

การพัฒนาวิธีไฮดรอสเปส เพื่อวิเคราะห์สารปนเปื้อนอินทรีย์ที่ระเหยง่าย
และตัวทำละลายตกค้างอื่น ๆ ในยา



นางสาว ปราณอม ขาวเมฆ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต

ภาควิชาเคมี

บัณฑิตวิทยาลัย จุฬาลงกรณ์มหาวิทยาลัย

พ.ศ. 2538

ISBN 974-631-769-5

ลิขสิทธิ์ของบัณฑิตวิทยาลัย จุฬาลงกรณ์มหาวิทยาลัย

I16760141

DEVELOPMENT OF HEADSPACE METHOD FOR ANALYSIS OF ORGANIC VOLATILE
IMPURITIES AND OTHER RESIDUAL SOLVENTS IN DRUG

Miss Pranom Khaowmek

A Thesis Submitted in Partial Fulfillment of the Requirements

for the Degree of Master of Science

Department of Chemistry

Graduate School

Chulalongkorn University

1995

ISBN 974-631-769-5

Thesis Title Development of Headspace Method for Analysis of Organic
 Volatile Impurities and Other Residual Solvents in Drug

By Miss Pranom Khaowmek

Department Chemistry

Thesis Advisor Dr. Varaporn Leepipatpiboon



Accepted by the Graduate School, Chulalongkorn University in Partial Fulfillment
of the Requirements for the Master's Degree.

Santi Toongsuwan

..... Dean of Graduate School
(Associate Professor Santi Toongsuwan, Ph.D.)

Thesis Committee

Udom Kokpol

..... Chairman
(Associate Professor Udom Kokpol, Ph.D.)

Varaporn Leepipatpiboon

..... Thesis Advisor
(Dr. Varaporn Leepipatpiboon, D.Sc.)

Siri Varothai

..... Member
(Associate Professor Siri Varothai, Ph.D.)

Pipat Karntiang

..... Member
(Associate Professor Pipat Karntiang, Ph.D.)

Tasaneek Chokcharoenrat

..... Member
(Ms. Tasanee Chokcharoenrat, B.Sc. in Pharm.)

ปรานอม ขาวเมฆ : การพัฒนาวิธีเฮดสเปส เพื่อวิเคราะห์สารปนเปื้อนอินทรีย์ที่ระเหยง่ายและตัวทำละลายตกค้างอื่นๆ ในยา (Development of headspace method for analysis of organic volatile impurities and other residual solvents in drug)
อาจารย์ที่ปรึกษา : ดร. วราภรณ์ ลิขิตพัฒนไพบุลย์ , 168 หน้า ISBN 974-631-769-5

เทคนิคเฮดสเปสได้พัฒนาขึ้นมา เพื่อใช้วิเคราะห์สารปนเปื้อนอินทรีย์ที่ระเหยง่ายและตัวทำละลายตกค้างอื่นๆ ในยา เช่น เมธิลลีนคลอไรด์ คลอโรฟอร์ม เบนซีน ไตรคลอโรเอธิลีน และ 1,4-ไดออกเซน โดยทำการศึกษาและประเมินค่าปัจจัยต่างๆ ที่มีผลต่อความไว (sensitivity) และประสิทธิภาพของการสกัด (percent recovery) ผลการศึกษาพบว่า การใช้อุณหภูมิ 70°C เป็นเวลา 40 นาที ด้วยอัตราส่วนน้ำต่ออากาศ 5:5 ในขวดขนาด 10 มิลลิลิตร ปริมาตรของเฮดสเปสแก๊ส ที่นำเข้าสู่เครื่องแก๊สโครมาโตกราฟด้วยเครื่องอัดเฮดสเปส 1.00 มิลลิลิตร และใช้เกลือโซเดียมซัลเฟต 1.00 กรัม เป็นสภาวะที่เหมาะสมที่สุดของการวิเคราะห์โดยเทคนิคเฮดสเปส เทคนิคนี้สามารถตรวจวัดสารประเภทนี้ในตัวอย่างยาได้ที่ระดับต่ำที่สุดในช่วง 0.2 ส่วนในพันล้านส่วน (ppb) ถึง 0.2 ส่วนในล้านส่วน (ppm) (ยกเว้น 1,4-ไดออกเซน สามารถตรวจวัดได้ที่ระดับต่ำที่สุด 12.41 ส่วนในล้านส่วน) ความถูกต้องในการวิเคราะห์ด้วยเทคนิคนี้ พบว่ามีความผิดพลาดอยู่ร้อยละ 0.42 ถึง 5.06 เปอร์เซ็นต์ จากการสุ่มตัวอย่างยาเม็ดจำนวน 15 ตัวอย่างมาตรวจวัดด้วยเทคนิคนี้พบว่าตัวอย่างที่เก็บมา 3 ตัวอย่างมี เมธิลลีนคลอไรด์อยู่ในช่วง 38.10 ถึง 202.10 ไมโครกรัมต่อกรัม และ 1 ตัวอย่างตรวจพบว่ามี คลอโรฟอร์มในปริมาณ 957.10 นาโนกรัมต่อกรัม และตรวจพบตัวทำละลายอินทรีย์อื่นๆ เจือปนอยู่ได้แก่ ไฮโดรคาร์บอน, เมธิลเอมีน, เพนทานอน, เดตราคลอโรเอธิลีน และคาร์บอนไดซัลไฟด์ เป็นต้น



