CHAPTER III
LITERATURE ON ANTIDIABETIC DRUGS AND DRUG INVESTIGATED

Diabetes mellitus is a chronic metabolic disorder characterized by a high blood glucose concentration – hyperglycemia (fasting plasma glucose greater than 7m mol/lit, or plasma glucose greater than 11.1 mmol/lit 2hrs after a meal) –caused by insulin deficiency, often combined with insulin resistance. Hyperglycemia occurs because of uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal muscle with reduced glycogen synthesis. When the renal threshold for glucose reabsorption is exceeded, glucose spills over into the urine (glycosuria) and causes an osmotic diuresis (polyuria), which in turn, results in dehydration, thirst and increased drinking. Insulin deficiency causes wasting through increased breakdown and reduced synthesis of proteins. Diabetic ketoacidosis is an acute emergency. It develops in the absence of insulin because of accelerated fat breakdown.

Various complications developed as a consequence of the metabolic derangements in diabetes, often over many years. Many of these are the result of disease of blood vessels, chronic renal failure.

There are two main types of diabetes mellitus

1. Type 1 diabetes (previously known as insulin dependent diabetes mellitus (IDDM) or juvenile onset diabetes).
2. Type 2 diabetes (previously known as non-insulin dependent diabetes mellitus (NIDDM) or maturity onset diabetes.
In Type 1 diabetes, there is an absolute deficiency of insulin resulting from autoimmune destruction of β-cells. Without insulin treatment such patients will ultimately die with diabetic ketoacidosis. Main reason of causing disease is genetic factor, viral infection.

Type 2 diabetes is accompanied both by insulin resistance (which precede over disease) and by impaired insulin secretion, each of which are important in its pathogenesis. Such patients are often obese and usually present in adult life, the incidence rising progressively with age as β-cells function declines. The treatment is initially dietary although oral hypoglycemic drugs usually become necessary and about one-third of patients ultimately requires insulin treatment.

**Oral hypoglycemic agents (OHA):**

Use of oral hypoglycemic agents (OHA) is now established in the management of diabetic state. In 1942, Janbon and coworkers discovered that p-aminobenzenesulfonamide – isopropyl thiadiazole (a sulfonamide) induced hypoglycemia. Loubatieres subsequently found that the compound was showing not any hypoglycemic activity when used in pancreatectomized animals. He, therefore, suggested that the hypoglycemic action was the result of stimulation of the pancreas to secrete insulin. At a later date a drug called Tolbutamide found its place in therapeutic armamentarium and it became popular for the management of certain diabetic patients. Tolbutamide is a member of the class of drugs referred to as sulphonylureas.
Advantages of oral therapy in diabetes

1. Patient acceptability
2. Ease of administration
3. No need of exogenous insulin – hence decreased insulin antigenicity
4. Insulin – being endogenous – physiological major action on liver and less at periphery
5. Less frequent and less severe hypoglycemia when compared to insulin therapy

Disadvantages

1. Less of medical supervision
2. Disinclination towards potential dangers of diabetes
3. Drug interactions
4. Toxic reactions – though rare could be serious
5. Limitations of dosage and inflexible dosage
6. Increased incidence of therapeutic failure with the passage of time

Drugs used as oral hypoglycemic agents

1. Sulphonylureas
   a) First generation sulphonyl ureas
      Ex: Tolbutamide, chlorpropamide, acetohexamide, tolaamide
   b) Second generation sulphonylureas
      Ex: Glibenclamide, glipizide, Gliclazide
   c) Third generation sulphonylureas
      Ex: Glimepiride
2. **Biguanides**
   Ex: Buformin, metformin, Phenformin

3. **L – Glucosidase inhibitor**
   Ex: Acarbose, Meglitol

4. **Thiazolidine diones**
   Ex: Pioglitazone, Rosiglitazone

5. **Short acting insulinotropic agents (or) Meglitinide agents**
   Ex: Repaglinide, Nateglitinide

**Mechanism of action of sulphonylureas:**

The principle action of sulphonylureas is on β-cells. Stimulating insulin secretion and thus reducing plasma glucose. High affinity receptors for sulphonylureas are present on the \( K_{\text{ATP}} \) channels in β-cell plasma membrane and the binding of various sulphonylureas parallels their potency in stimulating insulin release. The drugs reduce the \( K^+ \) permeability of β-cells by blocking \( K_{\text{ATP}} \) Channels, causing depolarization, calcium ions and thus insulin is released.

