Research Article **www.ijcps.com**

International Journal of
Chemical and Pharmaceutical Sciences
2019, Mar., Vol. 10 (1)

ISSN: 0976-9390
IJCPS

Nanoemulsion based intranasal delivery of paliperidone hydrchloride for nose to brain targeting

[1] Sarjak P Pathak[*], [2] Shailesh T Prajapati and [3] Chetna D Modi.

[1] Technology transfer department, Torrent Pharmaceutical, Indrad,Mehsana, Gujarat, India.

[2] Principal, Kalol institute of pharmacy, Kalol, Gandhinagar, Gujarat, India.

[3] Faculty of Pharmacy, SSSRGI, Vadasama, Mehsana, Gujarat, India.

[*] **Corresponding Author:** E-Mail**:** Sarjak.pathak62@gmail.com

Received: 30th April 2019, Revised and Accepted: 5th May 2019

ABSTRACT

Paliperidone nano emulsion, as nasal drug delivery system was prepared to produce quick effect compare to oral route. Solubility of drug was determined in different vehicles. Pseudo ternary phase diagram generated using Acrysol E 150 as oil, Plurololeique cc 497 as a co-surfactant, and Labrasol as a surfactant. The Different formulations were prepared by the spontaneous emulsification method and were further characterized for their physicochemical properties like pH, conductivity, Globule size and zeta potential, Viscosity,Drug content, percentage transmittance & refractive index. *Ex vivo* Diffusion study of the optimized batch was carried out using goat nasal mucosa. Histpathological study of the optimized batch was studied. Optimized formulation having the mean globule size 31.1 nm and zeta potential -29.7 mV. In Histopathlogical study formulation treated mucosa did not shown any damage to the epithelium layer.

Keywords: Paliperidone, Nanoemulsion, Spontaneous emulsification, Nasal ciliotoxicity.

1. INTRODUCTION

Schizophrenia is one of the psychotic mental disorders and affects an individual's thoughts, behaviors, and social functioning. The major problem in treating mental disorders is due to the inability of the therapeutic agents to surpass the blood brain barrier (BBB) and the blood cerebrospinal fluid barrier. One of the possibilities to overcome this barrier is drug delivery to brain using novel drug delivery systems like nanoemulsions exploring nanotechnology[1-5].

Paliperidone (PALI) is an atypical antipsychotic agent that belongs to the class of benz-isoxazole and approved for the treatment of schizophrenia[1-5]. It is a lipophilic drug having oral bioavailabity of 28 %. This is primarily attributed to its poor aqueous solubility, and high lipophilicity and extensive first pass metabolism. Considering the limitations, a strategy which will increase PALI solubility, reduce its first pass metabolism and overcome BBB through delivering PALI directly to the target site is highly desirable. The utility of nanoemulsions (NEs) has been successfully established in optimizing the therapeutic performance of many lipophilic drugs. Recently, increasing attention has been focused on nanoemulsion based drug delivery due to their ease of preparation with biocompatible formulation components, unique properties such as smaller droplet size (50–200 nm), increased drug solubility, and improved mucosal permeation, which further justifies rational of this study.

An alternative route, intranasal drug delivery system has now been recognized as a reliable route for the administration of drugs next to parenteral and oral routes. The olfactory region of the nasal mucosa provides a direct connection between the nose and the brain. The advantages of nasal route are rapid absorption; higher bioavailability reduced first pass metabolism, non-invasive administration, and self-medication as well as improved patient compliance[1-5]. It is also reported in our earlier studies that absorption of PALI through transnasal route was more efficient when given in an oil based formulation (microemulsion)[3-4]. These studies outcomes

render PALI as a potent candidate for lipid based systems such as nanoemulsion for intranasal delivery. However, these formulations may suffer from drawbacks such as rapid nasal mucocilliary clearance of PALI. To get the better of this, many research groups have demonstrated the use of a potent mucoadhesive system which improves the nasal residential time and prolongs the intimate contact of drug with nasal mucosa with improved absorption.

Taken together, this information has led our research group to a formulated mucoadhesivenanoemulsion of PALI with the aim of improving its solubility and transnasal delivery.

