CHAPTER IV
DEVELOPMENT OF NATURAL RUBBER MATRIX USING IN ELECTRICAL STIMULI TRANSDERMAL DRUG DELIVERY APPLICATION

4.1 Abstract

Transdermal patch was developed to be used in a transdermal drug delivery system under applied electrical potential. Double centrifuge natural rubber latex (DCNR) was utilized to fabricate the DCNR films and blended with plasticizers to improve the permeation of indomethacin (IN) as an anionic model drug. DCNR film was prepared by the UV-curing method for crosslinking the natural rubber. The protein in DCNR was removed p by using the saponification method to reduce the skin allergic effect. The amount of IN permeation was studied under the effects of the type of plasticizers namely ethylene glycol (EG), propylene glycol (PG), and glycerol (GLY), the amounts of plasticizer, and the electrical potentials from 0-9 V. The IN permeation was studied using a pig skin as the membrane placed on the Modified-Franz diffusion cell. The efficiency of the plasticizers on the amount of IN permeation was ranked as follows: EG>PG>GLY. The amount of IN permeation increased with increasing amount of plasticizer. Moreover, the amount of IN permeation under applying electrical potential was enhanced because of the electro-repulsive force between the negatively charged drug molecule and the negatively charged electrode in addition to the pure Fickian diffusion.

Keywords: Drug delivery, Natural rubber, Ionic drug, Electrical potential, Plasticizer

4.2 Introduction

Transdermal drug delivery system (TDDS) is an important method to transport the drug into the body for the direct treatment at the site which avoids the first pass metabolism. TDDS consists of an adhesive patch which contains the specific dose of drug inside. There are many types of the matrix for drug release patch such as polymer hydrogel (Chansai *et al.*, 2009, Paradee *et al.*, 2012),

polyurethane (Sintov *et al.*, 1988, Sharma *et al.*, 1988), poly(vinyl alcohol) (Juntanon *et al.*, 2008), polyacrylamide (Niamlang and Sirivat, 2009), and especially elastomeric materials such as polydimethylsiloxane elastomer (Carelli *et al.*, 1989), silicone rubber (Soulas *et al.*, 2011, Golomb *et al.*, 1990), and natural rubber latex (NR).

NR obtained from *Hevea brasiliensis* is the elastomeric material that is widely used as a raw material to produce many types of product such as condoms, gloves, tubes, and other medical devices. NR can be used in many applications including the matrix in drug delivery application because it is low cost, biocompatible material, high flexibility, and available material etc. Natural rubber membranes have been used in the controlled releases of urea by graft with modified starch (Riyajan *et al.*, 2012), nicotine (Suksaeree *et al.*, 2012, Pichayakorn *et al.*, 2012), metronidazole (Herculano *et al.*, 2011), and protein (Herculano *et al.*, 2009). However, using NR as the matrix of topical patch must overcome the drug permeation into skin due to the macromolecule size and the drug hydrophilicity. The amount of drug release is improved by blending the natural rubber matrix with plasticizers or polymers into the natural rubber matrix (Pichayakorn *et al.*, 2012). The suitable type and concentration of plasticizer affect mechanical properties and permeability of drugs (Alexander *et al.*, 2012). Many types of plasticizers were used to improve the ability of drug permeation from matrices such as propylene glycol (Patel *et al.*, 2009), myristic acid (Gondaliya and Pundarikakshudu, 2003), and dibutylphthalate (Suksaeree *et al.*, 2012). However, protein in natural rubber molecule is the main cause of allergic effect to human skin (Sussman *et al.*, 2002) when using the natural rubber products such as rubber dental prosthesis (Warshaw, 1998), latex gloves (Cormio *et al.*, 1993), and heal care products (Abraham *et al.*, 2002). In recent years, many of researchers solved the allergic problem by removing protein from the natural rubber. There are many methods to deal with protein such as coating with polymer (Kanjanathaworn *et al.*, 2013), treating with urea (Kawahara *et al.*, 2004), and incubation with enzyme (Kawahara *et al.*, 2004).

Electrical potential (EP) is a physical method to improve and control drug release through the layers of skin (Kotnik *et al.*, 2012, Haberl *et al.*, 2013). An ionic drug was used in the drug delivery system by using EP to control the characteristic,

rate, and kinetic of drug release (Paradee *et al.*, 2012). Juntanon and co-worker showed the increasing amount of sulfosalicylic acid released from poly(vinyl alcohol) hydrogel with increasing the electrical potential 0 to 5 V (Juntanon *et al.*, 2008). EP affected the amount of drug release due to the electro-repulsive force between the drug charge and the electrode (Niamlang and Sirivat, 2009).

In this work, the effects of plasticizer type, plasticizer, and electrical potential on the topical drug permeation through pig skin from double centrifuge natural rubber (DCNR) matrix were investigated. The deproteinized natural rubber was prepared from DCNR and then the nitrogen content was evaluated. Comparison of IN permeation from DCNR and DPNR was studied. Ethylene glycol (EG), propylene glycol (PG), and glycerol (GLY) were used as the plasticizers blended with the natural rubber due to their compatibility and non-toxicity property (Suyatma *et al.*, 2005). Electrical potentials were applied to the topical patchs from 0-9 V. The surface morphology of IN-loaded natural rubber films before and after permeation through the pig skin was investigated by SEM.

4.3 Experimental

4.3.1 Materials

Double-centrifuge natural rubber latex (DCNR1; Thai Easter Rubber Co., Ltd) was used as the matrix of transdermal patch with trimethylol-propane tris(3-mercaptopropionate) (TMPTMP; Aldrich), and 2-Methyl-4'-(methylthio)-2-morpholino propiophenone (MMMP; Aldrich) as the crosslinking agent and photoinitiator, respectively. Indomethacin (IN; Aldrich) was used as an anionic model drug. Ethylene glycol (EG; POCH), propylene glycol (PG; MERCK), and glycerol (GLY; CARLO ERBA) were used as the plasticizers. Sodium chloride (NaCl; CARLO ERBA), sodium phosphate dibasic (Na_2HPO_4, biology glade; Calbiochem), potassium chloride (KCl, biology glade; Calbiochem), and potassium phosphate monobasic (KH_2PO_4, biology glade; Calbiochem) were used to prepare a phosphate-buffer saline solution at the pH of 7.4. Methanol (MeOH, AR glade; Lobachemie), hexane (analysis glade; ACl Labscan), toluene (AR; QRëC), dimethyl

sufoxide (DMSO, synthesis glade; MERCK), and distilled water were used as solvents.

4.3.2 Preparation of Deproteinized Natural Rubber Latex

Deproteinized natural rubber (DPNR1) was prepared for decreasing the amount of protein in the rubber latex via a saponification method. A solution was prepared by mixing sodium hydroxide (NaOH) (1.5 g per 100 mL DCNR) and sodium dodecyl sulfate (SDS) (2 g per 100 mL DCNR1). The solution was continuously stirred for 3 h at 60 °C. Then, the distilled water was added into the solution at volume ratio of DCNR1: distilled water of 1:5 and stirred for 30 min at room temperature. This solution was centrifuged at 8000 rpm for 60 min to separate rubber layer content and water layer content from each other.

