Journal of
Food and Pharmaceutical Sciences

*Original Article*

# Application Simplex Lattice Design on Optimizing Formula of Ketoprofen Matrix Patch Transdermal

**Eka Indra Setyawan[1]*, Achmad Fudholi[2], Akhmad Kharis Nugroho[2]**

[1]Faculty of Mathematics and Natural Science, Udayana University, Bali, Indonesia
[2]Faculty of Pharmacy, Gadjah Mada University, Yogyakarta, Indonesia.
*Corresponding author: Eka Indra Setyawan | Email: indrasetyawan@ymail.com

Received: 8 August 2019; Revised: 22 August 2019; Accepted: 26 September 2019; Published: 29 September 2019

**Abstract:** Ketoprofen is a propionic acid derivative that has anti-inflammatory, analgesic, and antipyretic activity. Transdermal patch dosage form is the right choice for ketoprofen in an effort to minimize side effects, improving patient compliance and ensure the achievement of therapeutic targets. This study aimed to optimize the formulation of ketoprofen matrix patch transdermal. The optimizing process was analyzed by simplex lattice model. Determination of the level of ketoprofen released was carried out by spektrophotometer UV-Vis. Interpretation of the dissolution profile can be seen visually fit between the model constructed from the zero-order approximation, first-order, Higuchi, Korsmeyer-Peppas, Weibull, Hixson-Crowell and Baker-Lonsdale. The results provide information that a combination of MC and HPMC polymers have a significant influence on increasing the patch weight, patch thickness, loss on drying and dissolution efficiency and insignificant effect against folding endurance. The optimal formula is generated by a combination of HPMC:MC (0.1:0.9) and produces a patch matrix with weight, thickness, drying loss, and DE were 0.68 g, 0.36 mm, 12.42%, and 23.21%, respectively. The release kinetic of ketoprofen followed Korsmeyer-Peppas model through the mechanism of non-Fickian diffusion.

**Keywords:** transdermal; ketoprofen; optimizing; release kinetic

## 1. INTRODUCTION

Ketoprofen (3-benzophenyl) -propionic acid is a propionic acid derivative that has anti-inflammatory, analgesic, and antipyretic activities. Ketoprofen is able to inhibit arachidonic acid metabolism through the cyclooxygenase pathway. Ketoprofen is commonly used to relieve pain in patients with musculoskeletal disorders, namely osteoarthritis, rheumatoid arthritis, and traumatic pain in patients who experience acute low back pain or soft tissue disorders [1].

Ketoprofen is reported to have side effects greater than the side effects of analgesics such as propionic acid derivatives such as ibuprofen. The maximum concentration of ketoprofen in plasma on oral use (Cpmax) occurs after use for 1-2 hours, half-life (t1/2) of 2 hours, and plasma drug levels are 98% [2]. Transdermal administration of ketoprofen patches is expected to improve patient compliance compared to oral administration because it can minimize the frequency of drug consumption.

The advantages of patch dosage form are; 1) Avoiding first-pass metabolism; 2) Reducing the side effect by decreasing the peak of plasma level; 3) Reducing the occurrence of fluctuations; 4)

Applicable for the drugs with a short half-life and short therapeutic range; 5) Easily stopped if there are symptoms of poisoning; 6) Reducing the frequency of drug use, thereby increasing patient compliance [3]. Transdermal dosage form is able to maintain uniform plasma drug concentrations during use. Patches are preferred over intravenous administration because they do not cause pain and damage tissue. A drug requirements to be made in the dosage form include; 1) Short half-life; 2) Does not have a toxic effect on the skin; 3) Molecular weight less than 500 Da; 4) Has a partition coefficient of 1-3 [4,5].

The drug release ability of the matrix is one of the important things that greatly affects the success of a patch. The drug particles have to dissolve to be molecules form that can diffuse through the matrix, and then the drug will penetrate through the skin. There are 2 transdermal patch systems, namely the matrix or monolithic type and the membrane or reservoir system [6]. This type of membrane consists of backing layer, drug reservoir, membrane controlling and adhesive. This type of matrix is composed of a backing layer, polymeric drug reservoir, and adhesive. Sometimes in the system, there are only a backing layer and drugs that have been mixed with adhesive [7,8].

