Chapter 1 Introduction

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 language based learning disability and affects approximate 3–7% of people. (1-3) Definition describes by the British Dyslexia Association is "a learning difficulty which predominantly affects word reading and spelling skill" and is categorized by "difficulties in memory, phonological cognizance, and speed of verbal processing ". (4) According to American Academy of Pediatrics, ADHD is a neurobehavioral disorder most frequently occurring in childhood and approximately effecting 3-5% of population. Children with ADHD show symptoms of hyperactivity, inattention, distractibility and impulsivity. (5) For disorders like Dyslexia and ADHD, medication options remain limited. However, there is much that can be done to attenuate these disorders and reduce the extent of disability. Medicine is generally not used to treat dyslexia. Since it is a condition and not a disease, the underlying problem cannot be treated medically. Occasionally, medicines are used for co-existing conditions like dyslexia and ADHD. (6) Approximate around 25% of kids with ADHD have dyslexia, and less than 40% of kids with dyslexia may have ADHD. (7) Many pathophysiological key mechanisms of dyslexia have been identified in recent years, but drug treatment targeting one or a few of these mechanisms has failed to improve clinical outcome. Till date there is no effective approved medicine/ therapy to manage dyslexia and its consequences. Drug treatment is not beneficial for dyslexia but along with dyslexia if kid has ADHD, drug treatment for ADHD can progress in learning abilities. (6) The etiology of ADHD is unclear, although ADHD can be successfully managed, can't be cured, and with ages some symptoms may improve. (8, 9) According to a majority of medical research in the United States, as well as other countries, ADHD is today considered a chronic disorder and there are no therapy, however, some treatments are available. At present to treat the disorder is by stimulant medication. (10) Methods of treatment usually involve some combination of medication and psychotherapy. For dyslexia, medicine use are to improve cognitive function are 'nootropic' drugs; for balance and coordination, anti-motion drugs and for symptoms of low self-esteem, restlessness, and distractibility, stimulant drugs are used, example is Ritalin or Cylert. Learning disorders associated to ADHD, stimulant drugs may be more effective than for dyslexia. (11) Treatment for of dyslexia by Piracetam, a nootropic drug

are commonly used but reported a legal issues. (12) Stimulants have reported side effects like nervousness and insomnia, also have contra-indicated with use of monoamine oxidase inhibitors; furthermore, continue use may ironically depress the nervous system, adversely affect growth and may cause dependence. Stimulate the effects of alcohol and amphetamines.

FDA-approved ADHD medication dosage forms are oral, except for one methylphenidate patch. (13) Although the precise mechanisms involved in this disorder are not totally understood, stimulant medications recommend by current guidelines are d- and d,l-methylphenidate, dextroamphetamine, or mixed salts of amphetamine as first-line treatments for kids act as norepinephrine and dopamine reuptake inhibitors. (3, 13, 14) Approximately 80% response rates are similar for short and/or chronic treatment. (15, 16) The common side effect of Amphetamines and Methylphenidate are delayed sleep onset, headache, decreased appetite, abdominal pain and jitteriness. (17) With reasonable symptoms of ADHD, CNS stimulants can be useful where psychological interventions have been unavailable. (18) The choice of medication should take into consideration co-morbid conditions (such as tic disorders, Tourette syndrome and epilepsy), the adverse effect profile, potential for drug misuse, tolerance and dependence; preferences of the child and care taker. Methylphenidate hydrochloride and Atomoxetine are used for the management of ADHD however, Dexamphetamine sulfate and lisdexamphetaminemesi-late are an alternative in children who do not respond to the former drugs. (19) Reported potential side effects of the stimulants include nervousness and insomnia, and are contra-indicated with epilepsy, allergies, blood pressure problems, or with use of monoamine oxidase (MAO) inhibitors. Long-term use of stimulants in children is reported to adversely affect growth, may ironically depress the nervous system or lead to loss of consciousness. By reducing natural levels of stimulants in the brain, they may also cause dependence. Newer non-amphetamine drugs show more access than amphetamine stimulant drug to treat ADHD. (20)

