Permeation Study of Indomethacin from Polycarbazole/Natural Rubber Blend Film for Electric Field Controlled Transdermal Delivery

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ABSTRACT: Transdermal drug delivery is an alternative route to transport the drug into the blood system. This method has been continuously developed to overcome limitations and is now suitable for a wide variety of drug molecules. In this work, the influences of electric field and conductive polymer were investigated for developing a unique drug delivery system from double-centrifuged natural rubber (DCNR) matrix. Indomethacin (IN) was loaded into polycarbazole (PCz) as a conductive polymer drug host to promote the efficient transportation of the drug. The IN-loaded PCz was blended with DCNR to form a transdermal patch. The permeation of IN through the PCz/NR film and pig skin was carrried out by a modified Franz diffusion cell. The IN diffused from DCNR film by the diffusion controlled combined with erosion mechanism depending on the pore formation period. The drug permeation increased with decreasing cross-link ratio because of more accessible pathways for the drug permeation. Moreover, an electric field and the inclusion of PCz as the drug carrier dramatically improved the diffusion of the drug from the membrane by through the electrorepulsive force and electro-reduced PCz expansion. Thus, the PCz/DCNR films are shown here as a potential transdermal patch under applied electric field.

Keywords: polycarbazole; natural rubber film; indomethacin; electric field strength; controlled release; electroporation; diffusion; transdermal drug delivery; permeability; iontophoresis

INTRODUCTION

Transdermal drug delivery systems (TDDSs) are designed specifically to control the delivery of active drugs through a matrix over a period of time after adhering onto the skin.[1] These systems avoid the first-pass metabolism and any pain occurred by the mechanical injection. Moreover, TDDS can control the drug levels in blood not possible in conventional drug delivery systems.[2] A polymer matrix is generally employed to the controlled release system because of the diversity of polymer structures that can be specifically modified to control the release mechanism of the drug molecule.[3]

Natural rubber (*cis*-1, 4-polyisoprene) (NR) obtained from *Hevea brasiliensis* has been used as transdermal patches because of its biocompatibility, high mechanical resistance, capability to form a film, and natural stimulant of angiogenesis.[4] NR was fabricated into a film to control the release rate of metronidazole,[4] and NR was blended with hydroxypropylmethyl cellulose for preparation of nicotine matrix films.[5] However, poor mechanical properties of the rubber occurred by the photodegradation under a strong sunlight,[6] and this effect can be prevented by cross-linking. The UV curing system in the presence of a photoinitiator and a cross-linking agent uses a short time, operates at low temperature, and it efficiently enhances the mechanical properties of NR.[7]

A conductive polymer can be blended with a NR to provide desirable properties for using in TDDS. Polycarbazole (PCz) is one of many candidate conductive polymers. It possesses unique electrical, electrochemical, and optical properties.[8] PCz is synthesized by the chemical method because of the possibility of bulk synthesis and morphology control.[9]

In this work, PCz/NR blend films were prepared by the UV irradiation using trimethylolpropane tris(3-mercaptopropionate) as a cross-linking agent and 2-methyl-4-(methylthio)-2-morpholdino propiophenone as a photoinitiator. The aim of this work is to investigate the electrical and thermal properties, morphology, and swelling property of drug matrix films. Indomethacin (IN) was used as an anionic drug and the release and permeation behaviors of the films were investigated under the effects of cross-linking degree and electrical potential. In particular, the drug release behaviors and mechanism from the pristine cross-linked NR and IN-loaded PCz/NR blends were systematically investigated and compared here.

EXPERIMENTAL

Materials

Carbazole (Cz; Merck, Hohenbrunm, Germany), ammonium persulfate (APS; Sigma–Aldrich, Louis, USA), and hydrochloric acid (HCl, AR; RCI Labscan, Bangkok, Thailand) as a monomer, an oxidizing agent, and a dopant, respectively, were used in the polymerization of PCz. Double-centrifuged natural rubber (DCNR; Thai Eastern Rubber

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Company, Ltd., Rayong, Thailand) was successfully utilized to fabricate a DCNR film with trimethylol-propane tris(3-mercaptopropionate) (TMPTMP; Aldrich, Louis, USA), 2-methyl-4-(methylthio)-2-morpholdino propiophenone (MMMP; Aldrich, Louis, USA) acting as a cross-linking agent and a photoinitiator, respectively. IN (Sigma–Aldrich, Louis, USA) was used as an anionic drug. Potassium chloride (KCl), potassium phosphate monobasic (KH_2PO_4), and sodium phosphate dibasic (Na_2HPO_4, research grade) were obtained from Calbiochem, Darmstadt, Germany. Potassium sodium chloride (NaCl) was purchased from Carlo Erba, Strada Rivoltana, Italy. All chemicals were employed for the preparation of a phosphate-buffered saline (PBS) (pH 7.4). Ammonia solution (NH_3; EMSURE, Billerica, USA), dichloromethane (DCM, ACS; Burdick & Jackson, Ulsan, Korea), hexane (AR; RCI Labscan, Bangkok, Thailand), hydrogen peroxide (H_2O_2; QRëC, Newzealand), methanol (MeOH, AR; Lobachemie, Mumbai, India), polyethylene glycol (PEG; Sigma–Aldrich, Louis, USA), sodium hydroxide (NaOH, AR; Lobachemie, Mumbai, India), toluene (AR; QRëC, Newzealand), and distilled water were used as solvents.