The matrix system, the polymer material will bind and control the release rate of the drug In the membrane system, the drug release rate is controlled by the membrane which acts as a barrier. The membrane system generally provides a drug release rate that follows the zero order. There are two types of polymers used as carriers in the matrix system, namely, hydrophilic polymers such as hydroxy propyl methyl cellulose, hydroxy propyl cellulose and polyvinylpyrolidone, and hydrophobic polymers such as ethyl cellulose, methyl cellulose, polyethylene and polyvinyl chloride. The hydrophilic polymers causes the dissolution medium to easily penetrate into the matrix, so that drug diffusion is fast, while the hydrophobic polymers will decrease the rate of drug release. In order for the drug release to be effective, it is necessary to modify the properties of the polymer by using a mixture of the two polymers. The effect of this modification causes the formation of pores [9].

Previous studies have been conducted to study the combined effect of the two polymers in assisting drug release. Vijayan et al, [10], observed that the combination of hydroxy propyl methyl cellulose (HPMC) with methyl cellulose (MC) 1:1 w/w in the losartan patch resulted in drug transport of 75.96% for 24 h higher than the combination of HPMC with Eudragit® RS100 and HPMC with ethyl cellulose (EC) were 45.55% and 61.33%, respectively. Kahinata et al. [11], the combination of HPMC with MC (1:1 w/w) showed that the amount of valsartan transported was 87.55% higher than the combination of HPMC with Eudragit® RS100, HPMC with Eudragit® RL100 and HPMC with EC were 52.24%, 71.25%, and 63.5%, respectively. Kumar et al. [12], a combination of 3% HPMC and 2% MC produced a ketorolac thromethamine patch with a constant release rate and a long enough duration so as to reduce the frequency of drug use. Therefore, it is important to conduct research on patch formulation using a combination of HPMC and MC polymers to increase the amount of transport and ketoprofen flux, so that it is expected to be able to provide a therapeutic effect.

## 2. MATERIALS AND METHODS

### *2.1. Materials*

Ketoprofen is purchased from Sigma-Aldrich (Singapore), hydroxy propyl methyl cellulose (HPMC), methyl cellulose (MC), and Eudragit® RL100 is given from PT. Menjangan Sakti (Indonesia), ethanol and crystal menthol are purchased from Bratchem (Indonesia).

*2.2. Instruments*

Electric scale (Adventurer® Ohaus ARC120), UV-Vis spectrophotometer (Genesys® 10S), sonicator (Transonic® 570), magnetic stirrer (Stuart® cb162), pH meter (Hanna® HI 8314), Franz diffusion cell.

*2.3. Methods*

2.3.1. Validation method

Determination of the maximum wavelength of ketoprofen was carried out by dissolving 100 mg of ketoprofen in a PBS solution of pH 7.4 (100 mL) and then diluting it 10 times. The scanning process is carried out in the range of 200-400 nm. The same process was carried out for the scanning process of the blank matrix patch [13].

The concentrations series of the standard solution of ketoprofen (0.5-5 μg/mL) were prepared for use in the linearity test, limit of detection (LoD) and limit of quantitation (LoQ). The standard addition method is used to test the accuracy and precision. The accuracy test is expressed as the percent of recovery and the precision test is expressed as the percent of the relative standard deviation (% RSD)..

2.3.2. Matrix patch transdermal formulation

The ketoprofen matrix patch was made using a matrix controled system which was printed with a circular petri glass with an inner diameter of 5.7 cm. All ingredients are weighed according to the formula established as follows (Table 1).

