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Introduction
Central nervous system and the brain are delicate yet complex organs and persistently, advancement in the field of Science and Technology is evolving efficient ways to protect it. Unfortunately, the same mechanisms that protect it against intrusive chemicals can also upset the therapeutic interventions. A large number of existing pharmaceutical compounds are rendered ineffective in the treatment of cerebral diseases due to inability to effectively deliver and sustain them within the brain. Therefore, innovative methods that can enhance drug delivery to the brain are of great interest. Despite of aggressive research, patients suffering from fatal and/or debilitating central nervous system (CNS) diseases, such as epilepsy, migraine, brain tumors, HIV encephalopathy, cerebrovascular diseases and neurodegenerative disorders, far outnumber those dying of all types of systemic cancer or heart disease (Misra et al., 2003). The clinical failure of much potentially effective therapeutics is often not due to a lack of drug potency but rather to shortcomings in the method by which the drug is delivered. Treating CNS diseases is particularly challenging because a variety of formidable obstacles often impede drug delivery to the brain and spinal cord. By targeting drugs at their desired site of action, toxicity can be reduced concurrently with improvisation in the treatment efficiency. In response to the insufficiency in conventional delivery mechanisms, scientists are aggressively pursuing the research on the development of new strategies for delivering the drug molecules efficiently and effectively to brain and CNS (Bodor N et al., 2003). Recent advances in the field of brain-targeting, rational drug design approach and drug delivery to CNS are helpful to encounter the complexity of the problems to some extent. However, research is ongoing across the globe for successful brain targeting of drug compounds. Despite enormous advances in the area of brain research, brain and central nervous system disorders remain the world's leading cause of disability, and account for more hospitalizations and prolonged care than almost all other diseases combined. The major problem in drug delivery to brain is the presence of the BBB. Drugs that are effective against diseases in the CNS and reach the brain via the blood compartment must pass the BBB (Begley D J., 1996; Schlossauer B et al., 2002). Despite successful examples of drug delivery to the CNS, but only some have reached the phase wherein safe and effective human applications were demonstrated. As pharmacological strategies improve, there will be less need for invasive procedures
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for treating CNS diseases. Considerable strides have been made in intravascular delivery and neurosurgical invasive procedures to deliver therapeutic substances into the brain.

