



Research Article

Formulation and In-Vitro Penetration Test of Ketoprofen Patch with Addition Aloe vera Powder (*Aloe vera* L.) Bioenhancer

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ABSTRACT

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) which is generally used to reduce pain and inflammation. The main obstacle in administering drugs via transdermal is the low penetration of drugs through the skin. *Aloe vera* contains lignin compounds which are thought to be bioenhancer. This research aims to formulate ketoprofen and *aloe vera* powder in form patch and compare penetration patch with and without the addition of aloe vera powder. Preparation patch 3 formulas were made with different ratios of HPMC E5 and Eudragit E100 polymers F1 (6:2), F2 (8:2), F3 (10:2). Formula 3 is the best formula with a comparison of HPMC E5 and Eudragit E 100 of 10:2. Formula 3 has a thin, dry patch and is easy to remove from the mold. F3 then remade with additions bioenhancer by 5 % and patch without additions bioenhancer. The results of the physical quality test showed that the formula with and without the addition of aloe vera as an enhancer has uniform weight, thickness, pH and folding resistance which meets the requirements for patch preparation. Franz diffusion cell result for patch preparations with the addition of aloe vera showed a better penetration value than without the addition of aloe vera with a cumulative value of 92.5815 $\mu\text{g}/\text{cm}^2$ and a total flux of 260.4355 $\mu\text{g}/\text{cm}^2$ hour.

Keywords: *Aloe vera*; Bioenhancer; Franz Diffusion Test; Ketoprofen; Patch**INTRODUCTION**

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) that can reduce prostaglandin synthesis by inhibiting the cyclooxygenase enzyme. Generally used to reduce pain, inflammation, and stiffness caused by various conditions such as rheumatoid arthritis, osteoarthritis, and stomach cramps associated with menstruation (Yani et al., 2020). When used orally, ketoprofen has an elimination half-life of 1-4 hours which can cause the frequency of drug use to become more frequent. Ketoprofen has greater side effects on the digestive tract compared to other anti-inflammatory groups, ranging from dyspepsia to bleeding (Setyawan et al., 2015). Therefore, to overcome these side effects, it is necessary to provide alternatives for administering ketoprofen, one of which is transdermal (Yani et al., 2020).

A transdermal drug delivery system (TDDS) is a delivery system that carries drug products through the skin into the body. One of the known ones is a

transdermal patch, which is a dosage form with an adhesive that is applied to the skin to deliver a certain dose through the skin and into the bloodstream (Mali et al., 2015). Transdermal preparations have several advantages, including being more comfortable to use because they are non-invasive, easy for patients to use themselves, and avoid first-pass metabolism drugs, can be an alternative to drugs that irritate the gastrointestinal tract and are designed for a frequency of use once a day or less frequently (minimum dose repetition) thereby increasing patient compliance (Mita et al., 2018).

The main obstacle in administering drugs via transdermal is the low penetration of drugs through the skin. The effectiveness of a patch is determined by the ability of drug penetration and drug release from the matrix patch past the stratum corneum (Setyawan et al., 2015). Penetration enhancer or enhancer is a compound added to topical and transdermal preparations which can reduce skin resistance and increase skin permeability thereby increasing drug

penetration through the skin (Almira et al., 2021). The enhancer used in this research was aloe vera powder (*Aloe vera* L.). Aloe vera contains lignin compounds which can increase drug penetration. The enhancer function is to increase the solubility of the drug inside the stratum corneum by changing the partition of the drug in the stratum corneum and influencing drug diffusion across the stratum corneum by interfering with the complex properties of skin lipids (Sharma et al., 2015).

Based on Bhutkar's research results (2019) 3 % concentration of aloe vera gel can increase the penetration of lidocaine gel into the skin by 79.18 %. Then for preparation patch candesartan cilexetil (CC) with a 10 % aloe vera gel concentration can increase penetration by 98.8 % within 12 hours. This increase in penetration is caused by the complex attraction effect that forms between the drug and the enhancing agent (lignin). This indicates that aloe vera has potential as a bio enhancer (Sharma et al., 2016), so this research was made using bioenhancer aloe vera powder (*Aloe vera* L.) with a concentration of 10 %.

