-PERMEATION STUDY OF INDOMETHACIN FROM POLYCARBAZOLE/NATURAL RUBBER BLEND FILM FOR ELECTRIC FIELD CONTROLLED TRANSDERMAL DELIVERY

.

Pornwalai Thorngkham

A Thesis Submitted in Partial Fulfilment of the Requirements for the Degree of Master of Science The Petroleum and Petrochemical College, Chulalongkorn University in Academic Partnership with The University of Michigan, The University of Oklahoma, and Case Western Reserve University

2014

Thesis Title:	Permeation Study of Indomethacin from
	Polycarbazole/Natural Rubber Blend Film for Electric Field
	Controlled Transdermal Delivery
By:	Pornwalai Thorngkham
Program:	Polymer Science
Thesis Advisor:	Prof. Anuvat Sirivat

Accepted by The Petroleum and Petrochemical College, Chulalongkorn University, in partial fulfilment of the requirements for the Degree of Master of Science.

· /N College Dean

(Asst. Prof. Pomthong Malakul)

Thesis Committee:

Annatserinal

(Prof. Anuvat Sirivat)

Ratana Rujiravanit

(Assoc. Prof. Ratana Rujiravanit)

(Dr. Sumonman Niamlang)

ABSTRACT

5572015016: Polymer Science Program

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

Thesis Advisor: Prof. Anuvat Sirivat 164 pp.

Keywords: Polycarbazole/ Natural rubber film/ Controlled drug release

The transdermal drug delivery system (TDDS) is an alternative route to the transport of medical species into the blood system through the skin. This method has been continuously developed and improved to overcome limitations and is now suitable for a wide variety of drug molecules. In this work, the influence of the electric field and conductive polymer used for the drug delivery system was investigated. Indomethacin, an anti-inflammatory drug, was loaded into polycarbazole (PCz), which is a conductive polymer to promote the efficient transportation of the drug. The drug-loaded PCz was blended with natural rubber (NR) to form a transdermal patch. The permeation of indomethacin in phosphate-buffered saline (PBS) buffer (pH 7.4) through PCz/DCNR film was carrried out by a modified Franz diffusion cell at a maintained temperature at 37 °C. UV-visible spectrometer was used to detect the amount of drug released. The results confirmed that an electric field can improve the diffusion of drug from a membrane through the skin by generating electrorepulsive force.

บทคัดย่อ

พรวลัย ทองคำ : การควบคุมการปลคปล่อยยาภายใต้กระแสไฟฟ้าจากพอลิคาร์บาโซล/ ยางธรรมชาติ (Permeation Study of Indomethacin from Polycarbazole/Natural Rubber Blend Film for Electric Field Controlled Transdermal Delivery) อ. ที่ปรึกษา : ศ.คร. อนุวัฒน์ ศิริวัฒน์ 164 หน้า