ภาควิชา.....เคส.....
สาขาวิชา.....เคสวิเคราะห์.....
ปีการศึกษา.....2537.....

ลายมือชื่อนิสิต.....*ปรานอม ขาวเมฆ*.....
ลายมือชื่ออาจารย์ที่ปรึกษา.....*วราภรณ์ ลิขิตพัฒนไพบุลย์*.....
ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....



C525138 : MAJOR CHEMISTRY

KEY WORD : HEADSPACE ANALYSIS / RESIDUAL SOLVENT / ORGANIC VOLATILE IMPURITY

PRANOM KHAOWMEK : DEVELOPMENT OF HEADSPACE METHOD FOR ANALYSIS OF ORGANIC VOLATILE IMPURITIES AND OTHER RESIDUAL SOLVENTS IN DRUG. THESIS ADVISOR : Dr. VARAPORN LEEPIPATPIBOON , D.Sc. 168 pp. ISBN 974-631-769-5

A headspace technique was developed for the determination of organic volatile impurities and other residual solvents i.e., methylene chloride , chloroform , benzene , trichloroethylene and 1,4 dioxane in drug samples. The various factors having the effect on sensitivity and percent recovery were studied. The temperature of 70 °C , equilibration time of 40 minutes , the liquid to gas phase volume ratio of 5:5 in 10 mL vial for headspace , 1.00 mL of injection volume , and salting out with 1.00 g. of anhydrous sodium sulfate were chosen as the optimal headspace analysis condition for the analysis of the organic volatile impurities and other residual solvents in drug. The method detection limit of this technique is in the range of 0.2 ppb to 0.2 ppm for all studied compound (except 12.41 ppm for 1,4-dioxane). The accuracy of this technique was also studied and the percent errors are in the range of 0.42 - 5.06 % at the ppm level of concentration. Moreover , the developed technique was also applied to analyse fifteen drug samples from thirteen companies. Chromatographic and mass spectral analysis detected methylene chloride in the concentration of 38.10 - 202.10 µg/g and chloroform in the concentration of 957.10 ng/g. Other volatile solvents found were i.e., cyclohexane , methylamine, pentanone , ethanol, tetrachloroethylene and carbondisulfide.

ภาควิชา.....เคมี.....

สาขาวิชา.....เคมีวิเคราะห์.....

ปีการศึกษา.....2537.....

ลายมือชื่อผู้ผลิต.....Pranom Khaowmek.....

ลายมือชื่ออาจารย์ที่ปรึกษา.....Varaporn Leeppatpiboon.....

ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

ACKNOWLEDGEMENT

The author would like to take this opportunity to convey the most sincere thanks and appreciation to her advisor Dr. Varaporn Leepipatpiboon. This work would not be completed without her kindness, guidance, and assistance. She is also grateful to Miss Tasanee Chokcharoenrat for her helpful and pharmaceutical knowledge.

She is grateful to the National Research Council of Thailand for the financial support. Thank to the staffs in the instrumental laboratory in Chemistry Building 3, Department of Chemistry, Faculty of Science, Chulalongkorn University and Department of Forensic Medicine, Faculty of Medicine Chulalongkorn University for their permission of using the gas chromatograph and mass selective detector, respectively.

