CONTENTS

	Page
CONTENTS	vi
LIST OF TABLES	viii
LIST OF FIGURES	X
LIST OF ABBREVIATIONS AND SYMBOLS	xi
CHAPTER	
1. INTRODUCTION	
1.1 General introduction	1
1.2 Tuberculosis	3
1.3 Stability study	5
1.4 Rifampicin	8
1.5 Isoniazid	10
1.6 Ethambutol	11
1.7 Pyrazinamide	12
2 EXPERIMENTAL	
2.1 Apparatus and instruments	13
2.2 Chemicals	13
2.3 Samples	14
2.4 Analytical method	14
2.5 Samples preparation	16
2.6 Drug quality	16
2.7 Non-isothermal stability	16
2.8 Program validation	17
2.9 Isothermal stability	17
2.10 Statistical data analysis	18
3 RESULTS AND DISCUSSIONS	
3.1 Analytical method	19
3.2 Method validation	21
3.3 Non-isothermal stability study	22
3.4 Program validation	24
3.5 Drug quality	26

CONTENTS (Continued)

	Page
3.6 Isothermal stability study	27
4 CONCLUSIONS	50
REFERENCES	51
VITAE	57

LIST OF TABLES

Гable	Page
1. Guideline for tuberculosis treatment	5
2. Results of linearity from 5 replications of antituberculosis drugs	20
3. Results of accuracy and precision	21
4. Kinetic parameters from non-isothermal stability	23
5. Percentage of the amount of anti-tuberculosis drugs before	
the isothermal stability study	26
6. ANOVA of percentage of rifampicin remaining from	
isothermal stability	27
7. Pairwise comparisons between temperature to time (months)	
of rifampicin	28
8. Pairwise comparisons between temperature to relative humidity	
of rifampicin	29
9. ANOVA of percentage of ethambutol remaining from	
isothermal stability	30
10. Multiple comparison temperature of ethambutol	31
11. Pairwise comparisons between relative humidity to	
time (month) of ethambutol	32
12. ANOVA of percentage of pyrazinamide remaining from	
isothermal stability	33
13. Pairwise comparisons between temperature to	
time (months) of pyrazinamide	35
14. Pairwise comparisons between temperature to relative humidity	
of pyrazinamide	36
15. ANOVA of percentage of isoniazid remaining from	
isothermal stability	37
16. Pairwise comparisons between temperature to relative humidity	
of isoniazid	39
17. Predicted kinetic parameters of antituberculosis drugs from isothermal	
stability at 30°C by using Arrhenius equation	41

LIST OF TABLES (Continued)

Table	Page
18. Constants from nonlinear regression (hooke-Jeeves and Quai-newton	
estimated method) and extrapolated shelf-lives at 30°C	42

LIST OF FIGURES

Fig	Figure	
	1. Chemical structures of rifampicin and its decomposition products	10
	2. Chromatogram of rifampicin and indomethacin	19
	3. Chromatogram of isoniazid and pyrazinamide	20
	4. Reaction of ethambutol and cupric ion in basic medium	20
	5. Concentration change in isoniazid pyrazinamide and rifampicin	23
	6. Concentration change in ethambutol	23
	7. Plot of simulated E_a/R versus E_a/R recovery	25
	8. Plot of A simulated versus A recovery	25
	9. Plot of T90 simulated versus T90 recovery	26
	10. Percentage of rifampicin remaining versus time at nine conditions	
	from isothermal stability	28
	11. Percentage of ethambutol remaining versus time at nine conditions	
	from isothermal stability	32
	12. Percentage of pyrazinamide remaining versus time at nine conditions	
	from isothermal stability	35
	13. Percentage of isoniazid remaining versus time at at nine conditions	
	from isothermal stability	38
	14. Correlation of the predicted shelf-lives of antituberculosis drugs (T90%)	
	at 25 and 30°C by the Arrhenius method and the Yoshioka method.	44
	15. Compared Arrhenius method and Yoshioka method for predicting percentage	
	of ethambutol remaining after isothermal-stability study at nine conditions	46
	16. Compared Arrhenius method and Yoshioka method for predicting percentage	
	of isoniazid remaining after isothermal-stability study at nine conditions	47
	17. Compared Arrhenius method and Yoshioka method for predicting percentage	
	of pyrazinamide remaining after isothermal-stability study at nine conditions	48
	18. Compared Arrhenius method and Yoshioka method for predicting percentage	
	of rifampicin remaining after isothermal-stability study at nine conditions	49

LIST OF ABBREVIATIONS AND SYMBOLS

ANOVA Analysis of variance

BCS Biopharmaceutic Classification System

BP British Pharmacopoeia

°C Degree Celsius

E_a Activation energy

FDC Fixed dose combination

HPLC High performance liquid chromatography

mg Milligram
ml Milliliter
μg Microgram
R Gas constant

R² Coefficient of determination

RH Relative humidity

RSD Relative standard deviation

SD Standard deviation
SSE Sum of square error

USP the United States Pharmacopoeia

UV Ultraviolet

w/w Weight by weight