ระบบน้ำส่งยาผ่านทางผิวหนังถูกพัฒนาเพื่อเพิ่มประสิทธิภาพของการรักษา โดย หลีกเลี่ยงการถูกทำลายของยาจากระบบทางเดินอาหาร หรือการเกิดเมตาบอลิซึมของยาที่ตับ ้นอกจากนี้ยังช่วยรักษาระดับปริมาณยาในเลือดให้คงที่ แต่เนื่องจากธรรมชาติของผิวหนังที่เป็นเยื่อ เลือกผ่านจึงเป็นข้อจำกัคในการแพร่ผ่านของยาจากชั้นผิวหนังไปยังอวัยวะเป้าหมายและจำกัด ประเภทของยา ซึ่งทำให้ประสิทธิภาพในการรักษาลุคลง คังนั้นจึงได้มีการใช้กระแสไฟฟ้าเพื่อลุค ทำให้ระบบนี้สามารถใช้ได้กับยาหลากหลายชนิดและทำให้การรักษามี ข้อจำกัดคังกล่าว งานวิจัยนี้ศึกษาการปลคปล่อยยาอิน โคเมธาซินที่บรรจุในแผ่นยางธรรมชาติ ประสิทธิภาพดีขึ้น และแผ่นยางธรรมชาติผสมพอลิคาร์บาโซล โดยใช้ Modified-Franz diffusion cell ในฟอสเฟต บัฟเฟอร์ซาลืนที่ค่า พีเอช 7.4 อณหภมิ 37 องศาเซลเซียส ผลการทคลองพบว่าปริมาณยาอินโค เมธาซินลคลงเมื่อเพิ่มปริมาณสารเชื่อมขวางในแผ่นยางธรรมชาติ และปริมาณเพิ่มขึ้นเมื่อเพิ่ม ความแรงของกระแสไฟฟ้าเนื่องจากเกิดแรงผลักทางไฟฟ้าระหว่างประจุลบของยาและประจุลบ บนขั้วไฟฟ้าที่วางบนแผ่นยาง นอกจากนี้พบว่าพอลิคาร์บาโซลในแผ่นยางธรรมชาติผสมพอลิคาร์ บาโซลช่วยเพิ่มการแพร่ผ่านของยาอินโคเมธาซินผ่านผิวหนัง

iv

ACKNOWLEDGEMENTS

The author would like to thank all faculties who have provided invaluable knowledge to her, especially, Prof. Anuvat Sirivat who is her advisor.

The author would like to express her sincere appreciation to Assoc. Prof. Ratana Rujiravanit and Dr. Sumonman Niamlang for being on her thesis committee.

The author would like to thank all special senior students in the AS group and room 515, especially, to Ms. Nophawan Paradee for encouraging and helpful suggestions.

The author is grateful for the scholarship and funding of the thesis work provided by The Petroleum and Petrochemical College; and The National Center of Excellence for Petroleum, Petrochemicals, and Advanced Materials, Thailand.

Lastly, the sincerest appreciation is for her family for the love, understanding, ⁻ encouragement, and lovely friends.

TABLE OF CONTENTS

Р	A	G	E
-	А	٦V	Ľ

-

	Title Page	i	
	Abstract (in English)	iii	
	Abstract (in Thai)	iv	
	Acknowledgements	v	-
	Table of Contents	vi	
-	List of Tables	х	
	List of Figures	xiv	
	Abbreviations	xxi	
	List of Symbols	xxii	

CHAPTER

-

.

INTRODUCTION	1
LITERATURE REVIEW	3
2.1 Transdermal Drug Delivery System (TDDS)	3
2.2 Natural Rubber (NR)	6
2.3 Conductive Polymers	13
2.4 Polycarbazole (PCz)	19
2.5 Anti-inflammatory Drugs	22
EXPERIMENTAL	24
3.1 Materials	24
3.2 Methodology	25
3.2.1 Preparation of Indomethacin-loaded	
Double-Centrifuged Natural Rubber Films	25
3.2.2 Polymerization of Polycarbazole	25
3.2.3 Preparation of Indomethacin-doped Polycarbazole	25
	INTRODUCTION LITERATURE REVIEW 2.1 Transdermal Drug Delivery System (TDDS) 2.2 Natural Rubber (NR) 2.3 Conductive Polymers 2.4 Polycarbazole (PCz) 2.5 Anti-inflammatory Drugs EXPERIMENTAL 3.1 Materials 3.2 Methodology 3.2.1 Preparation of Indomethacin-loaded Double-Centrifuged Natural Rubber Films 3.2.2 Polymerization of Polycarbazole 3.2.3 Preparation of Indomethacin-doped Polycarbazole

-

.

