CHAPTER II

LITERATURES REVIEW

Human diabetes mellitus is a heterogeneous disorder. The most common types encountered clinically are Type 1 (insulin-dependent) diabetes mellitus (IDDM) and Type 2 (non-insulin-dependent) diabetes mellitus (NIDDM). The former is mainly characterized by β-cell destruction, which leads to profound deficiency of insulin secretion meanwhile the later is a major metabolic abnormalities which contributes to the hyperglycaemic state causing peripheral and hepatic insulin resistance and impaired insulin secretion.

The short term aim in treating diabetic patients is to control symptoms by restoring glycaemia to near normal levels. There is no doubt, however, that the most difficult goal is to prevent the long term micro- and macrovascular complications that affect both Type 1 and Type 2 diabetic patients (Marchetti and Navalesi, 1989: 101).

A. Glipizide

1. History

During the World War II, Janbon, a clinician from Montpelier treated typhoid fever with a new sulphonamide derivative, glyprothiazole (2254 RP). He found that many patients developed hypoglycaemia. The compound was extensively studied by Loubatieres (1957), and some derivatives were used in the treatment of diabetes mellitus in the mid-1950s. It was subsequently found that the elimination of an NH_2-moiety on the benzene ring and the opening of the heterocyclic nitrogen ring enhanced the therapeutic efficacy and reduced toxicity. The sulphonylurea drugs are derived from this latter molecule (Jackson and Bressler, 1981: 214; Marchetti and Navalesi,1989: 102).

A number of sulphonylureas are currently marketed in Thailand as oral hypoglycaemic agents. These include the older drugs such as chlorpropamide as well as 'second generation' agents namely glipizide, gliclazide, and glibenclamide (glyburide).

2. Chemistry and Stability

2.1 Chemistry

Glipizide is a sulfonylurea antidiabetic agent (Figure 1). Glipizide occurs as a whitish powder and is practically insoluble in water and in alcohol. The drug has a pK_a of 5.9 (Lunn, and Schmuff, 1997; Budavari, ed., 2001 and McEvoy, 2001).

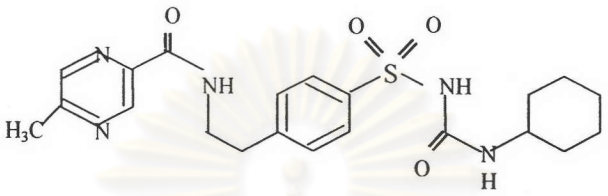

Figure 1 Chemical Structure of Glipizide

Chemical name	:	*N*-[2-[4-[[[(Cyclohexylamino)carbonyl]amino]sulfonyl] phenyl]ethyl]5-methylpyrazinecarboxamide
Synonym	:	glydiazinamide
Other name	:	1-cyclohexyl-3-[[*p*-[2-(5-methylpyrazinecarboxamido) ethyl]phenyl]sulfonyl]urea
CAS Registry No.	:	29094-61-9
Empirical formula	:	$C_{21}H_{27}N_5O_4S$
Molecular weight	:	445.54

2.2 Stability

Glipizide tablets should be stored in tight, light-resistant containers at a temperature less than 30^0C.

3. Pharmacology

3.1 Antidiabetic Effect

Sulfonylureas lower blood glucose in patients with type 2 diabetes by directly stimulating the acute release of insulin from functioning beta cells of pancreatic islet tissue by an unknown process that involves a sulfonylurea receptor on

the beta cell. Sulfonylureas inhibit the ATP-potassium channels on the beta cell membrane and potassium efflux, which results in depolarization and calcium influx, calcium-calmodulin binding, kinase activation, and release of insulin-containing granules by exocytosis, and effect similar to that of glucose.