4.3.3 Preparation of Indomethacin Loaded Natural Rubber Film

Trimethylol-propane tris(3-mercaptopropionate) (TMPTMP) (0.5 %wt of rubber) as the crosslinking agent and 2-Methyl-4'-(methylthio)-2-morpholino propiophenone (MMMP) (1 %wt of rubber) as the photoinitiator were dissolved in plasticizers namely propylene glycol (PG), glycerol (GLY), or ethylene glycol (EG) (10 mL) at 70 °C for an hour. Indomethacin (IN) (100 mg) was added in the solution and then stirred to obtain a yellow homogenous solution. After that, the yellow homogeneous solution was poured into 5 mL of DCNR1 or DPNR1 and continuously stirred at room temperature for 5 min. In case of DPNR preparation, polysorbate (TWEEN®20) (9 %v/v of DPNR1, 500 mg per 5 mL DPNR1) were added in the solution and then stirred. The solution was casted in a petri dish and inserted in a UV curing machine for curing under UV radiation for 10 min. The ingredients for preparing rubber patches are shown in Table 4.1.

4.3.4 Characterizations

Attenuated total reflection Fourier transform infrared spectroscopy (ATR-FTIR; Thermo Nicolet, Nexus 670) was used to identify the interaction between the rubber matrix, plasticizers, and IN. The samples were scanned at 64 scans with wave number range of 550-4000 cm^{-1}.

Thermal stability of rubber films was investigated by using a thermogravimetry analyzer (TG-DTA; Prekin Elmer, Pyris Diamond) to study the decomposition temperature. The rubber films were heated from 30 to 550 °C under nitrogen atmosphere at the heating rate of 10 °C/min.

Surface morphology, before and after permeation test, was investigated by a scanning electron microscope (SEM) at the magnifications of 50-1200 and acceleration voltage of 150 kV.

The nitrogen content was analyzed by a CHN analyzer (TruSpec Micro model of LECO Company). The calibration curve was created by using ethylenediaminetetraacetic acid (EDTA) which had a certain amount of nitrogen. The samples were wrapped with a foil cup before inserting into the analyzer. The samples were completely oxidized under oxygen atmosphere at 950 °C.

4.3.5 Preparation of Phosphate Buffered Saline Solution (PBS buffer)

NaCl (0.14 M), Na_2PO_4 (10 mM), KCl (2.68 mM), and KH_2PO_4 (1.84 mM) were mixed together in distilled water (800 mL). After a complete dissolution, an aqueous HCl (0.1 M) was added into the solution until the pH reached 7.4 and then distilled water was added until the volume was 1000 mL.

4.3.6 Preparation of Pig Skin Membrane

A pig skin (abdominal part) was used for the membrane permeation study. Hair on the pig skin surface and subcutaneous fat were removed by sharp razor blades until the thickness of the pig skin was about 0.2 cm. The prepared pig skin was cut into a circular shape with a diameter 2 cm, immersed in PBS buffer pH 7.4, and then kept at room temperature for 24 h before the permeation test.

4.3.7 Crosslinking Density of Natural Rubber film

The crosslinking density NR films were immediately studied after the crosslinking process following the ASTM D6814-02 procedure. The crosslinked DCNR film was cut to 1 cm^2 and weighed in air and MeOH (non-solvent). The square film was immersed in toluene for 5 days to obtain the equilibrium swelling state. Eq. (4.1) was used to calculate the crosslink density (Flory-Rehner equation);

$$\nu_e = \frac{-[\ln(1-V_r)+V_r+\chi_1 V_r^2]}{[V_1(V_r^{1/3}-V_r)/2]} \quad (4.1)$$

where ν_e is the number of chains in a real network per unit volume, V_1 is the molar volume of solvent (106.29 mL/mol), V_r is the polymer volume fraction in swollen state, and χ is the Flory interaction parameter of natural rubber (0.391). V_r can be calculated following Eq. (4.2):

$$V_r = \frac{\text{Weight of dry rubber / Density of dry rubber}}{\left(\frac{\text{Weight of dry rubber}}{\text{Density of dry rubber}}\right) + \left(\frac{\text{Weight of solvent absorbed by sample}}{\text{Density of solvent}}\right)} \quad (4.2)$$

The density of the dry rubber can be calculated using Eq. (4.3):

$$\text{Density at } 23 \pm 2\ ^\circ\text{C (g/mL)} = 0.7913 \times \frac{A}{A-B} \quad (4.3)$$

where A is the weight of specimen measured in air (g), B is the weight of specimen measured in MeOH (g), 0.7913 is the density of MeOH at 23 ± 2 °C (g/mL).

4.3.8 Drug Permeation

4.3.8.1 Actual Drug Content

IN-loaded NR with various amounts of IN and plasticizers with the areas of about 3.14 cm^2 and 12.56 cm^2 were immersed in 100 mL of hexane which was continuously stirred. For each sample, 0.3 mL of solution was collected. The amount of drug content was determined by using the UV-visible spectrophotometer (TECAN, InfiniteM200) at 324 nm of calibration curve.

4.3.8.2 Drug Permeation Study

The IN permeation from the rubber films was determined for the *in vitro* drug permeation study by using a Modified-Franz diffusion cell which consists of two part (donor compartment and receptor compartment). PBS buffer solution was added into the receptor compartment which was constantly stirred by a magnetic bar and temperature was controlled at 37 °C by water in a jacket around

this compartment. A prepared pig skin was placed on the receptor compartment followed by the rubber film. The effect of three plasticizers (EG, PG, and GLY), amount of plasticizers, and electrical potential (connected with DC-power supply, KETHLEY 1100 V Source Meter) at 0-9 V were studied for 48 h. For the electrical potentials of 0,3,5,7, and 9 the corresponding electrical fields are 0, 0.67, 1.11, 1.56, and 2 V/mm (electrical potential/ (sample thickness+ pig skin thickness)). For the effect of electrical potential to IN permeation, the cathode, negatively charged electrode, was placed on the rubber film and the receptor compartment, respectively. The PBS buffer solution was withdrawn from the receptor compartment at the amount of 3 x 0.1 mL several times during experimental period and then 0.3 mL of PBS buffer was into this solution. The amount of IN permeation was determined by the UV-visible spectrophotometer.

4.4 Results and discussion

4.4.1 DCNR Characterization

Crosslinking of the DCNR1 matrices was carried out to prepare IN loaded DCNR1 for studying the amount of IN permeation by using the UV radiation method. First, radicals were generated from MMMP and then the sulfide radicals were induced from TMPTMP. The sulfide radicals reacted with double bond in main chain of the natural rubber molecule (cis1 4-polyisoprene) (Choi *et al.*, 2005, Thorngkham *et al.*, 2015). The natural rubber was successfully cured via the UV-curing method which was confirmed by the crosslinking density data as shown in Table 4.2. The crosslinking density of the natural rubber with added plasticizers was increased because the plasticizers enhanced the movement of rubber molecule, thus, the crosslinking agent was more possibility to react with the rubber chain (Yasin *et al.*, 2005). Moreover, different types of plasticizer affect to the amount of crosslinking density due to the molecular size (Gioia and Guilbert, 1999), the number, and position of hydroxyl group (Spencer *et al.*, 1988). Crosslinking density of DPNR1 was higher than DCNR1 because the protein inside natural rubber molecule was removed, thus, the crosslinking agent was even more efficient to react with the rubber molecule.