**Table 1.** Formulation matrix patch transdermal of ketoprofen design by Simplex Latice Design (software used Design Expert ver.7)

| Formula | HPMC | MC | Ketoprofen (mg) | HPMC (mg) | MC (mg) | Eudragit® RL100 (mg) | Menthol (mL) | PEG 400 (mL) |
|---|---|---|---|---|---|---|---|---|
| 1 | 0 | 1 | 20 | 0 | 300 | 500 | 1 | 0.5 |
| 2 | 0.5 | 0.5 | 20 | 150 | 150 | 500 | 1 | 0.5 |
| 3 | 0.25 | 0.75 | 20 | 75 | 225 | 500 | 1 | 0.5 |
| 4 | 0.75 | 0.25 | 20 | 225 | 75 | 500 | 1 | 0.5 |
| 5 | 0 | 1 | 20 | 0 | 300 | 500 | 1 | 0.5 |
| 6 | 0.5 | 0.5 | 20 | 150 | 150 | 500 | 1 | 0.5 |
| 7 | 1 | 0 | 20 | 300 | 0 | 500 | 1 | 0.5 |
| 8 | 1 | 0 | 20 | 300 | 0 | 500 | 1 | 0.5 |

2.3.3. Matrix patch transdermal evaluation

Evaluation of the patch matrix is conducted by observing parameters such as matrix thickness, matrix weight, loss on drying, folding endurance, and percent of dissolution efficiency (% $DE_{300}$). Each parameter is analyzed to determine the optimum formula.

2.3.4. In vitro release study of ketoprofen

Determination of ketoprofen release was carried out using Franz diffusion cells without using a eradication membrane. The ketoprofen patch directly comes into contact with the

dissolution medium contained in the acceptor compartment of the diffusion cell. The dissolution medium used was a phosphate buffer saline solution (PBS) pH 7.4 (30 mL). Sampling was carried out at 15; 30; 45; 60; 75; 90; 105; 120; 150; 180; 210; 240; 270 and 300 minutes were taken as much as 1.0 mL and then diluted with PBS to 10.0 mL. Determination levels of ketoprofen released were carried out by spectrophotometer UV-Vis.

2.3.5. Drug content

The ketoprofen matrix patch was cut into an area of 1 $cm^2$ and dissolved in 100.0 mL of a PBS medium pH 7.4. The transdermal ketoprofen patch solution was taken of 1.0 mL and diluted with the addition of a PBS medium pH 7.4 to 5.0 mL. Furthermore, the absorption was measured using a spectrophotometer UV-Vis at its maximum wavelength

2.3.6. Determination of the release kinetic model of ketoprofen

Determination of the kinetics of the release of ketoprofen was carried out using a curve fitting approach between observations and predictions from the following equation model (Table 2).

**Table 2.** Release kinetic model equation

| **Release model tested** | |
|---|---|
| Higuchi | $Qt = Kh\sqrt{t}$ |
| Zero order | $Qt = Q_0 + K_0t$ |
| First order | $Qt\ unreleased = Q_0 \exp^{-K1t}$ |
| Baker-Lonsdale | $(3/2)[1-(1-(Qt/Q\sim)^{2/3}]-(Qt/Q\sim) = Kt$ |
| Hixson-Crowell | $Q_0^{2/3} - Qt\ unreleased^{1/3} = Kt$ |
| Weibull | $Qt/Q\sim = 1-\exp[-(t-Ti)^{\beta}/\alpha]$ |
| Korsmeyer-Peppas | $Qt/Q\sim = Kt^n$ |

## 3. RESULTS AND DISCUSSION

*3.1. Validation method*

The observations results showed that ketoprofen had a maximum wavelength at 262 nm, while the matrix absorption of each formula does not interfere with the maximum wavelength of the ketoprofen compound. Linearity is the ability of the analytical method to the respond directly. Linearity is usually expressed in terms of the variance around the direction of the linear regression line which is calculated based on the mathematical equation of the data obtained from the test results of the analyte in samples with various concentrations of the analyte. The results showed the correlation coefficient (r) of 0.9988, LoD was 0.04 μg/mL and LoQ of 0.12 μg/mL (figure 1). The results of the accuracy test (intra-day) with six times replication presented in the percent recovery value for addition 0.5 μg/mL (87.32-104.23%) with % RSD of 8.89%, 2.5 μg/mL (95.77-102.52%) with % RSD of 3.63%, and 5μg/mL (100.84-103.09%) with % RSD of 1.12%.