With chronic sulfonylurea treatment, insulin production is not increased and may return to pretreatment values, but insulin efficacy continues and is thought to involve extrapancreatic mechanisms to increase insulin sensitivity in target tissues, such as liver, muscle, and fat as well as in other cells, such as monocytes and erythrocytes. This can result in a decrease in hepatic glycogenolysis and gluconeogenesis (Jackson et al., 1981; Marchetti et al., 1989; USP DI, 2003)

On a weight basis, glipizide is one of the most potent of the sulfonylurea antidiabetic agents; although an exact dosage relationship does not exist, a daily glipizide dose of 5 mg controls blood glucose concentration to approximately the same degree as daily doses of acetohexamide 500 mg, chropropamide or tolazamide 250 mg, glyburide 2.5-5 mg, or tolbutamide 0.1-1 g (McEvoy, 2001).

3.2 Other Effects

Glipizide produces a mild diuresis effect by enhancement of renal free water clearance. Like other sulfonylureas, glipizide directly increases the secretion of pancreatic and gastric somatostatin and does not seem to have a direct effect on glucagons (USP DI, 2003).

4. Pharmacokinetics

4.1 Absorption

Glipizide is rapidly and completely absorbed from the GI tract. First-pass metabolism of glipizide appears to be minimal, and the absolute oral bioavailability of the drug is reported to be 80-100%.

4.1.1 Time to Peak Plasma Concentration (t_{max}) and Peak Plasma Concentration (C_{max})

Following 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. The hypoglycemic action of glipizide generally begins within 15-30 minutes and is maximal within 1-2 hours (McEvoy, 2001). However, many studies revealed that C_{max} was approximately 450-500 ng/mL (ranged 260-1117 ng/mL) (Balant, 1981; Zmeili et al., 1995; Kobylinska et al., 2000) with t_{max} of 1 to 3 hours after administration of the same dose of glipizide tablet (Brogden et al., 1979; Balant, 1981; Marchetti et al., 1989; Zmeili et al., 1995; Kobylinska, 2000).

4.1.2 Area Under the Concentration-time Curve (AUC)

In bioequivalence studies of glipizide, Zmeili et al. (1995) reported that the AUC_{0-12} was 2169.9-2278.8 ng.hr/mL (ranged 1261.3-4663.8 ng.hr/mL) whereas Kobylinska et al. (2000) found that the AUC_{0-24} was 1828.35-1934.86 ng.hr/mL and the $AUC_{0-\infty}$ was 2011.48-2126.13 ng.hr/mL

The area under the plasma concentration-time curve (AUC) for glipizide increases in proportion to increasing doses (McEvoy, 2001).

4.1.3 Delayed Absorption of Sulfonylurea

Food delays absorption of glipizide by 20-40 minutes but does not affect peak plasma concentration achieved or the extent of absorption of the drug. Therefore, glipzide should be taken 30 minutes before a meal (McEvoy, 2001). Neither is any information available on the important topic of interindividual variation in absorption. It appears that most of the effect of food can be attributed to delayed gastric emptying, as glipizide preparations dissolve poorly in acid, but rapidly in simulated intestinal fluid (Jackson and Bressler, 1989, cited in Wahlin-Boll et al., 1980)

By impairing gastric motility and gastric emptying, hyperglycemia may significantly delay sulfonylurea absorption. Glipizide plasma concentration has been shown to be reduced by 50% with plasma glucose concentrations over 198 mg/dL (11 mmole/L) (USP DI, 2003).

4.1.4 Double Peaks in Oral Concentration-time Profiles

A few reports indicate that biphasic peak plasma concentrations may occur in some patients, suggesting that the drug may undergo enterohepatic circulation (McEvoy, 2001). The double peak is not expected to affect the accuracy of the measurements for the reason that comparison between the formulations is based on the overall C_{max}, t_{max} and AUC (Zmeili, 1995: 44, cited in Suttle et al., 1992).

4.2 Distribution

Distribution of glipizide into human body tissues and fluids has not been fully characterized.

Following IV administration of glipizide in mice, highest concentrations of the drug were attained in the liver and blood, with lower concentrations in the lungs, kidneys, adrenals, myocardium, salivary glands, and retroscapular fat. The drug was not detected in the brain or spinal cord.

