NOVEL THERAPEUTIC STRATEGIES FOR MANAGEMENT OF DYSLEXIA AND ADHD

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TITLE: NOVEL THERAPEUTIC STRATEGIES FOR MANAGEMENT OF DYSLEXIA AND ADHD

Dyslexia and Attention Deficit-Hyperactivity Disorder (ADHD) like disorder can be distressing for patients and their families. Dyslexia is the most common learning disability based on language and Affects all over the world about 3-7 % population. For disorders like Dyslexia and ADHD, medication options remain limited. Medicine is generally not used to treat dyslexia. Since it is a condition and not a disease. Occasionally, medicines are used for co-existing conditions like dyslexia and ADHD. In developed nation, 70-80% of people with poor reading skills, are likely dyslexic. Nearly the same percentage of males and females have dyslexia. Thomson (1984), of the University of Birmingham, England, pointed out that dyslexics have memory deficits, specifically a smaller storage capacity than normal readers. According to American Academy of Pediatrics, ADHD is a neurobehavioral disorder most frequently occurring in childhood. Children with ADHD present with symptoms of hyperactivity, inattention, distractibility and impulsivity. Approximately 11% of children 4-17 years of age (6.4 million) have been diagnosed with ADHD as of 2011. ADHD is the most prevalent childhood developmental disorder and is also of unclear neurobiological aetiology. The stimulant drugs may be more effective for learning disorders related to ADHD or ADD.

Modafinil, stimulant drug, is practically insoluble and therefore bioavailability has not been reported and Vinpocetine is insoluble in water having very low bioavailability. Lipid-based formulations have attracted great deal of attention to enhance solubility and thereby improve the oral bioavailability of poorly water soluble drugs. Infact, the most favored approach is to incorporate lipophilic drugs into inert lipid vehicles such as microemulsions, self-emulsifying formulations, self-microemulsifying formulations, and liposomes. Among these approaches, self-microemulsifying drug delivery system (SMEDDS) were used for lipophilic drug which is associated with poor water solubility and low bioavailability after the oral delivery. Microemulsion and mucoadhesive microemulsion are being use as a delivery system to enhance uptake of drug through nasal mucosa. Adding a mucoadhesive polymer to it helps in prolonging residence time at the site of application, providing a controlled rate of drug release for improved therapeutic outcome. Due to improved transport of drugs to the brain, intranasal delivery approach may be expected to reduce the wide distribution of drug to the non-targeted sites. SMEDDS is isotropic mixtures of an oil, surfactant, co-surfactant and drug, which emulsifies spontaneously and generates drug loaded oil droplets. Sometimes co-solvents were added to impart

better stability to the systems. The digestive motility of the stomach and intestine provides the agitation required for self-emulsification in vivo.

The aims of this study were to formulate a self-microemulsifying drug delivery system (SMEDDS) for oral delivery of BCS Class-II drug Modafinil; and Microemulsion and mucoadhesive microemulsion system are formulated with aim for nasal delivery of BCS Class-II drug Vinpocetine and were used for the treatment of Dyslexia and associated ADHD. The formulations were optimized by using D-Optimal Mixture Design and evaluating its *in-vitro* and *in-vivo* potential. Lipid-microemulsion formulations with particular emphasis on self-microemulsifying or self-emulsifying drug delivery systems (SMEDDS and SEDDS) to improve oral bioavailability of poorly water-soluble drugs. SMEDDS are isotropic mixtures of oil, surfactants, and co-surfactants that form fine microemulsions (i.e., SMEDDS) when introduced into an aqueous phase under gentle agitation.

Part-1

Analytical methods

The analytical methods used for the estimation of drug content in the developed formulation, and for the purpose of In-Vitro, Ex-Vivo and Stability studies were based on the UV Spectrophotometric and HPLC methods. Modafinil in solvent system doesn't produce any identical spectrum when scanned in the ultraviolet range between 200 and 400 nm. The scan showed absorption maxima at 225 nm, was chosen as the analytical wavelength but it was devoid of any sharp peak. Beer's law cannot be applied for a non characteristic peak. So, mathematical calculation can be used for conversion of these peaks to first order derivative for identical analytical method. Modafinil in ACN: Water (35:65) shows a characteristic spectrum when scanned in the ultraviolet range between 200 and 400 nm and converted to first order derivative spectra using UV-Probe software v.2.10. The scan shows absorption maxima at 232 nm and this wavelength was chosen as the analytical wavelength. Beer's law was obeyed between 5 and 20 µg/ml. Regression analysis was performed on the experimental data. Regression equation for standard curve and correlation coefficient signifying that a linear relationship between concentration and absorbance. Lower values of standard deviation also indicate the reproducibility of the analytical method. The method was validated for linearity, accuracy and precision. The validation parameter was found to meet the 'readily pass criteria' specify in the USP. The UV method was found to be linear in range of 5-20 µg/ml with r^2 value 0.999. Interference Study show that the mixture of excipients used