2. MATERIALS AND METHODS

Following materials and analytical instruments used in present investigation

Materials	Source of procurement
Paliperidone	Torrent pharmaceutical Ltd.
Labrafil M 1944	Gattefosse Saint-Priest, France
labrafac CC	Gattefosse Saint-Priest, France
labrasol,	Gattefosse Saint-Priest, France
plurololeique CC 497	Gattefosse Saint-Priest, France
lauroglycol 90	Gattefosse Saint-Priest, France
Polycarbophil AA-1	Lubrizol Advanced Material
Acrysol E-150	Finar Chemical Ltd
propylene glycol	Finar Chemical Ltd
Methanol	Finar Chemical Ltd
potassium dihydrogen phosphate	Finar Chemical Ltd
tween 80	Finar Chemical Ltd
Tween 20	Himedia Lab
Isopropyl myristate	Himedia Lab
Seasame oil	Qualikems
PEG 400	Central drug house
Propylene glycol	Central drug house

Instruments	Model specification
UV-visible spectrophotometer	(Shimadzu 1800, Kyoto, Japan)
Fourier transform Infrared Spectrophotometer	Spectrum GX FT-IR, Perkin Elmer, Norwalk, CT
pH meter	Control Dynamics
Conductivity meter	Control Dynamics, model APX-185
Zetasizer	Nano ZS, Malvern Instruments, UK
Brookfield Viscometer LVDV-IIIU	Brookfield Engineering LABS, Stoughton, MA
Diffusion cell	Orchid Scientifics, Nashik, India
Microscope	Polarizing Microscope RPL-55 Series, Radical Instruments, India
Sonicator	Vibra cell Bandelin RK 100 H,Germany

2.1. Method for Nanoemulsion preparation:

The PALI loaded NE (P-NE) were prepared by the dissolving PALI (5 mg/mL) in oil. Surfactants were weighed accurately and mixed with oil to form homogenous isotropic mixture. Required amount of water was added to the mixture to obtain PNE. PALI loaded mucoadhesive NE (PM-NE) was prepared by the addition of polycarbophil AA-1 (0.50 %, w/w) to P-NE and the dispersion stirred for 1 h. The composition of P-NE and PM-NE is shown in Table 1.

Each formulation contains paliperidone 5 mg/mL.

Preparation of solution

The PS (5 mg/mL) meant for the comparative evaluation was prepared by dissolving PALI (50 mg) in 10 mL of propylene glycol (PG).

3. RESULT AND DISCUSSION

NE formulation containing Paliperidone was successfully developed using for the purpose of improving its solubility and transnasal delivery, which can be further utilized for its preclinical evaluation. Screening of formulation components helped to identify the most suitable excipients, whereas phase diagrams gave a good idea about the concentrations of the formulation components that should be used to achieve NE. Collectively, the results demonstrate that PM13, due to its appropriate physicochemical properties, optimum surfactant and co-surfactant concentrations, highest diffusion coefficient, and free from nasal cilio toxicity may be more suitable for intranasal delivery which could be developed as a novel regime for intranasal administration of PALI.

Table - 1: The composition of the PALI loaded nanoemulsion and mucoadhesive nanoemulsion formulations

Ingredients (w/w)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	PM11	PM12	PM13
Acrysol E-150	2.38	2.08	1.85	1.70	1.56	1.43	1.75	2.05	2.4	2.3	1.70	1.56	1.43
Labrasol:plurol oleique cc 497 (3:1)	9.52	10.41	11.11	11.90	12.5	12.86	–	–	–	–	11.90	12.5	12.86
Tween 80:propylene glycol (1:1)	–	–	–	–	–	–	15.73	16.39	16.82	16.85			
polycarbophil AA-1											0.5 %	0.5 %	0.5 %
Distilled water	13.10	12.5	12.04	11.39	10.93	10.71	7.52	6.56	5.77	5.34	11.39	10.93	10.71

Table - 2: Calibration data of standard plot of paliperidone.

Conc. In mcg/ml	Absorbance 1	2	3	Avg. absorbance
0	0.0	0.0	0.0	0±0
2	0.112	0.116	0.115	0.114±0.002
4	0.187	0.179	0.185	0.183±0.004
6	0.206	0.211	0.212	0.209±0.003
8	0.356	0.348	0.352	0.352±0.004
10	0.397	0.392	0.391	0.393±0.003
20	0.628	0.631	0.631	0.630±0.001
30	0.943	0.938	0.936	0.939±0.003

Table - 3: Solubility Studies of Paliperidone in Oils and Surfactants/Co-surfactants

Oils/surfactants/co-surfactants	Concentration of PALI (mg/ml)
Labrasol®	0.618±0.062
Acrysol E-150	0.585± 0.002
Transcutol® HP	0.245±0.025
Tween® 80	1.913±0.084
Tween® 20	0.234±0.04
PEG 400	0.232±0.072
Captex 100	0.016±0.0005
oleic acid	0.005±0.0004

Table - 4: Results of Pseudoternary Phase Diagram for tween 80: propylene glycol (Smix)ratio (1:1)

