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Intranasal nanoemulsion of Olanzapine: A new prospective to treat psychosis

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ABSTRACT

Olanzapine nano emulsion, as nasal drug delivery system is prepared to produce quick effect compare to oral route. It exhibit faster and more complete dissolution than marketed tablet regardless of the type and pH of the dissolution medium. Solubility of drug is determined in different vehicles. Pseudo ternary phase diagram generated using Sesame oil as oil, Labrasol and tween 20 as a surfactant, and PEG 400 as a co-surfactant. Drug loaded nano emulsion formulations are prepared using an ultra sonication method and further characterization of their physicochemical properties like thermodynamic Stability Studies Droplet size and zeta potential, Transmission Electron Microscopy, Viscosity, Refractive index, percentage transmittance and pH done. In vitro release and *Ex vivo* Diffusion study of the optimized batch is carried out using goat nasal mucosa. Optimized formulation also carried out for the stability studies.

Keywords: Olanzapine, Nanoemulsion, Ultra sonification, Ex vivo diffusion, Intranasal.

1. INTRODUCTION

Schizophrenia is a heterogenous syndrome characterized by perturbation of language, perception, social activity, affection, and volition. Schizophrenic patients may present positive (conceptual disorganization, delusions, and hallucinations) or negative symptoms (loss of function, anhedonia, decreased emotional expression, impaired concentration, and diminished social engagement). Antipsychotic drugs (APDs), especially the atypical antipsychotic agents, are the cornerstones of acute and maintenance treatment of both positive and negative symptoms of schizophrenia.

Olanzapine is a novel antipsychotic agent with broad efficacy, and elicits response in both the positive and negative symptoms of schizophrenia. Compared with traditional antipsychotic agents, olanzapine causes a lower incidence of extrapyramidal symptoms and minimal perturbation of prolactin levels. Generally, olanzapine is well tolerated. The pharmacokinetics of olanzapine is linear and dose proportional within the approved dosage range. Olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3 b][1,5]benzodiazepine, a third atypical antipsychotic was approved by the Food and Drug Administration (FDA), in 1996, and is presently available as tablet, which after administration shows extensive first-pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Therefore, orally disintegrating wafers (Zydus, Gujarat, India) and intramuscular injection are available to overcome the bioavailability problems. But since the target site of the olanzapine is the brain, a strategy is thereby desirable, which not only improves the bioavailability by preventing extensive first-pass metabolism but also provides targeting to the receptor site and bypasses the blood–brain barrier (BBB), so as to achieve the desired drug concentration at the site of action, hence preventing the availability of drug at non-targeting sites and reducing the side effects.

Some studies have demonstrated that intranasal administration offers a practical, non-invasive, and an alternative route of administration for rapid drug delivery to the brain. It also offers the advantages of the drugs being administered simply, cost-effectively, and conveniently. Direct transport of drugs to the brain circumventing the brain barriers following intranasal administration provides a unique

feature and better option to target drugs to the brain. However, few formulation factors need to be addressed while designing drug delivery systems for intranasal administration. The formulation should be designed for targeting of the drug to the olfactory region of nasal cavity so as to provide its rapid transport across nasal mucosa, and mucoadhesion phenomenon further helps in drug permeation in the olfactory region along with longer residence time in the posterior nasal cavity by overcoming the nasal mucociliary clearance. Nanoemulsions by virtue of their lipophilic nature and low globule size are widely explored as a delivery system to enhance uptake across nasal mucosa and the addition of mucoadhesive agents such as polyelectrolyte polymer helps in the retention of the formulation on the nasal mucosa.

The objective of this investigation was to prepare and characterize olanzapine nanoemulsion and evaluate their performance. It was hypothesized that nanoemulsion based alternative drug delivery system will result in rapid nose-to-brain transport of olanzapine and greater transport and distribution into and within the brain. This can reduce the side effects, decrease the dose and frequency of administration, and perhaps even the cost of the therapy.

