EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 7
82-98
Year: 2016

QUALITY ASSESSMENT FOR TWO YEMENI GLIMIPRIDE BRANDS COMPARED TO THE ORIGINAL BRAND

Wafa Al-Madhagi*1, Ahmed Abdulbari Ahmed Albarakani[2], Abobakr Khaled Alhag[2], Zakaria Ahmed Saeed[2], Nahlah Mansour Noman[3] and Khaldon Mohamed[4]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Sana'a-University, Yemen.
[2]Department of Pharmacy, Faculty of Medicine and Health Sciences, Yemen Jordian University, Yemen.
[3]Department of Pharmacy, Faculty of Medicine and Health Sciences, Thamar University, Yemen.
[4]Department of Biomedical, Sana'a-University, Yemen.

*** Corresponding Author: Wafa Al-Madhagi**
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Sana'a-University, Yemen.

Article Received on 16/05/2016 **Article Revised on 06/06/2016** **Article Accepted on 27/06/2016**

ABSTRACT
The aim of the present study is to evaluate the effectiveness of Yemeni glimepride tablets in compare with amaryl 3mg as a reference drug. As result of this, this research would concern about evaluation of the Yemeni glimiperide (brand A and Glimaryl) in order to increase the Yemeni products to be competitive to amaryl the reference drug. According to quality control tests the brand A gave the minimum disintegration time but the tablets was friable so the hardness test were rejected as well as the weight variation. The hardness of brand gave significant difference with Amaryl that make the product is not accepted. The Glimaryl showed non-significant difference with Amaryl and close weight and weight variation. Glimaryl can be best alternative and comparative to the Amaryl.

KEYWORDS: glimipride, quality control, Yemeni glimipride.

INTRODUCTION
diabetes is the disruption in the body and the inability of Pancreas to secrete the right amount of insulin in addition to the lack of effectiveness of this insulin resulting Garret metabolic disorders be clarified for us the high proportion of sugar in the blood and if increased The level of sugar in the blood for a certain extent, the kidney cannot be preserved and then shows sugar in the urine and on this, the rise of blood sugar is the hallmark of diabetes. According to Statistics The number of people with diabetes in Yemen about 327 000 patients and is what constitutes about 1.5 percent of the total population of the country live 42% Palm cent of them below the poverty line, says adherent to the World Health the number of patients diabetes around the world is expected to increase 100 percent and diabetes affects more than 220 million people all over the world and is worth mentioning that about 80% of deaths occurring sugar in low and middle income countries. Diabetes showed serious complication as retinopathy, Peripheral Vascular Disease and Foot Ulcer and other complication that may threaten the human life. As result of this, this research would concern about evaluation of the Yemeni glimiperide in order to increase the Yemeni products to be competitive to amaryl the reference drug and the quality control tests would be done in Yemeni Jordanian University.

Literature Review
1. Diabetes Mellitus
Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia and abnormalities in carbohydrate, fat and protein metabolism.

It results from defects in insulin secretion, insulin sensitivity, or both. Chronic microvascular, macrovascular and neuropathic complications may ensue (B.WELL 2009).

1.1 Pathophysiology
There are four time of D.M that could according to cause as showed in table1. The most familiar's types are type 1 DM and type 2 DM.

Type 1 DM accounts for 5% to 10% of all diabetes cases. It generally develops in childhood or early adulthood and results from immune mediated destruction of pancreatic β-cells, resulting in an absolute deficiency of insulin.
- Hyperglycemia occurs when 80% to 90% of β-cells are destroyed.
- There is a long preclinical period (up to 9 to 13 years) marked by the presence of immune markers when β-cell destruction is thought to occur.
- The factors that initiate the autoimmune process are unknown, but the process is mediated by macrophages and T lymphocytes with circulating auto antibodies to

various β-cell antigens (e.g., islet cell antibody, insulin antibodies).

Type 2 DM accounts for as many as 90% of DM cases and is usually characterized by the presence of both insulin resistance and relative insulin deficiency.

 Type 2 DM occurs when a diabetogenic lifestyle presents (excessive calories, inadequate exercise, and obesity) and genetics or Uncommon causes of diabetes (1% to 2% of cases) include endocrine disorders (e.g., acromegaly, Cushing's syndrome), gestational diabetes mellitus (GDM), diseases of the exocrine pancreas (e.g., pancreatitis) and medications (e.g., glucocorticoids, pentamidine, niacin and α-interferon).

 Complication could be developed as Microvascular complications include retinopathy, neuropathy and Nephropathy or Macrovascular complications include coronary heart disease, stroke and peripheral vascular disease. (B.WELL 2009).

