Available online on 15.10.2020 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research

Open Access

Research Article

Comparison of In-vitro Penetration of Transdermal Patch Containing Pure Diclofenac Sodium and Nanoparticles as Analgesic and Anti-Inflammatory

Zakaria Nurmalia[1]*, Bangun Hakim[1], Harahap Urip[2]

[1]Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Sumatera Utara, Medan, Indonesia

[2]Department of Pharmacology, Faculty of Pharmacy, University of Sumatera Utara, Medan, Indonesia.

A B S T R A C T

Objective: Diclofenac sodium is a Non-Steroid Anti Inflammatory class of drug which has a weakness in oral use in the form of irritation of the digestive tract. This study aims to make transdermal patches containing pure sodium diclofenac and nanoparticles with ethyl cellulose (EC) and polyvinyl pyrrolidone (PVP) polymers and compare in-vitro penetration using Franz diffusion cells.

Design: This research is an experimental research which will be calculated cumulative penetration percent penetration of pure diclofenac sodium and nanoparticles from the transdermal patch for 8 hours.

Intervention: The variables that play a role in this research are pure diclofenac sodium and nanoparticles, both using and without enhancers

Main outcome measures: In this study, the main measurement is the absorbance value of diclofenac sodium using a spectrophotometer, which penetrates the skin on franz diffusion cells and is converted to percent cumulative penetration.

Result: Transdermal patches containing diclofenac sodium nanoparticles have a higher cumulative percent penetration (58.87 ± 0.7458%) than transdermal patches containing pure sodium diclofenac (46.6 ± 1.9438%), but not higher than transdermal patches containing pure sodium diclofenac with the addition of propylene glycol enhancers (67.59 ± 1.4675%). The three transdermal patch formulas did not differ significantly to the percent cumulative drug penetration ($p > 0.05$).Transdermal patches containing diclofenac sodium nanoparticles have a higher analgesic and anti-inflammatory effect than transdermal patches containing pure sodium diclofenac up to 480 minutes.

Conclusion: Transdermal patches containing sodium diclofenac nanoparticles have been shown to be able to increase drug penetration through the rabbit's stomach skin membrane in-vitro using Franz diffusion cells. Transdermal patches of pure diclofenac sodium and nanoparticles provided analgesic and anti-inflammatory effects that were significantly different from the negative control.

Keywords: Transdermal patch, pure diclofenac sodium, diclofenac sodium nanoparticle, in-vitropenetration, analgesic, anti-inflammatory.

A R T I C L E I N F O: Received 05 July 2020; Review Completed 02 Oct. 2020; Accepted 08 Oct. 2020; Available Online 15 Oct. 2020

Cite this article as:

Julianty S. M*., Arianto A., Yuandani, Determination of Sun Protection Factor of Blemish Balm Nanocream Containing Avobenzone, Octyl Methoxycinnamate, and Vitamin C, Asian Journal of Pharmaceutical Research and Development. 2020; 8(5):24-31. **DOI:** http://dx.doi.org/10.22270/ajprd.v8i5.843

***Address for Correspondence:**

Julianty S. M, Department of Pharmaceutical Technology, Faculty of Pharmacy, Universitas Sumatera Utara, Medan, 20155, Indonesia

INTRODUCTION

Diclofenac sodium is a non-steroidal anti-inflammatory class of drugs that is widely used to treat pain and inflammation, especially for various joint diseases such as gout, rheumatism and osteoarthritis[1]. Diclofenac inhibition of cyclooxygenase (COX) which can reduce prostaglandins in the gastric epithelium, causing gastrointestinal side

effects such as bleeding, peptic ulcers, nausea and vomiting, which can occur at any time when given orally[2]. Other than that, non-adherence of patients to the drug regimen is also a viewpoint in the design matrix transdermal patches are extended, where the reported incidence of non-compliance with the patient air amount from about 15% to 93% to the level of the average forecast of 50%[3], it's can be overcome with a form of Transdermal Drug Delivery System (TDDS) which is a drug delivery system that utilizes the skin as a place for drug entry.