Many advanced and effective approaches to CNS delivery of drugs have been emerged in recent years. Intranasal delivery products share approximately US$2 billion of the US pharmaceutical market. In the last decade almost half dozen of the filed nasal products were approved by USFDA, indicating the recent interest in this area. The systemic nasal delivery systems are increasing day by day in the market (Wermling D P et al., 2003). In addition to many currently marketed drugs that are ideal intranasal delivery candidates, biotechnology research is developing a whole range of therapeutic protein products that may greatly benefit from nasal administration. Although some growth has occurred in this delivery area in recent years, the popularity of systemic intranasal drug delivery is expected to rise considerably in the near future. Intranasal drug delivery is one of the focused delivery option for brain targeting as brain and nose compartments are connected to each other via olfactory route and via peripheral circulation. Realization of nose-to-brain transport and the therapeutic viability of the route can be traced from the ancient times and been investigated for rapid and effective transport in last two decades. Various models have been designed and studied by the scientists to establish the qualitative and quantitative transport through nasal mucosa to brain. The transport is also dependant on various formulation variables and physicochemical factors. The development of nasal drug products for brain targeting is still faced with enormous challenges. Better understanding in terms of properties of drug candidate, nose-to-brain transport mechanism and transport to and within the central nervous system is of utmost importance. The whole process of determining the development of suitable dosage form, its transport to and within CNS will lead to development of products meant for CNS targeting via intranasal route which are therapeutically effective, stable and safe (Misra et al., 2005). Intranasal route is noninvasive mode of drug administration in comparison to the other routes of administration. Intranasal drug delivery delivers the drug directly to the brain by circumventing BBB and reduces drug delivery to non targeted sites. Direct transport of drugs to the brain may lead to the administration of lower doses and in turn can reduce toxicity. Systemic dilution
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effect and first pass metabolism are also avoided (Illum Lisbeth, 2000). Direct transport could result rapid and/or higher uptake in brain, which provides an alternative option of self-medication in management of emergencies. However, the few limitations of intranasal delivery are low dose/volume especially when compounds have less aqueous solubility are difficult to formulate. High lipophilicity and preferably low molecular weight of drug are the prerequisites as it could influence the uptake across nasal mucosa (Chein et al., 1989). Drug compounds devoid of offensive/pungent odor/aroma and non-irritant nature are highly desirable to facilitate dosage form design for intranasal drug delivery systems. The other practical difficulties that have to be overcome include active degradation or alteration by enzyme, low pH of nasal epithelium, the possibility of mucosal irritation or the possibility of large variability caused by nasal pathology, such as common cold. One of the other major concerns of intranasal drug delivery is mucociliary clearance (Behl C R et al., 1998). The compounds or formulations administered may get cleared off from the nasal cavity which may lead to poor bioavailability of the drug compounds. Therefore, longer residence time as a function of longer retention of formulation in nasal cavity is desirable in order to achieve rapid and complete absorption of drug compounds (Ugwoke M I et al., 2001). Reports in the literature reveal that carbomer derivatives and chitosan are mucoadhesive compounds which can enhance absorption of drugs by increasing residence time inside the nasal cavity without altering the natural physiological processes of the nasal cavity/mucosa. These functional excipients are reported to open up the tight junctions of the interstitial spaces in the nasal mucosa cells. Weakly cross-linked polycrylates such as carbomers (FDA approved) are able to trigger the reversible opening up of the tight junctions between the nasal mucosa cells and allow paracellular transport of peptides (Luessen et al., 1996). Chitosan also have similar properties and open up the tight junctions. The possible mechanism may be by ionic charge transfer between the positive charges of the chitosan molecule and the negative charges (sulphate and sialine groups) of the glycocalix (Thanou et al., 2000). In addition to residence time of formulation inside the nasal cavity, a few formulation factors affect the rapid on set of action and complete absorption of the drug substance from a formulation when administered via intranasal route.
Microemulsion has been recently explored as an alternative drug delivery system through nasal route to demonstrate a possible alternative to IV administration and a promising approach for rapid onset delivery of CNS medications (Lianli Li et al., 2002). Since microemulsion is optically isotropic, thermodynamically stable system and imparts relatively more lipophilicity to the formulation, poorly water soluble drugs and drugs, which are more prone to hydrolysis can be successfully formulated and administered by microemulsion (Lawrence M Jayne et al., 2002). Moreover, conventional lipid emulsions for parenteral nutrition is that the particle size of the disperse lipid phase is such that the lipid is not assimilated well if administered rapidly. It has been observed that particles of the size found in the disperse phase of conventional lipid emulsions are removed from the blood stream via the reticuloendothelial cell system (RES) of the body. The RES identifies these particles as foreign and removes them by phagocytosis, a process which is limited by the ability of the RES cells to draw in and break down these large particles. Too-rapid administration of conventional lipid emulsions can overload this process and produce reduced metabolism and lipid toxicity. Smaller particles can bypass this mechanism and be taken up in some degree directly by a variety of metabolically active cells, resulting in faster assimilation and better utilization by the body. Thus, it would be desirable to provide a lipid for parenteral nutrition which has a particle size such that it is more readily and more safely assimilated by the body.

The brain and other nervous tissue, most cell membranes, and many microbial cell walls are rich in lipids, so that these drugs can be surprisingly effective, both as to potency and duration, if delivered intact to their intended sites of action. Ethyl laurate-based microemulsion system with polysorbate 80 as surfactant, propylene glycol and ethanol as co-solvents was developed by Lianli Li et al. for rapid onset intranasal delivery of diazepam. A fairly rapid nasal absorption for diazepam was observed through nasal mucosa with maximum plasma concentration reached within 2-3 minutes and about 50 % relative bioavailability compared to IV injection (Lianli et al., 2002).
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Hence, the aim of this investigation was envisaged to deliver anti-epileptic and anti-migraine therapeutic agents for the effective management of emergencies of status epileptics and migraine. It was hypothesized that microemulsion based nasal drug delivery system loaded with these drugs will selectively transport the drugs directly nose to the brain and will restrict its distribution the desired sites in the brain. It will help in rapid drug delivery to the brain, maximize therapeutic index, reduce side effects, and reduce dose/frequency of dosing and perhaps the cost of therapy.

