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การพัฒนาและการประเมินผลนอกกายของไดอะซีแพมไมโครอิมัลชัน  
ชนิดน้ำมันในน้ำเป็นระบบนำส่งยาฉีด



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ศูนย์วิทยทรัพยากร

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**DEVELOPMENT AND IN VITRO EVALUATION OF  
DIAZEPAM OIL IN WATER MICROEMULSION  
AS PARENTERAL DRUG DELIVERY SYSTEM**



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**ศูนย์วิทยทรัพยากร**  
**จุฬาลงกรณ์มหาวิทยาลัย**

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ยาฉีดไมโครอิมัลชันชนิดน้ำมันในน้ำได้เตรียมขึ้นเพื่อเพิ่มการละลาย และความคงตัวของยาไดอะซีแพม ไมโครอิมัลชันที่ศึกษาเตรียมโดยใช้น้ำมันถั่วเหลือง, ทวิน 20 หรือทวิน 80 เป็นสารลดแรงตึงผิว, กลีเซอริน หรือโพर्फีลีน กลัยคอล หรือ โพลีเอทิลีน กลัยคอล 400 เป็นสารลดแรงตึงผิวร่วม และน้ำสำหรับเตรียมยาฉีด จากการศึกษาคพบว่าทวิน 80 สามารถเกิดไมโครอิมัลชันชนิดน้ำมันในน้ำเมื่อใช้กลีเซอรินและโพลีเอทิลีน กลัยคอล 400 เป็นส่วนประกอบ กลีเซอรินซึ่งใช้เป็นสารลดแรงตึงผิวร่วมสามารถทำให้เกิดไมโครอิมัลชันได้ดีกว่าโพลีเอทิลีน กลัยคอล 400 ในขณะที่โพर्फีลีน กลัยคอล ไม่สามารถทำให้เกิดไมโครอิมัลชันได้ ในซูโด-เทอร์นารีเฟสไดอะแกรมพบว่าพื้นที่ที่เกิดไมโครอิมัลชันเพิ่มขึ้นเมื่ออัตราส่วนของสารลดแรงตึงผิวและสารลดแรงตึงผิวร่วมเพิ่มขึ้น ผลการทดสอบโดยการเจือจาง และการยอมสี พบว่าเป็นไมโครอิมัลชันเป็นชนิดน้ำมันในน้ำขนาดเส้นผ่านศูนย์กลางเฉลี่ยของไมโครอิมัลชันทั้งที่มียาไดอะซีแพมและไม่มียาอยู่ระหว่าง 50-100 นาโนเมตร ขนาดของไมโครอิมัลชันที่ไม่มียาไดอะซีแพมลดลง เมื่ออัตราส่วนของสารลดแรงตึงผิวและสารลดแรงตึงผิวร่วมเพิ่มขึ้น และขนาดเส้นผ่านศูนย์กลางเฉลี่ยของไมโครอิมัลชันเพิ่มขึ้นภายหลังจากการทำไรเซอโดยใช้หมอนิ่งอัดไอ การละลายของยาไดอะซีแพมในไมโครอิมัลชันชนิดน้ำมันในน้ำคือ 10 มิลลิกรัม/มิลลิลิตร ซึ่งเพิ่มขึ้นประมาณ 200 เท่า เมื่อเทียบกับการละลายของไดอะซีแพมในน้ำ แต่อย่างไรก็ตามไมโครอิมัลชันที่ได้มีความหนืดสูง โดยเฉพาะอย่างยิ่งเมื่อมียาไดอะซีแพมอยู่ในตัวรับ การปลดปล่อยยาจากไมโครอิมัลชันสามารถปลดปล่อยยาได้ยาวนานกว่า 48 ชั่วโมง ปริมาณยาที่ถูกปลดปล่อยจะเพิ่มขึ้นเมื่อความเข้มข้นของยาในไมโครอิมัลชันเพิ่มขึ้น แต่อย่างไรก็ตามรูปแบบการปลดปล่อยของยาไม่มีความแตกต่างอย่างมีนัยสำคัญ จลนศาสตร์การปลดปล่อยของยาเป็นแบบวิลบูลและคิวบ์รูท ภายหลังจากการทดสอบความคงตัวภายใต้สภาวะเร่ง พบว่าไมโครอิมัลชันมีความคงตัวทั้งทางกายภาพและเคมี

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KEY WORD: O/W MICROEMULSION / LIPOPHILIC DRUG / PHYSICOCHEMICAL CHARACTERISTICS / *IN VITRO* DRUG RELEASE / ENHANCE SOLUBILITY / ENHANCE STABILITY

RATTANASUDA NILNAKRA: DEVELOPMENT AND *IN VITRO* EVALUATION OF DIAZEPAM OIL IN WATER MICROEMULSION AS PARENTERAL DRUG DELIVERY SYSTEM. THESIS ADVISOR: ASSOC. PROF. GARNPIMOL C. RITTHIDEJ, Ph.D. 247 pp. ISBN 974-17-0899-8