Polymers are the main constituent components that play an important role in producing patches with good physical characteristics (Fatmawaty et al., 2017). Two types of polymers, namely polymers are not soluble in water (hydrophobic) and polymers that are soluble in water (hydrophilic). Hydrophobic polymers provide good flexibility and strength to preparation patches, while hydrophilic polymers can accelerate the solubility of drugs from the matrix (Fuzyanti et al., 2022). The research conducted by Rao et al. (2019) confirmed that the ketoprofen patch which used a combination of HPMC E5 polymer and Eudragit S100 produces a patch with characteristics of transparent, flexible, and smooth texture while the research by Maheshwari & Bharathi (2015) found that the repaglinide patch with a combination of Eudragit E100 polymer and PVP produces a strong film, smooth and flexible patch. Based on these results, this research will formulate the ketoprofen patch using a combination of HPMC E5 and Eudragit E100 polymers.

RESEARCH METHODS

Tools and Materials

The tools used in this research are glassware (Pyrex®), blender, petri dish, desiccator, grinder, filter, porcelain crucible, magnetic stirrer (IKA®), cellophane membrane, screw micrometer, oven (Mettler), pH meter (Ohaus®), knife, Franz diffusion cell (Orchid Scientific®), UV-Vis spectrophotometer (Thermo Scientific™), furnace (Daihan Scientific®), thermometer, analytical balance (LabPRO).

The materials used in this research were distilled water, aloe vera leaves, 96% ethanol, eudragit E100 (Evonik Industries), hydroxypropyl methylcellulose E5 (HPMC E5) (Coloron Asia Pacific Pte. Ltd), ketoprofen (Hubei Xunda Pharmaceutical Co., Ltd), potassium dihydrogen phosphate (KH₂PO₄), maltodextrin, methanol, sodium hydroxide (NaOH), methylparaben, propylene glycol.

Aloe vera Powder Preparation

Aloe vera powder was produced using 8-12 months fresh leaves. The aloe vera leaves were sorted to remove dirt and then washed with running water. The leaves were peeled, chopped, and blended then filtered to produce a liquid extract. About 8 % maltodextrin was added, and the mixture was stirred until homogeneous. The liquid extract obtained was dried using a vacuum dryer at a temperature of 60 °C until dry. Dried aloe vera extract was ground with the grinder and sifted to produce fine aloe vera powder (Permanasari et al., 2019). The aloe vera powder is then subjected to quality tests including organoleptic tests, yield, water content, and ash content.

Formulation and Preparation Ketoprofen Patch

This patch formula uses the active ingredient ketoprofen at 1.67%. Each patch made weighs around 3 grams or the equivalent of 50 mg of ketoprofen. The polymer ratio used is HPMC E5 and Eudragit E100 with variations in each formula: F1 (6:2), F2 (8:2), and F3 (10:2). Details of the patch formulation can be seen in Table 1.

Table 1. Formulation of Ketoprofen Patch

Material	Formula % (b/b)			Function
	F1	F2	F3	
Ketoprofen	1.67	1.67	1.67	Active substance
HPMC E5*	6	8	10	Polymer
Eudragit E100*	2	2	2	Polymer
Propylene Glycol	10	10	10	Plasticizer
Methyl Paraben	0.3	0.3	0.3	Preservative
Ethanol:aquadest (3:1) ad	100	100	100	Solvent

Table 2. Ketoprofen Patch Formula with Aloe Vera Powder Bioenhancer

Material	Formula % (b/b)		Function
	FA	FB	
Ketoprofen	1.67	1.67	Active substance
HPMC E5*	10	10	Polymer
Eudragit E100*	2	2	Polymer
<i>Aloe vera</i>	-	5	Bioenhancer
Propylene Glycol	10	10	Plasticizer
Methyl Paraben	0.3	0.3	Preservative
Ethanol:aquadest (3:1) ad	100	100	Solvent

Results patch with the best physical characteristics, namely F3 with a ratio of HPMC E5 and Eudragit E100 (10:2). Then it is remade with additions of bioenhancer aloe vera amounting to 5 % (FB) and patch without additions bioenhancer aloe vera as a comparison (FA). The formula in the patch content using bioenhancer aloe vera powder can be found in Table 2.

