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Physical Properties, Release and Penetration Tests of Membrane-Type Diclofenac Sodium Patch Using Nanostructured Lipid Carrier as Reservoir

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ABSTRACT

Diclofenac sodium, a Non-Steroidal Anti-Inflammatory medicine, is efficacious in treating osteoarthritis. However, it might cause adverse gastrointestinal symptoms and may lead to liver metabolic complications when used orally. Hence, the development of an efficacious treatment, specifically the diclofenac sodium patch with a membrane, is imperative. The goal of this research was to identify the optimal formulation for a membrane-type diclofenac sodium patch with Nanostructured Lipid Carrier (NLC) as a reservoir, using a solvent casting technique with HPMC 606 as the rate-controlling membrane. Diclofenac sodium patch with NLC Formula 1 was determined to be the most effective formula, as it showed good physical attributes such as drug content and drug homogeneity above 85%, spherical particles, a higher release flux of 12.246 ± 0.60 µg/cm^2/min$^{1/2}$ compared to Formula 2 and Formula 3, and the release kinetics in all formula followed the Higuchi model. Using the most optimal patch formula, a penetration test showed a higher flux penetration of 0.329 ± 0.01 µg/cm^2/min compared to the comparison, which involved a diclofenac sodium patch with physical mixture. The research suggested that diclofenac sodium patch with NLC holds significant potential as a transdermal drug delivery system.

***Keywords*:** Diclofenac sodium, Patch, Nanostructured Lipid Carrier, Physical Attributes, Release Test, Penetration Test.

Introduction

Diclofenac sodium, categorized as a Non-Steroidal Anti-Inflammatory Drug (NSAID), functions by impeding the activity of enzyme cyclooxygenase (COX).[1] It is commonly employed for the management of rheumatoid arthritis and osteoarthritis.[2] Nevertheless, when diclofenac sodium is used orally, it might cause gastrointestinal side effects and is metabolized by the liver through first-pass metabolism.[2,1] Transdermal administration of diclofenac sodium offers a promising alternative, with the patch being a specific version of this delivery mechanism.[3]

A patch is capable of administering accurate amounts of active chemicals transdermally, delivering them directly into the bloodstream for a predetermined period of time.[4] This method is non-invasive and has the potential to improve patient compliance.[5] There are two primary types of patches: matrix patches and membrane patches. Membrane-type patches provide benefits such as increased active ingredient concentration and controlled, uninterrupted medication release, enabling extended usage in comparison to matrix-type patches.[6]

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The effectiveness of a membrane-type patch depends on its capacity to release the drugs from the membrane and permeate the outermost layer of the skin, known as the stratum corneum. The amount of drug released is regulated by the solubility of the active ingredient. Diclofenac sodium is categorized as a class II substance in the Biopharmaceutical Classification System (BCS) and possesses a log P value of 1.13.[7] In order to enhance the absorption of substances into the skin, it is necessary to utilize a particular method of delivery such as Nanostructured Lipid Carrier (NLC).

NLC serves as a carrier system, composed of a mixture of solid and liquid lipids to encourage the creation of amorphous solids.[8] With a particle size ranging 10 to 1000 nm, NLC enhances penetration by increasing the surface area and promoting better interaction between the drug and the membrane, thereby augmenting absorption and skin penetration.[9]

In this research, membrane-type diclofenac sodium patches were produced using the solvent casting method, utilizing NLC as the drug reservoir, HPMC 606 as the rate-controlling membrane, propyleneglycol as the plasticizer, and menthol as the enhancer. The evaluation such as physical attributes, release and *in vitro* penetration tests. The release and penetration assessments were conducted utilizing a 5-paddle over disk device with a diffusion cell. A phosphate buffer saline pH 7.4 and 70% ethanol 85:15 (v/v) was used as the medium at a temperature of 37 ± 0.05°C. Measurement of diclofenac sodium levels was conducted by using UV spectrophotometer, with a maximum wavelength of 276.6 nm.

Material and Methods

Materials

Diclofenac sodium (Manufactured by PT. Dexa Medica, Indonesia); other materials used were stearic acid (Avantor Performance Materials Taiwan Co.,Ltd, Hsinchu), oleic acid (Marks & Nos Inc), Tween 80

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(PT. Kao, Indonesia), HPMC 606 (Shin-Etsu Chemical Co.,Ltd, Japan), propyleneglycol and menthol (PT. Brataco, Indonesia).