TDDS is a technique that is effective and interesting and challenging for the study. Over the past two decades, transdermal drug delivery has become a favaourite and an acceptable technology because it minimizes and avoids the limitations of the drug when administered by conventional and parenteral routes, such as bioavailability of drugs in plasma that show fluctuating concentrations, pain and discomfort levels[4]. The Transdermal patch defined as a drug adhesive patch that is placed on the skin to give a specific dose of the drug with a prescribed release rate in order to achieve blood flow[5]. However, the low skin permeability causes the limited number of drugs that can be given through the skin[6], so that in making the transdermal diclofenac sodium patch the appropriate polymer and plasticizer must be chosen as a drug matrix, as well as enhancers capable of increasing diclofenac sodium penetration so that it is able to penetrate the skin and reach the target area of treatment, but must release the drug gradually so that it becomes extended release[7]. In addition to these efforts, drug penetration through the skin can also be overcome by changing the shape of the drug, which is macro/microparticles into nanoparticles[8]. To increase the therapeutic effect and decrease side effects of the drug, the substance/molecule of the active drug must be controlled for its release in the affected part. Increased drug development or drug release strategies can be understood and overcome nanotechnology. Nanoparticles have emerged as one of the choices for excellent and most promising drug delivery systems[9].

The surface of nanoparticles can be easily adapted to targeted tissue or organs. The development of nanoparticles in the transdermal route has recently been in great demand as an effective alternative and is able to improve patient compliance better because of its non-invasive nature and allows the administration process independently[10]. Nanotechnology represents the design, synthesis, characterization, and application of materials and devices at the atomic or molecular level of 1–1000 nm in size[11].

The business of making a diclofenac sodium transdermal matrix al patch is designed to be able to release the drug extensively. It has been reported that the use of a combination of polymer Ethylcellulose (EC) and Polyvinyl pyrrolidone (PVP) with plasticizer propylene glycol is able to provide drug penetration in vitro[12,2]. The use of propylene glycol in addition to being a plasticizer is also able to act as an enhancer with a concentration of 5 - 30% [13].

In this study, transdermal patches are made with active ingredients pure diclofenac sodium and nanoparticles with or without the use of enhancers, and will be compared in-vitro penetration and analgesic-antiinflammatory activity. The Transdermal patch is made by the solvent evaporation method, using EC and PVP polymers.

MATERIALS AND METHODS

Material

Diclofenac sodium BP procured from Mega Fine Pharma (P). Ltd., EC (EC), PVP and propylene glycol procured from Shanghai Honest Chem CO. Ltd., methanol, phosphate buffer pH 7,4, and carrageenan obtained from Laboratory of North Sumatera University.

Table: 1. Formula of Transdermal patch

Ingrediant	Formula (mg)		
	F1	F2	F3
Pure diclofenac sodium	1,8	-	1,8
Diclofenac sodium nanoparticle	-	1,8	-
Ethylcellulosa	50	50	50
Polyvinyl Pirolidon	12,5	12,5	12,5
Propylene glycol (PG) (%b/b of total polimer)	-	-	6,25 (10%)
Methanol	5 ml	-	5 ml
Chloroform	-	5 ml	-

Preparation of Diclofenac Sodium Nanoparticle

Diclofenac sodium nanoparticles are made using a milling ball. Diclofenac sodium powder was mashed with a milling ball (Retsch brand pm 200) for 5 hours and then the particle size is measured using a particle size analyzer (Fritsch NanoTech).

Preparation of the diclofenac sodium transdermal patch matrix

Matrix type transdermal patches containing pure diclofenac sodium and nanoparticlewere prepared according to the formula in Table 1. Polymers (EC-PVP), drugs and plasticizers/enhancers (propylene glycol) were mixed in a methanol/chloroform. Mixing was done in a beaker and

stirring slowly for 20-30 minutes with a magnetic stirrer so that the mixture is homogeneous. Then the resulting solution was poured in a 4 cm^2 mould and the solvent was removed by storage at 40 ° C for 45 minutes[14].

Drug-excipient incompatibility Test with FT-IR

Examination of the interaction between diclofenac sodium with each polymer was carried out by FT-IR. Each diclofenac sodium and polymer were dispersed in potassium bromide and the spectrum is measured using IR spectroscopy at wavelengths of 400 - 4000 cm-1[15].

Matrix Thickness Test

Patch thickness measurements were carried out using a a screw micrometer and performed at three different points, and then the average thickness was calculated[16].

Uniformity Test Weight of the matrix

Weights test was carried out to see the uniformity of patch weights by weighing five patches one by one, then calculating the average weights [16].

Moisture Content Test

Moisture Content Test was done by means of patch the prepared each weighed (initial weight) and stored in a desiccator containing silica gel at room temperature for 24 hours. The patch was then re-weighed (final weight), then the water content was calculated.