She wishes to appreciate the director of Scientific and Technological Research Equipment Centre , Chulalongkorn University for his encouragement. She greatly appreciated Miss supanee Hiruntanakijakul and Mr. Wutichai Yentongchai for their help and guidance during the course of this study.

Finally, the author is greatly indebted and deeply grateful to her parents and the family members for their encouragement and understanding throughout the entire course of study.



CONTENTS

	PAGE
ABSTRACT (IN THAI).....	IV
ABSTRACT (IN ENGLISH).....	V
ACKNOWLEDGEMENTS.....	VI
CONTENTS.....	VII
LIST OF TABLES.....	XIII
LIST OF FIGURES.....	XVIII
CHAPTER I : INTRODUCTION	
Problem Definition	1
Literature Review.....	4
Hypothesis.....	15
The Purpose of the Study.....	16
CHAPTER II : THEORY	
Basic Theory of Headspace Analysis.....	17
Sensitivity of Headspace Analysis Technique.....	24
Method of Increasing the Analytical Sensitivity of Headspace Analysis Technique.....	25
1. Temperature.....	25
2. Phase Ratio.....	27
3. Injection Volume.....	28
4. Salting Out Effect.....	30

	PAGE
Pharmaceutical Formulation.....	31
Pharmaceutical Tablets.....	31
1. Diluents.....	31
2. Binders and Adhesives.....	32
3. Disintegrates.....	33
4. Lubricants, Antiadherents and Glidants.....	33
5. Colors, Flavors and Sweeteners.....	34
Orally Ingested Tablets.....	35
1. Sugar- and Chocolate-Coated Tablets.....	35
2. Film-Coated Tablets.....	36
 CHAPTER III : EXPERIMENTAL.	
Apparatus.....	38
Chemicals.....	39
1. The Standard of Volatile Organic Compounds.....	39
2. Organic Solvents.....	39
3. Salts.....	40
4. Double Distallated Water.....	40
Preparation of the Standard Solutions.....	40
1. The Standard Solution for the Headspace Study Using GC with FID as a Detector.....	40
1.1 The Single Component Standard Stock Solution of Methylene chloride, Chloroform, Benzene, Trichloroethylene and 1,4-dioxane in Dimethyl sulfoxide(DMSO).....	40

1.2	The Single Standard Solution of Methylene chloride Chloroform, Benzene, and Trichloroethylene in Dimethyl sulfoxide (DMSO).....	41
1.3	The Standard Mixture Solution of Methylene chloride Chloroform, Benzene, and Trichloroethylene and 1,4-Dioxane in Water.....	41
2.	The Standard Solution for the Headspace Study Using GC with ECD as a Detector.....	42
2.1	The Single Component Standard Stock Solution of Methylene chloride , Chloroform , Benzene , Trichloroethylene and 1,4-dioxane in Dimethyl sulfoxide(DMSO).....	42
2.2	The Single Standard Solution of Methylene chloride , Chloroform, Benzene, and Trichloroethylene in Dimethyl sulfoxide (DMSO).....	43
2.3	The Standard Mixture Solution of Methylene chloride , Chloroform, Benzene, and Trichloroethylene and 1,4-Dioxane in Water.....	43
3.	The Standard Solution for the Calibration Curve Using GC with FID as a Detector.....	43
3.1	The Single Component Standard Stock Solution of Methylene chloride , Chloroform , Benzene , Trichloroethylene and 1,4-dioxane in Dimethyl sulfoxide(DMSO).....	43

4. The Standard Solution for the Calibration Curve Using GC with ECD as a Detector.....	44
Gas Chromatographic Condition.....	45
The Study of the Various Parameters on the Sensitivity of Headspace Technique Using FID as a Detector.....	47
1. Temperature.....	47
2. Equilibration Time.....	48
3. Liquid to Gas Phase Volume Ratio.....	49
4. Salting Out Effect.....	49
Method Detection Limit.....	51
Quantitative Headspace Analysis.....	51
1. The External Standardisation Method.....	51
1.1 When the Distribution Coefficient, K , of the Interested Compounds is Known.....	52
1.2 When the Distribution Coefficient, K , of the Interested Compounds is not Known.....	52
The Determination of Equilibration Concentration of the Interested Compound in Gas Phase Using External Standardization Method.....	53
The Study of Precision of Automated Headspace Technique for Determination Volatile Organic Compounds in Aqueous Solution.....	59
1. The Procedure for the Study of Precision of Each Volatile Organic Compound Using GC with FID as a Detector.....	59

