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Review Article

Review on Anti Diabetic Drug - Glibenclamide and Their New Formulation Approches

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ABSTRACT

Diabetes is a disease that occurs when your blood sugar or glucose level was not into the normal blood sugar or glucose level. Various drugs uses in the Treatment of Diabetes Type-2 and act by lower your blood sugar in a variety of ways. Sulphonylureas were discovered by Auguste Loubatières as the first pharmacological family of oral anti-diabetic drugs (OADs) is a kind of oral medication that works to regulate blood sugar levels in people with type 2 diabetes by stimulating insulin synthesis in the pancreas, which increases the efficacy of insulin in the body are typically divided into two generations (1st Generation and 2nd Generation). Glibenclamide, commonly known as Glyburide, is a kind of 2nd generation Sulphonylureas used in the treatment of type 2 diabetes mellitus**.** The creation of a novel formulation including both chemicals provides significant efficiency and compliance benefits, as well as operating as a multi-target medication system. The enhancement of the solublity and formulate Enhanced formulation like Transdermal patches, Inhalers, Misopourous silica.

INTRODUCTION

Diabetes is a disease that occurs when your blood sugar or glucose level was not into the normal blood sugar or glucose level (140 mg/dL) [1, 2], the occurrence of this disease is due to the irregular secretion of the Insulin from the pancreas to the body [1].

Diabetes is also referred as borderline diabetes, which imply that someone does not have diabetes or that they have a less serious disease; however every case of diabetes is serious [3].

Diabetes Types

(a) Type-1 Diabetes:

Type 1 diabetes is considered to be caused by an autoimmune reaction (the body mistakenly fights itself) that prevents your body from producing insulin. Type 1 diabetes affects around 5-10% of all diabetics [4].

(b) Type-2 Diabetes: When you have type-2 diabetes, your body does not use insulin properly and cannot maintain normal blood sugar levels. Type 2 diabetes affects 90-95 percent of diabetics [1, 4].

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It's generally takes many years of time to develop and is generally diagnosed in adulthood (but more and more in children, teens, and young adults). Type-2 diabetes can be avoided or postponed by making healthy lifestyle changes such as decreasing weight, eating nutritious foods, and getting enough exercise [4].

Symptoms of Diabetes:

(a) Type-1 Diabetes

Type 1 diabetes can include:

- extreme hunger
- increased thirst
- unintentional weight loss
- frequent urination
- blurry vision
- tiredness
- It may also result in mood changes.

(b) Type-2 Diabetes

Type 2 diabetes can include:

- increased hunger
- increased thirst
- increased urination
- blurry vision
- tiredness
- sores that are slow to heal

Causes of Diabetes:
Different Types of causes can be responsible for having each type of diabetes.

(a) Type-1 Diabetes
Doctors aren't sure what causes type 1 diabetes. The immune system wrongly assaults and kills insulin-producing beta cells in the pancreas for unknown reasons [2].

Some people's genes may have a role. It's also conceivable that a virus triggers the immune system's response [2].

(b) Type-2 Diabetes
Type 2 diabetes is caused by a mix of hereditary and environmental factors. Being overweight or obese also raises your risk. Carrying additional weight, particularly around the abdomen, makes your cells more resistant to the effects of insulin on blood sugar [2].

This disease runs in families. Family members share genes that make them more prone to type 2 diabetes and obesity [2].

Treatment of Diabetes:
Doctors treat diabetes with a few different medications.

(a) Type-1 Diabetes
The First and common Medication for type-1 diabetes is insulin. It acts as a substitute for the hormone that your body is unable to manufacture. The four most frequent kinds of insulin are as follows. They differ in terms of how soon they begin to operate and how long their effects last: Rapid-acting insulin begins to function within 15 minutes and has a half-life of 3 to 4 hours. Short-acting insulin begins working within 30 minutes and lasts for 6 to 8 hours. Intermediate-acting insulin begins working within 1 to 2 hours and lasts for 12 to 18 hours.

(b) Type-2 Diabetes
With the help of proper exercise and diet type-2 diabetes can be controlled. If changing your lifestyle isn't enough to decrease your blood sugar, you'll need to take medication (Table 1).