Parenteral o/w microemulsion was prepared to enhance the solubility and stability of diazepam. Soybean oil, tween 20/tween 80 as a surfactant, glycerin/propylene glycol/polyethylene glycol 400 as a cosurfactant and water for injection were used. The results indicated that tween 80 could form o/w microemulsions with glycerin and polyethylene glycol 400. Glycerin was a better cosurfactant than polyethylene glycol 400 while propylene glycol could not form microemulsion. The area of microemulsion in pseudo-ternary phase diagram increased with the increasing weight ratio of surfactant to cosurfactant. The results from dilution and dye solubility tests showed that the microemulsions were o/w type. The mean droplet diameters of microemulsion with and without diazepam were in between 50-100 nm. The size of microemulsion without diazepam decreased with the increasing ratio of surfactant to cosurfactant. And the mean droplet diameter increased after autoclaving. The solubility of diazepam in o/w microemulsions was found to be 10 mg/ml, which was about 200 fold increase compared with the solubility in water. However, the viscosity of microemulsions was high especially when loaded with diazepam. The drug diffusion from microemulsions was sustained more than 48 hours. The amount of drug diffusion increased when increasing the drug concentration in microemulsion. However, the diffusion patterns showed no significant difference ( $p > 0.05$ ) between formulations containing drug 5 mg/ml and 10 mg/ml. The drug diffusion kinetic was best fitted with Weibull model and cube root model. After accelerated stability testing, microemulsions still showed good physical and chemical stability.

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Field of study ....Industrial Pharmacy..... Advisor's signature .....*G. C. Ritthidej*.....  
Academic year .....2002..... Co-advisor's signature .....

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## CONTENTS

	Page
ABSTRACT (THAI) .....	iv
ABSTRACT (ENGLISH) .....	v
ACKNOWLEDGEMENTS .....	vi
CONTENTS .....	vii
LIST OF TABLES .....	viii
LIST OF FIGURES .....	xiv
LIST OF ABBREVIATIONS .....	xxiv
CHAPTER	
I    INTRODUCTION .....	1
II   LITERATURE REVIEW .....	4
III  MATERIALS AND METHODS .....	29
IV  RESULTS .....	44
V   DISCUSSION AND CONCLUSION .....	125
REFERENCES .....	144
APPENDICES .....	153
VITA .....	247

ศูนย์วิทยทรัพยากร  
จุฬาลงกรณ์มหาวิทยาลัย

## LIST OF TABLES

Table	Page
1. Composition of intravenous fat emulsions (in grams).....	12
2. Composition of ingredients in oil dispersion of 1:1.5 surfactant:cosurfactant.....	32
3. Composition of ingredients in oil dispersion of 1:1 surfactant:cosurfactant.....	32
4. Composition of ingredients in oil dispersion of 1:0.7 surfactant:cosurfactant.....	33
5. Composition of ingredients in oil dispersion of 1:0.5 surfactant:cosurfactant.....	33
6. The formability of microemulsion systems.....	46
7. Composition of o/w microemulsions.....	47
8. The microemulsion type and non-birefringent property of the microemulsion with and without diazepam.....	51
9. The physical appearances of the microemulsions with and without diazepam both before and after sterilization by autoclaving.....	54
10. The pH, viscosity, and refractive index of the investigated microemulsions.....	55
11. Comparison of the particle diameter obtained by a computerized program and manual observation.....	62
12. Mean particle sizes of the microemulsions before and after autoclaving.....	98
13. The coefficient of determination of microemulsion preparations in various drug diffusion kinetics calculated from total drug diffusion data.....	109
14. The diffusion rate of microemulsions from cube root model.....	110
15. The physical appearances, pH, and refractive index of microemulsion preparations after stability testing.....	114
16. The mole of surfactant and cosurfactants in each ratio of microemulsion system.....	129
b1 The relationship between absorbances and concentrations of diazepam in mixture of 80% v/v phosphate buffer and 20% v/v propylene glycol at 231 nm.....	165
b2 Data of accuracy of diazepam assayed by the HPLC method.....	167
b3 Data of within run precision of diazepam assayed by the HPLC method.....	168
b4 Data of between run precision of diazepam assayed by the HPLC method.....	168
b5 Data of calibration curve of standard solutions of diazepam.....	170
c1 The viscosity of microemulsions.....	172



