Intranasal mucoadhesive microemulsion of mirtazapine: Pharmacokinetic and pharmacodynamic studies

Hetal P Thakkar, Arpita A Patel, Nirav P Chauhan

Department of Pharmacy, Faculty of Technology and Engineering, The M. S. University of Baroda, Kalabhavan, Vadodara, Gujarat, India

The aim of this investigation was to prepare and characterize mirtazapine microemulsion for intranasal delivery, to determine its brain drug delivery using pharmacokinetic studies, and assess its performance pharmacodynamically for the antidepressant activity. Mirtazapine microemulsion of different compositions were prepared by water titration method and characterized for globule size and zeta potential. Microemulsion with maximum drug solubilization, lowest globule size and lowest zeta potential was considered optimal and taken for further studies with or without addition of chitosan, a mucoadhesive agent. Pharmacokinetics of optimized mirtazapine microemulsion, mucoadhesive microemulsion and mirtazapine solution were studied in brain and blood of male Wistar rats post intranasal and oral administration. Despair Swim test, locomotor activity and plus maze test were carried out in rats in order to compare therapeutic activity of the drug formulation for oral and intranasal route. Brain/blood uptake ratios were found to be highest for mirtazapine mucoadhesive microemulsion (MMME) followed by mirtazapine microemulsion (MME) post-intranasal administration compared to oral delivery of microemulsion. Significant ($P < 0.05$) reduction in assessed pharmacodynamic parameters was observed after intranasal administration of MMME against control group. This investigation demonstrates a more rapid and larger extent of transport of mirtazapine into the brain with intranasal MMME, which may prove useful in treating depression.

Key words: Antidepressant, blood-brain barrier, blood-brain ratio, brain targeting, nasal delivery

INTRODUCTION

Anxiety and depression are the growing problems in many nations of the world. Generalized anxiety disorder (or GAD) 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 400 million 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 the 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 via 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 of dose, systemic dilution...
and first pass metabolism of the drug.\textsuperscript{[2]} Nasal delivery route is convenient, patient friendly, and also prevents risk of gastrointestinal tract irritation.\textsuperscript{[3]} Direct nose to brain transport results into rapid and/or higher uptake in the brain, which provides an alternative option of self-medication in the management of emergencies.\textsuperscript{[4]}

Conventionally, drugs can be 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 have been explored as drug delivery system for intranasal delivery.\textsuperscript{[5]} However, their toxicity/irritancy on the nasal mucosa cells due to the presence of a variety of polymers/excipients is a major concern. Microemulsions are one such novel formulation which is optically isotropic and thermodynamically stable system composed of oil, water, surfactant (and/or co surfactant).\textsuperscript{[6]} Microemulsions offer several advantages like high solubilization of lipophilic drugs, stable, easy to prepare and handle stabilization of hydrolytically susceptible compounds. Microemulsions provide large area for better absorption of drugs due to smaller globule size. Various drugs such as Sumatriptan,\textsuperscript{[7]} Zolmitriptan,\textsuperscript{[8]} Cabergoline,\textsuperscript{[9]} Clonazepam,\textsuperscript{[10]} Nimodipine,\textsuperscript{[11]} Tacrine,\textsuperscript{[12]} and Diazepam\textsuperscript{[13]} have been successfully delivered via nasal route in the form of microemulsion and 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 nasal mucosa and ensuring efficient absorption of drug.\textsuperscript{[14]} 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 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. It is also used to treat anxiety by increasing central noradrenergic and serotonergic (5-HT1) neurotransmission, act primarily as a potent antagonist at postsynaptic 5-HT2 and 5-HT3 (serotonergic) and central noradrenergic receptors. Mirtazapine is rapidly absorbed following oral administration but due to high first-pass metabolism, its absolute bioavailability is only 50%.\textsuperscript{[15]}

In the light of above facts, an alternative drug delivery system is needed which can selectively target Mirtazapine to the brain. Due to preferential transport of drugs to the brain, intranasal delivery approach may be expected to reduce the wide distribution of 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 nasal cavity. The aim of this investigation was to prepare and characterize mirtazapine microemulsion for intranasal delivery, to determine its brain drug delivery using pharmacokinetic studies, and assess its performance pharmacodynamically for the antidepressant activity. The research work was carried out with objectives in mind to provide rapid drug delivery to the brain, to reduce side effects and maximize therapeutic index and to reduce dose and dosing frequency.

