Original Article

Formulation and optimization of mucoadhesive microemulsion containing mirtazapine for intranasal delivery

Abstract

Background: Mirtazapine, an antidepressant drug, has absolute bioavailability of only 50% due to high first pass metabolism. **Aim:** The purpose of this study was to develop and optimize mucoadhesive microemulsion containing mirtazapine for intranasal delivery. **Materials and Methods:** Based on solubility study, Capmul Medium chain Monoglyceride, Tween 80 and polyethylene glycol (PEG) 400 were selected as oil, surfactant and co surfactant respectively. Microemulsions were prepared using water titration method. 3:1% w/w ratio (Tween 80: PEG 400) was selected for formulation development. The prepared microemulsions were optimized for globule size, zeta potential, % transmittance and polydispersity index. The optimized batch was further characterized for % drug content, conductivity and transmission electron microscopy. **Results and Conclusion:** All the parameters showed the suitability of microemulsion of mirtazapine for intranasal delivery. Chitosan (0.5% 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. mirtazapine mucoadhesive microemulsion showed the highest percentage of diffusion (57.11 ± 0.710%) after 210 min during *in-vitro* drug diffusion study through sheep nasal mucosa, followed by mirtazapine microemulsion (46.08 ± 0.674%) and finally by mirtazapine solution (17.63 ± 0.612%).

Key words:
Intranasal, microemulsion, mirtazapine, optimization

Introduction

Anxiety and depression are the growing problems in many nations of the world. Generalized anxiety disorder is characterized by excessive, exaggerated anxiety and worry about everyday life events with no obvious reasons while 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.[1]

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.[2,3] Hence, scientists are exploring the novel approaches so that delivery of the drugs can be enhanced and/or restricted to the brain and CNS.

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

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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.

Mirtazapine is an antidepressant drug used for the treatment of moderate to severe depression. It is the only tetracyclic antidepressant that has been approved by the Food and drug administration to treat depression and anxiety. Mirtazapine is a potent antagonist at postsynaptic 5-HT2 and 5-HT3 (serotonergic) and central noradrenergic receptors and acts by increasing central noradrenergic and serotonergic (5-HT1) neurotransmission. Absolute bioavailability of mirtazapine is only 50% due to high first-pass metabolism. Common side-effects of mirtazapine include dizziness, blurred vision, sedation, dry mouth, constipation, nightmares, joint pain, muscle pain, back pain, etc.[19]

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 mirtazapine 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

Mirtazapine was gifted by Sun Pharma Advanced Research Centre, Vadodara, India. Capmul MCM was gifted by Abitec Corporation Limited, Janesville, USA. Tween 80 and polyethylene glycol (PEG) 400 were purchased from the standard deviation (SD) fine chemicals. Mumbai, India. Chitosan was gifted by Indian Sea Foods Limited, Cochin, India. Other chemicals were of analytical grade and purchased from SD Fine chemicals, Mumbai, India.

Methods

Solubility determination

Solubility of mirtazapine 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 (Model: RIS 24BL, Make: Remi Equipments, Mumbai, India) for 72 h. The samples were then centrifuged at 8000 revolutions per minute (RPM) (Model: R4C, Make: Remi Equipments, Mumbai, India) for 10 min and the drug content in the supernatant was analyzed using ultraviolet (UV) spectrophotometric method (UV 1700, Shimadzu, Japan) at λmax of 292 nm after suitable dilution with methanol.[20]

Construction of the phase diagram

The phase diagrams with different ratios of surfactant: Co surfactant (1:1, 2:1, 3:1, 4:1% w/w) with selected oil were 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 added drop wise to each oil-Smix mixture under constant stirring. After equilibrium, the samples were visually checked and determined as being clear microemulsions. Phase diagrams were constructed using Chemix software (Chemix school, version 3.6).

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 (26 mg) in the oil-Smix mixture, then titrated with water on the magnetic stirrer (Remi instrument, Mumbai, India) at 150 RPM for 10 min.

