CHAPTER I

INTRODUCTION

Nasal drug delivery is commonly associated with the topical treatment of local conditions such as allergic rhinitis and symptoms of common colds. Recently, there has been a growing interest in the nasal route for systemic delivery of drugs, particularly those having low oral bioavailabilities due to degradation in the gastrointestinal tract and/or hepatic first-pass metabolism. Enzymatic degradation is a major problem when considering the oral delivery of therapeutically active peptides and proteins (Banga and Chien, 1988). The most efficient route of administration currently available for these drugs is by injection. However, the parenteral route has several disadvantages. The pain associated with injections often results in low patient acceptability, especially when chronic therapy is required. Careful patient education and training is essential to enable self-administration and avoid possible complications. In contrast, the nasal route is easily accessible and has good patient acceptance. The nasal mucosa is one of the most permeable and highly vascularized sites for drug administration, thereby ensuring rapid absorption and onset of therapeutic action. It also bypasses hepatic first-pass metabolism and has a smaller dilution effect than the GI-mucosa (Hussain, 1998). It has been explored as an alternative route for the delivery of drugs with poor oral bioavailability as well as for biosensitive and high molecular weight (MW) compounds such as steroids, peptides, proteins, and vaccines. However, like other routes, nasal delivery also has its limitations. The permeability of drugs is not only affected by the intrinsic characteristics of the nasal membrane but also by the characteristics of the drug and dosage form being delivered.

Several nasal drug delivery systems are available on the market such as nasal drops for multiple and single-dose administration, aqueous nasal sprays, nasal gel pumps, nasal aerosols and powders. Selection of the delivery system depends upon the drug being used, proposed indication, patient population and marketing preferences. For example, aqueous nasal sprays are more preferred than the non-aqueous system for peptide drugs intended for systemic administration due to better compatibility and stability.

A large number of proteins and peptides are delivered through the nasal cavity such as oxytocin, buserelin, desmopressin, calcitonin, insulin, luteinizing hormone – releasing hormone and growth hormone. Some of these peptides have long been available in the market for clinical use. Calcitonin (CT), in particular, has long been used for the treatment of osteoporosis and other bone-related disorders. It is currently used in Europe and has been approved for clinical use in the United States by the FDA.

CT is a polypeptide hormone produced naturally by cells in the thyroid gland. It plays a part in controlling the amount of calcium in the body, by regulating the formation and breakdown of bone. The commercial form of CT nasal spray contains synthetic salmon CT, previously known as salcatonin, which has the same effects as the natural human hormone and is used to prevent bone breakdown.

Bone is not a static structure. There is a continual turnover over bone in the body; bone is formed by cells called osteoblasts, and is broken down by cells called osteoclasts. In osteoporosis, the breakdown of bone becomes faster than the formation of bone. This causes the bones to become weak and brittle and prone to fracture. CT works by inhibiting the action of the osteoclasts. This slows the increased breakdown of bone in osteoporosis, and therefore helps keep the bones strong.

CT is currently used in the treatment of postmenopausal osteoporosis, Paget's disease and malignant hypercalcemia (Avioli, 1996). Due to the chronic nature of the diseases for which CT is used, a nasally administered dosage form would increase the clinical use of CT and improve the patient compliance. Because of its polypeptide nature, CT is susceptible to degradation by enzymes in the gastrointestinal tract as well as inactivation by the first pass hepatic metabolism, leading to extremely poor oral bioavailability. Its oral bioavailability was reported to be only 0.22 % (Baluom, 1997) and the parenteral dosage form had been the only choice of administration before the introduction of nasal CT as an alternative delivery system.

Among the different forms of CT available for clinical use (human, salmon, porcine, chicken and eel CT), salmon CT is one of the most potent and commonly utilized in commercial preparations. Highly purified synthetic salmon CT injections have been available for several years. Its potency, based on the hypocalcemic effect in rats, is assigned in international units (IU), as defined by the international standard for salmon CT established by the World Health Organization (WHO) in 1974.

Salmon CT has been used in clinical trials since the early 1970s when the first injectable formulation was approved for use in various European countries. The safety of injectable salmon CT was further established by wider clinical trials, leading to the 1986 FDA approval for its use in the United States (Avioli, 1996).

As an alternative to the parenteral route, researchers have studied various mucosae in order to effectively deliver salmon CT with better patient compliance. The most common routes include nasal (Derose et al., 1974; Reginster et al., 1985; Kurose et al., 1987), rectal (Buclin et al., 1987), pulmonary (Yamamoto et al., 1997), vaginal (Rochira et al., 1996), as well as oral and implant delivery systems (Stevenson and Tan, 2000). However, the nasal route appears to be a highly attractive alternative to the invasive parenteral injection and provides direct access of the drug to the systemic circulation. Because of its higher permeability, avoidance of hepatic first-pass metabolism and ease of administration, nasal administration of synthetic salmon CT has been extensive by studied and developed into a commercial nasal spray.

Recently, in the PROOF (Prevent recurrence of osteoporosis fractures) study, 1,255 women with established osteoporosis were randomized to receive either placebo or intranasal salmon CT at doses of 100, 200, or 400 IU per day for 5 years. It was found that intranasal salmon CT at 200 IU per day significantly reduced the risk of vertebral fractures by 33% to 36% by comparison with placebo (Chesnut, 2000).

Currently, there is evidence that CT can significantly reduce bone pain in osteoporosis. The analgesic effect of CT is probably due to a direct effect of the hormone on the central nervous system (CNS). CT has been shown to provide a rapid and persistent analgesic effect, which appears to be independent of its action on bone (Gennari, 2002). However, a more precise biochemical mechanism of CT-induced analgesia needs further investigation.

Salmon CT nasal spray has been available in Thailand since 1998. According to the Siriraj Hospital Pharmacy department, the total value of purchase in 2004 was 2,800 bottles (200 IU) equivalent to 9,500,000 Baht. The limited use of salmon CT in Thailand, despite its enormous clinical benefits, is attributed to the prohibitively high cost of the product. Currently, the retail value of a 200 IU per puff nasal spray is about 3,400 Baht. And this bottle can be used for only 14 puffs. It is thus very interesting to investigate the possibility of the local manufacture of salmon CT nasal spray in Thailand. Availability of a bioequivalent product locally manufactured at a much more economical price would

definitely increase the usage of this product in Thailand and consequently help relieve many symptoms associated with hypercalcemia in many patients who require this medication.

Therefore, the purpose of this study was as follows:

1. To formulate salmon CT nasal spray preparations at a strength of 100 and 200 IU per puff

2. To evaluate the *in vitro* characteristics of the formulated nasal sprays such as percent labeled amount, uniformity of weight per spray, degradation product, pH and sterility, under two different storage conditions (30° and 4° C)

3. To assess the bioequivalence in healthy volunteers of the formulated nasal spray in comparison with the innovator product