Preparation of Diclofenac Sodium NLC
The diclofenac sodium NLC was produced by using an Ultra-turrax homogenizer (Ika T-25) to blend it at 75℃ between the lipid phase (stearic acid and oleic acid with ratio such as 6:4, 7:3, 8:2) and diclofenac sodium.[10] This mixture was then agitated at 3800 rpm for 5 min. Conversely, solutions of surfactants composed from Tween 80 and phosphate buffer saline pH 6.0 ± 0.05 were prepared and warmed to 75°C. These solutions were then combined with the lipid phase using the homogenizer at 13000 rpm for 5 min in 2 cycles.[11] During the cooling phase, the mixture was stirred at 50 rpm until it reached 25℃ using a hotplate stirrer (Cimarec).[12]

Preparation of Diclofenac Sodium Patch
Patches were made using formula enlisted on Table 1. The patch was shaped using a circular mold with an inner diameter of 3.8 cm, resulting in a surface area of 11.335 cm^2. 2% diclofenac sodium is the concentration utilized.[13] The NLC as the reservoir, was poured into the mold and allowed to dry for 48 hours. Subsequently, a rate-controlling membrane solution, composed of HPMC 606, propyleneglycol, and menthol, was applied onto the dried patch by mixing at 500 rpm for 5 min. The patch was then dried again for 24 hours. Finally, the dried patch was carefully taken out of the mold and stored in a desiccator.[14]

Thickness Evaluation
This examination is conducted to assess the thickness of each patch formulation using thickness gauge digital. The thickness of each patch was evaluated at three different positions, and the average is computed.[15]

Weight Uniformity Evaluation
Three patches from each formulation were randomly selected and weighed using an analytical balance (Ohaus), followed by the calculation of the mean weight, SD and RSD.[15]

Moisture Content Evaluation
The patches were weighed and then positioned inside a desiccator with silica gel for 24 hours at room temperature. Subsequently, the patches were weighed again until a consistent weight is achieved. The % moisture content computation is as follows:[16]

$$\%MC = \left(\frac{initial\ weight - final\ weight}{final\ weight}\right) \times 100\%$$

Drug Content Evaluation
The evaluation of the active ingredient content involved dissolving the patch preparation in 100 mL of phosphate buffer saline pH 7.4 ± 0.05, supplemented with 70% ethanol. The solution was then stirred at 1000 rpm for 2 hours. Following this, centrifugation (Hettich Rotofix 32) was performed at 4000 rpm for a duration 10 min, after which 0.2 mL of the solution was extracted and dissolved in 10 mL of medium. The supernatant was analyzed using a UV Spectrophotometer (Hitachi) at a wavelength of 276.6 nm.[17]

Drug Homogeneity Evaluation
The assessment of the active ingredient content homogeneity within the patch entailed dividing each patch into four segments.[18] Each patch was dissolved in 100 mL of phosphate buffer saline at pH 7.4 ± 0.05, supplemented with 70% ethanol, and stirred at 1000 rpm for 2 hours. The solution was then centrifuged at 4000 rpm for 10 min, and 0.2 mL of the solution was extracted and dissolved in 10 mL of medium. The supernatant was examined using a UV Spectrophotometer at a wavelength of 276.6 nm.

Surface Morphology Evaluation
The surface morphology and form of the patch was examined through Scanning Electron Microscopy (SEM).[19]

Release and In Vitro Penetration Evaluation
The patch release and penetration tests were conducted utilizing a 5-paddle over disk apparatus equipped with a diffusion cell. For the release test, the cell was covered with a cellophane membrane, while for the penetration test, the cell was covered with abdominal skin from Wistar rats as a membrane. Then the membrane was placed in a dissolution test tube containing 500 mL medium. The experimental temperature was maintained at 37 ± 0.5°C, with the paddle revolving at 50 rpm. The absorbance of the samples was observed using a UV Spectrophotometer at a wavelength of 276.6 nm.[20]

Statistical Analysis
With a 95% confidence level, the physical characteristics of the patch were assessed using One-Way Analysis of Variance (ANOVA). Tukey HSD Post Hoc Test is continued to determine which groups are different if there is a significant difference in the ANOVA Test.