Optimization of parameters

Different batches of microemulsions were prepared by water titration method. The prepared batches were evaluated for zeta potential, globule size, polydispersity index (PDI) and % Transmittance. Optimized batch was selected on the basis of lower zeta potential, globule size and PDI and higher % transmittance.[21]

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 chitosan solution (1% w/w chitosan in acetate buffer pH 5) such that the final concentration of chitosan was 0.5% w/w in the formulation.

Characterization of microemulsion

Globule size determination

The globule size of mirtazapine microemulsion (MME) and mucoadhesive microemulsion was determined using photon correlation spectroscopy (Model: Nano zs, Malvern instruments, UK) at 633 nm. The globule size of microemulsion was determined after diluting it 10 times with distilled water.

Zeta potential determination

Malvern Zetasizer Nano zs was used to measure the zeta potential of the globules based on the electrophoresis and electrical conductivity of the formed microemulsion. The electrophoretic mobility (μm/s) of the particles was converted to the zeta potential by in-built software based on Helmholtz-Smoluchowski equation. Measurements were performed using small volume disposable zeta cell. Zeta potential was studied and recorded for MME and mirtazapine mucoadhesive microemulsion (MMME).

% Transmittance

The % transmittance of the microemulsion was checked against distilled water using UV-Visible spectrophotometer at λmax of 633 nm.

% Drug content

A definite volume of formulation, i.e., MME or MMME was taken in a 10 ml volumetric flask and diluted with methanol. The resultant solution was sonicated for 3 min at ambient temperature and the absorbance of the resultant solution was measured at λmax of 292 nm against placebo formulation treated in the similar manner as blank.

Transmission electron microscopy (TEM)

To perform TEM observations, a drop of diluted (1 in 10 dilution) microemulsion was directly deposited on the copper grid and observed after drying. The images were taken with Tecnai 200 charge coupled device camera operating at 200 kV and capable of point to point resolution.

Nasal toxicity study

Freshly excised sheep nasal mucosa was collected from a local slaughter house and was kept in phosphate buffer saline pH 6.4 for 15 min. Sheep nasal mucosa pieces having uniform thickness of 0.2 mm were taken. Mucosa treated with phosphate buffer pH 6.4 was taken as a negative control and the mucosa treated with isopropyl alcohol was taken as a positive control. Other two mucosae were treated with microemulsion and mucoadhesive microemulsion for 1 h separately. After 1 h, the both the mucosae were rinsed with phosphate buffer pH 6.4 and all of them were carried to the pathological laboratory in 10% formalin for the preparation of pathological slides. The sectioned tissue was then stained with hematoxylin and eosin. The prepared pathological slides were studied under an optical microscope at ×10 resolution for any sign of toxicity and the images were taken.

***In-vitro* drug release study**

The *in-vitro* drug diffusion study was performed using Franz diffusion cell of diameter 10 mm mounted with excised sheep nasal mucosa[22,23] of thickness (height) 0.2 mm. A total volume of 0.8 ml mirtazapine solution (MS) (MS in acetate buffer pH 5); MME and MMME were placed in the donor compartment along with 1.2 ml diffusion media. Receptor compartment contained 20 ml of acetate buffer pH 5 stirred with Teflon coated magnetic stirrer (120 RPM). A total volume of 1 ml sample was withdrawn from the receptor compartment at predetermined time intervals and analyzed using UV spectrophotometric method.[20] Each sample removed was replaced with an equal volume of acetate buffer pH 5. Each study was carried out for a period of 3.5 h and in triplicate. The mean cumulative values for percentage drug diffused and diffusion coefficients for mirtazapine were calculated for the formulations [Table 1].

Results and Discussion

Solubility study

Microemulsions are essentially clear systems and hence solubility of drug in all the components is necessary. The volume capacity of the nasal cavity is 7.5 mL per each nostril in humans. However, 150 μL per nostril is the maximum possible volume for convenient nasal administration.[23-25] Hence, it is necessary that the effective dose of the drug should be delivered within minimum volume of formulation. Hence, solubility study of mirtazapine was carried out in number of solvents which are generally regarded as safe (GRAS listed) for nasal administration. Based on solubility

data, Capmul MCM was selected as oil phase, Tween 80 as surfactant and PEG 400 as cosurfactant as these components showed better solubility for mirtazapine. Results are tabulated in Table 2.

