## TABLE OF CONTENTS

	Page
ACKNOWLEDGEMENTS	iii
THAI ABSTRACT	iv
ENGLISH ABSTRACT	vi
TABLE OF CONTENTS	viii
LIST OF TABLES	ix
LIST OF ILLUSTRATIONS	xiv
ABBREVIATIONS AND SYMBOLS	xviii
CHAPTER 1 INTRODUCTION	1
2 LITERATURE REVIEW	3
3 MATERIALS AND METHODS	28
4 RESULTS	40
5 DISCUSSION	70
6 CONCLUSIONS	79
REFERENCES	81
APPENDIX	85
<sup>VITA</sup> สิทธิ์มหาวิทยาลัยเชียงโ	125
Copyright <sup>©</sup> by Chiang Mai Univer	

## LIST OF TABLES.

Tabl	е	Page
2.1	Degree of substitution and Molar substitution of Methocels	19
2.2	The physical properties of various grade of HPMC	20
2.3	The Carbopol polymer analogues	22
2.4	The widerange of carmober's grades with different Viscosity	23
3.1	There main formulas of tranexamic acid hydrogel	31
3.2	The component of tranexamic acid hydrogels with various amount	32
	of release accelerants	30/-
4.1	The appearances of different hydrogel formulations	40
4.2	pH of tranexamic acid hydrogel patch formulations	41
4.3	Accuracy and precision of tranexamic acid calibration curve	42
4.4	Limit of detection of tranexamic acid	44
4.5	Tranexamic acid content in hydrogel patch preparations in the first day	45
	of storage comparing with spiking method measurement	
4.6	Tranexamic acid content of tranexamic acid patches in various storage	46
	conditions	
4.7	Reproducibility of formula J33 exhibited as % tranexamic acid released	48
4.8	Release of tranexamic acid from the hydrogels prepared with different	50
	gelling agents on the first day of storage	
4.9	Release of tranexamic acid from the hydrogels on the first day of room	51
	temperature storage and the 120 <sup>th</sup> day of 3 storage conditions; 4 °C,	
	Room temperature (RT) and 45°C	
4.10	Release of tranexamic acid from formula M35 and the formulas	. 54
	containing lactic acid (P1 and P4)	

## LIST OF TABLES (Continued)

Table		Page
4.11	Release of tranexamic acid from formula M35 and the formulae	54
	containing NMP (P7 and P8)	
4.12	Release of tranexamic acid from formula J33 and the formulae with	56
	NMP (P9, P10 and P11)	
4.13	The observed data of tranexamic acid hydrogel patches on 120 <sup>th</sup> day of storage	59
4.14	The average distance of rolling ball measured on the surface of patches	63
4.15	Friction coefficient (µ) of the patch surfaces	63
4.16	The quality of M35 patches examined on 1 <sup>st</sup> and 120 <sup>th</sup> day of storage	66
4.17	The quality of M38 patches examined on 1 <sup>st</sup> and 120 <sup>th</sup> day of storage	67
4.18	The outcomes of J33 patches examined on 1 <sup>st</sup> and 120 <sup>th</sup> day of storage	67
4.19	The irritation test of tranexamic acid hydrogel patches observed within 24 hours	68
4.20	The visual scoring evaluation on 24 hours after patches occlusion (day1)	69
	and 24 hours after patches removal (day2)	
Al	The intensities for intra-day calibration curve (n=5)	86
A2	The intensities for inter-day calibration curve (n=5)	86
А3	The intensities of calibration curve for the determination of LOD	87
A4	The intensity data of solution samples for LOD determination	87
A5	Accuracy and precision examination of 4.2 μg/ml solution sample measurement	87
В1	Initial (total) drug content /Day1 determination by spectrofluorimetric detection	88
B2	The intensities of calibration curve for drug content determination of the	88
	day30 patches	
ВЗ	The intensity data of 4°C-stored hydrogel patches	89
B4	The intensity data of RT-stored hydrogel patches	89
B5	The intensity data of 45°C-stored hydrogel patches	89
В6	The intensities of calibration curve for drug content assay of the day60 patches	90