In humans, small and very small amounts of glipizide are distributed into bile and into erythrocytes and saliva, respectively. Following IV administration of the drug, the volumes of distribution in the central compartment and at steady-state average 4.2-4.6 L (ranged 3.5-13.2 L) and 10.2-11.7 L (ranged 4.6-15.1 L), respectively, suggesting that the drug is distributed principally within extracellular fluid. According to USPDI, the volume of distribution (V_d) is 0.14-0.16 L/kg. The apparent volume of distribution of glipizide in man has been reported to be 11.5 to 25 L (Brogden et al., 1979).

At a concentration of 9-612 ng/mL, glipizide is approximate 92-99% bound to plasma proteins. Unlike the protein binding of some other sulfonylurea antidiabetic agents and like that of glyburide with higher affinity for binding to serum albumin than does glipizide. The protein binding of glipizide appears to be principally nonionic (McEvoy, 2001).

4.3 Elimination

After oral administration in healthy individuals or diabetic patients with normal renal and hepatic function, the terminal elimination half-life of glipizide

averages 3-4.7 hours (ranged 2-7.3 hours) (McEvoy, 2001) and increases to 2 to 5 after long term treatment (Marchetti et al., 1989; Wahlin-Boll et al., 1986)

The elimination rate constant of glipizide in plasma was 0.2-0.25 hr^{-1} (Zmeili et al., 1995; Kobyliska et al., 2000). Total plasma or serum clearance of glipizide reportedly averages 21-38 mL/hour per kg. Plasma clearance has been shown to be 2.4 to 3.0 L/h (McEvoy, 2001; Brogden et al., 1979).

Glipizide is almost completely metabolized, mainly in the liver. The drug is metabolized principally at the cyclohexyl ring to 4-trans-hydroxyglipizide. The drug is metabolized to non-active metabolites such as the 3-cis-hydroxy derivative, N-(2-acetylaminoethylphenylsulfonyl)-N'-cyclohexyl urea (DCDA), and at least 2 unidentified metabolites.

Glipizide and its metabolites are excreted principally in urine occurring within the first 6-24 hours after oral administration. They are also excreted in feces, apparently almost completely via biliary elimination. Only small amounts may be excreted in feces as unabsorbed drug. Approximately 60-90% of the 5-mg dose of glipizide is excreted in urine as unchanged drug and metabolites within 24-72 hours and about 5-20% is excreted in feces within 24-96 hours. In urine excretion within 24 hours, less than 10% of a dose is excreted as unchanged drug, about 20-60% as the 4-trans-hydroxy metabolite, 10-15% as the 3-cis-hydroxy metabolite, 1-2% as DCDA, and the remainder as unidentified metabolites.

Plasma glipizide concentration may be increased in patients with renal or hepatic insufficiency. However, the terminal elimination half-life of unchanged glipizide does not appear to be substantially increased in patients with impaired renal function (McEvoy, 2001).

5. Uses

Patients most likely to respond to sulfonylurea therapy are those with type 2 diabetes mellitus who have an onset of disease after 40 years of age, a duration of the disease less than 5-10 years before initiation of therapy, a body weight within 110-160% of ideal, a fasting plasma glucose concentration of less than 180 mg/dL, and no history of ketoacidosis and who require less than 40-50 units of insulin daily. Type 2

diabetic patients who are very obese or who have fasting blood glucose concentrations greater than 200 mg/dL may be less likely to respond to oral antidiabetic agents.

Combined therapy with insulin and oral antidiabetic agents may be useful in some patients with type 2 diabetes mellitus whose blood glucose concentrations are not adequately controlled with maximal dosages of the oral agent and for as a means of providing increased flexibility with respect to timing of meals and amount of food ingested (McEvoy, 2001).