Sulphonylureas:
Janbon et al. developed Sulfonylureas in 1942 after seeing that certain sulfonamides caused hypoglycemia in experimental animals. Carbutamide (1-butyl-3-sulfonylurea) was created as a result of this observation [5].

Carbutamide was the first sulfonylurea used to treat diabetes, but it was later pulled from the market due to bone marrow toxicity [5].

Sulphonylureas were discovered by Auguste Loubatières and his colleagues in France in the late 1950s as the first pharmacological family of oral anti-diabetic drugs (OADs) [6].

Sulphonylureas are Organic Compounds that are extensively employed for agricultural and medical purposes. Sulphonylureas are pharmaceutically utilised as an anti-diabetic drug for patients with Type 2 Diabetes Mellitus [4].

Table 1: Various drugs uses in the Treatment of Diabetes Type-2 and act by lower your blood sugar in a variety of ways

Types of drug	How they work	Example(s)
Alpha-glycosidase inhibitors	Slow your body's breakdown of sugars and starchy foods	Acarbose (Precose) and miglitol (Glyset)
Biguanides	Reduce the amount of glucose your liver makes	Metformin (Glucophage)
DPP-4 inhibitors	Improve your blood sugar without making it drop too low	Linagliptin (Tradjenta), saxagliptin (Onglyza), and sitagliptin (Januvia)
Glucagon-like peptides	Change the way your body produces insulin	Dulaglutide (Trulicity), exenatide (Byetta), and liraglutide (Victoza)
Meglitinides	Stimulate your pancreas to release more insulin	Nateglinide (Starlix) and repaglinide (Prandin)
SGLT2 inhibitors	Release more glucose into the urine	Canagliflozin (Invokana) and dapagliflozin (Farxiga)
Sulfonylurea	Stimulate your pancreas to release more insulin	Glyburide (DiaBeta, Glynase), glipizide (Glucotrol), and glimepiride (Amaryl)

Sulphonylureas are a kind of oral medication that works to regulate blood sugar levels in people with type 2 diabetes by stimulating insulin synthesis in the pancreas, which increases the efficacy of insulin in the body [7].

Drugs in This Class

The following drugs are all in the Sulphonylureas class (trade name first, generic name in brackets) [7]:

- Amaryl (Glimepiride)
- Daonil (Glibenclamide)
- Diamicron (Gilclazide)
- Diamicron MR (Gilclazide)
- Glibenese (Glipizide)
- Minodiab (Glipizide)
- Tolbutamide (Tolbutamide)

Various Generations of Sulphonylureas

Sulfonylureas were discovered in 1942, and by the 1960s, numerous Sulfonylureas were commercially accessible; they are typically divided into two families (or generations). Gilclazide, glipizide, Glibenclamide, and glimepiride are contemporary second-generation Sulfonylureas, whereas first-generation medicines (such as Tolbutamide and chlorpropamide) are no longer used [5].

a) First Generation:

Acetohexamide, chlorpropamide, tolazamide, and tolbutamide are first-generation sulfonylureas that are used in the treatment of type 2 diabetes [8].

The sulfonylureas are arylsulfonylureas with different sorts of substitutions at the two ends of the molecule. Sulfonylureas reduce blood glucose via increasing insulin production from pancreatic beta cells. They may also have extra-pancreatic hypoglycemia effects that are significant during long-term treatment. The first generation sulfonylureas have mostly been supplanted in routine usage by second generation drugs, which are more effective and are provided in lower dosages, primarily once daily [8, 9].

b) Second Generation:

Glyburide (also known as glibenclamide), gliclazide, glipizide, and glimepiride are oral hypoglycemic medicines that are commonly used in type 2 diabetes therapy. Second-generation sulfonylureas have powerful antidiabetic activities in individuals with noninsulin-dependent diabetes mellitus. In newly diagnosed or untreated individuals with noninsulin-dependent diabetes mellitus, the effects of glipizide medication on insulin sensitivity, glucose-mediated insulin production, and glucose utilisation were assessed [8, 10-11].

