

Index

Chapter 1	Introduction	1
Chapter 2	Literature review	11
2.1	Introduction: ADHD	12
2.1.1	Cause and symptoms	12
2.1.1.1	Causes	12
2.1.1.2	Symptoms	12
2.1.2	Diagnosis	13
2.1.3	Treatment	13
2.1.4	Patented product of Modafinil	14
2.2	Introduction: Dyslexia	15
2.2.1	Cause and symptoms	16
2.2.1.1	Causes	16
2.2.1.2	Symptoms	18
2.2.2	Diagnosis	18
2.2.3	Treatment	18
2.2.4	Patented product of Vinpocetin	21
2.3	Formulation approaches to improve oral bioavailability	21
2.4	Self-microemulsifying drug delivery system (SMEDDS)	22
2.4.1	Mechanism of self-emulsification	24
2.4.1.1	Enhanced dissolution/solubilization	24
2.4.2	Absorption mechanism for self-micro emulsification	25
2.4.3	Composition of SMEDDS	26
2.4.3.1	Oil	26
2.4.3.2	Surfactant	26
2.4.3.3	Co-surfactant	27
2.4.3.4	Co-solvent	28
2.4.3.5	Polymer	28
2.4.4	Formation of SMEDDS	28
2.4.4.1	Advantages of SMEDDS	29
2.4.4.2	Limitations of SMEDDS	29
2.4.5	Marketed formulation of SMEDDS	30
2.5	Nasal drug delivery system: An approach for brain targeting	30
2.5.1	Anatomy of the nasal cavity	31
2.5.1.1	Nasal vestibule	31
2.5.1.2	Respiratory section	31
2.5.1.3	Olfactory region	32
2.5.2	Nose to brain delivery	32
2.5.2.1	Advantages of nasal route	33
2.5.2.2	Disadvantages of nasal route	34
2.5.2.3	Mechanism of nasal absorption	34
2.5.2.4	Blood supply to nasal cavity	35
2.5.3	Strategies to improve nasal absorption	35
2.5.4	Mucoadhesive drug delivery system	35

2.5.4.1	Mechanism of mucoadhesion	35
2.5.4.2	Theories of mucoadhesion	36
2.5.4.3	Characteristics of ideal bioadhesive polymers	36
2.6	Basic concept of microemulsion	37
2.6.1	Background of microemulsion	37
2.6.2	Structure of microemulsions	37
2.6.3	Methods for constructing phase diagram	38
2.6.4	Preparation of microemulsion	39
2.6.4.1	Phase titration method	39
2.6.4.2	Phase inversion method	39
2.6.5	Advantages of microemulsion based systems	40
2.6.6	Limitations of microemulsion	40
2.6.7	Advanced method for characterization of mucoadhesive microemulsion	40
2.6.7.1	Scattering techniques for microemulsions characterization	40
2.6.7.2	Static light scattering techniques	40
2.6.7.3	Dynamic light scattering techniques	41
2.6.7.4	Nuclear magnetic resonance studies	41
2.6.7.5	Interfacial tension	41
2.6.7.6	Electrical conductivity measurements	41
2.6.7.7	Mucoadhesive strength	42
2.6.7.8	<i>In vitro</i> diffusion study of mucoadhesive microemulsion	43
2.6.7.9	<i>In vitro</i> permeation study of mucoadhesive microemulsion	43
2.7	Patented microemulsion product	44
2.8	References	45
Chapter 3	Drug and excipients profile	54
3.1	Drug profile	55
3.1.1	Physico-chemical property of the drug: Modafinil	56
3.1.2	Pharmacology	56
3.1.2.1	Indication	56
3.1.2.2	Mechanism of action	56
3.1.2.3	Pharmacokinetic profile	57
3.1.2.4	Pharmacodynamic profile	57
3.1.2.5	Adverse drug reaction	57
3.1.2.6	Drug interaction	58
3.1.3	Physico-chemical property of the drug: Vinpocetine	58
3.1.4	Pharmacology	59
3.1.4.1	Indication	59
3.1.4.2	Mechanism of action	59
3.1.4.3	Pharmacokinetic profile	61
3.1.4.4	Pharmacodynamic profile	62
3.1.4.5	Adverse drug reaction	62
3.1.4.6	Drug interaction	62
3.2	Excipients profile	63
3.2.1	Clove oil	63
3.2.2	Capmul MCM C8 oil	64