Quality Evaluation Patch

Organoleptic Test

The organoleptic examination was conducted visually without any tools. It focuses on assessing the color, odor, and shape of the dosage form patch. This method ensures a comprehensive evaluation of the patch's sensory attributes (Yusuf et al., 2020).

pH Test

Testing the pH of the preparation patch was carried out using a pH meter. Solution patch soaked in 10 mL of distilled water for two hours. Next, the electrode was dipped into a glass beaker containing the preparation solution patch.

Weight Uniformity Test

Uniformity of weight testing was conducted by weighing 5 patches randomly selected from each formula. Then, each patch was weighed, and the average weight was calculated. This process ensures the consistency of weight for each formula produced (Baharudin & Maesaroh, 2020).

Thickness Test Patch

The thickness of the patch was measured using a screw micrometer with an accuracy of 0.01 mm. Measurements were taken at three different points on the patch. Then, the average thickness of the patch was calculated from these measurements (Baharudin & Maesaroh, 2020).

Folding Resistance Test

The test for folding resistance involves repetitively folding the patch in a fixed position until it breaks. The number of folds achieved before breakage determines the folding resistance value. A folding

resistance value exceeding 200 folds meets the standard requirement (Yusuf et al., 2020).

Determination of Ketoprofen Rate

A total of one patch of ketoprofen containing ketoprofen equivalent to 50 mg was melted at a temperature of 60-70 °C with 75 % methanol solvent for 30 minutes. Next, it was put into a 100 mL measuring flask and added 75 % methanol to the mark. 2 mL of solution was pipetted then it was put into a 100 mL measuring flask, and 75 % methanol was added to the mark. The absorbance of the test solution was measured using a UV-Vis spectrophotometer at the wavelengths that were obtained (Yani, 2020).

Patch Ketoprofen Penetration Test

The penetration test was conducted using a Franz diffusion cell comprising donor and receptor compartments. The patch was placed in the donor compartment, while an EDP solution of 21.5 mL volume was introduced into the receptor compartment. A hydrated cellophane membrane was positioned between the donor and receptor compartments after approximately 12 hours. During operation of the Franz diffusion cell, the temperature was maintained at a constant 37 ± 0.5 °C, and liquid homogeneity was ensured using a magnetic stirrer at 500 rpm (Fitrianiingsih, 2022). The penetration test lasted for 6 hours. Samples were collected using a 3 mL pipette from the receptor compartment solution at intervals of 5, 10, 15, 20, 30, 60, 120, 180, 240, 300, and 360 minutes. Each sample was mixed with 3 mL of pH 7 phosphate buffer solution to maintain a consistent fluid volume. Subsequently, the sample solutions were analyzed for absorption using UV-Vis spectrophotometry with the EDP solution serving as the blank. Each formula underwent penetration testing twice.

Data Analysis

Statistical testing was performed to evaluate the significance of differences between ketoprofen patches with and without the addition of aloe vera powder as a bioenhancer. The data underwent analysis using One Way ANOVA (Analysis of Variance) conducted with SPSS version 24 software. This statistical method

allowed for the comparison of multiple groups to determine any significant effects of the bioenhancer on the patches' properties. The results were interpreted to ascertain the impact of aloe vera powder on the ketoprofen patch formulations.

RESULTS AND DISCUSSION

Quality Characteristics of Aloe Vera Powder

Organoleptic Test Results

The organoleptic examination of aloe vera powder was conducted visually, assessing its color, shape, and odor without the use of instruments. Results indicated that the powder was white, finely powdered, and had a distinctive aroma. Figure 1 illustrates the appearance of the aloe vera powder.



Figure 1. Aloe Vera Powder.

Yield Results, Water Content, and Ash Content

Yield is a comparison of the weight of the extract obtained with the weight of the raw material. The yield of aloe vera powder was 12.18 %, this result was greater than research by Permanasari et al (2019) due to the difference in drying time. Apart from that, the high yield of aloe vera powder was influenced by the addition of maltodextrin. The higher the amount of maltodextrin added, the more solids will be produced (Ghulvani, 2022). The yield of aloe vera powder is not less than 0.03 % (Kementerian Kesehatan RI, 2017).

