CHAPTER I

INTRODUCTION

Conventionally, the nasal route of delivery has been used for delivery of drugs for treatment of local diseases such as nasal allergy, nasal congestion, and nasal infection. Over the last decades, the nasal route has become increasingly important for systemic drug delivery. From 1998 to 2008, the number of nasally applied substances with systemic action on the US market increased from five to nine, the Rote Liste® 2008 counts nine products as well on the German market. New and established substances include small molecules and large peptide molecules(Wengst et al.,2010). A wide range of nasal products is in the market, mostly aimed for exploiting many advantages that include rapid absorption due to the coverage of the epithelial surface by numerous microvilli. The subepithelial layer is highly vascularized. The venous blood from the nose passes directly into the systemic circulation and therefore avoids the loss of drug by first-pass metabolism in the liver. It offers lower doses, more rapid therapeutic blood levels, quicker onset of action than oral and easier to administer than parenteral. However, the limitations of nasal delivery include: potential local tissue irritation; rapid mucocilliary clearance of therapeutic agent from the site of deposition resulting in a short span of time available for absorption; low permeability of the nasal membrane for the larger macromolecules; presence of proteolytic enzymes that may cause degradation in the nasal cavity and possible presence of pathological conditions such as colds or allergies which may alter nasal bioavailability. Strategies to overcome these limitations include: the use of nontoxic enhancers to improve the permeability of the nasal membrane to high molecular weight compound; the use of enzyme stabilizers that prevent degradation in the nasal cavity; and the use of bioadhesive polymers that increase residence time of the formulation in the nasal cavity thereby improving absorption. Since most absorption enhancers are possible irritation, damage and ciliotoxic effects on the nasal epithelial membrane, the strategy of using bioadhesive polymer is of much interest these days. Many bioadhesive polymers have been used for nasal drug delivery systems such as

carbopol, sodium carboxymethyl cellulose, hydroxypropyl cellulose, sodium hyaluronate, chitosan (Illum,1999). In this study, pectic polysaccharide from durian rinds was used for nasal drug delivery of bovine serum albumin which was a model protein. Pectic polysaccharide isolated from fruit-hulls of durian has been found to be useful in preparation of jellies and jam and as an excipient in pharmaceutical preparations (Umprayn et al.,1990). It has been found to be composed of pectin as the principal component and starch as a contaminant (Hokputsa et al.,2004). Pectin is one of the attractive biopolymer for a variety of pharmaceutical and biomedical application. It has shown promise in engineering drug carriers for oral drug delivery(Thirawong et al.,2008). Chemically, the structure of pectin has many hydrogen bond forming groups such as hydroxyl, carboxyl and amide groups. This may allow the interaction between pectin and biological mucus e.g. gastrointestinal mucus (Liu et al.,2003), thus it has mucoadhesive property to be used for nasal protein delivery.

Intranasal drugs have been delivered through dosage forms such as nasal drop, sprays, powder insufflations, topical gels, nasal pledgets, emulsions and ointments. Powder dosage forms of peptide and protein drugs can have advantages over liquid formulations. For instance, in powders the chemical stability of the drug is increased therefore a preservative in the formulation is not required. Moreover, it is possible to administer larger amounts of drug and excipients, and it was better absorbed than in solution (Schipper et al.,1993). Consequently, many reports have been published on spray drying of peptide and protein drugs (Moses et al.,1983; Schipper et al.,1993; Callens et al.,2000; Matsuyama et al.,2007; Kusonwiriyawong et al.,2009). Numerous techniques can be used to dry protein and obtain protein powders with desirable characteristics such as freeze-drying, supercritical fluid drying and spray drying. Although freeze-drying is the most widely used technique, spray drying has been in the pharmaceutical industry for almost 50 years (Snyder et al.,2008) and become a mainstream process to stabilize proteins as an attractive alternative to freeze drying. When appropriately formulated, proteins endure the spray drying process in spite of the thermal and shear stress involved (Maa et al.,1998; Kusonwiriyawong et al.,2008). Furthermore, spray-dried particles of appropriate size, shape and density for nasal delivery can be produced.

This study was thus aimed at investigating the feasibility of spray dried pectic polysaccharide microparticles of various physicochemical properties for protein delivery through nasal route. For this purpose, bovine serum albumin was used as a model protein. The permeation of protein through nasal cell line was explored. Two types of commercial pectin were also prepared and studied for comparison.

The objectives of this study were:

1. To develop mucoadhesive microparticles with pectic polysaccharide from durian fruit-hulls by spray drying technique.
2. To evaluate physicochemical and permeation properties of produced pectic polysaccharide microparticle.
3. To study the stability of protein after spray drying process.