for formulation shown interference and so we cannot use UV spectroscopy method for this formulation analysis or release study. Value of Correlation coefficient 0.992 was obtained which indicates that absorbance and concentration of the drug were linearly related and Beer's law was found to be obeyed between 2.5-20 µg/ ml in HPLC. The method is highly sensitive and not interfering with excipients' analysis, it can be conclude that this analytical method can be used for the analysis of Modafinil in SMEDDS. The method was validated for linearity, accuracy and precision. Estimation of Modafinil in Plasma using RP-HPLC was also validate and r^2 found to be 0.995 in the range of 1-20 µg/ml. No interference was observed in the HPLC estimation.

Preparation and characterization of formulation

Solubility study of modafinil in various oils, surfactants, and co-surfactants was determined by addition of an excess amount of drug; initially 20 mg of drug was taken in 2 ml of each of oil, surfactant or co-surfactant in glass vial.. Followed by gentle heating at 40^0C in water bath to facilitate the solubilization using cyclomixer; vortex for 10 min. It was kept in isothermal shaker for 48 h at 37^0C to attain equilibrium. The equilibrated samples were then centrifuged at 5000 rpm for 15min. The amount of modafinil was determined in oils, surfactants or co-surfactants using HPLC. All studies were repeated thrice, with similar observations 15 min at room temperature (25^0C). Among the components screened, the clove oil and PEG-400 demonstrated highest solubility for modafinil and hence, were selected as oil and co-surfactant respectively. Tween-80 and Tween-20 both had high solubility for drug with no significant difference and hence were further evaluated for emulsification efficiency of clove oil according to procedure described under methods. Based on transmittance the tween 80 was selected as a surfactant. Higher monophasic region was found for both Smix ratio 3:1 and 2:1 but did not show much difference and hence they were further optimized using drug loading efficiency of formulation. Smix ratio was selected on basis of globule size, PDI, % transmittance and stability on dilution of drug loaded SMEDDS. With Smix ratio 3:1, incorporation of 100 mg drug was stable after 4 h but with the increase in amount upto 125 mg small amount of drug precipitated out after 4 h.

D-optimal mixture experimental design was applied to optimize the formulation variables; oil phase X1 (Clove oil), surfactant X2 (Tween-80) and co-surfactant X3 (Polyethylene glycol-400). All the batches were optimized on the basis of globule size (Y1) and % transmittance (Y2). To evaluate the thermodynamic stability, modafinil loaded SMEDDS were subjected to heating cooling cycle (40^0C and 45^0C), centrifugation test and freeze thaw cycle (-21^0C and $+25^0$C). Robustness of SMEDDS to dilution

was performed by diluting (100 times) specified quantity of formulation with various media like water, 0.1 N HCl and pH 7.4 phosphate buffers. The diluted microemulsions were stored for 24 h at RT and observed for phase separation or drug precipitation.

SMEDDS were diluted (10, 50, 100 times) with distilled water and % transmittance at 650 nm using UV spectrophotometer. SMEDDS was diluted 100 times with aqueous phase and globule size, polydispersity index (PDI), zeta Potential of the dispersion were determined using (clear disposable zeta cell) Malvern Zeta Sizer Nano ZS 90. Viscosities of the modafinil SMEDDS and diluted SMEDDS (10 and 100 times dilution in aqueous phase) were measured (Brookfield digital Viscometer, DV1) at 25^0C temperature. Spindle 64 was selected and rotated at 100 rpm for measurement. Assay, conductantce and cloud point was measure. Morphology of SMEDDS was analysed by TEM.

