



## Research Article

### Essential Oil based Microemulsions for Intranasal Delivery of Venlafaxine HCl

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#### ABSTRACT

An aim of the study was to develop microemulsion based intranasal delivery of venlafaxine HCl for effective treatment of depression by targeting brain. Saturation solubility studies were carried out to determine the solubility of drug in various oils, surfactants and co-surfactants. Microemulsions were prepared using eucalyptus oil as oil phase, tween 80 and ethanol as surfactant and co-surfactant respectively. Pseudo-ternary phase diagrams were plotted to determine the formation of microemulsion using water titration method. Drug loaded microemulsions were further characterized for *in vitro* and *ex vivo* drug diffusion studies, zeta potential, polydispersibility index, pH, viscosity and stability studies at various temperatures. Differential Scanning Calorimetry and Fourier Transform Infra Red Spectroscopy were done to verify any drug excipient incompatibility. Microemulsion with Smix: oil ratio 1:1 (F1) was found to be stable having pH of  $6.2 \pm 0.2$  with viscosity of  $90.0 \pm 2$  cps. *In vitro* and *ex vivo* studies results showed  $98.33 \pm 0.39$  and  $81.58 \pm 1.56$  percent of drug diffusion respectively for a period of 6h as compared to other formulations. The microemulsion (F1) showed a good average globule size of 218.9 nm, polydispersity index of 0.372 and zeta potential of -23.4 mV. Studies showed absence of interaction between drug and excipients. The above results indicated good diffusion properties of developed microemulsions for a period of 6h. A polydispersity index and zeta potential value indicates uniform distribution of globules and good stability of microemulsions. Microemulsion based intranasal delivery of Venlafaxine HCl could be a potential delivery to treat depression.

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## INTRODUCTION

Microemulsions have been widely studied to enhance the bioavailability of the poorly soluble drugs. Microemulsions have very low surface

tension and small droplet size which results in high absorption and permeation. Microemulsion systems are being increasingly investigated for transdermal, ocular, nasal, pulmonary, vaginal,

rectal and intravenous drug delivery (Talegaonkar *et al* 2008). A lot of study and research have been done over the microemulsions as a potential drug delivery system (Senthil *et al* 2011, Kantaria *et al* 2003). The characteristics such as increased drug solubilization, better thermodynamic stability and the ease of manufacturing gives microemulsions the edge over the other formulations (Tenjarla 1999, Constantinides 1995). Microemulsion systems have a great diversity and can be used to deliver the drugs by different routes (Gasco 1997, Gasco *et al* 1989).

Venlafaxine hydrochloride is extensively metabolized in the liver via CYP2D6 and so has low oral bioavailability of 45%. Venlafaxine is a unique antidepressant, and is referred to as a serotonin norepinephrine-dopamine reuptake inhibitor. Venlafaxine and its active metabolite, Odesmethylvenlafaxine (ODV) inhibit the neuronal uptake of norepinephrine, serotonin and to a lesser extent dopamine<sup>8</sup>. Essential oils are lipophilic in nature and thus can pass the BBB through olfactory route and show their potential effects. Inhaled aromatherapy is a popular and gentle treatment to reduce mild anxiety<sup>9</sup>. Therefore, a drug molecule can be transferred quickly across the single epithelial cell layer directly to the systemic blood circulation without first-pass hepatic and intestinal metabolism. The effect is often reached within 5 min for smaller drug molecules<sup>10</sup>. Treating a depressed patient is not easy while he refuses to swallow or administer a drug by other route, hence nasal spray is a preferred route of administration having quick onset of action, patient compliance and ease of administration.

The present study is an attempt to design microemulsion based formulation of venlafaxine hydrochloride for intranasal application which would help to retain high concentration of drug in brain, improve bioavailability by avoiding hepatic first pass metabolism and exert quick onset of action which is required for patients suffering from depression. The intranasal sprays are more patient compliant as compared to oral route, it would help to maximize therapeutic index, reduce dose and dosing frequency.

## MATERIALS AND METHODS

**Materials:** Venlafaxine hydrochloride was obtained as a gift sample by Wockhardt limited, Aurangabad, Maharashtra, India, Tween 80, Propylene glycol, Isopropyl myristate, polyethylene glycol 400 were purchased from S. D. Fine Chemicals Ltd, Mumbai, India. Eucalyptus oil and Castor oil were purchased from Sreeji Aroma Mumbai, India, and Capmul MCM was generous gift sample form ABITEC Corporation USA, Nasal sprays pump was obtained as gift sample from Valois India Pvt. Ltd. All the other reagents and solvents used were of analytical grade.

