



INDEX

Sr.No.	TOPIC	Page No.
	Title Page	
	Certificate	
	Declaration	
	Acknowledgements	
	List of Tables	I-VI
	List of Abbreviations	VII-IX
	CHAPTER 1. INTRODUCTION	1-30
1.1.	Microemulsion	02
1.1.1.	Microemulsion formation and phase behavior	06
1.1.1.1.	Theories of microemulsion formation	06
1.1.1.2.	Phase behavior	07
1.1.1.3.	The role of surfactant	09
1.1.2.	Microemulsion characterization	11
1.1.3.	Microemulsion optimization	12
1.2.	Inclusion complex	12
1.2.1.	Cyclodextrins	13
1.2.2.	Inclusion compound and concept	17
1.2.3.	Mechanism of formation of inclusion complex	19
1.2.4.	Advantage of inclusion complex	19
1.2.5.	Study of comlexation and dilution effects	21
1.2.6.	Effect on dissolution and bioavailability	22
1.3.	Research envisaged	24
1.4.	References	26
	CHAPTER 2. DRUG PROFILE AND LITERATURE REVIEW	31-72
2.1.	Drug profile	31
2.1.1.	Drug profile of Cilostazol	31
2.1.1.1.	Nomenclature and physico-chemical properties	31
2.1.1.2.	Pharmacology	31
2.1.1.2.1.	Pharmacodynamic properties	31
2.1.1.2.2.	Mechanism of action	32
2.1.1.2.3.	Pharmacokinetics	32
2.1.1.2.4.	Therapeutic indications	33
2.1.1.2.5.	Adverse effects	33
2.1.1.2.6.	Contraindications	34
2.1.1.2.7.	Dose and administration	34
2.1.1.2.8.	Over dose	35
2.1.2.	Drug profile of Tadalafil	35
2.1.1.1.	Nomenclature and physico-chemical properties	35
2.1.1.2.	Mechanism of action	36
2.1.2.3.	Pharmacokinetics	36
2.1.2.4.	Dose and administration	37

2.1.2.5.	Overdose	38
2.2.	Literature Review	39
2.3.	References	63
CHAPTER 3. DEVELOPMENT OF FORMULATION FOR CILOSTAZOL		73-200
3.1.	Analytical method development of Cilostazol	73
3.1.1.	Estimation of Cilostazol by Spectrophotometry	73
3.1.1.1.	Methodology	73
3.1.1.1.1.	Reagents	73
3.1.1.1.2.	Instrument	73
3.1.1.1.3.	Preparation of working stock solution	73
3.1.1.1.4.	Preparation of standard solution	74
3.1.1.1.5.	Determination of analytical wavelength for Cilostazol	74
3.1.1.1.6.	Calibration curve	74
3.1.1.2.	Method Validation	75
3.1.1.2.1.	Linearity	75
3.1.1.2.2.	Accuracy	76
3.1.1.2.3.	Precision	76
3.1.1.2.4.	Limit of detection and Limit of quantification	80
3.1.1.3.	Result and discussion	80
3.1.1.4.	Estimation of Cilostazol (Formulation/Diffusion/Dissolution Medium)	81
3.1.1.4.1.	Preparation of working stock solution of Cilostazol	81
3.1.1.4.2.	Calibration curve of Cilostazol for inclusion efficiency measurement	81
3.1.1.4.3.	Calibration curve of Cilostazol for phase solubility measurement	81
3.1.1.4.4.	Calibration curve of Cilostazol for dissolution measurement	82
3.1.1.4.5.	Estimation of Cilostazol from its formulation	83
3.1.1.4.6.	Calibration curve of Cilostazol for diffusion measurement	83
3.1.1.4.7.	Estimation of Cilostazol (Drug retention and accelerated conditions)	83
3.1.1.4.8.	Interference of the excipients used	83
3.1.2.	Estimation of Cilostazol by HPLC method	85
3.1.2.1.	Introduction	85
3.1.2.2.	Methodology	85
3.1.2.2.1.	Material and Reagents	85
3.1.2.2.2.	Apparatus	85
3.1.2.2.3.	Preparation of working stock solution	85
3.1.2.2.4.	Chromatographic conditions	85
3.1.2.2.5.	Preparation of calibration curve	86
3.1.2.2.6.	Procedure for pharmaceutical formulations	86
3.1.2.3.	Result and discussion	86
3.1.3.	Estimation of Cilostazol in human plasma by HPLC method	92
3.1.3.1.	Methodology	92
3.1.3.1.1.	Reagents	92
3.1.3.1.2.	Apparatus	92