The determination of moisture content was conducted using the gravimetric method to establish

the minimum moisture content limit in aloe vera powder. The results of the moisture content determination for aloe vera powder were $6.6575\% \pm 0.26$. Based on the obtained results, it has met the quality requirement of not exceeding 10 % (Kementerian Kesehatan RI, 2017). High moisture content ($>10\%$) can lead to microbial growth and may reduce the stability of aloe vera powder (Utami et al., 2017).

Table 3 displays the results of water content and ash content from the tested samples. The purpose of determining the ash content was to ascertain the total mineral content from the initial processing of the material to the formation of the extract. The ash content determination result of aloe vera powder was $4.6172\% \pm 0.30$. This result meets the quality requirements, where the ash content of dry aloe vera extract should not exceed 5 %. (Kementerian Kesehatan RI, 2017). The higher the ash content obtained, the higher the mineral content in aloe vera powder, which can become toxic. Toxic (inorganic) minerals that accumulate in the body over a long period can disrupt the circulatory, nervous, and kidney systems (Utami et al., 2017).

Evaluation of Ketoprofen Patch Quality

Organoleptic Test Results

The organoleptic examination is conducted visually without tools to identify the color, odor, shape, and appearance of ketoprofen patches. Different ratios of HPMC E5 and Eudragit E100 polymers were used, namely F1 (6:2), F2 (8:2), and F3 (10:2). The results of the organoleptic test for the ketoprofen patches can be seen in Figure 2.

Table 3. Yield, Water Content, and Ash Content of Aloe Vera

Test parameters	Results (%)	Requirement (%)
Yield	12.18	≥ 0.03 (Kementrian Kesehatan RI, 2017)
Water Content	6.6575 ± 0.26	≤ 10 (Kementrian Kesehatan RI, 2017)
Ash Content	4.6172 ± 0.30	≤ 5 (Kementrian Kesehatan RI, 2017)

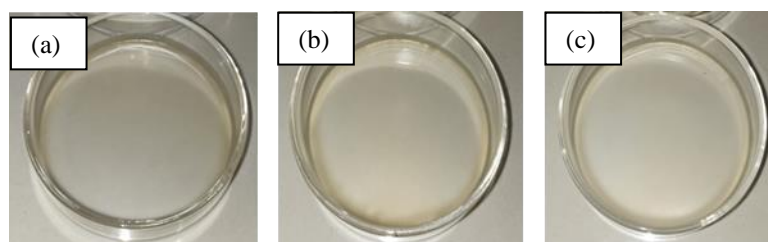


Figure 2. Ketoprofen Patch with Different Ratios of HPMC E5 and Eudragit E100. Formula 1 (6:2) (a), Formula 2 (8:2) (b) and Formula 3 (10:2) (c).

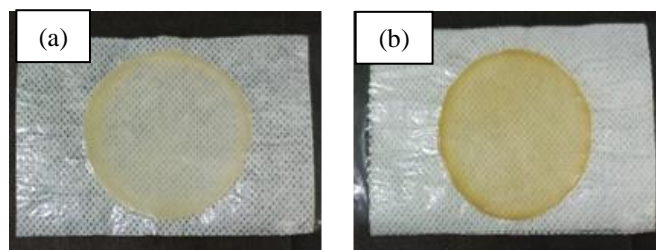


Figure 3. Patch Ketoprofen, (a) FA, (b) FB

F1 produces a thin and wet patch which makes it easy to tear but difficult to remove from the mold, after the drying process. F2 produces a thin and wet patch which makes it difficult to remove from the mold. F3 produces a thin and dry patch which makes it easy to lift from the mold and is a bit sticky. The difference in results is due to the different ratios of HPMC E5 and Eudragit E100 polymers used.

Based on the results of the organoleptic test, F3 with the ratio of HPMC E5 and Eudragit E100 (10:2) produces the form patch which is thin, dry, and easy to remove from the mold. Then it is remade with additions of bioenhancer aloe vera amounting to 5 % as FB and without the addition of aloe vera as FA. Organoleptic test results patch Ketoprofen with and without bio-enhancers can be found in Figure 3.