## LIST OF TABLES (Cont.)

Table	Page
c2 The refractive index of microemulsions before stability testing .....	173
c3 The refractive index of microemulsions after stability testing.....	174
c4 The viscosity of compounds.....	174
c5 The refractive index of compounds.....	175
c6 The content of diazepam in microemulsions before stability testing.....	175
c7 The content of diazepam in microemulsions after stability testing.....	176
d1 Particle size distribution of Formulation T1 G1.5 O8 before autoclaving.....	184
d2 Particle size distribution of Formulation T1 G1.5 O8 after autoclaving.....	184
d3 Particle size distribution of Formulation T1 G1.5 O6 before autoclaving.....	185
d4 Particle size distribution of Formulation T1 G1.5 O6 after autoclaving.....	185
d5 Particle size distribution of Formulation T1 G1.5 O4 before autoclaving.....	186
d6 Particle size distribution of Formulation T1 G1.5 O4 after autoclaving.....	186
d7 Particle size distribution of Formulation T1 G1.5 O4 D5 after autoclaving.....	187
d8 Particle size distribution of Formulation T1 G1.5 O4 D10 after autoclaving....	187
d9 Particle size distribution of Formulation T1 G1 O8 before autoclaving.....	188
d10 Particle size distribution of Formulation T1 G1 O8 after autoclaving.....	188
d11 Particle size distribution of Formulation T1 G1 O6 before autoclaving.....	189
d12 Particle size distribution of Formulation T1 G1 O6 after autoclaving.....	189
d13 Particle size distribution of Formulation T1 G1 O4 before autoclaving.....	190
d14 Particle size distribution of Formulation T1 G1 O4 after autoclaving.....	190
d15 Particle size distribution of Formulation T1 G1 O4 D5 after autoclaving.....	191
d16 Particle size distribution of Formulation T1 G1 O4 D10 after autoclaving.....	191
d17 Particle size distribution of Formulation T1 P0.7 O8 before autoclaving.....	192
d18 Particle size distribution of Formulation T1 P0.7 O8 after autoclaving.....	192
d19 Particle size distribution of Formulation T1 P0.7 O6 before autoclaving.....	193
d20 Particle size distribution of Formulation T1 P0.7 O6 after autoclaving.....	193
d21 Particle size distribution of Formulation T1 P0.7 O4 before autoclaving.....	194
d22 Particle size distribution of Formulation T1 P0.7 O4 after autoclaving.....	194
d23 Particle size distribution of Formulation T1 P0.7 O4 D5 after autoclaving.....	195
d24 Particle size distribution of Formulation T1 P0.7 O4 D10 after autoclaving...	195

## LIST OF TABLES (Cont.)

Table	Page
d25 Particle size distribution of Formulation T1 P0.5 O8 before autoclaving.....	196
d26 Particle size distribution of Formulation T1 P0.5 O8 after autoclaving.....	196
d27 Particle size distribution of Formulation T1 P0.5 O6 before autoclaving.....	197
d28 Particle size distribution of Formulation T1 P0.5 O6 after autoclaving.....	197
d29 Particle size distribution of Formulation T1 P0.5 O4 before autoclaving.....	198
d30 Particle size distribution of Formulation T1 P0.5 O4 after autoclaving.....	198
d31 Particle size distribution of Formulation T1 P0.5 O4 D5 after autoclaving.....	199
d32 Particle size distribution of Formulation T1 P0.5 O4 D10 after autoclaving....	199
d33 Particle size distribution of Formulation T1 G1.5 O4 D5 after stability testing.....	200
d34 Particle size distribution of Formulation T1 G1.5 O4 D10 after stability testing.....	200
d35 Particle size distribution of Formulation T1 G1 O4 D5 after stability testing...	201
d36 Particle size distribution of Formulation T1 G1 O4 D10 after stability testing.....	201
d37 Particle size distribution of Formulation T1 P0.7 O4 D5 after stability testing.....	202
d38 Particle size distribution of Formulation T1 P0.7 O4 D10 after stability testing.....	202
d39 Particle size distribution of Formulation T1 P0.5 O4 D5 after stability testing.....	203
d40 Particle size distribution of Formulation T1 P0.5 O4 D10 after stability testing.....	203
e1 The dissolution of diazepam from commercial diazepam injection (10 mg/ 2ml).....	230
e2 The dissolution of diazepam from Formulation T1 G1.5 O8 D5.....	230
e3 The dissolution of diazepam from Formulation T1 G1.5 O8 D10.....	231
e4 The dissolution of diazepam from Formulation T1 G1.5 O6 D5.....	231
e5 The dissolution of diazepam from Formulation T1 G1.5 O6 D10.....	231
e6 The dissolution of diazepam from Formulation T1 G1.5 O4 D5.....	232