Amt. of water (µl)	Oil : Smix ratio								
	1:9	2:8	3:7	4:6	5:5	6:4	7:3	8:4	9:1
10	+	+	+	+	+	+	+	-	-
20	+	+	+	+	+	+	+	-	-
25	+	+	+	+	+	+	-	-	-
35	+	-	-	-	-	-	-	-	-
45	+	-	-	-	-	-	-	-	-
55	+	-	-	-	-	-	-	-	-
65	+	-	-	-	-	-	-	-	-
80	-	-	-	-	-	-	-	-	-
100	-	-	-	-	-	-	-	-	-
120	-	-	-	-	-	-	-	-	-
150	-	-	-	-	-	-	-	-	-
185	-	-	-	-	-	-	-	-	-

235	-	-	-	-	-	-	-	-	-
300	-	-	-	-	-	-	-	-	-
400	-	-	-	-	-	-	-	-	-
550	-	-	-	-	-	-	-	-	-
900	-	-	-	-	-	-	-	-	-
2000	-	-	-	-	-	-	-	-	-

Table - 5: Results of Pseudoternary Phase Diagram for tween 80: propylene glycol (Smix)ratio (2:1)

Amt. of water (µl)	Oil : Smix ratio								
	1:9	**2:8**	**3:7**	**4:6**	**5:5**	**6:4**	**7:3**	**8:4**	**9:1**
10	+	+	+	+	+	+	+	-	-
20	+	+	+	+	+	+	+	-	-
25	+	+	+	+	+	+	+	-	-
35	+	+	+	+	+	+	+	-	-
45	+	+	+	+	+	+	+	-	-
55	+	-	-	-	-	-	-	-	-
65	+	-	-	-	-	-	-	-	-
80	+	-	-	-	-	-	-	-	-
100	+	-	-	-	-	-	-	-	-
120	+	-	-	-	-	-	-	-	-
150	+	-	-	-	-	-	-	-	-
185	+	-	-	-	-	-	-	-	-
235	-	-	-	-	-	-	-	-	-
300	-	-	-	-	-	-	-	-	-
400	-	-	-	-	-	-	-	-	-
550	-	-	-	-	-	-	-	-	-
900	-	-	-	-	-	-	-	-	-
2000	-	-	-	-	-	-	-	-	-

Table - 6: Results of Pseudoternary Phase Diagram for tween 80: propylene glycol (Smix)ratio (3:1)

Amt. of water (µl)	Oil : Smix ratio								
	1:9	2:8	3:7	4:6	5:5	6:4	7:3	8:4	9:1
10	+	+	+	+	+	+	+	+	+
20	+	+	+	+	+	+	+	+	+
25	+	+	+	+	+	+	-	-	-
35	+	+	+	-	-	-	-	-	-
45	+	+	-	-	-	-	-	-	-
55	+	-	-	-	-	-	-	-	-
65	+	-	-	-	-	-	-	-	-
80	-	-	-	-	-	-	-	-	-
100	-	-	-	-	-	-	-	-	-
120	-	-	-	-	-	-	-	-	-
150	-	-	-	-	-	-	-	-	-
185	-	-	-	-	-	-	-	-	-

235	-	-	-	-	-	-	-	-	-
300	-	-	-	-	-	-	-	-	-
400	-	-	-	-	-	-	-	-	-
550	-	-	-	-	-	-	-	-	-
900	-	-	-	-	-	-	-	-	-
2000	-	-	-	-	-	-	-	-	-

Table - 7: Results of Pseudoternary Phase Diagram for labrasol: plurol oleique CC 497 (Smix)ratio (1:1)

Amt. of water (µl)	Oil : Smix ratio								
	1:9	2:8	3:7	4:6	5:5	6:4	7:3	8:4	9:1
10	+	+	+	+	+	+	+	+	+
20	+	+	+	+	+	+	+	+	+
25	+	+	+	+	+	+	-	-	-
35	+	+	+	+	+	-	-	-	-
45	+	+	+	+	-	-	-	-	-
55	+	+	+	-	-	-	-	-	-
65	+	+	-	-	-	-	-	-	-
80	+	+	-	-	-	-	-	-	-
100	+	+	-	-	-	-	-	-	-
120	+	-	-	-	-	-	-	-	-
150	+	-	-	-	-	-	-	-	-
185	+	-	-	-	-	-	-	-	-
235	+	-	-	-	-	-	-	-	-
300	+	-	-	-	-	-	-	-	-
400	-	-	-	-	-	-	-	-	-
550	-	-	-	-	-	-	-	-	-
900	-	-	-	-	-	-	-	-	-
2000	-	-	-	-	-	-	-	-	-

Table - 8: Results of Pseudoternary Phase Diagram for labrasol: plurol oleique CC 497 (Smix)ratio (2:1)