2. MATERIALS AND METHODS

Following materials and analytical instruments used in present investigation

Materials	Source of procurement
Olanzapine	Sun Pharmaceutical
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

Drug loaded nanoemulsion formulations were prepared using an ultrasonication method. Separately, in the oil phase, consisting of 10 ml of sesame oil, the drug was added to the oil phase and stirred with the help of magnetic stirrer. The surfactant and cosurfactant mixture was prepared by Smix ratio (1:1, 1:2, 1:3, 2:1, etc.). Gradually, the Smix (2:1) was added to the oil phase under stirring conditions (Table 1). The oil droplet particle size in the course emulsion formed was further reduced by ultrasonication at 21% amplitude and 50% duty cycle using sonicator (Sonic – vibra cell Bandelin RK 100 H,Germany) ultrasound instrument for 10 minutes.

Table - 1: Composition of olanzapine nanoemulsion

Name of excipients	Amount of excipients in ml & mg					
	NE1	NE2	NE3	NE4	NE5	NE6
Sesame oil	10	10	10	10	15	15
Labrasol+Tween20	33.3	30	32	20	34	31.7
PEG 400	16.7	15	16	20	17	15.8
Water	40	45	42	50	34	37

3. RESULTS AND DISCUSSION

Olanzapine was successfully formulated as Nanoemulsion formulation. It exhibited faster and more complete dissolution of a than marketed tablet regardless of the type and pH of the dissolution medium. Also, it showed a significant result in Ex vivo as well as in vitro dissolution study.

Table - 2: Calibration Curve data of olanzapine

Conc. In mcg/ml	Absorbance			Avg. absorbance
	1	2	3	
0	0.0	0.0	0.0	0±0
5	0.469	0.481	0.476	0.475±0.0060
10	0.831	0.818	0.819	0.823±0.0072
15	1.162	1.173	1.166	1.167±0.0055
20	1.476	1.482	1.486	1.482±0.0050
25	1.731	1.732	1.735	1.733±0.0021
30	2.079	2.085	2.083	2.083±0.0030
35	2.368	2.379	2.375	2.374±0.0055
40	2.619	2.622	2.629	2.623±0.0051

Table - 3: Solubility of drug in different Oils, surfactant and cosurfactant.

Name of oils	Solubility (mg/ml)	Name of surfactant and cosurfactant	Solubility (mg/ml)
Castor oil	16.96±4.29	Gelucire	28.28±0.32
IPM	10.65±2.05	Tween 80	15.65±0.35
Captex 355	4.43±0.32	Tween 20	20.26±0.23
Olive oil	6.51±0.02	Labrasol	30.28±0.32
Sesame oil	48.25±0.021	Span 20	16.22±0.25
Capmul MCM	29.82±4.22	Labrasol+ Tween 20	42.23±2.73
Caproyl 90	24.53±0.60	PEG 300	35.80±1.02
Captex 200	5.25±0.02	PEG 400	40.41±0.27

Table - 4: Visual observation during aqueous phase titration for phase diagram constraction using s_{mix} ratio

OIL: SMIX(ml)	Observation made after each addition of aqueous phase (ml)									
	5	10	15	20	25	30	35	40	45	50
1:1	NE	NE	NE	NE	NE	NE	NE	NE	NE	E
1:2	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
1:3	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
1:4	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

1:5	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
1:6	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
1:7	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
2:1	NE	NE	NE	NE	NE	NE	NE	NG	NG	NG
3:1	NE	NE	NE	NG	NG	EG	EG	E	E	E
4:1	NE	NG	EG	E	E	E	E	E	E	E
5:1	EG	EG	E	E	E	E	E	E	E	E
6:1	EG	E	E	E	E	E	E	E	E	E
7:1	E	E	E	E	E	E	E	E	E	E
1:1	NE	NE	NE	NE	NE	NE	NE	NE	NE	E

Table - 5: Thermodynamic stability test of different selected NE formulation

Formulation code	Freezthraw cycle		Centrifu-gation	Heat and cooling cycle		Dispersibility tests	Inference
	4^0C	45^0C		-21^0C	+25^0C		
NE 1	√	√	√	√	√	A	Pass
NE 2	√	√	√	√	√	A	Pass
NE 3	√	√	√	√	√	A	Pass
NE 4	√	√	√	√	√	A	Pass
NE 5	√	√	√	√	√	A	Pass
NE 6	√	√	√	×	√	B	Pass

Table - 6: Droplet size, Zeta potential and polydispersity determination of NE Formulation