Moisture Uptake Test

Moisture uptake testing was done to see the extent of the ability of the polymer to absorb water. Patches of 4 cm^2 are weighed and placed in a petri dish containing 10 ml of distilled water. The increase in patch weight is then determined at a certain time interval until a constant weight is observed, then the percent of moisture uptake was calculated [17].

$$\text{Percentage moisture uptake} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100$$

Folding Endurance Test

The folding endurance test was performed that calculated the number of folds needed to break the polymer patch. This test aims to illustrate the strength of patches and checks how efficiently the use of plasticizers provides flexibility. This test involves the simple phenomenon of being patched repeatedly in the same place until broken. Thus, it can be seen the number of patches that can be folded at the same place without cracking/damage. The greater the amount of folding strength, the more elastic the shape of the matrix so that it is more comfortable to use [16].

Penetration Test in vitro

Preparation of Rabbit Skin Membrane

Male rabbits (1.5 kg) were obtained from the animal house of North Sumatra University. In the beginning, animals were sacrificed by excessive chloroform inhalation. The abdominal rabbit skin hair is carefully removed by removing the subcutaneous fat layer with a scalpel. The prepared skin is then washed with distilled water and dried with sterile gauze. The skin is wrapped in aluminium foil and stored at −30˚C. The trial permit was approved by the Ethics Committee of the Faculty of Biology, University of North Sumatra.

Determination of Maximum Wavelength and Calibration Curves

Sodium diclofenac solution was made with a concentration of 10 µg / ml using phosphate buffer and then the absorption was measured at a wavelength of 200 - 400 nm.from the standard solution (100 µg/ml) each pipette 0.1; 0.2; 0.4; 0.6; 0.8; 1.0; 1.2; 1.4; 1.6; 1.8; 2.0; 2.2 and 2.4 ml, then put into a 10 ml volumetric flask and a phosphate buffer of pH 7.4 is added to the limit mark, so that a series of solutions with a concentration of 1-24 ppm was obtained. Uptake was measured at the maximum wavelength of absorption of diclofenac sodium.

In-vitro Penetration with Franz Diffusion Cell

The penetration test is carried out using a modified vertical type Franz diffusion cell. The donor portion contains the transdermal patch containing pure sodium diclofenac and nanoparticle preparation. The dividing membrane between the donor compartment and the acceptor is rabbit skin. Rabbit skin is placed between the donor compartment and the acceptor compartment with the dermis side facing the acceptor compartment. The acceptor compartment contains a pH phosphate buffer of 4.7 ml of 21 ml and is stirred with a low-speed magnetic stirrer at 37 ± 0.5°C. Observations were carried out for 8 hours, and samples were taken at 30, 60, 120, 180, 240, 300, 360, 420, and 480 minutes. Each time 1 ml of the solution was taken into the acceptor compartment was put into a 10 ml measuring flask and Phosphate buffer is added to the boundary mark, then add 1 ml of phosphate buffer back into the acceptor compartment to meet the volume. Then the absorption of the diclofenac sodium sample was determined on a spectrophotometer with a maximum wavelength of absorption.

Analgesic Activity

Analgesic testing was using male rats (200-220 g)and with the plantar test method[18]. The experimental used 24 animals which were divided into four groups, each was six rats. The first group was negative control (patches without drug), the second group was the transdermal patches containing pure diclofenac sodium, the third group was the transdermal patches containing nanoparticle, and the fourth group was the transdermal patches containing pure diclofenac sodium with enhancer. The patch placed on the back of the animal which has been shaved 4 cm x7 cm for 30 minutes. Then, the animals were put into a plantar test room, and infrared light was given to the soles of the feet. The pain response will be timed for each animal licking or lifting its legs. Measurements were carried out for 480 minutes.

Anti-inflammatory Activity

Anti-inflammatory testing was carried out using the paw edemaa method using 24 male rats (200-220 g) which were divided into four groups. The first group was negative control (patches without drug), the second group was the transdermal patches containing pure diclofenac sodium, the third group was the transdermal patches containing nanoparticle, and the fourth group was the transdermal

patches containing pure diclofenac sodium with enhancer. Animal feet were induced using 1% carrageenan as much as 0.05 ml so that the feet became swollen. the preparation was attached 1 hour before induction on the back of the animal that has been shaved[18]. Foot edemaa volume will be measured using a plestymometer, and measurement is carried out for 480 minutes. Furthermore, the data obtained from the results of the study are processed with statistics, namely Analysis of variance (ANOVA).

RESULT AND DISCUSSION

Particle Size Analyzer Result

The size of the diclofenac sodium particle produced by milling ball tested with a particle size analyzer was between 10 - 400 nm. This figure showed that the diclofenac sodium powder had become a nanoparticle (Figure 1.)

