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# Transdermal patch loading diclofenac sodium for anti-inflammation therapy using a rat paw oedema model

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**ABSTRACT:** The anti-inflammatory effect of transdermal delivery of a diclofenac sodium patch was evaluated. The patch matrix consists of ethyl cellulose N-20 and polyvinyl pyrrolidone K-30 to control the drug release. In this study, the patches were prepared with ethyl cellulose N-20 (EC-N20) and polyvinylpyrrolidone K-30 (PVP K-30) at weight ratio of 6:4 and 7:3 for EC/PVP-6/4 and EC/PVP-7/3 patches, respectively. The anti-inflammatory effect was determined by evaluating the swelling of rat's paw oedema that was induced with 1% carrageenan suspension. The results showed that the high concentration of PVP K-30 resulted in less rigid patch with pore structures. In addition, it improved the anti-inflammatory effect of diclofenac sodium resulted in higher efficacy of EC/PVP-6/4 than that of EC/PVP-7/3. There were no significant differences on drug stability observed for both formulations. It can be concluded that controlling diclofenac sodium released from patch using PVP K-30 could give benefits for anti-inflammation therapy.

## 1 INTRODUCTION

Diclofenac sodium is a Non-Steroidal Anti-Inflammatory Drug (NSAID) that is widely used to relieve pain and inflammation. Diclofenac sodium has fast absorption by oral administration, but only about 60% of the total drug amount reaches the systemic circulation. This phenomenon is caused by the first-pass metabolism that occurs in the liver (Chuasuwana et al. 2008). The half-life of diclofenac sodium is very short, which is approximately two hours. Moreover, it produces severe side effects on the gastrointestinal tract i.e. stomach ulcers. Transdermal delivery may provide an alternative solution to overcome this problem.

Recently, commercial transdermal products of diclofenac sodium available on the market are mostly in topical liquids, gels or creams that are applied directly to the skin. However, these products provide only short-term pharmacological effects. The use of transdermal patch can provide many advantages for delivery of diclofenac sodium. The patch can control the drug release, so it can be used for long-term drug administration to achieve systemic dosing (Rathbone et al. 2002). The use of patch can also avoid gastrointestinal irritation, minimize pain, and bypass the hepatic first-pass metabolism. Moreover, due to its ability to control the release of drugs for extended and safe use, it reduces the occurrence of fluctuations and being beneficial for drugs that have very short half-life times and narrow therapeutic ranges. Thereby, it can increase the patient compliance (Kumar & Philip 2007).

It has been known that diclofenac sodium has low molecular weight, which is less 500 daltons, and partition coefficient or Log P of 1.1–1.3 (Kweon et al. 2004, Chuasuwan et al. 2008). These properties have been reported to be ideal for drug delivery using transdermal patch (Rathbone et al. 2002).

Polymer has an important role in regulating the release of the drug in the matrix-patch type. Modification of polymer properties using combination of hydrophilic and lipophilic polymers, such as polyvinyl-pyrrolidone (PVP) and ethyl cellulose (EC) is useful for achieving good drug release rate (Kandavilli et al. 2002, Rathbone et al. 2002). To improve drug penetrated into the skin, the addition of permeation enhancers, such as menthol, can be considered.

In this study, we evaluated the anti-inflammatory effects of diclofenac sodium patch at a dose of 14.13 mg/7.065 cm<sup>2</sup>. The patch was prepared with combination of EC N-20 and PVP K-30 at weight ratio of 6:4 and 7:3. These formulations also contain menthol and polyethylene glycol (PEG)-400 as they were previously reported as important components to prepare patch using the controlled matrix method (Hendradi et al. 2011). The anti-inflammatory effect was then evaluated by determine the thickness of oedema on hind paw of Wistar rats that was induced by injecting carrageenan suspension. Moreover, stability of patch was also determined as they likely affect the therapeutic effects of the preparation.

## 2 METHODS

### 2.1 Materials

Diclofenac sodium was purchased from Aarti Drug Ltd. (Tarapur, India). Ethyl cellulose (EC) N-20 was bought from Dow Chemical Company (Midland, USA). Polyvinylpyrrolidone (PVP) K-30 was a product of ISP Pte. Ltd. (Singapore). All other chemicals are the finest grade available.

### 2.2 Preparation of diclofenac sodium patch

Diclofenac sodium patch was prepared by using the controlled matrix method as previously reported (Hendradi et al. 2011). The patch composed of polymeric matrix, plasticizer, and penetration enhancer as shown in Table 1. The patches had surface area of 7.065 cm<sup>2</sup>. The formulation was generated in triplicates.

