DESIGN AND EVALUATION OF ORAL ANTIDIABETIC AGENTS AS BILAYERED TABLETS

INTRODUCTION

Diabetes mellitus is a chronic endocrine metabolic disorder characterized by a high blood glucose concentration level. Deficiency of insulin secretion resulting in hyperglycemia an increased blood sugar level. Fasting plasma glucose levels are ≥ 7.0mmol/L. and ≥11.1mmol/L two hours after meal. Hyperglycemia occurs because of uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal system with reduces glucogen synthesis. In this condition there are disturbance of carbohydrates, protein and lipid metabolism. Diabetes mellitus involves not only a deficiency of insulin but also an excess of certain other hormones, such as growth hormone, glucocorticoid and glucagon. Thus not only the pancreas are involves in the glucose homeostasis but also anterior pituitary gland and the adrenal cortex. When the renal threshold for glucose reabsorption is exceeded, glucose spills over into the urine called glycosuria and causes osmotic diuresis called polyuria, which in turn results in dehydration, thirst and increased drinking of water called polydipsia. Insulin deficiency causes wasting through increased breakdown and reduced synthesis of proteins.

In diabetes mellitus plasma immunoreactive glucagon concentrations are increased and the normal suppression of glucagon by hyperglycemia is also impaired. In diabetes capillary basement membrane thickening occurs which leads to the various complications like microangiopathy, neuropathy, nephropathy, retinopathy, atherosclerosis etc.

The World Health Organization (WHO) has classified diabetes mellitus as follows:

There are two main types of diabetes mellitus:

1. Type I diabetes also called as insulin-dependent diabetes mellitus. (IIDM). or juvenile-onset diabetes.
2. Type II diabetes also called as non-insulin dependent diabetes mellitus. (NIDDM). Or maturity-onset diabetes.

Others:
1. Type III diabetes mellitus.
2. Type IV diabetes mellitus also called as gestational diabetes mellitus.

In type I diabetes there is an absolute deficiency of insulin resulting from autoimmune destruction of bête cells where absolute deficiency of insulin and there is no circulation of insulin in plasma and thus insulin replacement is required. Without insulin treatment such patients will ultimately die with diabetic ketoacidosis. Diabetic ketoacidosis is an acute emergency it is developed in the absence of insulin because if accelerated breakdown of fat to acetyl –CoA, which is converted to acetoacetate and beta-hydroxybutyrate which causes acidosis and a ketone. Type I diabetes patients are usually young (children and adolescents) and not obese when they first develop the symptoms. There is an inherited predisposition with 10 fold increased incidence in first-degree relatives of an index case and strong associations with particular histocompatibility antigens (HLA) types.

Type-II diabetes is accompanied both by insulin resistance which precedes overt disease and by impaired insulin secretion, each or it is important in its pathogenesis. Such patients are often obese and usually present in adult life, the incidence rising progressively with age as beta cell function declines. Individuals with type II diabetes may not require insulin to survive, but 30% or more will benefit from insulin therapy to control blood glucose. Certain individuals initially diagnosed for both type I and II diabetes but later slowly progressing to type I diabetes are called latent autoimmune diabetes of adults (LADA) and they will ultimately require full insulin replacement therapy.

Type Two diabetes is characterized by pancreatic beta cell dysfunction and insulin resistance in the liver and peripheral tissues like skeletal muscle, adipose tissue. Because beta cell dysfunction is progressive management of type II diabetes necessitates continued monitoring and therapy modification. Further, since it is often difficult to achieve and maintain glycemic control, multiple drug therapy is eventually required in most patients.
Persons with type II may not develop ketosis, but ketoacidosis may occur as the result of stress such as infection or the use of medication that enhance resistance to insulin like corticosteroids. Dehydration in untreated and poorly controlled individuals with type II diabetes can lead to a life threatening condition called nonketotic hyperosmolar coma. In this condition the blood glucose level may rise to 6 to 20 times the normal range and altered mental state develops or the person loses consciousness where urgent medical care and rehydration is required.

Type III diabetes mellitus is refers to multiple other specific causes of an elevated blood glucose level. The causes may be pancreatectomy, pancreatitis, non-pancreatic diseases and drug therapy.

Type IV diabetes mellitus is also called gestational diabetes (GDM) and is defined as any abnormality in glucose level noted for the first time during pregnancy. During pregnancy the placenta and placental hormones create an insulin resistance that is most pronounced in the last trimester. Risk assessment for diabetes is suggested starting at the first prenatal visit.

Insulin is synthesized as a precursor (prepro-insulin) in the rough endoplasmic reticulum. It is transported to the Golgi apparatus where it is modified to proinsulin and then to insulin and C-peptide. These are stored in granules in the Beta-cells. Secretion normally occurs in pulses every 15 to 30 minutes.