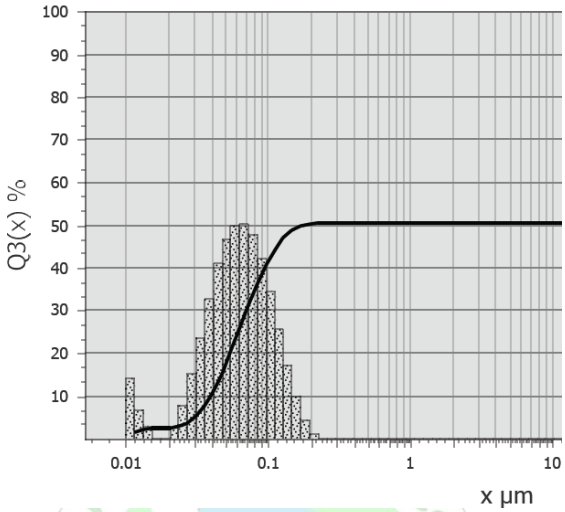

Figure: 1 Diclofenac sodium nanoparticle size measurements

Patch Matrix Thickness

Diclofenac sodium transdermal patch that has been made has a thickness between 0.16 ± 0.0003 to 0.18 ± 0.0002 mm. F1 and F2 do not use propylene glycol as an enhancer, while F3 uses propylene glycol 10%. The standard deviation of the three formulas is small (<1), so it can be stated uniform patch thickness.

Uniformity of Patch Matrix Weights

The weight of the diclofenac sodium patch matrix produced ranged from 80.8 ± 0.23 to 82.8 ± 0.07 mg. F3 has a slightly higher weight than F1 and F2, this is influenced by the addition of propylene glycol to F3, while F1 and F2 were not. A small standard deviation of the three formulas (<1) indicates that the patch weights were uniform.

Moisture Content of Matrix Patch

The Moisture content of transdermal patches of pure diclofenac sodium and nanoparticle produced ranged from 1.24 ± 0.01229 to 2.10 ± 0.4549%. A patch is said to be good if the patch has low water content, so the stability of the patch will be good, also not too dry and brittle[17].All three formulas show a small amount of moisture content.

Moisture uptake of Matrix Patch

Moisture uptake of transdermal patch of pure diclofenac sodium and nanoparticle ranged from 1.55 ± 0.0701 to 1.77 ± 0.4374%. Low water absorption will protect the patch from microbial contamination and avoid the formation of patches that are too thick[17].

Folding Endurance of Matrix Patch

Folding endurance F1, F2, and F3 were87, 95 and 246. F3 has a folding endurance value that is much higher than F1 and F2, due to the addition of propylene glycol to F3 as an enhancer. Apart from being an enhancer, propylene glycol also acts as a plasticizer which provides flexibility and elasticity to the patch. Folding endurance of F1 and F2 looks bad because there was no use of propylene glycol. The results of observations of diclofenac sodium transdermal matrix characteristics can be seen in Table 2.

Table: 2 Characteristics of the Diclofenac Sodium Transdermal Patch Matrix

Formula	Thickness (mm)	Weight (mg)	Moisture content (%)	Moisture uptake (%)	Folding Endurance
F1	0.16 ± 0.0003	80.8 ± 0.23	1.24 ± 0.1229	1.55 ± 0.0701	87
F2	0.17 ± 0.0002	81.3 ± 0.14	1.59 ± 0.4380	1.62 ± 0.5736	95
F3	0.18 ± 0.0002	82.1 ± 0.07	2.10 ± 0.4549	1.77 ± 0.4374	246

Maximum Wavelength of Diclofenac sodium

The results of measurements with a spectrophotometer show that sodium diclofenac provides maximum absorption at a wavelength of 276.6 nm. The curve of determining the maximum wavelength of diclofenac sodium can be seen in Figure 2.

