-off gel mask preparation

Evaluation of peel-off gel mask preparation included each formula's organoleptic, pH, spreadability, and drying time. The organoleptic test directly observed the mask's color, shape, and smell. The homogeneity test was

observed visually. The pH measurement was measured with a pH meter. Spreadability was determined by measuring the diameter of 1 gram of sample spread between two glass plates after one minute. Drying time was observed for 30 minutes to dry<sup>18</sup>.

## Determination of the optimum formula

The effect of variations in the concentrate level of PVA and HPMC on the preparation of red rice extract peel-off masks on the organoleptic test, pH test, spreadability test, and drying time test as parameters used to see the optimum formula by analyzing these parameters using the *Design Expert* software version 13 which the optimum formula was determined with a degree of *desirability* close to 1.

### Verification of the optimum formula

The optimum formula of red rice ethanol extract peel-off gel mask with varying concentrate levels of PVA and HPMC was verified by making the optimal formula predicted by *Design Expert* software version 13. The formula was then tested for accuracy by testing spreadability, pH, and drying time. The test results were then verified with a one-sample t-test to analyze the data.

## RESULTS AND DISCUSSION

### Preparation of red rice extract

The result of red rice extraction was a thick red extract with a distinctive rice odor and an extract yield of 1.715%. The resulting yield was greater than previous research, which amounted to 1.053%<sup>19</sup>. This was likely due to the re-maceration treatment in which there is a solvent change cycle so that the effectiveness of the withdrawal would be maximized<sup>20</sup>. The extraction using 96% ethanol because effective for extracting flavonoids<sup>21</sup>. The water content of the thick red rice extract produced was 13.69%. A good thick extract had a moisture content of 5-30%<sup>22</sup>.

### DPPH radical scavenging test

The IC<sub>50</sub> value obtained was 11.620 µg/mL (< 50 µg/mL), so it could be classified as a powerful antioxidant, as seen in Table 2. This was thought to be due to the content of anthocyanin compounds in red rice. The mechanism of anthocyanins were compounds that prevented or inhibited oxidation by capturing free radicals and then reducing oxidative stress by transferring single electrons or donating H-atoms<sup>23</sup>.

The antioxidant activity would be stronger, shown by the smaller IC<sub>50</sub> value calculated using a linear equation, with sample concentrate level as the x-axis and % inhibition as the y-axis<sup>24</sup>. Ethanol extract from red rice had strong oxidant

activity, as evidenced in research held by Oktaviani et al. (2019), that red rice extract had an antioxidant activity of 41 µg/mL, the smallest among white rice extract and black rice extract with 70% ethanol solvent. In this study, the IC<sub>50</sub> value was stronger because the solvent used was 96%; anthocyanins could dissolve nicely in ethanol because the polarity of the two substances was close, so the higher the concentrate level of ethanol solvent used, the higher the concentrate level of anthocyanins obtained<sup>26</sup>.

**Table 2.** 2,2-Diphenyl-1-Picrylhydrazyl Radical Scavenging Test Results

Concen trate (µg/mL)	Inhibition (%)	Equation (y=bx+a)	IC <sub>50</sub> (µg/mL)
5	41 ± 2.480	y = 1.4021x + 33.71	11.62
10	46.62 ± 1.442		
15	55.69 ± 2.111		
20	62.078 ± 1.184		
25	68.32 ± 0.391		

### Evaluation of peel-off gel mask preparation of red rice ethanol extract with varying concentrate levels of HPMC and PVA by factorial design method

#### 1. Organoleptic test

Both twelve red rice ethanol extract peel-off gel masks had a red color with a distinctive aroma of tea tree oil that dominated, which was homogeneous. However, there were differences in consistency in the red rice ethanol extract peel-off gel mask formula containing more PVA, which had a thicker consistency.

#### 2. pH test

The results of the evaluation of the peel-off gel mask of red rice ethanol extract were in Table 3. The pH of the resulting gel was between 5.54 and 6.22, so the peel-off gel mask was safe to be applied to the skin because this value was still within the skin pH range of 4.5-8.0 (SNI 16-4399-1996).