## LIST OF TABLES (Cont.)

Table	Page
e7 The dissolution of diazepam from Formulation T1 G1.5 O4 D10.....	232
e8 The dissolution of diazepam from Formulation T1 G1 O8 D5.....	232
e9 The dissolution of diazepam from Formulation T1 G1 O8 D10.....	233
e10 The dissolution of diazepam from Formulation T1 G1 O6 D5.....	233
e11 The dissolution of diazepam from Formulation T1 G1 O6 D10.....	233
e12 The dissolution of diazepam from Formulation T1 G1 O4 D5.....	234
e13 The dissolution of diazepam from Formulation T1 G1 O4 D10.....	234
e14 The dissolution of diazepam from Formulation T1 P0.7 O8 D5.....	234
e15 The dissolution of diazepam from Formulation T1 P0.7 O8 D10.....	235
e16 The dissolution of diazepam from Formulation T1 P0.7 O6 D5.....	235
e17 The dissolution of diazepam from Formulation T1 P0.7 O6 D10.....	235
e18 The dissolution of diazepam from Formulation T1 P0.7 O4 D5.....	236
e19 The dissolution of diazepam from Formulation T1 P0.7 O4 D10.....	236
e20 The dissolution of diazepam from Formulation T1 P0.5 O8 D5.....	236
e21 The dissolution of diazepam from Formulation T1 P0.5 O8 D10.....	237
e22 The dissolution of diazepam from Formulation T1 P0.5 O6 D5.....	237
e23 The dissolution of diazepam from Formulation T1 P0.5 O6 D10.....	237
e24 The dissolution of diazepam from Formulation T1 P0.5 O4 D5.....	238
e25 The dissolution of diazepam from Formulation T1 P0.5 O4 D10.....	238
f1 The result of 2 tailed paired-sample T test of pH between before and after autoclaving .....	239
f2 The result of 2 tailed paired-sample T test of validation of mean particle diameter between computerized program and manual observation (50 particles) .....	239
f3 The result of 2 tailed paired-sample T test of validation of mean particle diameter between computerized program and manual observation (50 particles) .....	239
f4 The result of 2 tailed paired-sample T test of validation of mean particle diameter between computerized program and manual observation (50 particles) .....	240

## LIST OF TABLES (Cont.)

Table	Page
f5 The result of 2 tailed paired-sample T test of mean particle diameter between before and after autoclaving of microemulsion without drug.....	240
f6 The result of ANOVA test of mean particle diameter after autoclaving of drug loaded microemulsions.....	240
f7 The result of ANOVA test of mean particle diameter after autoclaving of drug loaded microemulsions.....	241
f8 The result of ANOVA test of mean particle diameter after autoclaving of drug loaded microemulsions.....	241
f9 The result of ANOVA test of mean particle diameter after autoclaving of drug loaded microemulsions.....	242
f10 The result of 2 tailed paired-sample T test of dissolution profile between Formulation T1 G1.5 O8 D5 and T1 G1.5 O8 D10.....	242
f11 The result of 2 tailed paired-sample T test of dissolution profile between Formulation T1 G1.5 O6 D5 and T1 G1.5 O6 D10.....	242
f12 The result of 2 tailed paired-sample T test of dissolution profile between Formulation T1 G1.5 O4 D5 and T1 G1.5 O4 D10.....	243
f13 The result of 2 tailed paired-sample T test of dissolution profile between Formulation T1 G1 O8 D5 and T1 G1 O8 D10.....	243
f14 The result of 2 tailed paired-sample T test of dissolution profile between Formulation T1 G1 O6 D5 and T1 G1 O6 D10.....	243
f15 The result of 2 tailed paired-sample T test of dissolution profile between Formulation T1 G1 O4 D5 and T1 G1 O4 D10.....	243
f16 The result of 2 tailed paired-sample T test of dissolution profile between Formulation T1 P0.7 O8 D5 and T1 P0.7 O8 D10.....	244
f17 The result of 2 tailed paired-sample T test of dissolution profile between Formulation T1 P0.7 O6 D5 and T1 P0.7 O6 D10.....	244
f18 The result of 2 tailed paired-sample T test of dissolution profile between Formulation T1 P0.7 O4 D5 and T1 P0.7 O8 D10.....	244
f19 The result of 2 tailed paired-sample T test of dissolution profile between Formulation T1 P0.5 O8 D5 and T1 P0.5 O8 D10.....	244

## LIST OF TABLES (Cont.)

<b>Table</b>		<b>Page</b>
f20	The result of 2 tailed paired-sample T test of dissolution profile between Formulation T1 P0.5 O6 D5 and T1 P0.5 O6 D10.....	245
f21	The result of 2 tailed paired-sample T test of dissolution profile between Formulation T1 P0.5 O4 D5 and T1 P0.5 O8 D10.....	245
f22	The result of 2 tailed paired-sample T test of pH between before and after stability testing.....	245
f23	The result of 2 tailed paired-sample T test of refractive index between before and after stability testing.....	245
f24	The result of 2 tailed paired-sample T test of mean particle diameter between before and after stability testing.....	246


