

## OPTIMIZATION OF CARBOPOL 940 AND OLEIC ACID IN DICLOFENAC SODIUM BASE GEL USING FACTORIAL DESIGN 2<sup>2</sup> METHOD

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### ABSTRACT

*The aim of the present study was to determine the effect of carbopol 940, oleic acid and interaction of both in the value of viscosity and release rate and to find optimum formula of diclofenac sodium base gel which can produced viscoisity between 20 dPa.s - 200 dPa.s and rate release  $50\mu\text{g}/\text{cm}^2.\text{menit}^{1/2}$  -  $150\mu\text{g}/\text{cm}^2.\text{menit}^{1/2}$  using factorial design 2<sup>2</sup>. The level of carbopol 940 were 1,3% and 0,8% while the level of oleic acid were 5% and 20%. Analysis of the research used Design Expert 10 software. The results showed that carbopol 940 and oleic acid had significant effect in determining the viscosity response and the release rate. The addition of carbopol 940 and oleic acid l increased the viscosity response and the addition of carbopol 940 and oleic acid decreased the release flux response. There were 100 optimum compositions of combination of carbopol 940 between 0.8% to 1,194% and oleic acid between 5% and 19.95% which can be used to obtain sodium diclofenac base gel preparation with viscosity responses between 76,042 dPa.s -199,570 dPa.s and flux release responses from  $101,000\mu\text{g}/\text{cm}^2.\text{minute}^{1/2}$  until  $124,250\mu\text{g}/\text{cm}^2.\text{minute}^{1/2}$ .*

**Keyword :** carbopol 940, diclofenac sodium gel, factorial design, oleic acid.

### INTRODUCTION

Sodium is a non-steroid drug low soluble in water, and having excellent anti-inflammatory and analgesic effects. At the present time, it is used only in the form of oral preparations or suppositories exhibiting excellent anti-inflammatory and analgetic effects when so administered. However, side effects such as stomach and intestine problems, liver problems and kidney problems may occur, especially upon oral administration [1]. It also have 50% First Past Effect (FPE) in the liver and irritating the GI-tract [2]. Topical delivery

system are appropriate to attend that. Diclofenac sodium base gel have in-vitro rate release more good then in other such topical delivery as cream and ointment [3]. Further, gels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, compatible with several excipients, and water-soluble or miscible [4]. The necessary excipient for a gel is gelling agent that carbopol 940 are suitable cause It biocompatible and biodegradable for diclofenac sodium [1].

Diclofenac sodium is categorized into Biopharmaceutical Classification System (BCS) class 2<sup>nd</sup>. It has 13,4 in coefficient partition [2]. Meaning diclofenac sodium low soluble in water and high soluble in oil. So that, it is not good to penetrate in skin with gel administration almost the water. Suitable enhancer must be added to solve diclofenac sodium in gel and to increase penetration on the skin. Oleic acid match with diclofenac sodium because it can enhance sodium diklofenac more then other enhance such isopropyl miristat as castor oil, olive oil and isopropyl palmitat [5].

The goal of this research are to know impact of carbopol 940 and oleic acid and interaction of both to the value of viscosity and rate release and to find the optimum formula of carbopol 940 and oleic acid based on viscosity and rate release are appropriate using factorial design factorial 2<sup>2</sup> with Design Expert version 10 software. The respons of viscosity are between 20 dPa.s - 200 dPa.s and rate release responses from 50  $\mu\text{g}/\text{cm}^2 \cdot \text{minute}^{1/2}$  until 150  $\mu\text{g}/\text{cm}^2 \cdot \text{minute}^{1/2}$ .

## **MATERIAL AND METHOD**

### **Materials**

The material are diclofenac sodium as active ingredients, gelling agent carbopol 940 (Sumutomo Seika Chemicals), enhancer oleic acid (Avantor), tween 80 as emulsifying agent, propyl paraben and metyl paraben added as preservative and TEA as alkalizing agent.

### **Instrumentation**

The Instrumens are bekkar glass, mortar, stamper, stainless steel bowl, analytical scales, water bath, stopwatch, spread modification instrument, viscotester (*Viscometer Brookfield*), pH meter (*Denver*), *hot plate*, spectrophotometer UV-Vis (*Shimadzu UV-1800*), dissolution tester (*Erweka DT-700*), membrane cellophane, thermometer, ultrasonic, *SPSS* software dan Design Expert 10 software.

## Procedure

### Orientation level of each factor

Formula in this research based on factorial design formula  $2^2$  that have two factors are carbopol 940 and oleic acid and two level are low level (-1) and high level (+1) in each factor (table 1). The low level of carbopol 940 is 0,8% and high level is 1,3%. Further, oleic acid are 5% in low level and 20% in high level. The composition and concentration of diclofenac sodium base gel is in the table 2.

### Procedure of gel preparation

Carbopol 940 is dispersed in aquadest (1 gram of carbopol 940 is dispersed in 20 ml of aquadest) and let stand that on night. Add TEA to neutralize carbopol 940 and until seen transparant as gel. In the other, mix oleic acid and tween 80 and stir until homogen. Mix both mixture and add sodium diklofenac, propyl paraben, metyl paraben and aquades. Stiring the end mixture is until homogen.