Amt. of water (µl)	Oil : Smix ratio								
	1:9	2:8	3:7	4:6	5:5	6:4	7:3	8:4	9:1
10	+	+	+	+	+	+	+	+	+
20	+	+	+	+	+	+	+	+	+
25	+	+	+	+	+	+	-	-	-
35	+	+	+	+	+	-	-	-	-
45	+	+	+	+	-	-	-	-	-
55	+	+	+	-	-	-	-	-	-
65	+	+	-	-	-	-	-	-	-
80	+	+	-	-	-	-	-	-	-
100	+	+	-	-	-	-	-	-	-
120	+	-	-	-	-	-	-	-	-

150	+	-	-	-	-	-	-	-	-
185	+	-	-	-	-	-	-	-	-
235	+	-	-	-	-	-	-	-	-
300	+	-	-	-	-	-	-	-	-
400	-	-	-	-	-	-	-	-	-
550	-	-	-	-	-	-	-	-	-
900	-	-	-	-	-	-	-	-	-
2000	-	-	-	-	-	-	-	-	-

Table - 9: Results of Pseudoternary Phase Diagram for labrasol: plurol oleique CC 497 (Smix)ratio (3:1)

Amt. of water (µl)	Oil : Smix ratio								
	1:9	2:8	3:7	4:6	5:5	6:4	7:3	8:4	9:1
10	+	+	+	+	+	+	+	+	+
20	+	+	+	+	+	+	+	+	+
25	+	+	+	+	+	+	+	+	-
35	+	+	+	+	+	+	+	+	-
45	+	+	+	+	+	+	-	-	-
55	+	+	+	+	+	+	-	-	-
65	+	+	+	+	-	-	-	-	-
80	+	+	+	+	-	-	-	-	-
100	+	+	+	-	-	-	-	-	-
120	+	-	-	-	-	-	-	-	-
150	+	-	-	-	-	-	-	-	-
185	+	-	-	-	-	-	-	-	-
235	+	-	-	-	-	-	-	-	-
300	+	-	-	-	-	-	-	-	-
400	-	-	-	-	-	-	-	-	-
550	-	-	-	-	-	-	-	-	-
900	-	-	-	-	-	-	-	-	-
2000	-	-	-	-	-	-	-	-	-

Table - 10: Physicochemical parameters and cumulative percentage release of PALI loaded nanoemulsion formulations (mean ± SD, *n* = 3)

Formulation code	pH	Conductivity (mS/cm)	% transmittance	Refractive Index	Viscosity (cP)	Globule size (nm)	PDI[a]	Zeta potential (mV)	Drug content (%)	Percentage cumulative release (%)
P1	5.22 ± 0.01	0.110 ± 0.01	98.33 ± 0.51	1.336 ± 0.01	112.47 ± 1.20	117.3 ± 1.17	0.189 ± 0.01	−26.2 ± 1.53	99.00 ± 0.25	71.28 ± 0.53
P2	5.32 ± 0.01	0.121 ± 0.03	99.33 ± 0.59	1.340 ± 0.02	109.27 ± 0.60	98.9 ± 1.8	0.132 ± 0.02	−21.3 ± 1.68	97.93 ± 0.50	73.88 ± 0.77

P3	5.36 ± 0.01	0.130 ± 0.01	98.67 ± 0.55	1.336 ± 0.02	107.07 ± 0.42	58.5 ± 1.03	0.210 ± 0.02	−14.4 ± 2.07	98.60 ± 0.20	79.03 ± 0.24
P4	5.65 ± 0.02	0.108 ± 0.01	98.33 ± 1.00	1.337 ± 0.02	103.83 ± 0.35	43.2 ± 1.21	0.152 ± 0.15	−25.1 ± 1.21	99.47 ± 0.52	81.25 ± 1.11
P5	5.61 ± 0.01	0.151 ± 0.02	98.67 ± 0.58	1.341 ± 0.01	101.80 ± 0.61	32.3 ± 1.44	0.129 ± 0.01	−24.3 ± 1.89	99.73 ± 0.60	83.81 ± 0.18
P6	5.90 ± 0.01	0.124 ± 0.01	99.33 ± 0.60	1.336 ± 0.01	98.90 ± 1.60	28.8 ± 2.18	0.14 ± 0.02	−16.6 ± 1.34	99.47 ± 0.30	85.09 ± 0.78
P7	5.22 ± 0.01	0.165 ± 0.02	98.00 ± 1.00	1.336 ± 0.02	294.73 ± 1.38	72.2 ± 1.32	0.217 ± 0.02	−23.5 ± 2.1	98.20 ± 0.23	76.42 ± 0.60
P8	5.28 ± 0.01	0.107 ± 0.01	97.33 ± 0.62	1.336 ± 0.03	306.97 ± 0.51	83.5 ± 1.46	0.214 ± 0.02	−16.2 ± 1.78	98.00 ± 0.21	74.82 ± 0.68
P9	5.31 ± 0.02	0.140 ± 0.02	97.33 ± 0.67	1.335 ± 0.01	313.57 ± 0.47	121.8 ± 2.23	0.263 ± 0.02	−24.8 ± 1.38	98.07 ± 0.12	70.07 ± 0.86
P10	5.48 ± 0.02	0.146 ± 0.02	97.67 ± 1.53	1.337 ± 0.02	319.13 ± 1.59	137.5 ± 1.2	0.173 ± 0.01	−25.5 ± 1.45	98.60 ± 0.15	63.33 ± 0.49