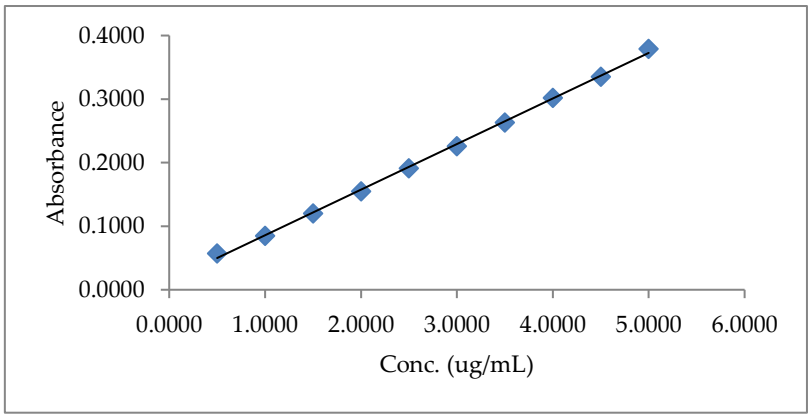


**Figure 1.** Standard calibaration curve of ketoprofen

*3.2. Matrix patch transdermal evaluation*

The observation of matrix weight for the eight formulas resulted in matrix weight was ranging from 0.638-0.846 g. Based on the results of the ANOVA statistical analysis, the eight formulas show a probability value of 0.0009 (< 0.05), so it can be concluded that each formula was significantly different so that it could be used as a response to the experimental design to determine and predicting the optimal formula. The effect of each component in the formula to the matrix weight can be illustrated by the following equation (Equation 1).

Weight = 0,77(A) + 0,63(B) + 0,46(A)(B)……..……..……..……..…….(1)

The quadratic equation above showed that HPMC (A) had the greatest contribution to the increase of matrix weight.

The observation results showed that the matrix thickness was in the range from 0.33-0.43 mm. Anova analysis resulted the p-value for the eight formulas was 0.0168 (< 0.05). The contribution of each component in the formula to the matrix thickness can be illustrated by the following equation (Equation 2).

Thickness = 0,40 (A) + 0,34(B) + 0,19(A)(B)……..……..…....…....……(2)

The quadratic equation above showed that HPMC (A) had the greatest contribution to the increase of matrix thickness.

Base on the results of the two parameters above can be said that, there was a relationship between the increase in the thickness of the matrix due to the addition of the matrix weight. The most dominant factor for the two parameters above was HPMC, HPMC is a hydrophilic polymer which is rich in free electrons, so that it is able to bind large amounts of water through hydrogen bonds. The large amount of bound water will have an impact on increasing the weight of the matrix and the thickness of the matrix.

The percentage of loss on drying of the matrix patch varies considerably, ranging from 8.71% to 15.46%. Based on the results of the ANOVA statistical analysis, each formula showed a significant difference from one another with p-value of 0.0001 (< 0.05). The contribution of each component in the formula to the loss on drying can be illustrated by the following equation (Equation 3).

% loss on drying = 8,76 (A) + 11,28(B) + 19,15 (A)(B)…..…….…….…..(3)

The quadratic equation above showed that interaction between HPMC (A) and MC (B) had the greatest contribution to the increase of loss on drying. An interaction of HPMC-MC was able to increase the permeability of the matrix so that the water was more easily diffuse out during the drying process.

Folding endurance test on the eight formulas did not show a significant difference. All formulas last more than 300 folds. Therefore, this parameter cannot be used further in determining the optimal formula.