These medications do not appear to promote insulin release from pancreatic beta cells in the same way as first-generation sulfonylureas do. Instead, they appear to act by sensitising beta cells to release insulin only when serum glucose levels are elevated. 824-2830 Although this increase in insulin secretion may be crucial in the patient's initial reaction to the medicine, plasma insulin levels have consistently returned to baseline levels over chronic treatment [8, 10].

Glibenclamide:

Glibenclamide, commonly known as Glyburide, is a kind of 2nd generation sulphonylurea used in the treatment of type 2 diabetes mellitus. It is an oral hypoglycemic medication that is indicated in conjunction with diet and exercise for the treatment of non-ketotic maturity onset diabetes mellitus [12].

General Chemistry:

a. Chemical Structure:

b. Chemical Formula: *C23 H28 Cl N3 O5 S*

c. Physical Properties: A white and off white crystalline powder.

d. Molecular Weight: 494.009 g-mol-1

e. Solublity: Partially soluble in water, readily soluble in dichloromethane, ethanol and dissolved in dilute solution of alkali alkaloids.

f. Melting Point: 165 -170 ℃

Mechanism:

The drug's mechanism of action is based on the blockage of ATP-sensitive K+ channels, which causes cell depolarization and insulin secretion. The drug's extrapancreatic effect in the liver, skeletal muscle, cardiac muscle, and smooth muscle sites is likewise based on the same mechanism (Fig. 1) [13].

Human Pharmacokinetics

a. Absorption

In gastrointestinal track it was observed the Glibenclamide is readily absorbed.

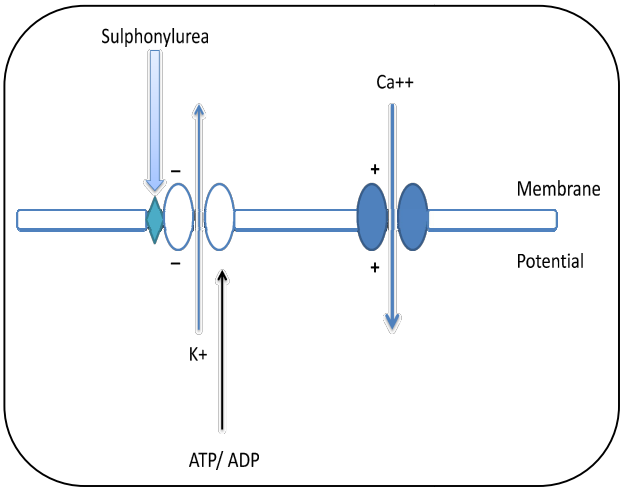

Figure 1: Mechanism of action of Sulfonylureas on ATP-sensitive K+ channels. The inhibition of K+ efflux from the cell leads to depolarization of the membrane potential, Ca++ influx and insulin release in the β-cell [13].

b. Half-Life

Half Life of Glibenclamide in general is 3-4 hours and in between 2-4 hours its Peak plasma concentrations occurs when orally administration**.**

c. Metabolism

It is almost entirely converted in the liver to weakly active metabolites and eliminated in equal parts through the bile and the kidneys, according to Goldfine and Maratos-Flier [14].

It is mostly metabolised by CYP3A4, then by CYP2C9, CYP2C19, CYP3A7, and CYP3A5.

Glyburide is metabolised by these enzymes to 4-trans-hydroxycyclohexyl glyburide (M1), 4-cis-hydroxycyclohexyl glyburide (M2a), 3-cis-hydroxycyclohexyl glyburide (M2b), 3-trans-hydroxycyclohexyl glyburide (M3), 2-trans-hydroxycyclohexyl glyburide (M4) (M5).