-

	3.2.4	Preparation of Indomethacin-doped Polycarbazole/	
		Double-centrifuged Natural Rubber Blend Films	25
	3.2.5	Preparation of Phosphate-Buffered Saline pH 7.4	26
3.3	Chara	acterizations	26
	3.3.1	Fourier Transforms Infrared Spectrometer (FTIR)	26
	3.3.2	Thermogravimetry Differential Thermal	
		Analyzer (TG-DTA)	26
	3.3.3	Scanning Electron Microscope (SEM)	26
	3.3.4	UV-visible Spectrophotometer (UV-visible)	26
	3.3.5	Two-point Probe Meter	27
	3.3.6	Swelling and Crosslink Density	27
	3.3.7	Drug Release Experiments	29

PERMEATION ST	TUDY OF INDOMETHACIN F	ROM		
POLYCARBAZO	POLYCARBAZOLE/NATURAL RUBBER BLEND			
FILM FOR ELEC	TRIC FIELD CONTROLLED			
TRANSDERMAL	DELIVERY	30		
4.1 Abstract		30		
4.2 Introduction		31		
4.3 Experimental		32		
4.4 Results and Dis	scussion	37		
4.5 Conclusions		45	~	
4.6 Acknowledgem	nents	45		
4.7 References		46		

.

V CONCLUSIONS

63

.

-

.

PAGE

viii

REFERENCES

64

.

APPENDIC	ES	70
Appendix A	Functional Groups of PCz Investigation	72
Appendix B	Thermal Properties of PCz and	
	Crosslinked DCNR Films	76
Appendix C	Determination of Degree of Swelling (%) of	
	LA, MA, and HA Films	81
Appendix D	Properties of Natural Rubber Latex	87
Appendix E	Determination of Degree of Swelling (%) and	
	Weight Loss (%) of DCNR Films	88
Appendix F	UV-visible Spectrum of Indomethacin (IN)	96
Appendix G	Calibration Curve of Indomethacin (IN)	97
Appendix H	Photographs of PCz and Crosslinked DCNR Film	99
Appendix I	Scanning Electron Microscope (SEM) Images	
	and Pore Size	102
Appendix J	Determination of Electrical Conductivity of	
	IN-doped PCz at Various Doping Levels	107
Appendix K	Release of IN from IN-doped PCz/DCNR	
	Investigation	109
Appendix L	Determination of the Crosslink Density of	
	Crosslinked DCNR Films	110
Appendix M	Determination of Actual Drug Content	113
Appendix N	Determination of Amounts and Diffusion	
	Coefficient of IN Permeated from Crosslinked	
	DCNR Film at Various Crosslink Ratios	
	in an Absence of Electric Field	114

Appendix O	Determination of Amounts and Diffusion	
	Coefficient of IN Permeated from IN-loaded	
	DCNR Films with 0.0032 Crosslink Ratio at	
	Various Electric Field Strengths under Cathode	125
Appendix P	Determination of Amounts and Diffusion	
	Coefficient of IN Permeated from IN-loaded	
	DCNR Film with 0.0032 Crosslink Ratio	
	at Various Electrode Polarities	139
Appendix Q	Determination of Amounts and Diffusion	
	Coefficient of IN Permeated from IN-loaded	
	PCz/DCNR Blend Film with 0.0032	
1.40	Crosslink Ratio at Various Electric Field	
	Strengths under Cathode	144
Appendix R	Determination of Amount and Diffusion	
	Coefficient of IN Released from IN-loaded	
	DCNR Film at 0.0048 Crosslink Ratio	
	without Electric Field	151
Appendix S	The Permeation and Release Times	155
Appendix T	Effect of Amount of IN-loaded into	
- B	the DCNR Film	156
Appendix U	Pore Area to Film Area Ratio	157
Appendix V	Preparation of Pigskin	163