Modafinil (Provigil) is the most commonly prescribed of the newer psychostimulant. As of 2004, however, researchers do not know exact mechanism of action of Modafinil. Available preclinical and clinical data on the abuse liability of Modafinil suggest a much

lower potential for abuse and dependency than amphetamine like stimulants commonly used for treating ADHD. (21) In 1998,U.S. FDA approved Modafinil for the treatment of narcolepsy and also for shift work sleep disorder and obstructive sleep apnea in 2003 but use offline for the treatment of ADHD. (21, 22) In addition to its wake promoting effects and ability to increase locomotor activity in animal, Modafinil produces psychoactive effects, memory enhancement, alteration in mood, perception, thinking and feelings which is also typical of other CNS stimulants in humans. (23) Therefore, Modafinil represents a valuable therapeutic option for the treatment of ADHD and Dyslexia associated with ADHD.

Vinpocetine was made available under the trade name Cavinton in 1978 and has been used widely in Japan, Hungary, Germany, Poland, and Russia for the treatment of cerebrovascular-related pathologies. (24) Vinpocetine is not approved in the United States for pharmaceutical use, but it can be sold as a dietary supplement. Vinpocetine is widely marketed as a supplement for vasodilation and as a nootropic for the improvement of memory, cerebral metabolism and cognition enhancing effects resulting in improved abilities to retain and recall information. (25)

Problem with Modafinil and Vinpocetine is; Modafinil is practically insoluble and therefore bioavailability has not been reported and Vinpocetine is having very low bioavailability (7%). There are many types of drug delivery carriers are being developed or in developing stage with an objective to improve drug bioavailability. Lipid-based formulations have attracted great deal of attention for poorly water soluble drugs to improve its oral bioavailability. 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 etc. Among these approaches, self-microemulsifying drug delivery system, self-emulsifying drug delivery systems (SMEDDS and SEDDS) and microemulsion were used for lipophilic drug which is associated with poor water solubility and low bioavailability after the oral delivery.

SMEDDS is an isotropic mixtures of an oil, surfactant, co-surfactant (or solubilizer), with drug(s) and ability to form microemulsion after dilution by external phase. SMEDDS spread readily in the GI tract, digestive motility provide the necessary agitation and GI

fluid provides the media for self microemulsification of the system. SMEDDS are not necessarily digested before the drug is absorbed as they present the drug in micro-emulsified form which can easily penetrate the mucin and water unstirred layer. (26) The drug is in a dissolved form and added advantage is the small droplet size that provides enormous surface area for drug absorption. Specific components of SMEDDS promote the intestinal lymphatic transport of drugs which is helpful to bypass first pass metabolism. The characteristic mechanisms for enhanced absorption of microemulsion system include increasing the membrane fluidity to facilitate transcellular absorption, opening of tight junction to allow paracellular transport of drug and inhibit P-gp efflux due to presence of surfactants. (27) Ease of manufacture and scale up is one of the most important advantage that make SMEDDS unique when compared to other drug delivery systems like solid dispersion, liposomes, nanoparticles etc.

Some of the suitable drug candidate identification for SMEDDS are; drug that undergoes first pass metabolism can be delivered effectively via SMEDDS. High dose of drug is not suitable for SMEDDS. Lipophilic nature drug compounds that display dissolution-rate-limited absorption, SMEDDS can offer an enhancement in rate and degree of absorption. Drug whose peak blood level achieved at somewhat high Tmax (>4 hr). Log P value should be high. High melting point drug is poor candidate for SMEDDS.

The nasal delivery looks to be a promising way to circumvent the obstacles for blood cerebrospinal fluid (BCSF) barrier and blood brain barrier (BBB), thus permitting direct drug delivery to the BioPhase of central nervous system (CNS). It is the only site in the human body where the nervous system is in direct contact with the surrounding environment. The nasal route, therefore, offers a potential for drugs targeting to the brain and provide more opportunities for the entry of drug in the CNS. Some of the advantages of nasal route are: (28, 29) It provides easy accessibility and needle free drug application. Self-administration of the drug is possible, improving patient compliance compared to parenteral routes, It provides good penetration, especially of lipophilic and low molecular weight drugs, It provides quick absorption and fast commencement of action due to a comparatively large absorptive surface and high vascularization. Nasal administration of

suitable drugs as alternative to parenteral administration would be effective in emergency therapy. It avoid the hepatic first-pass metabolism and hence potential for dose reduction compared to oral delivery. Potential of bypassing the CSF barrier and blood-brain-barrier. Direct delivery of vaccine to lymphatic tissue and secretory immune response at distant mucosal sites. Enhancing the bioavailability of larger drug molecules by means of absorption enhancer or other approach, i.e. Chitosan.