### Methods

**Selection of Excipients (Saturation Solubility Studies)**-Solubility of venlafaxine HCl was determined in various oils, surfactant and co-surfactants. Five ml of each component was taken in screw cap vials with excess quantity of drug. After sealing, vials were kept on orbital shaking water bath at 37°C for 48h (Bajaj *et al* 2011, Brahmaiah *et al* 2016). After equilibrium each test tube was centrifuged (Remi Equipments Pvt. Ltd Mumbai, India) at 3000 rpm for 15 min, solution was appropriately diluted with methanol and UV absorbance was measured at 224 nm against blank. Concentration of dissolved drug was determined using standard equation.

**Construction of Pseudo-Ternary Phase Diagram**-Venlafaxine HCl loaded microemulsions were prepared using aqueous titration method. Slow titration with the aqueous phase was performed for each combination of oil and Smix separately (Syed *et al* 2014, Masthan Rao *et al* 2015). Surfactant (Tween 80) and co-surfactant (Ethanol) were mixed (Smix) indifferent volume ratios (1:1, 1:2, 1:3, 2:1, 3:1). For each phase diagram, oil (Eucalyptus Oil) and specific Smix ratio were mixed thoroughly in various ratios from 9:1 to 1:9 in different glass vials. After each addition of the aqueous phase to the oil: Smix, visual observation was made. Pseudo ternary phase diagram was constructed using TriPlot (TriPlot version 4.1 trial edition) software based on the observations noted.

### Development of Microemulsion

The concentrations of oil, water, surfactant and co-surfactant were varied in each case keeping the concentration of drug constant (Vaishali *et al*

2015). Predetermined amount of drug was accurately weighed and dissolved in oil. Co-surfactant and surfactant were added to oily solution of the drug and mechanically stirred (Magnetic stirrer, Remi Equipment's Pvt. Ltd.) to form an emulsion. Water was added dropwise to the emulsion till the formation of a transparent solution which indicated formation of microemulsion.

#### **Drug Excipients Compatibility Studies**

**Fourier Transform Infrared Spectroscopy (FTIR) Studies**-FTIR spectrum of Venlafaxine Hydrochloride was recorded to determine any possible interactions that might occur between drug and other excipients during the development of formulation (Vaishali *et al* 2015, Sabrina *et al* 2014). These are generally analyzed on the single reflection ATR accessories; the infrared spectra of drug and formulation were recorded using Bruker Alpha E, FTIR spectrometers (Bruker Alpha E, Opus-7.0.122 and 8400S Shimadzu, Japan) equipped with an ATR (Attenuated Total Reflectance). The spectra were scanned at room temperature in transmission mode over the wave number range of 4000- 400  $\text{cm}^{-1}$ .

**Differential scanning calorimetric (DSC) studies**-Thermal analysis was performed using a differential scanning calorimetric (8400S Shimadzu, Japan) equipped with a computerized data station. The sample of pure drug was weighed and heated at a scanning rate of 10°C/min between 40 and 300°C and 40 ml/min of nitrogen flow. The differential scanning calorimetric analysis gives an idea about the interaction of various materials at different temperatures; it also allows us to study the possible degradation of the material.

#### **Characterization of Microemulsion**

**Physical appearance**- The developed Venlafaxine hydrochloride microemulsion formulations were inspected for their appearance, thermostability and accelerated stability studies (Salimi *et al* 2015, Arpan *et al* 2011)

**Measurement of pH**- The pH values of the developed microemulsions samples were measured by pH meter (Remi equipment Pvt. Ltd, India). The pH meter was calibrated before each use with buffer solution of pH 4.0, 7.0 and 9.0. The measurement of pH of the formulation

was done in triplicate and mean values were calculated.

**Measurement of viscosity**-The viscosities of developed microemulsions were measured with a Brookfield viscometer DV-II+ PRO, equipped with spindle no. LV1 having spindle code as 62 at ambient temperature and 100 rpm for 5 min (Borade *et al* 2013).

**Drug content determination**- Venlafaxine HCl content in developed microemulsions was measured by dissolving quantity equivalent to one spray of microemulsion in methanol by sonication (Borade *et al* 2013). Absorbance was measured after suitable dilution at 224 nm using UV/VIS spectrophotometer (UV1700 CE, Shimadzu Corporation, Japan).