2. The Procedure for the Study of Precision of Each Volatile Organic Compound Using GC with ECD as a Detector.....	60
The Study of Linearity of Automated Headspace Technique for Determination Volatile Organic Compounds in Aqueous Solution.....	60
1. The Procedure for the Study of Linearity of Each Volatile Organic Compound Using GC with FID as a Detector.....	61
2. The Procedure for the Study of Linearity of Each Volatile Organic Compound Using GC with ECD as a Detector.....	61
The Study of Accuracy of Automated Headspace Technique for Determination Volatile Organic Compounds in Aqueous Solution.....	62
1. The Procedure for the Study of Accuracy of Each Volatile Organic Compound Using GC with FID as a Detector.....	62
2. The Determination of Volatile Organic Compound in Real Samples..	63
Confirmation on the Structure of Volatile Organic Impurities and Other Residual Solvents by GC/MSD.....	69
CHAPTER IV: RESULTS AND DISCUSSIONS	
The Study of Temperature.....	70
The Study of Equilibration Time.....	78
The Study of Liquid to Gas Phase Volume Ratio.....	89
The Study of Salting Out Effect.....	96
The Precision of Headspace Analysis Technique.....	110
Method Detection Limit.....	113

	PAGE
The Linearity of Headspace Analysis Technique.....	115
The Accuracy of Headspace Analysis Technique.....	121
The Determination of Volatile Organic Compounds in Drug Samples...	123
CHAPTER V : CONCLUSION.....	155
REFERENCES.....	158
APPENDIX	
APPENDIX A.....	166
APPENDIX B.....	167
VITA.....	168

LIST OF TABLES

TABLE	PAGE
3.1 The desity of the standard of volatile organic compounds used in the headspace study.....	39
3.2 The measuring volume standard volatile organic compounds and the concentration of the single component standard stock solution in DMSO...41	
3.3 The measuring volume of standard volatile organic compounds and the concentration of the single component standard stock solution in DMSO...42	
3.4 The suitable GC conditions for the study of volatile organic compounds in mixture component solution using FID as a detector.....	45
3.5 The suitable GC conditions for the study of volatile organic compounds in mixture component solution using ECD as a detector.....	46
3.6 The GC/MSD condition for the confirmation on structure of volatile organic impurited in drug.....	69
4.1 The effect of temperature on the distribution coefficient and the equilibrium concentration of each volatile compound in gas phase with concentration of aqueous standard solution in lower level of ppm.....	72
4.2 The effect of temperature on the distribution coefficient and the equilibrium concentration of each volatile compound in gas phase with concentration of aqueous standard solution in higer level of ppm.....	73

4.3	The effect of temperature on the sensitivity of each volatile compound in gas phase with concentration of aqueous standard solution in lower level of ppm.....	74
4.4	The effect of temperature on the sensitivity of each volatile compound in gas phase with concentration of aqueous standard solution in higher level of ppm.....	75
4.5	The result of the effect of equilibration time on the peak area of 4.21 ppm methylene chloride.....	79
4.6	The result of the effect of equilibration time on the peak area of 12.63 ppm methylene chloride.....	80
4.7	The result of the effect of equilibration time on the peak area of 4.24 ppm chloroform.....	81
4.8	The result of the effect of equilibration time on the peak area of 12.73 ppm chloroform.....	82
4.9	The result of the effect of equilibration time on the peak area of 4.19 ppm benzene.....	83
4.10	The result of the effect of equilibration time on the peak area of 12.58 ppm benzene.....	84
4.11	The result of the effect of equilibration time on the peak area of 4.21 ppm trichloroethylene.....	85
4.12	The result of the effect of equilibration time in the peak area of 12.63 ppm trichloroethylene.....	86