**Table 3.** Results of pH Test, Spreadability, and Drying Time of Red rice Extract peel off Gel Mask

Run	Parameters			
	pH	Drying Time (minutes)	Spreadability (cm)	Viscosity (cps)
1	5.86 ±0.20	38.04 ± 0.93	8.33 ± 0.58	13410 ± 1016.02
2	5.79 ±0.02	17.18 ± 1.55	5.5 ±0.36	27940 ± 1412.34
3	6.22 ±0.07	15.87 ± 2.25	5.53 ±0.31	28470 ± 1287.91
4	6.16 ±0.07	15.78 ± 0.82	5.47 ±0.25	29280 ± 662.04
5	5.82 ±0.02	30.17 ±3.51	8.4 ±0.56	15470 ± 563.1
6	5.54 ±0.02	27.13 ± 2.91	6.76 ±0.32	25740 ± 1052.57
7	5.84 ±0.02	42.09 ± 0.29	8.23 ±0.25	21140 ± 1775.92
8	5.86 ±0.03	13.46 ± 1.38	5.06 ±0.21	28840 ± 1240.68
9	5.63 ±0.02	32.16 ±1.52	7.13 ±0.25	27730 ± 632.38
10	6.05 ±0.01	19.48 ±0.61	6.06 ±0.21	25940 ± 720.21
11	5.71 ±0.06	26.51 ± 4.62	7.9 ±0.1	25720 ± 1178.18
12	5.87 ±0.03	17.14 ± 1.19	5.2 ±0.1	27960 ± 441.93

Note: n = 3 replications

**Table 4.** Results of pH Test, Spreadability, and Drying Time of Red rice Extract peel off Gel Mask

Response	Model		Lack of Fit		Adjusted R <sup>2</sup>	Predicted R <sup>2</sup>	Adeq Precision
	F-value	P-value	F-value	P-value			
pH	45.96	< 0.0001*	1.47	0.2596**	0.8803	0.9177	16.212
Spreadability	62.32	< 0.0001*	2.33	0.1656**	0.8910	0.8414	15.656
Drying Time	25.90	0.0002*	2.69	0.1394**	0.7368	0.8191	10.279

Note : \*= significantly

\*\*= not significantly

From the analysis of *Design Expert* software version 13, the pH response in Table 4 had a model value of <0.0001 (significant) and a lack of fit of 0.2596 (insignificant). Predicted R<sup>2</sup> was quite compatible with Adjusted R<sup>2</sup>, which had a difference of less than 2, and Adeq Precision had a value of more than 4<sup>27</sup>.

Modelling of the pH response was shown in equation (1):

$$Y = 6.12 - 0.04 A + 0.09 B \dots\dots\dots(1)$$

**Equation 1.** Response modelling of the spreadability of red rice ethanol extract peel-off gel mask. Notes: Y=pH, A=PVA(%), B=HPMC(%)

Equation (1) showed that the pH value was generated only from the contribution of each ingredient; there was no interaction of ingredients that affected the pH of the

peel-off gel mask preparation.) As in Figure 1a, the contour plot displayed a linear line because no interaction between variables affected the response. It illustrated the distribution of data from the pH response of the combination of PVA and HPMC concentrate level variations, with blue indicating the highest data value and red as the lowest value of 5.54-6.22.