**Mechanism of action of Thiazolidinediones:**

Thiazolidinediones (Tzds) act to decrease insulin resistance. Their primary action is the regulation of genes involved in glucose and lipid metabolism and adipocyte differentiation. Tzds are ligands of peroxisome proliferator-activated receptor-gamma (PPAR-\( \gamma \)), part of the steroid and thyroid superfamily of nuclear receptors. These PPAR receptors are found in muscle, fat, and liver. PPAR-\( \gamma \) receptors are complex and modulate the expression of the genes involved in lipid and glucose metabolism, insulin signal transduction and adipocyte and other tissue differentiation.
Chemically, \((RS)-5-(4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl)thiazolidine-2,4-dione\)

Molecular formula: \(C_{19}H_{20}N_{2}O_{3}S\)

Molecular weight: 392.90 g/mol

Properties: Pioglitazone is an odorless white crystalline powder. It is soluble in N,N-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether.

Melting Point: \(188^0\) C

Pharmacokinetics:

Single oral dose of pioglitazone, 15 to 45 mg results in a \(C_{max}\) of \(4.1 \pm 0.12\) mg/l within 2 hours. Steady state concentrations are achieved after 2 days of administration of 15-45 mg of pioglitazone. Administration of pioglitazone with food \(C_{max}\) and \(T_{max}\). The volume of distribution is low due to extensive protein binding (85-97%). The half life of pioglitazone varies from 3-6 hours after single dose administration. Pioglitazone is
extensively metabolized to 7 metabolites predominantly excreted in the urine, the most abundant being the carboxylic acid. About 60-70% of the dose is excreted in the urine and 10-20% in the faeces.

**Pharmacokinetic parameters:**

- Oral bioavailability: 80%
- Bound in plasma: > 99%
- Half-life: 3-6 h
- Volume of distribution: 13 – 24 L/kg
- Daily dose: 15 – 60 mg
- Time for peak plasma concentration: 2

**Pharmacological properties:**

Pioglitazone is absorbed within 2 hours of ingestion; although food may delay uptake, total bioavailability is not affected. Pioglitazone is metabolized by CYP2C8 and CYP3A4 to active metabolites. The bioavailability of numerous other drugs also degraded by these enzymes may be affected by pioglitazone therapy, including estrogen-containing oral contraceptives; additional methods of contraception are advised. Pioglitazone may be taken once daily; the usual starting dose is 15–30 mg. Pioglitazone therapy reduces mortality and macrovascular events (myocardial infarction and stroke). Pioglitazone is approved as a monotherapy and in combination with metformin, sulfonylureas, and insulin for the treatment of type 2 diabetes.
Absorption: Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption.

Distribution: The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. Pioglitazone is extensively protein bound (>99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (>98%) to serum albumin.

Metabolism: Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of pioglitazone) and M-III (keto derivative of pioglitazone) are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. At steady state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the total peak serum concentrations and 20% to 25% of the total AUC.

Excretion and Elimination: Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the faeces. The mean serum half-life of pioglitazone and
total pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7 L/hr.

**Therapeutic uses:** Pioglitazone is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. Pioglitazone is used in the management of type–2 diabetes mellitus also known as non-insulin dependent diabetes mellitus (NIDDM) or adult onset diabetes. It decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output.