Before conducting drug release testing, it is necessary to determine the amount of drug content in the matrix. This determination aimed to see the number of drugs that are successfully contained in the formula as well as the basis for calculating the percent of dissolution efficiency (% DE300). The drug content was illustrated by percent of entrapment. The results showed that percent of entrapment varied from 95.80-105.38% for all formulas.

The dissolution efficiency is the ratio of the area under the dissolution curve in the square area of one hundred percent of the active substance dissolved in the medium at any given time. The use of DE parameters will be better if the time taken has shown that 90% of the active substance has dissolved in the medium, so that it describes a large part of the observable dissolution process. If you want to compare the dissolution results of one formula with the dissolution of another formula, the same DE must be used, meaning that the dissolution curves between these formulas are observed to be observed at the same time. As in the present experiment all formulas were observed for drug release within 300 minutes.

The results of the calculations from the experimental data show that the values varied, ranging from 19.28% to 31.80% with a p-value 0.0318 (< 0.05). The contribution of each component in the formula to the % $DE_{300}$ can be illustrated by the following equation (Equation 4).

% $DE_{300}$ = 24,53(A) + 20,84(B) + 28,79(A)(B)…..……..……...……...…...(4)

The quadratic equation above showed that interaction between HPMC (A) and MC (B) had the greatest contribution to the increase of % DE300. An interaction of HPMC-MC was able to increase the permeability of the matrix so that ketoprofen was more easily diffuse out during the test.

Desirability value is a value that indicates the achievement of a model used for the expected target, the magnitude of the desirability value ranges from 0 to 1. Based on the desirability value generated by the two formulas, the optimal formula is selected with the composition of HPMC and MC (0.1:0.9) (figure 2). The optimal formula was predicted produce a patch with a weight of 0.678 g, a patch thickness of 0.36 mm, a loss on drying 12.47% and a dissolution efficiency of 23.23%. The results of the verification test showed that there was not significant difference between the results of the model predictions and the results of the observation (Table 3).

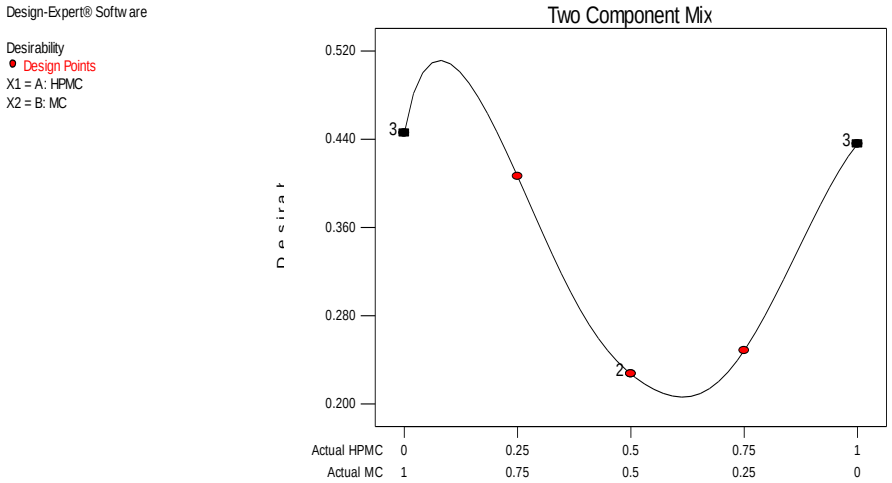


**Figure 2.** Graphic of the optimal formula of matrix patch transdermal

**Table 3**. Verification data between observed data and model prediction

| Parameters | Observation data Mean ± SD | Theoretical value | p-value |
|---|---|---|---|
| Matrix weight (g) | 0.68 ± 0.01 | 0.6775 | 0.796 |
| Matrix thickness (mm) | 0.36 ± 0.01 | 0.3585 | 0.681 |
| Loss on drying (%) | 12.42 ± 0.13 | 12.4699 | 0.541 |
| Dissolution efficiency (%) | 23.21 ± 1.03 | 23.2273 | 0.976 |