Table 1: Diclofenac sodium patch with NLC formula

Components	Formula 1 (6:4)	Formula 2 (7:3)	Formula 3 (8:2)
Diclofenac sodium NLC	22.67 mg	22.67 mg	22.67 mg
HPMC 606	1 mL	1 mL	1 mL
Propyleneglycol	53.3 mg	53.3 mg	53.3 mg
Menthol	1%	1%	1%

Result and Discussion

Organoleptic Test of Patch
Organoleptic assesment in this research was to assess whether the external appearance of the patch meets aesthetic criteria. This assessment was conducted using visual observation,[18] without the need for specialized tools, to evaluate the surface condition of the patch. The organoleptics data are presented in Figure 1. The white appearance of the patch was attributed to the color of diclofenac sodium. Notable variations in surface texture were not observed among Formula 1, Formula 2, and Formula 3. All formula exhibited a dry and a bit rough texture on their surfaces. Additionally, the diclofenac sodium patches in all formulation were odorless.

Thickness Test of Patch
Testing for patch thickness was conducted to ascertain the consistency of thickness across each patch. The pouring technique into the mold affected the thickness.[14] The thickness test outcomes of the diclofenac sodium patch with NLC are displayed in Table 2, demonstrating that each formula met the patch thickness criteria, which stipulated a maximum of 1 mm. Exceeding this thickness could hinder the release of the active substance from the patch.[21] Because the thicker it is, the effects will stay longer and the patch will be harder to remove the active ingredient. The research findings revealed the thickness order as Formula 1 < Formula 2 < Formula 3. As the quantity of lipids increases, it leads to an elevation in viscosity.[22] Where a solution is located will have an impact on how evenly it spreads throughout the mold. Since the spreading power of a thicker solution decreases,[23] the patches thickness increases as a result. Patch thickness influences drug release and flux. Increased thickness impacts the release duration, longer working time.[21] The One-Way ANOVA analysis followed by Tukey HSD analysis revealed a different thickness between Formula 1 with Formula 3 (Sig. = 0.026).

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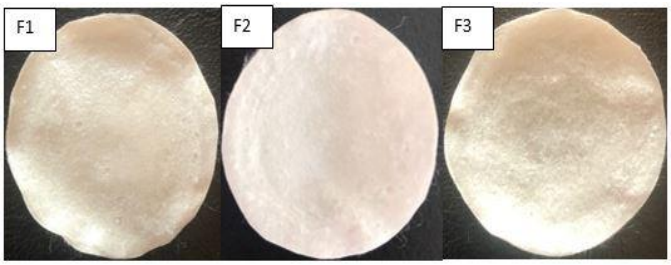

Figure 1: The result of organoleptic evaluation of diclofenac sodium patch with NLC on Formula 1, Formula 2 and Formula 3

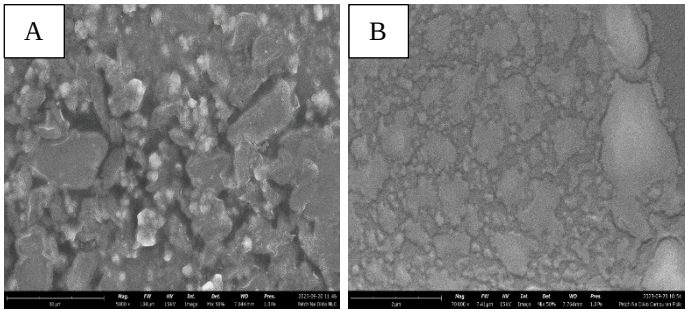

Figure 2: Surface morphology of (A) diclofenac sodium patch with NLC (Formula 1), (B) diclofenac sodium patch with physical mixture in magnification 5000x.

Weight Uniformity Test of Patch

This test was carried out to determine the uniformity of patch weights in each formula. Variations in patch weight among each formula may stem from uneven application of the patch material on its surface, resulting in certain areas with varying thicknesses. This unevenness can impact the overall weight of the patch. If the weight of the patch reduces from the stipulated weight, it is probable that one constituent has seen a reduction in weight. If the active ingredient was one of the elements that were lowered, it would have an impact on the quantity of active ingredient in the penetration tests. As a result, the weight was taken into consideration.[14] According to the data in Table 2, the patch weights in every formula demonstrated uniformity, as evidenced by a %RSD value of less than 5%.[24] There was a difference in the weight uniformity between Formula 1 and Formula 3 (Sig. = 0.036) according to the One-Way ANOVA analysis and Tukey HSD analysis.

