CHAPTER 1

INTRODUCTION

The term diabetes mellitus (DM) describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The detrimental effects of DM include long-term damage, dysfunction and failure of various organs. It is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications, increased risk of macrovascular complications (ischemic heart disease, stroke and peripheral vascular diseases), and diminished quality of life. Type 2 DM is the most common form of diabetes, characterized by disorders of insulin resistance and insulin secretion, either of which may be the predominant feature. Both are usually present at the time that the diabetes is clinically manifested (1). Recent estimates indicate there were 171 million people in the world with diabetes in the year 2000 and this is projected to increase to 366 million by 2030 (2).

Metformin HCl is an oral hypoglycemic drug approved for the treatment of type 2 DM in the U.S. since 1994. The drug has been widely used for more than three decades and is one of the two oral hypoglycemic agents in the World Health Organization (WHO) Model List of Essential Medicines in 2007 (the other being glibenclamide) (3). It is the first-line drug for diabetes, particularly in overweight and obese patients and those with normal kidney function (4, 5). In addition, it is the only antidiabetic drug that has been proven to reduce the cardiovascular complications of diabetes in a large study of overweight patients with diabetes (6). Metformin acts by decreasing hepatic glucose production, decreasing glucose absorption, and increasing glucose uptake into skeletal muscle. The use of metformin monotherapy has not been associated with hypoglycemia, however can lower fasting plasma glucose (FPG) by 60 to 70 mg/dL, lower hemoglobin A_{1c} by 1.5 to 2%, and decrease triglyceride concentrations as well as total and LDL cholesterol (6, 7). Metformin is also being

used increasingly in polycystic ovarian syndrome (8), non-alcoholic fatty liver disease (9) and premature puberty (10). Metformin is absorbed mainly from the small intestine. The drug does not bind to plasma proteins, and is rapidly excreted unchanged in the urine with a half-life ($t_{1/2}$) of about 4.0 – 8.7 h. The recommended daily dose is 2.5 g given three times a day with meals (5). The common adverse effects are gastrointestinal symptoms (11, 12, 13), which will be relieved by dosage reduction and rarely require discontinuation of treatment. Lactic acidosis can occur, but is extremely rare (occurrence of 3 cases per 100,000 patient-years) (13).

Recently, a generic preparation of metformin has been developed for clinical use with a lower cost. Although a generic and the reference preparations contain the same amount of the same active ingredient, they may differ from each other by manufacturing processes as well as content of excipient, which may affect the rate and extent of drug absorption. Therefore, the bioequivalence testing is mandated to confirm the bioavailability between the generic and the reference preparations in human subjects.

Bioequivalence is defined as the absence of significant differences in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available in the site of drug action when administered at the same molar dose under similar conditions in an appropriate designed study (14, 15). It could be done by comparing different variables of pharmacokinetic parameters including area under the concentration-time curve from time 0-t h, 0-∞ h ($AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$), maximal plasma concentration (C_{max}) and time to reach the maximal concentration (T_{max}) of the generic and original drugs by measuring and analyzing the extents of the drugs in biological fluids such as blood or plasma, in order to calculate the extent and the rate of drug absorption into the blood circulation (16). The result of this bioequivalence study will be useful for drug regulation authorities to consider whether the generic product should be approved for marketing and could be used as an effective alternative to the innovator product. It may serve to facilitate selecting and prescribing of metformin and to ensure that the patients will receive effective medical treatment with lower cost, and thus to minimize the cost of public heath care.

The rationale of the present study was to verify the bioequivalence of a generic metformin HCl 850 mg tablet to that of a reference formulation (Glucophage®). It was hypothesized that the generic metformin HCl is bioequivalent to the reference formulation.