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The effect of glycerin as penetration enhancer in a ketoprofen solid preparation–patch on *in vitro* penetration study through rat skin

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Abstract.

Context: The side effect of Ketoprofen in oral administration is gastrointestinal disorders and kidney failure. The transdermal route can solve this problem, and need penetration enhancer to increase the penetration into the skin. **Aims:** The aims of this study were to determine the effect of glycerin on the penetration of a ketoprofen patch. **Settings and Design:** Four formulas of solid ketoprofen–patch preparation with different amounts of glycerin as a penetration enhancer are tested statistically to observe the difference of rat skin penetration. **Methods and Material:** Ketoprofen make to be a solid dispersion, then evaluated of homogeneity and FTIR. Solid dispersion make to be a patch, then evaluated of organoleptic, weight homogeneity, thickness, folding endurance, assay, pH, moisture content, FTIR, a rate of *in vitro* penetration, and one–way ANOVA analysis. **Statistical analysis used:** One Way ANOVA Analysis. **Results:** Glycerin can increase the flux of ketoprofen patch and has different significant in a test with one-way ANOVA analysis. **Conclusions:** From this research can be concluded that the addition of glycerin in the formula patch can increase the rate of penetration of ketoprofen patch is described by the value of flux. The higher concentration of glycerin in the patch can increase the value of flux produced. Mechanism of glycerin as penetration enhancers by increasing the solubility of active ingredients and hydrate the stratum corneum. Glycerin also increases the value of patches for hygroscopic moisture.

Keywords: Glycerin, ketoprofen, patch, penetration enhancers, solid dispersion

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Introduction

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) used as analgesic and anti-inflammation. In oral administration, the side effect of ketoprofen is gastrointestinal disorders and kidney failure. Transdermal route of ketoprofen can be an alternative to avoid the side effects of oral administration.

In this study, the patch preparations made with the making of a matrix system because it produces a thin and elegant patch so convenient to use as well as the manufacturing process is easy, fast and cheap.

Ketoprofen is weakness insolubility. A solid dispersion can increase the solubility of ketoprofen. Stratum corneum which has a compact structure, so it makes the drug difficult to penetrate into the skin. Glycerin selected as penetration enhancers because it is more stable chemically and including in penetration enhancers cosolvent group. In the present study, the formula patch made in several groups with different concentration of glycerin to determine the effects of penetration enhancers based on the value of flux produced.

Materials and Methods

Instruments

The instruments used in this study is a spectrophotometer (Genesys 10S Uv-Vis), dissolution tester type paddle (Pharmeq), cell diffusion, pH meter (Elmetron), water bath, hot plate magnetic stirrer (Ika c-mag HS7), analytical balance (Centarus Scale), calipers, desiccator (Normax), oven (Mettler), moisture analyzer (Adam Equipment) and FTIR (Bruker).

Materials

The materials used in the study is ketoprofen (PT. Dexa Medica), hydroxypropyl methyl cellulose (Pt. Lawsim Zecha), ethyl cellulose (EC) (Pt. Lawsim Zecha), propylene glycol (PT. BRATACO Chemika), polyethylene glycol (PEG) (Pt. BRATACO Chemika), ethanol (PT. BRATACO Chemika), backing patch (PT. Hisamitsu Pharma Indonesia), and distilled water.

Methods

Preparation of solid dispersions of ketoprofen

The solid dispersion is made by fusing ketoprofen and PEG 6 000 1:9 at a temperature of $70\text{ }^{\circ}\text{C} \pm 5\text{ }^{\circ}\text{C}$ above the water bath and then immediately cooled on ice bath and saved in a desiccator for 24 h.

Evaluation of solid dispersions of ketoprofen

- Solid dispersion homogeneity test

Standard curve solid dispersion solution of ketoprofen in 96 % ethanol 1 mg L⁻¹, 2 mg L⁻¹, 3 mg L⁻¹, 5 mg L⁻¹, 10 mg L⁻¹, and 15 mg L⁻¹. Ketoprofen solid dispersion solution 7.5 mg L⁻¹ in 96 % ethanol and phosphate buffer scanned with spectrophotometer Uv-Vis in wavelength maximum. Calculated persen recovery levels.