CURRICULUM VITAE 164

-

LIST OF TABLES

TABL	BLE	
4.1	Comparison of diffusion coefficient and kinetic factor of drug	
	permeated from different matrix	50
4.2	Permeation and release time of IN permeated from IN-loaded	53
	DCNR films and PCz/DCNR blend films	
4.3	Pore size on a surface of DCNR films and PCz/DCNR films after	
	the permeation study	53
Al	The characteristic peaks of PCz	73
A2	Assignment bands of indomethacin	75
B1	The degradation temperature and weight loss (%) in TGA	
	thermograms of Cz monomer, PCz, dedoped PCz, IN,	
	and IN-doped PCz	78
B2	The degradation temperature and weight loss (%) of pure	
	DCNR film and of crosslinked DCNR with various curing times	79
B3	The degradation temperature and weight loss (%) of pure DCNR	
	film and of crosslinked DCNR with various crosslink ratios	80
C1	The value of degree of swelling (%) of LA, MA, and HA in	
	toluene with various curing times	84
C2	The value of degree of swelling (%) of LA, MA, and HA in	
	water with various curing times -	85
C3	The value of degree of swelling (%) MA in toluene and in acetate	
	buffer pH 5.5 with various curing times	86
DI	The characteristic of natural rubber latex	87
El	The value of degree of swelling (%) of crosslinked DCNR films in	
	with various crosslink ratios using 5 min of curing time and	
	0.45 %v/v photoinitiator	91

-

TABLE

-

PAGE

•

El	The value of degree of swelling (%) of crosslinked DCNR films in	
	pH 7.4 with various crosslink ratios using 5 min of curing time	
	and 0.45 %v/v photoinitiator	92
E3	The value of degree of swelling (%) and weight loss (%) of	
	crosslinked DCNR films in toluene with various curing time	
	using 0.0048 crosslink ratio	
	(Crosslinking agent: photoinitiator = 3: 1 %v/v rubber)	94
E4	The value of degree of swelling (%) and weight loss (%) of	
	crosslinked DCNR films in toluene and in PBS buffer pH 7.4	
	with various crosslink ratios using 5 min of curing time	95
G1	The absorbance of IN with various concentrations at 324 nm	98
11	Pore size on a surface of IN-loaded DCNR films and	
	IN-doped PCz/DCNR films after the permeation study	105
J1	Electrical conductivity of IN-doped PCz at various mole ratios	
	(IN: PCz)	108
L1	The crosslink density of the crosslinked DCNR film with various	
	crosslink ratios after immersion in toluene for 5 days	112
M1	The raw data of the determination of actual amount of IN in	
	the IN-loaded DCNR films and IN-doped PCz	113
N1	The absorbance intensity and amount of IN permeated from	
	crosslinked DCNR at 0.0008 crosslink ratio without	
ų.	an electric field	115
N2	The absorbance intensity and amount of IN permeated from	
	crosslinked DCNR at 0.0032 crosslink ratio without	
	an electric field	116
N3	The absorbance intensity and amount of IN permeated from	
	crosslinked DCNR at 0.0064 crosslink ratio without	
	an electric field	.117

N4	The diffusion coefficients (n_1) of IN permeated from various	
	crosslinked DCNR films, pH 7.4 at 37 °C, $E = 0 V$	123
N5	The diffusion coefficients (n_2) of IN permeated from various	
	crosslinked DCNR films, pH 7.4 at 37 °C, $E = 0 V$	124
0 <u>1</u>	The absorbance intensity and amount of IN permeated from	
	crosslinked DCNR at 0.0032 crosslink ratio under an absence of	
	electric field ($E = 0 V$)	126
02	The absorbance intensity and amount of IN permeated from	
	crosslinked DCNR at 0.0032 crosslink ratio under an electric	
	field ($E = 0.1 \text{ V}$)	127
03	The absorbance intensity and amount of IN permeated from	
	crosslinked DCNR at 0.0032 crosslink ratio under an electric	
	field ($E = 1 V$)	128
O4	The absorbance intensity and amount of IN permeated from	
	crosslinked DCNR at 0.0032 crosslink ratio under an electric	
	field ($E = 3 V$)	129
05	The absorbance intensity and amount of IN permeated from	
	crosslinked DCNR at 0.0032 crosslink ratio under an electric	
	field ($E = 5 V$)	130
06	The absorbance intensity and amount of IN permeated from	
	crosslinked DCNR at 0.0032 crosslink ratio under an electric	
	field $(E = 7 V)$.	131
07	The absorbance intensity and amount of IN permeated from	
	crosslinked DCNR at 0.0032 crosslink ratio under an electric	
	field ($E = 9 V$)	132
08	The diffusion coefficients (n_1) of IN permeated from	
	the IN-loaded DCNR films with various electric field strengths	
	at 0.0032 crosslink ratio, pH 7.4 at 37 °C	137

-

.