Psuedo 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, 4:1%w/w) were prepared and depending upon the microemulsion region the surfactant to co surfactant ratio was selected as 3:1 for further formulation development. The phase diagram is shown in Figure 1.

Table 1: *In-vitro* diffusion study of mirtazapine formulations

Time (min)	% drug diffused for MS	% drug diffused for MME	% drug diffused for MMME
5	0.0	0.89±0.181	1.41±0.213
15	0.11±0.156	2.67±0.387	7.56±0.344
30	0.27±0.231	5.82±0.412	10.2±0.423
45	1.52±0.298	8.55±0.467	16.17±0.489
60	2.08±0.322	11.51±0.524	21.76±0.549
90	5.27±0.385	15.98±0.568	27.77±0.586
120	8.61±0.461	20.73±0.588	31.18±0.602
150	11.52±0.524	25.19±0.614	46.11±0.633
180	16.31±0.557	40.28±0.665	50.2±0.651
210	17.63±0.612	46.08±0.674	57.11±0.710

MS – Mirtazapine solution; MME – Mirtazapine microemulsion; MMME – Mirtazapine mucoadhesive microemulsion

Table 2: Solubility data of mirtazapine in different solvents

Oil	Solubility* (mg/ml)
Capmul MCM	107.2±0.20
Capmul MCM C8	53.4±0.17
Captex 355	12.9±0.27
Miglyol 812	33.8±0.34
Labrafac lipophile	9.8±0.05
Labrafil 1944	11.6±0.23
Olive oil	11.8±0.18
Isopropyl myristate	17.8±0.42
Oleic acid	3.8±0.26
Tween 80	116.2±0.38
Tween 20	63.6±0.12
Acconon CC6	14.8±0.32
Labrasol	30.2±0.11
PEG 400	70.8±0.19
Transcutol P	38.8±0.14
PEG 600	13.4±0.35
Lauroglycol fcc	18.8±0.23
Plurol oleique CC 497	3.8±0.46
Lauroglycol 90	18±0.21

*Values are expressed as mean ± SEM of three estimations; SEM – Standard error of the mean

Preparation and optimization of microemulsion

Numbers of batches were prepared for the optimization of the microemulsion. The % oil and % Smix were varied and different batches were prepared. The prepared microemulsion batches were analyzed for zeta potential, globule size, PDI and % transmittance. The formulation, which had lesser globule size, PDI and zeta potential and higher % transmittance 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 lower globule size can provide enhanced interfacial area for drug release and absorption.[4,21] Lesser the PDI, more uniform the formulation is considered.[21] Lesser the zeta potential toward negative side (near to-30 mV), the more physical stability of the formulation one can expect.[21,26,27] In the same way, formulation with higher % transmittance was selected as it is indicative of isotropic and clear formulation. The result of the all the prepared batches is recorded in Table 3. From the Table, it shows that Microemulsion batch-7 was considered as optimized batch. It is having composition of 7% Capmul MCM, 45% Smix and 48% water. Mucoadhesive microemulsion was prepared with the same composition having 0.5% chitosan as mucoadhesive polymer. The detailed composition of optimized batch of MME and mucoadhesive microemulsion is shown in Table 4.

