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MICROEMULSION BASED NASAL TO BRAIN DELIVERY OF DRUG ACTING ON CNS

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Abstract: Background: Fluvoxamine, an antidepressant drug, has absolute bioavailability of only 53% due to high first pass metabolism. **Aim:** The purpose of this study was to develop and optimize mucoadhesive microemulsion containing Fluvoxamine for intranasal delivery. **Materials and Methods:** Based on solubility study, Acrysol K150, Tween 20 and polyethylene glycol (PEG) 400 were selected as oil, surfactant and co surfactant respectively. Microemulsions were prepared using water titration method. 2:1% w/w ratio (Tween 20:PEG 400) was selected for formulation development. The prepared microemulsions were optimized for globule size, zeta potential, pH, Viscosity and polydispersity index. The optimized batch was further characterized for% drug content, pH, viscosity and % drug diffusion. **Results and Conclusion:** All the parameters showed the suitability of microemulsion of Fluvoxamine for intranasal delivery. Carbapol 934P (0.3 % w/w) was used as a polymer for the preparation of mucoadhesive microemulsion to enhance the retention time in the nasal mucosa. Results of nasal toxicity study using excised sheep nasal mucosa showed comparatively no damage to epithelium and so formulation was considered safe for nasal administration. Fluvoxamine mucoadhesive microemulsion showed the highest percentage of diffusion (98.07 ± 0.710 %) after 24h during *ex-vivo* drug diffusion study through sheep nasal mucosa, followed by Fluvoxamine microemulsion (93.48 ± 0.674%) and finally by Fluvoxamine solution (70.57 ± 0.612%).

Keywords: Fast Dissolving Tablet, Mirtazapine, Indion 414, Avicelph102

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INTRODUCTION

Depression is the growing problems in many nations of the world. Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings and physical well being. All over the world there are 40 crore patients living with depression indicating its global prevalence. It impacts all aspects of everyday life including eating, sleeping, working, relationships, and how a person thinks about himself/herself. People who are clinically depressed cannot simply will themselves to feel better or just "snap out of it". If they do not receive appropriate treatment their symptoms can continue for weeks, months, or years.

The treatment of central nervous system (CNS) disorders is challenging because of a variety of formidable obstacles for effective and persistent delivery of drugs. Even though the drugs used for the treatment of CNS disorders are potent, their clinical failure is often not due to lack of drug efficacy but mainly due to shortcomings in the drug delivery approach. However, potent the drug may be, but if it cannot cross the blood brain barrier and reach the CNS in order to elicit its pharmacological action, it is ineffective.[1,2] Hence, to overcome the large number of barriers restricting the CNS drug delivery scientists are exploring the novel approaches so that delivery of the drugs can be enhanced and/or restricted to the brain and CNS. Various delivery strategies have been developed. Figure 1 briefly shows the various ways in which drug delivery to the brain has been tried. Out of all the strategies that have been listed, they can be categorized as invasive, noninvasive and miscellaneous techniques. Nasal drug delivery falls in the category of miscellaneous type. Current work is mainly focused on nasal to brain drug delivery so emphasis will be on nasal delivery in the following sections.

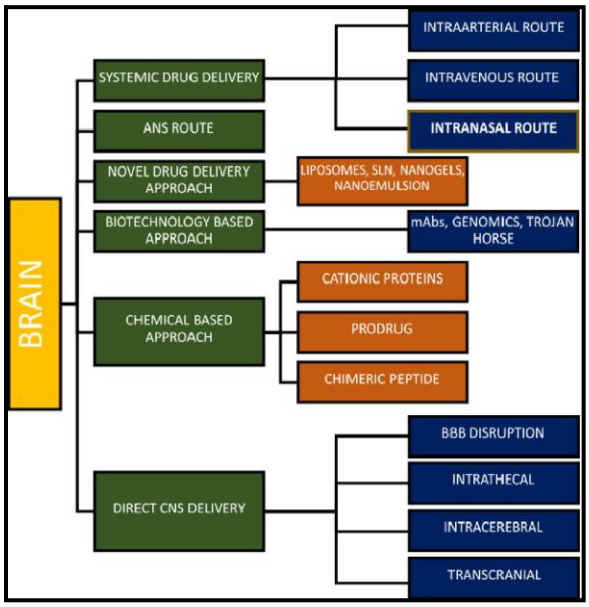

Figure 1: Various approaches for CNS drug delivery [3]

Intranasal drug delivery is one of the focused delivery options for brain targeting as brain and nose compartments are connected to each other through olfactory/trigeminal route via peripheral circulation.[4] Intranasal administration delivers drug directly to the brain circumventing the blood brain barrier and reduces drug distribution to the non targeted sites.[5,6] This may result in reduction in dose, systemic dilution and first pass metabolism of the drug.[7] Nasal delivery route is convenient, patient friendly and also prevents the risk of the gastrointestinal tract irritation.[8] Direct nose to brain transport results in rapid and/or higher uptake in the brain, which proves to be an alternative option of self-medication in the management of emergencies.[4]

Conventionally drugs were administered through intranasal route in the form of solutions, suspensions, gels, emulsions, powders etc. Such conventional dosage forms are having some disadvantages such as lack of dose precision, high particle size, high viscosity, lack of drug stability, solubility problem due to lipophilicity of drug etc. Some novel formulations such as microspheres, nanoparticles are also explored as drug delivery system for intranasal delivery.[9]

However, their toxicity/irritancy on the nasal mucosa cells due to the presence of a variety of polymers/excipients is a major concern. Microemulsion is one such novel formulation which is optically isotropic and thermodynamically stable system composed of oil, water, surfactant (and/or co surfactant).[10] Microemulsions offer several advantages like high solubilization of lipophilic drugs, stability, ease of preparation and stabilization of hydrolytically susceptible compounds. Microemulsions provide a large surface area for better absorption of drugs due to smaller globule size. Various drugs such as Sumatriptan,[11] Zolmitriptan,[12] Cabergoline,[13] Clonazepam,[14] Nimodipine,[15] Tacrine,[16] and Diazepam[17] have been successfully delivered through nasal route in the form of microemulsion and it resulted in improved drug absorption. In order to formulate a nasal formulation with desirable performance, it is advisable to focus on maximizing the residence time in the nasal mucosa and thus ensuring efficient absorption of drug.[18] Use of mucoadhesive polymers in the nasal formulations is expected to increase the residence time and thereby enhance the absorption of the drug.

