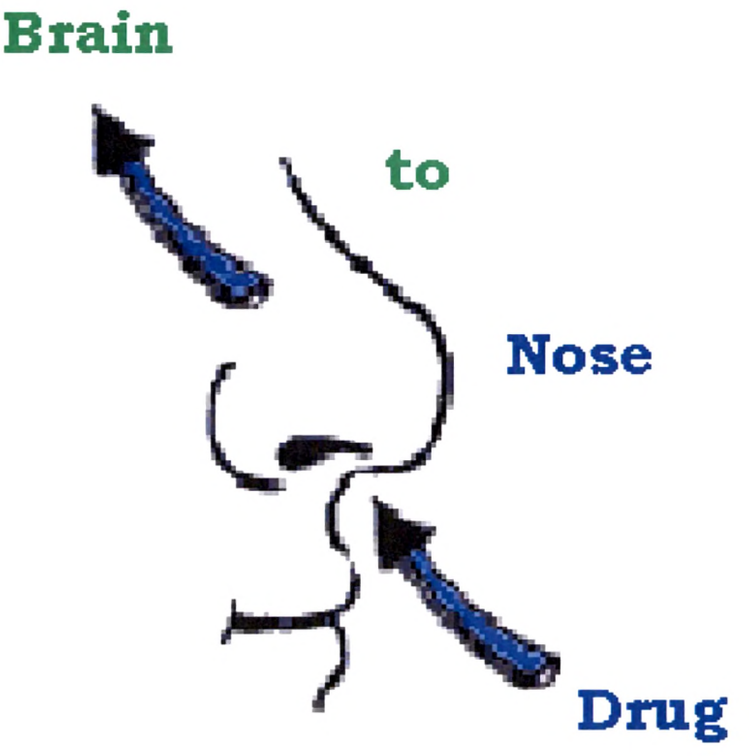

CHAPTER 1

INTRODUCTION

Despite enormous advances in brain research, brain and central nervous system (CNS) disorders remain the world's leading cause of disability, and account for more hospitalizations and prolonged care than almost all other diseases combined. Patients suffering from fatal and/or devastating CNS disorders, such as neurodegenerative disorders like Alzheimer's disease (AD), Parkinson's disease (PD) epilepsy, migraine, brain tumors, HIV encephalopathy, and cerebrovascular diseases, far outnumber of those are victimized from several types of systemic cancers and heart disease (Misra et al. 2003). Beyond loss of life, this broad category of disorders can have an overwhelming effect on the quality of life for the surviving patient and can lead to serous social and economic burdens on society. CNS disorders contribute to as much as 35% of the disease burden in the seven major pharmaceutical markets (US, Japan, France, Germany, Italy, Spain and UK) as measured in terms of daily-adjusted life years. The worldwide patient population with CNS disorders is steadily rising, both in terms of prevalence and in terms of treatment, driven by an aging population, improving diagnostic techniques, increasing physician and patient awareness and a gradual shift away from the social stigma traditionally attached to many psychiatric conditions. The CNS disorders could increase their share of the total global burden of disability and mortality from 10.5% in 1990 to 15% in 2020 (a larger proportionate increase than even cardiovascular disease) as reported by the 1990 Global Burden of Disease Study (www.who.int accessed August 12, 2002). Thus, the treatment of CNS disorders is the greatest challenge and largest potential growth sector of the pharmaceutical industries. A large number of therapeutic agents are found to be ineffective in the treatment of CNS disorders because of variety of formidable obstacles in effective drug delivery and maintenance of therapeutic concentrations in CNS for prolonged period (Vyas et al. 2005a). Frequently, the molecule is too large or has polar functional groups and the blood-brain barrier (BBB) limits its access to the CNS (Talegaonkar and Mishra 2004). The delivery of drugs to CNS is a challenge in the treatment of CNS disorders (Graff and Pollack 2005). The clinical failure of most of compounds active in CNS disorders is often not due to a lack of drug efficacy but mainly due to shortcomings in the drug delivery approach. The method of delivering a drug to the CNS has an impact on the drug's commercial potential. Thus, the market of CNS drug delivery technology is directly linked to the CNS drug market. General methods that can enhance drug delivery to the brain are, therefore, of great interest. Hence, scientists are exploring the novel approaches so that delivery of the drugs can be enhanced and/or restricted to the brain and CNS.

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 and Buchwald 2003). Many advanced and effective approaches to CNS delivery of drugs have emerged in recent years. Intranasal (i.n.) drug delivery is one of the focused delivery option for brain targeting as brain and nose compartments are connected to each other via olfactory/trigeminal 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. 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 effect and first pass metabolism are also avoided (Illum 2000). Direct transport also results into rapid and/or higher uptake in the brain, which provides an alternative option of self-medication in management of emergencies. However, the development of nasal drug products for brain targeting is facing enormous challenges. The nose-to-brain transport is also dependant on various formulation variables and physicochemical factors. Better understanding in terms of properties of drug candidate, nose-to-brain transport mechanism and transport to and within the CNS is of utmost importance. 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 i.n. drug delivery systems. Further, the low dose/volume, especially with compounds having poor aqueous solubility makes it difficult to formulate i.n. delivery of such compounds. 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. In addition to this, a few formulation factors affect the rapid on set of action and complete absorption of the drug substance from a formulation when administered via i.n. route. 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 i.n. route which are therapeutically effective, stable and safe (Vyas et al. 2005a).