**In vitro diffusion study**- Franz diffusion cell was used for the drug release studies; venlafaxine HCl loaded microemulsion spray was sprayed onto the surface of dialysis membrane (Hi Media Laboratories Pvt. Ltd, Mumbai, India). Dialysis membrane was clamped between the donor and the receptor chamber of diffusion cell. Receptor chamber was filled with freshly prepared SNF (Simulated Nasal Fluid) solution. Receptor chamber was stirred by magnetic stirrer. Samples were collected at suitable time interval, and analyzed for drug content by UV-Visible spectrophotometer at 224 nm after appropriate dilutions. The cumulative amount of drug released across the dialysis membrane was determined as a function of time

**ExVivo Drug Diffusion Studies**-The *ex vivo* drug diffusion studies of the developed microemulsion was carried out using a Franz diffusion cell and freshly excised nasal mucosa of a sheep (. Sheep nasal mucosa was obtained from freshly excised nose of sheep from slaughter house. This sheep nasal mucosa was cleansed with double distilled water and then soaked in simulated nasal fluid and was fixed onto the Franz diffusion cell of 3.14  $\text{cm}^2$  diffusion area and then clamped. The developed formulation of equivalent to dose of 25mg was applied onto the nasal mucosa in donor compartment and in the receptor compartment was filled with SNF. During the experiment the diffusion cell was maintained at body temperature and stirring rate was maintained at

600 rpm using magnetic stirrer. The aliquots of 3ml were withdrawn at fixed time points such as 15 min, 30 min, 45 min, 60 min, 120 min, 180 min, 240 min, 300 min, and 360 min from the receptor compartment. The volumes of samples withdrawn were immediately replaced with equal volumes of SNF to maintain the sink condition. These samples were analyzed for UV-Visible spectrophotometer at 224nm.

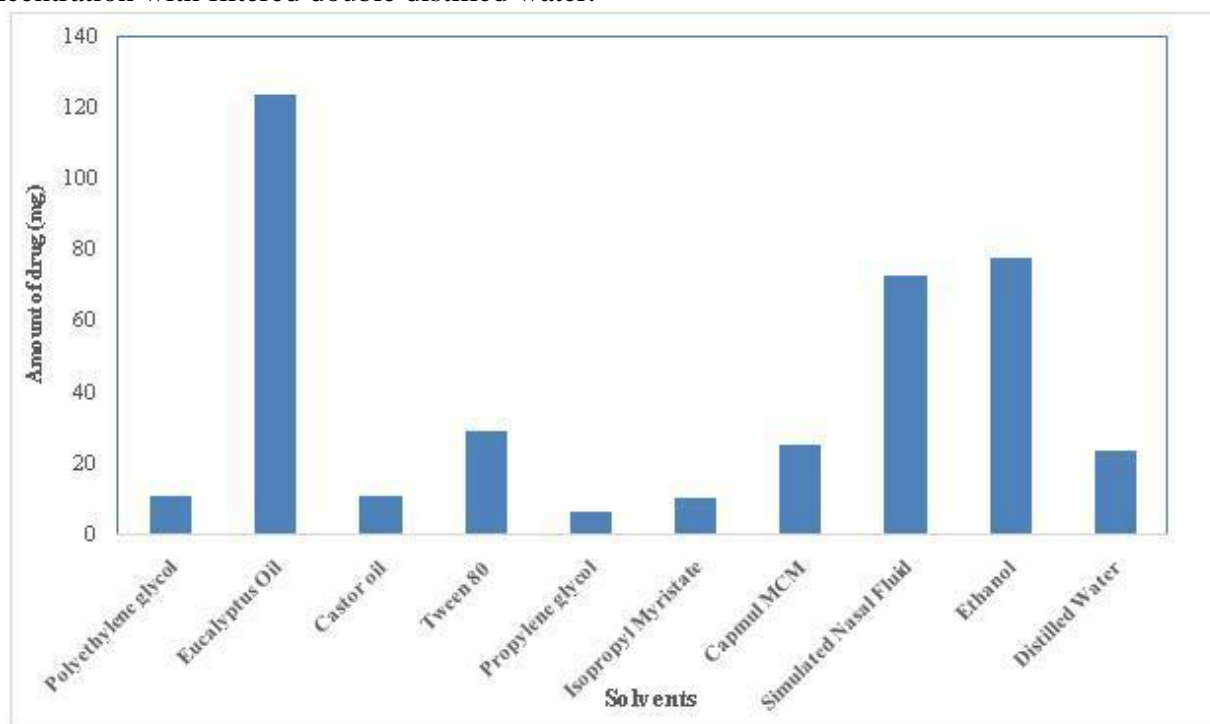
### Characterization of the Optimized Formulation

**Measurement of Particle size and Zeta Potential-** The mean droplet size and zeta potential was determined by dynamic light scattering or photon correlation spectroscopy technique using analyzer (HORIBA scientific nanoparticle analyzer SZ-100). Developed formulation was diluted to a suitable concentration with filtered double distilled water.

