PREFACE

Parkinson's disease (PD), one of the most common neurodegenerative disorders is characterized by the loss of neurons in nigrostriatal dopaminergic pathway. Currently, PD affects millions of people around the world and is incurable to date. Hence, there is a need for novel PD targets along with suitable experimental models to investigate new therapeutic compounds. β-Glucocerebrosidase (GCase) encoding gene GBA1 mutations constitute major risk factor in early-onset PD, but only account for 5-10% PD cases. Reduced GCase enzymatic activity is found in sporadic PD also. Since PD is mostly a sporadic disorder, thus GCase is emerging as serious risk factor. However, there is no established non-genetic animal model to validate GCase enzymatic activity in PD. With the aim of developing such model, the construct and face validity of 6-hydroxydopamine (6-OHDA)-induced hemiparkinson's model was considered and the model was evaluated to mimic GCase deficiency. The thesis introduces the validation of 6-OHDA-induced hemiparkinson's model to evaluate the compounds targeting GCase activity for management of PD symptoms.

Due to therapeutic limitations and several adverse effects associated with currently used drugs, it is crucial to search for safe and effective options for treatment of PD. Ambroxol, an FDA (Food and drug administration)-approved drug is used against respiratory diseases as mucolytic therapy. It is currently in clinical trial to stimulate GCase activity in PD [ClinicalTrials.gov Identifier NCT02914366 and NCT02941822]. There is unavailability of reports indicating ambroxol-induced modulation of PD symptoms using *in vivo* PD models probably due to lack of non-

genetic models. Rebamipide, an anti-ulcer drug crosses blood brain barrier in rats and has shown neuroprotective effects *in vitro*. Additionally, it acts as anti-oxidant and reported to provide mitochondrial protection in various disease models *in vivo* and *in vitro.* Therefore, rebamipide may also act against oxidative stress, mitochondrial dysfunction and related GCase deficiency like factors involved in PD pathogenesis, and hence, may be repurposed for PD. Overall, the thesis focuses on the action of ambroxol and rebamipide against 6-OHDA-induced changes in GCase enzymatic activity and PD symptoms. The mechanism of drugs is also explained. Considering the major role of GCase in PD pathogenesis, the thesis also introduces rebamipide as a potent GCase activator.

Disease-modifying medications are unmet medical requirement in the treatment of neurodegenerative disorders. Due to unavailability of medical intervention to alter the disease-course by slowing and arresting its progression, the progressive death of dopaminergic neurons in substantia nigra pars compacts leads to two to three times increased mortality within 20 years from the onset of disease compared to general community. Therefore, the thesis aims to assess the disease-modifying potential of ambroxol and rebamipide for the first time using hemiparkinson's model *in vivo*.

Among the newer methodologies for administration of drugs is the use of transdermal approaches. Currently, several drugs are available as transdermal patch systems for neurodegenerative disorders. Transdermal drug delivery has advantages over other routes because transdermal patches deliver drugs directly into the circulatory system, bypassing the gastrointestinal system. Rebamipide shows characteristics for transdermal delivery, such as partition coefficient, molecular

weight, lipophilicity, low oral bioavailability and hydrophobicity. It may be an ideal candidate for transdermal administration to obtain the desired pharmacological effects with low doses. Therefore, the technique is used to overcome the observed disadvantages of rebamipide against 6-OHDA-induced toxicity, including the requirement of high dose and frequent administration. Transdermal patches containing low rebamipide dose were formulated and characterized for its compatibility and efficacy compared to high oral dose against 6-OHDA toxicity. The thesis establishes high potency of rebamipide-loaded transdermal patches, indicating the highly economical treatment and patient compliance.

To summarize, the thesis demonstrates the validation of 6-OHDA-induced hemiparkinson's model to evaluate the compounds targeting GCase activity for management of PD symptoms. Rebamipide proved to be a GCase activator. Ambroxol and rebamipide were found to be effective against 6-OHDA toxicity and are potential disease-modifying candidates. The study proved that transdermal delivery of rebamipide is advantageous over oral route against PD model in terms of its low dose and frequency along with high potency and economical treatment.

Keywords:

Parkinson's disease; 6-hydroxydopamine; β-glucocerebrosidase; Ambroxol; Rebamipide; Nuclear factor erythroid 2-related factor 2; Disease-modifying agents; Transdermal Patches.