3.1.3.1.3.	Preparation of working stock solution	92
3.1.3.1.4.	Plasma calibration standard	92
3.1.3.1.5.	Sample extraction procedure	92
3.1.3.1.6.	System suitability study	92
3.1.3.1.7.	Chromatographic conditions	93
3.1.3.2.	Result and discussion	93
3.1.3.2.1.	Assay validation	93
3.1.3.2.2.	Extraction yield	93
3.1.3.2.3.	Stability	94
3.1.3.3.4.	System suitability	94
3.1.4.	References	97
3.2.	Microemulsion	99
3.2.1.	Preparation of oral microemulsion of Cilostazol (CME)	102
3.2.1.1.	Solubility of Cilostazol in various oil/surfactant/co-surfactant	102
3.2.1.2.	Preparation of Cilostazol microemulsions	103
3.2.2.	Characterization	107
3.2.2.1.	Appearance	107
3.2.2.2.	Stability as per stomach condition and pH determination	107
3.2.2.3.	Globule size determination	107
3.2.2.4.	Zeta potential determination	107
3.2.2.5.	Viscosity measurement	108
3.2.2.6.	Electroconductivity measurement	108
3.2.2.7.	% Transmittance measurement	108
3.2.2.8.	Active ingredient analysis	108
3.2.3.	Physical stability	112
3.2.4.	Chemical stability (Drug retention studies)	114
3.2.5.	Drug diffusion study	116
3.2.5.1.	Experimental design	117
3.2.5.1.1.	Dialysis bag technique	117
3.2.5.1.2.	Intestinal permeability study	118
3.2.6.	Result and discussion	124
3.2.7.	Reference	129
3.3.1.	Preparation of inclusion complexes	132
3.3.1.1.	Material and reagents	132
3.3.1.2.	Preparation of Cilostazol inclusion complexes	132
3.3.2.	Characterization of prepared Cilostazol-cyclodextrins inclusion complexes	134
3.3.2.1.	Phase solubility study	134
3.3.2.2.	Inclusion efficiency study	134
3.3.2.3.	IR spectroscopy study	134
3.3.2.4.	Differential scanning calorimetry	135
3.3.2.5.	X-ray powder diffraction study	135
3.3.3.	Dissolution study of Cilostazol-cyclodextrins inclusion complexes	157
3.3.3.1.	Introduction	157

3.3.3.2.	Experimental design	159
3.3.4.	Chemical stability of Cilostazol-cyclodextrin inclusion complex	187
3.3.5.	Results and discussion	190
3.3.6.	References	198
CHAPTER 4. DEVELOPMENT OF FORMULATION FOR Tadalafil		201-326
4.1.	Analytical method development for Tadalafil	201
4.1.1.	Estimation of Tadalafil by Spectrophotometry	201
4.1.1.1.	Methodology	201
4.1.1.1.1.	Reagents and Instrument	201
4.1.1.1.2.	Preparation of working stock solution	201
4.1.1.1.3.	Preparation of standard solution	201
4.1.1.1.4.	Determination of UV absorbance maxima for Tadalafil	202
4.1.1.1.5.	Calibration curve	202
4.1.1.2.	Method Validation	203
4.1.1.2.1.	Linearity	203
4.1.1.2.2.	Accuracy	203
4.1.1.2.2.1.	Intra-day accuracy of the study	204
4.1.1.2.2.2.	Inter-day accuracy of the study	204
4.1.1.2.3.	Precision	204
4.1.1.2.3.1.	Intra-day precision of the assay	205
4.1.1.2.3.2.	Inter-day precision of the assay	205
4.1.1.2.4.	Limit of detection and Limit of quantification	208
4.1.1.3.	Results and Discussion	208
4.1.1.4.	Estimation of Tadalafil (Formulation/Diffusion/Dissolution Medium)	209
4.1.1.4.1.	Preparation of working stock solution of Tadalafil	209
4.1.1.4.2.	Calibration curve of Tadalafil for inclusion efficiency measurement	209
4.1.1.4.3.	Calibration curve of Tadalafil for phase solubility measurement	209
4.1.1.4.4.	Calibration curve of Tadalafil for dissolution measurement	209
4.1.1.4.5.	Estimation of Tadalafil from its formulation	209
4.1.1.4.6.	Calibration curve of Tadalafil for diffusion measurement	210
4.1.1.4.7.	Estimation of Tadalafil (Drug retention and accelerated conditions)	210
4.1.1.4.8.	Interference of the excipients used	210
4.1.2.	Estimation of Tadalafil by HPLC	212
4.1.2.1.	Introduction	212
4.1.2.2.	Methodology	212
4.1.2.2.1.	Material and reagents	212
4.1.2.2.2.	Apparatus	212
4.1.2.2.3.	Preparation of working stock solution	212
4.1.2.2.4.	Chromatographic conditions	212
4.1.2.2.5.	Preparation of calibration curve	213
4.1.2.2.6.	Procedure for pharmaceutical formulations	213
4.1.2.3.	Results and discussion	213
4.1.3.	Estimation of Tadalafil in human plasma by HPLC	219