Formulation code	Partical size(nm)	Polydispersity Index (PDI)	Zeta potential (mV)
NE 1	76.53	0.150	-26.5
NE 2	62.89	0.141	-39.0
NE 3	84.29	0.169	-21.9
NE 4	90.38	0.186	-18.4
NE 5	83.33	0.167	-22.4
NE 6	89.60	0.178	-19.2

Table - 7: Viscosity, Refractive index, %Transmittance and pH determination of NE formulation

Formulation code	Viscosity (cp)	Refractive index (RI)	% Transmittance	pH
NE 1	23.40	1.31	98.96	5.3±0.16
NE 2	19.36	1.36	99.40	5.7±0.36
NE 3	25.53	1.37	98.63	4.8±0.15
NE 4	27.69	1.40	96.55	5.6±0.67
NE 5	25.02	1.29	97.23	5.0±0.25
NE 6	26.98	1.39	98.25	5.4±0.50

Table - 8: In vitro release profile of olanzapine formulation in 1.2 pH buffer.

Time IN HR	Cumulative % drug release							
	NE1	NE2	NE3	NE4	NE5	NE6	TABLET	Suspension
0	0	0	0	0	0	0	0	0
0.5	3.85	9.76	5.07	7.67	3.15	4.05	1.54	1.2
1	9.45	17.41	12.35	14.52	10.28	13.25	2.47	2.19
2	12.65	22.04	16.55	19.52	13.12	15.62	3.74	3.27
3	16.42	30.57	21.39	25.76	16.32	19.94	4.36	3.94
4	19.93	37.05	27.48	32.45	22.26	25.92	9.04	7.84
6	31.4	46.7	37.65	39.78	35.68	40.56	12.35	10.63
8	39.61	56.36	46.87	50.02	43.64	48.38	16.27	15.82
10	49.75	67.31	57.35	62.18	54.81	59.71	21.74	17.63
12	53.78	76.61	64.76	68.27	59.47	60.31	29.85	27.53
18	59.32	88.45	72.67	78.68	65.65	68.93	39.61	34.03
24	65.62	96.33±0.70	84.86	90.34	76.53	80.32	48.20±1.43	40.28±2.63

Table - 9: In vitro release profile of olanzapine formulation in 6.8 pH buffer

Time in hrs	Cumulative % drug release							
	NE1	NE2	NE3	NE4	NE5	NE6	TABLET	Suspension
0	0	0	0	0	0	0	0	0
0.5	2.46	8.45	4.19	6.45	2.18	3.8	1.09	1.03
1	8.73	16.43	10.02	12.89	8.07	12.11	1.44	1.35
2	11.45	21.95	15.07	17.83	11.84	13.45	2.68	2.45
3	16.54	28.65	19.72	23.03	15.48	17.15	3.38	2.93
4	18.65	35.67	25.05	30.73	20.95	23.94	8.76	7.52
6	29.7	44.67	35.6	38.04	33.68	38.65	11.9	9.84
8	37.65	56.8	43.59	48.72	41.63	46.73	15.46	14.48
10	47.32	66.43	55.08	60.25	52.81	57.85	20.76	15.42
12	52.56	72.54	67.58	66.9	57.47	58.32	28.98	26.36
18	56.7	85.63	68.95	76.35	63.1	66.52	38.08	32.71
24	63.43	92.43	83.99	88.32	74.53	78.44	46.83	38.29

Table - 10: Stability studies of optimized nanoemulsion (NE 2)

Time (Months)	Temperature (^{0}C)			
	4.0±0.5		25.0±0.5	
	Particle size in µm	RI± SD	Particle size in µm	RI± SD
0	62.89	1.36	62.89	1.36
1	62.89	1.36	64.82	1.39
2	62.89	1.36	69.48	1.40
3	64.82	1.37	69.48	1.40

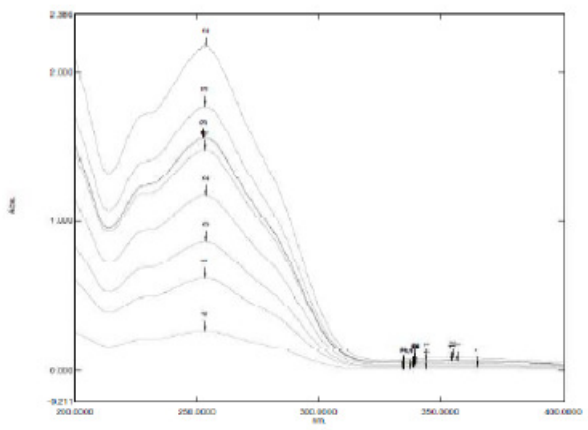

Figure - 1: UV-VIS Spectra of Olanzapine.

