CHAPTER I

INTRODUCTION

Peptide/protein therapeutics have obviously gained interests not only on scientific, but also medical establishments. With on-going technological advancement in genomic field, peptides or proteins have been recognized to play essential roles in a number of normal physiological and pathophysiological systems, thus the increasing demand of utilizing peptide therapeutics for specific treatment of human illness has been substantially propelled. The trend in peptide development pipeline demonstrates that peptides have been engineered to increase half-life, be selective to target cells, or improve blood-brain barrier (BBB) penetration (1). In 2013, approximately 90 peptide-based drugs have been approved in the global market, and nearly 597 therapeutic peptides have been in the clinical trials and preclinical studies (2). Additionally, worldwide marketing value categorizing only on peptide/protein therapeutics is predicted to reach close to $27.3 billion by 2018 (2).

Focusing on the central nervous system (CNS), several peptides show great promises for treatment variety of neurodegenerative diseases such as seizure, psychological disorders, ischemia, multiple sclerosis, Alzheimer's disease, Parkinson's disease, and pain syndrome (3-12). However, one major drawback for clinical utilization of such peptides is the invasive administration route in order to overcome BBB and get through the brain. Such typical routes are subcutaneous, intravenous, intrathecal, intracarotid, intracerebral, intracerebroventricular, and intracranial injections (7, 10, 13, 14) which are not practical if chronically used.

Another problem is the instability of peptides including physical and chemical instability during manufacturing processes, storage, or distributions. High temperature, shear stress, pH, light, oxidation, and hydrolysis cause denaturation or aggregation of peptides in both solution and solid state (15-17) resulting in changes of protein structure and biological function. However, aggregation of protein in solid state depends on moisture content, temperature, and formulation (18).

Fortunately, intranasal administration is one of the alternative routes which is less invasive and able to target drug to the brain. Avoiding first pass hepatic mechanism, rapid onset of action, and self-medication are other advantages. There are several reports by different research groups exploring the directly nose-to-brain transport of various drugs including small molecules and macromolecules such as carbamazepine (19), ribavirin (20), zolmitriptan (21), peptide T (22), nerve growth factor (NGF) (23-25), insulin-like growth factor-I (IGF-I) (12, 26), erythropoietin (EPO) (27), Interferon beta-1b (28, 29), oxytocin (30), insulin (31-34), and exendin (35, 36).

However, one of the major limitations of intranasal drug delivery is mucociliary clearance (MCC), a defense mechanism to prevent noxious stimuli adhering to nasal mucosa (37). Consequently, MCC causes low drug permeation due to short residence time of drug in nasal cavity resulting in low bioavailability (38, 39). Therefore, in order to increase residence time, mucoadhesive polymers have been suggested such as cellulose derivatives, polyacrylates, starchs, and chitosans (40). Various studies (39-43) demonstrated useful information relating to mucoadhesive nasal formulation. In addition to utilizing mucoadhesive polymer, it was found that powder formulation can beneficially promote mucoadhesive properties (44). Enabling high drug concentration at the absorption site, avoiding preservative used, providing higher drug loading per delivery dose, improving stability of products and minimizing temperature-damaged products during distribution or storage are other advantages of powder formulations (45-48). Higher nasal relative bioavailability of mucoadhesive powder would be obtained (39, 42). Moreover, powder formulations had additional benefit to limit oxidation from aqueous environment (39).

Therefore, with interesting on peptide/protein therapeutics and intranasal delivery system, especially powder dosage form, this study was aimed to formulate dry powder formulations with a novel technique and to investigate the feasibility of such powder formulations on various physicochemical properties, mucoadhesion, release study, and permeation study using two types of nasal mucosae; olfactory and respiratory mucosae, for protein delivery by using BSA as a model protein.

The ultimate goals of this present study were then;

1. To formulate dry protein powder for intranasal delivery using novel low energy technique (powder casting method) and following by different milling processes
2. To elucidate the mechanism of powder film formation by powder casting method
3. To evaluate physicochemical properties, mucoadhesive properties, protein integrity, and *in vitro* release of the powder formulations
4. To determine protein permeability of the powder formulation via olfactory and respiratory mucosae.