4.1.3.1.	Methodology	219
4.1.3.1.1.	Reagents	219
4.1.3.1.2.	Apparatus	219
4.1.3.1.3.	Preparation of working stock solution	219
4.1.3.1.4.	Plasma calibration standards	219
4.1.3.1.5.	Sample extraction procedure	219
4.1.3.1.6.	System suitability study	219
4.1.3.1.7.	Chromatographic conditions	220
4.1.3.2.	Results and discussion	220
4.1.3.2.1.	Assay validation	220
4.1.3.2.2.	Extraction yield	221
4.1.3.2.3.	Stability	221
4.1.3.2.4.	System suitability study	221
4.1.4.	Estimation of Tadalafil by spectrofluorophotometric method	224
4.1.4.1.	Methodology	224
4.1.4.1.1.	Material and reagents	224
4.1.4.1.2.	Instrument	224
4.1.4.1.3.	Preparation of working stock solution	224
4.1.4.1.4.	Preparation of stock solution	224
4.1.4.1.5.	Determination of analytical wavelength for Tadalafil	224
4.1.4.1.6.	Procedure for pharmaceutical formulation	225
4.1.4.1.7.	Preparation of Tadalafil working stock solution in spiked human plasma	225
4.1.4.1.8.	Plasma calibration standards	225
4.1.4.2.	Results and discussion	225
4.1.5.	References	231
4.2.1.	Preparation of oral microemulsion of Tadalafil (TME)	233
4.2.1.1.	Solubility of Tadalafil in various Oils/Surfactants/Co-surfactants	233
4.2.1.2.	Preparation of Tadalafil microemulsions	233
4.2.2.	Characterization	239
4.2.2.1.	Appearance	239
4.2.2.2.	Stability as per stomach condition and pH determination	239
4.2.2.3.	Globule size determination	239
4.2.2.4.	Zeta potential determination	239
4.2.2.5.	Viscosity measurement	240
4.2.2.6.	Electroconductivity measurement	240
4.2.2.7.	% Transmittance measurement	240
4.2.2.8.	Active ingredient analysis	240
4.2.3.	Physical stability	245
4.2.4.	Chemical stability (Drug retention studies)	247
4.2.5.	Drug diffusion study	250
4.2.5.1.	Experimental design	251
4.2.5.1.1.	Dialysis bag technique	251
4.2.5.1.2.	Intestinal permeability study	252
4.2.6.	Result and discussion	257

4.2.7.	Reference	262
4.3.1.	Preparation of inclusion complexes	264
4.3.1.1.	Material and reagents	264
4.3.1.2.	Preparation of Tadalafil inclusion complexes	264
4.3.2.	Characterization of prepared Tadalafil-cyclodextrins inclusion complexes	265
4.3.2.1.	Phase solubility study	265
4.3.2.2.	Inclusion efficiency study	265
4.3.2.3.	IR spectroscopy study	265
4.3.2.4.	Differential scanning calorimetry	265
4.3.2.5.	X-ray powder diffraction study	265
4.3.3.	Dissolution study of Tadalafil-cyclodextrins inclusion complexes	286
4.3.4.	Chemical stability	314
4.3.5.	Results and discussion	317
4.3.6.	References	325
CHAPTER 5. PHARMACOKINETIC STUDY		327-345
5.1.	Pharmacokinetic analysis	327
5.1.1.	Pharmacokinetic steps for calculating pharmacokinetic parameters	327
5.2.1.	Pharmacokinetic study for Cilostazol Microemulsion (CME 2), Marketed formulation (Pletoz-50) and Pure Cilostazol.	329
5.2.1.1.	Calculation of dose of drugs in rabbits	329
5.2.1.2.	Pharmacokinetic study of Cilostazol microemulsion	330
5.2.2.	Pharmacokinetic study of Cilostazol-DM-β-CD inclusion complex (1:3) prepared by co-precipitation method, Marketed formulation (Pletoz-50) and Pure Cilostazol.	333
5.2.2.1.	Experimental design	333
5.2.3.	Pharmacokinetic study for Tadalafil oral Microemulsion (TME 3), Marketed formulation (Tadora-20) and Pure Tadalafil.	336
5.2.3.1.	Calculation of dose of drugs in rabbits	336
5.2.3.2.	Experimental design	336
5.2.4.	Pharmacokinetic study of Tadalafil-β-CD inclusion complex (1:3) prepared by kneading method, Marketed formulation (Tadora-20) and Pure Tadalafil.	339
5.2.4.1.	Experimental design	339
5.3.	Results and discussion	342
5.4.	References	345
Chapter 6. Summary and Discussion		346-361
6.1.	Summary and conclusion	346
6.2.	References	361