Along with the parent molecule, the M1 and M2b metabolites are considered active [15].

d. Protein Binding

Glyburide is 99.9% bound to protein in plasma with >98% accounted for by binding to serum albumin [15].

e. Elimination

The Excretion or elimination of Glibenclamide is through urine (50%) and feces (50%) and mainly excreted in the metabolites [15].

f. Toxicity

Patients who have taken an overdose may experience hypoglycemia. Mild hypoglycemia should be addressed with oral glucose and changes to medicine dosages or meal plans. Severe hypoglycemia can cause unconsciousness, seizures, and neurological damage. This should be treated in the hospital right away with intravenous glucose and monitored for 24-48 hours [15].

Pharmacodynamics:

Glyburide is a second-generation sulfonylurea8 that increases intracellular potassium and calcium ion concentrations by closing ATP-sensitive potassium channels on beta cells. 7 Glibenclamide has a lengthy duration of action because it is administered once daily, as well as a broad therapeutic index because patients begin with dosages as low as 0.75mg and can be increased to as high as 10mg or more. 9, 12 Patients on glyburide should be warned of an elevated risk of cardiovascular mortality, similar to that reported with tolbutamide, another sulfonylurea [15].

Glibenclamide interacts with great affinity to the SUR-1 subunits of the b-cell potassium sensitive ATP Channel (K-ATP Channel) [14].

Marketed Formulation:

Table 2: Glibenclamide 5mg Brands in India [14]

Company	Product	Price (Rs.)
Sanofi Aventis	Tab Daonil-5mg Tab	12
Ciple	Glinil 5 Mg Tablet 10s	10.48
Aristo Pharma	Glybovin-5mg Tab	6.25
USV	Glyboral Tablet 10s	6.10
Zydus Cadila	Betanase-5mg	4

Effects:

a. Effects on Secretion of Insulin:

In both normal and diabetic circumstances, glibenclamide enhances basal insulin output. The rise in insulin secretion in response to glucose, on the other hand, was not statistically significant. Glibenclamide, on the other hand, exhibited neither activating or inhibitory impact on pancreatic Glucokinase activity in both diabetic and normal rats. However, in diabetic rats, the activity of this enzyme was much lower than in normal rats [16]. Glibenclamide had a disproportionate effect on insulin production at low-normal glucose [17]. It increases GH production by regulating GHRH and

somatostatin actions in pituitary cells [18]. Glibenclamide has been found to have an insulin tropic action on human islets at low and high glucose concentrations [19].

b. Effects on Blood Glucose Level:

In hyperglycemic situations, Glibenclamide lowers blood glucose by boosting insulin synthesis from the pancreas's existing beta cells [20]. Glibenclamide dosage increases do not result in a proportionate increase in insulin production or a proportional drop in blood glucose concentration [21].

When Glibenclamide and exercise were combined, the rise in blood insulin levels was mitigated, and insulin levels dropped after activity began. Thus, in moderately hyperglycemic Type 2 diabetes patients, exercise reduces the Glibenclamide-induced rise in blood insulin. Nonetheless, exercise has a significant hypoglycemic impact in Type 2 diabetes individuals using Glibenclamide [22].

c. Effects on b Granulates of Islet of Langerhans:

At low glucose concentrations, the pure human -cell aggregates retained appropriate glucagon secretion capabilities, but failed to react to changes in ambient glucose concentration. The addition of pure -cells, but not released components from -cells at low or high glucose concentrations, partially restored -cell response to glucose with controlled glucagon secretion. The EphA stimulator ephrinA5-fc was unable to match -cells' inhibitory action on glucagon secretion. Glibenclamide reduced glucagon production from islets as well as - and -mixed cell aggregations [23]. Glibenclamide promotes the replication of pancreatic -cells. However, Glibenclamide's impact on -cell replication was transient (lasting up to 15 days) [24].

d. Effects on Glucose Content of Liver:

In diabetic patients, hepatic CAT and SOD activities were dramatically lowered, and GLUT1 expression was discovered to be impacted by glucose and insulin levels. Treatment with glibenclamide corrected the alterations seen in diabetic liver tissues. However, renal CAT and SOD activities were unaffected by diabetes, indicating that Glibenclamide may directly boost hepatic CAT and SOD activity [25].