Fluvoxamine is an antidepressant drug used for the treatment of moderate to severe depression. Fluvoxamine is a potent and selective serotonin reuptake inhibitor with around 100-fold affinity for the serotonin transporter over the norepinephrine transporter.[19] It has negligible affinity for the dopamine transporter or any other receptor, with the sole exception of the σ_1 receptor.[20] It behaves as a potent agonist at this receptor and has the highest affinity of any SSRI for doing so.[20] This may contribute to its antidepressant and anxiolytic effects and may also afford it some efficacy in treating the cognitive symptoms of depression. Fluvoxamine's only FDA approved indication is in the treatment of OCD,[21] although in other countries (e.g. Australia,[22] UK[23] and Russian Federation[24]) it has indications for MDD, as well.

Fluvoxamine has been found to be useful in the treatment of MDD, and anxiety disorders such as panic disorder, social anxiety disorder, post-traumatic stress disorder (PTSD), and obsessive-compulsive spectrum disorders. Fluvoxamine is indicated for children and adolescents with OCD.[25] The drug works long-term, and retains its therapeutic efficacy for at least a year.[26] It has also been found to possess some analgesic properties in line with other SSRIs and tricyclic antidepressants.[27][28][29] Some evidence shows fluvoxamine may be a helpful adjunct in the treatment of schizophrenia, improving the depressive, negative, and cognitive symptoms of the disorder.[30] Its actions at the sigma receptor may afford it a unique advantage among antidepressants in treating the cognitive symptoms of schizophrenia.[31]

In the light of the above facts, an alternative drug delivery system is needed, which can selectively target the candidate drug to the brain. Due to preferential transport of the drug to the brain, intranasal delivery approach may be expected to reduce the wide distribution of the drug to the non-targeted sites such as systemic/peripheral circulation. The delivery system must be meticulously designed to provide rapid transport of the drug across nasal mucosa and longer residence time in the nasal cavity. The aim of this investigation was to deliver Fluvoxamine in the form of mucoadhesive microemulsion through nasal route for the effective treatment of CNS disorders like anxiety and depression. The research work was carried out with objectives in mind to provide rapid drug delivery to the brain, to reduce side effects, maximize therapeutic index and to reduce the dose and dosing frequency.

MATERIALS AND METHODS

Materials

Fluvoxamine was gifted by Torrent Pharmaceutical Limited, Ahmedabad, India. Corel Chemicals, Ahmedabad, India, gifted Acrysol K150. Tween 20 was purchased from the SD fine chemicals Limited, Mumbai, India. Polyethylene glycol (PEG) 400 was purchased from Himedia Private Limited, Mumbai, India. Carbopol 934P was gifted by Lubrizol, Ohio, USA. Other chemicals were of analytical grade andpurchased from SD Fine chemicals Limited, Mumbai, India.

Methods

Solubility determination

Solubility of Fluvoxamine was determined in various oils, surfactants and cosurfactants. Drug was added in excess to different oils, surfactants and co surfactants and shaken using mechanical shaker for 48 h. The samples were then centrifuged at 6000 revolutions per minute (RPM) for 15 min and the drug content in the supernatant was analyzed using ultraviolet (UV) spectrophotometric method at λ max of 254 nm after suitable dilution with methanol.

Selection of Surfactant and Co-Surfactant

300 mg of the surfactants was added to 300 mg of the selected oily phase. The mixtures were gently heated at 50°C for the homogenization of the components. Each mixture, 50 mg, was then diluted with distilled water to 50 mL in a stoppered conical flask. Ease of emulsification was judged by the number of flask inversions required to yield a homogenous emulsion. Emulsions were allowed to stand for 2 h and their % Transparency was evaluated at 650 nm by a double-beam UV-visible spectrophotometer using distilled water as a blank. The screening of the co-surfactant was conducted on the basis of % Transparency and ease of emulsification. Mixtures of 100 mg of the co-surfactant, 200 mg of the selected surfactant, and 300 mg of the selected oil were prepared and evaluated in a similar fashion as described in the above section on surfactant.

Construction of the phase diagram

The phase diagrams with different ratios of surfactant: Co-surfactant (1:1, 2:1, 3:1 % w/w) with selected oil was constructed to explore the microemulsion region. The area of the monophasic region was used as a tool for the selection of suitable surfactant and co surfactant mixture. Aliquots of each surfactant and co surfactant mixture (Smix) were mixed with oil at ambient temperature. For each phase diagram, the ratio of oil to the Smix was varied as 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9 (%w/w). Water was addeddrop wise to each oil-Smix mixture under constant stirring.After equilibrium, the samples were visually checked anddetermined as being clear microemulsions. Phase diagramswere constructed using SIGMA PLOT Software.

Preparation of microemulsion

Based on the phase diagram, the optimum Smix ratio was selected and the drug loaded microemulsions were prepared by dissolving the drug in the oil-Smix mixture, then titrated with water on the magnetic stirrer at 150 RPM for 10 min.

Optimization of parameters

Different batches of microemulsions were prepared by water titration method. Seven batches (F1-F7) were evaluated for Viscosity, pH, globule size, polydispersity index (PDI), % Drug Content and *in-vitro* Diffusion study. Optimized batch was selected on the basis of lower globule size and PDI and higher % Drug Diffusion.[32]

Screening of mucoadhesive agent

Mucoadhesive agents help to retain the formulation at site of administrationand prevent mucociliary clearance. Various polymers such as HPMC, Carbopol, and Chitosan in various

concentrations were evaluated formucoadhesion. For the study, dispersions of various concentrations ofmucoadhesive polymers were prepared by soaking them in water at roomtemperature for overnight and visually observed for their ability to form a film.After screening the polymers based on their gelling ability, they were incorporated in ME along with aqueous phase to form MME. The MME formed was further screened for globule size, zeta potential and Viscosity . Basedon these results the mucoadhesive polymer with specific concentration was finalized.

Preparation of mucoadhesive microemulsion

The mucoadhesive microemulsions were prepared by first preparing a microemulsion of the drug using minimum volume of external phase and then adding required volume of carbopol 934P solution such that the final concentration of carbopol 934P was 0.3 % w/w in the formulation.