In vitro dissolution study using USP type II apparatus

The dissolution test was performed in USP type-II dissolution apparatus according to United State Pharmacopoeia (USP 30) dissolution procedure for SMEDDS and drug (20 mg) separately. Apparatus was loaded with 900 ml with Phosphate buffer pH 6.8 containing 0.5% sodium lauryl sulphate at 37 ± 0.5^0C with paddle speed of 50 rpm. Each sample (5 ml) was withdrawn at predetermine interval of time and replaced sample by an equal volume of dissolution medium to maintain sink condition. Amount of dissolved modafinil was determined by RP-HPLC. In vitro dissolution study revealed that drug released from SMEDDS was more than 80% in less than 10 min, which was approximately 7 times higher compared to drug. SMEDDS shows almost complete drug release within 30 min whereas only 50% drug release from drug after 4 h. This performance of drug release from SMEDDS was due to the nano size of drug globule and size is inversely proportional to the surface area which is directly proportional to the dissolution. SMEDDS had smaller globule size and this system dealt with already dissolved form of the drug which facilitates improved drug release profile as compared to drug.

In vitro drug release study by diffusion using dialysis sac

Diluted SMEDDS (1 ml; 5 mg/ml) were filled into the activated dialysis sac which was folded and tied at both the ends with a thread, care was taken to ensure that there was no leakage of the content from the prepared sac. The sac was mounted like it was floating in glass beaker containing 1000 ml of phosphate buffer pH 6.8 (0.5% SLS). Here the sac was acting as a reservoir compartment and the respective media as the receptor compartment. The content of the beaker was stirred using teflon coated

magnetic bead and the beaker was covered with paraffin film to prevent evaporative loss of solution during the experimental run. At predetermined interval of time, specified quantity of sample (5 ml) was collected from receptor compartment and replaced the same volume with diffusion media. Amount of the drug release was determined using HPLC method. Same procedure was followed while performing drug release of drug suspension. All the studies were performed in triplicate. Study demonstrated that drug released from SMEDDS was enhanced compared to suspension

Ex vivo drug permeability study by using isolated stomach and intestine (duodenum)

Sprague Dawley male rats were euthanized; the tissues of stomach and duodenum were isolated carefully and cleaned.1ml of diluted SMEDDS (5 mg/ml) were instilled in to the stomach and it was carefully tied at both the end to avoid leakage of the formulation. Further it was suspended in the organ bath with continuous aeration at 37^0C; receptor compartment (organ tube) was filled with 0.5% SLS in 0.1 N HCL. At predetermined time intervals, samples were withdrawn from the receptor compartment. Fresh buffer was used to replenish the receptor compartment. The samples were analyzed by HPLC method. The experiment was performed in triplicate. The same procedure was repeated for drug suspension (5 mg/ml). The whole experiment was also repeated for both SMEDDS and drug suspension in phosphate buffer pH 7.4 containing 0.5% SLS using duodenum, at predetermined time intervals samples were withdrawn from the receptor compartment and analyzed by HPLC method. The experiment was performed in triplicate. The observation demonstrated that release of drug was faster from the intestine in comparison to the stomach. This confirmed that better absorption of drug from the intestinal region was due to the small globule size of microemulsion formed after administration of SMEDDS, high surface area of the intestine and more number of the absorption site.

Pharmacokinetic study in animals

Sprague Dawley rats (weight approximately 350-360 g) were fasted overnight prior to experiment but water was available ad libitum. 24 rats were divided into 4 groups. Each group was administered different dosage form via oral gavage. The dose of Modafinil administered was 10.3 mg/kg using a dose volume of 0.41 ml/kg. Blood samples (0.5 ml) were collected from the retro-orbital plexus at predetermine interval into the heparinized tubes post dose under light anesthesia. The plasma was collected by centrifugation at 4000 rpm, 4^0C for 10 min. The collected plasma was stored at -20^0C until further analysis by HPLC. At all the indicated time points, the modafinil concentrations in rats plasma

treated with SMEDDS were significantly higher than those treated with suspension. The pharmacokinetic parameters for modafinil drug suspension, marketed formulation (converted to suspension) and SMEDDS were calculated. The Cmax, AUC, MRT and Relative Bio-availability (Fr) for SMEDDS were significantly higher than that of drug suspension and marketed formulation. This indicated that SMEDDS achieved higher amount of drug in a short time lapse to the systemic circulation after oral administration. The higher Cmax was achieved with higher values of AUC, MRT and Fr observed in SMEDDS which suggested improvement in the rate and extent of drug concentration in the systemic circulation.