The test results for formula B showed that the patch was transparent brown. This coloration was due to the addition of 5 % aloe vera as a bioenhancer, which contains maltodextrin as a filler. Under certain pH and temperature conditions, maltodextrin can undergo a Maillard reaction. This reaction with amino acids results in a yellow or brownish hue. Thus, the color change in the patch is attributed to this chemical process (Rowe et al., 2009).

Weight Uniformity, Thickness, pH, and Folding Resistance Test

Physical quality testing was carried out on the parameters of weight uniformity, pH, folding resistance, and patch thickness. The results of physical quality testing can be seen in Table 4. A weight uniformity test was carried out to determine the similarity of each patch weight that has been made and produce a relatively uniform product that will affect the

dose in each dosage unit. Weight uniformity testing was carried out to determine the similarity of patch weight. Based on the results of the weight uniformity test, FA has an average weight of 0.58 grams and FB weighs 0.85 grams, meeting the requirements, namely having a good standard deviation (SD) value, of ≤ 0.05 (Baharudin & Maesaroh, 2020). A small SD value identifies that each patch has several active substances that do not differ in many fields (Fatmawaty et al., 2017). FB has a greater value than FA, this is because of the addition of aloe vera as an enhancer which will affect weight.

The thickness test has a role in the physical properties of the patch and can influence the process of releasing matrix active substances. The thicker patch takes a longer time to release the active substance. The test results showed patch has a thickness, namely formula A 0.17 mm and formula B 0.21 mm. Formula B was thicker than Formula A, this was due to the addition of aloe vera as a bioenhancer. The greater the number and type of components added, the higher the thickness and weight of the patch. The thickness patch generally ranges from 0.15 to 0.21 mm (Yusuf et al., 2020).

The testing of pH was carried out to determine whether the preparation was a patch made by the physiological pH of the skin namely 4.5-6.5 (Amalia et al., 2023). Based on the results of the pH testing that has been carried out, it met the requirements because it was included in the pH range that did not irritate the skin. Aloe vera has a pH range from 4.87-5.91, which causes Formula B with the addition of aloe vera to have a lower pH than Formula A. Apart from that, eudragit E 100 in the preparation also affects the pH of the preparation because it is acidic.

Table 4. Weight Uniformity, Thickness, and pH Test of Ketoprofen Patch

Test parameters	Mean Results \pm SD	
	FA (without aloe vera)	FB (5% aloe vera)
Weight Uniformity Test (g)	0.58 \pm 0.01	0.85 \pm 0.03
Thickness Test (mm)	0.17 \pm 0.01	0.21 \pm 0.01
pH Test	5.95 \pm 0.01	5.93 \pm 0.02
Folding Resistance	205	212

The folding resistance test was carried out to determine the elasticity and flexibility patch folded at the same angle. According to Yusuf et al. (2020), the number of folding resistances is ≥ 200 times. Test results showed that both formulas had a folding resistance of ≥ 200 times. This showed that the combination of HPMC E5 and Eudragit E100 as polymers with the addition of propylene glycol as a plasticizer can provide good film characteristics, difficult to break and tear. FB has a higher value caused by an increase in its thickness value.

Determination of Ketoprofen Content in The Patch

Determination of ketoprofen levels is conducted to ascertain the amount of ketoprofen present in the patch preparation. This analysis was performed twice for each formula to ensure accuracy. The results provide insight into the ketoprofen content across different formulations. Detailed information on the ketoprofen content can be found in Table 5. Results of determining the ketoprofen levels in patch formulas with and without the addition of aloe vera powder as a bioenhancer have a level of more than 90 %. Formula A has a ketoprofen content of 45.32 mg and Formula B has a ketoprofen content in the patch of 46.40 mg.

Penetration Test of Ketoprofen Patch

Penetration testing ketoprofen patch in vitro was carried out using the Franz diffusion cell method using a synthetic membrane, namely the cellophane membrane. Before carrying out the penetration test, the

cellophane membrane was soaked using an EDP solution for ± 12 hours. The aim is to prevent the formation of deposits on the membrane caused by the decrease of ketoprofen (Fitrianiingsih, 2022). The cumulative amount describes the amount of ketoprofen that penetrates the receptor fluid. The cumulative amount of ketoprofen can be seen in Figure 4.