3.2.3	Polysorbate-80 (Tween 80)	65
3.2.4	Polyethylene glycol-400	66
3.2.5	Chitosan	67
3.3	References	67
Chapter 4	Analytical method	70
4.1	Introduction	71
4.2	Analytical method development: Modafinil	71
4.2.1	UV Spectrophotometric instrument and software	72
4.2.2	HPLC instrumentation and conditions	72
4.3	Estimation of Modafinil in UV visible spectroscopy	72
4.3.1	Preparation of stock solution	72
4.3.2	Determination of λ_{max}	73
4.3.3	First order derivative in UV spectrophotometer	73
4.3.4	Preparation of calibration plot using first order derivative	73
	UV-spectroscopy	
4.4	Analytical method validation for the estimation of Modafinil using UV-spectrophotometer	73
4.4.1	Accuracy of an analytical method	74
4.4.2	Precision of an analytical method	74
4.4.3	Limit of detection (LOD) and limit of quantification (LOQ)	75
4.4.4	Linearity and range	75
4.4.5	Stability of an analytical method	76
4.5	Interference study	76
4.6	HPLC method for determination of Modafinil	76
4.6.1	Chemicals and reagents	77
4.6.2	Mobile phase preparation	77
4.6.3	Preparation of stock solution	77
4.6.4	Preparation of calibration plot of Modafinil by HPLC method	78
4.7	Analytical method validation for the estimation of Modafinil by HPLC	78
4.8	Calibration plot for Modafinil in plasma	78
4.8.1	Estimation of Modafinil in plasma	78
4.9	Results and discussion	79
4.9.1	Determination of λ_{max} and calibration plot for Modafinil	79
4.9.2	Calibration plot using first order derivative UV spectroscopy	79
4.9.3	Validation of analytical method	81
4.9.4	Solution stability of an analytical method	82
4.9.5	Interference study	82
4.9.6	Calibration of Modafinil by HPLC method	83
4.9.7	Validation of Modafinil by HPLC method	84
4.9.8	Solution stability of a HPLC analytical method	86
4.9.9	Interference study of Modafinil with excipients in formulation	86
4.9.10	Calibration plot of Modafinil in plasma using HPLC	87
4.10	Analytical method development: Vinpocetine	89

4.11	Estimation of Vinpocetine by UV spectroscopy	90
4.11.1	Preparation of stock solution	90
4.11.2	Determination of λ_{\max}	90
4.11.3	Preparation of calibration plot by UV spectroscopy	90
4.12	Analytical method validation for the estimation of vinpocetine using UV spectrophotometer	90
4.13	Interference study	91
4.14	Estimation of Vinpocetine in formulation using UV-spectrophotometer	91
4.15	Estimation of Vinpocetine in diffusion media	91
4.16	Estimation of Vinpocetine in plasma by HPLC method	91
4.16.1	Chemicals and reagents	92
4.16.2	Mobile phase preparation	92
4.16.3	Preparation of stock solution	92
4.16.4	Preparation of calibration plot of Vinpocetine by HPLC method	93
4.17	Analytical method validation for the estimation of Vinpocetine by HPLC	93
4.18	Estimation of Vinpocetine in plasma	93
4.18.1	Calibration plot of Vinpocetine in plasma	93
4.18.2	Estimation of Vinpocetine in brain homogenate	94
4.19	Results and discussion	95
4.19.1	Determination of λ_{\max} and calibration plot for Vinpocetine	95
4.19.2	Validation of analytical method	96
4.19.3	Stability of an analytical method	97
4.19.4	Interference study	98
4.19.5	Estimation of Vinpocetine in diffusion media	98
4.19.6	Calibration plot of Vinpocetine by HPLC method	99
4.19.7	Validation of Vinpocetine by HPLC method	100
4.19.8	Solution stability of HPLC analytical method	102
4.19.9	Estimation of Vinpocetine in brain homogenate	106
4.20	References	107
Chapter:5 (Part- A)	Formulation and development of oral SMEDDS	109
5.1	Introduction	110
5.2	Materials and instruments	111
5.3	Preformulation studies	112
5.3.1	Characterization of drug	113
5.3.1.1	Organoleptic characterization	113
5.3.1.2	Melting point determination	113
5.3.1.3	FT-IR study of pure drug	113
5.3.1.4	Thermal behavior of drug by DSC	113
5.3.2	Screening of excipients based on the solubility study	113
5.3.2.1	Solubility determination	114
5.3.2.2	Screening of excipients based on the emulsification efficiency	115
5.3.3	Drug-excipients compatibility study using FT-IR	115