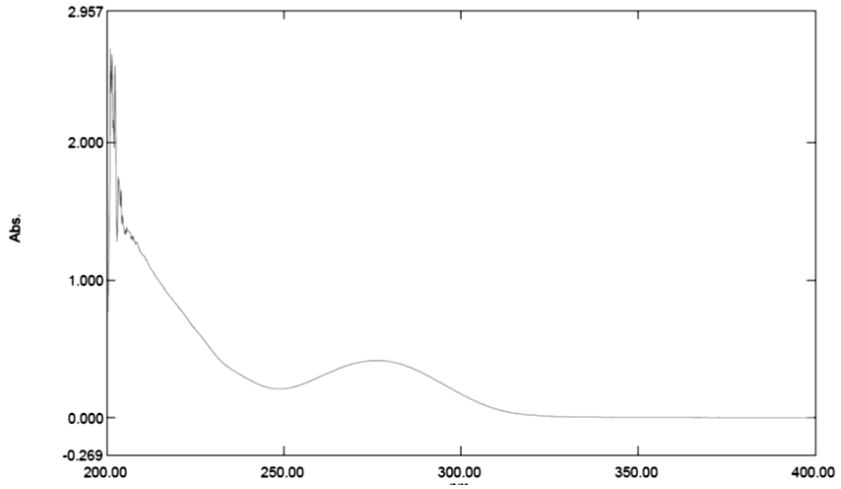

Figure: 2 Diclofenac sodium wavelength curve

Calibration Curve of Diclofenac Sodium

The results of the measurement of the standard diclofenac sodium curve obtained a linear regression equation that is y = 0.0188x-0.0127 with a linear value of r^2 = 0.9969. The results of the diclofenac sodium standard curve can be seen in Figure 3.

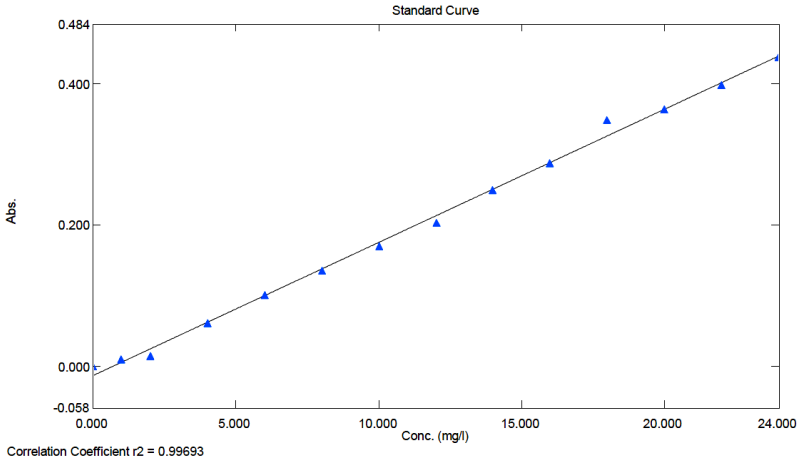

Figure: 3 Diclofenac sodium calibration curve

Penetration of the Transdermal Patch Matrix

Figure 4. showed that F1, F2, F3 began to experience penetration in the 480th minute by 46.6 ± 1.9438, 58.87 ± 0.7458, and 67.59 ± 1.4675. The results of this penetration show that the penetration rate of F2 is higher than F1, which means the utilization of nanoparticles can increase the diclofenac sodium penetration of the transdermal patch. Nanoparticle powder size can more easily cross the stratum corneum and then enter the epidermis and dermis. lipophilic drugs such as diclofenac sodium penetrate through the trans-epidermal route that is inter-cellular skin layer[19]. From this result it can also be seen, that f3 has a higher percent penetration than F1 and F2. F3 is a transdermal patch containing pure diclofenac sodium with the addition of a 10% propylene glycol enhancer. The use of enhancers aims to increase the penetration of the drug from the patch so that the drug more easily crosses the skin layer.

The film used in making the diclofenac sodium patch matrix in the form of ethyl cellulose and PVP has a role in the drug release system in the form of a matrix patch. Ethyl cellulose is a neutral lipophilic polymer that plays a role in holding the drug in the matrix, so it is not necessarily released from the patch, and the process of drug diffusion will be slow [20]. PVP polymers are hydrophilic polymers that can increase drug release, so the drug can immediately diffuse and come off the patch matrix to then be slowly carried across the skin and into blood vessels. PVP functions to form a pore that can increase the release of diclofenac sodium from the matrix[19].Anova One Way

statistical test results showed that the three formulas do not significantly differ in the cumulative percent penetration of the drug ($p > 0.05$).