  
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## LIST OF FIGURES

Figure	Page
1. Oil-in-water (o/w), bicontinuous, and water-in-oil (w/o) microemulsion structures. The filled larger circle (●) represent the surfactant, and the smaller empty circles (○) represent the cosurfactant (from Swarbrick and Boyland, 1994).....	1
2. Triangular phase diagram showing micellar, microemulsion, and liquid crystalline regions (from Swarbrick and Boyland, 1994).....	9
3. Effect of molecular moieties and solution conditions on the CPP of a surfactant and the resulting range of possible surfactant aggregates in water or aqueous solution (from Lawrence and Rees, 2000).....	15
4. The chemical structure, molecular formula and molecular weight of diazepam (from MacDonald et al., 1972).....	27
5. Hydrolysis of diazepam (from MacDonald et al., 1972).....	28
6. Schematic diagram of the apparatus of the <i>in vitro</i> diffusion studies.....	39
7. Asymmetrical chromatographic peak.....	42
8. Pseudo-ternary phase diagram of the system of soybean oil (O), water for injection (W), tween 80 (T), and glycerin (G) at tween 80:glycerin ratio 1:1.5 (A), 1:1 (B), 1:0.7 (C), and 1:0.5 (D). The shaded area represents the microemulsion.....	48
9. Pseudo-ternary phase diagram of the system of soybean oil (O), water for injection (W), tween 80 (T), and polyethylene glycol 400 (P) at tween 80:polyethylene glycol 400 ratio 1:0.7 (A) and 1:0.5 (B). The shaded area represents the microemulsion.....	50
10. The viscosity of microemulsions with and without diazepam.....	57
11. Comparison of the pH of microemulsions both before and after autoclaving....	60
12. The TEM photomicrograph of the Formulation T1 G1.5 O8 before autoclaving (1mm from picture equivalent to 33.33 nm).....	63
13. Particle size distribution of Formulation T1 G1.5 O8 before autoclaving.....	63
14. The TEM photomicrograph of the Formulation T1 G1.5 O8 after autoclaving (1mm from picture equivalent to 33.33 nm).....	64
15. Particle size distribution of Formulation T1 G1.5 O8 after autoclaving.....	64

## LIST OF FIGURES (Cont.)

Figure	Page
16. The TEM photomicrograph of the Formulation T1 G1.5 O6 before autoclaving (1mm from picture equivalent to 58.82 nm).....	65
17. Particle size distribution of Formulation T1 G1.5 O6 before autoclaving.....	65
18. The TEM photomicrograph of the Formulation T1 G1.5 O6 after autoclaving (1mm from picture equivalent to 33.33 nm).....	66
19. Particle size distribution of Formulation T1 G1.5 O6 after autoclaving.....	66
20. The TEM photomicrograph of the Formulation T1 G1.5 O4 before autoclaving (1mm from picture equivalent to 58.82 nm).....	67
21. Particle size distribution of Formulation T1 G1.5 O4 before autoclaving.....	67
22. The TEM photomicrograph of the Formulation T1 G1.5 O4 after autoclaving (1mm from picture equivalent to 33.33 nm).....	68
23. Particle size distribution of Formulation T1 G1.5 O4 after autoclaving.....	68
24. The TEM photomicrograph of the Formulation T1 G1.5 O4 D5 after autoclaving (1mm from picture equivalent to 33.33 nm).....	69
25. Particle size distribution of Formulation T1 G1.5 O4 D5 after autoclaving.....	69
26. The TEM photomicrograph of the Formulation T1 G1.5 O4 D10 after autoclaving (1mm from picture equivalent to 33.33 nm).....	70
27. Particle size distribution of Formulation T1 G1.5 O4 D10 after autoclaving.....	70
28. The TEM photomicrograph of the Formulation T1 G1 O8 before autoclaving (1mm from picture equivalent to 33.33 nm).....	72
29. Particle size distribution of Formulation T1 G1 O8 before autoclaving.....	72
30. The TEM photomicrograph of the Formulation T1 G1 O8 after autoclaving (1mm from picture equivalent to 58.82 nm).....	73
31. Particle size distribution of Formulation T1 G1 O8 after autoclaving.....	73
32. The TEM photomicrograph of the Formulation T1 G1 O6 before autoclaving (1mm from picture equivalent to 58.82 nm).....	74
33. Particle size distribution of Formulation T1 G1 O6 before autoclaving.....	74
34. The TEM photomicrograph of the Formulation T1 G1 O6 after autoclaving (1mm from picture equivalent to 58.82 nm).....	75
35. Particle size distribution of Formulation T1 G1 O6 after autoclaving.....	75

## LIST OF FIGURES (Cont.)

Figure	Page
36. The TEM photomicrograph of the Formulation T1 G1 O4 before autoclaving (1mm from picture equivalent to 33.33 nm).....	76
37. Particle size distribution of Formulation T1 G1 O4 before autoclaving.....	76
38. The TEM photomicrograph of the Formulation T1 G1 O4 after autoclaving (1mm from picture equivalent to 33.33 nm).....	77
39. Particle size distribution of Formulation T1 G1 O4 after autoclaving.....	77
40. The TEM photomicrograph of the Formulation T1 G1 O4 D5 after autoclaving (1mm from picture equivalent to 33.33 nm).....	78
41. Particle size distribution of Formulation T1 G1 O4 D5 after autoclaving.....	78
42. The TEM photomicrograph of the Formulation T1 G1 O4 D10 after autoclaving (1mm from picture equivalent to 33.33 nm).....	79
43. Particle size distribution of Formulation T1 G1 O4 D10 after autoclaving.....	79
44. The TEM photomicrograph of the Formulation T1 P0.7 O8 before autoclaving (1mm from picture equivalent to 33.33 nm).....	82
45. Particle size distribution of Formulation T1 P0.7 O8 before autoclaving.....	82
46. The TEM photomicrograph of the Formulation T1 P0.7 O8 after autoclaving (1mm from picture equivalent to 33.33 nm).....	83
47. Particle size distribution of Formulation T1 P0.7 O8 after autoclaving.....	83
48. The TEM photomicrograph of the Formulation T1 P0.7 O6 before autoclaving (1mm from picture equivalent to 58.82 nm).....	84
49. Particle size distribution of Formulation T1 P0.7 O6 before autoclaving.....	84
50. The TEM photomicrograph of the Formulation T1 P0.7 O6 after autoclaving (1mm from picture equivalent to 58.82 nm).....	85
51. Particle size distribution of Formulation T1 P0.7 O6 after autoclaving.....	85
52. The TEM photomicrograph of the Formulation T1 P0.7 O4 before autoclaving (1mm from picture equivalent to 33.33 nm).....	86
53. Particle size distribution of Formulation T1 P0.7 O4 before autoclaving.....	86
54. The TEM photomicrograph of the Formulation T1 P0.7 O4 after autoclaving (1mm from picture equivalent to 33.33 nm).....	87
55. Particle size distribution of Formulation T1 P0.7 O4 after autoclaving.....	87