Table: 1 Etiologic classification of diabetes mellitus

TABLE 77-1 Etiologic Classification of Diabetes Mellitus

1. Type 1 diabetes[a] (β-cell destruction, usually leading to absolute insulin deficiency)
- Immune mediated
- Idiopathic

2. Type 2 diabetes[a] (can range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

3. Other specific types
- Genetic defects of β-cell function
  - Chromosome 20q, HNF-4α (MODY1)
  - Chromosome 7p, glucokinase (MODY2)
  - Chromosome 12q, HNF-1β (MODY3)
  - Chromosome 13q, insulin promoter factor (MODY4)
  - Chromosome 17q, HNF-1β (MODY5)
  - Chromosome 2q, neurogenic differentiation 1/b-cell e-box transactivator 2 (MODY6)
  - Mitochondrial DNA
  - Others
- Genetic defects in insulin action
  - Type 1 insulin resistance
  - Leprechaunism
  - Rabson-Mendenhall syndrome
  - Lipoatrophic diabetes
  - Others
- Diseases of the exocrine pancreas
  - Pancreatitis
  - Trauma/pancreatectomy
  - Neoplasia
  - Cystic fibrosis
  - Hemochromatosis
  - Fibrocalculous pancreatopathy
  - Others
- Endocrinopathies
  - Acromegaly
  - Cushing's syndrome
  - Glucagonoma
  - Pheochromocytoma
  - Hyperthyroidism
  - Somatostatinoma
  - Aldosteronoma
  - Others
- Drug- or chemical-induced
  - Vacor (pyriminil)
  - Pentamidine
  - Nicotinic acid
  - Glucocorticoids
  - Thyroid hormone
  - Diazoxide
  - β-Adrenergic agonists
  - Thiazides
  - Phenytoin
  - Interferon alpha
  - Others
- Infections
  - Congenital rubella
  - Cytomegalovirus
  - Others
- Uncommon forms of immune-mediated diabetes
  - "Stiff-man" syndrome
  - Anti-insulin receptor antibodies
  - Others
- Other genetic syndromes sometimes associated with diabetes
  - Down's syndrome
  - Klinefelter's syndrome
  - Turner's syndrome
  - Wolfram's syndrome
  - Friedreich's ataxia
  - Huntington's chorea
  - Laurence-Moon-Biedel syndrome
  - Myotonic dystrophy
  - Porphyria
  - Prader-Willi syndrome
  - Others

4. Gestational diabetes mellitus (GDM)

[a]Patients with any form of diabetes can require insulin treatment at some stage of their disease. Such use of insulin does not in itself classify the patient.

Adapted with permission from Report of the Expert Committee.[1]

Table: 2 pharmacokinetics of various insulins (B.WELL 2009)

TABLE 19-4 Pharmacokinetics of Various Insulins Administered Subcutaneously

Type of Insulin	Onset	Peak (hours)	Duration (hours)	Maximum Duration (hours)	Appearance
Rapid-acting					
Aspart	15–30 minutes	1–2	3–5	5–6	Clear
Lispro	15–30 minutes	1–2	3–4	4–6	Clear
Glulisine	15–30 minutes	1–2	3–4	5–6	Clear
Short-acting					
Regular	30–60 minutes	2–3	3–6	6–8	Clear
Intermediate-acting					
NPH	2–4 hours	4–6	8–12	14–18	Cloudy
Long-acting					
Glargine	4–5 hours	–	22–24	24	Clear
Detemir	2 hours	6–9	14–24	24	Clear

NPH, neutral protamine Hagedorn.

1.2 Clinical presentation

 Individuals with type 1 DM are often thin and are prone to develop diabetic ketoacidosis if insulin is withheld.
 Polyuria, polydipsia, polyphagia and weight loss.
 Patients with type 2 DM are often asymptomatic.
 Lethargy, polyuria, nocturnal and polydipsia can be present on diagnosis.
 Significant weight loss is less common

1.3 Diagnosis

Screening for type 2 DM should be performed every 3years in all adults beginning at the age of 45.Testing should be considered at an earlier age and more frequently in individuals with risk factors (e.g., family history of DM, obesity, signs of insulin resistance).

 The recommended screening test is a fasting plasma glucose (FPG) where Normal FPG is less than 100 mg/dL (5.6 mmol/L). Impaired fasting glucose is defined as FPG of 100 to 125 mg/dL (5.6 to 6.9 mmol/L). Impaired glucose tolerance is diagnosed when the 2-hour post load sample of the oral glucose tolerance test is between 140 and 199 mg per dL (7.8 to 11.0 mmol/L).

1.4 The goals of therapy in DM are to

1) Ameliorate symptoms of hyperglycemia.
2) Reduce the onset and progression of microvascular and macrovascular complications.
3) Reduce mortality, and improve quality of life.