TABLE

O9 The diffusion coefficients (n_2) of IN permeated from		
	the IN-loaded DCNR films with various electric field strengths	
	at 0.0032 crosslink ratio, pH 7.4 at 37 °C	138
PI	The diffusion coefficients (n_1) of IN permeated from crosslinked	
	DCNR films under the cathode, the anode, and the absence of	
	electric field, pH 7.4 at 37 °C	142
P2	The diffusion coefficients (n ₂) of IN permeated from crosslinked	
_	DCNR films under the cathode, the anode, and the absence of	
	electric field, pH 7.4 at 37 °C	143
Q1	The diffusion coefficients (n_1) of IN permeated from PCz/DCNR	
	blend films under the cathode, the anode, and the absence of	
	electric field, pH 7.4 at 37 °C	149
Q2	The diffusion coefficients (n_2) of IN permeated from PCz/DCNR	
	blend films under the cathode, the anode, and the absence of	
	electric field, pH 7.4 at 37 °C	150
S1	Permeation and release time of IN permeated from IN-loaded	
	DCNR films and PCz/DCNR blend films	155

.

-

-

. .

xiii

PAGE

LIST OF FIGURES

FIGURE PAGE 2.1 Skin structure consists of the skin's outermost layer. 3 2.2 Drug concentrations at site of therapeutic action after delivery by 5 an injection and a temporal controlled release system. 2.3 Drug delivery from an ideal distribution controlled release 6 system. 2.4 The structure of *cis* 1,4-polyisoprene. 7 2.5 The structure of the common conductive polymers. 14 2.6 Mechanism of electrical conductivity in PA as emblements of CPs. 14 2.7 The chemical structures for (a) poly (2,7 carbazole) and (b) poly (3,6 carbazole). 19 2.8 The structure of some glucocorticoids. 22 2.9 The structure of common NSAIDs. 23 4.1 Crosslink density of crosslinked DCNR film with various crosslink ratios. 54 4.2 FT-IR spectrum of: a) PCz; b) IN; and c) IN-doped PCz. 55 4.3 TGA thermograms of: a) PCz; b) IN; and c) IN-doped PCz. 55 Amount of IN permeated from crosslinked DCNR film with 4.4 various crosslink ratios (mol_{TMPTMP}/mol_{isoprene}) versus time t under absence of electric field, pH 7.4, 37 °C. 56 4.5 Amount of IN permeated from crosslinked DCNR film with various crosslink ratios (mol_{TMPTMP}/mol_{isoprene}) versus time t under absence of electric field, pH 7.4, 37 °C. 57 4.6 Amounts of IN permeated from IN-loaded DCNR film versus time^{1/2} with various crosslink ratios under absence of electric field, pH 7.4, 37 °C. 58