[a]Polydispersity Index

Table - 11: Drug release profile of nanoemulsion formulations

Time in min	Cumulative % Drug release									
	P1	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**	**P10**
30	5.24	4.65	8.43	6.73	7.35	8.46	6.72	6.14	4.56	2.55
60	11.65	12.35	18.03	13.52	21.22	19.73	14.81	12.35	10.66	9.05
120	22.96	26.89	39.93	38.32	39.45	38.73	43.08	29.74	19.25	20.36
180	63.85	46.63	59.48	50.75	56.63	60.45	47.8	52.49	43.55	37.71
240	71.28	73.88	79.03	81.25	83.81	85.06	76.42	74.82	70.07	63.33

Table - 12: Characterization parameters of PALI solution (PS) and optimized PALI mucoadhesive nanoemulsion (PMNE)

Formulation code	pH	Conductivity (mS/cm)	Viscosity (cP)	Globule size (nm)	PDI[a]	Zeta potential (mV)	Drug content (%)
PS	5.51 ± 0.03	–	–	–	–	–	99.34 ± 0.35
PM11	5.61 ± 0.02	0.110 ± 0.01	124.27 ± 1.10	47.4 ± 2.11	0.210 ± 0.01	−31.3 ± 1.54	99.75 ± 0.68
PM12	5.68 ± 0.02	0.121 ± 0.01	119.47 ± 0.65	43.3 ± 1.24	0.143 ± 0.02	−32.9 ± 1.70	99.15 ± 0.61
PM13	5.97 ± 0.02	0.130 ± 0.01	116.73 ± 0.95	31.1 ± 1.44	0.178 ± 0.04	−29.7 ± 1.14	99.60 ± 0.53

[a]Polydispersity Index

Table - 13: Cumulative amount of drug permeated per unit area versus time profile of PS, PM11, PM12 and PM13

Time in min	Cumulative amount of drug			
	PM11	PM12	PM13	PS
30	354	463	579	781
60	486	581	853	945
120	978	1146	1363	1432
180	1257	1378	1485	1562
240	1423	1584	1867	2143

Table - 14: Steady state flux, enhancement ratio, diffusion co-efficient and modeling parameters of PALI solution (PS) and paliperidone loaded mucoadhesive nanoemulsions (PM11, PM12 and PM13) (mean ± SD, *n* = 3)

Formulation	Steady state flux (Jss) (µg/cm²/min)	Enhancement ratio (E_r)	Diffusion co-efficient (cm²/min)	Modeling parameters		
				Zero-order (r^2)	First-order (r^2)	Higuchi (r^2)
PS	4.573 ± 0.21	1.00	$1.84 \times 10^{-5} \pm 0.013 \times 10^{-5}$	0.9112	0.8826	0.9805
PM11	3.544 ± 0.27	0.77	$1.42 \times 10^{-5} \pm 0.019 \times 10^{-5}$	0.9211	0.9718	0.9746
PM12	4.679 ± 0.50	1.03	$1.89 \times 10^{-5} \pm 0.015 \times 10^{-5}$	0.9329	0.9634	0.9897
PM13	5.072 ± 0.13	1.10	$2.04 \times 10^{-5} \pm 0.022 \times 10^{-5}$	0.9438	0.9387	0.9877

Table - 15: Results of stability testing of the PALI nanoemulsion (P-NE) and PALI mucoadhesive nanoemulsion containing 0.5 % (w/w) polycarbophil (PM-NE) (*n* = 3) for 6 months

Test	P6	PM13
% Assay	99.47 ± 0.306	99.6 ± 0.529
% Transmittance	99.33 ± 0.58	–
Globule size (nm)	28.8 ± 2.18	31.1 ± 1.44
Polydispersibility Index	0.140 ± 0.025	0.178 ± 0.035
Zeta potential (mV)	−16.6 ± 1.34	−29.7 ± 1.14