- Test FTIR solid dispersion

Solid dispersion of ketoprofen and pure ketoprofen scanned with FTIR.

Preparation of ketoprofen patch

Weighed solid dispersion of ketoprofen which is equivalent to 25 mg of ketoprofen, diluted with 95 % ethanol, glycerin and PEG 400 is then mixed in the EC and HPMC previously been diluted with 95 % ethanol. The mixture is poured into molds containing backing and dried in an oven at a temperature of 60 °C for 24 h. Then stored in a desiccator for 24 h.

Tabel 1. Formulation of ketoprofen patch

Material	Function	Formula (mg)			
		0	1	2	3
Solid dispersion	Active ingredient	250 *	250 *	250 *	250 *
EC	Hydrophobic polymer	150	150	150	150
HPMC	Hydrophilic polymer	150	150	150	150
Glycerin	Penetration enhancers	0	100	150	200
PEG 400	Plasticizer	200	200	200	200
total		750	850	900	950

* 250 mg solid dispersion equivalent to 25 mg of ketoprofen

Evaluation of ketoprofen patch

Tests performed include

- Organoleptic

Visual observations include color, smell, shape, and surface conditions ketoprofen patch.

- Weight homogeneity

An amount 10 patches are weighed then seen its weight variation.

- Thickness

Measuring five different points using a caliper and then calculated the average thickness.

- Folding endurance

Folding dosage patch on the same spot repeatedly until it breaks. Patch is good if it has a folding endurance value > 300.

- pH

Submerge patch with 5 mL of distilled water free CO₂ then tested using a pH meter.

- Assay

Patch extracted using a magnetic stirrer for 120 min with 95 % ethanol. Extraction results obtained diluted to 10 µg mL⁻¹, then observed using UV-Vis spectrophotometer to determine the absorbance value at a wavelength of maximum with 96 % ethanol as a blank.

- Moisture content

Moisture content test is done by means of a moisture analyzer at a temperature of 100 °C.

- FTIR patch test

The solid dispersions ketoprofen patch tested using FTIR.

- The rate of penetration in vitro test

Patch inserted at the center of the disc, skin-mounted between the compartment diffusion cell with the epidermal facing the donor compartment was placed into a dissolution testing apparatus. Dissolution medium is 475 mL of phosphate buffer saline pH 7.4 ± pH 0.05 and 25 mL of 95 % ethanol at 37 °C ± 0.5 °C which a rotation speed of 5.25 rad s⁻¹ are performed for 8 h. Samples were taken from the receptor compartment as much as 5 mL at 0 min, 15 min, 30 min, 45 min, 60 min, 90 min, 120 min, 180 min, 240 min, 300 min, 360 min, 420 min, and 480 min and then analyzed using spectrophotometer UV-Vis at the maximum wavelength. Flux value is calculated by the Formula (1):

$$J = dm (S.dt)^{-1} \quad (1)$$

(J = flux, M = the amount of active ingredient that is transported, S = area of skin and t = time.)

One Way ANOVA analysis

The results of the flux values were analyzed by one-way ANOVA to determine the relationship between the concentration of glycerin with flux.