Status epileptics, a neurological disorder, require quick management of seizures in order to avoid permanent damage to the brain. Clonazepam, a benzodiazepine derivative is used widely in the treatment of status epileptics. Clonazepam is preferred over other benzodiazepines due to its longer duration of action (24 h) (Rey et al., 1999). Clonazepam is the drug of choice in suppression of the myoclonic seizures and it acts by increasing the effectiveness of the inhibitory neurotransmitter, gamma amino butyric acid, within the central nervous system. Presently, clonazepam is available on the market in tablet and injectables dosage form (Revotril, Roche, USA, http://www.fda.gov/cder/foi/nda/index.htm). These formulations are designed to release clonazepam in peripheral circulation which limits the drug uptake across brain barriers and results in drug distribution to non-targeted sites (Misra et al., 2003). Although intravenous administration is probably the most rapid way to seizure suppression, an alternative route of drug delivery is highly needed since oral and/or intravenous routes for delivering drugs are sometimes non-supportive, delaying and/or inconvenient (Rey et al., 1999) for instance, because of delay in hospitalization of the patient/non-availability of hospital facility or non-supportive patient condition for oral ingestion of a tablet dosage form (Lianli et al., 2002). Earlier studies have demonstrated that intranasal administration offers a practical, non-invasive and an alternative route of administration for drug delivery to brain (Wermling et al., 2001; Dorman et al., 2002; Dragphia et al., 1995). Intranasal drug delivery also has the advantages that drugs can be administered simply, cost effectively and conveniently (Liu et al., 2001). Direct transport of drugs to the brain circumventing the brain-barriers following intranasal administration provides a unique feature and better option to target drugs to brain (Illum, 2003; Illum, 2000).
Migraine attack is a troublesome physiological condition associated with throbbing, intense headache in one half of the head. During an attack, the blood vessels in the brain dilate and then draw together with stimulation of nerve endings near the affected blood vessels. These changes to the blood vessels are probably what cause the pain, but migraine is still a poorly understood condition or phenomenon (Humphray P P et al., 1991). Sumatriptan and zolmitriptan, triptan derivatives are serotonin (5-hydroxytryptamine) agonist available in the market in form of oral tablets and subcutaneous injection for the treatment of migraine. These drugs are also available in rectal suppository dosage form for the treatment of migraine attacks. A substantial proportion of the migraine patients have gastric stasis and suffer severe nausea and/or vomiting. These circumstances may lead to erratic absorption of sumatriptan from the gastrointestinal tract and may result in ineffective treatment (Fuseau E et al., 2002). Moreover, the situation will lead to delaying or inconveniency in oral ingestion of the dosage form. Hence, sumatriptan delivered by the conventional routes stated above may result into ineffective treatment of migraine. References on animal studies (rat and rabbits) cited in the literature indicated that orally ingested triptan undergoes first pass metabolism which results in poor bioavailability for instance less than 40% whereas in humans it was found less than 14% (Kathleen Parfitt., 1999). In animal species, circulating sumatriptan gets cleared rapidly by metabolism and renal clearance with a half life of 1-2 h. Moreover, the passage of triptan across the blood-brain barrier is very poor although evidence of detection of some drug in cerebrospinal fluid following high intravenous doses has been cited in the literature. In light of above facts, designing of an alternative drug delivery system is imperative which can target the drug to the site of action (brain) may be useful and effective for the treatment of migraine. An alternative intranasal delivery approach may also be expected to reduce the first pass metabolism due to poor and/or restricted distribution of the drug to the non targeted sites such as systemic/peripheral circulation.

The emphasis was placed on with an objective to alter the pharmacokinetic of the therapeutic agents by targeting the drugs specifically at the site of action from nose-to-brain.
The proposed plan of research includes

I. Review of literature with respect to intranasal drug delivery, brain targeting approaches, microemulsions, mucoadhesive agents, and analytical profiles for selected therapeutic agents, numerical simulation techniques for optimization, various \textit{in vitro/in vivo} models for evaluation of intranasal drug delivery, radiolabeling and estimation, gamma scintigraphy images and electron microscopic investigation of biological fluids/tissues/organs.

II. Preparation of solutions containing selected drugs, preparation of microemulsions containing selected drugs and optimization of microemulsions with the help of pseudo ternary phase diagrams and titration technique.

III. Characterization of microemulsions loaded with selected therapeutic agents to evaluate parameters such as globule size determination, zeta potential determination, physical and chemical drug retention assessment at accelerated and under stress conditions.

IV. Incorporation of penetration enhancers, mucoadhesive agents, and combinations thereof to maximize nose-to-brain delivery.

V. \textit{In vitro} diffusion studies of drug solutions/microemulsions across nasal mucosa of sheep using Franz diffusion cell.

VI. Radiolabeling of the selected formulations and optimization for its suitability to carry out \textit{in vivo} studies.

VII. \textit{In vivo} studies in rats to ascertain nose-to-brain transport of drugs and establish the transport mechanism for the nasal mucosa using transmission electron microscopy/ Fourier transform infrared/ differential scanning calorimetry.

VIII. Derivation of Drug targeting efficiency and direct nose-to-brain transport of various formulations for the preliminary assessment of targeting efficiency.

The Gant chart (Figure 1.1) illustrates the activities to be performed and corresponding timelines against each activity.
Figure 1.1 Project management cycle illustrating activities to be performed and corresponding timelines
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