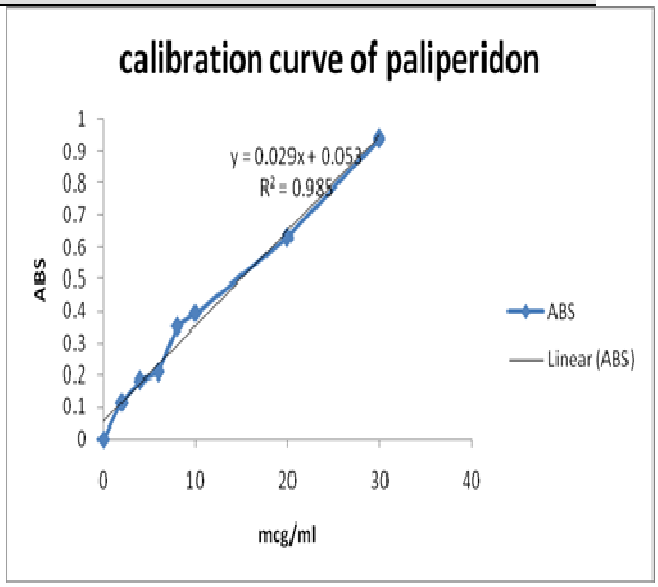


Figure - 1: calibration curve of paliperidon.

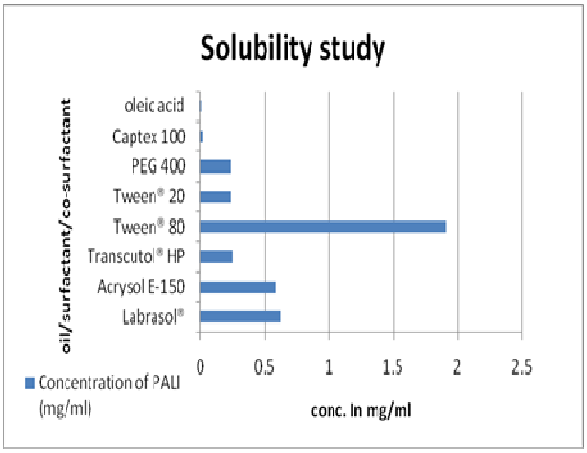
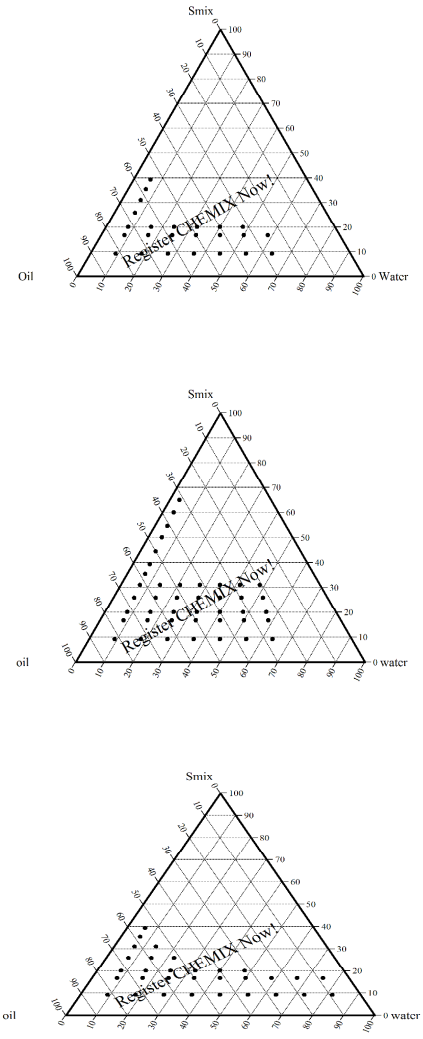
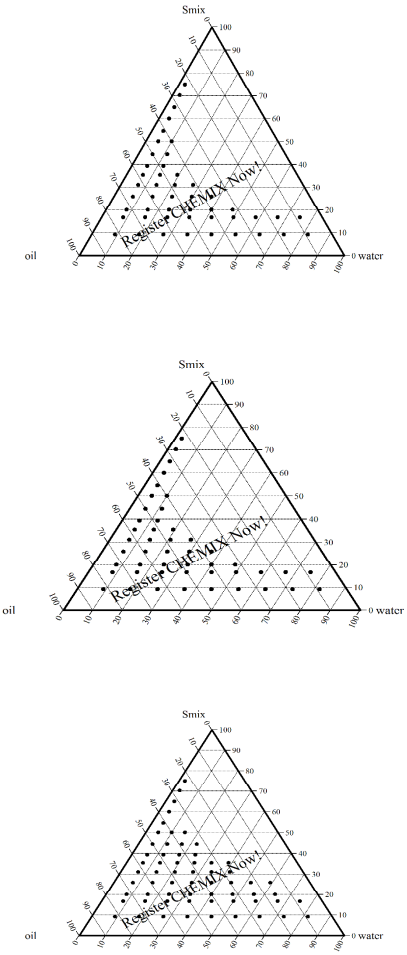


Figure - 2: Solubility Studies of Paliperidone.