### 2.3 Evaluation of physical characteristics of diclofenac sodium patch

#### 2.3.1 Organoleptic properties

The organoleptic properties of diclofenac sodium patch were evaluated by visual observation of physical appearances and colour of patch, and smelling of its odour.

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#### 2.3.2 Moisture content

The Moisture Content was determined by weigh measurement of patch before and after desiccation. The patch was put in a safety cabinet and its mass was weighed. Then, this patch was put in a silica gel desiccator and allowed to stand for 24 hours. After 24 hours, the patch was removed from desiccator and measured for its weight. The moisture content (%) of patch was calculated as follows:

$$\% \text{Moisture Content} = \frac{w_1 - w_2}{w_2} \times 100 \%$$

Table 1. The formulation of diclofenac sodium patch.

Component	Use	Formulation	
		EC/PVP-6/4	EC/PVP-7/3
Diclofenac sodium	Active drug	14 mg	14 mg
EC N-20	Polymeric matrix	169 mg	197 mg
PVP K-30	Polymeric matrix	113 mg	85 mg
PEG-400	Plasticizer	73 mg	73 mg
Menthol	Penetration enhancer	4 mg	4 mg

which  $w_1$  is diclofenac sodium patch's weight before being put in the desiccator, and  $w_2$  is diclofenac sodium patch weight after being put in a desiccator for 24 hours (Patel et al. 2009, Hendradi et al. 2011).

### 2.4 Surface morphology and homogeneity of diclofenac sodium concentration of patch

Determination of surface homogeneity test of patch was evaluated using scanning electron microscopy. The homogeneity of diclofenac sodium concentration in patch was carried out by dividing the patch into four equal parts. Each part was then measured for its level of diclofenac sodium in phosphate buffer saline (PBS) pH 7.4 using UV spectrophotometer at  $\lambda$  of 276 nm. The measurement was in triplicates.

### 2.5 Evaluation of anti-inflammatory effects in rats

All animal experiments were performed through approval of ethical clearance committee of Universitas Airlangga, Indonesia. The Wistar rats with age of two months old were used as the experimental animals. They were divided into four groups, which each group consists of 4 animals. The negative control groups were treated with placebo patches prepared with the combination of EC N-20 and PVP K-30 at weight ratio of 7:3 and 6:4 for EC/PVP-6/4 and EC/PVP-7/3 groups, respectively, and do not contain diclofenac sodium. The treatments groups received diclofenac sodium patches with a dose of 14.13 mg/7.065 cm<sup>2</sup>/rat

and prepared with combination of EC N-20 and PVP K-30 in the weight ratio of 7:3 and 6:4 for EC/PVP-6/4 and EC/PVP-7/3 groups, respectively.

The anti-inflammatory effect of diclofenac sodium patches were evaluated using rat's paw oedema model as previously reported (Hendradi et al. 2003). The patches were applied onto the abdominal skin of the rats. At one hour later, the left rear foot plantar tissue of Wistar rat (two months old) was injected with suspension of carrageenan for oedema induction. The anti-inflammatory effect was determined by measuring the thickness of rat hind paw with the long sliding every 0.5 hours.

#### 2.6 Stability of diclofenac sodium patch

Physical stability test of diclofenac sodium patch was conducted for three months, which were at day 7, 21, 54 and 84, by visual observation of consistency, physical appearances, and odour. In addition, the chemical stability tests were also carried out by determining the diclofenac sodium concentration

of patch during the same interval periods using spectrophotometric method at 276 nm. The measurements were in triplicates.

## 2.7 Data analysis

The anti-inflammatory effect of patch on reduction of inflammation was calculated using the following formula:

$$\% \text{ anti-inflammatory effect} = \frac{H_t - H_0}{H_0} \times 100 \%$$

which  $H_t$  is the thickness of swollen rat hind paw after carrageenan injection at determined measurement time, and  $H_0$  is the thickness of swollen rat hind paw before rats were injected with carrageenan (Hendradi et al. 2003). The significance of differences on reduction of inflammation was statistically analyzed using one-way analysis of variance. A  $p$  value of 0.05 or less was considered significant.

## 3 RESULTS AND DISCUSSIONS

In this study, we prepared diclofenac sodium patch prepared with different weight ratio of PVP K-30 and EC N-20 to control the release of drug. Reducing the concentration of PVP K-30 showed enhanced anti-inflammatory effects on rat's hind paw oedema.