5.3.4	Screening of surfactant: co-surfactant ratio based on pseudo ternary phase diagram	115
5.3.5	Optimization of Smix ratio by maximum drug loading capacity	116
5.4	Formulation of SMEDDS	116
5.5	Optimization of SMEDDS by D-Optimal mixture design	116
5.5.1	Optimization of formulation	117
5.5.2	Statistical analysis	118
5.6	Result and discussion	119
5.6.1	Organoleptic characteristics	119
5.6.2	Melting point determination	119
5.6.3	FT-IR study of pure drug	119
5.6.4	Thermal behavior of drug by DSC	120
5.6.5	Screening excipients based on solubility study	121
5.6.6	Screening of excipients based on emulsification efficiency	125
5.6.7	Drug-excipients compatibility studies	125
5.6.8	Screening of surfactant: co-surfactant (Smix) ratio based on pseudo ternary phase diagram	126
5.6.9	Optimization of Smix ratio based on maximum drug loading capacity	128
5.6.10	Finalization of concentration range for the SMEDDS formulation	129
5.6.11	Optimization of SMEDDS using D-Optimal Mixture Design	129
5.6.12	ANOVA analysis for response Y1: globule size	130
5.6.12.1	Mathematical model for globule size (Y1)	132
5.6.12.2	Contour and 3D surface plot	133
5.6.13	ANOVA analysis for response Y2: % transmittance	134
5.6.13.1	Mathematical model for % transmittance (Y2)	136
5.6.13.2	Contour and 3D surface plot	137
5.6.14	Numerical optimization	138
5.6.15	Graphical optimization	139
Chapter 5 (Part- B)	Formulation and development of NTB microemulsion	141
5.7	Introduction	142
5.8	Materials and instruments	143
5.9	Preformulation studies	143
5.9.1	Screening excipients	144
5.9.1.1	Screening of excipients based on the solubility study	144
5.9.1.2	Solubility determination	144
5.9.1.3	Screening of excipients based on the emulsification efficiency	144
5.9.2	Drug-excipients compatibility study using FT-IR	144
5.9.3	Screening of surfactant: co-surfactant (Smix) ratio based on pseudo ternary phase diagram	144
5.10	Formulation of microemulsion & mucoadhesive microemulsion	144