Globule size analysis was performed at 25°C with an angle of detection of 90°. Size, Polydispersity index of microemulsions was obtained directly from the instrument

### RESULTS AND DISCUSSION

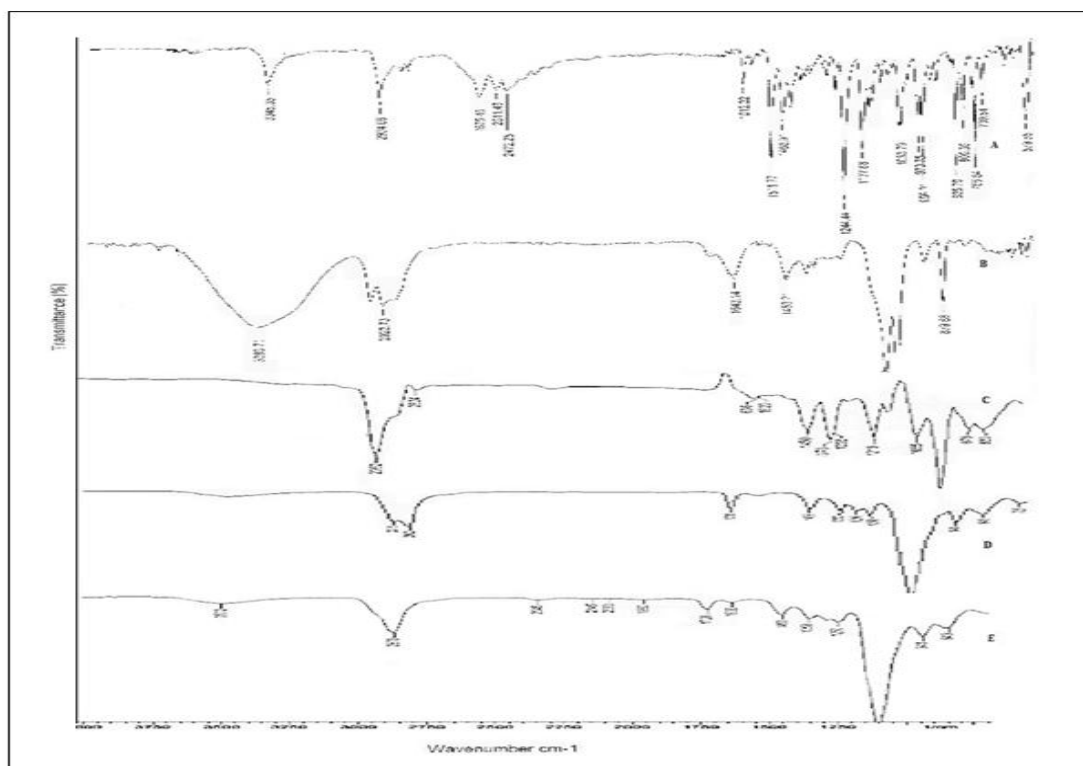
**Saturation Solubility studies-**As seen in (Fig.1), among the selected oils that were screened, maximum solubility of venlafaxine hydrochloride was found in Eucalyptus oil followed by Capmul MCM, Isopropyl myristate and castor oil. Drug got solubilized more in Tween 80 and propylene glycol used as surfactants. While ethanol followed by simulated nasal fluid and distilled water showed reasonable solubilizing potential for venlafaxine hydrochloride.