The organoleptic evaluation shows that diclofenac sodium patch EC/PVP-6/4 that was prepared with EC N-20 and PVP K-30 at weight ratio of 6:4, respectively, had more flexible consistency (Table 1). It may be because of the low amount of PVP K-30. Since PVP K-30 is a hygroscopic and hydrophilic polymer, it may cause the patch absorbing water molecules from the air, thus becoming more flexible than EC/PVP-7/3.

Moreover, EC/PVP-6/4 had more transparent appearance than EC/PVP-7/3, as shown in Fig. 1 A,B. It is because the use of less amount of EC, which is a water insoluble hydrophobic polymer, than that of EC/PVP-6/4. Both formulations have the minty fresh smell (Table 1) due to the addition of menthol as penetration enhancer in patch.

Table 2. Organoleptic properties of diclofenac sodium patch at day 0.

Formulation	Consistency	Appearance	Odour
EC/PVP-6/4	Less rigid	Transparent	Minty fresh
EC/PVP-7/3	Rigid	Less transparent	Minty fresh

By using scanning electron microscopy (SEM), it can be seen that EC/PVP-6/4 patch have more pores and larger pore size than EC/PVP-7/3 patch as shown in Fig. 2. Since EC N-20 is a hydrophobic polymer, the low amount of this polymer in EC/PVP-6/4 resulted in hydrophilic patch with extensive pore structures (Fig. 2 A,B). On the other hand, the high amount of EC N-20 in EC/ PVP-7/3 produced tightened structures, thus having small amount of pore with relative small pore size (Fig. 2C,D). The addition of diclofenac sodium had no effect on the physical structures of patches.

The moisture content analysis indicates that EC/PVP-6/4 patch had slightly higher moisture content than EC/PVP-7/3 (Table 3). It is due to the PVP K-30 content, which is a hygroscopic polymer. However, the difference between these two patch formulations was negligible.



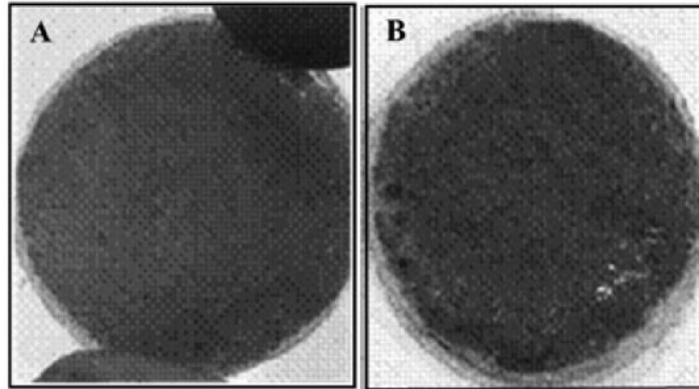


Figure 1. Physical appearances of diclofenac sodium patch prepared with EC N-20 and PVP K-30 at weight ratio of 6:4 and 7:3 for EC/PVP-6/4 (A), and EC/PVP-6/4 (B), respectively.

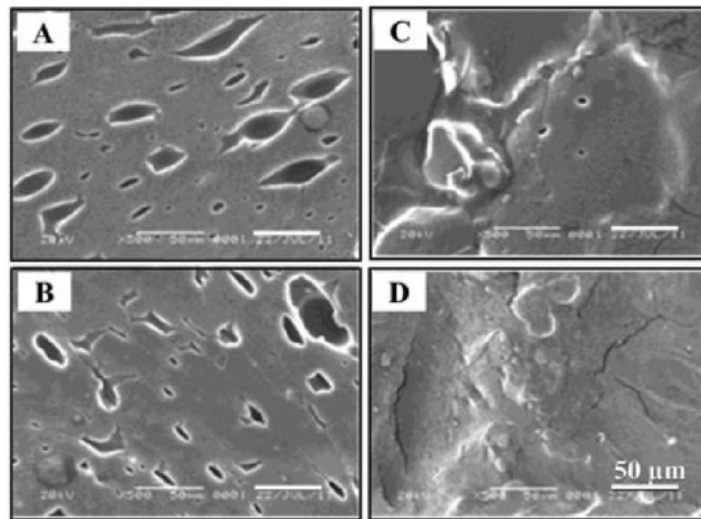


Figure 2. Scanning electron microscope (SEM) pictures of matrix type patch prepared with EC N-20 and PVP K-30 at weight ratio of 6:4 for EC/PVP-6/4 placebo patch (A), EC/PVP-6/4 loading diclofenac sodium (B), and 7:3 for EC/PVP-7/3 placebo patch (C), and EC/PVP-6/4 containing diclofenac sodium (D). Scale bar is 50 µm.

Table 3. Moisture content (%) and drug homogeneity of diclofenac sodium patches at day 0 (n = 3).