4.13	The result of the effect of equilibration time on the peak area of 99.26 ppm 1,4-dioxane.....	87
4.14	The result of the effect of equilibration time on the peak area of 297.79 ppm 1,4-dioxane.....	88
4.15	The effect of liquid to gas phase ratio on the distribution coefficient and the equilibrium concentration of each volatile compound in gas phase with concentration of aqueous standard solution in lower level of ppm.....	90
4.16	The effect of liquid to gas phase ratio on the distribution coefficient and the equilibrium concentration of each volatile compound in gas phase with concentration of aqueous standard solution in higher level of ppm.....	91
4.17	The effect of liquid to gas phase ratio on the sensitivity of each volatile compound in gas phase with concentration of aqueous standard solution in lower level of ppm.....	92
4.18	The effect of liquid to gas phase ratio on the sensitivity of each volatile compound in gas phase with concentration of aqueous standard solution in higher level of ppm.....	93
4.19	The results of salting out effect on the percent recovery of each volatile compound in mixture solution with concentration of aqueous standard in lower level of ppm using FID as a detector.....	97
4.20	The results of salting out effect on the percent recovery of each volatile compound in mixture solution with concentration of aqueous standard in higher level of ppm using FID as a detector.....	98

4.21	The results of salting out effect on the percent recovery of each volatile compound in mixture solution with concentration of aqueous standard in lower level of ppb using ECD as a detector.....	100
4.22	The results of salting out effect on the percent recovery of each volatile compound in mixture solution with concentration of aqueous standard in higher level of ppb using ECD as a detector.....	100
4.23	The percent recovery of each volatile compound at two concentration levels in mixture solution with anhydrous sodium sulfate.....	107
4.24	The sensitivity of each volatile compound at two concentration levels in mixture solution with anhydrous sodium sulfate.....	108
4.25	The optimum headspace analysis condition used in the investigation of the method detection limit, the precision, the accuracy and analyses of the real drug samples using FID and ECD as a detector	109
4.26	The precision of automated headspace analysis technique using FID as a detector.....	111
4.27	The precision of automated headspace analysis technique using ECD as a detector.....	112
4.28	The method detection limit of each volatile compound in aqueous solution using FID as a detector.....	114
4.29	The method detection limit of each volatile compound in aqueous solution using ECD as a detector.....	114

4.30	The results of linearity of the concentration range and the correlation coefficient of each volatile compound using FID as a detector.....	116
4.31	The results of linearity of the concentration range and the correlation coefficient of each volatile compound using ECD as a detector.....	116
4.32	The results of the analysis of synthetic unknown solution by external standard method and using FID as a detector.....	121
4.33	The concentration of the interested volatile organic compounds in fifteen drug samples using gas chromatograph equipped with ionization detector and electron capture detector.....	125
4.34	The other volatile organic compounds in fifteen drug samples using gas chromatograph equipped with ionization detector and mass selective detector	126

LIST OF FIGURES

FIGURE	PAGE
3.1 The calibration curve of methylene chloride in dimethyl sulfoxide using FID as a detector.....	55
3.2 The calibration curve of chloroform in dimethyl sulfoxide using FID as a detector.....	55
3.3 The calibration curve of benzene in dimethyl sulfoxide using FID as a detector.....	56
3.4 The calibration curve of trichloroethylene in dimethyl sulfoxide using FID as a detector.....	56
3.5 The calibration curve of 1,4-dioxane in dimethyl sulfoxide using FID as a detector.....	57
3.6 The calibration curve of methylene chloride in dimethyl sulfoxide using ECD as a detector.....	57
3.7 The calibration curve of chloroform in dimethyl sulfoxide using ECD as a detector.....	58
3.8 The calibration curve of trichloroethylene in dimethylsulfoxide using ECD as a detector.....	58
3.9 The external standard calibration curve of methylene chloride using FID as a detector.....	65

3.10	The external standard calibration curve of chloroform using FID as a detector.....	65
3.11	The external standard calibration curve of benzene using FID as a detector.....	65
3.12	The external standard calibration curve of trichloroethylene using FID as a detector.....	66
3.13	The external standard calibration curve of 1,4-dioxane using FID as a detector.....	67
3.14	The external standard calibration curve of methylene chloride using ECD as a detector.....	67
3.15	The external standard calibration curve of chloroform using ECD as a detector.....	68
3.16	The external standard calibration curve of trichloroethylene using ECD as a detector.....	68
4.1	The effect of temperature on the distribution coefficient of each volatile organic compound with concentration of aqueous standard solution in lower level of ppm.....	76
4.2	The effect of temperature on the distribution coefficient of each volatile organic compound with concentration of aqueous standard solution in higher level of ppm.....	76
4.3	The effect of temperature on the sensitivity of each volatile organic compound with concentration of aqueous standard solution in lower level of ppm.....	76