-

PAGE

4.7	Amounts of IN permeated from IN-loaded DCNR film versus		
	time ^{1/2} at various electric field strengths, at 0.0032 crosslink ratio,		
	pH 7.4, 37 °C.	58	
4.8	Diffusion coefficients (n1) of IN permeated from IN-loaded		
	DCNR film and IN-doped PCz/DCNR film versus time ^{1/2} at		
	various electric field strengths, at 0.0032 crosslink raio,		
	рН 7.4, 37 °С. –	59	
4.9	Diffusion coefficients (n2) of IN permeated from IN-loaded		
	DCNR film and IN-doped PCz/DCNR film versus time ^{1/2} at		
	various electric field strengths, at 0.0032 crosslink ratio, pH 7.4,		
	37 °C.	60	
4.10	SEM micrographs of crosslinked DCNR film with 0.0032		
	crosslink ratio before and after the permeation study with and		
	without electric field.	61	
4.11	Pore area to film area ratio of IN-loaded DCNR films as a		
	function of time under 0 and 3 V of the electric field strengths.	62	
Al	FT-IR spectra of Cz monomer and PCz.	72	
A2	FT-IR spectra of PCz, dedoped PCz, IN-doped PCz, and IN.	74	
Bl	TGA thermograms of Cz monomer, PCz, and dedoped PCz.	76	
B2	TGA thermograms of IN, PCz, and IN-doped PCz.	77	
B3	TGA thermograms of pure DCNR film and of crosslinked DCNR		
	at various curing times.	79	
B4	TGA thermograms of pure DCNR film and of crosslinked DCNR		
	with various crosslink ratios.	80	
Cl	Degree of swelling (%) of different crosslinked NR films		
	including LA film, MA film, and HA film in toluene with		
	various curing times.	80	

-

xvi

C2	Degree of swelling (%) of different crosslinked NR films	82
	including LA film, MA film, and HA film in water with various	
	curing times.	
C3	Degree of swelling (%) of crosslinked MA film in toluene and in	83
	acetate buffer pH 5.5 with various curing times.	
El	Degree of swelling (%) of crosslinked DCNR films in toluene	
	and in PBS buffer pH 7.4 with various crosslink ratios using 5	
	min of curing time and $0.45 $ %v/v photoinitiator.	88
E2	Degree of swelling (%) and weight loss (%) of crosslinked	
	DCNR films in toluene with various curing time using 0.0048	
	crosslink ratio (Crosslinking agent: photoinitiator = 2: 1 mole	
	ratio)	89
E3	Degree of swelling (%) and weight loss (%) of crosslinked	
	DCNR films in toluene and in PBS buffer pH 7.4 with various	
	crosslinking agents using 5 min of curing time (Crosslinking	-
	agent: photoinitiator = 2: 1 mole ratio).	90
F1	The UV-visible spectrum of IN.	96
Gl	The calibration curve of IN dissolved in MeOH/H ₂ O at 324 nm.	97
H1	Chemical polymerization of Cz: (a) recently mixing of oxidizing	
	agent and Cz monomers; (b) after stand for l2 h; (c) after stirred	
	for 7 h; (d) dried PCz after stand for 12h; (e) dried PCz after	
	stirred for 7 h; (f) dedoped PCz.	99
H2	Swelling test of crosslinked NR films with various curing times:	
	(a) 0 min; (b) 3 min; (c) 5min; and (d) 10 min in toluene.	100
H3	Crosslinked DCNR films with 0.0032 crosslink ratio using	
	curing time at: (a) 0 min; (b) 3 min; (c) 5min; (d) 10 min; 5min	
	containing of (e) loaded IN; (f) of loaded ibuprofen in GLY; (g)	
	loaded ibuprofen in Si; (h) loaded IN in PEG; and (i) loaded	
	ibuprofen in PEG.	101