Characterization of microemulsion

Globule size determination

Formulations (F1 to F7) each of 1 ml was diluted with 100 ml of water in a volumetric flask. The volumetric flask was inverted twice to ensure complete dispersion of the formulation. After ensuring complete dispersion of the formulation the droplet size of resultant microemulsion was determine by Zetasizer Nano Series (Malvern Instruments, UK). Light scattering was monitor at 25°C at 90° angle.

pH

A 10% dispersion of the formulation was prepared in distilled water and pH was determined by using pH meter standardize with standard buffers of pH 4 and pH 7.4.

Zeta potential determination

Zeta potential of the formulation was measured by using Malvern Zetasizer (Malvern Instruments, UK). Zeta sizer measures the potential ranges from -120 to +120 V. For measurement of zeta potential 2 gm of formulation was diluted with milliQ water (100 ml). Zeta potential is essentially useful for assessing flocculation since electrical charges on particles influence the rate of flocculation.

% Drug Content

Microemulsion formulation was analyzed for drug content by U.V. spectrophotometer (Shimadzu, UV1800) at 254 nm by taking 1ml of microemulsion and diluted with methanol appropriately. Experiment was performed in triplicate for each sample.

In-vitro drug permeation study

In order to estimate the amount of drug permeated in given time period, *in-vitro* permeation study through dialysis membrane was performed for the formulated Microemulsion system. *In-vitro* permeation study was performed for drug loaded microemulsion. Dialysis membrane (cellulose membrane) was soaked in phosphate buffer (pH 6.4). The pre-soaked dialysis membrane was fixed between donor and receptor compartment of Franz diffusion cell (22 ml) and secured in position and thermo-stated at 37±0.5 ^{o}C using water bath, stirred magnetically at 400 rpm. The prepared formulations (1 ml) were applied on the donor side of the membrane. Samples were withdrawn from the receptor fluid at predetermined time intervals up to 24 hours and replaced by equivalent amount of temperature equilibrated buffer. After appropriate dilution the sample was analyzed by UV-Vis spectrophotometer using phosphate buffer 6.4 as blank at 254 nm. The drug release was compared for the different formulations.

***Ex-vivo* drug permeation study**

The freshly excised sheep nasal mucosa, except the septum part was collected from a local slaughter house. The superior nasal membrane was identified and separated from the nasal cavity and made free from adhered tissues. Maintaining the viability of the excised nasal tissue during the experimental period is important. Therefore the mucosa was carefully removed within 20 min of sacrificing the animal, and immediately immersed in ice cold phosphate buffer saline pH 6.4 and aerated. *Ex-vivo* permeation study was carried out using Franz Diffusion Cell (22 ml). The receptor compartment was filled with 22 ml of simulated nasal fluid and stirred magnetically at 400 rpm. The receptor compartment was maintained at 37±0.5 ^{o}C throughout the study period. Mucosal preparation was mounted on receptor compartment of Franz Diffusion cell having a permeation area of 2cm^2 with the mucosal side facing the donor compartment and secured using a clamp, taking care to avoid entrapment of air bubble beneath the membrane. The tissue sample was allowed an incubation period of 15 min to attain 37 ^{o}C. The formulations (1 ml) were uniformly spread over the mucosal surface after the incubation period. Permeation study was performed for a period of 24 hours. At predetermined time intervals, 1 ml of aliquot was withdrawn and replaced with thermo-stated receptor medium. The aliquots were diluted suitably using simulated nasal fluid and drug content determined using UV-vis spectrophotometric method. Amount of drug permeated was calculated from the calibration curve and compared for different formulations.

Histopathology studies

Nasal mucosa of the animals without any dosing, animals dosed with Fluvoxamine Mucoadhesive Microemulsion system and one treated with isopropyl alcohol (control) were excisedand fixed in 10% formalin for histopathological studies.[33] Five micrometer sectioning of the nasal mucosa was done followed by staining with haemotoxylin and eosin. Microscopic examination was done for all possible anatomical changes.

Results and Discussion

Microemulsions are essentially clear systems and hence solubility of drug in all the components is necessary. It is necessary that the effective dose of the drug should be delivered within minimum volume of formulation. Hence, solubility study of Fluvoxamine was carried out in number of excipients that are generally regarded as safe (GRAS listed) for nasal administration. Based on solubility, Acrysol K 150 was selected as oil phase, Tween 20 as surfactant and PEG 400 as cosurfactant as these components showed better solubility for Fluvoxamine. Results are tabulated in Table 1 and Figure 2.

Table 1: Solubility Data of Fluvoxamine in Various Excipients

Vehicle	Function in Microemulsion	Solubility (mg/ml)*
Oleic acid	Oil	33.84±0.262
Acrysol K150	Oil	60.53±0.215
Castor oil	Oil	29.59±0.20
IPM	Oil	24.80±0.02
Tween 80	Surfactant	11.75±0.055
Tween 20	Surfactant	77.66±0.197
Span 80	Surfactant	29.33±0.065
Span 20	Surfactant	18.56±0.025
Propylene glycol	Co-Surfactant	11.56±0.052
IPA	Co-Surfactant	19.87±0.076
PEG-400	Co-Surfactant	89.36±0.052
Ethanol	Co-Surfactant	51.55±0.0305

*Values are mean ±SD (n=3)