Pharmacodynamic study: Morris water maze test

Effect of formulation on learning and memory capacities has been evaluated by morris water maze test. Morris water maze is a circular pool, 90 cm in diameter, 45 cm in height, with a plain inner surface. The pool was filled to a height of 25 cm with water. The pool was divided into 4 quadrants of equal area and was centered in one of the 4 quadrants of the pool and submerged just below the water surface (hidden 1 cm below water). The rat was placed into the maze (made opaque with white color) such that it could escape from water onto the platform and the time (in seconds) taken by the rat was measured as escape latency. The first experimental day was dedicated to swimming training for 60s in the presence of the platform. On the 2nd day, the rats were given three trial sessions with the platform in place. The time interval between 1st and 2nd trial sessions was 15 s while last trial session was performed after 30 min of 2nd trial.

For each trial sessions, rat was placed every time in the water facing the pool wall in one of the pool quadrants. The entry point was changed in a different order each day, the trial lasted until the rat found the platform, escape latency (indicative of Learning and Intact Reference Memory) was measured, it was permitted to remain on it for 15 s, after 15 s on the platform the animals were placed back in the water (in previous position) and allowed to search for platform (retained in previous position).

Escape latency (indicative of Short-term Working Memory i.e., second test)was recorded. But if the rat did not locate the platform within 60 s, it was placed on the platform for 20 s. The rat was dried by a dry towel and returned to a cage. During each trial session, the time taken to find the hidden platform (latency) was recorded. After the last training trial sessions, the platform was removed from the pool and rats were allowed to swim for 60 s to search for it. A record was kept for the number of crossing of

region of the pool where the platform had been previously placed. The animals were divided into four groups with six animals per group. Each group, except group-I, received modafinil 10.3 mg/kg orally, 15 min before conducting experiment each day and on eight day received saline. Group I received saline (0.9% sodium chloride, 10 ml/kg) for seven days and on eight day received modafinil.
Group II received modafinil suspension, group III SMEDDS, group IV modafinil marketed formulation (converted to suspension). All groups received preparation for seven days from beginning of the experiment as an oral supplementation. On 7th day, rats treated with modafinil showed significant difference ($P < 0.05$) in percentage time spent in quadrant where platformwas previously placed compared to the saline treated rats. This demonstrated that rats treated with modafinil learned the task by the seventh day of training whereas saline rat did not. On 8^{th} day despite the drug reversal, modafinil rat continued to perform much better than saline rats. This study demonstrated that saline treated animals did not result in noticeable improvement in learning and memory capacities compared with modafinil. Also, rats treated with modafinil remembered this training when tested with saline (no drug on 8th day) and rats treated with saline remained unaware of the location of the platform when tested with drug on 8th day. This study results demonstrated no significant improvement in learning and memory capacities with Modafinil formulation in comparison to saline and marketed formulation.

Stability study

The SMEDDS samples were stored in amber colored container and subjected to stability studies at 25^0C/60% relative humidity (RH) and 40^0C/75% RH. Samples were withdrawn at specified intervals of time, analyzed for drug content and for different characterization parameters. SMEDDS did not show changes in physical appearance during real time and accelerated stability conditions. SMEDDS exhibited good stability even on dilution with no signs of drug precipitation or cloudiness. Self emulsification time and % transmittance did not show drastic change. There was no significant decrease in modafinil concentration, indicates that drug remains stable in SMEDDS. Z-average size and zeta potential did not show major change during real time and accelerated stability study. Hence system was found to be capable of producing stable microemulsion on dilution with uniform globule size. No noticeably change in zeta potential indicated that it did not show change in the excipients property. These results of stability at RT revealed that SMEDDS were stable at RT. And accelerated stability study demonstrated, SMEDDS were stable for acceptable long term real time stability.

Conclusion

In the present investigation attempt was made to increase the bioavailability of Modafinil and to achieve uniform drug release by developing SMEDDS formulation. D-Optimal mixture design was applied for the optimization of SMEDDS formulation. It was found to spontaneously form microemulsion with mild agitation when exposed to aqueous fluid. SMEDDS was characterize for various parameters and found to be satisfactory, robust to dilute and thermodynamically stable formulation. The in-vitro and ex-vivo drug release suggested that there was uniform and greater drug release from Modafinil SMEDDS as compared plain drug suspension without any effect of pH of different media. TEM images were also revealed that the formulation of globules of microemulsion with uniformity of SMEDDS formulation. The Stability study confirmed the stability of SMEDDS formulations. In- vivo pharmacokinetic studies of SMEDDS formulation clearly showed that the Modafinil loaded SMEDDS exhibited improved pharmacokinetic properties compared to the Plain drug suspension and Modified marketed formulation. Finally based on the above results it can be concluded that the SMEDDS is suitable for improving the dissolution rate as well as bioavailability of poorly water soluble drug Modafinil. Thus, it can be concluded that orally administered modafinil SMEDDS increased oral bioavailability and improved learning and memory capacity in healthy rats. Therefore, SMEDDS of Modafinil can be used to improve memory in Dyslexic and ADHD patients so that it can manage the disorder. From this study, it was concluded that lipid based formulation, SMEDDS seems to be a promising drug delivery system for the BCS class -II drug.