**Fig. 1: Saturation Solubility Studies of Venlafaxine Hydrochloride in Various Solvents and Oils**

**FTIR analysis-**The FTIR spectrum of Venlafaxine hydrochloride is characterized by the absorption peaks at 3345.35, 2934.06, 1244.44 and 956.01 $\text{cm}^{-1}$  (Fig. 2). From the obtained formulation spectrum, H-bonded O-H bond stretch of medium broad peak at 3383.71 $\text{cm}^{-1}$ . Aromatic C-H bond stretch was

found to be medium narrow peak at 2923.73 $\text{cm}^{-1}$ . Phenolic C-O bond stretch was found to be strong narrow peak at 1086.45 $\text{cm}^{-1}$  and Primary Amine C-N bond stretch was found to be medium narrow peak at 1046.02 $\text{cm}^{-1}$ . The final formulation F1 correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

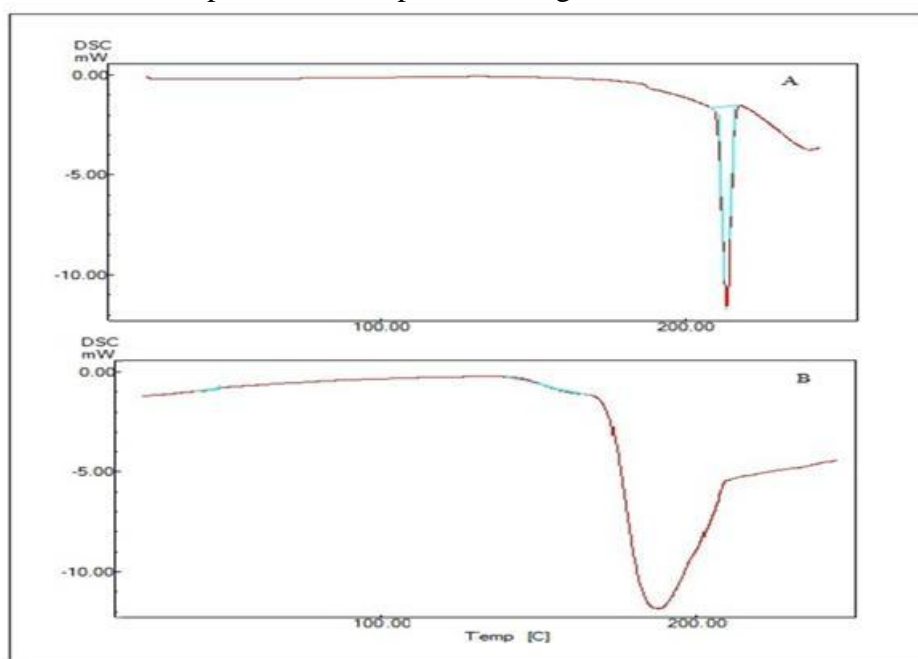


**Fig. 2: FTIRs of (A) Pure Drug Venlafaxine, (B) Formulation (F1), (C) Eucalyptus Oil, (D) Tween 80, (E) Smix**

#### Differential Scanning Calorimetry (DSC)

The DSC thermograms of venlafaxine HCl and developed microemulsion formulation are shown in **Fig. 3**. Thermogram of venlafaxine showed melting endotherm at 213.3°C. Thermal behavior of Venlafaxine HCl with excipients showed peak