Characterization of microemulsion

The drug loaded microemulsion and mucoadhesive microemulsion were prepared and characterized for their pH, globule size, zeta potential, conductivity, % transmittance, % drug content and the results are recorded in Table 5. As per the result of qualitative and conductivity tests, prepared microemulsion were found to be o/w type. Globule size of prepared microemulsion was found to be in nano range (below 50 nm). Nano globule size can help in enhanced permeation through nasal mucosa as well as result in enhanced interfacial area for drug release and absorption. The PDI is the measure of uniformity of the formulation. Less than 1 and near to 0.1 PDI is desirable for the formulation. Both microemulsion and mucoadhesive microemulsion showed PDI less than 1 and hence can be considered as uniform formulation. The zeta potential was found to be on the negative side for MME therefore the physical stability of the formulation on storage can be expected. For mucoadhesive microemulsion zeta potential was towards positive side because of presence

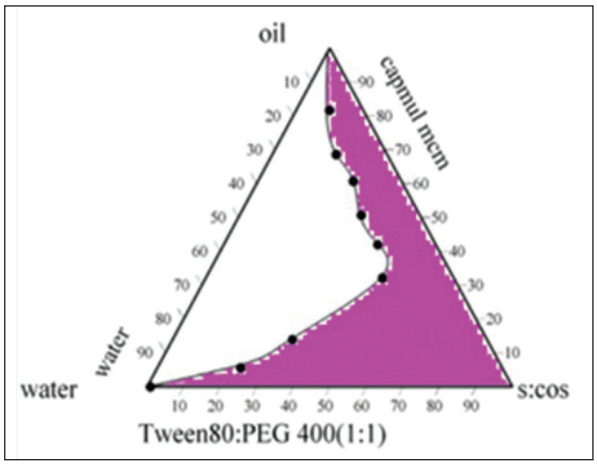

Figure 1a: Phase diagram 1 (surfactant: Co-surfactant ratio 1:1)

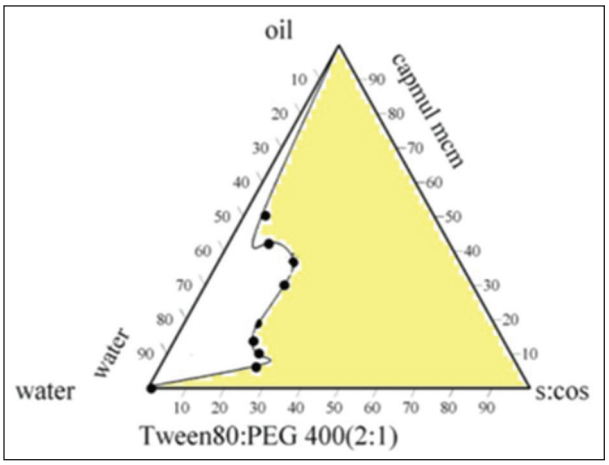

Figure 1b: Phase diagram 2 (surfactant: Co-surfactant ratio 2:1)

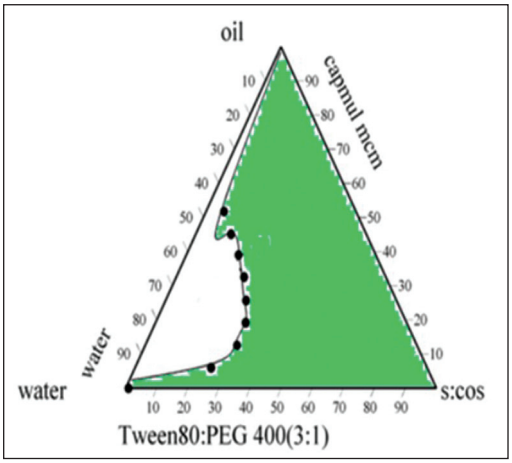

Figure 1c: Phase diagram 3 (surfactant: Co-surfactant ratio 3:1)

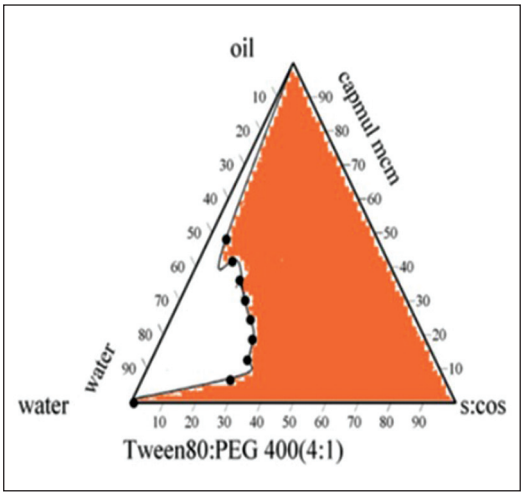

Figure 1d: Phase diagram 4 (surfactant: Co-surfactant ratio 4:1)