### Evaluation of gel

Organoleptic test for evaluation gel are colour, smelling and homogeneity by surface of glass. Other test are pH test using pH meter instrument and spread test making two mirror. For spread test, put 1 gram of gel into surface of mirror and put other mirror and others having total of both 125 gram on the gel.

### Viscosity test

50 gram gel diclofenac sodium was tested using viscometer *Brookfield. Spindle*. The required value of viscosity are between 20 dPa.s - 200 dPa.s because this viscosity can spread well and comfortably to its wearer [6].

### Rate release test

Membrane cellophane rinse with buffer phosphate pH  $7,4 \pm 0,05$  during  $\pm 12$  hours. The diffusion instrumen is prepared with 500 ml buffer phosphate pH  $7,4 \pm 0,05$  in the chamber (receptor compartement). 1 gram sample (gel) is plased in cakram and is closed with membrane cellophane (donor compartement). The diffusion cell is maintained at  $37^0$  C and the solution in the receptor chamber is stirred continuously at 100 rpm. At 0, 5, 15, 30, 45, 60, 90, 120, 150, 180, and 240 minutes, 5 ml of the solution is removed from receptor compartment and replaced immediately with an equal proportions of fresh buffer phosphate. The samples are analyzed in UV – Visible spectrophotometer after suitable dilutio. Flux

release is the slope from regression line the cumulative amount of sodium diclofenac vs  $\sqrt{\text{times}}$  in steady state condition.

## RESULTS AND DISCUSSION

### Evaluation of gel

All of the formula had white colour and having aroma like an oleic acid. All developed gels showed good homogeneity with absence of lumps. The pH of all the four formulations were in the range of 6,48 to 6,53 that suits the skin pH, indicating skin compatibility. Then, the spreadability of formulations ranged from 5,53 to 6,83 cm. The values of spreadability indicate that the gel is easily spreadable with minimal of shear.

### Viscosity

The viscosity of all the four formulations ranged from 75,83 to 230,83 dPa.s. Gels with high viscosity do not easily extrude from the tube whereas, low viscous gels may flow quickly and hence suitable viscosity is required to extrude a gel. Carbopol 940 and oleic acid had positive effect to gel viscosity. It means that addition of carbopol 940 and oleic acid would increase the viscosity of gel. Carbopol 940 has bigger effect than oleic acid to viscosity value. It causes carbopol 940 having high viscosity 40.000 – 60.000 cp [7]. The effect value was shown in table 3 and the contour plot 2D of factor effect also in figure 1.

### Release rate

The flux of all the four formulations ranged from 94,15 to 124,25  $\mu\text{g}/\text{cm}^2 \cdot \text{minute}^{1/2}$ . With increasing time, also increase the drug release from the gel. Carbopol 940 and oleic acid have negative effect to the flux (table 4). Increasing carbopol 940 and oleic acid would decrease the flux. It is shown in contour plot 2D in figure 2. Blue area shows the low value of flux while red area shows the high value of flux.

Having rigid character, carbopol makes the gel become thicker. This causes active ingredient having lipophilic character difficult to leave the gel system then it penetrates the cellophane membrane. The function of oleic acid is an enhancer. It can enhance diclofenac sodium and increase rate release in appropriate amount [8]. This research may use the appropriate amount in 5% of oleic acid. Increasing enhancer oleic acid can decrease rate release of diclofenac sodium that causes too much of it and saturates in the gel system. So that will disturb the diclofenac sodium to exit and then permeate the cellophane membrane.

### Optimization of carbopol 940 and oleic acid using design factorial 2<sup>2</sup>

Factorial Design for two factors at two levels with -1 and +1 equivalent to a 2<sup>2</sup> factorial design was chosen as the experimental design. This is an effective second-order experimental design associated with a minimum number of experiments to estimate the influence of individual variables (main effects) and their second-order effects. To investigate the factors systematically, a full factorial design was employed. The coded and actual factors was shown in table 5. The effect on viscosity(Y1) was observed to be significant by ANOVA and the polynomial equation was found as follows:

- Final equation in terms of coded factors:  $Y1 = 165,21 + 77,29X1 + 11,88X2$
- Final equation in terms of actual factors:  $Y1 = -179,20833 + 309,16667*\text{carbopol 940} + 1,58333*\text{asam oleat}$

The positive sign for coefficient of X1 (carbopol 940) indicates that as carbopol 940 increases, viscosity increases. And also the positive sign for coefficient of X2 (oleic acid) indicates that as oleic acid increases, viscosity increases. The effect on release rate (Y2) was observed to be significant by ANOVA and the polynomial equation was found as follows:

- Final equation in terms of coded factors:  $Y1 = 110,56 - 4,60X1 - 10,45X2 - 1,36X1X2$
- Final equation in terms of actual factors:  $Y1 = 137,78787 - 9,34178*\text{carbopol 940} - 0,63397*\text{asam oleat} - 0,72364*\text{carbopol 940}*\text{asam oleat}$

The negative sign for coefficient of X1(carbopol 940) indicates that as the carbopol 940 increases, the rate release (Y2) also increases. And also is same for sign in for coefficient of X2 (oleic acid).