6. Plasma Concentration and Clinical Effects

There is no simple relationship between plasma concentrations of sulphonylureas and hypoglycaemic effect. The correlations usually being found only when samples were drawn within a few hours after administration of the drug. In addition, despite even double plasma drug concentrations, no difference in plasma glucose level could be found (Brogden et al., 1981, cited in Wahlin-Boll et al., 1986). This supports the notion that an increase in sulphonylurea dose cannot compensate for increased energy intake (Balant, 1981; Marchetti et al., 1989; Haaber et al., 1993).

7. Dosage and Administration

Initial oral administration, 5-mg glipizide tablet is usually administered once a day thirty minutes before breakfast to achieve the maximum reduction in postprandial blood glucose concentration, with dosage being changed by 2.5 to 5 mg every several days as needed.

For maintenance oral dose, the drug up to 40 mg a day is administered thirty minutes before meals. Single daily doses are adequate with 15 mg or less but may be divided when necessary, while larger doses should be divided into two doses a day and taken thirty minutes before meals (USP DI, 2003).

8. Precautions to Consider

If patients are sensitive to one of the sulfonylureas or cross-sensitivity to other sulfonamide- or thiazide-type medications, they may be sensitive to the other sulfonylureas also (USPDI, 2003).

9. Adverse Effects

9.1 Hypoglycemia

Hypoglycemia, defined as blood glucose of less than 60 mg/dL or symptoms associated with hypoglycemia, may occur as a result of excessive glipizide dosage. However, since the development of hypoglycemia is a function of many factors, including diet, or exercise without adequate caloric supplementation, this effect may occur in some patients receiving usual dosages of the drug (McEvoy, 2001). In addition, drugs with longer half-lives, such as first-generation sulfonylurea agents, are higher risk of hypoglycemia (Harmel and Mathur, 2004).

The symptoms of hypoglycemia are often divided into two categories (Table 1). The first category results from the brain getting a reduction in fuel source (the brain needs glucose as its fuel). These are known as neuroglycopenic symptoms. The second category results from the body's response to the physiologic stress of having low levels of circulating blood glucose. This is known as the neurogenic response, and occurs before the neuroglycopenic symptoms in most case.

The neurogenic symptoms include shakiness, palpitations, anxiety and nervousness, sweating, and hunger, whereas the neuroglycopenic symptoms include confusion, drowsiness, weakness, incoordination, odd behavior, and more severe symptoms such as coma and seizure.

In general, this amount of oral 10 g glucose has been shown to raise plasma glucose from 58 to 122 mg/dL over 45 minutes, with peak response at 15 minutes, and a decline resulting by 60 minutes.

9.2 GI Effects

Adverse GI effects such as nausea, anorexia, vomiting, pyrosis, gastralgia, diarrhea, and constipation are the most common adverse reactions to glipizide conventional tablets, occurring in about 1-2% of patients. Glipizide-induced adverse GI effects appear to be dose related and may subside following a reduction in dosage or administration of the drug in divided doses.

Table 1 Signs and Symptoms of Hypoglycemia

Autonomic[a]	Neuroglucopenic[b]
Weakness	Headache
Sweating	Hypothermia
Tachycardia	Visual disturbances
Palpitations	Mental dullness
Tremor	Confusion
Nervousness	Amnesia
Irritability	Seizures
Tingling of mouth and fingers	Coma
Hunger	
Nausea[c]	
Vomiting[c]	

[a]Caused by increased activity of the autonomic nervous system.

[b]Caused by decreased activity of the central nervous system.

[c]Unusual.

9.3 Dermatologic Effects and Hepatic Effects

If allergic skin reactions including pruritus, erythema, eczema, urticaria, and morbilliform or maculopapular eruptions and glipizide-associated jaundice occur, the drug should be discontinued.

9.4 Other Adverse Effects

Like other sulfonylureas, weight gain and the syndrome of inappropriate secretion of antidiureic hormone (SIADH) have occurred in patients receiving glipizide.

10. Drug Interaction

Numerous drugs have been reported to interact with sulphonylureas leading to either potentiation or attenuation of the latter's hypoglycemic action through

pharmacokinetic and/or pharmacodynamic interactions (Marchetti and Nayaksi, 1989).