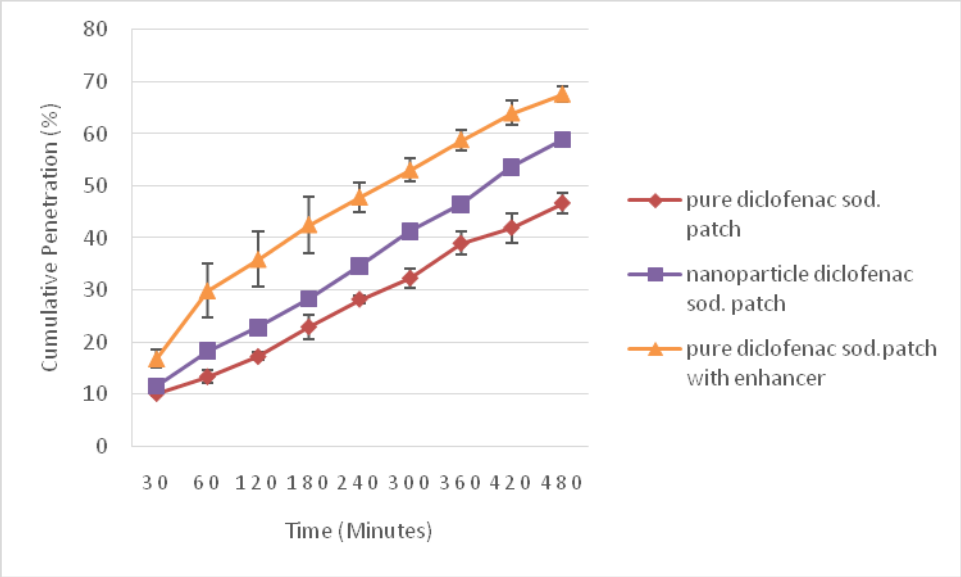

Figure: 4 Penetration of the transdermal patch containing pure diclofenac sodium and nanoparticle

Analgesic Activity

The analgesic activity test results showed that the use of the pure diclofenac sodium patch group in rats was able to increase the pain response value up to 480 minutes and showed significantly different results when compared to the negative control group ($p < 0.05$). Likewise, the diclofenac sodium nanoparticlepatch group and the pure diclofenac sodium patch group with the addition of enhancer, were able to increase the pain response value in experimental animals and showed significantly different results from the negative control group ($p < 0.05$). The highest increase in pain response value was shown by the fourth group that is the pure diclofenac sodium patch with the addition of an enhancer, but these results were not significantly different from the diclofenac sodium nanoparticle patch group and the pure diclofenac sodium patch group without enhancers ($p > 0.05$). Likewise, the diclofenac sodium nanoparticle patch group was seen to be higher in increasing the pain response value of experimental animals, but not significantly different from the pure diclofenac sodium patch group without enhancers ($p > 0.05$). The graph of the analgesic activity test results can be seen in Figure 5.

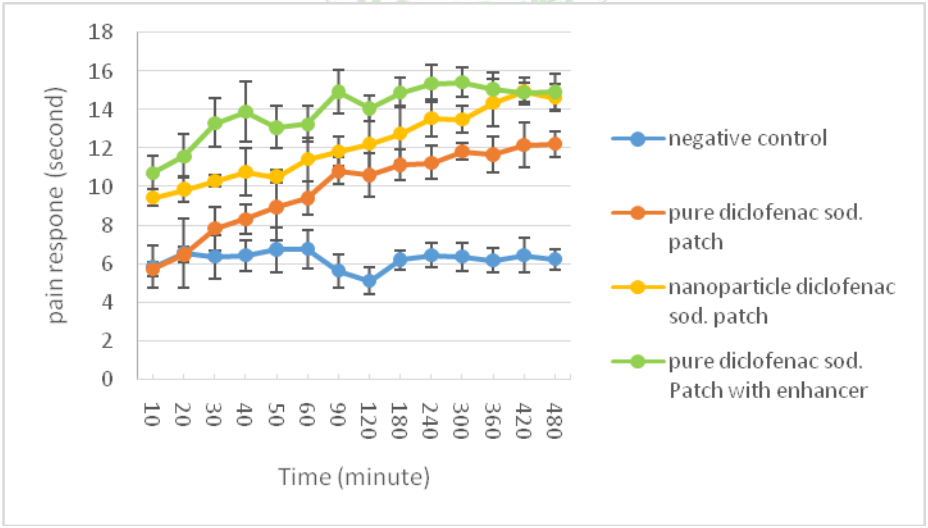

Figure: 5 Graph of the analgesic activity test

The ability of the patch to increase the value of the pain response indicates that the activity is better as an analgesic, because the use of the patch is able to deliver diclofenac sodium across the skin so that it is in the systemic system and provides an inhibiting effect on pain induction that has been given. The use of PVP polymer as a patch matrix serves to help the drug penetrate into the skin because it is hydrophilic, while ethyl cellulose serves to hold the drug from being released slowly. The nanoparticle form of diclofenac sodium is able to increase its penetration power because of its nanoparticle size, making it easy to enter skin cells and penetrate them[11]. The use of propylene glycol

enhancers appears to be able to increase the ability of the drug to enter the system more quickly and give effect. This is due to the hydrophilic nature of propylene glycol[21].