Insulin is released from pancreatic beta cells at a low or steady basal rate an in much higher stimulated rate in response to glucose. There is a steady basal release of insulin and secretion is increased as a response to a rise in blood glucose. Other stimulants of insulin release are sugars mannose, amino acids leucine, arginine, hormones such as glucagon-like polypeptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), glucagon, cholecystokinin and vagal activity. On the other end inhibitory effect of insulin release include somatostatin, leptin and chronically evaluated glucose and fatty acid levels. Insulin is made up of two polypeptide chains A and B. chain A is made up of 21 amino acids and chain B basic chain of 30 amino acids linked by two disulfide –S-S- bridges. The molecular weight is 6000 and normal pancreas secrets about 50 units daily.

Insulin is the main hormone controlling the intermediary metabolism, having actions on liver, muscle and fat. It is an anabolic hormone its overall effect is to conserve
the fuel by facilitating the uptake and storage of glucose, amino acids and fats after a meal. Insulin influences glucose metabolism in most tissues like liver where it inhibits glycogenolysis (glycogen breakdown) and gluconeogenesis (synthesis of glucose from non-carbohydrate sources.) while stimulating glycogen synthesis. Insulin does not enter cells to produce effects but it binds to special protein molecules called receptors on cell surface membrane of target cells. Glucose enters beta cells via a membrane transporter called Glut-2 and its subsequent metabolism via glucokinase (rate limiting enzyme) that acts as glucose sensor linking insulin secretion to extracellular glucose.

Insulin exhibits:

1. Gluoregulatory effects by increased glucose uptake by peripheral tissues, inhibits glycogen breakdown so reduces hepatic glucose release and it favors storage of glucose as glycogen. Insulin prevents glucose formation from proteins, amino acids and fats.

2. Lipid regulatory effect: it decreases the release of free fatty acids from fat cells. Suppresses hepatic ketogenesis in the liver cells.

3. Protein regulatory effect: it increases muscle amino acids uptake and protein synthesis (protein anabolism)

So insulin reduces blood sugar, consequently a fall in plasma insulin increases blood glucose.

**Mechanism of action of Metformin Hydrochloride:**

Metformin improves hyperglycaemia primarily by suppressing glucose production by the liver (hepatic gluconeogenesis). The "average" person with type 2 diabetes has three times the normal rate of gluconeogenesis; metformin treatment reduces this by over one third. Metformin activates AMP-activated protein kinase (AMPK), an enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats; activation of AMPK is required for metformin's inhibitory effect on the production of glucose by liver cells. Research published in 2008 further elucidated metformin's mechanism of action, showing activation of AMPK is required for an increase in the expression of SHP, which in turn inhibits the expression of the hepatic gluconeogenic genes PEPCK and Glc-6-Pase. Metformin is frequently used in research along with AICAR as an AMPK agonist. The mechanism by which biguanides increase the activity of AMPK remains uncertain; however, research suggests that metformin
increases the amount of cytosolic AMP (as opposed to a change in total AMP or total AMP/ATP).

In addition to suppressing hepatic glucose production, metformin increases insulin sensitivity, enhances peripheral glucose uptake (by phosphorylating GLUT-4 enhancer factor), increases fatty acid oxidation, and decreases absorption of glucose from the gastrointestinal tract. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors. AMPK probably also plays a role, as metformin administration increases AMPK activity in skeletal muscle. AMPK is known to cause GLUT4 deployment to the plasma membrane, resulting in insulin-independent glucose uptake. Some metabolic actions of metformin do appear to occur by AMPK-independent mechanisms; a 2008 study found "the metabolic actions of metformin in the heart muscle can occur independent of changes in AMPK activity and may be mediated by p38 MAPK- and PKC-dependent mechanisms.

**Mechanism of action of Glimepiride:**

Glimepiride is a medium-to-long acting sulfonylurea antidiabetic drug. Sulfonylureas bind to an ATP-dependent K⁺ (K_{ATP}) channel on the cell membrane of pancreatic beta cells. This inhibits a tonic, hyperpolarizing efflux of potassium, thus causing the electric potential over the membrane to become more positive. This depolarization opens voltage-gated Ca^{2+} channels. The rise in intracellular calcium leads to increased fusion of insulin granule with the cell membrane, and therefore increased secretion of (pro)insulin.

There is some evidence that sulfonylureas also sensitize β-cells to glucose, that they limit glucose production in the liver, that they decrease lipolysis (breakdown and release of fatty acids by adipose tissue) and decrease clearance of insulin by the liver.

The K_{ATP} channel is an octameric complex of the inward-rectifier potassium ion channel K_{ir}6.2 and sulfonylurea receptor SUR1 which associate with a stoichiometry of K_{ir}6.2α/SUR14.

Glimepiride acts as an insulin secretagogue. It lowers blood sugar by stimulating the release of insulin by pancreatic beta cells and by inducing increased activity of intracellular insulin receptors.