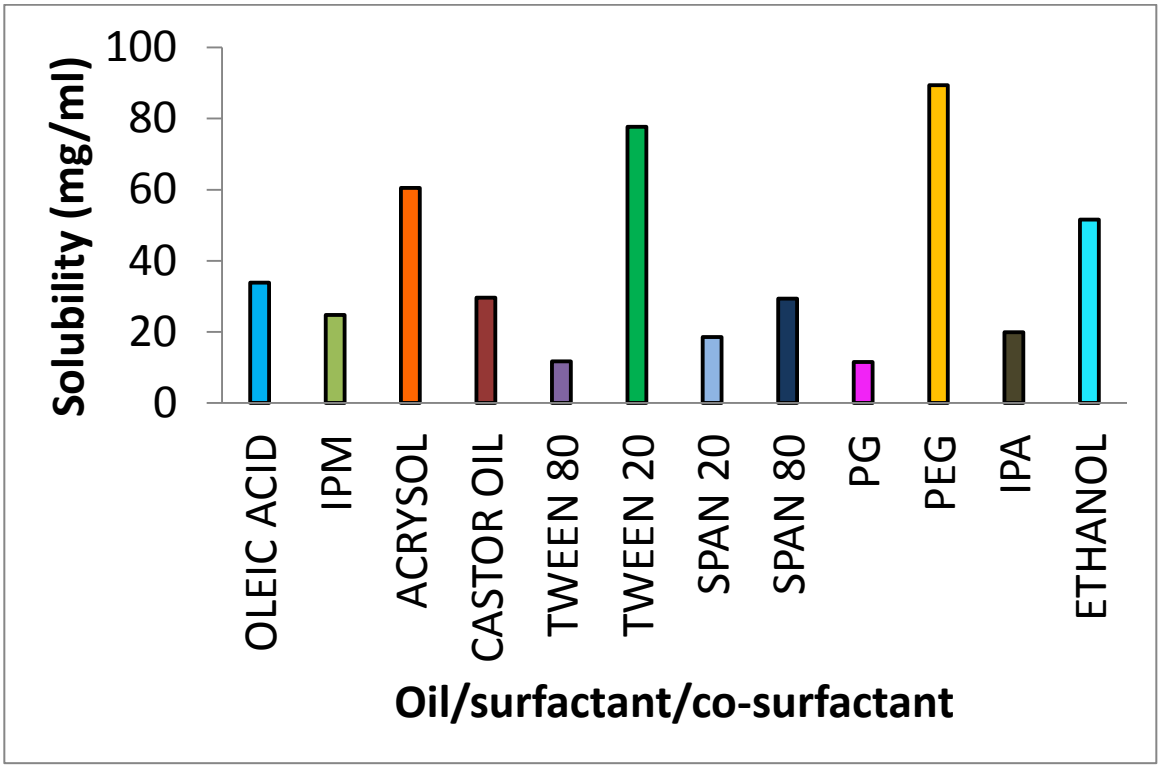

Figure 2: Solubility study of Fluvoxamine in Various vehicles

SELECTION OF SURFACTANT AND CO-SURFACTANT

Non-ionic surfactants are generally considered less toxic than ionic surfactants. In this study, the two surfactants (Tween 80, Tween 20) were compared. The well-formulated microemulsion is dispersed within seconds under gentle stirring conditions, which ultimately depends on the emulsification ability of the surfactant.

Results showed that the oily phase Acrysol K 150 exhibited the highest emulsification efficiency with Tween 20 [% Transparency: 98.58, 6 flask inversions] for the homogenous emulsion formation. On the other hand, Acrysol K 150 showed poor emulsification properties with other surfactant employed, requiring a higher number of flask inversions (as shown in Table 2). The results suggested the use of Acrysol K 150 as an oily phase with Tween 20 as a surfactant for further study. Addition of a co-surfactant to the surfactant-containing formulation was reported to improve dispersibility and drug absorption from the formulation. In the present investigation, two co-surfactants, namely, PEG-400 and ethanol were compared. As shown in Table 2 Acrysol K 150 exhibited good emulsification with all co-surfactants, with PEG-400 showing the maximum transmittance (98.80%).

Table 2: %Transparency of various surfactants and Co-surfactants

Surfactant/Co-surfactant	% Transparency	No. Of Inversion
Tween 20	98.58	6
Tween 80	97.19	14
PEG-400	98.80	9
Ethanol	96.75	17

Pseudo ternary phase diagram

In microemulsion system surfactant and co surfactant get preferentially adsorbed at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence. The selection of oil and surfactant and the mixing ratio of oil to S/CoS, play an important role in the formation of the microemulsion. This can be ascertained by pseudo ternary phase diagram as it differentiates the microemulsion region from that of macroemulsion region. By preparing phase diagram, microemulsion region can be obtained. Phase diagrams with different weight ratios of surfactant:Co surfactant (1:1, 2:1, 3:1 % w/w) were prepared and depending upon the microemulsion region the surfactant to co surfactant ratio was selected as 2:1 for further formulation development. The phase diagram is shown in Figure 3.

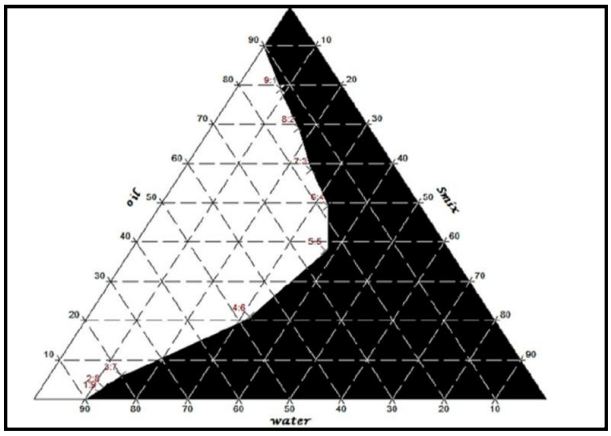

Figure 3(a): Surfactant:Co-surfactant (1:1)

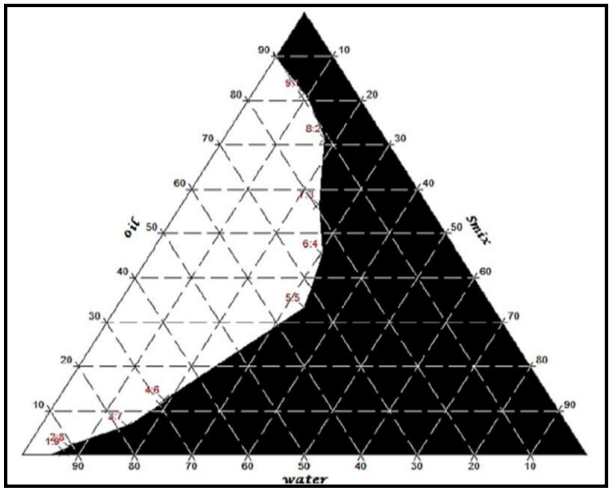

Figure 3(b): Surfactant:Co-surfactant (2:1)