4.4	The effect of temperature on the sensitivity of each volatile organic compound with concentration of aqueous standard solution in higher level of ppm.....	77
4.5	The effect of equilibration time on the peak area of 4.21 ppm methylene chloride.....	79
4.6	The effect of equilibration time on the peak area of 12.63 ppm methylene chloride.....	80
4.7	The effect of equilibration time on the peak area of 4.24 ppm chloroform.....	81
4.8	The effect of equilibration time on the peak area of 12.73 ppm chloroform.....	82
4.9	The effect of equilibration time on the peak area of 4.19 ppm benzene.....	83
4.10	The effect of equilibration time on the peak area of 12.58 ppm benzene.....	84
4.11	The effect of equilibration time on the peak area of 4.21 ppm trichloroethylene.....	85
4.12	The effect of equilibration time on the peak area of 12.63 ppm trichloroethylene.....	86
4.13	The effect of equilibration time on the peak area of 99.26 ppm 1,4-dioxane....	87
4.14	The effect of equilibration time on the peak area of 297.79 ppm 1,4-dioxane..	88
4.15	The distribution coefficient of each volatile organic compound with concentration of aqueous standard solution in lower level of ppm versus liquid to gas phase ratio.....	94
4.16	The distribution coefficient of each volatile organic compound with concentration of aqueous standard solution in higher level of ppm versus liquid to gas phase volume ratio.....	94

4.17	The effect of liquid to gas phase volume ratio on the sensitivity of each volatile organic compound with concentration of aqueous standard solution in lower level of ppm	95
4.18	The effect of liquid to gas phase volume ratio on the sensitivity of each volatile organic compound with concentration of aqueous standard solution in higher level of ppm	95
4.19	The effect of salting out on the distribution coefficient of each volatile organic compound in mixture solution with concentration of aqueous standard solution in lower level of ppm using FID as a detector.....	99
4.20	The effect of salting out on the distribution coefficient of each volatile organic compound in mixture solution with concentration of aqueous standard solution in higher level of ppm using FID as a detector.....	99
4.21	The effect of salting out on the distribution coefficient of each volatile organic compound in mixture solution with concentration of aqueous standard solution in lower level of ppb using ECD as a detector.....	101
4.22	The effect of salting out on the distribution coefficient of each volatile organic compound in mixture solution with concentration of aqueous standard solution in higher level of ppb using ECD as a detector.....	101
4.23	The effect of salting out on the sensitivity of each volatile organic compound in mixture solution with concentration of aqueous standard solution in lower level of ppm using FID as a detector.....	102

4.24	The effect of salting out on the sensitivity of each volatile organic compound in mixture solution with concentration of aqueous standard solution in higher level of ppm using FID as a detector.....	102
4.25	The effect of salting out on the sensitivity of each volatile organic compound in mixture solution with concentration of aqueous standard solution in lower level of ppb using ECD as a detector.....	103
4.26	The effect of salting out on the sensitivity of each volatile organic compound in mixture solution with concentration of aqueous standard solution in higher level of ppb using ECD as a detector.....	103
4.27	The effect of salting out on the percent recovery of each volatile organic compound in mixture solution with concentration of aqueous standard solution in lower level of ppm using FID as a detector.....	104
4.28	The effect of salting out on the percent recovery of each volatile organic compound in mixture solution with concentration of aqueous standard solution in higher level of ppm using FID as a detector.....	104
4.29	The effect of salting out on the percent recovery of each volatile organic compound in mixture solution with concentration of aqueous standard solution in lower level of ppb using ECD as a detector.....	105
4.30	The effect of salting out on the percent recovery of each volatile organic compound in mixture solution with concentration of aqueous standard solution in higher level of ppb using ECD as a detector.....	105

4.31	The linearity concentration ranges of methylene chloride in aqueous solution using FID as a detector.....	117
4.32	The linearity concentration ranges of chloroform in aqueous solution using FID as a detector.....	117
4.33	The linearity concentration ranges of benzene in aqueous solution using FID as a detector.....	118
4.34	The linearity concentration ranges of trichloroethylene in aqueous solution using FID as a detector.....	118
4.35	The linearity concentration ranges of 1,4-dioxane in aqueous solution using FID as a detector.....	119
4.36	The linearity concentration ranges of methylene chloride in aqueous solution using ECD as a detector.....	119
4.37	The linearity concentration ranges of chloroform in aqueous solution using ECD as a detector.....	120
4.38	The linearity concentration ranges of trichloroethylene in aqueous solution using ECD as a detector.....	120
4.39	The gas chromatogram of standard mixture in aqueous solution.....	129
4.40	The gas chromatogram of (A) Amoxicillin (Beechem Co.,Ltd.) and (B) Amoxicillin+standard mixture in aqueous solution.....	130
4.41	The gas chromatogram of (A) Aspirin (Unichem Co.,Ltd.) and (B) Aspirin + standard mixture in aqueous solution.....	131

