CHAPTER I

INTRODUCTION

Prevalence of diabetes in adults worldwide was increased and estimated to be 4.0% in 1995 and to rise to 5.4% by the year 2025. It is higher in developed than in developing countries. For Thailand, the increase will be around 1.3%, from 0.9 million in 1995 to 1.9 million in 2025 (King, Aubert, and Herman, 1998).

Diabetes mellitus (DM) are divided into insulin-dependent diabetes mellitus (IDDM) and noninsulin-dependent diabetes mellitus (NIDDM), which have replaced type 1 and type 2 DM. Type 1 DM is characterized by insulin deficiency and a tendency to develop ketosis, where as type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. In general, type 2 DM patient is more than type 1 DM patient (Braunwald et al., 2002).

Sulfonylurea is one of the antidiabetic agents that acts by directly stimulating the acute release of insulin from functioning beta cells of pancreatic islet tissue and increases insulin sensitivity in target tissue. As for other second-generation sulfonylureas, the potency of glipizide is greater than that of first-generation agents. It is used as adjunctive therapy to diet and exercise in the treatment and control of certain patients with type 2 diabetes. For avoidance of hypoglycemia and hyperglycemia, the goal of treatment is to control normal fasting whole blood glucose and plasma glucose about 80 to 120 mg/dL and 90 to 130 mg/dL, respectively (USP DI, 2003).

Glipizide is rapidly and completely absorbed from the GI tract. The absolute oral bioavailability of the drug is reported to be 80-100%. After oral administration of single 5 mg-dose of glipizide in fasting and nonfasting individuals, the drug appears in plasma 15-30 minutes and average peak plasma concentration of approximately 310-450 ng/mL usually are attained within 1-3 hours. Food delays absorption of glipizide by 20-40 minutes but does not affect peak serum concentration achieved or

the extent of absorption of the drug. Therefore, glipzide should be taken 30 minutes before a meal. In healthy individuals or diabetic patients with normal renal and hepatic function, the terminal elimination half-life of glipizide averages 3-4.7 hours (range: 2-7.3 hours) and total plasma or serum clearance of glipizide reportedly averages 21-38 mL/hour per kg. Glipizide is almost completely metabolized, mainly in the liver. The drug is metabolized principally at the cyclohexyl ring to 4-trans-hydroxyglipizide and excreted mainly in urine. They are also excreted in feces, apparently completely via biliary elimination (McEvoy, 2001).

The most frequently reported side effects are gastrointestinal upset, such as abdominal pain, nausea, vomiting, vertigo, weight gain, skin reactions and symptoms of hypoglycaemia, (Brogden et al., 1979).

At present, Thai government has the ultimate scenario of a universal healthy coverage policy called "30-Bath Health Policy" so as to normalize services underling equity and comparable standard in patients without considering about the people's economic status (อัมมาร สยามวาลา, 2001).

However, the innovator's product is more expensive than the generic products. Therefore, to reduce health cost, the patients will usually receive the generic products more than innovator's product. So, if the generic products have a quality, efficiency and safety equally to the innovator's product, the physicians will have a confidence to prescribe the generic products which will be benefit to patients in term of good product with low cost.

In the early 1990s, the regulatory requirements for average bioequivalence (ABE) have been started in USA.

In 2000, the office of Food and Drug Administration of Thailand declared "Criteria and Guideline for the Bioequivalence study of Generic Drugs" to direct the procedure of bioequivalence study (Thai FDA, 2000).

During the last decade, two concept about population bioequivalence (PBE) and individual bioequivalence (IBE) have been discussed (US Food and Drug Administration, Center for Drug Evaluation and Research (CDER), 1997, 1999, 2000, 2001). In addition, replicate crossover design is not only used to find out PBE and

IBE and have many advantages more than conventional design, but also the design provides a more accurate and reliable assessment of ABE. However, the bioequivalence study of glipizide by using replicate crossover design has never been assessed.

Therefore, this study was conducted to compare average bioavailability of a generic product of 5 mg glipizide tablet relative to an innovator's product (Minidiab®) by using replicate crossover design.

Objectives: To

1. Compare the bioavailability of generic product of 5 mg glipizide tablet in Thailand to the innovator's product in Thai healthy volunteers.
2. Compare the pharmacokinetic parameters of glipizide obtained from healthy Thai volunteers to those previously published in the journals.