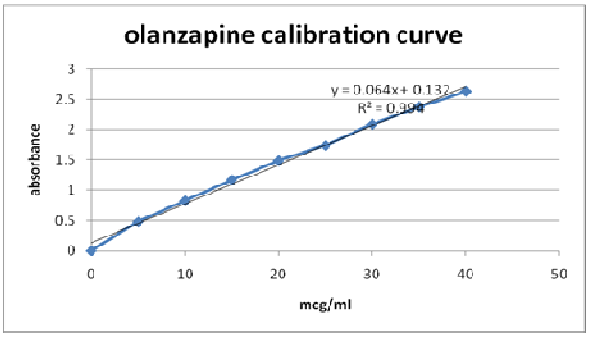

Figure - 2: Calibration curve of olanzapine.

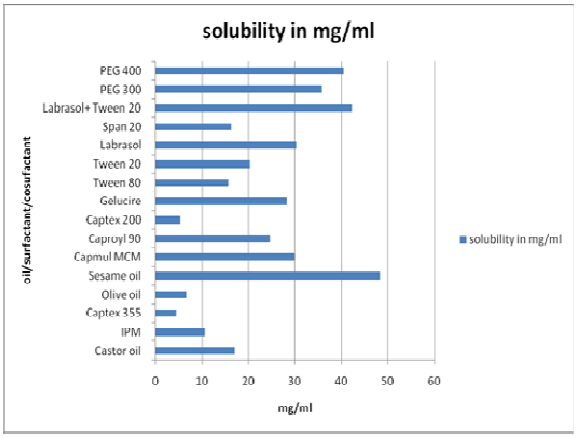

Figure - 3: Solubiltiy study of olanzapine.

Figure - 4: Visual observations of transparent and easily flowable o/w nanoemulsions made by different oil and Smix ratio.

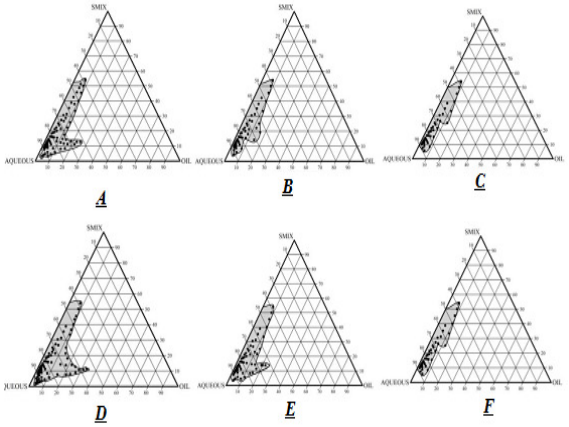

Figure - 5: Nanoemulsion region (A) s_{mix}1:1 (B) s_{mix}1:2 (C) s_{mix}1:3 (D) s_{mix}2:1 (E) s_{mix}3:1 (F) s_{mix}4:1.

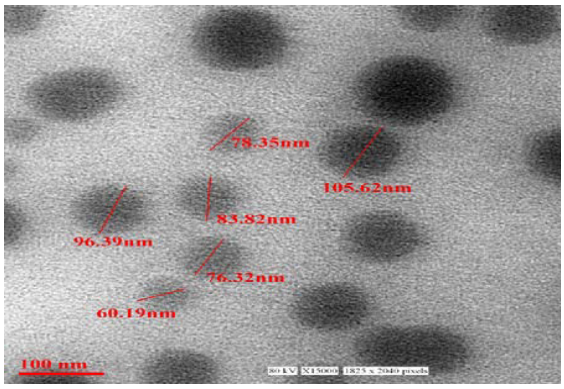

Figure - 6: Droplet sizes of NE formulation are determination by TEM.