## LIST OF FIGURES (Cont.)

Figure	Page
56. The TEM photomicrograph of the Formulation T1 P0.7 O4 D5 after autoclaving (1mm from picture equivalent to 33.33 nm).....	88
57. Particle size distribution of Formulation T1 P0.7 O4 D5 after autoclaving.....	88
58. The TEM photomicrograph of the Formulation T1 P0.7 O4 D10 after autoclaving (1mm from picture equivalent to 33.33 nm).....	89
59. Particle size distribution of Formulation T1 P0.7 O4 D10 after autoclaving.....	89
60. The TEM photomicrograph of the Formulation T1 P0.5 O8 before autoclaving (1mm from picture equivalent to 33.33 nm).....	90
61. Particle size distribution of Formulation T1 P0.5 O8 before autoclaving.....	90
62. The TEM photomicrograph of the Formulation T1 P0.5 O8 after autoclaving (1mm from picture equivalent to 58.82 nm).....	91
63. Particle size distribution of Formulation T1 P0.5 O8 after autoclaving.....	91
64. The TEM photomicrograph of the Formulation T1 P0.5 O6 before autoclaving (1mm from picture equivalent to 33.33 nm).....	92
65. Particle size distribution of Formulation T1 P0.5 O6 before autoclaving.....	92
66. The TEM photomicrograph of the Formulation T1 P0.5 O6 after autoclaving (1mm from picture equivalent to 33.33 nm).....	93
67. Particle size distribution of Formulation T1 P0.5 O6 after autoclaving.....	93
68. The TEM photomicrograph of the Formulation T1 P0.5 O4 before autoclaving (1mm from picture equivalent to 33.33 nm).....	94
69. Particle size distribution of Formulation T1 P0.5 O4 before autoclaving.....	94
70. The TEM photomicrograph of the Formulation T1 P0.5 O4 after autoclaving (1mm from picture equivalent to 33.33 nm).....	95
71. Particle size distribution of Formulation T1 P0.5 O4 after autoclaving.....	95
72. The TEM photomicrograph of the Formulation T1 P0.5 O4 D5 after autoclaving (1mm from picture equivalent to 33.33 nm).....	96
73. Particle size distribution of Formulation T1 P0.5 O4 D5 after autoclaving.....	96
74. The TEM photomicrograph of the Formulation T1 P0.5 O4 D10 after autoclaving (1mm from picture equivalent to 33.33 nm).....	97
75. Particle size distribution of Formulation T1 P0.5 O4 D10 after autoclaving.....	97

## LIST OF FIGURES (Cont.)

Figure	Page
76. Comparison of the mean particle size of microemulsion in tween80: glycerin systems before and after autoclaving.....	99
77. Comparison of the mean particle size of microemulsion in tween80: polyethylene glycol 400 systems before and after autoclaving.....	99
78. The diffusion profile of commercial diazepam injection.....	101
79. The percentage of drug diffusion from commercial diazepam injection at different time interval.....	101
80. The diffusion profiles of diazepam microemulsions containing 1:1.5 of tween 80:glycerin.....	102
81. The percentage of drug diffusion from diazepam microemulsions containing 1:1.5 of tween 80:glycerin at different time interval.....	102
82. The diffusion profiles of diazepam microemulsions containing 1:1 of tween 80:glycerin.....	106
83. The percentage of drug diffusion from diazepam microemulsions containing 1:1 of tween 80:glycerin at different time interval.....	106
84. The diffusion profiles of diazepam microemulsions containing 1:0.7 of tween 80:polyethylene glycol 400.....	107
85. The percentage of drug diffusion from diazepam microemulsions containing 1:0.7 of tween 80:polyethylene glycol 400 at different time interval.....	102
86. The diffusion profiles of diazepam microemulsions containing 1:0.5 of tween 80:polyethylene glycol 400.....	108
87. The percentage of drug diffusion from diazepam microemulsions containing 1:0.5 of tween 80:polyethylene glycol 400 at different time interval.....	108
88. The TEM photomicrograph of the Formulation T1 G1.5 O4 D5 after stability testing (1 mm from picture equivalent to 33.33 nm).....	115
89. Particle size distribution of Formulation T1 G1.5 O4 D5 after stability testing.....	115
90. The TEM photomicrograph of the Formulation T1 G1.5 O4 D10 after stability testing (1 mm from picture equivalent to 58.82 nm).....	116