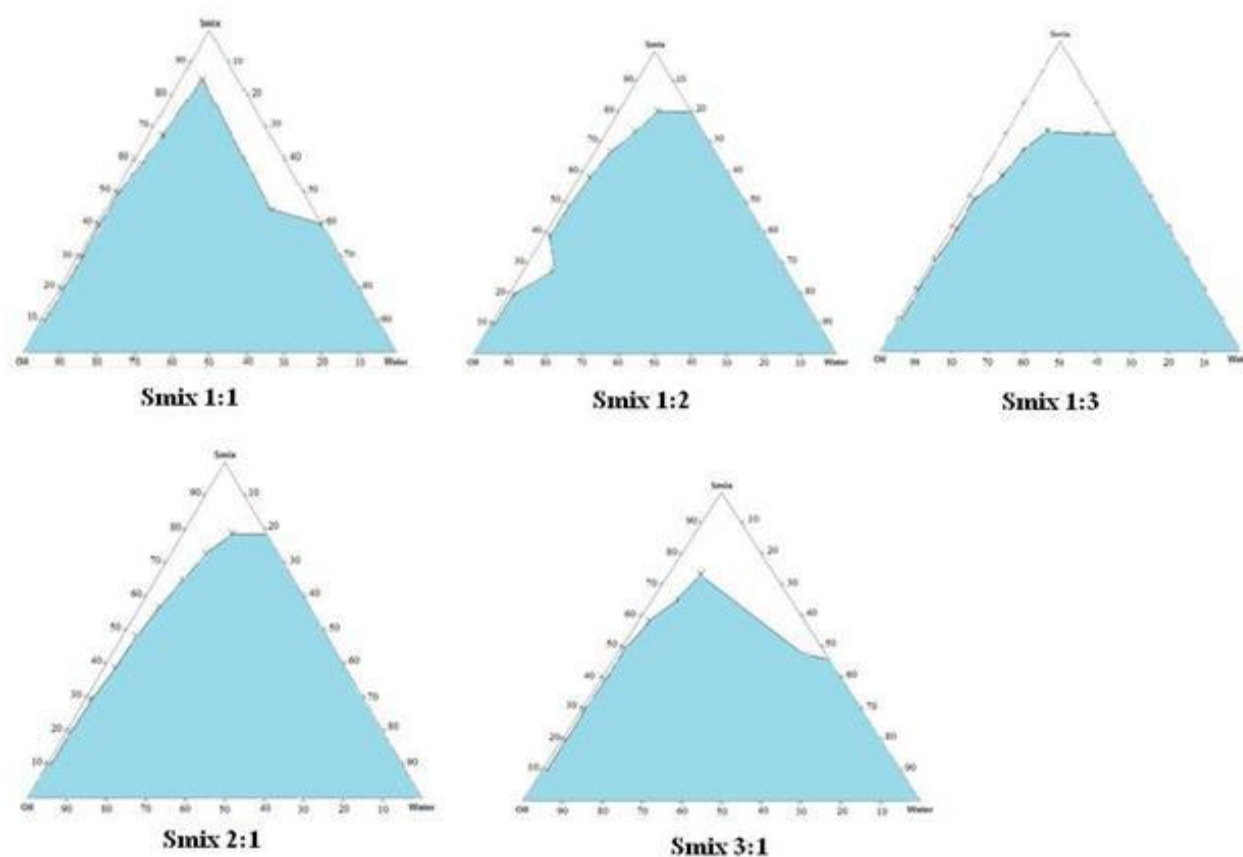
endotherm at 180.7°C. The endothermic change and broadening of peak from 185°C to 180°C might be due to loading of excipient complex. This indicates there was slight change but no significant change in melting endotherm of pure drug.



**Fig. 3: DSC Thermograms of Pure Drug (A) and Microemulsion Formulation F1 (B)**

**Construction of pseudo-ternary phase diagram-**As depicted from figure 4, pseudo-ternary phase diagrams revealed that the maximum proportions of water was incorporated in microemulsion systems when the surfactant to

cosurfactant ratios was 1:1 and 3:1, hence the same ratios were selected for microemulsion formulations. **Fig. 4** represents pseudo-ternary phase diagrams of various ratios.



**Fig. 4: Pseudoternary Phase Diagrams for Various Formulations**

**Development of Microemulsion Formulations-**From pseudo ternary phase diagram microemulsions prepared using Smix ratios of 1:1, 3:1 and Smix:Oil ratios of 4:1 and 9:1

weight ratios of Eucalyptus oil/ Tween 80/ Ethanol were selected for further studies. The general formula for formulating both the ratios is given in **Table 1**.

**Table 1: Formulae for best microemulsion formulations**

Components	Formulations	
	F1	F2
Venlafaxine HCl (mg)	25	25
Tween-80/ Ethanol (ml)	4.1	4.7
Eucalyptus Oil (ml)	1.1	0.5
Double distilled water (ml)	4.4	4.7

**Evaluation of optimized micro-emulsion formulations-**The optimized formulation was

evaluated for parameters like appearance, pH, viscosity stability of emulsions and drug content.

**Table 2: Evaluation of Optimized Microemulsion Formulations of Venlafaxine Hydrochloride**

Tests	Microemulsion	
Physical Appearance	Transparent	
pH	6.2±0.2	
Viscosity (cps)	90.0±2	
Stability by temperature and centrifugation	<b>F1</b>	<b>F2</b>
	Stable and no separation	Unstable, separated
	Stable, no separation	Stable
	Stable and no separation	Unstable, separated
Drug Content	93.46%	

From the data given in **Table 2** it can be seen that venlafaxine hydrochloride microemulsion formulation F1 showed good stability at various temperatures ranges (4°C, 25°C and 37°C) with no signs of phase separation, flocculation, and precipitation when compared to F2 which was unstable showing phase separation. So further studies were carried out using microemulsion formulation F1. The pH values for microemulsions were found to be in the range of 6.2±0.2. The viscosities of developed

microemulsions were measured and value of the samples was low and found to be 90.0±2 cps. Sample exhibited Newtonian flow behavior, which shows it has low viscosity; drug content was evaluated and was found to be 93.46%. The image of formulation F1 is given in Fig. 5.