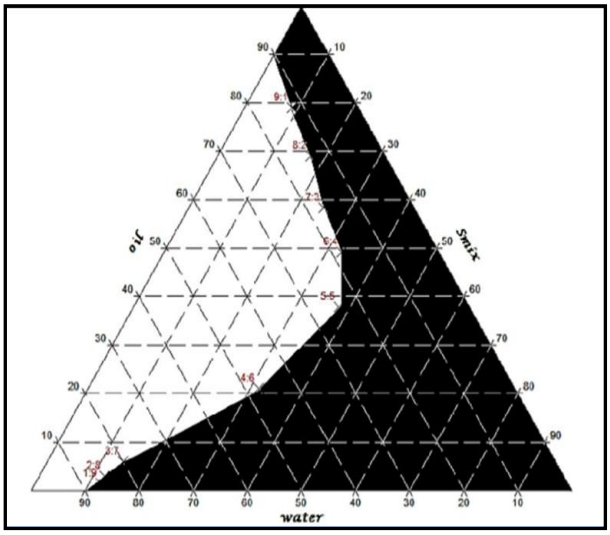

Figure 3(c): Surfactant:Co-surfactant (3:1)

Preparation and optimization of microemulsion

Numbers of batches (F1-F7) were prepared for the optimization of the microemulsion. The % oil and % S mix were varied and different batches were prepared. The prepared microemulsion batches were analyzed for globule size, PDI, pH, viscosity and % drug diffusion. The formulation, which had lesser globule size and PDI and higher % drug content and % drug diffusion from among all the batches, was selected as an optimum batch. The reason for selecting lower globule size was that it increases the permeation through the nasal mucosa as well as lowerglobule size can provide enhanced interfacial area for drug release and absorption. Lesser the PDI, more uniform the formulation is considered. In the same way, formulation with higher% drug diffusion as shown in Figure 4 and drug content was selected. The result of the all

the prepared batches is recorded in Table 3. From the Table, it shows that Microemulsion batch-5 (F5) was considered as optimized batch. It is having composition of 19 % Acrysol K150, 33 % S mix and 48% water. Mucoadhesive microemulsion was prepared with the same composition having 0.3 % carbopol 934P as mucoadhesive polymer. The detailed composition of optimized batch of Microemulsion and mucoadhesive microemulsion is shown in Table 4.

Table 3: Evaluation of microemulsion

FORMULATION	Globule size (nm)	PDI	*pH	Viscosity	*(% Drug Diffusion)	(% Drug Content)
F1	71.91±0.24	0.328	6.4±0.215	63±0.002	83.45±0.213	99.72±0.12
F2	42.48±0.21	0.510	6.5±0.045	75±0.20	86.08±0.334	98.67±0.57
F3	53.21±0.23	0.494	6.2±0.180	71±0.005	84.83±0.392	98.46±0.36
F4	37.25±0.18	0.268	6.2±0.138	77±0.10	89.15±0.523	99.02±0.18
F5	29.21±0.24	0.262	6.5±0.005	68±0.004	93.48±0.674	99.87±0.21
F6	39.92±0.21	0.369	6.7±0.230	66±0.140	87.95±0.588	99.37±0.59
F7	34.80±0.23	0.307	6.6±0.197	75±0.006	91.73±0.219	99.42±0.34

(*Values are mean ±SD (n=3))

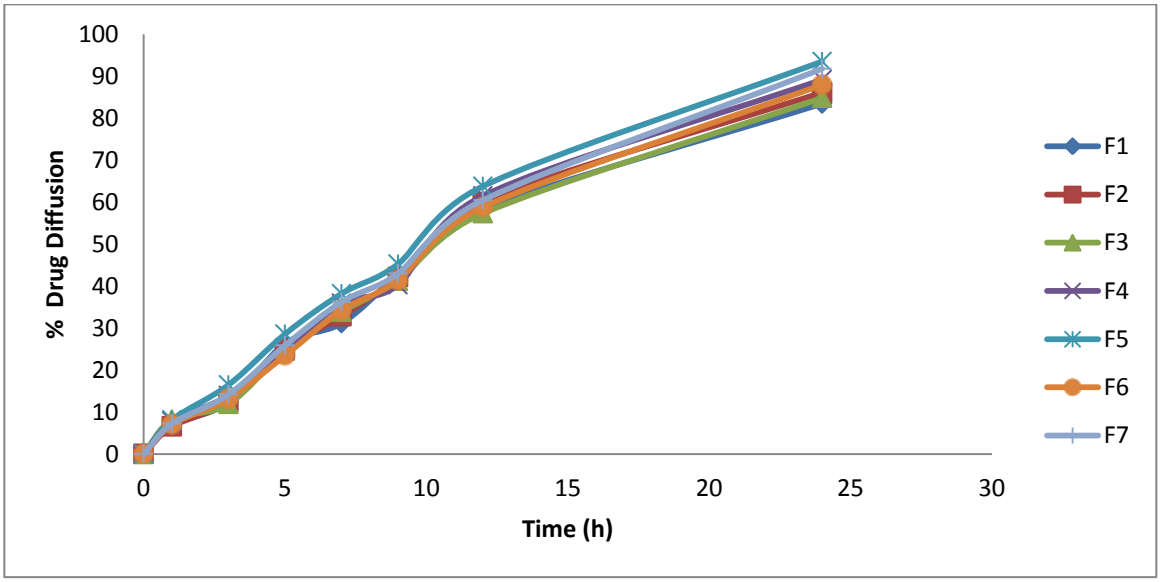

Figure 4: % Drug Diffusion of Different Batches of Microemulsion

Table 4: Optimized batch of microemulsion and mucoadhesive microemulsion

Components	Quantity (% w/w)	
	Microemulsion %	Mucoadhesive microemulsion %
Acrysol K150	18 %	18 %
Tween 20	22 %	22 %
PEG 400	10 %	10 %
Water	50 %	49.7 %
Carbopol 934P	-	0.3 %

Characterization of microemulsion

The drug loaded microemulsion and mucoadhesive microemulsion were prepared and characterized for their pH, globule size as shown in Figure 5 and 6, zeta potential as shown in Figure 7 and 8, % drug content, % drug diffusion as shown in Figure 9 and the results are recorded in Table 5.