Potentiation of sulphonylurea action due to pharmacokinetic mechanisms may be achieved by displacement from plasma protein binding sites, enzymatic inhibition or enzymatic induction of hepatic metabolism or reduction of urinary excretion.

Pharmacodynamic interactions have been claimed to explain the potentiation of sulphonylurea action by monoamine oxidase inhibitors (increased insulin secretion, decreased gluconeogenesis), and short term ethanol administration (decreased gluconeogenesis).

11. Preparations

Glipizide oral conventional tablets dosages are 5, 10 mg and extended release tablets are 2.5, 5 and 10 mg.

B. Bioavailability and Bioequivalence

1. History

Bioequivalence was first used in the approval of generic products in Canada in the 1970s and was defined there in 1973. However, the publication in 1977 of the US regulations on bioavailability and bioequivalence was a landmark that led to abbreviated new drug applications (ANDA) (Smith, 2003). In1992, the US Food and Drug Administration (US FDA) published its first guidance on statistical procedures for providing evidence of bioequivalence in average bioavailability between the generic drug product and the innovator drug product that replaces the animal toxicology, clinical efficiency, and pharmacokinetic bioavailability studies (Chow and Shao, 2002: 108-109; Shargel, Wu-Pong, and Yu, 2005: 453-479)

As indicated in the guidance, a standard two-sequence, two-period (2x2) crossover design with similar experimental conditions were used to prove bioequivalence. Two formulations of the same drug or two drug products are said to be bioequivalent in average bioavailability if the 90% confidence interval of the ratio of means of the primary pharmacokinetic parameters such as AUC and C_{max} are within the interval of 80 and 125% based on log-transformed data. It assumed that

they will provide the same therapeutic effect or that they are therapeutically equivalent (Chow and Liu, 2002).

Up to date, the idea of drug interchangeability usually classified as drug prescribability and drug switchability have been described in recently published guidance for industry: statistical approaches to establishing bioequivalence (US FDA, 2001). Drug prescribability is referred to as the physician's choice for prescribing and appropriate drug product for his or her new patients among an innovator drug product and a number of its generic drug products. On the other hand, drug swithchability is related to the switch from an innovator drug product to a generic product within the same subject whose concentration of the active ingredients has been titrated to a steady, efficacious, and safe level. For the object to assess drug prescribability and drug interchangeability, population bioequivalence (PBE) and individual bioequivalence (IBE) are recommended, respectively (Chow and Liu, 2002).

In 2000, the US FDA issued a guidance of general considerations of bioavailability and bioequivalence studies for orally administered drug products, added the option of using replicate designs for bioequivalence study for modified-release dosage forms and highly variable drug products (within-subject coefficient of variation $\geq$ 30%).

The replicated crossover design not only allows estimates both of bioequivalence; IBE and PBE, but also provides a more accurate and assessment of average bioequivalence (ABE).

2. Bioavailability

Bioavailability refers to the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of action.

The area under the drug concentration-time curve (AUC) is used as a measure of the total amount of unaltered drug that reaches the systemic circulation.

Relative (apparent) availability is the availability of the drug from a drug product (A) as compared to a recognized standard (B).

$$\text{Relative availability} = \frac{[AUC]_A}{[AUC]_B}$$

The absolute availability of drug is the systemic availability of a drug after extravascular administration (eg, oral, rectal, transdermal, subcutaneous) compared to IV dosing. After oral administration of a drug, *F* (which is fraction of the dose to be absorbed) may vary from a value of 0 (no drug absorption) to 1 (complete drug absorption) (Sharger, et al, 2005: 453-479).

$$\text{Absolute availability} = F = \frac{[AUC]_{PO}/\text{Dose}_{PO}}{[AUC]_{IV}/\text{Dose}_{IV}}$$

Several *in vivo* and *in vitro* methods can be used to measure product quality bioavailability and to establish bioequivalence. In descending order of preference, these include pharmacokinetic, pharmacodynamic, clinical observations, and *in vitro* studies (US FDA, 2003).