Statistic analysis

One Way ANOVA Analysis

Result

Ketoprofen solid dispersion homogeneity test

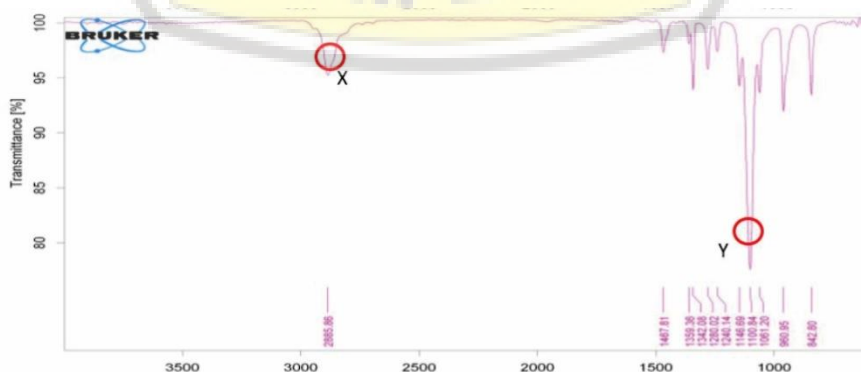
Percent recovery levels of ketoprofen in solid dispersion obtained is 96.302 %.

Table 2. The result of the solid dispersion concentration og ketoprofen

Decision point	Levels (mg L ⁻¹)	% Recovery
1	7.272	96.96
2	7.214	96.19
3	7.199	95.99
4	6.922	92.29
5	7.564	100.08
Mean	96.302 %	
± SD	± 2.78	
CV	2.89 %	

FTIR test of solid dispersion ketoprofen

Ketoprofen solid dispersion FTIR results showed the addition of alkane CH functional group at wave number 2 886.90 cm⁻¹ and the functional group COC at wave number 1 104.37 cm⁻¹ in the X and Y. Both the functional group is a functional group of the base used is PEG 6 000.



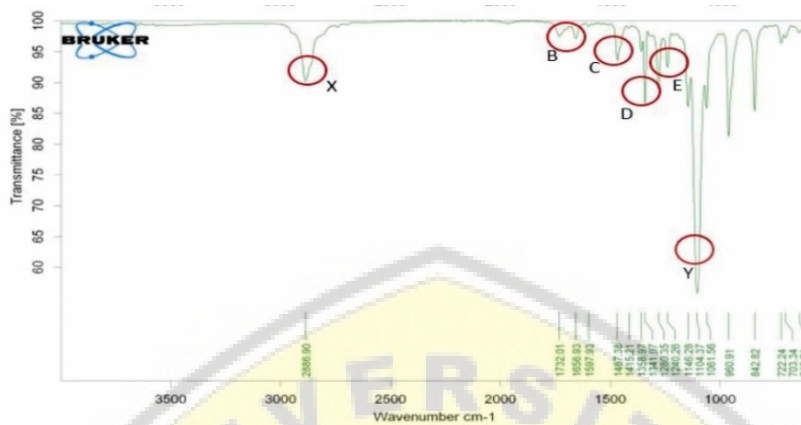


Figure 1. FTIR spectra of pure and solid dispersion ketoprofen.

Organoleptic test

Results of the organoleptic test showed ketoprofen patches are round, white, odorless with dry surface conditions, slightly shiny and not cracked.

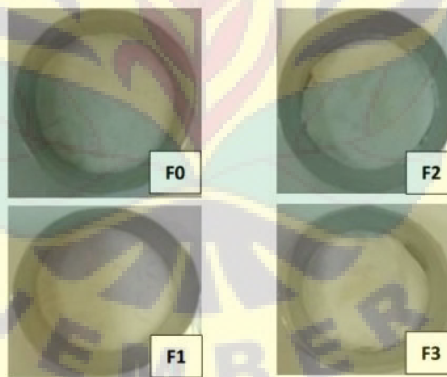


Figure 2. Patch solid dispersion of ketoprofen

Weight homogeneity

The test results showed that the weight of patch preparations average weight loss of between 3.1 % to 5.17 %.

Table 2. The weight of ketoprofen patch

	Weight patches (g)			
	Formula 0	Formula 1	Formula 2	Formula 3
Average	0.736 3	0.834 5	0.885 5	0.935 6
± SD	± 0.002 4	± 0.002 6	± 0.003 7	± 0.002 8

Thickness

The thickness of the patch obtained in this study ranged from 0.329 cm to 0.399 cm.