# LIST OF TABLES (Continued)

Table		Page
В7	The intensity data of 4°C-stored hydrogel patches	90
B8	The intensity data of RT-stored hydrogel patches	90
B9	The intensity data of 45°C-stored hydrogel patches	91
	The intensities of calibration curve for drug content assay of the day90 patches	91
	The intensity data of 4°C-stored hydrogel patches	91
B12	The intensity data of RT-stored hydrogel patches	92
B13	The intensity data of 45°C-stored hydrogel patches	92
B14	The intensities of calibration curve for drug content assay of the day 120 patches	92
B15	The intensity data of 4°C-stored hydrogel patches	93
B16	The intensity data of RT-stored hydrogel patches	93
B17	The intensity data of 45°C-stored hydrogel patches	93
Cl	The intensity data of calibration curve for formula M35	94
C2	The intensity data of calibration curve for formula M38	94
C3	The intensity data of calibration curve for formula J33/1 <sup>st</sup> . P10 and P11	95
C4	The intensity data of calibration curve for formula J33/2 <sup>nd</sup>	95
C5	The intensity data of calibration curve for formula J33/3 <sup>rd</sup>	95
C6	The intensity data of calibration curve for formula P1 and P4	96
C7	The intensity data of calibration curve for formula P7, P8 and P9	96
C8	Total content of tranexamic acid in hydrogel formula J33	97
C9	The intensities measured from the samples of J33/1 <sup>st</sup>	97
C10	% tranexamic acid release from J33/1 <sup>st</sup>	98
C11	% tranexamic acid release from J33/2 <sup>nd</sup>	98
C12	% tranexamic acid release from J33/3 <sup>rd</sup>	99
C13	% tranexamic acid release from M35	100
C14	% tranexamic acid release from M38	101

# LIST OF TABLES (Continued)

Table		Page
C15	The intensities of 4°C stored hydrogel samples	102
C16	% tranexamic acid release from M35/4°C	102
C17	% tranexamic acid release from M38/4°C	103
C18	% tranexamic acid release from J33/4°C	103
C19	The intensities of RT stored hydrogel samples	104
C20	% tranexamic acid release from M35/RT	104
C21	% tranexamic acid release from M38/RT	105
C22	% tranexamic acid release from J33/RT	105
C23	The intensities of 45°C stored hydrogel samples	106
C24	% tranexamic acid release from M35/45°C	106
C25	% tranexamic acid release from M38/45°C	107
C26	% tranexamic acid release from J33/45°C	107
C27	Total content of the accelerant formulae	108
C28	% tranexamic acid release from P1	109
C29	% tranexamic acid release from P4	109
C30	% tranexamic acid release from P7	110
C31	% tranexamic acid release from P8	110
C32	% tranexamic acid release from P9	111
C33	% tranexamic acid release from P10	111
C34	% tranexamic acid release from P11	112
Dl	The data of adhesive examination by manual model	113
E1	Statistical data of M35, M38 and J33: The intensity description	116
E2	One way ANOVA: Examination of gel base interference	116
E3	Post Hoc tests: Examination of gel base interference	117
F4	Post Hoc tests: M35 content	110

### LIST OF ILLUSTRATIONS

Figu	re	Pag
2.1	Chemical structure of Tranexamic acid	3
2.2	Dendrites of melanocyte in basal layer of the epidermis	4
2.3	Process of melanin synthesis	5
2.4	Partial energy diagram (Jablonski diagram)	7
2.5	Derivatization reaction of primary amine with NDA in presence of cyanide ion	8
	Cross section through the skin	11
2.7	Examples of dosage forms used in topical delivery	12
2.8	Schematic illustration of drug release and absorption across the skin tissues	13
	for localized therapeutic action or for systemic medication in the tissues	
	remote from the site of topical drug application	
2.9	Partitioning and diffusion processes involved in solute penetration through the	13
	Stratum corneum	
2.10	Examples of suggested penetration enhancers: aprotic solvents and	14
	Pyrroridone derivatives	
2.11	Franz diffusion cell, a hydrodynamically well-calibrated skin permeation cell	16
	consisting of two compartments arranged vertically position	
2.12	Horizontal diffusion cells	16
2.13	Chemical structures of Methocel® products	18
2.14	General structure of Carbomer (Carbopol)	21
2.15	Carbomer gel network structures	22
3.1	Diagram of patch making	30
3.2	a) Arrangement of horizontal diffusion cells with the patches, b) the diffusion	36
	systems and fluid sampling during the diffusion process	