The FTIR spectra of IN, DCNR1 and DPNR1 patches with and without adding the drug are shown in Figure 4.1. The peaks of the aromatic ring are at 754-840 and 1011-1014 cm^{-1}. The peaks of the C-H stretching, C-H vibration and C_{sp3}-H vibration are at 926-929 cm^{-1}, 1401 cm^{-1}, and 2919-2926 cm^{-1}, respectively. The other peaks are at 1087-1089 cm^{-1} (O-H stretching), 1222-1224 cm^{-1} (C-CO-O vibration), 1310 cm^{-1} (C-O vibration), 1375 cm^{-1} (C-N vibration), 1714 cm^{-1} (C=O vibration), 1655 cm^{-1} (C=C stretching), and 3356 cm^{-1} (O-H vibration) (Herculano *et al.*, 2009, Pichayakorn *et al.*, 2012, Taoudi *et al.*, 2000, Dupeyron *et al.*, 2013). Moreover, the FT-IR spectra of DPNR1 with and without adding drug show the decreases of the N-H vibration peak at 1650-1658 cm^{-1} relative to the DCNR1; the peak can be assigned to the α-helix of protein (Kong and Yu, 2007). In addition, the disappearance of the C=O stretching peak for DPNR1 at 1714-1737 cm^{-1}, relative to pure DCNR1, can be referred to the removal of phospholipid in rubber (Sansatsadeekul*et al.*, 2011 and Nawamawat *et al.*, 2010). The model drug IN was successfully loaded into the natural rubber film. The peaks at 1222-1224 cm^{-1} and 1308-1310 cm^{-1} can be assigned to the C-CO-O and C-O vibrations of the IN molecule. Moreover, the peak at 1714 cm^{-1} which can be referred to the C=O group appeared when IN was added into rubber matrix. Hence, there was an interaction between IN and the matrix occurred.

Protein in DCNR1 was completely removed by using the saponification method as verified by the nitrogen contents of DCNR1 and DPNR1 in Table 4.2 and confirm by FT-IR result. Amount of nitrogen in natural rubber is generally related to the amount of protein in the natural rubber (Nawamawat *et al.*, 2010). From Table 4.2, the nitrogen content of DPNR1 decreases after removing protein from DCNR1. Moreover, the nitrogen content increases with an addition IN because the IN structure consists of nitrogen atoms.

The thermal stability of IN and IN loaded natural rubber was determined by using the thermogravimetric analyzer. The thermogram of IN showed one degradation step at 250-350 °C (Aw *et al.*, 2012) and the remaining char. The 10EG_DCNR1 and 300IN-10EG_DPNR thermograms showed two degradation steps at 40-150 °C and 350-450 °C. In first step, the degradation corresponds to the evaporation of moisture. The second degradation step can be referred to the

degradation of natural rubber backbone and the pyrolysis of EG (Lee *et al.*, 2008). The TGA result did not confirm the existence of IN inside the rubber patch because there were few drug inside the rubber patch. However, the existence of IN inside the rubber patch was confirmed by the nitrogen content and the FT-IR result.

4.4.2 Actual amount of drug

The actual amounts of IN in IN-loaded_NR1 are shown in Table 4.3. The actual amounts of IN in the three plasticizers can be ranked as follow: PG>EG>GLY. Different types of plasticizer have different hydrophilicity values. The plasticizer which has higher hydrophilicity value is referred to the lower solubility system between rubber and plasticizer. Hence, the hydrophillicity produced the differences in the actual amount of IN that can be loaded inside the rubber matrix and subsequently the amount of drug permeation. The amounts of IN in 200IN-10EG_DCNR1 matrix and 200IN-10EG_DPNR1 matrix are 4.2 and 3.5 mg, respectively (sample size at 3.14 cm^2). Moreover, by increasing the 200IN-10EG_DPNR1 size from 3.14 to 12.56 cm^2, the initial amount of IN in the sample increased about 4 times from 3.5 to 14.1 mg.

4.4.3 Release kinetic of IN-loaded DCNR film

To study the mechanism of IN permeation from IN-loaded_DCNR1 film with various conditions, the IN permeation data were analyzed by using the Korsmeyer-Peppas model as in Eq. (4.4).

$$\frac{M_t}{M_\infty} = kt^n \qquad (4.4)$$

where M_t is the amount of IN permeation form IN-loaded_DCNR1 film at time (mg). M_∞ is the total amount of IN permeation (mg). k value is the kinetic constant (h^{-n}), t is the permeation time (h), and n is the diffusion scaling exponent.

The drug permeation mechanisms can be identified by the scaling exponent (n) which was obtained from the slope between $\ln(M_t/ M_\infty)$ versus ln(time) as shown in Figure 4.2. The n value can be identified into three regimes namely the Quasi

Fickian diffusion, the anomalous transport, and the Super Case II transport. At the n value less than 0.5, the drug permeation mechanism is controlled by the Quasi Fickian diffusion (Mahmoodi *et al.*, 2010, Pasparakis *et al.*, 2006, Pradhan *et al.*, 2008). At the n value between 0.5-1, the drug permeation mechanism is controlled by the anomalous transport caused by the pure diffusion and matrix swelling including the complex flows (Bisquert and Compte, 2001, Lowman and Peppas, 2000). At the n value more than 1, the drug permeation mechanism was controlled by the Super Case II transport due to the relaxation and erosion mechanism of polymer matrix (Sriamornsak *et al.*, 2007).

The n values of IN permeation of IN-loaded_DCNR1 at various types of plasticizer (EG, PG, and GLY) and various amounts of plasticizers with and without applied electrical potential suggest one diffusion stage, as shown in Table 4.3. The n values of 100IN-10GLY_DCNR1, 100IN-10PG_DCNR1, 100IN-5EG_DCNR1, 100IN-10EG_DCNR1, and 100IN-15EG_DCNR1 are 0.66, 0.78, 0.60, 0.90, and 0.85, respectively. These n values are between 0.5-1 which can be referred to the anomalous transport due to pure diffusion and matrix swelling (Bisquert and Compte, 2001, Lowman and Peppas, 2000). The n values under applied electrical potential of 300IN-10EG_DCNR1 from 0-9 V are 1.42, 1.35, 1.27, 1.43, and 1.59, respectively. Hence, the n values are more than 1, thus, the IN permeation can be referred to the Super Case II transport caused by the erosion of rubber matrix. The surface morphologies are shown in Figures 4.3 which identify the roughness and pores on the rubber patches with and without drug due to the erosion of rubber matrix. The matrix erosion occurred without applied electrical potential more severe roughness and more pores appeared with increasing electrical potential. The roughness and pore were generated from the diffusion of plasticizer which leaked from the surface of rubber patch, consistent with a previous study (Pichayakorn *et al.*, 2012).

The amounts of IN permeation were force-fitted with the Higuchi's equation of the Fickian diffusion of drug (n = 0.5) (Higuchi, 1963, Serra *et al.*, 2006) using Eq. (4.5), (4.6), and (4.7).

$$\frac{M_t}{M_\infty} = kt^{1/2} \quad (4.5)$$

$$Q = \frac{M_t}{A} = 2C_0\left(\frac{Dt}{\pi}\right)^{1/2} \quad (4.6)$$

$$M_t = k_H M_\infty t^{1/2} = 2C_0 \left(\frac{D^{1/2}}{\pi^{1/2}}\right) A\, t^{1/2} \quad (4.7)$$

where M_t/M_∞ is the fractional drug release, k_H is the Higuchi kinetic constant (t^{-n}), t is releasing time (h), Q is the amount of drug release per unit area (g/cm^2), and D is the diffusion coefficient of drug (cm^2/s).