The concept of microemulsion was introduced by Hoar and Schuleman in 1940s. Microemulsions are thermodynamically stable system and can solubilize both hydrophilic and lipophilic drugs including drugs that are relatively insoluble in both aqueous and hydrophobic solvents. It improve the effectiveness of drug, rendering the total dose to be reduced and hence lowering side effects. Moreover, are easy to prepare and requires no significant energy involvement during preparation and emulsification. Drug, in its already dissolved form is left for next step of diffusion. Recently, microemulsion and mucoadhesive microemulsion are being studied as a delivery system to enhance uptake of drug through nasal mucosa. Adding 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. (28, 29) 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 such as systemic/ peripheral circulation. The delivery system must be meticulously designed to provide preferential and rapid transport of drug across nasal mucosa and provide an alternative option of self-medication.

Research Envisaged

ADHD is a neuro-behavioral disorder that affects mental well being and social status of a person whereas dyslexia is a learning disability associated with reading and speaking. At present, there is no FDA approved treatment for dyslexia. The therapeutics selected for the study i.e. Modafinil and Vinpocetine may prove to be effective in managing dyslexia coexisting with ADHD, as they will exert their stimulant and nootropic action respectively. Drug selected for the study, Modafinil is administered orally and Vinpocetine is administered nasally. Therapeutic effect produced by; (i)

Modafinil may exert its stimulant effects by decreasing GABA-mediated neurotransmission, (30) although this theory has not yet been fully evaluated; several studies also suggest that an intact central alpha-adrenergic system is essential for Modafinil's activity and (ii) Vinpocetine increases the concentration of acid AMP, serotonin and ATP in tissues, thus favoring brain function. Along with medicine, treatment should include parent and classroom education, and/or behavioral therapy.

The objective of this study was to formulate a self-microemulsifying drug delivery system (SMEDDS) for oral delivery of BCS Class-II drug Modafinil, and formulate Microemulsion and mucoadhesive microemulsion system for nasal delivery of BCS Class-II drug Vinpocetine. This both formulations were optimized by using D-Optimal Mixture Design and evaluating its *in vitro* and *in vivo* potential. Lipid formulations with particular emphasis on microemulsion, self-microemulsifying (SMEDDS) drug delivery system can be formulated to improve oral bioavailability of poorly water soluble drugs of BCS class-II. The main objective is to improve the bioavailability of poor water soluble drug and analyze its performance by *in vivo* study.

Hence, the aim of this investigation was envisaged to deliver Modafinil via oral route (SMEDDS) and Vinpocetine via nasal route (Microemulsion) for the effective manage of disorders like dyslexia and ADHD.

Hypothesis

It was hypothesized that SMEDDS promote the intestinal lymphatic transport of drugs which is helpful to bypass first pass metabolism and enhanced absorption of drug thus lipid based formulations can enhance permeation of water insoluble and less lipophilic drug thereby increasing bioavailability. Further, Microemulsion and mucoadhesive microemulsion via intranasal delivery will selectively and effectively deliver drugs to the brain, and will avoid first pass metabolism of drug result in reduction of the dose of the drug and drug associated systemic side effects by delivering drug directly to the target organ and minimizing systemic exposure of the drug.

Proposed plan of research

1. Review of literature with reference to disorders like dyslexia and ADHD, delivery system based approaches for oral and intranasal delivery of drugs like nanoparticles, microemulsion, SMEEDS, mucoadhesive agents, nasal gel, etc., analytical profile and physicochemical properties of the selected therapeutic agents.
2. Preparation of formulations containing selected drugs, optimization and characterization of formulations with the help of factorial design approach and evaluation of stability of the formulations.
3. *In vitro* studies of optimized formulations.
4. *In vivo* Pharmacokinetic and pharmacodynamic performance studies of the drug formulation on suitable animal models.

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