Moisture Content Test of Patch

The purpose of testing a moisture content test is to assess the patch stability, because air is a place where organisms grow, patch preparations with too much air in them may become unstable, and to prevent it from becoming brittle or drying out.[25] The moisture content in this patch will facilitate the releasing process when applied to the skin. Nevertheless, an elevated water content can lead to the destabilization of the patch formulation. The results confirmed that all formulations met the stipulated criteria for ideal patch moisture content, maintaining a range is 1-10%.[26] The outcomes displaying the proportion of moisture content are presented in Table 2. One-Way ANOVA statistical examination Sig. the value obtained was 0.000 (<0.05) which shows the difference in moisture content in the three patch formula.

Drug Content Test of Patch

The objective of the drug content test is to verify that the diclofenac sodium present in the patch falls within the designated range. This concentration range of 85-115% for drug content ensures controlled release and effective skin penetration.[21] The outcomes of this test are outlined in Table 2. The findings indicate that only Formula 1 satisfies the specified criteria by consistently maintaining active ingredient levels above 85%. This is attributed to the influence of the concentration of liquid lipids used in the production of NLC. Higher concentrations of liquid lipids enable the incorporation of medicinal ingredients.[10] As a result, increased drug incorporation in the NLC system resulting in a higher drug content seen in patches with more of it. Furthermore, multiple other research have indicated that the drug released from the patch exhibits a clear correlation with the rise in moisture content.[27] Consequently, we discovered that formula containing more moisture i.e Formula 1 exhibited more drug content.

Drug Homogeneity Test of Patch

Following the assessment of the diclofenac sodium drug content in each patch formulation, an evaluation was conducted to assess their homogeneity. It is thought that the drugs release can happen concurrently in every area of the patch if the drug is evenly distributed.[20] The drug homogeneity percentage results displayed in Table 2, demonstrated variations in levels across all formula indicated by %CV values exceeding 6%. This suggests an uneven distribution of diclofenac sodium on the patch. Formula 1 remains the only formulation that complies with the active ingredient level requirements of 85-115%.[21] There was a difference in patch homogeneity between Formula 1 and Formula 2 (Sig. = 0.033), and Formula 1 and Formula 3 (Sig. = 0.026) according to the One-Way ANOVA analysis and Tukey HSD analysis.

Surface Morphology Test of Patch

Figure 2 displays the findings about the surface morphology. SEM study at 5000x magnification reveals that the diclofenac sodium patch with NLC Formula 1 exhibits uniformly distributed round particles, in contrast to the diclofenac sodium patch with physical mixture used for comparison. The diclofenac sodium patch with NLC Formula 1 contains diclofenac sodium that is enclosed within the NLC system. The particles in the patch, which are round and white, serve as a representation of the active ingredient. The diclofenac sodium patch with NLC Formula 1 exhibited the presence of surface holes, which therefore impacted the drug's release from the formulation.[28] This is in line with the highest release flux value obtained by diclofenac sodium patch with NLC Formula 1 in this research. The pores on the patch facilitate drug release from the matrix, as the presence of big pores enhances the drug's ability to exit.[29]

Table 2: The result of physical attributes of diclofenac sodium patch with NLC

Formula	Flatness (%)*	Thickness (mm)*	Weight Uniformity (mg)*	Moisture Content (%)*	Drug Content (%)*	Drug Homogeneity (%)*
Formula 1	0	0.89 ± 0.02	701.8 ± 25.68	4.36 ± 0.25	89.51 ± 5.85	93.73 ± 6.16
%RSD	0	1.72	3.66	5.69	6.53	6.58
Formula 2	0	0.94 ± 0.03	721.1 ± 7.12	3.52 ± 0.14	76.00 ± 4.76	72.20 ± 7.86
%RSD	0	3.41	0.99	3.98	6.27	10.89
Formula 3	0	0.96 ± 0.02	748.37 ± 12.95	2.21 ± 0.17	75.15 ± 8.14	71.24 ± 14.01
%RSD	0	2.18	1.73	7.62	10.83	19.66

*Data is calculated as the mean value obtained from three separate replications ± SD.