**Adverse reactions:** Hypoglycemia, resumption of ovulation, congestive heart failure, Hepatic effects like idiosyncratic hepatotoxicity.; Gastrointestinal disturbances - Nausea, diarrhoea, gastric pain, constipation, Vomiting, Metallic taste in mouth

**Indications:**

pioglitazone is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes (non-insulin dependent diabetes mellitus, NIDDM). Pioglitazone is indicated for monotherapy. Pioglitazone is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent does not result in adequate glycemic control. Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise. These efforts are important not only in the primary treatment of type 2 diabetes, but also to maintain the efficacy of drug therapy.

**Over dosage and treatment:**

Hypoglycaemia may occur in case of an over dosage. As a consequence of their improved insulin sensitivity may cause risk for pregnancy. Very rarely it causes hepatotoxicity in case of over dosage.
Dosage and administration:

Pioglitazone may be initiated at 15 mg or 30 mg once daily and can be increased to 45 mg once daily in increments for patients who respond inadequately to the initial dose.

Packing and Storage:

Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed, and protect from moisture and humidity.
NEED FOR CONTROLLED RELEASE OF PIOGLITAZONE

Pioglitazone is an effective oral anti–diabetic agent that belongs to the thiazolidone diones drug class. Pharmacological studies indicate that pioglitazone improves glycemic control while reducing circulating insulin level\textsuperscript{1}. Pioglitazone has short biological half-life of 3-6 hours and is eliminated rapidly.\textsuperscript{2} Therefore control release (CR) products are needed for pioglitazone to prolong its duration of action and to improve patience compliance; there are few reports\textsuperscript{3} on the formulation of pioglitazone employing coated granules and matrix tablets. The drug also causes gastrointestinal disturbances such gastric pain, constipation, nausea and vomiting if present in larger concentration in g.i. tract. Controlled release formulation is also needed for pioglitazone for better control of blood glucose levels to prevent hypoglycemia and enhance clinical efficacy, to reduce g.i. disturbances and to enhance patient compliance. No controlled release formulations of pioglitazone are available commercially.

PAST WORK ON PIOGLITAZONE

1. Formulation and evaluation of bilayer floating-mucoadhesive tablets of pioglitazone HCl\textsuperscript{4}

This study was performed to design a bilayer resioselective floating – mucoadhesive tablet (BFMT) containing pioglitazone hydrochloride to prolong the gastric residence time and increase the drug bioavailability. Bilayer floating drug delivery system (FDDS) comprised of two layers, i.e. a floating layer consisting of HPMC K15M, sodium bicarbonate, and a sustained release (SR) layer of pioglitazone hydrochloride, HPMC K15M: Carbopol 940 in different ratios and dicalcium phosphate. The sustained layer was compressed and granules of the floating layer were added to it. The prepared tablets were evaluated in terms of their precompression parameters, physical characteristics, \textit{in vitro}
release, buoyancy and buoyancy lag-time. The results of the in vitro release studies showed that the optimized formulation F4 could sustain drug release 89.47±1.57% for 12 h and remain buoyant for >12 h. The release followed Higuchi kinetics with $R^2 = 0.9866$ indicating anomalous release. The in vitro drug release from the tablet was controlled by the amount of HPMC K15M and Carbopol 940 in the sustained release layer. The concentration of HPMC K15M significantly affects the drug release rate, buoyancy lag-time, and swelling characteristics of the tablets. Optimized formulation F4 showed no significant change in physical appearance, drug content, total buoyancy time or in vitro dissolution study after storage at 45 °C/75% RH for three months. The tablet formulations were found to be economical and may overcome the drawbacks associated with the drug during its absorption.