*3.4. Determination of release kinetic of ketoprofen*

The release mechanism of ketoprofen from transdermal patches can be determined using a drug release equation model such as; zero order, order one, Higuchi, Korsmeyer-Peppas, Weibull, Hixson-Crowell and Baker-Lonsdale (table 2). The result of curve fitting (figure 3) showed that the release of ketoprofen visually followed the Korsmeyer-Peppas model. The Korsmeyer-Peppas model derives from a simple relationship that describes drug release of the polymeric system. This equation uses the value (n) to determine the characteristics of drug release and is used when the drug release mechanism is unknown or has more than one release mechanism. If n = 0.5, it means that the drug release follows Fickian diffusion, i.e. the diffusion rate is smaller than relaxation, n = 1, the release of the drug occurs through relaxation, where diffusion is faster than relaxation and if 1 > n > 0.5, the behavior follows non-Fickian diffusion, where the rate of diffusion and erosion of the polymer is balanced [14,15].

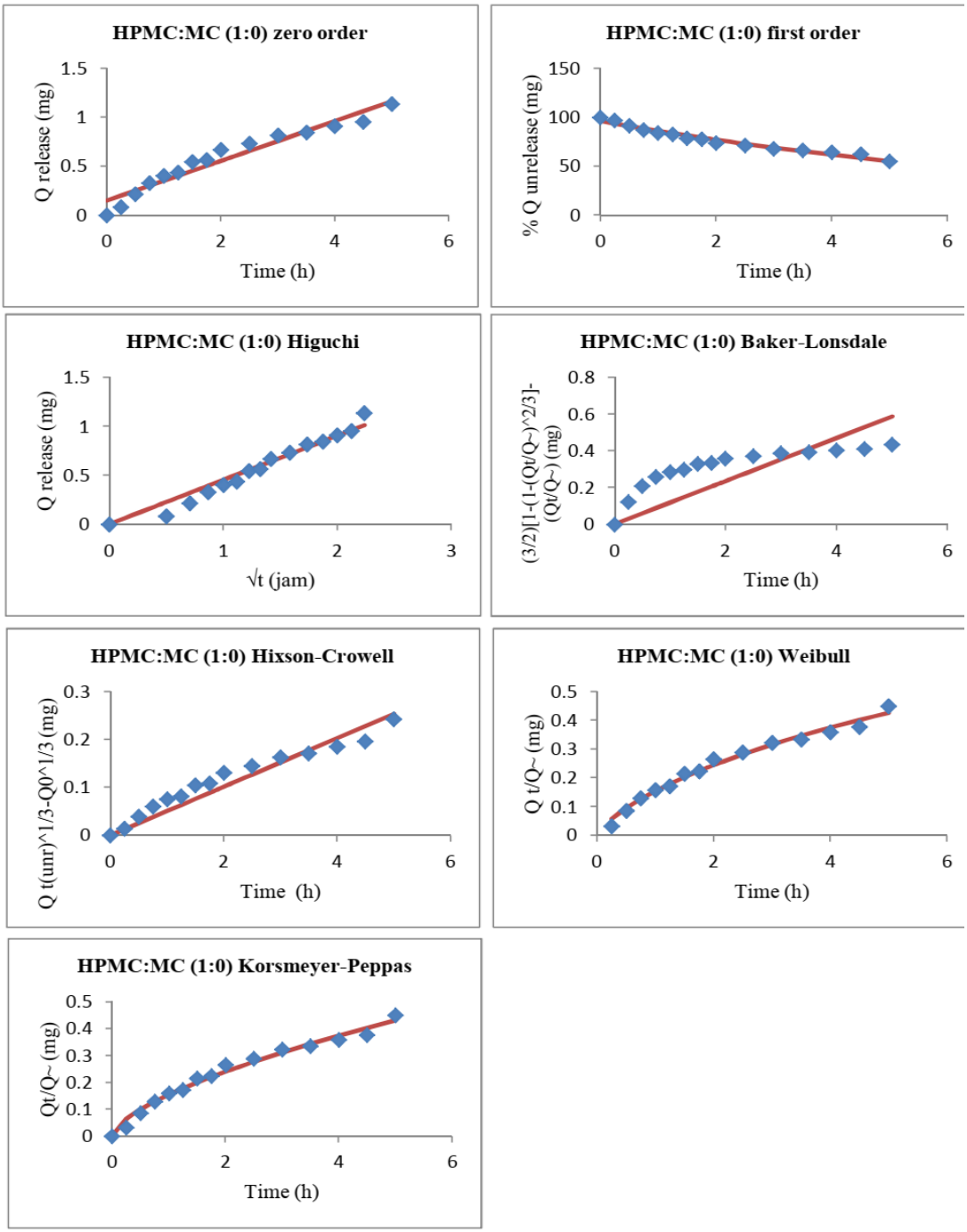


**Figure 3.** Curve fitting between oberserved data (blue pattern) and kinetic model (red line) of ketoprofen release from formula with combination of HPMC-MC (1:1) analyzed by Solver

The analysis results of the Korsmeyer-Peppas model obtained dissolution rate (k) and diffusion exponentials which indicate the drug release mechanism (n) as shown in the following table 4.

**Table 4.** Dissolution rate and diffusion exponentials of Korsmeyer-Peppas analyzed by Solver

| Formula | Korsmeyer-Peppas | |
|---|---|---|
| | k | n |
| HPMC:MC (1:0) | 0.15 | 0.64 |
| HPMC:MC (1:0) | 0.12 | 0.74 |
| HPMC:MC (0:1) | 0.14 | 0.55 |
| HPMC:MC (0:1) | 0.12 | 0.59 |
| HPMC:MC (0.5:0,5) | 0.20 | 0.58 |
| HPMC:MC (0.5:0.5) | 0.13 | 0.79 |
| HPMC:MC (0.75:0.25) | 0.17 | 0.68 |
| HPMC:MC (0.25:0.75) | 0.16 | 0.70 |