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Table 3: Drug release kinetics of diclofenac sodium patch with NLC

Formula	Zero order	First order	Higuchi	Korsmeyer-Peppas
Formula 1	r = 0.8584	r = 0.6631	r = 0.9640	r = 0.9171
Formula 2	r = 0.8393	r = 0.6554	r = 0.9519	r = 0.8776
Formula 3	r = 0.9084	r = 0.7128	r = 0.9676	r = 0.8971

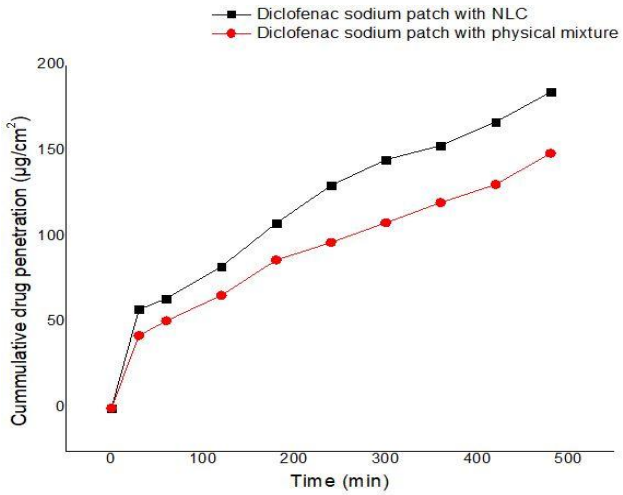

Figure 4: The result of *in vitro* penetration flux of diclofenac sodium patch with NLC and physical mixture (Mean ± SD, N=3)

Release Study of Patch

Figure 3 illustrates the release flux of diclofenac sodium from the patch. According to release studies, Formula 1 have release flux 12.246 ± 0.60 µg/cm²/min$^{1/2}$, so released 0,0122% of its load, Formula 2 have release flux 11.545 ± 0.86 µg/cm²/min$^{1/2}$, so released 0,0115% of its load, and Formula 3 have release flux 11.241 ± 0.12 µg/cm²/min$^{1/2}$, so released 0,0112% of its load. Thus, the release flux in the Formula 1 is greater than that in the Formula 2 and Formula 3. Patches are normally expected along with releases. This is because the patch component uses a rate-controlling membrane, which may deliver regulated drug release for an extended amount of time.[30]

Table 3 illustrates the release kinetics of the diclofenac sodium patch with NLC. The diclofenac sodium patch release pattern was evaluated by fitting the release data to different release kinetic models, such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. Subsequently, to analyze the release pattern, the correlation coefficient (r) was examined to identify the model with the closest correlation coefficient (r) value to one. The Higuchi model was chosen as the appropriate kinetic model for the diclofenac sodium patch with NLC due to its correlation coefficient (r) value being the closest to one. The correlation coefficient (r) values for the Higuchi model were found to be Formula 1 0.9640, Formula 2 0.9519, and Formula 3 0.9676. In patch formulations, the typical release pattern aligns with the Higuchi model. The Higuchi model is often applied to transdermal drug delivery devices such as patches,[31] where the release of the active ingredient is dependent on time. As time prolongs, the active ingredient's release slows down due to an increased diffusion distance for the active ingredient.[32] Diffusion is the main drug release mechanism in the Higuchi model.[33]

In Vitro Penetration Study of Patch

Considering the results of the physical attributes, Formula 1 was selected as the best formula for the ensuing penetration test. The diclofenac sodium penetration flux value from the patch is depicted in Figure 4. The penetration test results showed that the penetration flux for the diclofenac sodium patch with NLC was higher than diclofenac sodium patch with physical mixture, which was 0.329 ± 0.01 µg/cm^2/min and 0.261 ± 0.01 µg/cm²/min, respectively. This occurred because NLC lipid particles' small size guarantees close interaction with the stratum corneum and may enhance the quantity of drug that penetrates the skin.[34] According to further research, NLC's unique structure allows it to maintain extremely close contact with the stratum corneum, forming an occlusive layer of skin that increases the quantity of drug that can permeate.[35] The skin pore size is around 200-300 nm,[36] but the diclofenac sodium patch with physical mixture has a size in the micrometer range, resulting in reduced skin penetration ability.

Conclusion

In conclusion, NLC demonstrates promise as a drug reservoir for patch. Among the formulations, Formula 1 of the diclofenac sodium patch with NLC exhibits good physical attributes and higher release flux of 12.246 ± 0.60 µg/cm²/min$^{1/2}$ compared to Formula 2 and Formula 3. Besides that, the model kinetics of release in all formula followed the Higuchi model. The penetration flux values from Formula 1 was 0.329 ± 0.01 µg/cm^2/min higher than the diclofenac sodium patch with physical mixture was 0.261 ± 0.01 µg/cm²/min.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.\

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