

LIST OF FIGURES

Figure No.	Title	Page
2.1	Location of barrier sites in the CNS. Barriers are present at three main sites: 1) the brain endothelium forming the blood-brain barrier (BBB), 2) the arachnoid epithelium forming the middle layer of the meninges, and 3) the choroid plexus epithelium which secretes cerebrospinal fluid (CSF) forming blood-cerebrospinal fluid barrier (BCB). In each site, the physical barrier is caused by tight junctions that reduce the permeability of the paracellular (intercellular cleft) pathway.	15
2.2	Anatomy of nose: cross sectional sketch illustrating (A) the vestibular, (B) the respiratory, and (C) the olfactory region.	29
2.3	Mechanisms of Transnasal Transport to the Brain.	33
2.4	Possible transport routes: nasal mucosa to brain/CNS	33
2.5	Nasal Delivery devices and dosage forms	36
2.6	Critical physicochemical factors need to be considered prior to designing intranasal drug delivery systems	36
2.7	Mucociliary clearance of the nose	43
2.8	Schematic representation of the most common self-association structure resulting by the association of surfactant with oil, water or combinations thereof	65
2.9	Schematic representations of three most commonly observed microemulsion structures (A) oil-in-water, (B) bicontinuous, and (C) water-in-oil microemulsion.	65
2.10	A hypothetical pseudo ternary phase diagram depicting various microstructural features observed during microemulsion formation	71
2.11	Chemical structure of Tacrine HCl	83
2.12	Chemical structure of Donepezil HCl	87
3.1	Calibration curve of tacrine free base in methanol at 326 nm	118
3.2	Calibration curve of donepezil free base in methanol at 313 nm	129
4.1	Pseudo-ternary phase diagram representing the three phases and various ME points where three phases intercepts.	147
4.2	Pseudo-ternary phase diagrams for TME 1 (System 1) showing ME regions (Shaded) at S: CoS ratio 1:1, 2:1 and 3:1	150
4.3	Pseudo-ternary phase diagrams for TME 2 (System 2) showing ME regions (Shaded) at S: CoS ratio 1:1, 2:1 and 3:1	151
4.4	Pseudo-ternary phase diagrams for TME 3 (System 3) showing ME regions (Shaded) at S: CoS ratio 1:1, 2:1 and 3:1	152
4.5	Pseudo-ternary phase diagrams for TME 4 (System 4) showing ME regions (Shaded) at S: CoS ratio 1:1, 2:1 and 3:1	153
4.6	Pseudo-ternary phase diagrams for DME 1 (System 1) showing ME regions (Shaded) at S: CoS ratio 1:1, 2:1 and 3:1	161