For Optimized Microemulsion:

			Size (d.nm):	% Intensity	Width (d.nm):
Z-Average (d.nm):	29.21	Peak 1:	21.41	61.0	7.631
PDI:	0.262	Peak 2:	152.5	33.1	54.86
Intercept:	0.952	Peak 3:	4554	6.0	849.8

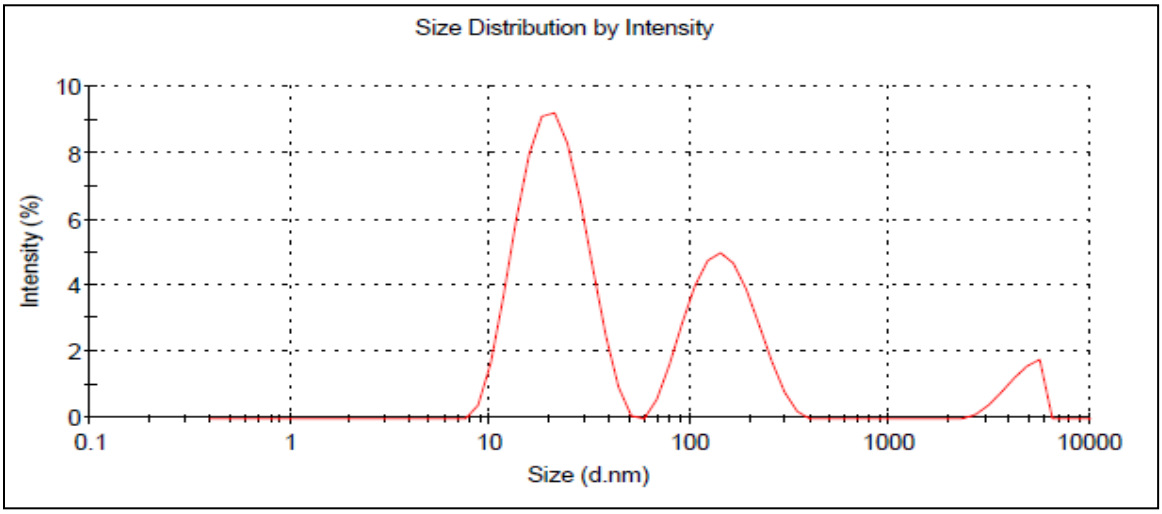

Figure 5: Globule Size of F5 (Optimized Microemulsion)

For Mucoadhesive Microemulsion:

			Size (d.nm):	% Intensity	Width (d.nm)
Z-Average (d.nm):	35.92	Peak 1:	52.17	100.0	34.10
PDI:	0.264	Peak 2:	0.000	0.0	0.000
Intercept:	0.936	Peak 3:	0.000	0.0	0.000

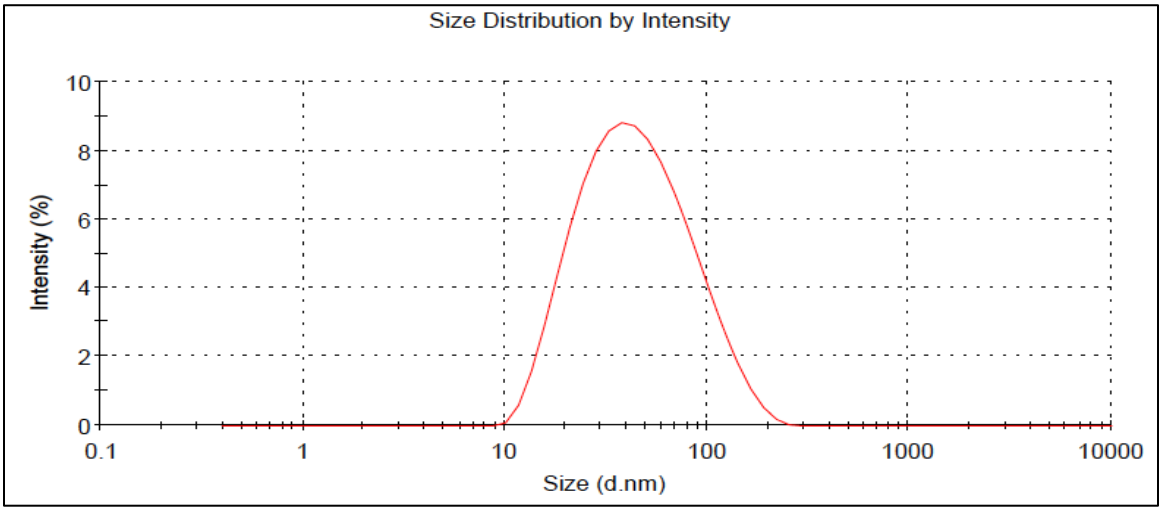

Figure 6: Globule Size of Mucoadhesive Microemulsion

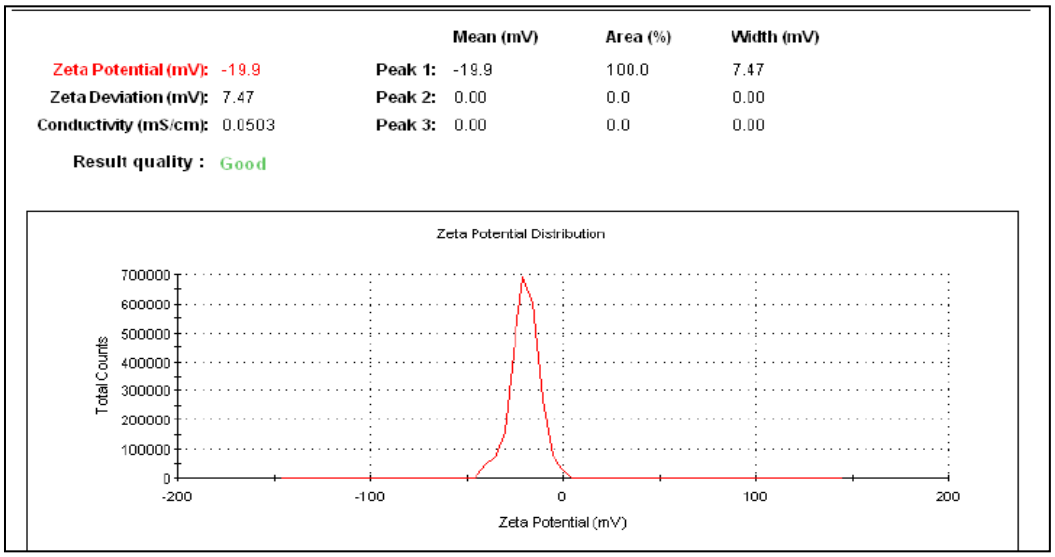

Figure 7: Zeta Potential for F5 (Optimized Microemulsion)