**MATERIALS AND METHODS**

**Materials**

Mirtazapine was gifted by Sun Pharma Advanced Research Center, Vadodara, India. Capmul MCM (Glyceryl Monocaprylate) was gifted by Abitec Corporation Limited, Janesville, USA. Tween 80 and PEG 400 were purchased from SD Fine chemicals Mumbai, India. Labrafac PG, Labrafac Lipophile, Plurol Oleique CC 497, Labrafac 1444, Transcutol P, Transcutol HP, Labrosol were gifted by Gattefosse, France. Chitosan was gifted by Indian Sea Foods Limited, Cochin, India. Other reagents were of analytical grade and purchased from SD Fine chemicals, Mumbai, India.

**Preparation and characterization**

The mirtazapine solution (MS- 7% w/w mirtazapine) was prepared by dissolving the required quantity of drug in distilled water with constant stirring. The drug-loaded microemulsions (MME- 26% w/w mirtazapine) were prepared by completely dissolving mirtazapine in a mixture of oil Capmul MCM (O- 7% w/w), surfactant Tween-80 (S- 33.75% w/w), and co-surfactant, Polyethylene Glycol 400 (CoS- 11.25% w/w). Distilled water was added gradually with continuous stirring to obtain transparent and homogenous mirtazapine microemulsion (MME) [Table 1], (transmittance at 630 nm >98%). No heating was applied during the preparation of microemulsion.

The mucoadhesive microemulsion (MMME) was prepared by adding chitosan solution (1% w/w in acetate buffer pH 5) with stirring, to the continuous phase such that the final content of chitosan in the formulations was 0.5% w/w. Mirtazapine was estimated using UV-Visible spectroscopy (Shimadzu 1601, Japan) at 292 nm against methanol as blank after confirming the noninterference of excipients in the absorbance region of Mirtazapine.

The drug-loaded microemulsions and mucoadhesive microemulsions were characterized for globule size,\textsuperscript{[20]} (Nano ZS, Malvern Instruments), zeta potential,\textsuperscript{[20]} (Nano ZS, Malvern Instruments), assay (Shimadzu 1601, Japan), pH (Systronics 335, India) and viscosity (Brookfield HADV III+).

**Pharmacodynamic activity**

All the experimental procedures were approved by the Institutional Animal Ethics Committee (IAEC) of The Maharaja Sayajirao University of Baroda and were in accordance with

**Asian Journal of Pharmaceutics - January-March 2013**

37
the Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India.

**Elevated plus maze test**
The Plus-Maze (LE842, EB Instruments, Florida) consists of two open arms, 50 × 10 × 40 cm, and two enclosed arms, 50 × 10 × 40 cm, with an open roof, arranged so that the two open arms are opposite to each other. The maze is elevated to a height of 50 cm. The mice (Swiss Albino; 20-25 g body weight) were housed in pairs for 10 days prior to testing in the apparatus. Groups consist of 3 mice for each dose. In Group-I (control) 0.1 ml of saline was administered orally. In Group II (standard), mirtazapine drug solution in distilled water and in Group III (marketed), Mirtazapine tablet suspension (Mirtaz 15 mg, Sun Pharmaceuticals Industries Ltd, Vadodara, India) in distilled water was administered orally with dose equivalent to 0.125 mg (0.1ml). Mirtazapine microemulsion (Group IV) and mirtazapine mucoadhesive microemulsion (Group V) were administered intranasally using micropipette with dose equivalent to 0.125 mg (20 µl). After 30 min, mice from each group were placed in the center of the maze one by one for 5 min, facing one of the enclosed arms. During 5 min test period, the following measures were taken: The number of entries into and time spent in the open and enclosed arms; the total number of arm entries. Comparison of number of entries in open arm and time spend in open arm of each group was done statistically.[22]

**Despair swim test**
Mice were individually forced to swim inside a vertical Plexiglas cylinder (height: 40 cm; diameter: 18 cm, containing water up to 15 cm of height maintained at 25°C). Mice placed in the cylinders for the first time were initially highly active, vigorously swimming in circles, trying to climb the wall or diving to the bottom. After 2-3 min, activity begins to subside and to be interspersed with phases of immobility or floating of increasing length. After 5-6 min immobility reaches a plateau where the mice remain immobile for approximately 80% of the time. After 15 min in the water, the mice were removed and allowed to dry in a heated enclosure (32°C) before being returned to their home cages. They were again placed in the cylinder 24 h later and the total duration of immobility was measured during a 5 min test. Immobility time of each mice in each group was recorded. Mice were divided in total 5 groups and dose was administered by the same procedure mentioned in the Plus Maze test. Each mice from each group was again placed in the cylinder and the total duration of immobility was measured during 5 min period. Immobility time and % recovery from the immobility was recorded for each mouse, in each group. Comparison of % recovery from the immobility for each group was done statistically.[21]