**Fig. 5: Developed Micro-emulsion Formulation (F1)**

**In-vitro diffusion studies-**From the Fig. 6 it is evident that the developed microemulsion formulation showed a drug release of  $98.33 \pm 0.39$  in 6h which indicates good diffusion through the

membrane. The high values obtained for diffusion studies may be due to the presence of ethanol and eucalyptus oils both acting as penetration enhancers.

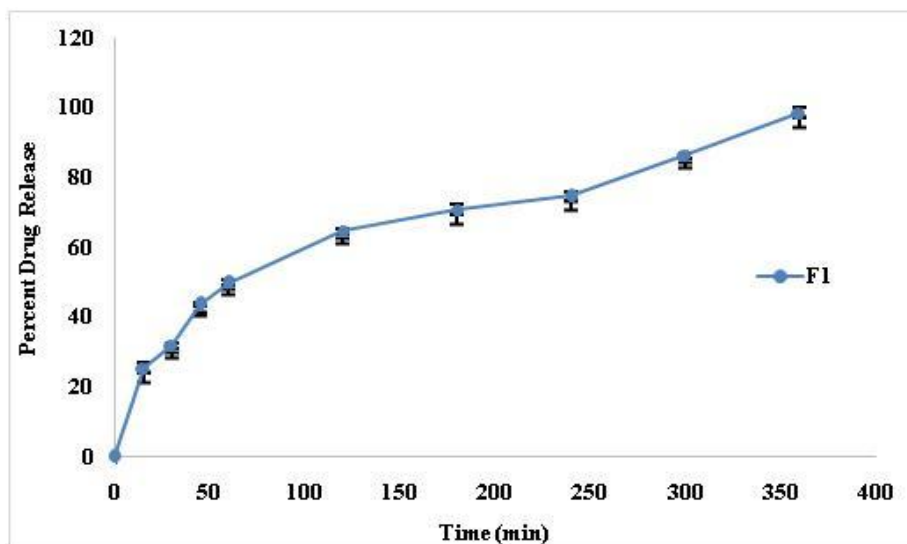


Fig. 6: *In vitro* Percent Drug Diffused, Formulation F1 Mean  $\pm$  SD n=3

**Ex-vivo diffusion studies-** Developed formulation F1 showed higher drug release across the sheep nasal mucosa almost  $81.58 \pm 1.56$  percent of drug was diffused over a period of 6h

as observed in Fig.7. Combined effect of natural penetration enhancer like eucalyptus oil and ethanol being strong penetration enhancer resulted in more drug diffusion across the nasal mucosa.