## LIST OF FIGURES (Cont.)

Figure	Page
91. Particle size distribution of Formulation T1 G1.5 O4 D10 after stability testing.....	116
92. The TEM photomicrograph of the Formulation T1 G1 O4 D5 after stability testing (1 mm from picture equivalent to 33.33 nm).....	117
93. Particle size distribution of Formulation T1 G1 O4 D5 after stability testing.....	117
94. The TEM photomicrograph of the Formulation T1 G1 O4 D10 after stability testing (1 mm from picture equivalent to 33.33 nm).....	118
95. Particle size distribution of Formulation T1 G1 O4 D10 after stability testing.....	118
96. The TEM photomicrograph of the Formulation T1 P0.7 O4 D5 after stability testing (1 mm from picture equivalent to 33.33 nm).....	119
97. Particle size distribution of Formulation T1 P0.7 O4 D5 after stability testing.....	119
98. The TEM photomicrograph of the Formulation T1 P0.7 O4 D10 after stability testing (1 mm from picture equivalent to 33.33 nm).....	120
99. Particle size distribution of Formulation T1 P0.7 O4 D10 after stability testing.....	120
100. The TEM photomicrograph of the Formulation T1 P0.5 O4 D5 after stability testing (1 mm from picture equivalent to 33.33 nm).....	121
101. Particle size distribution of Formulation T1 P0.5 O4 D5 after stability testing.....	121
102. The TEM photomicrograph of the Formulation T1 P0.5 O4 D10 after stability testing (1 mm from picture equivalent to 33.33 nm).....	122
103. Particle size distribution of Formulation T1 P0.5 O4 D10 after stability testing.....	122
104. Comparison of the mean particle size of microemulsions between before and after stability testing.....	123
105. The content of diazepam in microemulsions in tween 80:glycerin systems before and after stability testing.....	124

## LIST OF FIGURES (Cont.)

Figure	Page
106. The content of diazepam in microemulsions in tween 80:polyethylene glycol 400 systems before and after stability testing.....	124
107. Possible structure of surfactant film formation in tween 80:glycerin systems.....	127
108. Possible structure of surfactant film formation in tween 80: polyethylene glycol 400 systems.....	128
109. Possible structure of surfactant film formation in tween 80: propylene glycol systems.....	130
110. The viscosity of microemulsions.....	138
b1 The UV spectrum of diazepam in mixture of 80% v/v phosphate buffer pH 7.4 and 20% v/v propylene glycol .....	164
b2 Calibration curve of diazepam in mixture of 80% v/v phosphate buffer pH 7.4 and 20% v/v propylene glycol at 231 nm.....	165
b3 The HPLC chromatogram of (A) internal standard; and (B) diazepam.....	168
b4 The HPLC chromatograms of the standard solutions of diazepam (RT- 4.057-4.07 minutes) and the internal standard (furosemide; RT = 2.290-2.292 minutes).....	169
b5 Calibration curve of diazepam assay by HPLC method.....	170
b6 The HPLC chromatograms of the standard solutions of diazepam and the internal standard (furosemide) for calculated resolution and tailing factor ..	171
d1 The TEM photomicrographs of the Formulation T1 G1.5 O8 before autoclaving.....	204
d2 The TEM photomicrograph of the Formulation T1 G1.5 O8 after autoclaving.....	204
d3 The TEM photomicrograph of the Formulation T1 G1.5 O6 before autoclaving .....	204
d4 The TEM photomicrograph of the Formulation T1 G1.5 O6 after autoclaving.....	205
d5 The TEM photomicrograph of the Formulation T1 G1.5 O4 before autoclaving.....	205

## LIST OF FIGURES (Cont.)

Figure	Page
d6 The TEM photomicrograph of the Formulation T1 G1.5 O4 after autoclaving.....	206
d7 The TEM photomicrograph of the Formulation T1 G1.5 O4 D5 after autoclaving.....	207
d8 The TEM photomicrograph of the Formulation T1 G1.5 O4 D10 after autoclaving.....	207
d9 The TEM photomicrograph of the Formulation T1 G1 O8 before autoclaving .....	207
d10 The TEM photomicrograph of the Formulation T1 G1 O8 after autoclaving.....	208
d11 The TEM photomicrograph of the Formulation T1 G1 O6 before autoclaving.....	209
d12 The TEM photomicrograph of the Formulation T1 G1 O6 after autoclaving.....	210
d13 The TEM photomicrograph of the Formulation T1 G1 O4 before autoclaving .....	211
d14 The TEM photomicrograph of the Formulation T1 G1 O4 after autoclaving.....	211
d15 The TEM photomicrograph of the Formulation T1 G1 O4 D5 after autoclaving .....	212
d16 The TEM photomicrograph of the Formulation T1 G1 O4 D10 after autoclaving .....	212
d17 The TEM photomicrograph of the Formulation T1 P0.7 O8 before autoclaving .....	213
d18 The TEM photomicrograph of the Formulation T1 P0.7 O8 after autoclaving .....	213
d19 The TEM photomicrograph of the Formulation T1 P0.7 O6 before autoclaving.....	214
d20 The TEM photomicrograph of the Formulation T1 P0.7 O6 after autoclaving .....	215