The cumulative amount of ketoprofen that penetrates the skin is the highest of the preparations patch ketoprofen is in formula B with the addition of bioenhancer 5 % aloe vera powder was 92.5815 $\mu\text{g}/\text{cm}^2$ and the lowest was formula A without the addition of aloe vera powder, namely 80.7635 $\mu\text{g}/\text{cm}^2$. Analysis results in One Way ANOVA results obtained a p-value of $0.000 \leq 0.05$, which means there is a significant difference, in addition, bioenhancer aloe vera powder on the cumulative value or amount of ketoprofen penetrated.

The points produced on the graph depict the penetration rate or the amount of active substance that passes through the membrane per time (Figure 5). The highest value was found in formula B with the addition of 5 % aloe vera powder bioenhancer, namely 260.4355 $\mu\text{g}/\text{cm}^2.\text{hour}$, and the lowest was in formula A without the addition of bioenhancer, amounting to 210.3072 $\mu\text{g}/\text{cm}^2$. Analysis results in One Way ANOVA results obtained a p-value of $0.000 \leq 0.05$, which means there is a significant difference between the formulas in the value quickly or the amount of ketoprofen that passes through the membrane per time.

Table 5. Ketoprofen Content in Patch

Formula	Ketoprofen content in patch (mg)	Ketoprofen content in patch (%)
FA (without aloe vera)	45.32	90.65
FB (5 % aloe vera)	46.40	92.82

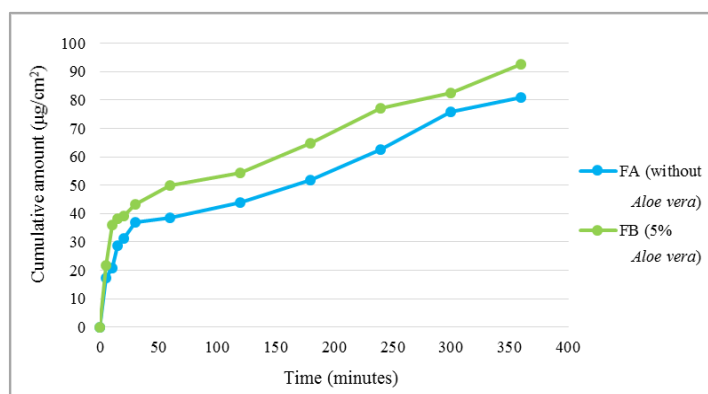


Figure 4. Cumulative Amount of Ketoprofen.

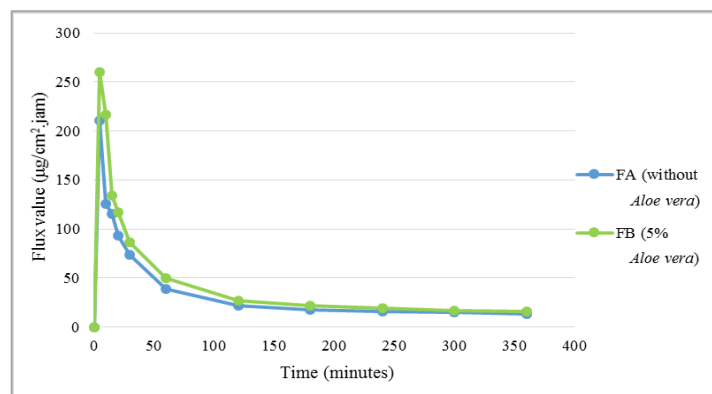


Figure 5. Flux Value of Ketoprofen.

CONCLUSION

Preparation formula patch ketoprofen with a combination of polymer HPMC E5 and Eudragit E100 in a ratio of 10:2 (F3) produces the best physical quality. Preparation patch ketoprofen with the addition of bioenhancer 5 % aloe vera powder showed the best penetration test with a cumulative amount of 92.5815 µg/cm² and flux value of 260.4355 µg/cm².hour.

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