(A) , (B), (C)

Figure - 3: The pseudo ternary phase diagrams of the Acrysol E-150, tween 80: propylene glycol (Smix), water system at the 1:1 (A), 2:1 (B) and 3:1 (C) weight ratios of Smix (Km) at ambient temperature. The dark area represents nanoemulsion region.



(A),(B),(C)

Figure - 4: The pseudo ternary phase diagrams of the Acrysol E-150, labrasol: plurol oleique CC 497 (Smix), water system at the 1:1 (A), 2:1 (B) and 3:1 (C) weight ratios of Smix (Km) at ambient temperature. The dark area represents nanoemulsion region.

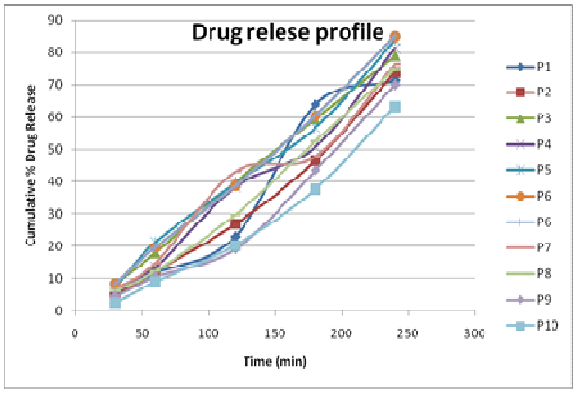


Figure - 5: Cumulative percentage release of nanoemulsion formulations P1 to P10.

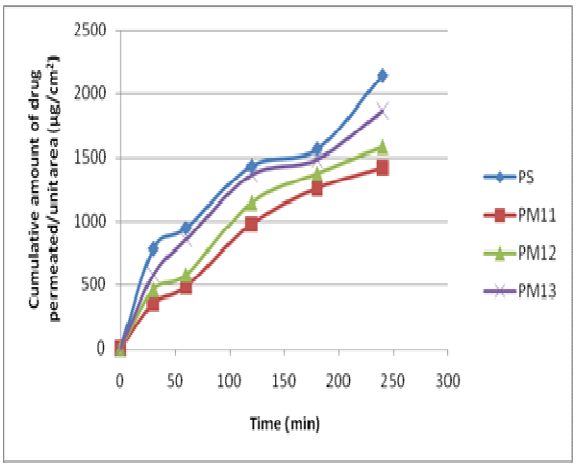


Figure - 6: Cumulative amount of drug permeated per unit area versus time profile of PS, PM11, PM12 and PM13.

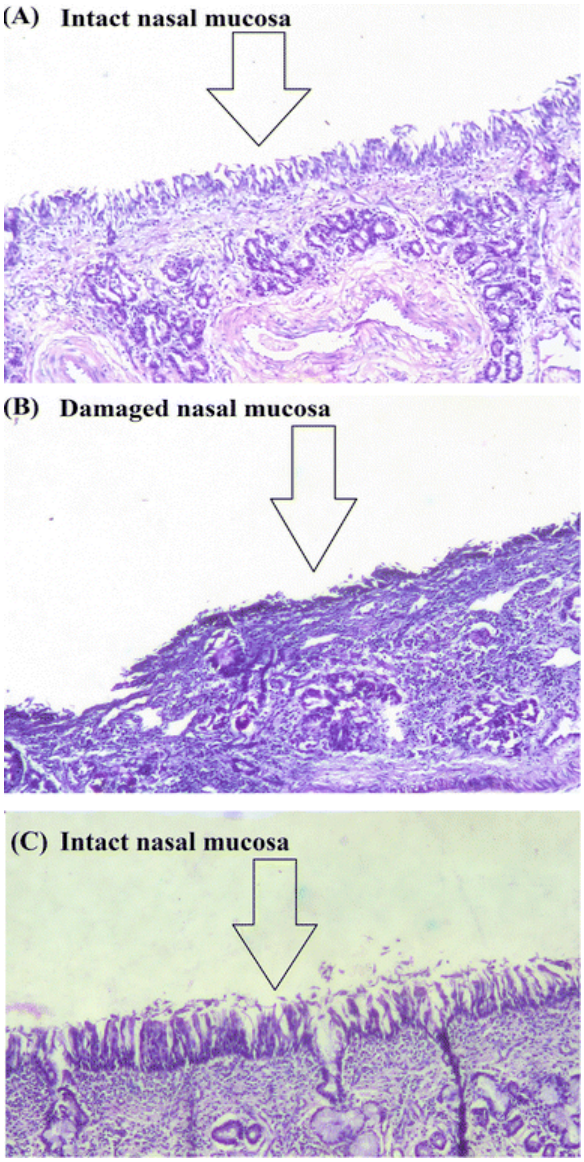


Figure - 7: Photographs of goat nasal mucosa demonstrating histological characteristics when treated with (a) phosphate buffer saline pH 6.4 (b) isopropyl alcohol and (c) paliperidone loaded mucoadhesive nanoemulsion.