The Higuchi kinetic constant (k_H) are determined by the slope of M_t/M_∞ versus square root of time ($t^{1/2}$) as shown in Table 4.3. The k_H values of IN-loaded with various types and amounts of plasticizer in DCNR with and without electrical potential were then used to calculate the diffusion coefficient value (D) as in Eq. (4.7).

4.4.4 Effect of Type of Plasticizers

The amounts of IN permeation from the three types of plasticizer (PG, GLY, and EG) were identified as in the percentages of initial IN amounts in rubber matrix as shown in Table 4.3. 100IN-10EG_DCNR1 shows the highest amount of IN permeation, follow by 100IN-10PG_DCNR1 and 100IN-10GLY_DCNR1 at 20 (0.65 mg), 15 (0.52 mg), and 12% (0.31 mg), respectively. The time to obtain permeation equilibrium of 100IN-10PG_DCNR1, 100IN-10GLY_DCNR1, and 100IN-10EG_DCNR1 are 7.5, 6, and 6 h. respectively. The amount of IN permeation increases with adding the plasticizer because the plasticizer inside the matrix could reduce the intermolecular force between the polymer back-bone (Kumar and Gupta, 1998), increase the mobility of polymer chain (Meier *et al.*, 2004), and to induce pathway for drug transportation within the patch (Pichayakorn *et al.*, 2012). The driving force of IN permeation is through the drug concentration gradient between the drug concentration inside the rubber matrices and PBS buffer in the receptor compartment (Gondaliya and Pundarikakshudu, 2003). Hence, the

plasticizers acted as the drug carrier for enhancing transportation of IN through the pig skin membrane. The GLY showed the highest hydrophilicity followed by EG and PG (Wypych, 2011). The EG acting as the plasticizer provided the highest amount of drug permeation due to the higher hydrophilicity than PG. In contrast, GLY provided the lowest amount of drug permeation due to the lowest concentration gradient. The D values of IN permeation were calculated from Eq. (4.4) (Table 4.3). The D value from the 100IN-10EG_DCNR1 is the highest when compared with 100IN-10GLY_DCNR1 and 100IN-10PG_DCNR1. Hence, 100IN-10EG_DCNR1 was chosen to study the IN permeation under the effects of various amounts of plasticizer and electrical potential.

4.4.5 Effect of Amount of Plasticizer

Figure 4.4 shows the amounts of IN permeation from 100IN-5EG_DCNR1, 100IN-10EG_DCNR1, and 100IN-15EG_DCNR1 at 15% (0.49 mg), 20% (0.65 mg), and 23% (0.60 mg), respectively of the initial amounts of IN in the patches. The time to obtain permeation equilibrium of 100IN-5EG_DCNR1, 100IN-10EG_DCNR1, and 100IN-15EG_DCNR1 are 10, 6, and 7.5 h, respectively. The percentage of IN permeation increases with increasing amount of plasticizer. The amount of IN permeation of 100IN-10EG_DCNR1 is higher than 100IN-5EG_DCNR1 because the more pathways were generated with adding more plasticizer (Meier *et al.*, 2004, Pichayakorn *et al.*, 2012). In contrast, the amount of IN permeation of 100IN-15EG_DCNR1 is lower than 100IN-10EG_DCNR1 because the initial amount of IN content of 100IN-15EG_DCNR1 is lower than 100IN-10EG_DCNR1. This is due to the phase separation between the excessive plasticizer and the rubber matrix. Hence, the concentration gradient of 100IN-15EG_DCNR1 decreases due to the decrease of IN inside the rubber matrix as shown in Table 4.3. The D values under the effect of amount of plasticizer are also shown in Table 4.3. The D value of 100IN-10EG_DCNR1 shows the highest because of the higher initial amount of IN when comparing with 100-15EG_DCNR1. Moreover, the D value of 100IN-10EG_DCNR1 is greater than 100IN-5EG_DCNR1 because the higher amount of EG in the rubber matrix.

4.4.6 Effect of Electrical Potential

The electrical potential was varied from 0 to 9 V by using a cathode as a negatively charged electrode placed on the natural rubber patch. The amounts of IN permeation of 300IN-10EG_DCNR1 under applied electrical potential are shown in Table 4.3. The amounts of IN permeation at 0, 3, 5, 7, and 9 V are 28% (2.03 mg), 29% (2.10 mg), 36% (2.59 mg), 43% (3.11 mg), and 55% (3.97 mg), respectively (Figure 4.5). The times to obtain permeation equilibrium under applied electrical potential conditions at 0, 3, 5, 7, and 9 V are 2.8, 2.8, 2.4, 2.4, and 2.2 h, respectively. The amount of IN permeation increases with increasing electrical potential. The main driving force of the drug molecule from the matrix was generated from the electro-repulsive force between negatively charged drug molecule and the negatively charged electrode, the so-called "electro-repulsive force" (Thorngkham *et al.*, 2015), in addition to the pure Fickian diffusion. Moreover, applying electrical potential also generated the aqueous pathway within the pig's skin membrane which improved the transportation of drug through membrane (Weaver *et al.*, 1999). Furthermore, D values of IN permeation increases with increasing electrical potential due to the electro-repulsive driving force.

Throngkam and co-worker (2015) studied the effect of electrical potentials control IN permeation from DCNR and PCz/DCNR matrix. The n of samples under applied electrical potentials at 0-9 V were between 1.22-1.77 which can be referred to the Super Case II transport (Throngkam *et al.*, 2015). Comparison of IN permeable mechanism in this work, the IN permeation from 300IN-10EG_DCNR1 under applied electrical potentials at 0-9 V shows the same permeable mechanism (Super Case II) in all cases as the scaling exponent n in the present work is higher than 1. The D values of 300IN-10EG_DCNR are higher than those of DCNR or PCz/DCNR due to the improvement of rubber matrix by adding the plasticizer.

4.4.7 Effect of Types of Rubber Matrix

The protein inside natural rubber molecule causes the human skin allergic effect (Yip *et al.*, 2000). In the present work, the protein was successfully removed by using the saponification method which was confirmed by the decrease in nitrogen content of DPNR1 after the saponification of DCNR1. The amount of IN

permeation of 200IN-10EG_DCNR1 and 200IN-10EG_DPNR1 are 47% (1.98 mg) and 77% (2.69 mg), respectively as shown in Figure 4.6. The times to obtain permeation equilibrium of 200IN-10EG_DCNR1 and 200IN-10EG_DPNR1 are 6 and 8.5 h, respectively. The amount of IN permeation of 200IN-10EG_DPNR1 was higher than 200IN-10EG_DCNR1 because the H-bonding between the drug, protein and phospholipid in the natural rubber DPNR1 patch was lower in strength (Nowak et al., 1992) as confirmed by the FT-IR result (Figure 4.1). Moreover, the TWEEN®20 inside 200IN-10EG_DPNR1 acted as the plasticizer to induce drug pathway resulting in improved IN permeation (Cappel and Keruter, 1991). In this work, the amount of TWEEN20 (9% v/v or 10.6% w/w) was limited to a minimum in the rubber patch preparation to avoid the skin irradiation problem. In the previous work, with increasing amount of nonionic surfactant (TWEEN80) above 1% w/w, the interaction between micelles and drug occurred. Hence, the higher drug solubility by surfactant micelles above a certain concentration decreased the drug penetration efficiency (Shokri *et al.*, 2001). Furthermore, the permeation behaviour was further determined by the n value. The n values of 200IN-10EG_DCNR1 (1.32) and 200IN-10EG_DPNR1 (1.01) correspond to the Super Case II and anomalous transport behaviour, respectively. Moreover, the D values of 200IN-10EG_DCNR1 and 200IN-10EG_DPNR1 are 3.13×10^{-6} and 9.43×10^{-6} $cm^2.s^{-1}$, respectively as shown in Table 4.3. A factor of 3 increase in the D value is obtained after the saponification.