The results showed that the dissolution rate were in the range of 0.12-0.20 mg/h and the diffusion exponential value (n) were in the range of 0.55-0.79. Based on the value of (n), the release kinetic of ketoprofen followed non-Fickian diffusion, where the rate of diffusion and erosion of the polymer is balanced. This erosion mechanism is caused by the presence of MC which is a water-insoluble polymer so that the penetration of water into the polymer due the swelling of the matrix. Meanwhile, the diffusion mechanism is caused by the penetration of the dissolution medium into the pores of the matrix produced by HPMC (hydrophilic polymer) so that it will dissolve ketoprofen. Increasing the volume of media in the matrix will cause the matrix to swell and the drug will diffuse out accordingly. To determine the diffusion rate and relaxation rate, the Peppas-Sahlin equation is used to determine both parameters (Equation 5).

$$Qt/Q\sim = kd \times t0{,}5 + kr \times t \quad \ldots\ldots(5)$$

By using the Peppas-Sahlin equation model assisted by a Solver, the diffusion and relaxation rate values are obtained as shown in the table 5. Thus, based on the Korsmeyer-Peppas model approach which is strengthened by the Peppas-Sahlin model, it can be concluded that the ketoprofen release process from the patch follows a non-Fickian diffusion process (transport anomaly) with a balanced diffusion rate and relaxation rate.

**Table 5**. The diffusion and relaxation rate of Peppas-Sahlin analyzed by Solver

| Formula | Peppas-Sahlin | |
|---|---|---|
| | **k(diff.)** | **k(relax.)** |
| HPMC:MC (1:0) | 0.04 | 0.04 |
| HPMC:MC (1:0) | 0.04 | 0.04 |
| HPMC:MC (0:1) | 0.04 | 0.04 |
| HPMC:MC (0:1) | 0.03 | 0.03 |
| HPMC:MC (0.5:0.5) | 0.05 | 0.05 |
| HPMC:MC (0.5:0.5) | 0.05 | 0.05 |
| HPMC:MC (0.75:0.25) | 0.05 | 0.05 |
| HPMC:MC (0.25:0.75) | 0.05 | 0.05 |

## 4. CONCLUSION

The optimal formula is generated by a combination of HPMC:MC (0.1:0.9) and produces a patch matrix with weight, thickness, drying loss, and DE were 0.68 g, 0.36 mm, 12.42%, and 23.21%, respectively. The release kinetic of ketoprofen followed Korsmeyer-Peppas model through the mechanism of non-Fickian diffusion.