5.11	Optimization of microemulsion by D-Optimal mixture design	145
5.11.1	Optimization of formulation	146
5.11.2	Statistical analysis	146
5.11.3	Optimization of chitosan concentration for microemulsion system	146
5.12	Result and discussion	147
5.12.1	Organoleptic characteristics	147
5.12.2	Melting point	147
5.12.3	FT-IR study of pure drug	147
5.12.4	Thermal behaviour of drug by DSC	148
5.12.5	Screening excipients based on solubility study	149
5.12.6	Screening of excipients based on emulsification efficiency	151
5.12.7	Drug excipients compatibility studies	151
5.12.8	Screening of surfactant: co-surfactant (Smix) ratio based on pseudo ternary phase diagram	152
5.12.9	Finalization of concentration range for the microemulsion formulation	154
5.12.10	Optimization of microemulsion using D-Optimal Mixture design	154
5.12.11	ANOVA analysis for response Y1: globule size	156
5.12.11.1	Mathematical model for globule size(Y1)	158
5.12.11.2	3D surface plot	159
5.12.12	ANOVA analysis for response Y2: % transmittance	160
5.12.12.1	Mathematical model for % transmittance (Y2)	161
5.12.12.2	3D surface plot	162
5.12.13	Numerical optimization	162
5.12.14	Graphical optimization	164
5.12.15	Optimized batch of Vinpocetine microemulsion	165
5.12.16	Maximum drug loading in optimized batch of microemulsion	165
5.12.17	Optimization of chitosan concentration for mucoadhesive microemulsion	166
5.12.18	Optimized formula for microemulsion and mucoadhesive microemulsion system	167
5.13	References	168
Chapter 6 (Part- A)	Characterization of oral SMEEDS	171
6.1	Introduction	172
6.2	Characterization of oral SMEDDS	172
6.2.1	Thermodynamic stability testing	172
6.2.1.1	Heating cooling cycle	172
6.2.1.2	Centrifugation test	172
6.2.1.3	Freeze thaw cycle stress test	172
6.2.2	Self emulsification time	172
6.2.3	Robustness to dilution	173
6.2.4	Dye solubility study	173

6.2.5	Globule size	173
6.2.6	Zeta potential	174
6.2.7	pH measurement	174
6.2.8	Percentage transmittance	174
6.2.9	Conductance	174
6.2.10	Viscosity	174
6.2.11	Cloud point	175
6.2.12	Assay	175
6.2.13	Transmission electron microscopy (TEM)	175
6.3	Result and discussion	176
6.3.1	Thermodynamic stability testing	176
6.3.2	Self emulsification time and dispersibility grade assessment	176
6.3.3	Robustness to dilution	176
6.3.4	Dye solubility study	177
6.3.5	Globule size and zeta potential determination	177
6.3.6	pH measurement	178
6.3.7	Percentage transmittance	178
6.3.8	Conductance	179
6.3.9	Viscosity	179
6.3.10	Cloud point	179
6.3.11	Assay	180
6.3.12	TEM	180
Chapter 6 (Part- B)	Characterization of NTB microemulsion	181
6.4	Introduction	182
6.5	Characterization of ME and MME	182
6.5.1	Thermodynamic stability testing	182
6.5.2	Robustness to dilution	182
6.5.3	Dye solubility study	182
6.5.4	Globule size measurement	182
6.5.5	Zeta potential measurement	183
6.5.6	pH measurement	183
6.5.7	Percentage transmittance	183
6.5.8	Conductance	183
6.5.9	Viscosity	183
6.5.10	Cloud point	183
6.5.11	Assay	184
6.5.12	Histopathology study	184
6.5.13	Transmission electron microscopy (TEM)	184
6.6	Result and discussion	185
6.6.1	Thermodynamic stability testing	185
6.6.2	Robustness to dilution	185
6.6.3	Dye solubility study	186
6.6.4	Globule Size and zeta potential determination	184
6.6.5	pH measurement	188
6.6.6	Percentage transmittance measurement	188
6.6.7	Conductance	189