Table 3: Results of globule size, PDI, zeta potential and % transmittance

Batch no.	% of oil	% of Smix (3:1)	% transmittance at 633 nm	Globule size (nm)	Zeta potential (mV)	PDI
ME 1	5	40	98.12±0.12	29.85±0.24	−14.9±0.22	0.512
ME 2	5	45	98.05±0.18	31.14±0.21	−14.1±0.23	0.498
ME 3	5	50	98.17±0.22	26.65±0.25	−13.9±0.24	0.491
ME 4	5	55	98.24±0.27	23.81±0.23	−14.8±0.22	0.483
ME 5	5	60	98.28±0.12	28.82±0.18	−14.0±0.21	0.421
ME 6	7	40	99.57±0.26	15.29±0.22	−14.48±0.24	0.319
ME 7	7	45	99.93±0.24	13.71±0.21	−16.9±0.22	0.214
ME 8	7	50	99.27±0.28	16.21±0.24	−15.24±0.21	0.298
ME 9	7	55	99.89±0.14	14.71±0.22	−15.93±0.18	0.328
ME 10	7	60	99.63±0.29	15.62±0.18	−14.38±0.14	0.321
ME 11	9	40	98.63±0.22	22.18±0.21	−14.16±0.14	0.417
ME 12	9	45	99.84±0.27	15.17±0.22	−11.8±0.18	0.459
ME 13	9	50	98.4±0.24	20.57±0.21	−8.55±0.16	0.412
ME 14	9	60	99.20±0.28	18.56±0.23	−10.09±0.21	0.465

PDI – Polydispersity index; ME – Microemulsion; Smix – Surfactant and co-surfactant mixture

of mucoadhesive polymer chitosan. The formulations are not expected to pose any problem due to electrostatic interaction between the microemulsion and nasal mucosa on intranasal administration. The % drug content was more than 99% for both microemulsion and mucoadhesive microemulsion, which indicates very high drug entrapment

efficiency of the system. More than 99% transmittance indicated that the microemulsion is optically clear and isotropic system. TEM image of the MME is shown in Figure 2. The globule size was found to be 13.91 nm, which was in correlation with the globule size obtained by zetasizer.

Nasal toxicity study

The prepared mirtazapine formulations were subjected to nasal toxicity study to evaluate the safety of the ingredients used in the formulation. The optical microscopy images of nasal mucosa treated with mirtazapine formulations are shown in Figure 3. The nasal mucosa treated with isopropyl alcohol (mucociliary toxic agent) showed complete destruction of epithelial layer while nasal mucosa treated with microemulsion and mucoadhesive microemulsion were found to be intact without any damage to the epithelial layer. Thus prepared formulations were found to be safe on nasal mucosa. However, further toxicity studies have to be conducted prior to clinical application of the prepared formulations.

Table 4: Optimized batch of microemulsion and mucoadhesive microemulsion

Components	Quantity (% w/w)	
	Microemulsion %	Mucoadhesive microemulsion %
Capmul MCM	7	7
Tween 80	33.75	33.75
PEG 400	11.25	11.25
Water	48	47.5
Chitosan	—	0.5

PEG – Polyethylene glycol; MCM – Medium chain Monoglyceride

Table 5: Characterization of microemulsion

Parameter	Microemulsion	Mucoadhesive microemulsion
% assay	99.8±0.14	99.43±0.14
% transmittance at 633 nm	99.93±0.08 nm	Not determined
Globule size	13.71±0.22 nm	21.47±0.22 nm
PDI	0.214	0.359
Zeta potential	−16.9±0.21 mV	5.98±0.21 mV
Conductivity	0.128±0.012 mS/cm	0.251±0.012 mS/cm
Ph	6.39±0.26	5.92±0.26
Mg/mL of mirtazapine in ME	26 mg/ml	26 mg/ml