Glibenclamide can influence GLUT1 expression and insulin levels in both severely and slightly diabetic patients. Glibenclamide can protect the liver from the effects of severe hyperglycemia [26].

e. Effects on Thyroid Function

Long-term Glibenclamide medication does not have any effects on thyroid in type 2 diabetes patients, and there is no relationship between Glycemic management and thyroid hormones or TSH [27].

Solublity Enhancement Approches:

a. Chitosan-Based Delivery Systems:

Glibenclamide was encapsulated in the matrix of novel polymeric systems based on Chitosan. The polymeric systems were synthesized as micro particles utilizing the ionic gelation process using penta sodium tripolyphosphate (TPP) as a cross linking agent [28].

The developed polymeric systems demonstrated a positive drug release profile, with an increased percentage of release.

b. By using Misopourous Silica:

Misopourous silica has emerged as a formulation enabler for poorly soluble active medicinal compounds (APIs). Unlike other formulations, Misopourous silica generally does not prevent supersaturated API precipitation. To improve absorption from the gastrointestinal (GI) tract, an appropriate precipitation inhibitor (PI) should be added [29].

Solid dispersions, Complexation with cyclodextrin, self-micro emulsifying drug delivery systems, and adsorption on carriers such as Misopourous silica and magnesium aluminometasilicate are among the strategies used. Adsorption onto Misopourous silica has shown significant promise in improving the solubility of poorly soluble Glibenclamide [30].

c. PLGA Based Nanoparticles:

One of the most successful biodegradable polymeric nanoparticles is poly (lactic-co-glycolic acid) (PLGA) (NPs). Because of its controlled and sustained release qualities, minimal toxicity, and biocompatibility with tissue and cells, the US FDA has authorised it for use in drug delivery systems [31].

Controlled release biodegradable Glibenclamide NPs can be efficiently prepared by emulsification solvent evaporation method suitably modulating processing variables [32].

d) Micellization:
One of the most difficult parts of medication research is improving the oral bioavailability of such weakly water-soluble medicines. To increase the solubility of weakly water-soluble medicines in an aqueous media, many approaches are applied. The surfactant Micellization approach was utilized in this work to improve the solubility of weakly water-soluble medicines.

To encapsulate the Glibenclamide, a carbohydrate-based nonionic surfactant that was produced in the lab was utilized. It was discovered that Glibenclamide's water solubility raised several folds [33].

New Formulation Approches:
a. Glibenclamide Nano-suspension Inhaler:
Because of its noninvasive nature, the lung is an appealing target for drug delivery because it can provide not only local lung effects but also potentially high systemic bioavailability, avoidance of first-pass metabolism, more rapid onset of therapeutic action, and the availability of a large surface area [34].

Because of the uniform distribution of medication dosage among the alveoli and the improved solubility and dissolution rate of the drug, nanoparticles in pulmonary drug administration are regarded as a promising technique [34].

Glibenclamide is a second-generation sulfonylurea that has been used in the treatment of non-insulin-dependent diabetic mellitus for many years, because of Glibenclamide's high hepatic first-pass metabolism and clinical efficacy at low dosages [34].

This inhaler application may provide an effective alternative to its oral dosage forms by the creation of nanosuspension for targeted administration of Glibenclamide as a hypoglycemic agent to the lung in an aerosol dosage form [34].

b. Glibenclamide Transdermal Patches
Glibenclamide's main activity is on beta cells, where it stimulates insulin production and thereby lowers plasma glucose. Many Sulfonylureas, including glipizide, have been linked to severe and even deadly hypoglycemia and gastrointestinal disturbances such as nausea, vomiting, heartburn, anorexia, and increased hunger following oral administration [35].

Because of the risk of hypoglycemia, Glibenclamide is best avoided in the elderly and in individuals with even modest renal impairment. Patient compliance is particularly critical because these medications are often designed to be used for an extended length of time [35].

Transdermal drug delivery has a number of advantages over oral administration, including reduced side effects, improved patient compliance, and elimination of the first-pass effect, sustained drug delivery, and interruption or termination of treatment when needed. A better performance of the Glibenclamide transdermal patches in comparison to oral administration could be due to day-to-day Glycemic control on long-term use [35].

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