**Locomotor activity**
Mice with average weight of 25 g were taken and deprived of food and water for 24 h before the test. Three mice were taken per time point. Dose of the drug was administered in all 5 groups as per the method given in Elevated Plus Maze test. After 120 min, the locomotor activity was measured for 10 min by placing the animals in digital photoactometer. Number of counts for each mouse in each group was recorded and comparison of mean of each group was done statistically.[21]

**Pharmacokinetic activity**
The study was performed to check the effectiveness of intranasal delivery of mirtazapine microemulsion and mirtazapine mucoadhesive microemulsion as compared to oral delivery of mirtazapine microemulsion. For pharmacokinetic study one group was selected for Mirtazapine microemulsion given orally and two groups for intranasal route, in which one group received mirtazapine microemulsion and other group received mirtazapine mucoadhesive microemulsion. In each group, five Wistar rats of average weight 240-270 g were selected. Pharmacokinetic data was calculated by Kinetta software (Version 4.10, Innaphase, Philadelphia, PA) and comparison of pharmacokinetic parameters such as Area Under Curve (AUC), Cmax, Tmax, T1/2, Mean Residence Time (MRT) was done statistically by one way ANOVA method using software Graph Pad Prism software (Version 5, California, USA).

For the oral administration, each animal received Mirtazapine microemulsion (0.2 ml) dose equivalent to 1.275 mg by oral gavage.

The MME (50 µl) containing 1.275 mg mirtazapine (equivalent to 5 mg/kg body weight) was administered in each nostril. Formulations were instilled into the nostrils with the help of micropipette (10-100 µl) attached with low density poly ethylene (LDPE) tubing, having 0.1 mm internal diameter at the delivery site. The rats were held from the back in slanted position during nasal administration.

The rats were sacrificed humanely at different time intervals and the blood was collected using cardiac puncture. Subsequently, brain and other organs (liver, spleen, intestine, kidney and tail) were dissected, washed twice using normal saline, made free from adhering tissue/fluid, and weighed. Pharmacokinetic parameters for mirtazapine formulations were calculated.[23] Estimation of the amount of mirtazapine was done by HPLC.

**Statistical analysis**
The data was analyzed by Graph Pad Prism software (Version 5, California, USA) and the statistical comparison of results was performed using One way ANOVA followed by a Bonferroni’s Multiple Comparison test.

**RESULTS AND DISCUSSION**

**Preparation and characterization**
The mirtazapine microemulsions (MME) and Mirtazapine mucoadhesive microemulsions (MMME) were prepared...
by water titration method and the composition of the optimized formulation is shown in Table 1. The optimized batch was characterized for globule size, zeta potential, Assay, pH, viscosity and the results are recorded in Table 1. The results show that addition of chitosan had an effect on the globule size, pH, viscosity and zeta potential of microemulsions. Chitosan being a cationic polymer increased the zeta potential from -16.9 mV to 5.98 mV in mucoadhesive microemulsions which is thought to improve the stability of formulation by preventing aggregation. An increase in viscosity of the microemulsion was observed after addition of Chitosan, from 125.8 ± 0.24 cPs to 249.3 ± 0.24 cPs. Chitosan being mucoadhesive polymer, its incorporation in the microemulsion will retain the formulation on the nasal mucosa for longer period of time. Increased viscosity of MMME would result in decrease of nasal drainage after administration and increased residence time would allow the greater absorption of drug from the formulation through the nasal mucosa. The similar kind of result was obtained with Sumatriptan, Cabergoline and Clonazepam. The pH of the mucoadhesive microemulsions was observed to be shifted from 6.39 ± 0.26 to 5.92 ± 0.26, on incorporation of chitosan making it more biocompatible intranasally as normal physiological pH of human nasal mucosa is being reported to be between 4.5 and 6.5. The formulation pH is reported to have profound effect on the mucoadhesive property of polymers used. Chitosan having a pKa of 6.5 is more soluble and, hence, has better mucoadhesion at formulation pH 5.5. Globule size of the MME and MMME was found to be 14.17 ± 0.14 nm and 23.79 ± 0.62 nm, respectively. The globule size of the optimized formulation was lower enough for the permeation through nasal mucosa and moreover lower globule size increases the interfacial area for drug absorption and release.