PDI – Polydispersity index; ME – Microemulsion

In-vitro drug diffusion study

The prepared formulations of mirtazapine were subjected to *in-vitro* drug diffusion studies through excised sheep nasal mucosa for 210 min. The % cumulative drug diffused across nasal mucosa from the formulations were calculated and recorded in Table 1. The MMME showed higher % drug release [Figure 4] as compared to MME, which was reflected in higher diffusion coefficient value than MME. This may be explained by bio-adhesion and absorption enhancement property of chitosan across the mucosal membrane by opening tight epithelial junctions of the mucosal membranes like nasal membrane and although, MS showed lowest % of drug diffused as compared to MME and MMME because of lesser nasal retention time of MS.

Results and Conclusion

Microemulsion of mirtazapine was prepared and optimized by using *in-vitro* parameters like particle size, PDI, zeta potential, pH, conductivity, % drug content. Optimal microemulsion contains Capmul MCM as oil phase, Tween 80 as a surfactant and PEG 400 as co surfactant. The % weight ratio of surfactant to co surfactant was selected as 3:1. The developed optimal microemulsion containing mirtazapine had globule size 12.3 nm, PDI 0.214, zeta potential – 16.9 mV, % transmittance 99.93%. Mucoadhesive microemulsion was also developed using 0.5% chitosan. Nasal toxicity study was carried out in an excised sheep nasal mucosa to

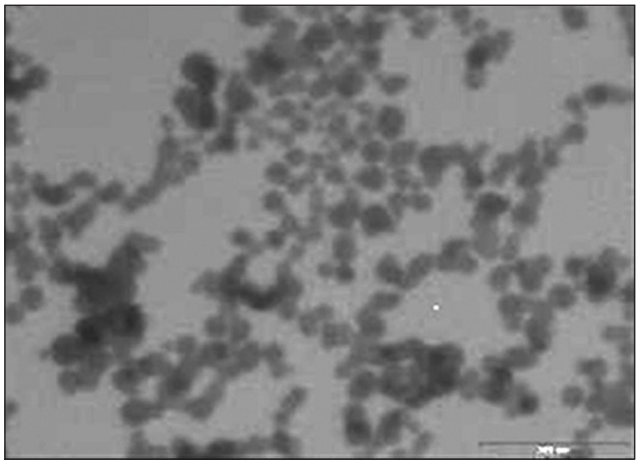

Figure 2: Transmission electron microscopy image of mirtazapine microemulsion

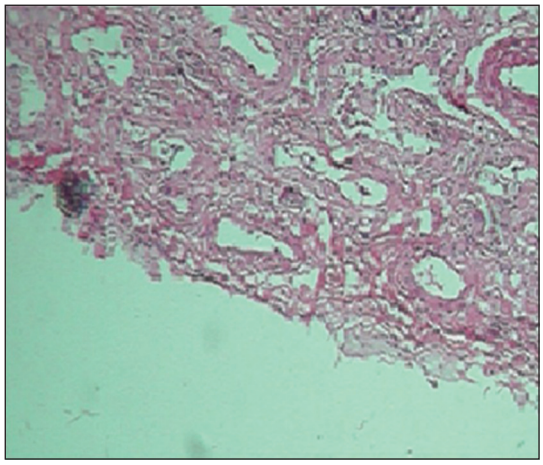

Figure 3a: Nasal mucosa treated with Iso propyl alcohol (positive control)

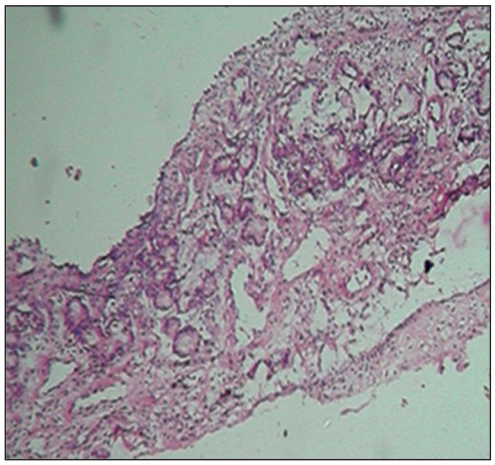

Figure 3b: Nasal mucosa treated with phophate buffer saline pH 6.4 (negative control)