Formulation	Moisture content (%)	Drug homogeneity (%)
EC/PVP-6/4	12.81 ± 0.65	100.22 ± 0.61
EC/PVP-7/3	10.95 ± 0.11	98.56 ± 0.83

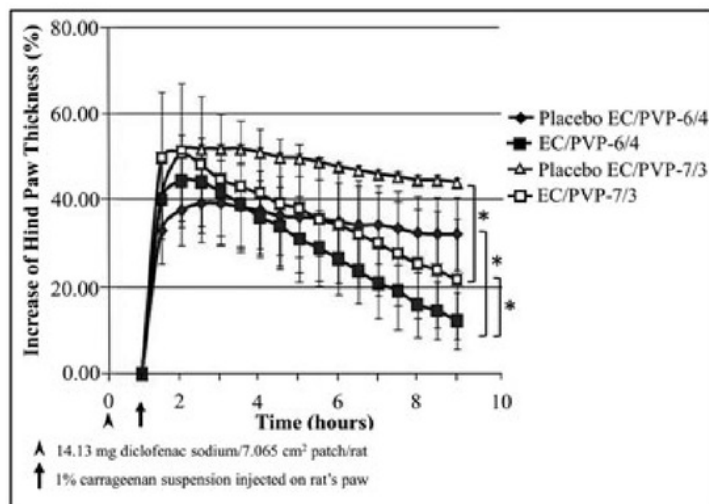


Figure 8 The anti-inflammatory effect of diclofenac sodium-loaded patch on the carrageenan-induced rat paw oedema (n = 4). Each value represents mean  $\pm$  S.D. (n = 4). \* $P < 0.05$ .

Moreover, drug homogeneities of the two patch formulations were  $98.56 \pm 0.83$  and  $100.22 \pm 0.61\%$ ; these results show that both formulations produced homogeneous diclofenac sodium patches and meet product homogeneity requirements with percent of variation coefficient less than 2% (Departemen Kesehatan 2014).

In the in vivo study, there were significant differences on oedema reduction between diclofenac sodium-containing patch applications and placebo patches. Moreover, a significant higher increase in the anti-inflammatory effects was observed in the EC/PVP-6/4 treatment group than that of EC/PVP-7/3 (Fig. 3). It is possibly due to the large pores present in EC/PVP-6/4 patch enable drug to be dissolved, released, and readily penetrate into the skin, thus causing reduction of the inflammation. On the other hand, the tightened patch pore structure of EC/PVP-7/3 limits this process producing weaker anti-inflammatory effects than that of EC/PVP-6/4, although the concentration of diclofenac sodium released from this patch formulation was still able to cure the inflammation. In addition, according to the calculation of area under curve (AUC) of swelling thickness of rat's hind paw, it can be seen that administration of EC/PVP-6/4 patch into abdominal skin of rats produced the largest decrease on the paw oedema as shown in Fig. 4. Beside the pores, the use of menthol as penetration enhancer also plays important roles in enhancing anti-inflammatory effects of diclofenac sodium patch. It has been known that menthol affects the integrity of stratum cor-neum layers, thus improving the penetration of diclofenac sodium.

After storage at room temperature, the stability was evaluated at day 7, 21, 56 and 84. There were no changes observed in the organoleptic properties between patches determined at observation day and those of day 0 (Table 2). The consistency, physical appearances and odour of EC/PVP-6/4 and EC/PVP-7/3 patches were similar. Moreover, the moisture contents of patches, either EC/PVP-6/4 or EC/PVP-7/3, during observation periods had no significant differences from that of the day 0, as shown in Fig. 5. The moisture contents were about 11% and 13% for EC/PVP-6/4 and EC/PVP-7/3, respectively.

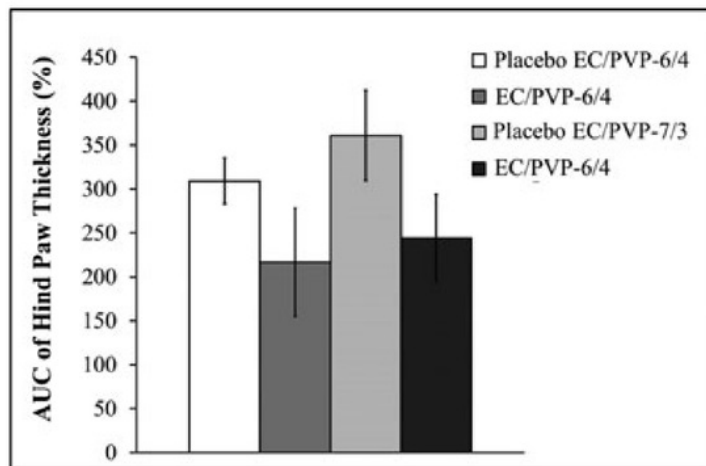


Figure 4. The areas under curve (AUC) of hind paw thickness of carrageenan suspension-induced rat oedema after topical administration of the placebo and diclofenac sodium-loaded patches onto abdominal skin (n = 4).