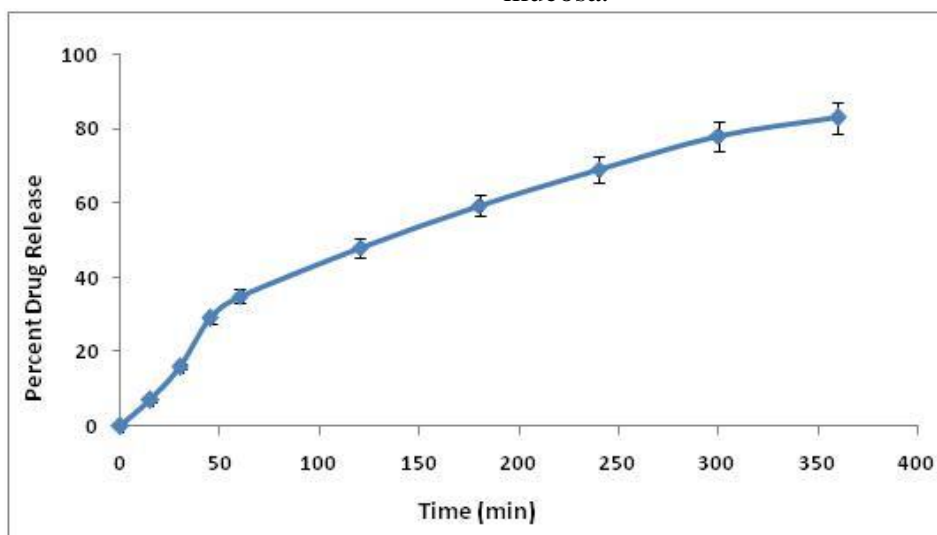


Fig. 7: *Ex-vivo* Percent Drug Diffused, Formulation F1  $\pm$  SD n=3

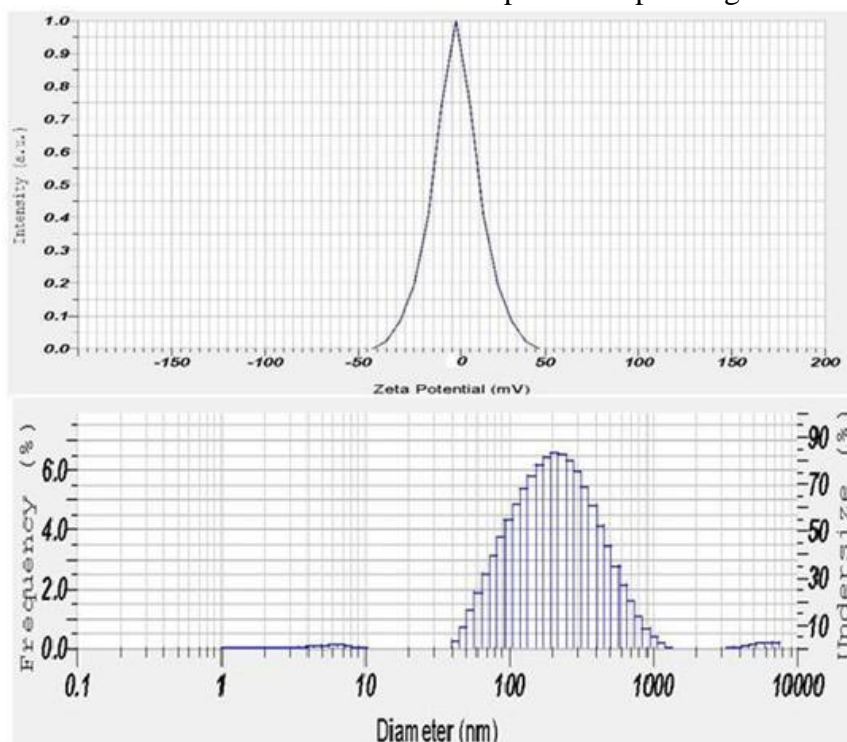
**Characterization of the Optimized Formulation- Measurement of Particle Size and Zeta Potential-**The developed microemulsion

formulation F1 was analyzed for the measurement of particle Size, polydispersity index (PDI) and zeta potential. All measurements are carried out at scattering angle of  $90^\circ$  and  $25^\circ\text{C}$  temperatures (Fig. 8). The average droplet



size of developed microemulsion was found to be  $218.9 \pm 1.7$  nm with low value of polydispersity index of 0.372. This signifies the uniformity of the droplet size in the formulation. Our obtained value of polydispersity index of the microemulsion formulation indicates uniformity of droplet size within the formulation. Because of the presence of Tween-80 as an emulsifier leads

to shift of the share plane position in electric double layer and hence a reduction in the magnitude of zeta potential. Zeta potential of developed microemulsion was  $-23.4$  mV with a conductivity of  $0.123$  mS/cm, low negative zeta potential indicates that the emulsion may be stable since non-ionic interactions between droplets are operating.



**Fig. 8: Zeta Potential of the Microemulsion Formulation (F1)**

## CONCLUSION

From the results obtained in the studies it can be concluded that the developed microemulsion may have better absorption capacity through nasal delivery and can be efficiently used to treat major depressive disorder.

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## CONFLICT OF INTEREST

Authors declare no conflict of interest.

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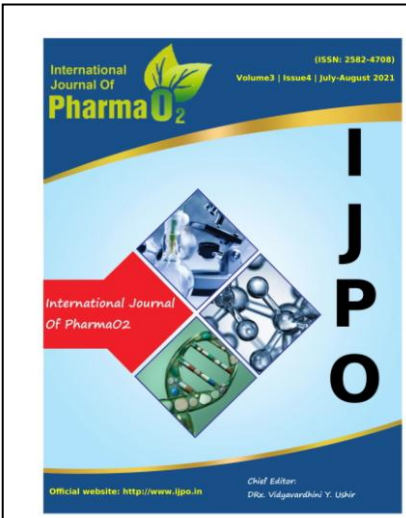
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