Suksaeree and co-worker studied the D value of nicotine. The transdermal patch was prepared by blending DPNR with hydroxypropylmethyl cellulose (HPMC) and dibutylphthalate (DBP) to improve the permeation efficiency. The D values of nicotine permeation from DPNR patch with various types of backing layer were 3.5×10^{-3}-9.1×10^{-3} $cm^2.h^{-1}$ (9.7×10^{-7}-2.5×10^{-6} $cm^2.s^{-1}$) (Suksaeree *et al.*, 2012). From the result in this work, the D value of IN from 200IN-10EG_DPNR1 is higher than nicotine patch because 200IN-10EG_DPNR1 was added with a higher amount of plasticizer (10 mL of EG) relative to the nicotine patch (10 phr of DBP). Moreover, the presence of surfactant (TWEEN®20) also improved the IN permeation. Hence, the diffusion efficiency from DPNR matrix is shown here by adding the plasticizer and surfactant into the rubber matrix.

4.4.8 Effect of Electrical Potential for DPNR Matrix

The electrical potentials were applied to 200IN-10EG_DPNR1 (sample size 12.56 cm^2) to study the amount of IN permeation. The amounts of IN permeation of 200IN-10EG_DPNR are shown in Figure 4.7. Under applied electrical potentials, the amounts of IN permeation are 37% (5.22 mg), 50% (7.07 mg), 59% (8.38 mg), 76% (10.73 mg), and 86% (12.19 mg) at the electrical potential of 0, 3, 5, 7, and 9 V, respectively. The increase in the sample size from 3.14 to 12.56 cm^2 affects the amount of IN permeation (at E = 9 V) by about 4 times (2.69 to 12.19 mg). The electro-repulsive force enhances the efficiency of IN permeation under applied electrical potential. Furthermore, the permeation of 200IN-10EG_DPNR1 at 0-9 V shows the n values between 0.54-0.70. Hence, the permeation behaviour of this rubber matrix corresponds to the anomalous transport of the pure Fickian diffusion and the matrix swelling. The surface morphology are shown in Figure 4.3e-4.3h. Moreover, the D value of 200IN-10EG_DPNR1 increases with increasing electrical potential.

4.5 Conclusions

The crosslinked IN-loaded plasticizers_DCNR1 were successfully prepared by the UV irradiation method. The deproteinized process successfully removed protein from DCNR1 which was confirmed by the decrease in the nitrogen content from 0.20 to 0.01 %wt. Using EG as the plasticizer showed the highest amount of IN permeation when compared with PG and GLY system. Hence, EG is the most suitable candidate of plasticizer for studying the IN permeation. Amount of IN permeation from IN-loaded EG_DCNR1 increased with increasing the amount of EG up to 10 mL but decreased with increasing the amount of EG up to 15 mL, using initially 5 mL DCNR. Hence, the optimum volume of EG was 10 mL using initially 5 mL DCNR. The IN permeation of 300IN-10EG_DCNR1 increased with increasing electrical potential. Moreover, the amount of IN permeation was improved due to TWEEN®20 inside DPNR matrix and the increase in the sample size. The IN permeation mechanisms were identified by the scaling exponent n which changed from the anomalous transport to Super Case II transport by applying electrical

potential in the case of DCNR matrix. However, the IN permeation mechanisms of DPNR matrix under applied electrical potentials showed only the anomalous transport behavior. The time to equilibrium of IN permeation in all cases was in the range of 2.2-10 h. The diffusion coefficients of IN increased with applying electrical potential due to the electro-repulsive force between the negatively charged drug and the negatively charged electrode.

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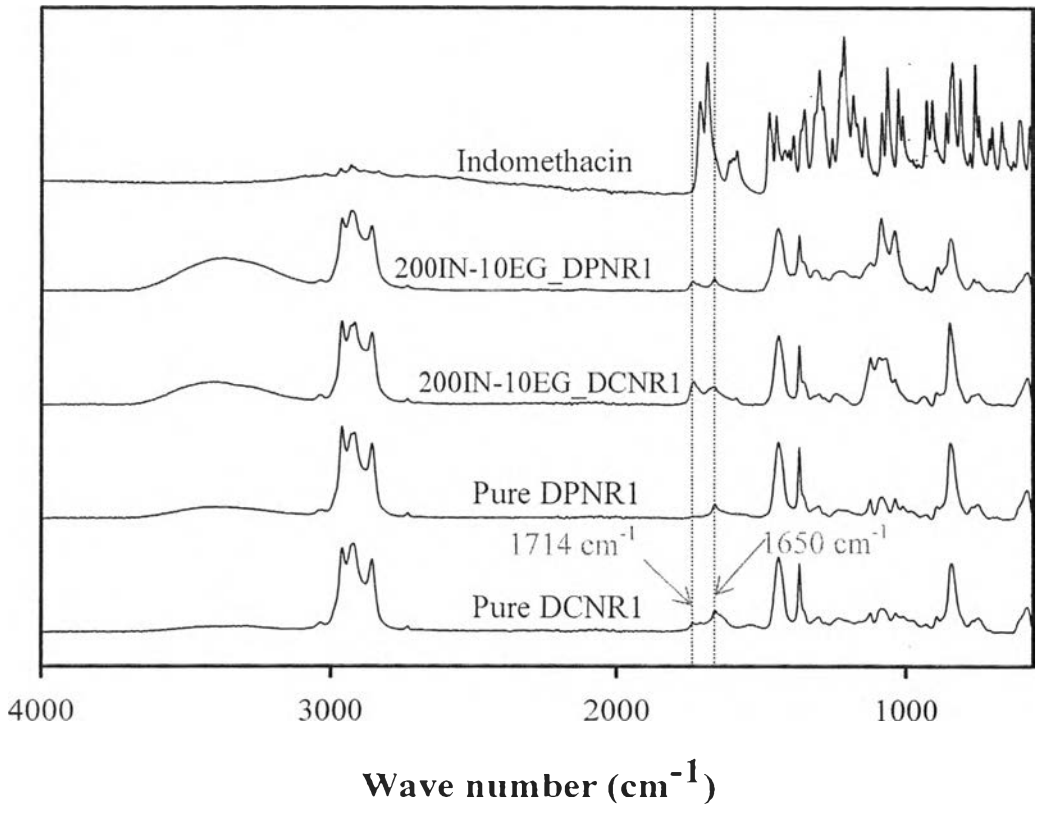

Figure 4.1 FT-IR spectra of DCNR1 and DPNR1 patches.

