4. SCOPE AND PLAN OF WORK

4.1 Scope of Work

The present treatment strategies in AD offer primarily symptomatic benefits, providing temporary cognitive improvement and deferred decline with little or no evidence of slowing disease progression. AChEIs are associated with gastrointestinal adverse effects like nausea and vomiting that most commonly lead to discontinuation of treatment in patients affected by this type of dementia. Further, there is no effective therapy targeting OS and neuroinflammation in AD. Curcumin, a plant derived polyphenol with multitude of pharmacological properties, has been found to exert beneficial effects on experimental models of AD. However, clinical therapeutic efficiency of CUR is hampered by poor aqueous solubility, low oral absorption, rapid metabolism and instability in alkaline medium. Thus, alternative route of drug administration may provide benefits to oral dosing of AChEIs or neuroprotective molecules like CUR. So far, limited attempts have been made to investigate adjunctive therapies for management of AD. A combination of AChEI with a neuroprotective therapy may be a useful approach to improve cognitive deficits as well as effectively control OS and neuroinflammation.

Nanomedicine offers a promising approach to overcome the limitations of conventional drug delivery systems. The most important property of nanocarriers in context of AD is their ability to target the drugs to brain with minimization of drug distribution to non-target sites. Nanocarriers have ability to have intimate contact and transcend the mucosal barriers. IN route is considered as an alternative to parenteral treatment in terms of achieving absolute bioavailability and to achieve direct nose-to-brain transport.

It is expected that intranasal delivery using lipid based nanocarriers will improve the brain uptake and pharmacokinetics of DZP and CUR. Apart from cholinergic replacement, an adjunctive therapy utilizing a neuroprotective molecule could be superior in terms of controlling OS and neuroinflammation thereby affording complete treatment of AD.
4.2 Plan of Work

Stage I: Preformulation studies

- Selection of drugs
- Analytical and bioanalytical method development by reverse phase high performance liquid chromatography (RP-HPLC)
- Solubility and partition coefficient studies of drugs
- Solubility and stability of drug in simulated nasal fluid (SNF)
- Compatibility study of drug and lipid by fourier transform infra-red spectroscopy (FTIR) and differential scanning calorimetry (DSC) analysis

Stage II: Formulation studies

- Construction of pseudoternary phase diagrams
- Formulation and optimization NE and MNE using DoE approach
- Study on the effect of process/formulation variables
- Formulation and optimization of NLC using DoE approach

Stage III: Evaluation of lipid nanocarriers

- Particle/globule size, zeta potential
- Drug loading and entrapment efficiency
- Drug content, refractive index, % transmittance, viscosity, conductivity and pH
- Thermodynamic stability studies
- Surface morphology by transmission electron microscopy (TEM) and scanning electron microscopy (SEM)
- Crystalline behavior of drug and lipid by DSC and powder X-ray diffraction (PXRD)
- *In vitro* release by dialysis bag method and release kinetics
- *Ex vivo* diffusion by sheep nasal mucosa and release kinetics

Stage IV: Toxicity assessment

- *In vitro* cytotoxicity assay
- *In vitro* hemolytic toxicity
- Nasal ciliotoxicity studies

Stage V: Stability studies

- Stability Studies of NE/MNE and NLC at 4°C and 25°C
Stage VI: Pharmacokinetic and brain uptake studies
- Pharmacokinetics of developed formulations in albino Wistar rats

Stage VII: Pharmacodynamic studies
- Induction of AD using ICV-STZ model
- Evaluation of effect of nanoformulations on memory functions using radial arm maze (RAM) task
- Measurement of AChE activity and OS markers in frontal cortex and hippocampus
- Histopathological analysis of frontal cortex and hippocampus