Pharmacodynamic study
The results of elevated plus maze test, despair swim test and locomotor activity test are shown in Table 2 for oral and intranasal route. Elevated Plus Maze is well established paradigm and has a long and successful history in assessing depression like behavior in rodents. The model is based on natural aversion of rodents for open spaces (afraid possibly of falling off). Rodents tend to avoid the open areas, especially when they are brightly lit, favoring darker, and more enclosed spaces. After administering the drug, the number of entries of mice in open arm increased in all four groups with respect to control group. MME (i.n) and MMME groups (i.n) showed significant (P < 0.05) increase in number of entries [Figure 1] and time spent in open arm [Figure 2] with respect to standard and marketed formulation. Mirtazapine being an antidepressant, by decreasing the depression, increases the open arm exploration time and number of entries of the mice in elevated plus maze apparatus.

In despair swim test, it was suggested that initially mice forced to swim in a restricted space from which they cannot escape are induced to a characteristic behavior of immobility and depression. This behavior reflects a state of despair which was found to be reduced by mirtazapine, which can be observed as % recovery of immobility data. Both mirtazapine microemulsion and Mirtazapine mucoadhesive microemulsion group showed significant (P < 0.05) increase in % recovery of immobility with respect to standard and marketed formulation [Figure 3] which is an indicative of better antidepressant activity for MME and MMME through intranasal route.

The similar types of results were obtained in the locomotor activity tests [Table 2] Mirtazapine microemulsion group and Mirtazapine mucoadhesive microemulsion group showed significant (P < 0.05) increase in % recovery of immobility with respect to standard and marketed formulation [Figure 4]. Thus, MMME given intranasally was found superior in terms of brain uptake.

Pharmacokinetic study
The concentration of mirtazapine in blood, as well as brain following oral and intranasal administration for
The increased brain $T_{1/2}$ of drug when administered intranasally ($T_{1/2} = 4.40 \pm 0.01$ h) compared to oral ($T_{1/2} = 1.12 \pm 0.04$ h) demonstrates that mirtazapine concentrations in the brain will be sustained for a long time (3 to 4 h) as evident from the plateau-like curve as depicted in Figure 5, which is desirable for drug to have therapeutic effect for a prolong period of time and is not the case with intravenous administration.

Also, brain $T_{1/2}$ of mirtazapine changed with formulations in the order of microemulsion < mucoadhesive microemulsion. This may be attributed to the presence of surfactants in microemulsion system acting as permeation enhancers by reducing interfacial tension across the mucosal membrane and the prolonged dilation of tight junctions of nasal mucosa by the mucoadhesive polymer. Chitosan felicitating paracellular drug transport also.

The pharmacokinetic parameters such as $C_{max}$, $AUC_{0-240}$, $AUC_{0-\infty}$, $K_e$, $K_{e1}$ ($L/h$), and $T_{1/2}$ (h) were calculated using Kinetica software (Version 4.10, Innaphase, Philadelphia, PA) and results are recorded in Table 4 and shown in Figure 5.

At 0.5 h the brain/blood ratio for MME (Oral) was found to be 0.0 compared to the 0.517 and 0.547 for MME (Intranasal) and MMME (Intranasal) respectively. The brain/blood ratio at 1 hour for MME (Intranasal) and MMME (Intranasal) was found to be respectively 8 and 9 folds higher compared to the MME (Oral). This can be attributed to direct nose to brain transport by by-passing the blood brain barrier due to unique connection between the nose and CNS.

MME (Intranasal) and MMME (Intranasal) showed 11-folds and 14-folds higher $C_{max}$ (brain) and 18-folds and 20-folds various formulations is shown in Table 3 and Figure 5. The concentrations of mirtazapine in brain following i.n. administration of MME and MMME were found to be significantly ($p < 0.05$) higher (5.903 ± 0.02 µg/ml and 6.647 ± 0.17 µg/ml) at all sampling time points when compared to oral (0.457 ± 0.06 µg/ml) administration of MME. The brain/blood ratio of the drug at all time points for the formulations were calculated and are recorded in Table 3.