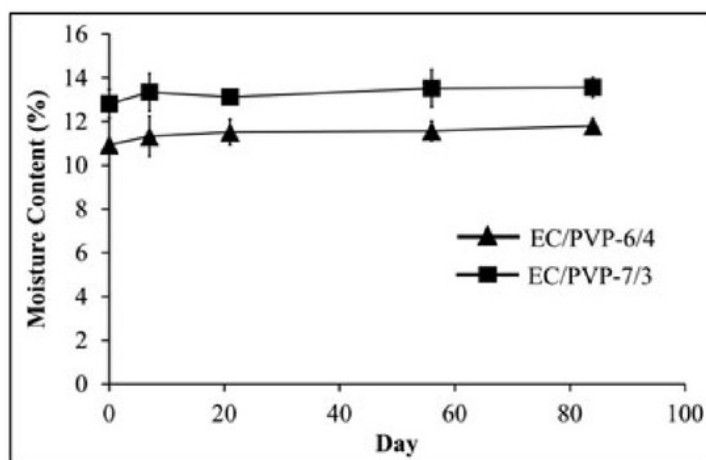
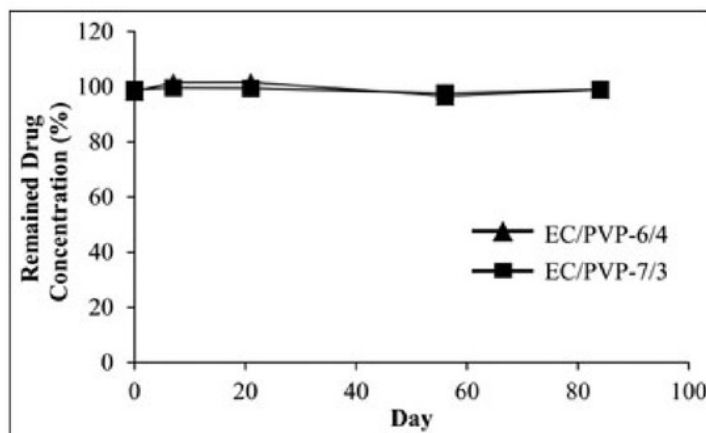


Figure 5. The stability evaluation for moisture content (%) of diclofenac sodium-loaded patches i.e. EC/PVP-6/4 and EC/PVP-7/3 stored at room temperature (25°C) for 84 days (n = 3).





**Figure 6. The concentration of diclofenac sodium loaded in EC/PVP-6/4 and EC/PVP-7/3 patches during the storage at room temperature (25°C, n = 3).**

In addition, it can be seen that the concentration of diclofenac sodium in the patches were stable until 84 days stored at room temperature, which were still within the range of 95–105% (Figure 6). This result suggests that the use of different ratio of EC N-20 and PVP K-30 in patch formulation have no different effects on chemical stability of the drug and both of them could maintain the stability of diclofenac sodium loaded in the patches.

The use of EC N-20 and PVP K-30 as polymeric matrix with menthol addition in patch could improve transdermal delivery of diclofenac sodium. It produced transdermal patch with good organoleptic properties, physically and chemically stable during storage at room temperature, and importantly, improved anti-inflammatory effects of diclofenac sodium on rat's paw edema by topical administration. Mostly, drug penetration into the skin is very limited, thus being the great problem for achieving good drug therapy. It is important to design a carrier for controlling drug release and enhancing skin drug penetration in an appropriate manner for achieving high drug efficacy. However, further investigation is still required to evaluate physicochemical interaction of EC N-20 and PVP K-30 for enhancing the therapeutic outcomes of patch loading diclofenac sodium.

#### 4 CONCLUSIONS

In this study, to deliver diclofenac sodium for anti-inflammation therapy, we prepared patches using combination of EC N-20 and PVP K-30 as polymeric matrix and evaluated their anti-inflammatory effects using rat paw oedema model. High reduction on paw swelling was achieved in EC/PVP-6/4 patch that was prepared with the high amount of PVP K-30. This finding suggested that EC N-20 and PVP K-30 at weight ratio of 6:4, respectively, can act as an excellent polymeric matrix for transdermal patch.

#### ACKNOWLEDGEMENTS

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