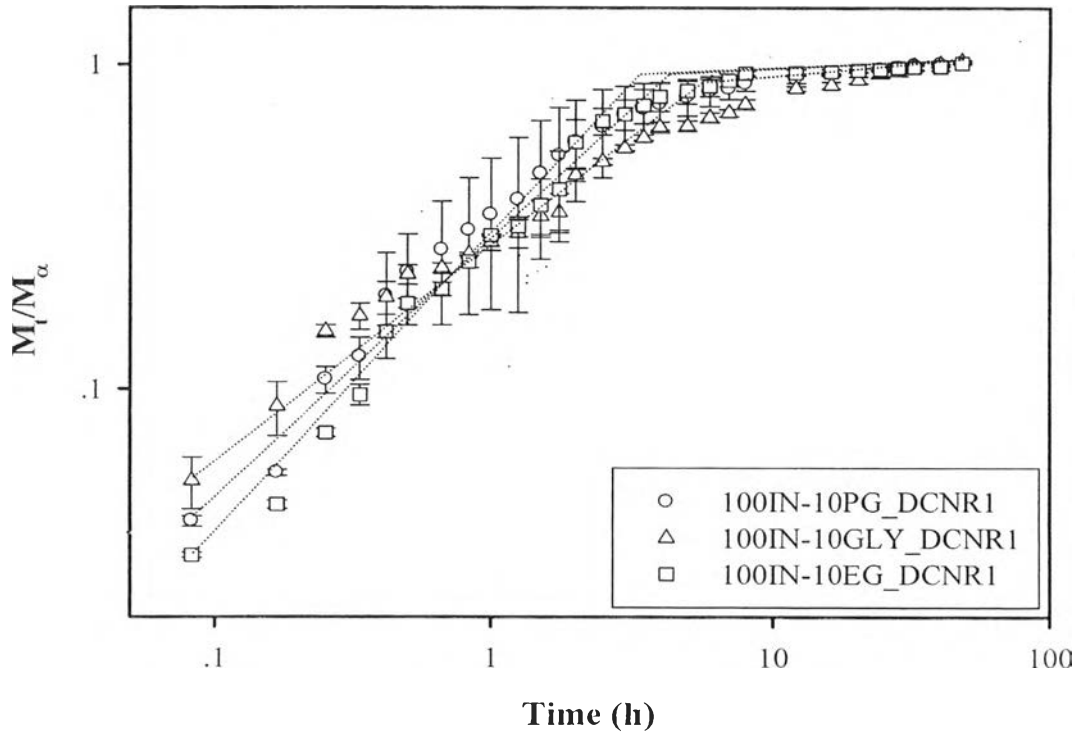

Figure 4.2 Plots M_t/M_∞ versus time of various plasticizers (sample area 3.14 cm^2) under an absence of electrical potential, pH 7.4, 37 °C.

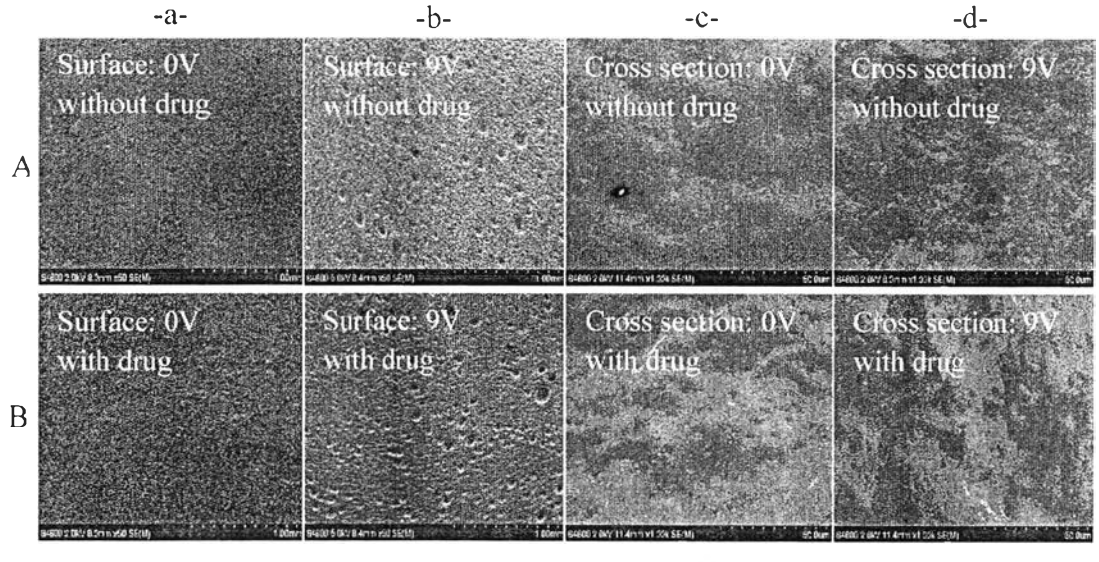

Figure 4.3 SEM micrograph of: (A) 10EG_DCNR1 and (B) 300IN-10EG_DCNR1 (a and b: surface of rubber patch after permeation test without and with apply electrical potential (9 V), respectively, c and d: cross section of rubber patch after permeation test without and with apply electrical potential (9 V), respectively).

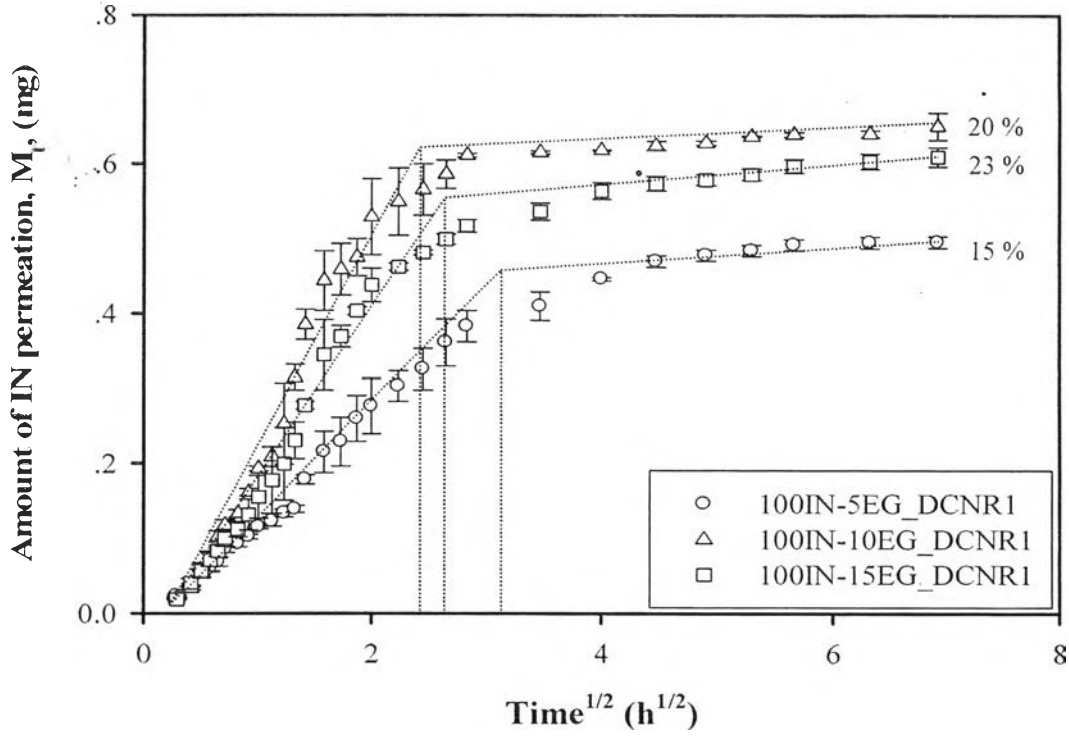

Figure 4.4 Amounts of IN permeated from IN loaded EG_DCNR1 (sample area 3.14 cm^2) at various amounts of EG versus time $t^{1/2}$ under an absence of electrical potential, pH 7.4, 37 °C .