Figure No.	Title	Page
4.7	Pseudo-ternary phase diagrams for DME 2 (System 2) showing ME regions (Shaded) at S: CoS ratio 1:1, 2:1 and 3:1	162
4.8	Pseudo-ternary phase diagrams for DME 3 (System 3) showing ME regions (Shaded) at S: CoS ratio 1:1, 2:1 and 3:1	162
5.1	Franz Diffusion Cell	192
5.2	Cumulative % drug diffused for different tacrine microemulsions at different time intervals. Error bars represent SD (n=3)	195
5.3	Mean flux ($\mu\text{g}/\text{min}$) and diffusion coefficient (cm^2/sec) of different tacrine microemulsions	196
5.4	Cumulative % drug diffused for different donepezil microemulsions at different time intervals. Error bars represent SD (n=3)	199
5.5	Mean flux ($\mu\text{g}/\text{min}$) and diffusion coefficient (cm^2/sec) of different donepezil microemulsions	200
5.6	Comparison of cumulative % drug diffused for Tacrine Solution (TS), Tacrine Microemulsion (TME 1(05)) and Tacrine Mucoadhesive Microemulsion (TCP 0.5 %). Error bars represent SD (n=3)	205
5.7	Comparison of Mean flux ($\mu\text{g}/\text{min}$) and diffusion coefficient (cm^2/sec) for Tacrine Solution (TS), Tacrine Microemulsion (TME 1(05)) and Tacrine Mucoadhesive Microemulsion (TCP 0.5 %)	205
5.8	Comparison of cumulative % drug diffused for Donepezil Solution (DS), Donepezil Microemulsion (DME 2(05)) and Donepezil Mucoadhesive Microemulsion (DCP 0.5 %). Error bars represent SD (n=3)	208
5.9	Comparison of Mean flux ($\mu\text{g}/\text{min}$) and diffusion coefficient (cm^2/sec) for Donepezil Solution (DS), Donepezil Microemulsion (DME 2(05)) and Donepezil Mucoadhesive Microemulsion (DCP 0.5 %)	209
6.1	Effect of pH on labeling efficiency of $^{99\text{m}}\text{Tc}$ -TS/TME/TMME. Results are the mean of three separate experiments. Error bar represents SD	215
6.2	Effect of stannous chloride concentration on labeling efficiency of $^{99\text{m}}\text{Tc}$ -TS/TME/TMME. Results are the mean of three separate experiments. Error bar represents SD	215
6.3	Effect of variable molar concentrations of DTPA on radiolabeled $^{99\text{m}}\text{Tc}$ -tacrine complexes. Percentage transchelation was measured using ITLC-SG. Results are mean of three separate experiments. Error bar represents SD	217
6.4	Effect of pH on labeling efficiency of $^{99\text{m}}\text{Tc}$ -DS/DME/DMME. Results are the mean of three separate experiments. Error bar represents SD	220
6.5	Effect of stannous chloride concentration on labeling efficiency of $^{99\text{m}}\text{Tc}$ -DS/DME/DMME. Results are the mean of three separate experiments. Error bar represents SD	220

Figure No.	Title	Page
6.6	Effect of variable molar concentrations of DTPA on radiolabeled ^{99m}Tc -donepezil complex. Percentage transchelation was measured using ITLC-SG. Results are mean of three separate experiments. Error bar represents SD	221
7.1	Tacrine concentration in mice (n = 3) (A) blood and (B) brain at different time intervals following ^{99m}Tc -TS _{i.v.} , ^{99m}Tc -TS _{i.n.} , ^{99m}Tc -TME _{i.n.} and ^{99m}Tc -TMME _{i.n.} administrations. Error bars represents SD	230
7.2	Gamma scintigraphy images of rabbit showing the presence of radioactivity into the brain (arrows). (A) ^{99m}Tc -TS _{i.v.} (100 μCi); (B) ^{99m}Tc -TS _{i.n.} (100 μCi); (C) ^{99m}Tc -TME _{i.n.} (100 μCi); and (D) ^{99m}Tc -TMME _{i.n.} (100 μCi)	236
7.3	Donepezil concentration in mice (n = 3) (A) blood and (B) brain at different time intervals following ^{99m}Tc -DS _{i.v.} , ^{99m}Tc -DS _{i.n.} , ^{99m}Tc -DME _{i.n.} and ^{99m}Tc -DMME _{i.n.} administrations. Error bars represents SD	241
7.4	Gamma scintigraphy images of rabbit showing the presence of radioactivity into the brain (arrows). (A) ^{99m}Tc -DS _{i.v.} (100 μCi); (B) ^{99m}Tc -DS _{i.n.} (100 μCi); (C) ^{99m}Tc -DME _{i.n.} (100 μCi); and (D) ^{99m}Tc -DMME _{i.n.} (100 μCi)	245
8.1	Effects of different tacrine formulations after i.v. and i.n. administration on the escape latency achieved during the Morris water maze test in mice (n=4). (A) Saline-treated Mice and (B) Scopolamine-treated Mice. Error bars represent SD (n=4)	255
8.2	Effects of different donepezil formulations after i.v. and i.n. administration on the escape latency achieved during the Morris water maze test in mice (n=4). (A) Saline-treated Mice and (B) Scopolamine-treated Mice. Error bars represent SD (n=4)	257