4.42	The gas chromatogram of (A) Aspent A.D.(Unichem Co.,Ltd.) and (B) Aspent A.D.+ standard mixture in aqueous solution.....	132
4.43	The gas chromatogram of (A) Vitamin B1,6,12(Mearck Co.,Ltd.) and (B) Vitamin B1,6,12 + standard mixture in aqueous solution.....	133
4.44	The gas chromatogram of (A) Vitamin B1,6,12(Olic Co.,Ltd.) and (B) Vitamin B1,6,12 + standard mixture in aqueous solution.....	134
4.45	The gas chromatogram of (A) Vitamin B1,6,12(P.P. Lab Co.,Ltd.) and (B) Vitamin B1,6,12 + standard mixture in aqueous solution.....	135
4.46	The gas chromatogram of (A) Vitamin B1,6,12(Takada Co.,Ltd.) and (B) Vitamin B1,6,12 + standard mixture in aqueous solution.....	136
4.47	The gas chromatogram of (A) Vitamin B1,6,12(MearckCo.,Ltd.) and (B) Vitamin B1,6,12 + standard mixture in aqueous solution.....	137
4.48	The gas chromatogram of (A) Brofen (Parke-Davis Co.,Ltd.) and (B) Brofen + standard mixture in aqueous solution.....	138
4.49	The gas chromatogram of (A) Ibuprofen (Parke-Davis Co.,Ltd.) and (B) Ibuprofen +standard mixture in aqueous solution.....	139
4.50	The gas chromatogram of (A) Clamosin (Biolab Co.,Ltd.) and (B) Clamosin + standard mixture in aqueous solution.....	140
4.51	The gas chromatogram of (A) Erythromycin (Pharmaceutical Organisation) and (B) Erythromycin + standard mixture in aqueous solution.....	141
4.52	The gas chromatogram of (A) Erythromycin (Abbott Co.,Ltd.) and (B) Erythromycin + standard mixture in aqueous solution.....	142

4.53	The gas chromatogram of (A) Erythromycin (Sevipharm Co.,Ltd.) and (B) Erythromycin + standard mixture in aqueous solution.....	143
4.54	The gas chromatogram of (A) Fuben 500 (TO Co.,Ltd.) and (B) Fuben 500 + standard mixture in aqueous solution.....	144
4.55	The gas chromatogram of (A) Erythromycin (Sevipharm Co.,Ltd.) and (B) Erythromycin + standard mixture in aqueous solution.....	145
4.56	The gas chromatogram of (A) Stresstab 600 + Zinc (F.E.Zuellig Co.,Ltd.) and (B) Stresstab 600 + Zinc + standard mixture in aqueous solution.....	146
4.57	The gas chromatogram with MSD detection for headspace of Amoxicillin drug sample in aqueous solution.....	147
4.58	The mass spectrum for headspace of Amoxicillin drug sample with the retention time of 2.35 min.	148
4.59	The gas chromatogram with MSD detection for headspace of Clamosin drug sample in aqueous solution.....	149
4.60	The mass spectrum for headspace of Clamosin drug sample with the retention time of 2.34 min.	150
4.61	The gas chromatogram with MSD detection for headspace of Erythromycin (Pharmaceutical Organisation Co.,Ltd.) drug sample in aqueous solution.....	151
4.62	The mass spectrum for headspace of Erythromycin (Pharmaceutical Organization Co.,Ltd.) drug sample with the retention time of 2.34 min.....	152

4.63	The gas chromatogram with MSD detection for headspace of Erythromycin (P.P. Lab Co.,Ltd.) drug sample in aqueous solution.....	153
4.64	The mass spectrum for headspace of Erythromycin (P.P. Lab. Co.,Ltd.) drug sample with the retention time of 3.42 min.	154