Microemulsion has been recently explored as an alternative drug delivery system through nasal route to demonstrate a possible alternative to intravenous (i.v.) administration and a promising approach for rapid onset delivery of CNS medications (Lianli et al. 2002; Vyas 2005b; Vyas et al 2006a; Vyas et al 2006b). 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 and Rees 2002).

Mucociliary clearance is also one of the other major concerns of i.n. drug delivery (Behl 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 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. 1995). 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).

Alzheimer's disease is a highly disabling neuropsychiatric disorder characterized by an irreversible deterioration of memory and intellectual behavior. While the etiology of AD remains unknown, evidence has been presented that the hippocampus (an essential brain structure for memory and learning) is one of the principal areas affected by AD (Marx 1991). A specific loss of cholinergic neurons and deficits of choline acetyltransferase have been suggested to play a major role in the primary cognitive symptoms of the disease. Decreased central cholinergic activity has received major attention from investigators in search of biochemical approach that supports a pharmacotherapy for the disease. Inhibition of acetylcholinesterase is a promising approach and the most common

method under investigation for the treatment of AD (Giacobini 1993). Tacrine (1,2,3,4-tetrahydro-9-aminoacridine), a potent, centrally active, reversible cholinesterase inhibitor, was the first drug approved by the USFDA in 1993 for treating the symptoms of mild to moderate AD (Small 1992; Davis and Powchik 1995; Giacobini 1998). Presently tacrine is available in the market as oral capsule dosage forms. However, peroral administration of tacrine is associated with low bioavailability, extensive hepatic first pass effect, rapid clearance from the systemic circulation, a short elimination half life (Telting-Diaz and Lunte 1993), large inter individual differences (Hartvig et al. 1990; Lou et al. 1996), a reversible dose dependent hepatotoxicity and peripheral cholinergic side effects (O'Brien et al. 1991; Farlow et al. 1992; Sathyan et al. 1995). Its clinical uses have been limited due to associated cholinergic, hepatic, and gastrointestinal adverse reactions (Abramowicz 1993; Qizilbash et al. 2000; Yang et al. 2001). A recent study had shown that gastrointestinal side effects, such as diarrhea, anorexia, dyspepsia, and abdominal pain, and raised serum liver enzymes were the major reasons for its withdrawal (Qizilbash et al. 2000). Hence, alternative route of tacrine delivery that selectively target tacrine directly to the various regions of brain is needed for the treatment of AD.

Donepezil hydrochloride (2,3-Dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1*H*-inden-1-one hydrochloride) is a specific, reversible acetyl choline esterase inhibitor used widely for the palliative treatment of mild to moderate dementia of the Alzheimer's type. Doenpezil was approved by FDA in 1996. Presently donepezil is available in the market as oral film coated or orally disintegrating tablets in the strength of 5 and 10 mg. Donepezil HCl is well absorbed from the gastrointestinal tract, maximum plasma concentrations being achieved within 3 to 4 h. It is about 95% bound to plasma proteins, mainly albumin. It undergoes partial metabolism via the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP2D6, to 4 major metabolites. Over 10 days, about 57% of a single dose is recovered from the urine as metabolites, and about 15% from the faeces; 17% of the drug remains unchanged and is excreted in urine; 28% remains unrecovered suggesting accumulation. The elimination half-life is about 70 h. Steady-state concentrations are achieved within 3 weeks of the start of therapy. The most frequently reported side effects associated with donepezil include headache, generalized pain, fatigue, dizziness, nausea, vomiting, diarrhoea, loss of appetite, weight loss, muscle cramping, joint pain, insomnia, and increased frequency of urination.

Previous experience with the nasal delivery of neuropeptides (Gozes et al. 1996) and neurotropic factors (Frey et al. 1997; Chen et al. 1998; Capsoni et al. 2002; Thorne et al.

2004; De Rosa et al. 2005), and monosialoganglioside (Kumbale et al. 1999) to rats has shown that the nose could be a possible administration route for these potential drugs in treating AD. Therefore, the nasal route for delivering tacrine/donepezil to the brain appears to be an attractive alternative to conventional administration route for the management of AD.

RESEARCH ENVISAGED

Hence, the aim of this investigation was envisaged to deliver cholinesterase inhibitors (Tacrine/Donepezil - anti-alzheimer's therapeutic agents) via nasal route for the effective management of AD. It was hypothesized that microemulsion based nasal drug delivery system loaded with these drugs will result in to selective and effective nose-to-the brain transport and will restrict its distribution to 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.

The proposed plan of research includes

I. Review of literature with special reference to CNS disorder, drugs and market; Alzheimer's disease, its prevalence, etiology and treatment; i.n. drug delivery, brain targeting approaches, microemulsions, mucoadhesive agents, and analytical profiles for selected therapeutic agents, various *in vitro/in vivo* models for evaluation of i.n. 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 mucoadhesive agents to optimized microemulsion based drug delivery to increase residence time in nasal cavity and maximize nose-to-brain delivery.

V. *In vitro* diffusion studies of drug solutions/microemulsions/mucoadhesive microemulsions across nasal mucosa of sheep using Franz diffusion cell.

VI. Radiolabeling of the selected formulations and optimization for its suitability to carry out *in vivo* studies.

VII. *In vivo* biodistribution studies, gamma scintigraphy studies to ascertain nose-to-brain transport of drugs.

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

IX. Pharmacodynamic evaluation to evaluate efficacy of developed formulations on learning and memory capacities.

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