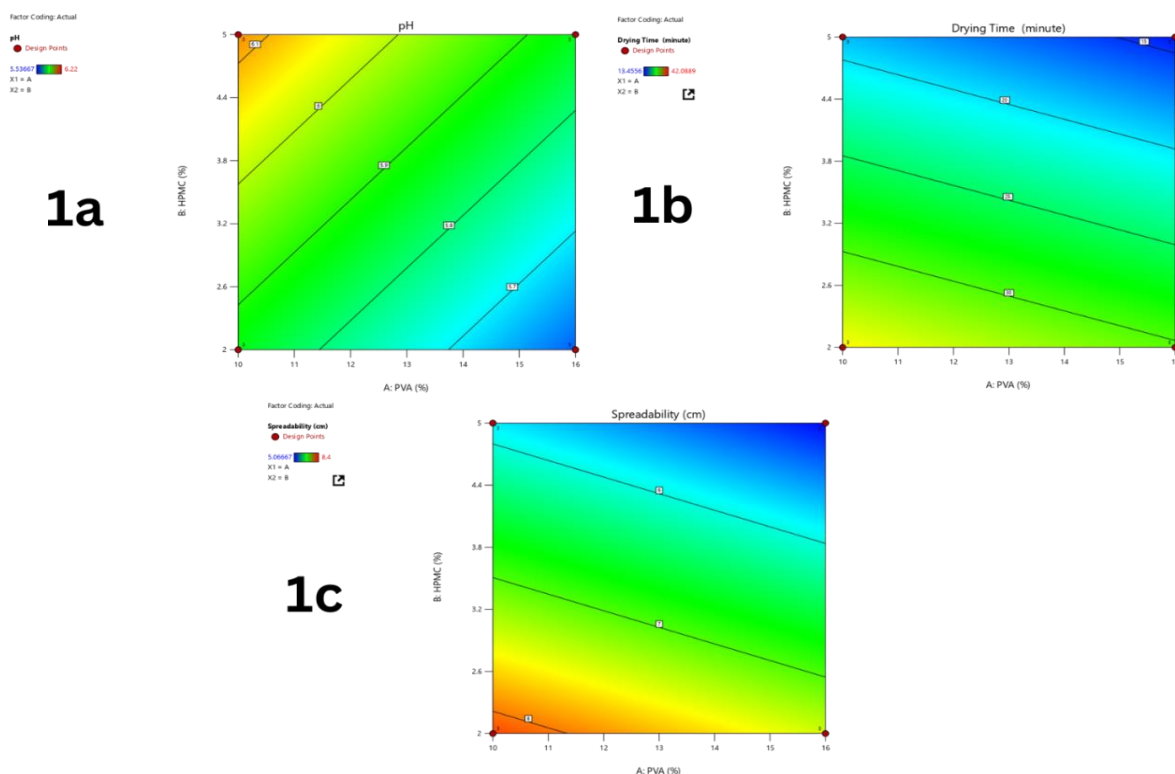
#### 1. Drying Time Test

The concentrate level of PVA and HPMC affected the drying time, where the range of time needed to dry is 13.46 - 42.09 minutes, which could be seen in the evaluation results of the red rice ethanol extract peel-off gel mask (Table 3). A good drying time of a peel-off gel mask was 15-30 minutes. Run 7 had a drying time of

$42.09 \pm 0.293$  minutes, which exceeded the limit of good drying time. Run 3 had the best drying time of  $15.78 \pm 0.824$  minutes because, according to Partuti et al. (2021), the best value of peel-off gel drying time

illustrating that adding PVA and HPMC reduces the drying time. Drying time could be affected by viscosity; the higher the viscosity, the faster the drying time<sup>9</sup>.

Due to the higher concentrate level of



**Figure 1. Contour plot of evaluation response of red rice ethanol extract peel-off gel mask.**  
**Description:** pH (1a), drying time (1b), and spreadability (1c) of red rice ethanol extract peel-off gel mask.

was 15 minutes after application to the skin.

The model value of drying time was 0.0002 (*significant*), and the *lack of fit* was 0.1394 (*insignificant*). Drying time had a difference value of *Predicted R<sup>2</sup>* with *Adjusted R<sup>2</sup>* owned by each response, which was less than 2. *Adeq Precision* value greater than 4 indicated adequate signal, and the model could navigate the design space. The drying time equation was obtained as follows:

$$Y = 53.54 - 0.77A - 5.4B \dots\dots\dots(2)$$

**Equation 2.** Modelling the pH response of red rice ethanol extract peel-off gel mask. Notes: Y = pH, A = PVA (%), B = HPMC (%)

Equation (2) showed that PVA and HPMC had a negative response,

PVA, the drying time was faster. This was due to the increased content of attracted water in each formula, which impacted faster film formation<sup>29</sup>. PVA's molecules attracted solvents to enlarge their molecular size (expand), increased liquid resistance and the ability to flow and spread, and a large amount of solvent attracted by PVA decreased the drying time of the gel<sup>11</sup>.