Part-2

Aim of present work was to formulate microemulsion system for nose to brain delivery of water insoluble drug Vinpocetine and evaluating its *in vitro*, *ex vivo* and *in vivo* potential for management of ADHD and Dyslexia. Vinpocetine has low bioavailability due to its first pass metabolism and after oral administration; its absorption is limited by its low dissolution rate due to very low aqueous solubility. Hence, optimization of the concentration of permeation enhancer with oil and minimum concentration of surfactant, co-surfactant on the formulation of stable drug loaded microemulsion system for nasal administration were investigated.

Analytical Method:

The analytical methods used for the estimation of drug content in the developed formulation, and for the purpose of In-Vitro, Ex-Vivo and Stability studies were based on the UV Spectrophotometric and HPLC methods. Beer's law was obeyed between 4 to 20 µg/ml range. None of the excipients were found to be interfering in analysis of vinpocetine, therefore UV spectroscopy method was used for study. To study pharmacokinetic parameter of drug HPLC method was used. Beer's law was obeyed between 1 to 20µg/ml. The HPLC method for vinpocetine was further analysed at lower concentrations, in plasma and in brain homogenate.

Preparation and characterization of formulation

Solubility study for vinpocetine in different types of oils, surfactants, and co-surfactants was determined by adding an excess amount of drug using cyclomixer. All studies were repeated thrice. The ratio of various components was obtained by construction of phase diagram. For the optimization of the formulation D-optimal mixture design was applied using Design Expert software. Then concentration of permeation enhancer, chitosan, was optimized for the drug loaded microemulsion. Vinpocetine loaded microemulsion and mucoadhesive microemulsions were characterized for thermodynamic stability testing, robustness on dilution (effect of pH and dilution factor), dye solubility, droplet size, zeta potential, pH, viscosity, % transmittance, conductance, viscosity, cloud point, assay, TEM and histopathology analysis. Vinpocetine loaded ME and MME were checked for nasal toxicity study (Histopathology Study) and result shows both of them were safe for nasal mucosa.

In vitro drug release profile:

The *in vitro* drug release profile for Vinpocetine ME and MME were performed by diffusion sac method for 9 hrs in 10 % methanolic phosphate buffer saline PH 6.4. The *in vitro* release profile through dialysis sac shows that release of Modafinil from MME is high as compared to drug solution and ME. It may be due to presence of permeation enhancer in the MME formulation. The kinetic pattern of the diffusion was studied by fitting % drug diffused in given time in different order kinetics like zero order, first order and higuchi order. Regression coefficient of all formulations in different orders were compared and found that the release pattern of Vinpocetine from the formulations across the nasal mucosa followed by higuchi order rather than zero order and first order.

Ex vivo drug release profile:

The ex-vivo drug release profile for Vinpocetine suspension, ME and MME were performed by using isolated nasal mucosa for 4 hrs in 10 % methanolic phosphate buffer saline PH 6.4. MME formulation have additional of permeation enhancer which shows improved diffusion of drug compared to ME.

In vivo Pharmacokinetic Study:

In vivo study was performed to compare pharmacokinetic data of optimized ME and MME formulation with compared to oral suspension. Formulation of ME/MME dose was administered through nostril, while for oral suspension dose was administered through oral gavage to Male Sprague-Dawley rats. The plasma concentration vs time curve in male Sprague-Dawley rats after a single dose of ME/MME of vinpocetine through nostril was compared to vinpocetine oral suspension, at all the time points, the vinpocetine concentrations in rat plasma treated with ME/MME were significantly higher than those treated with oral suspension. The Cmax, AUC, MRT and Relative Bio-availability (Fr) for ME, MME were significantly higher than that of drug suspension. This indicated that ME and MME achieved higher amount of drug in a short time lapse to the systemic circulation after nasal administration, hence increase of bioavailability. Also, Intranasal administration of ME and MME showed highest Cmax (brain) compared to orally administered suspension formulation.