Anti-Inflammatory Activity

The results of the anti-inflammatory activity test showed that the use of the pure diclofenac sodium patch group in rats was able to reduce the value of foot edemaa volume up to 480 minutes and showed significantly different results when compared to the negative control group ($p < 0.05$). Likewise, the diclofenac sodium nanoparticlepatch group and the pure diclofenac sodium patch group with the addition of enhancer, were able to decrease the edemaa volume value of the experimental animals' feet and showed significantly different results from the negative control group ($p < 0.05$). The highest decrease in foot edema volume value was shown by the fourth group, namely the pure diclofenac sodium patch with the addition of enhancers, but these results were not significantly different from the diclofenac sodium nanoparticlepatch group and the pure diclofenac sodium patch group without enhancers ($p > 0.05$). The three patch groups appeared to have almost the same anti-inflammatory effect ($p > 0.05$), but the pure diclofenac sodium patch group without enhancers was the lowest group in reducing the volume of foot edemaa. These results indicated that the use of nanoparticle diclofenac sodium was much better at increasing the permeation of the drug through the skin compared to the pure form, but the effect was almost similar to that of the pure diclofenac sodium patch group with the addition of the enhancer.The graph of the analgesic activity test results can be seen in Figure 6.

.

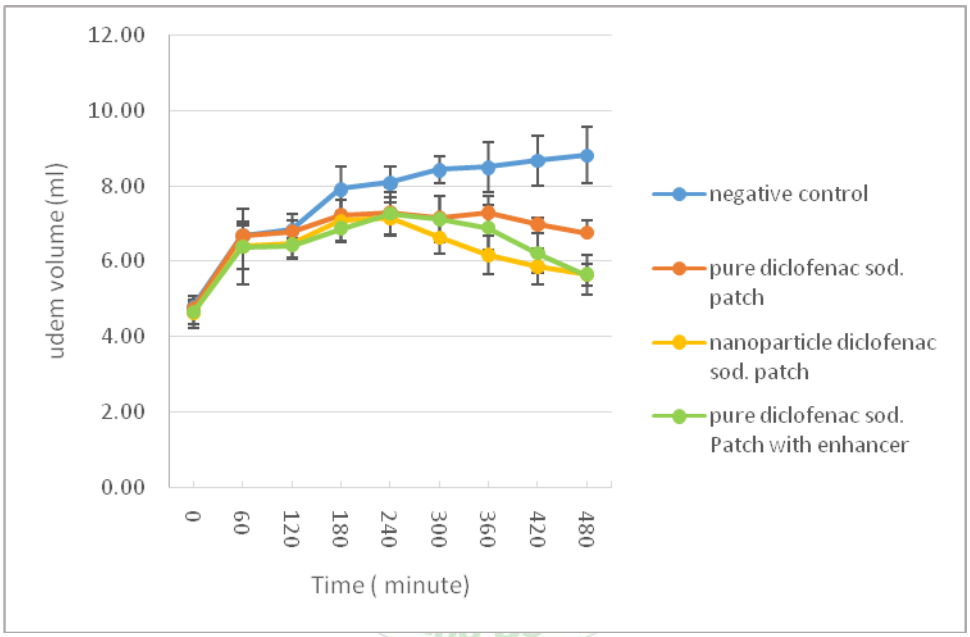

Figure: 6. The graph of the anti-inflammatory activity test

CONCLUSION

Transdermal patches containing sodium diclofenac nanoparticles have been shown to be able to increase drug penetration through the rabbit's stomach skin membrane in vitro using Franz diffusion cells compared to its pure form. Transdermal patches of pure diclofenac sodium and nanoparticles are able to provide analgesic and anti-inflammatory effects in experimental animals, the form of nanoparticles is better at providing these effects than the pure form.

ACKNOWLEDGEMENT

The author would like to thank the physical pharmacy laboratory and pharmacology faculty of pharmacy at the North Sumatra University of Medan, for the support of tools and materials in this study.