There were 100 optimum composition combinations of carbopol 940 between 0.8% to 1,194% and oleic acid between 5% to 19.95% which can be used to obtain viscosity from 76,042 dPa.s -199,570 dPa.s and the flux from 101,000  $\mu\text{g}/\text{cm}^2.\text{menit}^{1/2}$  - 124,250  $\mu\text{g}/\text{cm}^2.\text{menit}^{1/2}$ . That show in overlay plot on figure 3. The optimum formula in yellow area.

### CONCLUSION

It may be concluded that Factorial Design can be used for a systematic approach for designing and optimizing the desired formulation based on different process variables. Carbopol 940 and oleic acid have positive effect to viscosity and negative effect to rate release. With increasing carbopol 940 and oleic acid, the viscosity decreases while the rate

release increases. The equation of coded factor or actual factor can be used to find the value of viscosity and rate release that you wanted.

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**Table 1.** The formula based on design factorial  $2^2$  method

Name of formulas	Factors	
	Carbopol 940	Oleic acid
1	-1	-1
a	+1	-1
b	-1	+1
ab	+1	+1

**Table 2.** Composition and concentration of sodium diclofenac base gel

Materials	Function	1 (%)	a (%)	b (%)	ab (%)
Sodium Diklofenac	Active ingredient	1	1	1	1
Carbopol 940	Gelling agent	0,8	1,3	0,8	1,3
TEA	Alkalizing agent	0,4	0,65	0,4	0,65
Asam oleat	Enhancer	5	5	20	20
Tween 80	Emulsifying agent	2	2	2	2
Metyl paraben	Preservative	0,18	0,18	0,18	0,18
Propyl paraben	Preservative	0,02	0,02	0,02	0,02
Aquadest		Ad 100	Ad 100	Ad 100	Ad 100

**Table 3.** Effect value of each factor and of both interaction to viscosity of gel

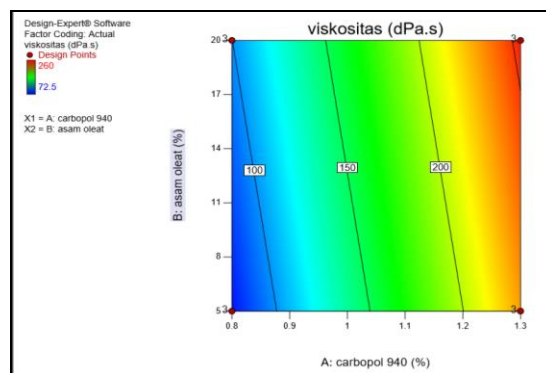
Factors	Value of Effect	p-value ANOVA	Contribution (%)
Carbopol 940	154,58	< 0,0001	97,44
Oleic Acid	23,75	< 0,0001	2,30
Interaction	-0,42	-	-

**Table 4.** Effect value of each factor and of both interaction to value of rate release (flux)

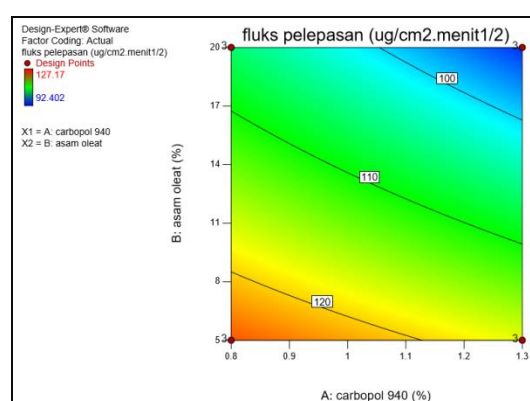
Factors	Effect	p-value ANOVA	Contribution (%)
Carbopol 940	-9,19	0,0006	15,32
Asam oleat	-20,91	< 0,0001	79,24
interaksi	-2,71	0,1452	1,34

**Table 5.** Correlation of actual and coded values of levels

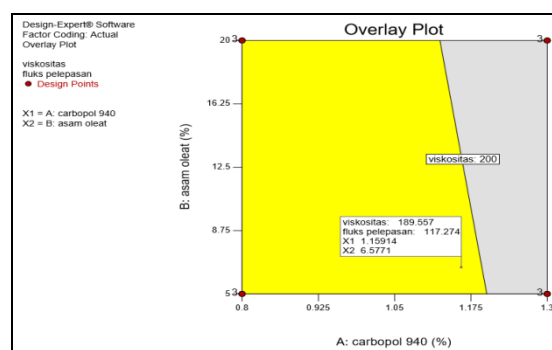
Level factor	Coded factor	Actual factor	
		Carbopol 940 (X1)	Oleic acid (X2)
High level	-1	0,8%	5%
Low level	+1	1,3%	20%



**Figure 1.** Contour plot 2D showing the factor to viscosity response



**Figure 2.** Contour plot 2D showing the factor to rate release response



**Figure 3.** Overlay plot optimum formula