# LIST OF ILLUSTRATIONS (Continued)

Figu	ne 90818186	Page
3.3		39
	hydrogel surface	
4.1	Calibration curve of tranexamic acid	43
4.2	Fluorescence intensities investigated by derivatization of 50.4 µg/ml	43
4.3	The fluorescence spectra of tranexamic acid derivatized with NDA	45
	tranexamic acid standard solution (♦) and reagent blank (O)	
4.4	% Drug remained of hydrogel formula M35 stored in 4°C (:),	3 47
	room temperature ( ) and 45°C ( )	
4.5	% Drug remained of hydrogel formula M38 stored in 4°C ( ),	47
	room temperature ( ) and 45°C ( )	
4.6	% Drug remained of hydrogel formula J33 stored in 4°C ( :),	48
	room temperature ( ) and 45°C ( )	
4.7	Triplicate release profiles of tranexamic acid from formula J33;	49
	1 <sup>st</sup> profile ( $\bullet$ ), 2 <sup>nd</sup> profile ( $\square$ ), 3 <sup>rd</sup> profile ( $\triangle$ )	
4.8	Release profiles of tranexamic acid from the hydrogels on the first day	50
	of storage; formula M35 (■), M38 (O) and J33 (▲)	
4.9	Release profiles of tranexamic acid from hydrogel formula M35 on first day	52
	of storage (*) and three profiles investigated from 120th day of various	
	storage conditions; 4 °C ( $\square$ ), room temperature (O) and 45 °C ( $\blacktriangle$ )	
4.10	Release profiles of tranexamic acid from hydrogel formula M38 on first day	52
	of storage (•) and three profiles investigated from 120th day of various	e
	storage condition; 4 °C ( $\square$ ), room temperature (O) and 45 °C ( $\blacktriangle$ )	
<b>4.11</b>	Release profiles of tranexamic acid from hydrogel formula J33 on first day	53
	of storage (*) and three profiles investigated from 120th day of various	
	storage condition; 4 °C (□), room temperature (O) and 45 °C (▲)	

# LIST OF ILLUSTRATIONS (Continued)

]	Figure		Page
	4.12	Release profiles of tranexamic acid from hydrogel formula M35 (■) and the	55
		formulas with lactic acid; P1 (O) and P4 ( A)	
	4.13	Release profiles of tranexamic acid from hydrogel formula M35 (■) and the	55
		formulas with NMP; P7 (O)and P8 (A)	
	4.14	Release profiles of tranexamic acid from hydrogel formula J33 (▲) and the	56
		formulas with NMP; P9 (○), P10 ( □ ) and P11 (♦)	
	4.15	Higuchi plot of tranexamic acid released from hydrogel formula J33,	57
		the repeated profiles; $1^{s'}(\spadesuit)$ , $2^{nd}(\blacksquare)$ and $3^{rd}(\triangle)$ .	
	4.16	Higuchi plot of tranexamic acid released from hydrogels on day1;	58
		M35 (♦), M38 (■)and J33 (△).	
	4.17	Higuchi plot of tranexamic acid released from hydrogel formula J33 on	58
		day I ( $\spadesuit$ ), day 120/4°C ( $\blacksquare$ ), day 120/RT ( $\triangle$ ) and day 120/45°C (O).	
	4.18	Formula M35 patch, One-day stored at RT	60
	4.19	Formula M35 patch, 120 days-stored at 4°C	60
	4.20	Formula M35 patch, 120 days-stored at RT	60
	4.21	Formula M35 patch, 120 days-stored at 45°C	60
	4.22	Formula M38 patch, One-day stored at RT	61
	4.23	Formula M38 patch, 120 days-stored at 4°C	61
	4.24	Formula M38 patch, 120 days-stored at RT	61
	4.25	Formula M38 patch, 120 days-stored at 45°C	61
	4.26	Formula J33 patch, One-day stored at RT	62
	4.27	Formula J33 patch, 120 days-stored at 4°C	62
	4.28	Formula J33 patch, 120 days-stored at RT	62
	4.29	Formula J33 patch, 120 days-stored at 45 °C	62