6.6.8	Viscosity measurement	189
6.6.9	Cloud point measurement	190
6.6.10	Assay	190
6.6.11	Histopathology study	190
6.6.12	TEM	191
6.7	References	192
Chapter 7 (Part- A)	<i>In vitro & Ex vivo</i> drug release study for oral SMEDDS	194
7.1	Introduction	195
7.1.1	<i>In vitro</i> drug release	195
7.1.2	<i>Ex vivo</i> drug permeability study	195
7.2	Materials and instrumentation	196
7.3	<i>In vitro</i> dissolution study	196
7.4	<i>In vitro</i> diffusion study	197
7.4.1	Activation of dialysis membrane	197
7.4.2	<i>In vitro</i> diffusion study through dialysis bag	197
7.5	<i>Ex vivo</i> drug permeability study using isolated tissue of rat	198
7.6	Result and discussion	199
7.6.1	<i>In vitro</i> dissolution using USP type II apparatus	199
7.6.2	<i>In vitro</i> drug diffusion study by dialysis sac	201
7.6.3	<i>Ex vivo</i> drug permeability study	202
Chapter 7 (Part-B)	<i>In vitro & Ex vivo</i> drug release study for NTB microemulsion	206
7.7	Introduction	207
7.7.1	<i>In vitro</i> drug release	207
7.7.2	<i>Ex vivo</i> drug permeation study	207
7.8	Materials and instrumentation	208
7.9	<i>In vitro</i> drug release study by diffusion through dialysis bag/sac	209
7.9.1	Activation of dialysis membrane	209
7.9.2	<i>In vitro</i> drug release studies	209
7.10	<i>Ex vivo</i> drug permeation study by using isolated sheep nasal mucosa	209
7.10.1	Determination of diffusion coefficient (D)	210
7.11	Result and discussion	211
7.11.1	<i>In vitro</i> drug diffusion	211
7.11.2	<i>Ex vivo</i> drug permeability study	212
7.12	References	214
Chapter 8 (Part- A)	<i>In vivo</i> pharmacokinetic	215
8.1	Introduction	216
8.2	Material and instrument	216
8.3	Animals	217
8.4	Administration and blood collection	217
8.5	Analysis of blood samples	218
8.6	Pharmacokinetic parameters	218
8.7	Result and discussion	219
Chapter 8 (Part- B)	<i>In vivo</i> pharmacokinetic	221

8.8	Introduction	222
8.9	Material and instrument	222
8.10	Animals	222
8.11	Administration and blood collection	223
8.12	Analysis of blood samples	224
8.13	Pharmacokinetic parameters	224
8.14	Statistical analysis	224
8.15	Result and discussion	225
8.16	References	228
Chapter 9 (Part- A)	Stability study for oral SMEDDS	230
9.1	Introduction	231
9.2	Stability study of Modafinil SMEDDS	231
9.2.1	Parameters for stability study	231
9.3	Result and discussion	232
Chapter 9 (Part- B)	Stability study for NTB microemulsion	235
9.4	Stability study of ME and MME	236
9.5	Parameters for stability study	236
9.6	Result and discussion	237
9.7	Reference	242
Chapter 10	Pharmacodynamic study	243
10.1	Introduction	244
10.2	Animal	244
10.3	Experimental method	245
10.3.1	Administration of formulation	245
10.3.2	Morris water maze test	246
10.4	Result	247
10.4.1	Learning and memory effect of Modafinil formulations by oral administration	247
10.4.2	Learning and memory effect of Vinpocetine formulations by Intranasal	253
10.2	References	259
Chapter 11	Summary and conclusion	261
11.1	Summary	262
11.1.1	Analytical method	262
11.1.2.	Formulation and optimization of Modafinil SMEDDS	263
11.1.3	Characterization of Modafinil SMEDDS	263
11.1.4	Drug release study	264
11.1.4.1	<i>In vitro</i> drug release profile	264
11.1.4.2	<i>Ex vivo</i> drug release profile	264
11.1.5	<i>In vivo</i> pharmacokinetic study	265
11.1.6	Stability studies	265
11.1.7	Pharmacodynamic study	266
11.2	Conclusion	266
11.3	Summary	268
11.3.1	Analytical method	268

11.3.2	Formulation and optimization of Vinpocetine microemulsion	269
11.3.3	Characterization of Vinpocetine loaded ME and MME	269
11.3.4	Drug release study	270
11.3.4.1	<i>In vitro</i> drug release profile	270
11.3.4.2	<i>Ex vivo</i> drug release profile	270
11.3.5	<i>In vivo</i> pharmacokinetic study	271
11.3.6	Stability studies	271
11.3.7	Pharmacodynamic study	271
11.4	Conclusion	272