2. In vivo bioequivalence of oral antidiabetic agents: Pioglitazone tablets

The study was designed to evaluate the bioequivalence of two pioglitazone (CAS 112529-15-4) formulations. The trial was performed in 26 healthy male volunteers with the aim of comparing a new generic product (tablets containing 30 mg pioglitazone hydrochloride, test) with the originator product (reference). The trial was performed according to an open, crossover design in one study centre. In each of the two study periods (separated by a wash-out of 14 days) a single oral dose of 30 mg (test or reference) formulation was administered. Blood samples were taken up to 120 h post dose, the plasma was separated and the concentrations of pioglitazone and its principal active metabolite hydroxypioglitazone were determined by LC-MS-MS method. AUC$_{0\text{-inf}}$, AUC$_{0-t}$, C$_{\text{max}}$, and T$_{\text{max}}$ were calculated for both formulations. The mean C$_{\text{max}}$ of pioglitazone ranged between 1.01 μg/ml and 1.05 μg/ml, while the mean AUC$_{0\text{-inf}}$ and AUC$_{0-t}$ ranged between 10.89 μg x h/ml and 10.98 μg x h/ml as well as between 10.56 μg
x h/ml and 10.62 μg x h/ml for the test and reference formulations, respectively. The median ∫ₘₐₓ for the test tablets was 1.50 h and for the reference was 1.75 h. The ratios test/reference formulation for AUC₀–ₐₐ₃, AUC₀–₄ and Cₘₐₓ were 99.70%, 100.13% and 99.17%, respectively. Furthermore, the 90% geometric confidence intervals of the mean ratio of ln-transformed AUC₀–ₐₐ₃ were narrow and symmetrical around 100%, i.e. 90.59% to 109.72%, for AUC₀–₄, 90.69% to 110.55%, whereas for Cₘₐₓ they were 87.52% to 112.37%. As in the case of pioglitazone, mean values of the principal bioequivalence parameters of hydroxypioglitazone did not differ significantly after administration of the test and reference formulations. In the light of the present study it can be concluded that the two evaluated pioglitazone formulations, i.e. test formulation of pioglitazone hydrochloride and reference formulation, are bioequivalent in terms of the rate and extent of absorption.

3. Formulation and evaluation of pioglitazone hydrochloride floating drug delivery system

The objective of the present study was to develop a hydrodynamically balanced system of pioglitazone hydrochloride (HCl), by non-effervescent and effervescent techniques. Various grades of polymers (e.g. HPMC K-100M, HPMC K-4M, HPMC K-30, HPMC K-15, SCMC and MC) were used alone and in combination. Sodium bicarbonate (NaHCO₃) was used as a gas generating agent in effervescent technique. All the tablets were prepared by wet granulation technique. Various trial studies were carried out to fix the concentration of polymers and NaHCO₃. From the studies, it was found that 60 per cent of polymer concentration and 20mg of NaHCO₃ provided good tablet floating behaviour and also the possible shortest lag time was achieved.
4. Design and in vitro evaluation of mucoadhesive microcapsules of pioglitazone

Mucoadhesive microcapsules of pioglitazone were prepared using sodium alginate as a shell forming polymer and carbopol 974, HPMC, Sodium CMC as a Mucoadhesive polymer for the potential use of treating acute and chronic diabetes mellitus. Large spherical microcapsules with a coat consisting of sodium alginate and a Mucoadhesive polymer could be prepared by orifice-ionic gelation process. The microcapsules were found to be discrete, spherical, free flowing. The microcapsules were uniform in size, with size range of 300 to 600 µm. The SEM photographs indicated that microcapsules were spherical and completely covered with the coat polymer and microcapsule encapsulation efficiency was in the range of 80-93%. Pioglitazone release from the microcapsules was studied in phosphate buffer of pH 7.4 and pH 1.2 for 24 hours. Pioglitazone release from the microcapsules was slow and followed zero-order kinetics. Microcapsules of alginate-carbopol in phosphate buffer oh pH 7.4 gave slow release compared to others. The slower increasing release rate observed in order Sodium alginate: Carbopol< Sodium alginate: Sodium CMC< Sodium alginate: HPMC. The microcapsules with a coat consisting of alginate and a Mucoadhesive polymer exhibited good mucoadhesive properties in the in vitro wash-off test. The wash-off was faster at intestinal pH than at gastric pH. The Mucoadhesive microcapsules are thus suitable for oral controlled release of pioglitazone.
REFERENCES