#### LIST OF ILLUSTRATIONS (Continued)

Figure	अभिनाम् ।	Page
4.30	The friction coefficient ( $\mu$ ) on the patch surfaces; formula M35 ( $\phi$ ),	64
	M38 (o) and J33 (A), stored in laminated aluminum foils at room temperature	
4.31	The friction coefficient ( $\mu$ ) on the patch surfaces; formula M35 ( $\blacklozenge$ ),	64
	M38 (o) and J33 (A), stored in zip-locked plastic bags at room temperature	
4.32	Comparison of friction coefficient of hydrogel formula M35 stored in	65
	laminated aluminum foils (♦) and zip-locked plastic bags (□)	
4.33	Comparison of friction coefficient of hydrogel formula M38 stored in	65
	laminated aluminum foils (♦) and zip-locked plastic bags (□)	
4.34	Comparison of friction coefficient of hydrogel formula J33 stored in	66
	laminated aluminum foils (♦) and zip-locked plastic bags (□)	
D1	Diagram of adhesive model exhibiting the factors of friction coefficient	114
	UNIT	

# ลิขสิทธิ์มหาวิทยาลัยเชียงใหม่ Copyright<sup>©</sup> by Chiang Mai University All rights reserved

#### ABBREVIATIONS AND SYMBOLS

% = Percentage

Trade name of product

2-ME = 2-Mercaptoehtanol

2-P = 2-Pyrrolidone

AA = Arachidonic acid

av = Average

°C = Degree Celsius

CBI = Cyanobenz [f] isoindoles

cGMP = Cyclic of Guanosin-5-phosphoric acid

cm = Centimeter

cm<sup>2</sup> = Square centimeter

cm<sup>3</sup> = Cubic centimeter

CN = Cyanide ion

Co., Ltd. = Company limited

conc = Concentration

cP = Centipoise

DMAA = Dimethylacetamide

DMF = Dimethylformamide

DMSO = Dimethylsulfoxide

Em SBW = Emission slit bandwidth

et al = And others

etc = et cetera, and all the others

Ex SBW = Excitation slit bandwidth

exp = Exponential relation

#### ABBREVIATIONS AND SYMBOLS (Continued)

°F = Degree Fahrenheit

 $f^*$  = The stress

g = gram

GC = Gas chromatography

HPLC = High performance liquid chromatography

HPMC = Hydroxypropylmethylcellulose

 $I_0$  = The power of the excitation source

KCN = Potassium cyanide

kg = Kilogram

= liter

LOD = Limit of detection

Molar concentration, mole per liter

m<sup>2</sup> = square meter

m<sup>3</sup> = cubic meter

mg = Milligram

min = Minute

ml = Milliliter

mm = Millimeter

mPa = millipascal

Mw = Molecular weight

NDA = Naphthalene-2,3-dicarboxaldehyde

nm = nanometer

NMP = N-methylpyrrolidone

NSIADs = Nonstroidal anti-inflammatory drugs

OPA = o-phthaladehyde

Pa = Pascal

PBS = Phosphate buffer saline

#### ABBREVIATIONS AND SYMBOLS (Continued)

PG = Propylene glycol

PGE, = Prostaglandin E,

pH = The negative logarithm of the hydrogen ion concentration

Ph.Eur. = European Pharmacopoeia

pK<sub>a</sub> = Negative log of ionization constant of acid

PMT = Photo multiplier tube

PVP = Polyvinyl pyrrolidone

R<sup>2</sup> = Coefficient of determination

RSD = Relative standard deviation

RT = Room temperature

 $S_0$  = Vibrational level of ground state

S<sub>t</sub> = Vibrational level of excited state

SC = Stratum corneum

SD = Standard deviation

sec = Second

temp = Temperature

TNBS = 2,4,6-trinitrobenzenesulfonic acid

trans-AMCA = trans-4-(Aminomethyl) cyclohexane carboxylic acid

UV = Ultraviolet

w/w = weight by weight

 $\alpha$  = Elongation of the polymer

Of The quantum efficiency of an analyte

E = Molar absorptivity

 $\lambda_{\rm em}$  = Emission wavelength

 $\lambda_{ex}$  = Excitation wavelength

 $\mu$  = Friction efficiency

 $\mu g = Microgram$ 

μl = Microliter