The aim of the present work was to develop and evaluate nanostructured lipid carriers (NLC) containing duloxetine hydrochloride (DLX) for the treatment of major depressive disorders (MDD). DLX is the first line drug in the treatment of depression (MDD). It is effective in the treatment of both emotional and physical symptoms of depression. DLX possesses poor oral bioavailability owing to extensive hepatic first pass metabolism and acid labile at gastric pH (1 - 2). Depression is a mental disorder and is amongst the leading causes of disability worldwide. It is caused due to disturbances in monoaminergic (e.g., norepinephrine, serotonin) transmission in brain. DLX maintain the level of neurotransmitters including serotonin and norepinephrine (SNRI) in the synaptic cleft by inhibiting its reuptake in the pre-synaptic neuron. The delivery system was designed to be delivered through nasal route to target the brain with maximum therapeutic activity negligible discomfort (non-invasive) and side effects and better patient compliance. Therefore the work also aimed at enhancement of its bioavailability in brain, circumventing liver and gastric pH via the nasal route of drug administration.

The study can be summarized as follows:

1. Physicochemical characterization and identification of procured DLX by organoleptic properties, solubility, loss on drying, partition coefficient, UV spectroscopy, FTIR spectroscopy and differential scanning calorimetry.
2. An analytical method using UV spectrophotometry was developed and validated for determining drug entrapment efficiency, drug loading and in-vitro release.
3. HPLC method was developed and validated for the analysis of in-vitro (drug release) and in-vivo (plasma and brain homogenates) samples.
4. Glyceryl monostearate and capryol PGMC were selected as solid (fat) and liquid (oil) lipids respectively for the development of the NLC formulations for intranasal delivery.
5. The NLC formulations for nose-to-brain delivery were developed successfully to satisfactory levels in terms of particle size, particle shape, particle size distribution, zeta potential, drug entrapment, drug loading and in vitro studies (drug release and permeation studies).
6. The in vitro release of DLX from lyophilized DLX-NLC was found to be 73.38 ± 3.32 % and the release followed Higuchi release kinetics.
7. The in vitro release of DLX from DLX-NLC dispersion was found to be 76.75 ± 4.49 % and it followed first order kinetics.
8. The *in vitro* permeation studies exhibited a maximum of 74.75 ± 2.33 % and 72.92 ± 3.21 % after 24 h, of DLX was permeation from DLX-NLC dispersion and lyophilized DLX-NLC respectively.

9. The DLX-NLC formulations were evaluated *in vivo* for pharmacodynamic studies for depression by forced swimming test (FST) and locomotor activity test (LAT). The intranasal DLX-NLC significantly increased the total swimming, climbing time and locomotor activity when compared with control and significantly reduced the immobility period.

10. The results of estimation of DLX after performing the FST revealed that the brain concentration was much higher with intranasal DLX-NLC (467.312 ± 49.12 ng/g) than DLX solution formulation (123.937 ± 54.11 ng/g).

11. The *in vivo* nasal permeation studies exhibited better permeation of DLX-NLC than DLX (solution) and its permeation rate was increased may be because of surfactant action. The estimated amount of DLX was found to be higher in DLX-NLC when compared with DLX solution in brain as well as in plasma.

12. The radiolabeling efficiency of DLX and DLX-NLC was found to be 98.41±0.96 and 98.87±0.82 at 30 min, and it was found to be stable in saline and serum respectively.

13. The biodistribution studies for nasal DLX-NLC formulations were performed to compare the amount of drug reaching in various vital organs. The biodistribution of radiolabeled DLX-NLC administered via intranasal route was compared with a positive control of radiolabeled DLX given intranasally. From the biodistribution data of DLX-NLC and DLX solution administered via intranasal route it was observed that NLC formulations resulted in a higher % of radioactivity/g in the brain as compared with the DLX (p < 0.05).

14. The DLX-NLC exhibited higher distribution not only in brain but also in other organs as compared to pure DLX solution. The higher distribution of DLX-NLC than DLX solution after intranasal administration may be explained because of nanoparticulate nature of NLC, lipophilicity of NLC and enhancement in permeation/absorption by the surfactant and co-surfactant added during the preparation of NLC.

15. The intranasal administration exhibited about 8- times higher concentration of DLX in brain when compared with the intravenous administration of DLX solution. The higher concentration of DLX in brain may be explained on the basis of direct pathway of transport (neuronal and non-neuronal) from nose to brain.
16. The intranasal route revealed significantly higher concentration of DLX in the brain than intravenous administration. The superiority of this route for nose to brain delivery over the other routes may be attributed to the shortest path to reach the brain (Neuronal/extracellular pathway), circumvent BBB, bypass hepatic first pass metabolism, avoidance of degradation at gastric pH (DLX is acid labile) and avoidance of binding by plasma protein.

17. The pharmacokinetic parameters after intranasal administration of DLX-NLC were, $C_{\text{max}} = 10.75 \pm 1.73 \%$/g, $AUC_{0-24} = 111.69 \pm 7.27 \text{ h } %/g$, $AUC_{0-\infty} = 180.91 \pm 8.31 \text{ h } %/g$, $AUMC_{0-24} = 1615.32 \pm 22.42 \%.$h$^2$/ml and $K_{el} = 0.055 \pm 0.0012 \text{ h}^{-1}$ in brain homogenate. In plasma the pharmacokinetic parameters were, $C_{\text{max}} = 6.45 \pm 1.34 \%$/g, $AUC_{0-24} = 68.91 \pm 9.16 \%$/g, $AUC_{0-\infty} = 147.93 \pm 11.17 \text{ h } %/g$, $AUMC_{0-24} = 1043.64 \pm 33.51 \%.$h$^2$/ml and $K_{el} = 0.038 \pm 0.0018 \text{ h}^{-1}$. The direct transport percentage (DTP = 86.80 %) and drug targeting efficiency (DTE = 757.74 %) values were determined for the DLX-NLC formulations and compared with DLX solution. The higher DTP % and DTE % suggested that DLX-NLC formulation has a better brain targeting efficiency than DLX solution when administered intranasally.

18. Stability studies revealed results on changes in the particle size, zeta potential and drug loading of DLX-NLC formulations after time intervals of 0, 1 (30 days), 2 (60 days), and 3 (90 days) months. Storage temperature affected the NLC stability and it was found that DLX-NLCs were more stable at 4 °C than room temperature. Moreover, the lyophilized NLCs were more stable than the NLC dispersions. The shelf life of DLX-NLC formulation was found to be 2.19 years when determined using Arrhenius plot.

In conclusion, we developed DLX-NLC formulations for targeting the brain for the treatment of CNS disorders including depression. DLX-NLC formulation was developed for intranasal delivery. This provided a non-invasive route by which rapid and efficient direct nose to brain delivery of DLX can be affected to target DLX in brain for treatment of major depressive disorders (MDD). The delivery system is useful to avoid probable systemic side effects due to DLX. Consequently, the present study visibly established that intranasal DLX-NLC is a suitable method for targeting brain for the treatment of behavioural disorders. It may also be used as an effective method for the treatment of other CNS disorders.