The pharmacokinetic parameters such as $C_{max}$, $AUC_{0-240}$, $AUC_{0-\infty}$, $T_{max}$, $K_e$ ($L/h$), and $T_{1/2}$ (h) were calculated using Kinetica software (Version 4.10, Innaphase, Philadelphia, PA) and results are recorded in Table 4 and shown in Figure 5.
higher AUC (Brain) compared to MME (Oral). Higher Cmax and AUC (Brain) were observed for MMME (Intranasal) compared to MME (Intranasal) demonstrating the role of mucoadhesive agent. This may be attributed to longer residence time of the mucoadhesive microemulsion in the nasal cavity. These observations are in consistence with reported findings, indicating that intranasal microemulsion enhance nose to brain transport of the drugs.[11-14]

**CONCLUSION**

Microemulsion containing Capmul MCM, Tween 80, PEG 400 showed highest solubilization for mirtazapine. The optimized formulation was characterized for globule size, zeta potential, pH, Assay, Viscosity, % Transmittance and all the physicochemical properties of the optimized microemulsion and mucoadhesive microemulsion showed the suitability of the formulation for intranasal administration.

Pharmacodynamic studies demonstrated profound increase in anti-depressant activity of mirtazapine when investigated in vivo in mice. The results of pharmacokinetic studies and increased brain $T_{1/2}$ illustrated selective nose to brain transport of mirtazapine.

Since mirtazapine is used in disorders such as depression and anxiety, the developed formulation can also find application in treatment of these diseases and may also demonstrate advantage over conventional formulation (tablet) by being more brain selective drug delivery and possibly reducing the dose and/or frequency of dosing and, hence, possibly the cost of therapy for treating the diseases. It may be noted that expected decrease in dosage regime in these diseases can help lowering of the systemic side effects of the drug. However, therapeutic benefits of intranasal mirtazapine over conventional therapies in these disorders need preclinical and clinical studies.

### Table 2: Pharmacodynamic activities of mirtazapine in mice

<table>
<thead>
<tr>
<th>Pharmacodynamic activities</th>
<th>Control (oral)</th>
<th>Standard (oral)</th>
<th>Marked formulation (oral)</th>
<th>Microemulsion (intranasal)</th>
<th>Mucoadhesive microemulsion (intranasal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of entries in open arm</td>
<td>4±1</td>
<td>7±3</td>
<td>7±1</td>
<td>11±2</td>
<td>11±2</td>
</tr>
<tr>
<td>Time spend in open arm (second)</td>
<td>65±8</td>
<td>82±4</td>
<td>75±6</td>
<td>117±20</td>
<td>142±18</td>
</tr>
<tr>
<td>% Recovery from the immobility</td>
<td>13.21±32</td>
<td>29.86±12.75</td>
<td>15.17±2.98</td>
<td>72.80±10.25</td>
<td>64.75±6.75</td>
</tr>
<tr>
<td>Number of counts in photoactometer</td>
<td>134.58±7.66</td>
<td>160.24±7.90</td>
<td>149.61±8.63</td>
<td>198.32±10.10</td>
<td>191.52±11.59</td>
</tr>
</tbody>
</table>

Values are expressed as a mean±SEM of three estimations. ** Indicates that the variation in the values between MME (IN) and MMME (IN) When compared to MME (ORAL) are significant (P<0.05)

### Table 3: Concentration (µg/ml) of MME (Oral), MME (Intranasal) and MMME (Intranasal) in Brain and blood (plasma) at predetermined time interval in Wistar rat