REFERENCES

1. Silva, N. H. C. S. et al. Bacterial cellulose membranes as transdermal delivery systems for diclofenac : In vitro dissolution and permeation studies. Carbohydr. Polym.2014; **106:**264–269.
2. Rajabalaya, R., Khanam, J. & Nanda, A. Design of a matrix patch formulation for long-acting permeation of diclofenac potassium. Asian J. Pharm. Sci.2008; **3**:30–39.
3. WHO. Chronic rheumatic conditions. World Health Organization (WHO) https://www.who.int/chp/topics/rheumatic/en/ (2019).
4. Sachan, R. &Bajpai, M. Transdermal Drug Delivery System: A Review. International Journal of Research and Development in Pharmacy and Life Sciences. 2013; 3:748–765.
5. Sheth, N. S. & Mistry, R. B. Formulation and evaluation of transdermal patches and to study permeation enhancement effect of eugenol. J. Appl. Pharm. Sci.2011; **01**:96–101.
6. Bhowmik, D., Pusupoleti, K. R., Duraivel, S. & Kumar, K. P. S.Recent Approaches in Transdermal Drug Delivery System. The Pharma Innovation-Journal.2013;2:99–108.
7. Rastogi, V., Pragya & Upadhyay, P. A Brief View On Antihypertensive Drugs Delivery Through Transdermal Patches. Int. J. Pharm. Sci. Res.2012; **3**:1955–1970.
8. Taghizadeh, S. M. &Bajgholi, S. A New Liposomal-Drug-in-Adhesive Patch for Transdermal Delivery of Sodium Diclofenac. Journal of Biomaterials and Nanobiotechnology. 2011; 576–581.
9. Singh, A. K., Yadav, T. P., Pandey, B., Gupta, V. & Singh, S. P. Chapter 15 - Engineering Nanomaterials for Smart Drug Release: Recent Advances and Challenges. Applications of Targeted Nano Drugs and Delivery Systems (Elsevier Inc., 2019). doi:10.1016/B978-

0-12-814029-1.00015-6.

10. Sharma, M. Chapter 18 - Transdermal and Intravenous Nano Drug Delivery Systems: Present and Future. Applications of Targeted Nano Drugs and Delivery Systems (Elsevier Inc., 2019). doi:10.1016/B978-0-12-814029-1.00018-1.
11. Bibi, N., Ahmed, N. & Khan, G. M. Chapter 21 - Nanostructures in transdermal drug delivery systems. Nanostructures for Drug Delivery (Elsevier Inc., 2017). doi:10.1016/B978-0-323-46143-6/00021-X.
12. Ashok, A.K. Fabrication and In-Vivo Evaluation of Lipid Nanocarriers Based Transdermal Patch Of Colchicine. Journal of Drug Delivery Science and Technology.2017; 41:444–453.
13. Yadav, V. Transdermal Drug Delivery System: Review. Int. J. Pharm. Sci. Res.2012; **3:**376–382.
14. Muñoz, M. D., Castán, H., Ruiz, M. A. & Morales, M. E. Design, development and characterization of transdermal patch of methadone. J. Drug Deliv. Sci. Technol. (2017) doi:10.1016/j.jddst.2017.04.011.
15. 15. Swain, R. P., Nagamani, R. & Panda, S. Formulation, in vitro Characterization and Stability Studies of Fast Dispersing Tablets of Diclofenac Sodium. J. Appl. Pharm. Sci.2015; 5:094–102.
16. Lakhani, P., Bahl, R. & Bafna, P. Transdermal Patches: Physiochemical And In-Vitro Evaluation Methods. Int. J. Pharm. Sci. Res.2015; **6.**
17. Mahajan, N. M. et al. Formulation development and evaluation of transdermal patch of piroxicam for treating dysmenorrhoea. J. Appl. Pharm. Sci.2018; **8:**35–41.
18. Lintang, K., Panal, S. & Aminah, D.Anti-Inflammatory Activity of Ethanol and Fraction of Buni Leaves (Antidesma Bunius L.) on White Rat in Carrageenan Induced Paw Inflammation. Asian Journal of Pharmaceutical Research and Development.2019;7:1–5.
19. Alkilani, A. Z., Mccrudden, M. T. C. & Donnelly, R. F. Transdermal Drug Delivery: Innovative Pharmaceutical Developments Based on Disruption of the Barrier Properties of the stratum corneum. Pharmaceutics.2015;**7**:438–470 (2015).
20. Parthasarathy, G., Reddy, K. B. & Prasanth, V. V. Formulation And Characterization Of Transdermal Patches of Naproxen With Various Polymers. Pharm. Glob. Int. J. Compr. Pharm.2011; **2:**1–3.
21. Walker, B. & Smith, E. W. The role of percutaneous. Adv. Drug Deliv. Rev. 1996; 295–301.