Table 4. Thickness of the patch test result

Replication	Thickness (cm)			
	Formula 0	Formula 1	Formula 2	Formula 3
1	0.320	0.352	0.370	0.400
2	0.316	0.352	0.366	0.396
3	0.322	0.354	0.370	0.402
Mean	0.329	0.353	0.370	0.399
± SD	± 0.002	± 0.001	± 0.004	± 0.003

Folding endurance

The test results showed that the folding endurance patch contained glycerin was appropriate additional requirements have folding endurance > 300 times.

Table 5. Folding endurance test results

Replication	Formula 0	Formula 1	Formula 2	Formula 3
1	< 300	> 300	> 300	> 300
2	< 300	> 300	> 300	> 300
3	< 300	> 300	> 300	> 300

pH test

The test results showed that the pH of the patch surface has met the criteria range that does not irritate the skin is pH 4.5 to pH 6.5.

Table 6. pH test result

Replication	pH			
	Formula 0	Formula 1	Formula 2	Formula 3
1	4.74	4.82	5.05	5.19
2	4.73	4.85	5.08	5.20
3	4.72	4.86	5.03	5.21
Mean	4.73	4.84	5.05	5.20
± SD	± 0.01	± 0.002	± 0.02	± 0.01

Moisture content

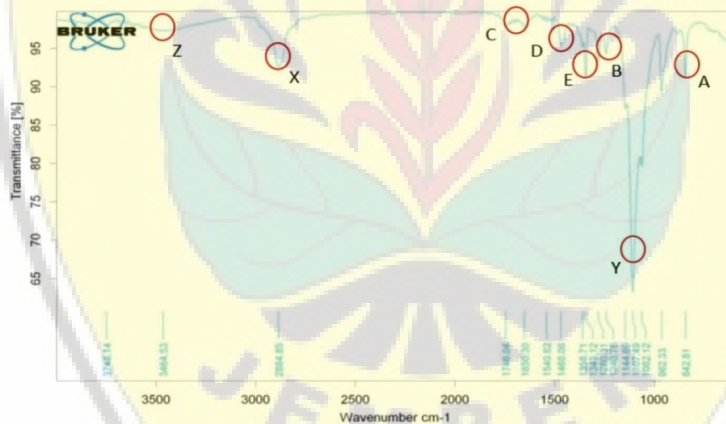
Values of the greatest MC is $F3 > F2 > F1 > F0$. The higher concentration of glycerin in the formula may increase the value of the MC because glycerin is hygroscopic.

Table 7. Test result moisture content

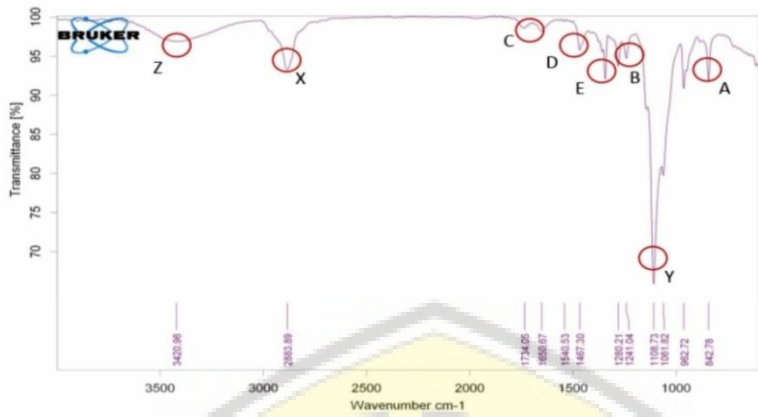
	Formula 0	Formula 1	Formula 2	Formula 3
1	2.9	3.0	3.25	3.9
2	2.9	3.1	3.3	3.9
3	2.8	2.9	3.25	4.0
Average ± SD	2.87 ±	3.00 ± 0.1	3.27 ± 0.03	3.39 ± 0.06
CV	0.06	3.333 %	0.887 %	1.468 %
	2.021 %			