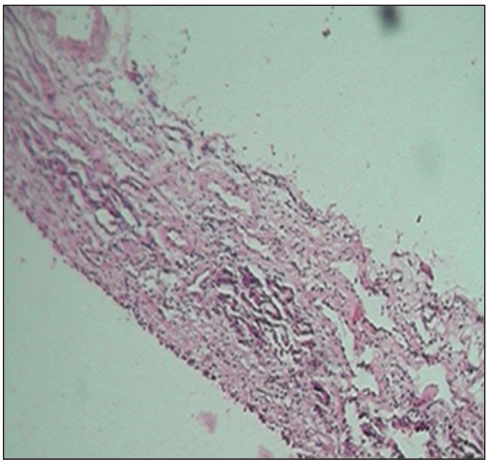

Figure 3c: Nasal mucosa treated with mirtazapine microemulsion

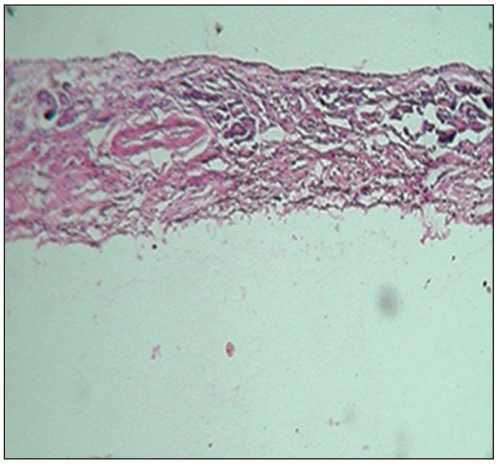

Figure 3d: Nasal mucosa treated with mirtazapine mucoadhesive microemulsion

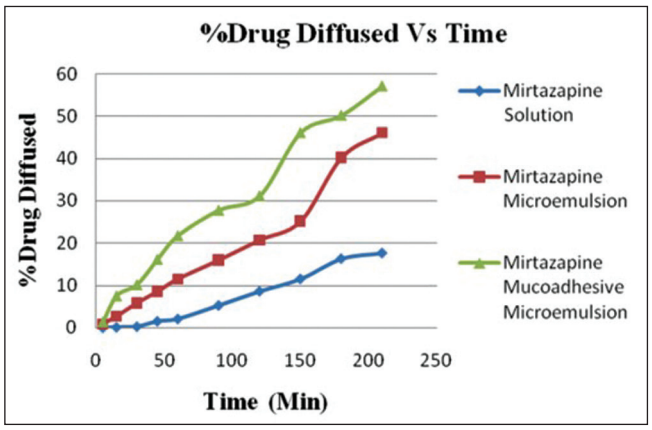

Figure 4: % drug diffused versus time

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 mirtazapine by nasal route.