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Organ/Tissue</th>
<th>0.5 h</th>
<th>1 h</th>
<th>1.5 h</th>
<th>2 h</th>
<th>4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>MME (oral)</td>
<td>Blood</td>
<td>0.8823±0.04</td>
<td>1.7509±0.03</td>
<td>2.1610±0.02</td>
<td>3.4484±0.01</td>
<td>4.5826±0.02</td>
</tr>
<tr>
<td>Brain</td>
<td>0.0</td>
<td>0.179±0.05</td>
<td>0.251±0.04</td>
<td>0.350±0.03</td>
<td>0.457±0.02</td>
<td></td>
</tr>
<tr>
<td>MME (IN)</td>
<td>Blood</td>
<td>1.468±0.01</td>
<td>6.847±0.08</td>
<td>5.766±0.05</td>
<td>4.678±0.03</td>
<td>4.037±0.03</td>
</tr>
<tr>
<td>Brain</td>
<td>0.759±0.04</td>
<td>5.903±0.01</td>
<td>5.003±0.07</td>
<td>4.117±0.05</td>
<td>3.528±0.01</td>
<td></td>
</tr>
<tr>
<td>MMME (IN)</td>
<td>Blood</td>
<td>1.564±0.03</td>
<td>7.313±0.06</td>
<td>6.545±0.07</td>
<td>5.599±0.01</td>
<td>4.745±0.02</td>
</tr>
<tr>
<td>Brain</td>
<td>0.856±0.04</td>
<td>6.647±0.01</td>
<td>5.720±0.04</td>
<td>4.917±0.02</td>
<td>4.213±0.01</td>
<td></td>
</tr>
<tr>
<td>MME (oral)</td>
<td>Brain/Blood</td>
<td>0</td>
<td>0.1022±0.02</td>
<td>0.1161±0.02</td>
<td>0.10149±0.03</td>
<td>0.0997±0.04</td>
</tr>
<tr>
<td>MME (IN)</td>
<td>Brain/Blood</td>
<td>0.517±0.04*</td>
<td>0.862±0.03*</td>
<td>0.867±0.02*</td>
<td>0.880±0.03*</td>
<td>0.873±0.04*</td>
</tr>
<tr>
<td>MMME (IN)</td>
<td>Brain/Blood</td>
<td>0.547±0.02*</td>
<td>0.908±0.03*</td>
<td>0.873±0.01*</td>
<td>0.878±0.01*</td>
<td>0.887±0.01*</td>
</tr>
</tbody>
</table>

Values are expressed as a mean±SEM of three estimations. ** Indicates that the variation in the values between MME (IN) and MMME (IN) When compared to MME (ORAL) are significant (P<0.05)

### Table 4: Pharmacokinetics of MME (Oral), MME (Intranasal) and MMME (Intranasal) in brain and blood (Plasma) at predetermined time interval in Wistar rat

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Organ/ Tissue</th>
<th>Cmax (µg/ml)</th>
<th>Tmax (hour)</th>
<th>AUC 0→240 (µg/ml*hour)</th>
<th>AUC 0→∞ (µg/ml*hour)</th>
<th>MRT (hour)</th>
<th>$T_{1/2}$ (hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MME (oral)</td>
<td>Blood</td>
<td>4.5826±0.45</td>
<td>4.0</td>
<td>8.03±0.3</td>
<td>11.92±0.18</td>
<td>16.62±0.04</td>
<td>13.29±0.07</td>
</tr>
<tr>
<td>Brain</td>
<td>0.457±0.06</td>
<td>4.0</td>
<td>8.07±0.02</td>
<td>1.1095±0.001</td>
<td>2.68±0.01</td>
<td>1.12±0.04</td>
<td></td>
</tr>
<tr>
<td>MME (IN)</td>
<td>Blood</td>
<td>6.847±0.03</td>
<td>1</td>
<td>16.92±0.04</td>
<td>40.9±0.07</td>
<td>7.24±0.02</td>
<td>4.68±0.03</td>
</tr>
<tr>
<td>Brain</td>
<td>5.903±0.02</td>
<td>1</td>
<td>14.50±0.06*</td>
<td>36.05±0.01*</td>
<td>7.05±0.01*</td>
<td>4.40±0.01*</td>
<td></td>
</tr>
<tr>
<td>MMME (IN)</td>
<td>Blood</td>
<td>7.3137±0.08</td>
<td>1</td>
<td>19.45±0.01</td>
<td>53.30±0.12</td>
<td>7.97±0.02</td>
<td>5.07±0.04</td>
</tr>
<tr>
<td>Brain</td>
<td>6.647±0.17</td>
<td>1</td>
<td>16.98±0.02*</td>
<td>46.68±0.02*</td>
<td>7.98±0.015*</td>
<td>5.10±0.03*</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as a mean±SEM of three estimations. ** Indicates that the variation in the values between MME (IN) and MMME (IN) When compared to MME (ORAL) are significant (P<0.05)
REFERENCES


How to cite this article: Thakkar HP, Patel AA, Chauhan NP. Intranasal mucoadhesive microemulsion of mirtazapine: Pharmacokinetic and pharmacodynamic studies. Asian J Pharm 2013;7:36-42.

Source of Support: Nil. Conflict of Interest: None declared.