## LIST OF FIGURES (Cont.)

Figure	Page
d21 The TEM photomicrograph of the Formulation T1 P0.7 O4 before autoclaving .....	216
d22 The TEM photomicrograph of the Formulation T1 P0.7 O4 after autoclaving .....	216
d23 The TEM photomicrograph of the Formulation T1 P0.7 O4 D5 after autoclaving .....	217
d24 The TEM photomicrograph of the Formulation T1 P0.7 O4 D10 after autoclaving .....	217
d25 The TEM photomicrograph of the Formulation T1 P0.5 O8 before autoclaving .....	218
d26 The TEM photomicrograph of the Formulation T1 P0.5 O8 after autoclaving .....	218
d27 The TEM photomicrograph of the Formulation T1 P0.5 O6 before autoclaving .....	219
d28 The TEM photomicrograph of the Formulation T1 P0.5 O6 after autoclaving .....	220
d29 The TEM photomicrograph of the Formulation T1 P0.5 O4 before autoclaving .....	221
d30 The TEM photomicrograph of the Formulation T1 P0.5 O4 after autoclaving .....	222
d31 The TEM photomicrograph of the Formulation T1 P0.5 O4 D5 after autoclaving.....	222
d32 The TEM photomicrograph of the Formulation T1 P0.5 O4 D10 after autoclaving .....	223
d33' The TEM photomicrograph of the Formulation T1 G1.5 O4 D5 after stability testing .....	223
d34 The TEM photomicrograph of the Formulation T1 G1.5 O4 D10 after stability testing .....	224
d35 The TEM photomicrograph of the Formulation T1 G1 O4 D5 after stability testing .....	225

## LIST OF FIGURES (Cont.)

Figure	Page
d36 The TEM photomicrograph of the Formulation T1 G1 O4 D10 after stability testing .....	226
d37 The TEM photomicrograph of the Formulation T1 P0.7 O4 D5 after stability testing .....	226
d38 The TEM photomicrograph of the Formulation T1 P0.7 O4 D10 after stability testing .....	227
d39 The TEM photomicrograph of the Formulation T1 P0.5 O4 D5 after stability testing .....	228
d40 The TEM photomicrograph of the Formulation T1 P0.5 O4 D10 after stability testing .....	229


  
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## LIST OF ABBREVIATIONS

°C	=	degree Celsius (centigrade)
%CV	=	percentage of coefficient of variation
CPP	=	the critical packing parameter
cps	=	centipoise
CTAB	=	hexadecyltrimethyl ammonium bromide
D	=	diazepam
DDAB	=	didodecyl ammonium bromide
et al.	=	et alii (and others)
FFA	=	free fatty acids
g	=	gram (s)
G	=	glycerin
HLB	=	hydrophile lipophile balance
HPLC	=	high-performance liquid chromatography
hr	=	hour (s)
i.e.	=	id est (that is)
IPM	=	isopropyl myristate
IV	=	intravenous
LM	=	lipid microemulsion
log	=	logarithm
LTCs	=	long chain triglycerides
MBGs	=	microemulsion-based organogels
mg	=	milligram (s)
ml	=	milliliter (s)
mm	=	millimeter (s)
MTCs	=	medium chain triglycerides
nm	=	nanometer (s)
No.	=	number of sample
o/w	=	oil in water
P	=	polyethylene glycol 400



## LIST OF ABBREVIATIONS (Cont.)

PG	=	propylene glycol
pH	=	the negative logarithm of the hydrogen ion concentration
pK <sub>a</sub>	=	the negative logarithm of its acid dissociation constant
psi	=	pound (s) per square inch
R <sup>2</sup>	=	coefficient of determination
RES	=	reticuloendothelial system
rpm	=	revolution (s) per minute
RT	=	retention time
O	=	soybean oil
SD	=	standard deviation
SEM	=	standard error of mean
SMEDDS	=	self-microemulsifying drug delivery system
T	=	tween 80
T20	=	tween 20
TEM	=	transmission electron microscopy
TPN	=	total parenteral nutrition
UV	=	ultraviolet
v/v	=	volume by volume
W	=	water for injection
w/o	=	water in oil
w/w	=	weight by weight
$\bar{X}$	=	mean value
μL	=	microliter (s)
μg	=	microgram (s)
μm	=	micrometer (s)
λ <sub>max</sub>	=	wavelength of maximum absorption