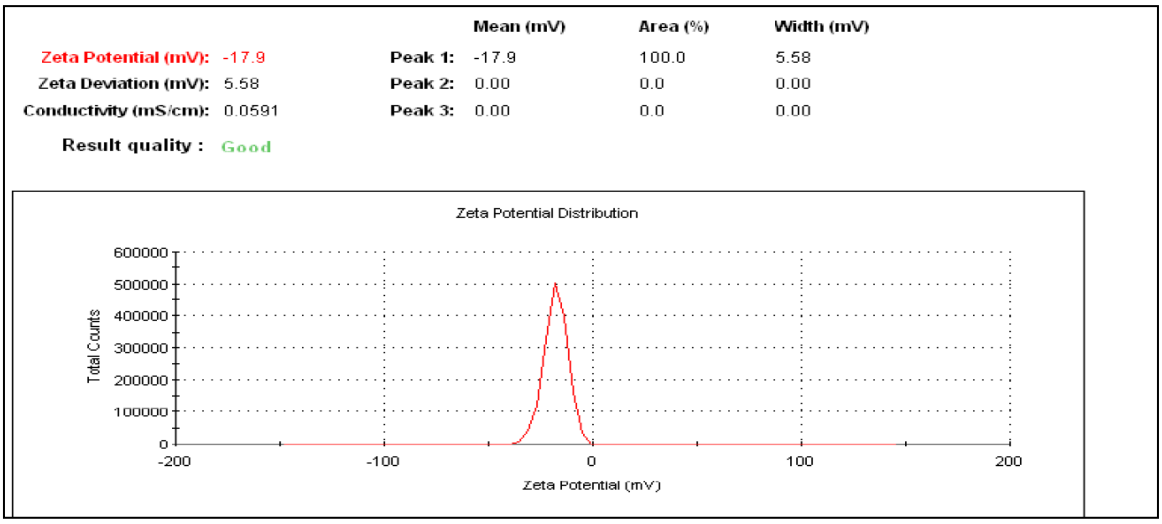

Figure 8: Zeta Potential for Mucoadhesive Microemulsion

Table 5: Characterization of microemulsion

Parameters	Microemulsion (F5)	Mucoadhesive microemulsion
% Drug Content	99.87±0.21	99.52±0.33
% Drug Diffusion	93.48±0.674	98.07 ± 0.710
Globule Size	29.21±0.24	35.92±0.37
PDI	0.262	0.264
Zeta Potential	-19.9	-17.9
pH	6.5±0.005	6.2±0.046
Viscosity	68±0.004	73±0.135

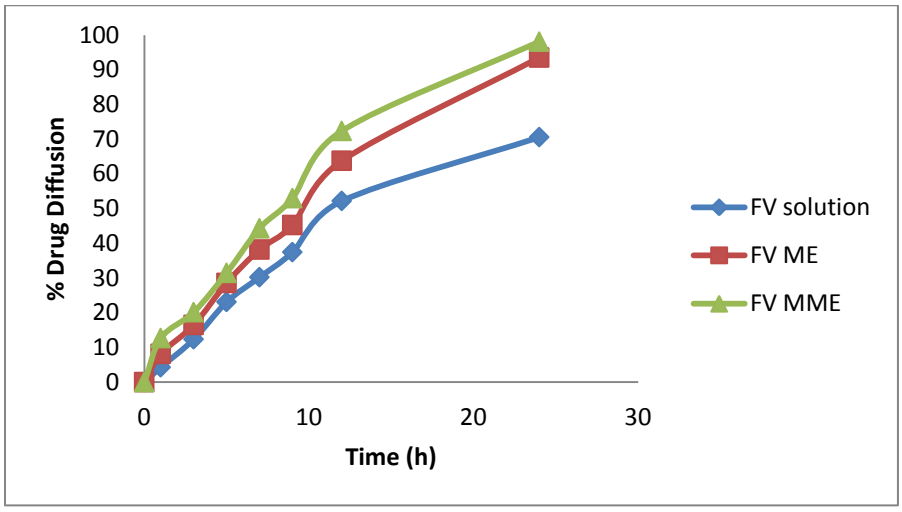

Figure 9: Comparison of % Drug Diffusion between microemulsion and Mucoadhesive Microemulsion

Histopathology studies

The microscopic observations indicate that the prepared Mucoadhesive Microemulsion has no effect on integrity of cells of nasal mucosa when compared with the untreated nasal mucosal sample (Figure 10). As shown in Figure 11, neither necrosis nor removal of cells of epithelium were observed from the nasal mucosa under 40X magnification. However, in case of isopropyl alcohol treated sample of nasal mucosa disruption of cell integrity and damage of the epithelial layer was observed, as shown in Figure 12. Thus the formulation seems to be safe with respect to nasal irritation