Acknowledgment

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References

1. Available from: http://www.en.wikipedia.org/wiki/Anxiety. [Last accessed on 2011 Jan 02].
2. Löscher W, Potschka H. Role of drug efflux transporters in the brain for drug disposition and treatment of brain diseases. Prog Neurobiol 2005;76:22-76.
3. Misra A, Ganesh S, Shahiwala A, Shah SP. Drug delivery to the central nervous system: A review. J Pharm Pharm Sci 2003;6:252-73.
4. Vyas TK, Shahiwala A, Marathe S, Misra A. Intranasal drug delivery for brain targeting. Curr Drug Deliv 2005;2:165-75.
5. Illum L. Transport of drugs from the nasal cavity to the central nervous system. Eur J Pharm Sci 2000;11:1-18.
6. Ugwoke MI, Verbeke N, Kinget R. The biopharmaceutical aspects of nasal mucoadhesive drug delivery. J Pharm Pharmacol 2001;53:3-21.
7. Pires A, Fortuna A, Alves G, Falcão A. Intranasal drug delivery: How, why and what for? J Pharm Pharm Sci 2009;12:288-311.
8. Wermeling DP, Miller JL, Rudy AC. Systematic intranasal drug delivery: Concepts and applications. Drug Deliv Technol 2002;2.
9. Joshi HM, Bhumkar DR, Joshi K, Pokharkar V, Sastry M. Gold nanoparticles as carriers for efficient transmucosal insulin delivery. Langmuir 2006;22:300-5.
10. Mehta SK, Kaur G, Bhasin KK. Incorporation of antitubercular drug isoniazid in pharmaceutically accepted microemulsion: Effect on microstructure and physical parameters. Pharm Res 2008;25:227-36.
11. Vyas TK, Babbar AK, Sharma RK, Singh S, Misra A. Preliminary brain-targeting studies on intranasal mucoadhesive microemulsions of sumatriptan. AAPS PharmSciTech 2006;7:E8.
12. Vyas TK, Babbar AK, Sharma RK, Misra A. Intranasal mucoadhesive microemulsions of zolmitriptan: Preliminary studies on brain-targeting. J Drug Target 2005;13:317-24.
13. Sharma G, Mishra AK, Mishra P, Misra A. Intranasal cabergoline: Pharmacokinetic and pharmacodynamic studies. AAPS PharmSciTech 2009;10:1321-30.
14. Vyas TK, Babbar AK, Sharma RK, Singh S, Misra A. Intranasal mucoadhesive microemulsions of clonazepam: Preliminary studies on brain targeting. J Pharm Sci 2006;95:570-80.

15. Zhang Q, Jiang X, Jiang W, Lu W, Su L, Shi Z. Preparation of nimodipine-loaded microemulsion for intranasal delivery and evaluation on the targeting efficiency to the brain. Int J Pharm 2004;275:85-96.
16. Jogani VV, Shah PJ, Mishra P, Mishra AK, Misra AR. Intranasal mucoadhesive microemulsion of tacrine to improve brain targeting. Alzheimer Dis Assoc Disord 2008;22:116-24.
17. Li L, Nandi I, Kim KH. Development of an ethyl laurate-based microemulsion for rapid-onset intranasal delivery of diazepam. Int J Pharm 2002;237:77-85.
18. Illum L. Nasal drug delivery — Possibilities, problems and solutions. J Control Release 2003;87:187-98.
19. Available from: http://www.en.wikipedia.org/wiki/Mirtazapine. [Last accessed on 2011 Mar 02].
20. Karaşen N, Altinöz S. Determination of mirtazapine in tablets by UV spectrophotometric and derivative spectrophotometric methods. J Pharm Biomed Anal 2000;24:11-7.
21. Patel ZB, Patel KS, Shah AS, Surti NI. Preparation and optimization of microemulsion of rosuvastatin calcium. J Pharm Bioallied Sci 2012;4:S118-9.
22. Willimann H, Walde P, Luisi PL, Gazzaniga A, Stroppolo F. Lecithin organogel as matrix for transdermal transport of drugs. J Pharm Sci 1992;81:871-4.
23. Du G, Gao Y, Nie S, Pan W. The permeation of nalmefene hydrochloride across different regions of ovine nasal mucosa. Chem Pharm Bull (Tokyo) 2006;54:1722-4.
24. Pires A, Fortuna A, Alves G, Falcão A. Intranasal drug delivery: How, why and what for? J Pharm Pharm Sci 2009;12:288-311.
25. Costantino HR, Illum L, Brandt G, Johnson PH, Quay SC. Intranasal delivery: Physicochemical and therapeutic aspects. Int J Pharm 2007; 337:1-24.
26. Available from: http://www.azonano.com/article.aspx?ArticleID=1234. [Last accessed on 2011 Jan 05].
27. Kaur P, Kim K. Pharmacokinetics and brain uptake of diazepam after intravenous and intranasal administration in rats and rabbits. Int J Pharm 2008;364:27-35.

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