PAGE

FIGURE

11 SEM micrographs of: (a) IN; (b) dedoped PCz at 10k; (c) dedoped PCz at 20k; (d) PCz at 10k; (e) PCz at 20k; (f) PCz at 35k; (g) IN-doped PCz at 10k; (h) IN-doped PCz at 20k; and (i) IN-doped PCz at 35k. 102 I2 SEM micrographs of: (a) pure DDNR film at 10k; (b) crosslinked DCNR film with 0.0032 crosslink ratio at 10k; (c) cross-section of crosslinked DCNR film with 0.0032 crosslink ratio at 10k; (d) IN; (e) IN-loaded DCNR film with 0.0032 crosslink ratio at 10k; (f) cross-section of IN-loaded DCNR film with 0.0032 crosslink ratio at 10k; (g) crosslinked DCNR film with 0.0032 crosslink ratio after the release study in PBS buffer pH 7.4 at 1k; (h) the crack of IN-loaded DCNR film with 0.0032 crosslink ratio before the release study in PBS buffer pH 7.4 at 1k; and (i) the crack of IN-loaded DCNR film with 0.0032 crosslink ratio after the release study in PBS buffer pH 7.4 at 1k. 103 13 SEM micrographs of crosslinked DCNR film with 0.0032 crosslink ratio: (a) before the permeation study; (b) after the permeation study without electric field; (c) after the permeation study under electric field; and (d) after the release study without electric field in PBS buffer pH 7.4 at 200 and 1k of magnification. 104 **I4** SEM micrographs of PCz/DCNR blend film with 0.0032 crosslink ratio after the permeation study at electric field strength of: (a) 0 V; (b) 1 V; (c) 3 V; (d) 5 V; and (e) 7 V, in PBS buffer pH 7.4, at 500 of magnification. 106 J1 Electrical conductivity of IN-doped PCz at various mole ratios (IN: PCz). 107 K1 UV-visible spectra of IN and IN released under E = 0 V and E = 3 V.109

PAGE

FIGURE

.

.

.

-

PAGE

Ll	The crosslink density of the crosslinked DCNR film with various	
	crosslink ratios.	111
NI	Amount of IN permeated from crosslinked DCNR film with	
	various crosslink ratios (mol _{TMPTMP} /mol _{isoprene}) versus time t	
	under an absence of electric field, pH 7.4, 37 °C.	114
N2	Amounts of IN permeated from IN-loaded DCNR film versus	
	time ^{1/2} with various crosslink ratios ($mol_{TMPTMP}/mol_{isoprene}$) under	
	an absence of electric field, pH 7.4, 37 °C.	120
N3	Amounts of IN permeated from IN-loaded DCNR film versus	
	time $^{1/2}$ with various crosslink ratios (mol _{TMPTMP} /mol _{isoprene}) in the	
	first region under an absence of electric field.	121
N4	Diffusion coefficients (n1) of IN from IN-loaded DCNR films	
	versus crosslink ratio ($mol_{TMPTMP}/mol_{isoprene}$) under an absence of	
	electric field, pH 7.4, 37 °C.	122
N5	Diffusion coefficients (n2) of IN from IN-loaded DCNR films	
	versus crosslink ratio $(mol_{TMPTMP}/mol_{isoprene})$ under an absence of	
	electric field, pH 7.4, 37 °C.	123
01	Amount of IN permeated from crosslinked DCNR film with	
	various electric field strengths at 0.0032 crosslink ratio, pH 7.4,	
	37 °C.	125
02	Amounts of IN permeated from IN-loaded DCNR film versus	
	time ^{1/2} with various electric field strengths at 0.0032 crosslink	
	ratio, pH 7.4, 37 °C.	134
O3	Diffusion coefficients (n1) of IN permeated from IN-loaded	
	DCNR film versus time ^{1/2} with various electric field strengths at	
	0.0032 crosslink ratio, pH 7.4, 37 °C.	135
O4	Diffusion coefficients (n2) of IN permeated from IN-loaded	
	DCNR film versus time ^{1/2} with various electric field strengths at	
	0.0032 crosslink ratio, pH 7.4, 37 °C.	136

