## TABLE OF CONTENTS

	Page
ACKNOWLEDGEMENT	iii
ENGLISH ABSTRACT	iv
THAI ABSTRACT	vi
LIST OF TABLES	ix
LIST OF ILLUSTRATIONS	xi
LIST OF ABBREVIATIONS	xii
INTRODUCTION	1
LITERATURE REVIEW	4
OBJECTIVES	8
MATERIALS AND METHODS	9
RESULTS	21
DISCUSSION	56
CONCLUSION	63
REFERENCES	64
APPENDIX	68
VITA	70

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

viii

## LIST OF TABLES

Table		Page		
1	The randomized schedule of drug administrations			
2	Demographic characteristics of 20 male healthy volunteers			
3	Various concentration of donepezil in plasma use for construction			
	calibration curve			
4	Intra-day assay validation of donepezil in plasma			
5	Inter-day assay validation of donepezil in plasma			
6	Recovery of donepezil and IS from plasma	26		
7	Freeze-thaw stability of donepezil in plasma	27		
8	Short-term stability of donepezil in plasma	27		
9	Long-term stability of donepezil in plasma	28		
10	Post-preparative stability of donepezil in plasma	28		
11	Stability of donepezil and IS in stock-solution	29		
12	Plasma donepezil concentrations (ng/mL) after oral administration of	32		
	5-mg the generic donepezil HCl			
13	Plasma donepezil concentrations (ng/mL) after oral administration of	34		
	5-mg Aricept <sup>®</sup>			
14	The mean, SD, %CV, maximum and minimum of plasma donepezil	36		
	concentrations (ng/mL) after oral administrations of 5-mg generic			
	donepezil HCl			
15	The mean, SD, %CV, maximum and minimum of plasma donepezil	- 37		
	concentrations (ng/mL) after oral administrations of 5-mg Aricept®			
16	Pharmacokinetic parameters after a single oral dose of 5-mg generic	38		
	donepezil HCl			
17	Pharmacokinetic parameters after a single oral dose of 5-mg $Aricept^{\mathbb{R}}$	39		
18	The clearance (CL/F) and Volume of distribution (Vd/F) of the	40		
	generic donepezil HCl (test) and Aricept <sup>®</sup> (reference)			

Table		Page
19	Comparison of donepezil pharmacokinetic parameters (C <sub>max</sub> and AUC)	41
	in individual volunteers after single oral administrations of 5-mg	
	generic donepezil HCl (test) and Aricept <sup>®</sup> (reference)	
20	ANOVA table and 90% confidence interval of the pharmacokinetic	42
	parameter [logarithmically transformed AUC <sub>0-t</sub> ]	
21	ANOVA table and 90% confidence interval of the pharmacokinetic	42
	parameter [logarithmically transformed AUC <sub>0-∞</sub> ]	
22	ANOVA table and 90% confidence interval of the pharmacokinetic	43
	parameter [logarithmically transformed C <sub>max</sub> ]	
23	ANOVA table and 90% confidence interval of the pharmacokinetic	43
	parameter [T <sub>max</sub> ]	

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

## LIST OF ILLUSTRATIONS

Figure		Page			
1A	Chromatograms of blank plasma				
1B	Chromatogram of donepezil 100 ng/mL and IS (ondansetron) in				
	human plasma				
2A	Chromatograms of donepezil and IS in plasmas, after 2-hour single	23			
	oral dose administration of the test product				
2B	Chromatograms of donepezil and IS in plasmas, after 2-hour single	23			
	oral dose administration of the reference product				
2C	Chromatograms of donepezil and IS in plasmas, after 2-hour single	23			
	oral dose administration of the blank plasma				
3	Calibration curve of donepezil in human plasma	24			
4	Pairwise plasma concentration-time profiles after oral administration	44			
	of 5-mg generic donepezil HCl and Aricept®				
5	Mean plasma concentration-time profiles after oral administration	54			
	of 5-mg generic donepezil HCl and Aricept <sup>®</sup>				
6	Plasma concentration-time curves of individual subjects (n=20)	55			
	after oral administration of 5-mg generic donepezil HCl				
7	Plasma concentration-time curves of individual subjects(n=20)	56			
	after oral administration of 5-mg Aricept <sup>®</sup>				

xi

## LIST OF ABBREVIATIONS

ACh	= 0	acetylcholine
AChE	=	acetylcholinesterase
AD	=	Alzheimer's disease
AUC <sub>0-∞</sub>	=	area under the concentration-time curve from administration
		and extrapolation to infinity
AUC <sub>0-t</sub>	= 4	area under the concentration-time curve from administration to
		time t
BMI	=	body mass index
BuChE	=	butyrylcholinesterase
BUN	=	blood urea nitrogen
%CV	+	percent coefficient of variation
°C	, =	degree Celsius
CBC	ŧ	complete blood count
ChE		cholinesterase
CI	÷.	confidence interval
CL	=	clearance
$C_{max}$	=	maximal plasma concentration
Conc	e l	concentration
CYP 450	3=U	cytochrome P-450
Vd	-0	volume of distribution
FDA 2	ŧ	Food and Drug Administration
F <sub>rel</sub>	=	relative bioavailability
GI	= 1	gastrointestinal tract
HPLC	=	high performance liquid chromatography
HC1	=	hydrochloride
h	=	hour
ht	=	height

IS	=	internal standard
kg	=	kilogram
L	=	liter
LFT	=	liver function test
LLOQ	=	lower limit of quantification
М	=	molar
mg	A	miligram
μL	=	microliter
mM 💽	=	milimolar
min	=	minute
mL	=	milliliter
mL/s	=	milliliter/second
mm	=	millimeter
ng	=	nanogram
rpm	=	round per minute
SD	=	standard deviation
Т	=	test
T <sub>1/2</sub>		half-life
T <sub>max</sub>		time to reach maximum concentration
R	=	reference
$V_d$	=	volume of distribution
WBC	=	white blood cell
jan	ธิ์เ	ู <sup>year</sup> าวิทยาลัยเชียงใหม่

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

xiii