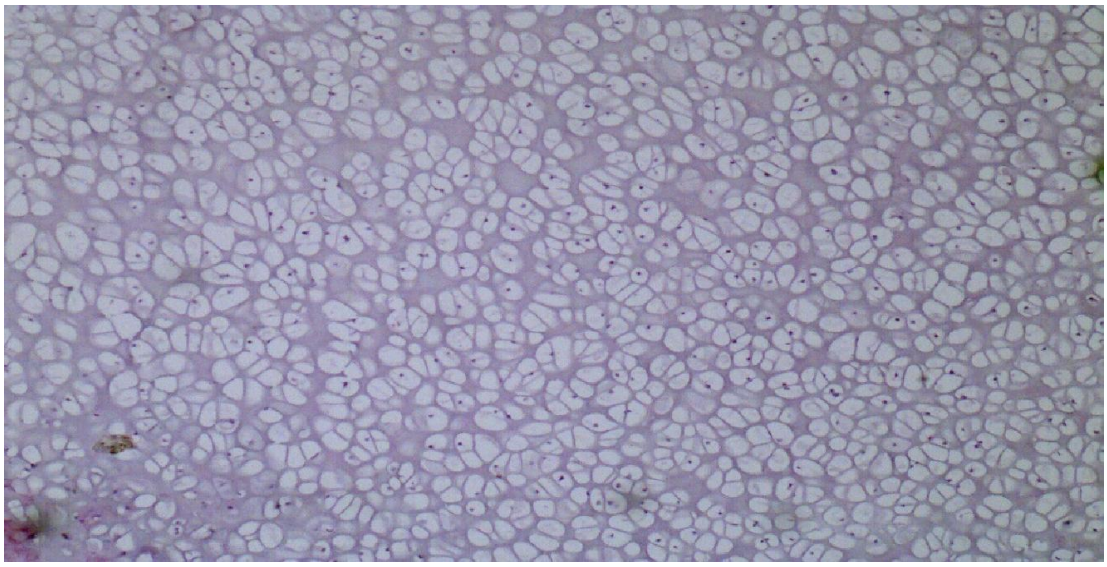

Figure 10: Histopathological section of intact (untreated) nasal mucosa

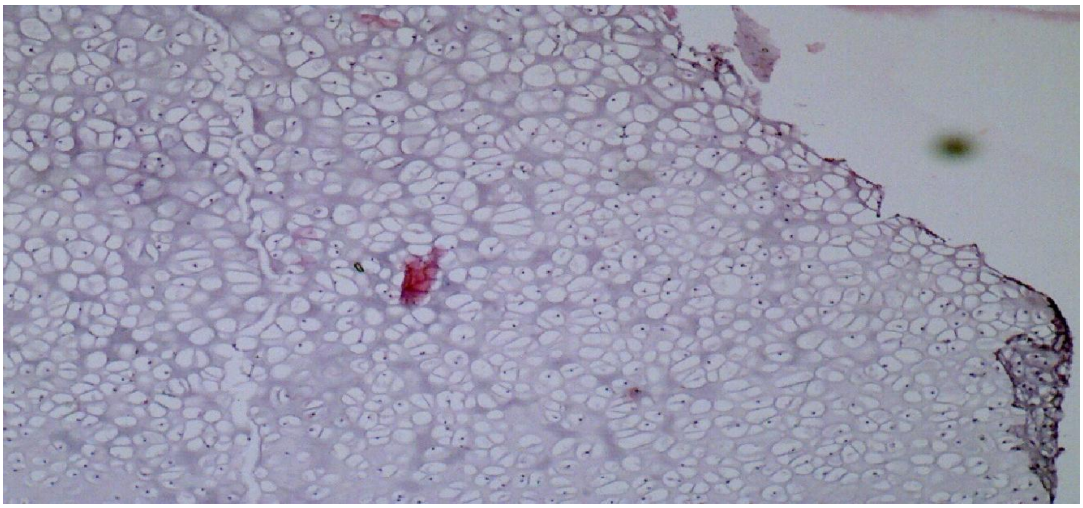

Figure 11: Histopathological section of nasal mucosa treated with Fluvoxamine Mucoadhesive Microemulsion

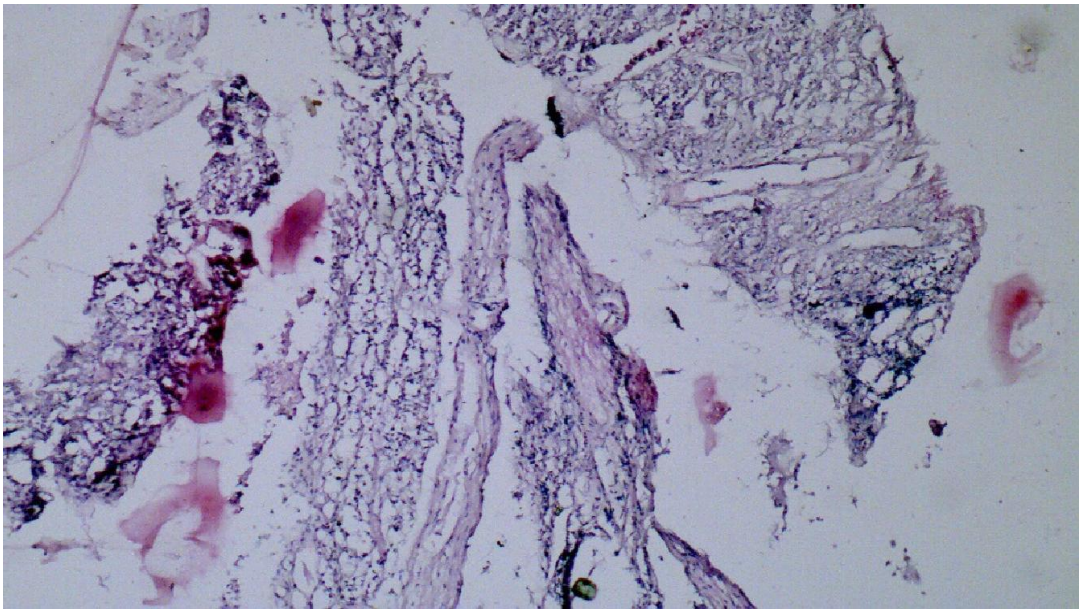

Figure 12: Histopathological section of nasal mucosa treated with Isopropy alcohol

CONCLUSION:

Microemulsion of Fluvoxamine was prepared and optimized by using *in-vitro* parameters like particle size, PDI, zeta potential, pH, % drug diffusion, % drug content. Optimal microemulsion contains Acrysol K150 as oil phase, Tween 20 as a surfactant and PEG 400 as co surfactant. The % weight ratio of surfactant to co surfactant was selected as 2:1. The developed optimal microemulsion containing Fluvoxamine had globule size 29.21 nm, PDI 0.262, zeta potential −19.9 mV, % drug content 99.87±0.21 and % drug diffusion 93.48±0.674. Mucoadhesive microemulsion was also developed using 0.3% Carbopol 934P. Nasal toxicity study was carried out in an excised sheep nasal mucosa to evaluate the effect of microemulsion components on nasal mucosa and the results showed that prepared formulations were safer for nasal administration. Our study illustrated the potential use of microemulsion system to administer Fluvoxamine by nasal route.

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