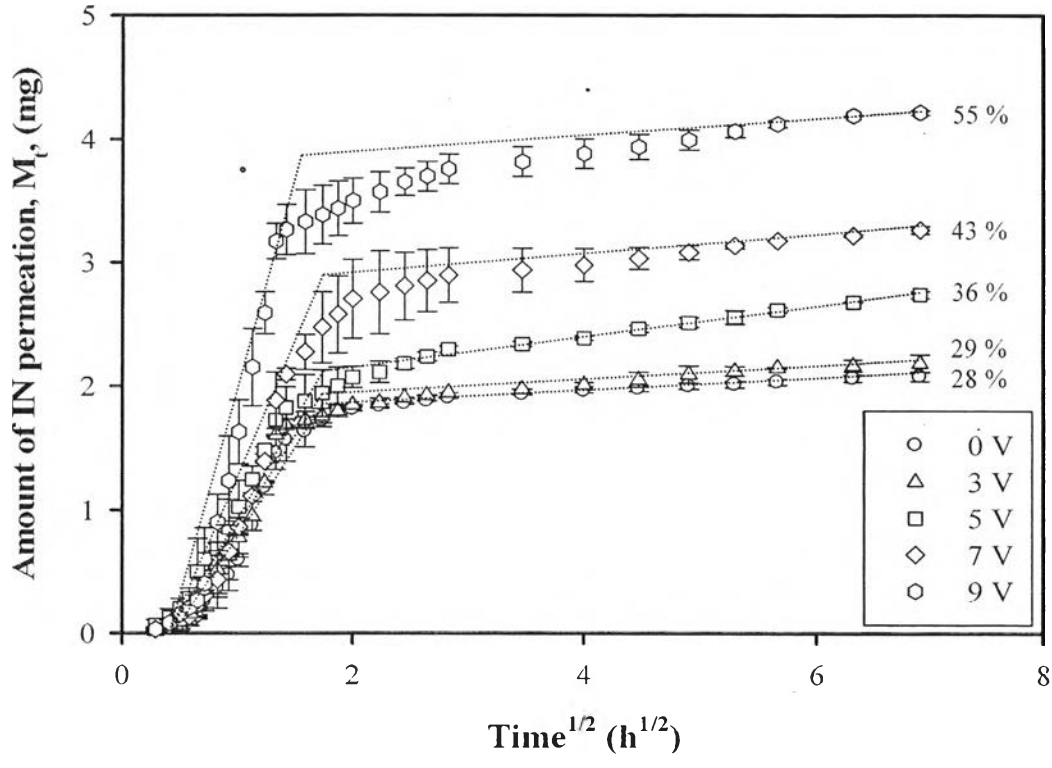

Figure 4.5 Amounts of IN permeated from 300IN-10EG_DCNR1 (sample area 3.14 cm^2) versus time $t^{1/2}$ at various electrical potentials (0-9 V) .

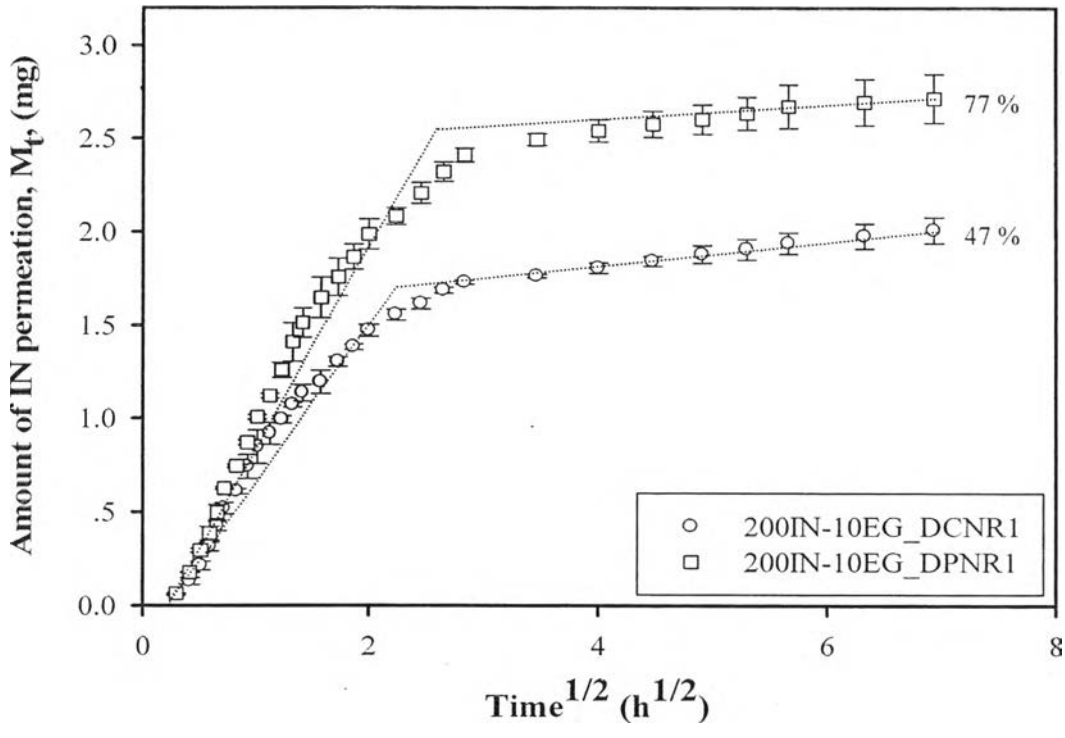

Figure 4.6 Amounts of IN permeated from 200IN-10EG_DCNR1, and 200IN-10EG_DPNR1 (sample area 3.14 cm^2) versus time $t^{1/2}$ under an electrical potential (9 V) , pH of 7.4, and at 37 °C.