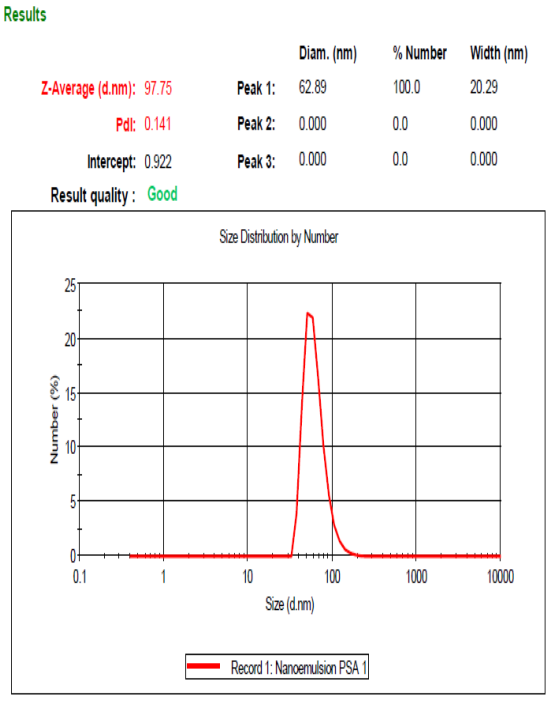

Figure - 7: Droplet size and polydispersity determination by zetasizer.

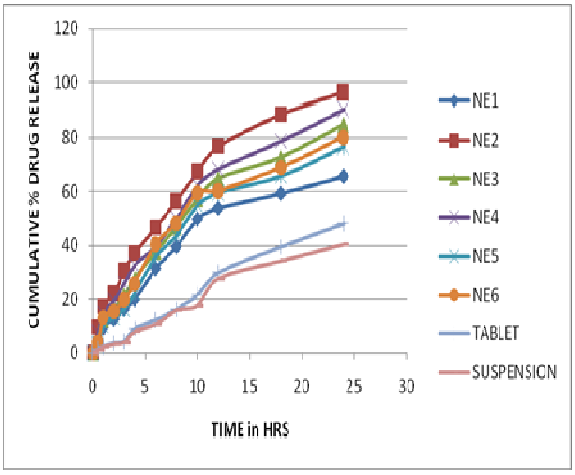

Figure - 8: In vitro release profile of olanzapine formulation in 1.2 pH buffer.

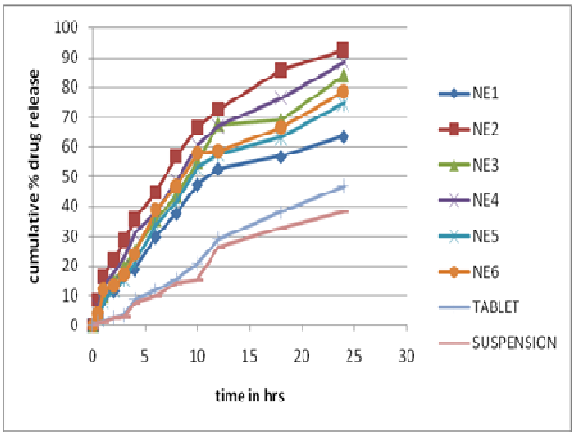

Figure - 9: In vitro release profile of olanzapine formulation in 6.8 pH buffer.

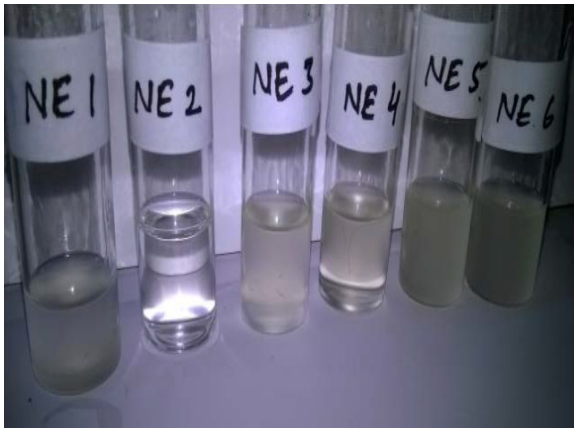

Figure - 10: Stability studies of optimized nanoemulsion at (4^{0}C) and (25^{0}C) for the period of 3 months.

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.

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