FTIR test patch

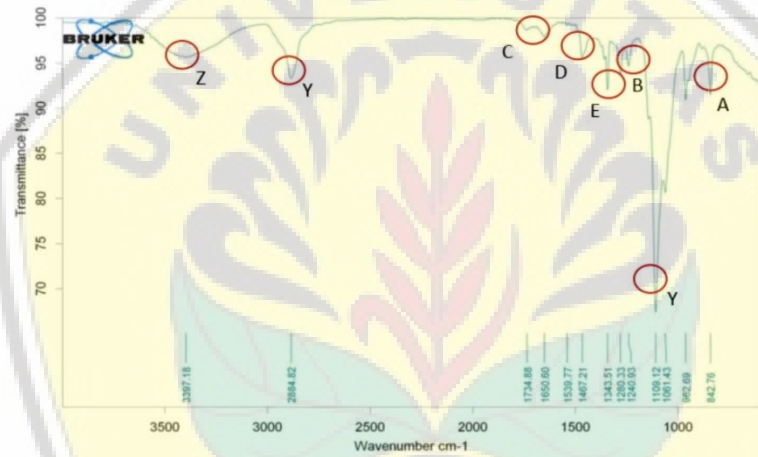
ketoprofen patch FTIR test results there is the addition of functional groups represented by the letters X, Y, Z is a functional group of additives patch (HPMC, EC, PEG 400).



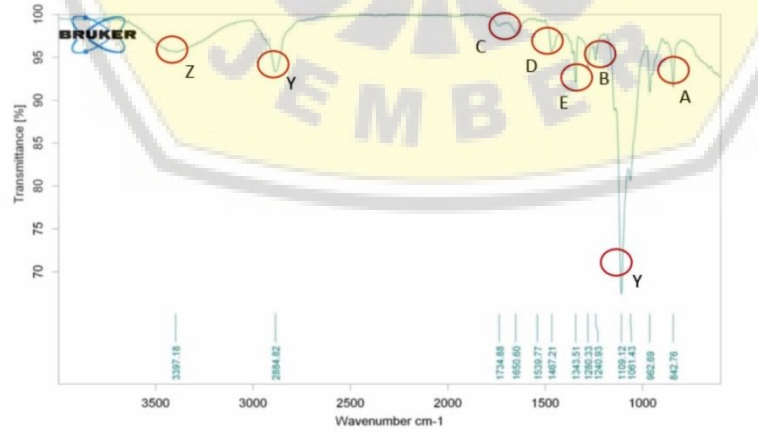
(a)



(b)



(c)



(d)

Figure 3. FTIR spectra patch (a) F0; (b) F1; (c) F2; and (d) F3

The in vitro penetration study

Based on data obtained flux, F0 has the smallest value among formula in the absence of the addition of glycerin as penetration enhancers. F3 has the highest flux values compared F0, F1, and F2 for the highest concentration of glycerin.