HPMC formed a hydrogel that accelerated drying time by increasing the number of polymer fibers that could hold more liquid and then bonding it like PVA. The amount of unbound liquid to evaporate was less, increasing the preparation's evaporation rate.<sup>9</sup>

Figure 1b was a contour plot of the *Design Expert's* factorial design method, representing the PVA and HPMC variables, with blue indicating the highest

value and red as the lowest value, 13.46 - 42.09. The contour plot displayed a linear line because no interaction between variables affected the response.

### 3. Spreadability Test

A good peel-off gel mask had a spreadability of 5-7 cm<sup>5</sup>. Run 5 had good spreadability with a value of 5.06667 cm, while Run 8 had a value of 8.4 cm, exceeding the range of good preparation requirements.

The spreadability response had a model value of <0.0001 (*significant*) and a *lack of fit* of 0.1656 (*insignificant*), which could be seen in the table. The *Predicted R*<sup>2</sup> value was quite following the *Adjusted R*<sup>2</sup> value, namely the difference in value owned by each response, which was less than 2, and *Adeq Precision* had a value > 4 (greater). This model could be accepted because it was *significant*. The equation produced by the spreadability response was:

$$Y = 10.96 - 0.12A - 0.77B \dots\dots\dots(3)$$

**Equation 3.** Modelling the spreadability response of red rice ethanol extract peel-off gel mask. Notes: Y = pH, A = PVA(%), B = HPMC(%)

Equation (3) predicted that the impact given by PVA and HPMC was equally negative, implying that adding both ingredients decreased the value of spreadability. This proved that the concentrate level of PVA influenced the spreadability of peel-off gel masks; the greater the concentration of PVA, the smaller the spreadability value<sup>30</sup>. The decrease in the spreadability value occurred due to the increased molecular size of PVA because it had attracted liquid and held it, thereby increasing the resistance of the preparation to flow and spread<sup>31</sup>. Research by Noval et al. (2020) showed the effect of HPMC on spreadability, namely, the higher the concentrate level of HPMC used in gel preparations, the smaller the diameter of

the resulting spread. This was because the more the gel was made, the thicker it would be, which reduced the ability to spread, so an increase in HPMC concentration could decrease gel dispersion. The higher the concentrate level of the gelling agent used, the lower the spreadability, where HPMC was a gelling agent<sup>32,33</sup>.

Figure 1c was a contour plot of the *Design Expert's* factorial design method representing the PVA and HPMC variables, with blue indicating the highest value and red as the lowest value of 5.07 - 8.4. The contour plot displayed a linear line because no interaction between variables affected the response.

### 4. Viscosity Test of Red rice Ethanol Extract Peel-Off Gel Mask

Viscosity influenced spreadability and drying time, as evidenced by the viscosity testing of formulas 2 and 8. These formulas had high viscosity and fast drying time, with a ratio of PVA and HPMC concentrations of 16: 5. The results of viscosity testing were presented in Table 3.

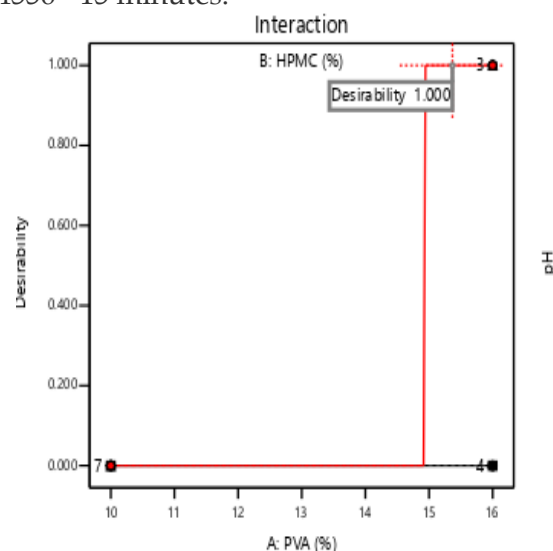
The viscosity of the preparation was influenced by the concentrate level of PVA and HPMC. Hydrogel occurred because HPMC expanded in water due to increasing the number of polymer fibers, which allowed it to hold more liquid and function as a gelling agent. HPMC gel formation occurred when macromolecules and solvent interacted, reducing the space between particles and forming cross-links between molecules. After that, the movement of the solvent was reduced, forming a gel mass. Thereafter, the active substance was retained in the gel matrix and released upon use<sup>34</sup>. As PVA attracted liquid and held it, its molecular size increased, resulting in increased resistance to flow and spread, increasing the viscosity of the preparation, which was inversely proportional to the value of spreadability<sup>31</sup>.