**Funding:** This research received no external funding
**Acknowledgments:** This research was supported by Udayana University, Gadjah Mada University, and PT. Menjangan Sakti
**Conflicts of interest:** The authors declare no conflict of interest.

### References

1. 1. Sekiya I, Morito T, Hara K, Yamazaki J, Ju YJ, Yagishita K, et al. Ketoprofen absorption by muscle and tendon after topical or oral administration in patients undergoing anterior cruciate ligament reconstruction. AAPS PharmSciTech. Springer; **2010**;11:154–8.
2. Ramchandani U, Balakrishnan S. Development and evaluation of transdermal drug delivery system of ketoprofen drug with chitosan for treatment of Arthritis. Eur J Appl Sci. **2012**;4:72–7.
3. Kumar R, Philip A. Modified Transdermal Technologies : Breaking the Barriers of Drug Permeation via the Skin. **2007**;6:633–44.
4. Williams AC, Barry BW. Penetration enhancers. Adv Drug Deliv Rev. Elsevier; **2004**;56:603–18.
5. Sapra B, Jain S, Tiwary AK. Percutaneous permeation enhancement by terpenes: Mechanistic view. AAPS J. 2008. p. 120–32.
6. Kakar S, Singh R, Rani P. A review on transdermal drug delivery. Innorginal Int J Sci. **2016**;3:1–5.
7. Reddy BV. Transdermal drug delivery systems: A review. Int J Chem Pharm Sci. **2015**;2:870–7.
8. Sharma N, Agarwal G, Rana AC, Bhat ZALI. A review : Transdermal drug delivery system : A tool for novel drug delivery system. Int J Drug Dev Res. **2011**;3:70–84.
9. Agarwal S, Murthy RSR. Effect of Different Polymer Concentration on Drug Release Rate and Physicochemical Properties of Mucoadhesive Gastroretentive Tablets. Indian J Pharm Sci. Wolters Kluwer -- Medknow Publications; **2015**;77:705–14.
10. Vijayan V, Sumanth MS, Šuman L, Vinay T, Srinivasrao D, Kumar KJ, et al. Development and Physiochemical, In-Vitro Evaluation of Antihypertensive Transdermal Patches. J Pharm Sci Res. **2010**;2:171–7.
11. Kashinata; Singh, Prashant; S S. Design and evaluation of transdermal film of valsartan by using modified polymer Design and evaluation of transdermal film of valsartan by using modified polymer. **2015**;5:2823–9.
12. Kumar De P, Mallick S, Mukherjee B, Sengupta S, Pattnaik S, Chakraborty S. Optimization of In - vitro Permeation Pattern of Ketorolac Tromethamine Transdermal Patches. Iran J Pharm Res IJPR. Shahid Beheshti University of Medical Sciences; **2011**;10:193–201.
13. Kuncahyo I, Choiri S, Fudholi Rohman AA, Martien R. Analytical method development of pitavastatin-loaded SNEDDS formulation: Multivariate analysis regarding ultraviolet spectrophotometry analysis. J.Food Pharm.Sci. **2019**,7(1):1-5.
14. Costa P, Lobo JMS. Evaluation of Mathematical Models Describing Drug Release from Estradiol Transdermal Systems. J Drug Deliv Pharm. **2003**;29:89–97.
15. Lobo MS, Costa P. Modeling and comparison of dissolution profiles ´. J Drug Deliv Pharm. **2001**;13:123–33.