Stability Studies:

The stability studies for Vinpocetine loaded ME and MME were carried out as per ICH guidelines. Chemical and physical stability of loaded formulations were assessed under different storage condition

like room temperature (25 ± 2 °C/75 ± 5 % RH) and accelerated temperature (40 ± 2 °C/75 ± 5 % RH). The studies were carried out for different time interval. The samples were evaluated for the parameters like Visual inspection, pH, Assay, % Transmittance, Z-average globule size and Zeta Potential.

No change in physical appearance was observed during stability studies. Both the formulations remain clear at all the storage conditions with no signs of precipitation. No significant change in pH, Assay, % T, Globule size and Zeta Potential was observed for both the formulations.

Pharmacodynamic Study

Water maze test: Learning and intact reference memory and short term working memory

Escape latency period in learning and intact reference memory (test 1) and short-term working memory (test 2) remained unchanged for the first 4 days of testing period in all the group of Vinpocetine. From 5th day onwards rat learned the location of the platform in all groups of vinpocetine, and there were no significant difference among them.

Water maze test on rats: Percentage time spent in each quadrant

On 6th day of trial, time spent in each quadrant differ for Vinpocetine loaded ME and MME. Vinpocetine loaded ME and MME spent more time in quadrant where platform was previously placed, indicating nasal group, ME and MME treated rats started to learned on day 4th. They made a correct choice on day 6 for both test-1, learning and intact memory and test-2, short term memory in both oral and nasal formulation as well for saline. On 7th day, rats treated with Vinpocetine show significant difference ($P<0.05$) in time spent in quadrant where platform was previously placed compared to the saline treated rats in the nasal formulations. This demonstrated that rats treated with Vinpocetine learned the task by the seventh day of training whereas rats treated with saline did not. The result did not show change on 8th day despite of drug reversal. This study demonstrated noticeable improvement in learning and memory capacities with vinpocetine ME and MME by nasal administration. Improvement was best with the nasal vinpocetine than oral formulations.

Conclusion:

The poor aqueous solubility and first pass metabolism of Vinpocetine leads to variable low oral bioavailability. Therefore, in the present investigation attempt was made to improve the permeability of Vinpocetine and to achieve uniform drug release by developing appropriate formulation for intra nasal application. ME and MME formulations were optimized by using D-Optimal Mixture design. Both of

them were characterized for various parameters and found to be transparent, the system had narrow size distribution and uniform particle size. The zeta potential values were found to be indicating good stability of Formulation. Histopathology study indicates that both the formulations were nontoxic. The *in vitro* and *ex vivo* drug release suggested that there was uniform and improved drug diffusion in ME, MME as compared to drug suspension. TEM image also revealed that the MME formulation has uniform globules and size of droplet was similar to the result obtained from the Zeta sizer. The stability study for the 6 months at accelerated condition and 12 months at room temperature confirmed the stability of ME and MME formulations. It shows that ME and MME have achieved higher Cmax, AUC and Relative Bioavailability (Fr) compared to suspension formulation which suggests improvement in rate and extent of drug concentration in the systemic circulation. The increased in AUC of the brain demonstrate selective nose to brain transport of drugs following intranasal delivery than oral delivery system. This result was also confirmed by the Pharmacodynamic study which represent that the Vinpocetine loaded ME and MME by nasal administration gave significant improvement in learning and memory than oral suspension.

Finally, the study can be concluded, that the MME is suitable for improving the diffusion as well as bioavailability of poorly water soluble drug. Furthermore, the results of the *in vivo* kinetic study illustrate that intranasal delivery a practical strategy to deliver drugs effectively to the brain. Also, the results demonstrate ME and MME a suitable delivery system to deliver drugs specifically to the brain. Therefore, it can be concluded that ME, MME can be used to increase solubility and permeation of poorly water soluble drug Vinpocetine by nasal route. Thus, the developed intranasal ME and MME would demonstrate advantage over conventional oral vinpocetine formulations in the management of brain disorders by being more brain selective with reduction in drug dose and/or frequency of dose and possibly the cost of therapy. Thus, the study confirmed that the intranasal administration of ME and MME formulation can be used as a possible alternative to traditional oral formulations of vinpocetine to improve its bioavailability which is helpful to manage Dyslexia and ADHD.