### Determination of optimum formula of peel-off gel mask with variation of HPMC and PVA concentration by factorial design method

The pH, spreadability and drying time responses were then used to determine the optimal formula by giving values and weights to each response presented in Table 5 below.

Goal, lower limit, and upper limit values of each response in Table 5 were determined from the varied minimum and maximum concentration ranges of PVA and HPMC, and the requirements for peel-off gel mask preparations were said to be good. The value of good spreadability in peel-off gel masks was 5-7 cm <sup>35</sup>, and a good pH value was in the range of 4.5 - 8 based on SNI 16-4399-1996. The best peel-off gel drying time value is 15 minutes after application to the skin <sup>36</sup>. Therefore, the

goal used is in the range of the fastest drying time of the preparation, namely 13.4556 - 15 minutes.



**Figure 4.** Desirability Curve of Optimum Formula with Variation of PVA and HPMC Concentrate Level

**Table 5.** Giving Value and Weight to the Response of Peel-Off Gel Mask with Variations in HPMC and PVA Concentration with Factorial Design Method

Name	Goal	Lower Limit	Upper Limit	Importance
A: PVA (%)	As in range	10	16	3
B: HPMC (%)	As in range	2	5	3
pH	As in range	4.5	8	3
Spreadability (cm)	As in range	5	7	3
Drying Time (minutes)	As in range	13.46	15	3

**Table 6.** Results of Physical Properties Test of Optimum Formula of Peel-Off Gel Mask with Various Concentrate Levels of HPMC and PVA with Factorial Design Method

Parameters	Replication 1	Replication 2	Replication 3	Average	SD
Drying Time (minutes)	13.10	15.65	14.75	14.50	1.29
Spreadability (cm)	5.5	5.9	5.3	5.57	0.31
pH	5.99	6.04	6.08	6.04	0.05
Viscosity (cP)	28680	29670	30000	29450	686.95

Verification of the results was analyzed using the normality test, namely *Shapiro-Wilk* and *one sample t-test*. After being analyzed, it resulted in a value  $<0.05$ , which meant a significant difference in the

the spreadability value and drying time. The optimum formula was obtained with a variation of PVA of 15.368% and HPMC of 4.989%.

**Table 7.** Comparison of Response Values of The Test Results of The Predicted Optimum Formula and The Optimum Formula of Peel-Off Gel Masks with Varying Concentrations of HPMC and PVA with Factorial Design Method

Parameters	SLD Prediction Value	Optimum Formula Value	Sig (2-tailed)
pH	5.89	$6.04 \pm 0.05$	0.03*
Spreadability (cm)	5.19	$5.57 \pm 0.31$	0.17**
Drying Time (minutes)	14.71	$14.50 \pm 1.29$	0.73**

Note : \*= significantly different

\*\*= not significantly different

pH response and had a value  $>0.05$ , which meant a significant difference in the response results of drying time and spreadability. The experimental pH test value with the predicted pH value from the software had a significant difference, so it was invalid to be used as the optimal formula. According to Noval et al. (2020), the difference in pH value could be caused by several possibilities, one of which was changes in the pH of the extract or storage preparation, the rise and fall of pH during storage occurred significantly, but was still within the normal pH range of the skin.

According to the physical evaluation carried out in this study, PVA as a film coating and HPMC as a gelling agent affected the physical characteristics of gel mask preparations made from red rice extract. In addition, PVA and HPMC affected drying time and spreadability.

Table 7 compares the test response values of the predicted optimal formula and the optimal preparation formula.

## CONCLUSION

Variations in the concentrate level of PVA and HPMC affected the physical properties of the Red Rice extract peel-off gel mask preparation. Increasing the PVA and HPMC concentrate levels could reduce

## Conflict of Interest

The authors declare no conflict of interest.

## Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article.

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