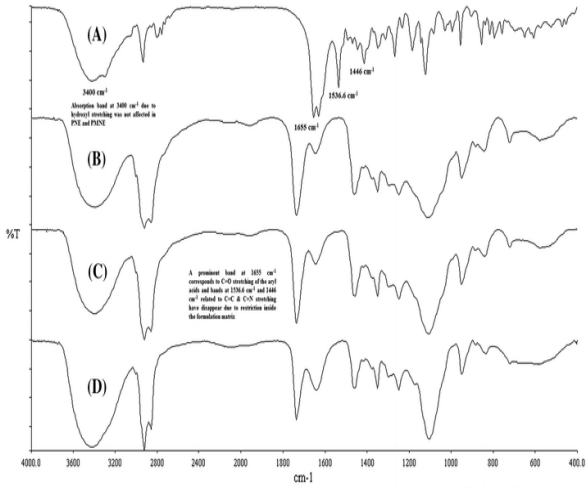


Figure - 8: Infra red spectra of (a) paliperidone (b) plain nanoemulsion (c) paliperidone loaded nanoemulsion and (d) paliperidone loaded mucoadhesivenanoemulsion.

4. CONCLUSION

This work consists of compatibility test, construction of the pseudo ternary phase diagram to know the range of nanoemulsion, selection of the formulation and incorporation of the drug, evaluation of the formulation, bioanalytical analysis and stability study. All results are promising and presented in tabulated form.

5. REFERENCES

1. Canuso CM et al. Paliperidone extended-release tablets in schizophrenia patients previously treated with risperidone. **IntClinPsychopharm** 2008; 23:209–215
2. Patel RB et al. UV SPECTROPHOTOMETRIC method development and validation: quantification of paliperidone in formulations and in vitro release study. **Anal Methods** 2010; 2:525–531
3. Patel RB et al. Paliperidone loaded mucoadhesivemicroemulsion in treatment of schizophrenia: formulation consideration. **J Pharm Inn** 2013; 8:195–204.
4. Patel RB et al. Risperidone microemulsion for transnasal delivery: pharmacodynamic and pharmacokinetic evaluation. **Pharm Nanotechnol** 2013; 1:44–53.
5. Kumar MS et al. Development of analytical method for risperidone by uv spectrophotometry. **Int. J. of pharma sci. and research** 2010 1(2):122-126.

6. Elshafeey AH et al. Intranasal microemulsion of sildenafil citrate: in vitro evaluation and in vivo pharmacokinetic study in rabbits. **AAPS Pharm Sci Tech** 2009 10:361–364.
7. Jogani VV et al. Intranasal mucoadhesivemicroemulsion of tacrine to improve brain targeting. Alzheimer **Dis AssocDisord**2008; 22:116–124.
8. Kumar M et al. Mucoadhesivenanoemulsion-based intranasal drug delivery system of olanzapine for brain targeting. **J Brain Targ** 2008; 16:806–814.
9. Patel MR et al. Effect of formulation components on the in vitro permeation of microemulsion drug delivery system of fluconazole. **AAPS Pharm Sci Tech** 2009 10:917–923.
10. Kumar M et al. Formulation and characterization of nanoemulsion based drug delivery system of risperidone. **Drug Dev Ind Pharm** 2009; 35:387–39
11. Azeem A et al.Nanoemulsion components screening and selection: a technical note. **AAPS Pharm Sci Tech** 2009; 10:69–76.
12. Borhade V et al. Clotrimazole nanoemulsion for malaria chemotherapy. Part I: preformulation studies, formulation design and physicochemical evaluation. **Int J Pharm** 2012; 431:138–148.
13. Pierre MB et al.Acrysol E-150 as optimizer of the skin delivery of 5-aminolevulinic acid in photodynamic therapy. **Pharm Res** 2006; 23:360–366.
14. Barakat NS et al. Carbamazepine uptake into rat brain following intra-olfactory transport. **J Pharm Pharmacol**2006; 58:63–72.
15. Jadhav SA et al. Stress degradation behavior of paliperidone, an antipsychotic drug, and development of suitable stability-indicating RP-LC method. **Chromatogr Res Int** 2011; 1–10.
16. Karasulu E et al. Permeation studies and histological examination of goat nasal mucosa following administration of different nasal formulations with or without absorption enhancers. **Drug Del** 2008; 15:219–225.
17. Sharma G et al. Intranasal cabergoline: pharmacokinetic and pharmacodynamic studies. **AAPS Pharm Sci Tech**. 2009; 10:1321–1330.