LIST OF EQUIPMENTS AND THEIR MAKE

Equipments/Apparatus	Make
Calibrated pipettes of 1.0 mL, 5.0 mL and 10.0 mL, volumetric flasks of 10 mL, 25 mL, 50 mL and 100 mL capacity. Beakers, funnels and other glassware.	Corning India Ltd. and Borosil, Mumbai, India.
Analytical balance (205A SCS, PBS 205)	Precisa, Switzerland and Mettler, USA.
pH meter	Systronics 335, India.
Cyclomixer	Remi Scientific Instruments, Mumbai, India.
Centrifuge (C-24)	Remi Scientific Instruments, Mumbai, India.
Photon Correlation Spectrophotometer (Nano ZS)	Malvern Instruments, UK.
Stirrers and Magnetic stirrers	Remi Scientific Instruments, Mumbai, India.
Instant Thin Layer Chromatography (ITLC)	Gelman Sciences Inc., Ann Arbor, MI, USA.
Single Positron Emission Computerized Tomography (Diacam, SPECT, LC 75-005)	Siemens AG; Erlanger, Germany.
Gamma Scintillation Counter (shielded well-type, Type GRS23C)	Electronics Corporation of India Ltd, Mumbai, India.
Software	WinNonlin, USA
UV-Visible double beam spectrophotometer (UV-1601)	Shimadzu, Japan.

LIST OF RAW MATERIALS AND THEIR SOURCE

Raw Material	Source
Tacrine HCl	Pfizer, USA
Donepezil HCl	Sun Pharma Advanced Research Center, Vadodara, India.
Propylene glycol	ISP Technologies, Mumbai, India.
Labrafil M 1944 CS	Gatteffose, France (Supplied by Colorcon Asia Pvt. Ltd., Goa, India)
Labrafac CC	Gatteffose, France (Supplied by Colorcon Asia Pvt. Ltd., Goa, India)
Transcutol P	Gatteffose, France (Supplied by Colorcon Asia Pvt. Ltd., Goa, India)
Cremophor RH 40	BASF, Mumbai, India.
Cremophor EL	BASF, Mumbai, India.
Captex 355	Abitec Corporation, Ohio, USA
Capmul MCM	Abitec Corporation, Ohio, USA
Polysorbate 80 (Tween 80)	ICI chemicals, Mumbai, India.
Carbopol 934 P	Noveon, Mumbai, India.
Chitosan	
Sodium pertechnetate, separated from molybdenum-99 (99m)	Board of Radiation and Isotope Technology (BRIT), Delhi, India.
Stannous chloride dehydrate ($\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$)	Sigma Chemical Co., St. Louis, MO.
Sodium bicarbonate	S.D. Finechem, Ahmedabad, India.
Glacial acetic acid	Rankem, Mumbai, India.
Acetone	S.D. Finechem, Ahmedabad, India.
Pyridine	S.D. Finechem, Ahmedabad, India.
Diethylene triamine penta acetic acid (DTPA)	Sigma Chemical Co., St. Louis, MO.
Ethyl alcohol (Absolute)	Alembic Ltd., Vadodara.
Sodium chloride	S.D. Finechem, Ahmedabad, India.
Disodium hydrogen phosphate	Merck Chemicals, Mumbai, India.

Raw Material	Source
Potassium dihydrogen phosphate	Merck Chemicals, Mumbai, India.
Sunflower Oil	Ranjit Chemicals, Mumbai, India.
Corn Oil	Ranjit Chemicals, Mumbai, India.
Methanol	Merck Chemicals, Mumbai, India.
Diethyl ether	S.D. Finechem, Ahmedabad, India.
Scopolamine hydrochloride	Sigma Chemical Co., St. Louis, MO.
0.45µm and 0.22 µm membrane filter (Nylon 66)	Millipore, France.