Plasma drug concentration method is the most direct and objective way to determine systemic drug bioavailability. An accurate description of plasma drug concentration-time profile of drug substance can be obtained using validated drug assay and this provide t_{max}, C_{max}, and AUC values. Other methods were used only if this quantitative of drug in plasma lack an assay with sufficient accuracy and/ or reproducibility. Exceptionally, the *in vitro*-studies method was used to assess bioavailability when there are correlation between the *in vitro* drug dissolution rate and *in vivo* drug bioavailability (Shargel, et al, 2005: 453-479).

3. Designs

3.1 Description of Crossover Designs

For bioavailability and bioequivalence studies, the crossover design is viewed favorably by the FDA because of the following advantages (Bolton, 1997: 384-425):

1. Each subject serves as his or her own control. It allows a within subject comparison between formulations.

2. It removes the intersubject variability from the comparison between formulations.

3. With a proper randomization of subjects to the sequence of formulation administrations, it provides the best unbiased estimates for the differences (or ratios) between formulations.

4. In practice, a crossover design, which can remove the intersubject variability from the comparison of average bioavailability between formulations, is often considered to be the design of choice if the number of formations to be compared is small, say no more than three (Chow and Liu, 2000).

3.2 Replicate Designs for Bioequivalence Studies

In 2000 FDA Guidance on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations, it states five potential advantages to what they term replicate study designs (Smith, 2003: 83-120). These are

1. Allow comparisons of within-subject variances for the test and reference product.

2. Indicate whether a test product exhibits higher or lower within-subject variability in the BA measures when compared to the reference product.

3. Suggest whether a subject-by-formulation (S*F) interaction may be present.

4. Provide more information about factors underlying formulation performance, and

5. Reduce the number of subjects needed in the BE study.

For replicated design study, the new guidance theoretically allows for 12 subjects, all subjects must complete the study (Kimanani et al, 2000:1103). In the 2001 FDA Guidance for Statistical Approaches to Establish Bioequivalence, it mentions only the following two replicate designs, neither of which has been previously mentioned in this entry such as the three-period design and the four-period design (Shargel et al., 2005). If the higher-order crossover design has more than two sequences, it may increase the chance of errors occurring in the randomization schedules (Chow and Liu, 2000).

Moreover, the replicated design study must be considerate about very time-consuming to complete the study, increasing the number of dropouts and the effect on the data due to possible changes in the subjects' physiological status over this longer time period (Chow and Shao, 2002: 108-109).

For the attractive design, many studies reported that high variability drug were study based on replicated crossover design such as two sequence dual design (Sechaud et al, 2002), four-period design with two sequences (Yacobi et al., 2000 and Joukhadar et al., 2003) and four-period design with four sequences (Meyer et al., 2000).

4. Statisticals

4.1 Log-Transformation of Data

The distribution of many biological parameters such as the C_{max} and the AUC values has a longer right tail than would be observed in a normal distribution.

Parametric analysis of C_{max} and AUC has become accepted practice to take a log transformation of these two variables.

4.2 Analysis of Variance (ANOVA)

A statistical difference between the pharmacokinetic parameters obtained from two or more drug products is considered statistically significant if there is a probability of less than 1 in 20 times or 0.05 probability ($p< 0.05$).

4.3 Confidence Intervals in Bioequivalence Studies

Presently, in Thailand, only average bioequivalence estimates are used to establish bioequivalence of genetic drug products.

The objective of a bioequivalence study is to compare bioavailability between two formulations (a test and a reference formulation) of a drug product with respect to the rate and extent of absorption. The primary hypothesis may be whether the difference in average bioavailability between a test and reference product in within $\pm$ 20% of the reference mean which arbitrary by appears to have been chosen

to satisfy clinical considerations. The confidence limits must lie between 0.8 and 1.25 based on the difference of the back-transformed averages of the log transformed AUC and C_{max} results (Bolton, 1997; Chow and Liu, 2000; Shargel et al, 2005).