-

-

-

P1	Amount of IN permeated from crosslinked DCNR film at 0.0032	
	crosslink ratio versus time t under the cathode, the anode, and the	
	absence of electric field, pH 7.4, 37 °C.	139
P2	The diffusion coefficients (n2) of IN permeated from IN-loaded	
	DCNR film versus time $^{1/2}$ with 0.0032 crosslink ratio under the	9
	cathode, the anode, and the absence of electric field, pH 7.4,	141
	37 °C.	
P3	The diffusion coefficients (n_2) of IN permeated from IN-loaded	
	DCNR film versus time ^{1/2} with 0.0032 crosslink ratio under the	
	cathode, the anode, and the absence of electric field, pH 7.4,	
	37 °C.	142
Q1	Amount of IN permeated from PCz/DCNR blend film at 0.0032	
	crosslink ratio versus time t at various electric field strengths, pH	
	7.4, 37 °C.	144
Q2	Amounts of IN permeated from IN-loaded DCNR film versus	
	time ^{1/2} with 0.0032 crosslink ratio at various electric field	
	strengths, pH 7.4, 37 °C.	146
Q3	Diffusion coefficients (n1) of IN permeated from IN-doped	
	PCz/DCNR blend film versus time $^{1/2}$ with various electric field	
	strengths at 0.0032 crosslink ratio, pH 7.4, 37 °C.	147
Q4	Diffusion coefficients (n2) of IN permeated from IN-doped	
	PCz/DCNR blend film versus time $^{1/2}$ with various electric field	
	strengths at 0.0032 crosslink ratio, pH 7.4, 37 °C.	148
R1	Amount of IN released from DCNR film at 0.0048 crosslink ratio	
	versus time t without electric field, pH 7.4, 37 °C.	151
R2	Log (M_t/M_{∞}) versus log time.	152
R3	Amounts of IN released from IN-loaded DCNR film versus	
	time ^{1/2} with 0.0048 crosslink ratio without electric field, pH 7.4,	
	37 °C.	154

-

.

4

FIGURE

-

PAGE

.

.

-

*

T1 Amount of IN permeated from IN-loaded DCNR		film at various	
	amount of drug loading under an applied electric	field strength of	
	5 V.	1	56
Ul	Pore area to film area ratio versus time of IN-load	led DCNR film	
	under 0 and 3 V of the electric field strength.	1	57
U2	Pore area to film area ratio versus time of DCNR film under 0		
	and 3 V of the electric field strength.	1	58
U3	SEM images of DCNR film after the permeation	study without	
	an electric field at 100 magnification.	1	59
U4	SEM images of IN-loaded DCNR film after the p	ermeation study	
	without an electric field at 50 magnification.	1	60
U5	SEM images of DCNR film after the permeation	study with an	
	electric field ($E = 3 V$) at 100 magnification.	1	61
U6	SEM images of IN-load DCNR film after the per	meation study	
	with an electric field ($E = 3 V$).	1	62
V1	A pigskin sample	- 1	63

ABBREVIATIONS

Avg	Average
CPs	Conductive Polymers
DCNR	Double-centrifuged Natural Rubber
FTIR	Fourier Transform Infrared Spectromerter
IN	Indomethacin -
PCz	Polycarbazole
SD	Standard deviation –
SEM	Scanning Electron Microscope
TG-DTA	Thermogravimetry Differential Thermal Analyzer
TDDS	Transdermal Drug Delivery System
UV-visible	UV-visible spectrophotometer

•

-

.

LIST OF SYMBOLS

Ms	weight of the sample after submersed in the buffer solution (g)
M _d	weight of sample after submersed in the buffer solution (g)
Mi	initial weight of the sample (g)
Ve	the number of chains in a real network per unit volume
Vı	the molar volume of solvent
Vr	the polymer volume fraction in swollen state
χ	the Flory interaction parameter of natural rubber
А	the weight of sample measured in air (g),
В	the weight of sample measured in MeOH (g),
M _t	amounts of drug release at time (mg)
M_{∞}	amounts of drug release at time infinity (mg)
M_{t}/M_{∞}	fractional of drug release
k	kinetic constant (h ⁻ⁿ)
k _H	Higuchi kinetic constant (h ⁻ⁿ)
n	diffusion scaling exponent
Q	amount of material flowing through a unit cross-section of barrier
	(g/cm^2)
C ₀	initial drug concentration in the film (g/cm^3)
D	diffusion coefficient of a drug (cm ² /s)
t	time (h)