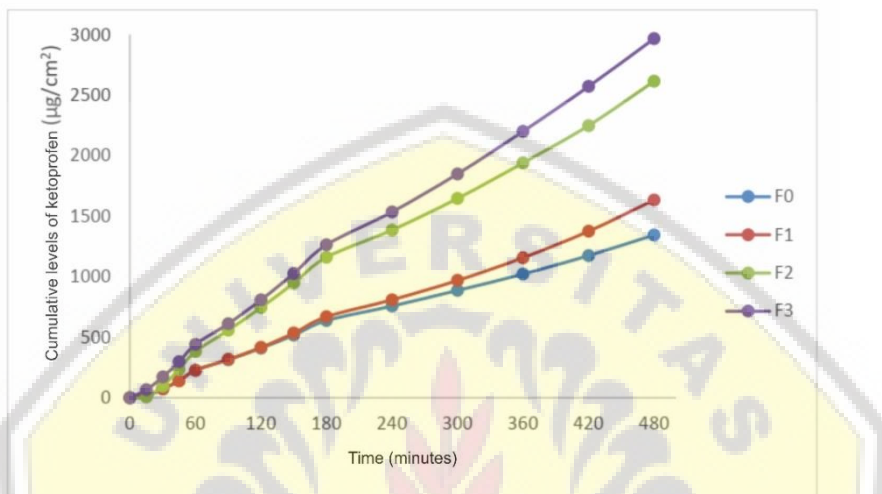


Figure 4. Graph of cumulative levels of ketoprofen patch

Table 8. Flux of ketoprofen patch

Formula	Flux ($\mu\text{g cm}^{-3} \text{min}^{-1}$)
0	2.334 ± 0.074 52
1	3.195 ± 0.300 82
2	4.835 ± 0.141 86
3	5.704 ± 0.254 02

One way ANOVA analysis

There are significant differences in the value of flux on a formula that contained glycerin and without glycerin.

Discussion

Ketoprofen patch has a different thickness. Thickness difference between formula is affected by the total amount of material used each formula is different. The weight of the patch in this study is lost during the mixing process in the cup and the preparation of a patch that sticks to the mold.

Factors affecting the folding endurance in preparation patch is plasticizer. In this study, PEG 400 is used as a plasticizer to improve the folding endurance of the preparation of the ketoprofen patch.

FTIR testing pure ketoprofen and ketoprofen solid dispersion shows no sign of a sharp shift in absorption bands at wave number ketoprofen solid dispersion and solid dispersion spectra are identified already entered into ketoprofen characteristic spectral range. Ketoprofen in the form of a solid dispersion by using a carrier material PEG 6 000 is not shaping interactions that can alter the function of ketoprofen group and does not affect the therapeutic effect of ketoprofen.

MC patch testing conducted to determine the water content in the preparation can effectiveness due to large water content can affect microbial growth and stability of the preparation. Good patch preparation has a water content of less than 10 %. Glycerin is hygroscopic easier to absorb moisture from the surrounding environment, thus affecting the MC.

Penetration test aims to determine the amount of ketoprofen are transported through the membrane per unit area and per unit time. The flux obtained from the slope value of cumulative levels of meloxicam regression results over time. Flux is calculated when the curve of cumulative levels of ketoprofen over time to form a linear curve. The mechanism of glycerin as penetration enhancers that can improve the solubility of drug ingredients that increase the diffusion of drugs across cell membranes and provide hydration to the skin effect which softens the keratin layer of the stratum corneum thereby increasing the amount of drug that penetrates through the skin.

The addition of glycerin as penetration enhancers with the number 0 mg, 50 mg, 100 mg, and 150 mg each patch on the preparation of solid dispersions ketoprofen transdermal patches can increase the value of the MC and ketoprofen flux values. Preparations ketoprofen patch with the number of 150 mg ketoprofen in research can produce qualified and MC biggest penetration rate with the MC of 1.43 % \pm 0.020 8 % and the rate of penetration of 1.126 g cm⁻² min⁻¹ \pm 0.085 g cm⁻² min⁻¹.

The penetration rate of patch test data analysis is one way ANOVA to determine the effect of glycerin on the flux generated. Statistical analysis by one-way ANOVA showed that every increase in the provision of glycerin concentration for all the formulas are F1, F2, and F3 causing an increase in the value of percent flux meaningful when compared with formula 0 that there are no additional glycerin. It is characterized by the value of $p = 0.000$ at one way ANOVA test, which means there is a significant difference to the value of percent glycerin adding flux. The higher concentration of glycerin in the patch, the patch flux value is also higher.

Conclusion

From this research can be concluded that the addition of glycerin in the formula patch can increase the rate of penetration of ketoprofen patch is described by the value of flux. The higher concentration of glycerin in the patch can increase the

value of flux produced. Mechanism of glycerin as penetration enhancers by increasing the solubility of active ingredients and hydrate the stratum corneum. Glycerin also increases the value of patches for hygroscopic moisture.

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