Preparation of IN-Loaded DCNR Films

The cross-linked DCNR was fabricated using UV irradiation in the presence of MMMP as a photoinitiator and TMPTMP as a cross-linking agent according to the procedure of Choi et al.[7] DCNR latex (5 mL, 0.0415 mol) was poured into the TMPTMP/MMMP mixture (mole ratio of TMPTMP:MMMP as 2:1) at various moles of cross-linking agent at 0.0004, 0.0016, and 0.0032 mol. After homogeneously stirring, the solution of 0.025 g of IN in PEG (2 mL) was added into the latex solution and continuously stirred for 30 min. Then, latex was casted on a petri dish and cured under UV irradiation for 5 min.

Synthesis of PCz

Polycarbazole was polymerized via the interfacial chemical polymerization according to the method of Gupta and Prakash.[9] Cz monomer (60 mM) in DCM (50 mL) was slowly poured on APS (1.2 M) and dissolved in HCl (0.5 M, 50 mL). The solution was left for 7 h. Then, the product was filtered and washed with distilled water and DCM. Then, it was dried at 65°C for 24 h under vacuum.

Preparation of IN-Doped PCz

Polycarbazole was dedoped with NH_3 solution (0.1 M). The dedoped PCz and IN were stirred in MeOH (50 mL). The mixture was stirred for 7 h and then filtered. The filtrate was cleanly washed with distilled water. The final product was dried in the oven at 65°C for 24 h.

Preparation of IN-Doped PCz/DCNR Blend Films

Indomethacin-doped PCz was added into the latex mixture consisting of DCNR latex, MMMP, TMPTMP, and PEG. The IN-loaded PCz/DCNR mixture was poured on a petri dish and then cured under a UV reactor for 5 min.

Preparation of Pig Skin Membrane

A pig abdominal skin was washed with a normal saline and hair and subcutaneous fat were removed to obtain the skin thickness of about 0.2 cm. The hairless pigskin was cut into a circle shape with diameter of 1.5 cm and then soaked in a PBS buffer of pH 7.4 overnight before the permeation study.

Characterizations

The PCz powder, IN powder, and IN-doped PCz powder were identified for functional groups using a FTIR spectrometer (Nicolet, Nexus 670). Samples were scanned with 64 scans over a wave number period of 400–4000 cm^{-1}. The powder sample was thoroughly grinded with anhydrous KBr. For the drug matrix films, ATR technique with ZnSe window was applied to investigate functional groups.

Thermogravimetry Differential Thermal Analyzer, TG-DTA (PerkinElmer, Pyris Diamond) was used to study the decomposition temperatures of PCz and IN-doped PCz. The sample of 5–10 mg was heated from 50°C to 900°C under a nitrogen atmosphere at a gas heating rate of 20°C/min.

Scanning electron microscope (S4800; Hitachi) was used to investigate the surface morphology of the DCNR films before and after the permeation study. Micrographs of the film were obtained using an acceleration voltage of 15 kV at various magnifications in a range of 200–1000.

For studying a cross-link density (ASTM D6814-02), the cross-linked 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. Equation (1) was used to calculate the cross-link density (Flory–Rehner equation):

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

where e is the number of chains in a real network per unit volume, V_1 is the molar volume of solvent, V_r is the polymer volume fraction in swollen state, and χ is the Flory interaction parameter of NR.

V_r was calculated following Eq. (2):

$$V_r = \frac{\text{Weight of dry rubber/density of dry rubber}}{\left(\frac{\text{Weight of dry rubber}}{\text{Density of dry rubber}}\right) + \left(\frac{\text{Weight of solvent absorbed by sample}}{\text{Density of solvent}}\right)} \quad (2)$$

and the density of the dry rubber was calculated using the Eq. (3):

$$\text{Density at } 23 \pm 2^\circ\text{C (g/mL)} = 0.7913 \times \frac{A}{A - B} \quad (3)$$

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

Spectrophotometric Analysis of Model Drug

The solution of IN in MeOH was prepared for a UV–visible spectrophotometer to identify the maximum absorption wavelength. The absorbance at the characteristic peak of IN was used to determine the amount of drug released from the calibration curve.

Determination of Drug Content

The IN-loaded DCNR and IN-doped PCz/DCNR films (film area of ~3.14 cm^2, thickness of ~0.2 cm) were immersed in hexane. The 0.3 mL of each solution was determined a drug content in

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