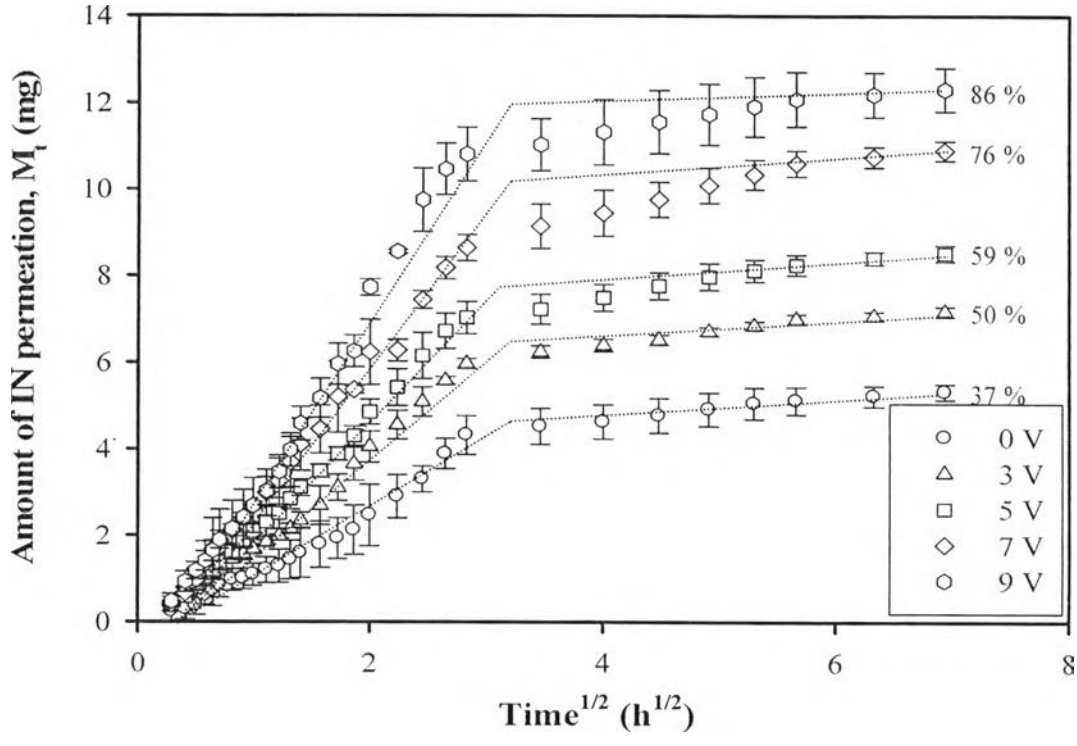

Figure 4.7 Amounts of IN permeated from 200IN-10EG_DPNR1 (sample area 12.56 cm^2), versus time $t^{1/2}$ at various electrical potentials (0-9 V) , pH of 7.4, and at 37 °C.

Table 4.1 Ingredients of IN-loaded_NR1 matrices with plasticizers, using the crosslinking agent of 0.3 %v/v and photoinitiator of 1 %wt, and with 5 mL of the rubber latex

Type of rubber	Amount of IN (mg)	Type of plasticizers	Amount of plasticizer (mL)	Sample name
DCNR	100	GLY	10	100IN-10GLY_DCNR1
		PG	10	100IN-10PG_DCNR1
		EG	5	100IN-5EG_DCNR1
			10	100IN-10EG_DCNR1
			15	100IN-15EG_DCNR1
	200		10	200IN-10EG_DCNR1
	300			300IN-10EG_DCNR1
DPNR	200			200IN-10EG_DPNR1

Table 4.2 Crosslinking density values and nitrogen contents of DCNR1 and DPNR1

Sample	ν_e	Nitrogen content (%wt)
DCNR1	$6.75\times10^{-6} \pm 1.21\times10^{-6}$	0.20573
10PG_DCNR1	$9.25\times10^{-6} \pm 7.71\times10^{-6}$	0.22056
10EG_DCNR1	$1.43\times10^{-5} \pm 8.89\times10^{-6}$	0.21536
10GLY_DCNR1	$1.13\times10^{-5} \pm 4.29\times10^{-6}$	0.21853
DPNR1	$1.01\times10^{-5} \pm 3.32\times10^{-6}$	0.01031
10EG_DPNR1	$2.38\times10^{-5} \pm 8.46\times10^{-6}$	0.01892

Table 4.3 Release kinetics and characteristic data

Sample name	Sample size (cm^2)	Actual amount drug (mg)	Electrical potential (V)	n	Higuchi		Diffusion coefficient (cm^2/s)	Time to equilibrium (h)	Amount of IN permeation (%) (mg)
					K_H (t^{-n})	r^2			
100IN-10GLY_DCNR1	3.14	2.7	0	0.66	0.35	0.943	8.15×10^{-8}	6	12 (0.31)
100IN-10PG_DCNR1		3.9		0.78	0.40	0.951	1.94×10^{-7}	7.5	15 (0.52)
100IN-5EG_DCNR1		3.3		0.60	0.29	0.990	1.03×10^{-7}	10	15 (0.49)
100IN-10EG_DCNR1		3.2		0.90	0.40	0.983	3.78×10^{-7}	6	20 (0.65)
100IN-15EG_DCNR1		2.6		0.85	0.35	0.993	2.93×10^{-7}	7.5	23 (0.60)
300IN-10EG_DCNR1		7.2		1.42	0.85	0.966	7.15×10^{-6}	2.8	28 (2.03)
			3	1.35	0.83	0.964	7.41×10^{-6}	2.8	29 (2.10)
			5	1.27	0.73	0.972	8.63×10^{-6}	2.4	36 (2.59)
			7	1.43	0.80	0.971	1.47×10^{-5}	2.4	43 (3.11)
			9	1.59	0.64	0.992	1.57×10^{-5}	2.2	55 (3.97)
200IN-10EG_DCNR1		4.2		1.32	0.45	0.986	3.13×10^{-6}	6	47 (1.98)
200IN-10EG_DPNR1		3.5		1.01	0.51	0.971	9.43×10^{-6}	8.5	77 (2.69)

200IN-10EG_DPNR1	12.56	14.1	0	0.62	0.32	0.985	1.37×10^{-5}	10	37 (5.22)
			3	0.54	0.33	0.896	2.64×10^{-5}	10	50 (7.07)
			5	0.65	0.46	0.934	7.19×10^{-5}	10	59 (8.38)
			7	0.67	0.41	0.921	9.46×10^{-5}	10	76 (10.73)
			9	0.70	0.36	0.934	9.44×10^{-5}	10	86 (12.19)
*DCNR_CR0.0008	3.14	0.79	0	1.77	0.17	0.954	4.39×10^{-7}	20-54	24 (0.170)
*DCNR_CR0.0032		0.72		1.70	0.11	0.951	2.11×10^{-7}		17 (0.123)
*DCNR_CR0.0064		0.85		1.76	0.08	0.932	9.61×10^{-8}		12 (0.085)
*DCNR_CR0.0032		0.72	0.1	1.48	0.11	0.952	2.32×10^{-7}		19 (0.136)
			1	1.22	0.17	0.933	4.46×10^{-7}		21 (0.150)
			3	1.64	0.18	0.922	6.32×10^{-7}		26 (0.186)
			5	1.41	0.23	0.985	1.00×10^{-6}		33 (0.232)
			7	1.44	0.25	0.976	1.19×10^{-6}		36 (0.254)
			9	1.62	0.27	0.985	1.42×10^{-6}		37 (0.264)

*Pornwalai Thorngkham *et al.* (2015) Permeation study of indomethacin from polycarbazole/natural rubber blend film for electric field controlled transdermal delivery. Pharmaceutics, Drug Delivery and Pharmaceutical Technology, DOI 10.1002/jps.2441

**CR is crosslinking ratio