1.5 Treatment

1.5.1 General approach

 Therapeutic strategies should attempt to match carbohydrate intake with glucose-lowering processes (usually insulin) and exercise Dietary intervention should allow the patient to live as normal life as possible.
 Cardiovascular risk factors should be managed aggressively (i.e.,smoking cessation, treatment of dyslipidemia, intensive blood pressure control, antiplatelet therapy).
 Diet and exercise.
 Self-monitoring of blood glucose (SMBG); and appropriate assessment of laboratory parameters. (B.WELL 2009).

1.5.2 Non-pharmacological therapy

A meal plan that is moderate in carbohydrates and low in saturated fat, with a focus on balanced meals is recommended.

Type 2 DM often requires caloric restriction to promote weight loss, bedtime and between-meal snacks are not usually needed if pharmacologic management is appropriate. Aerobic exercise can improve insulin resistance and glycemic control and may reduce cardiovascular risk factors Exercise should be started slowly in previously sedentary patients.

Older patients and those with atherosclerotic disease should have a cardiovascular evaluation prior to beginning a substantial exercise program.

1.5.3 Pharmacological therapy for type-I

All patients with type I DM require insulin, but the type and manner of delivery differ considerably among individual patients and clinicians. All of the insulins (with the exception of insulin glargine) have some degree of peak effect that must be considered in planning meals and activity Insulin glargine or insulin detemir is a feasible basal insulin supplement for most patients.

❖ **Type of insulin**

1. Regular insulin

Has a relatively slow onset of action when given subcutaneously, requiring injection 30 minutes prior to meals to achieve optimal postprandial glucose control and to prevent delayed postmeal hypoglycemia.

2. Lispro, aspart and glulisine insulins

 Analogs.
 More rapidly absorbed, peak faster, and have shorter durations of action than regular insulin.

This permits more convenient dosing within 10 minutes of meals (rather than 30 minutes prior) Produces better efficacy in lowering postprandial blood glucose than regular insulin in type1 DM and Minimizes delayed post meal hypoglycemia.

3. Neutral protamine hagedorn (NPH)

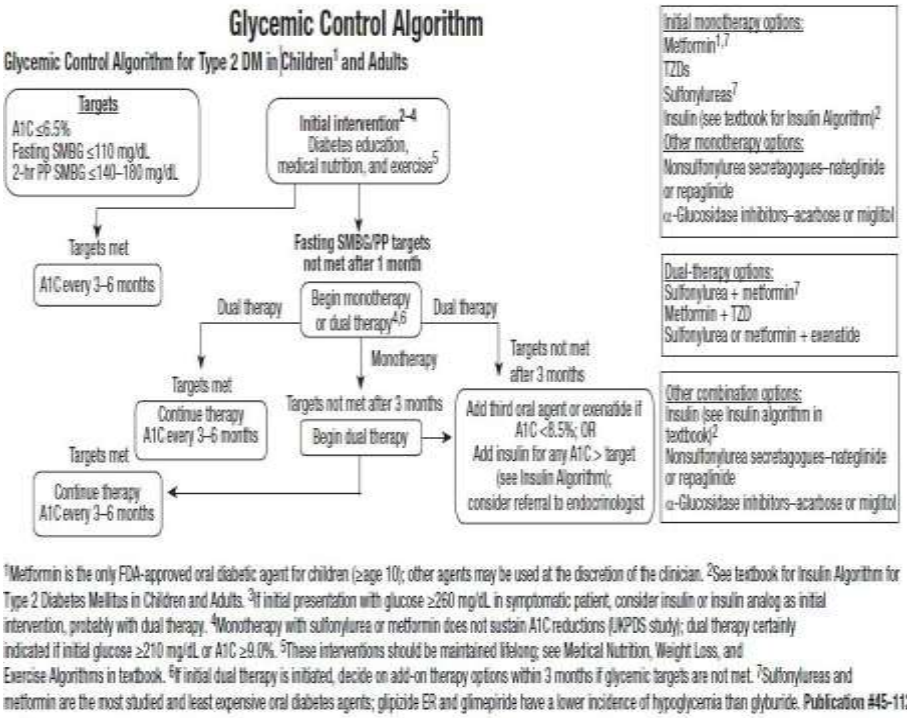
Intermediate-acting. Variability in absorption Inconsistent preparation by the pati, ilent. Pharmacokinetic differences may contribute to a labile glucose response, nocturnal hypoglycemia, and fasting hyperglycemia.

4. Glargine and detemir insulins

Long-acting ―peak less‖ human insulin analogs Less nocturnal hypoglycemia than NPH insulin when given at bedtime. In type 1 DM, the average daily insulin requirement is 0.5 to 0.6 units/kg. Higher doses (0.5 to 1 unit/kg) for acute illness or ketosis. In type 2 DM, a dosage range of 0.7 to 2.5 units/kg is often required for patients with significant insulin resistance. Hypoglycemia and weight gain are the most common adverse effects of insulin.

insulin, insulin lispro, insulin aspart, or **insulin glulisine**. Most patients require toal daily doses between 0.5 and 1 unit/kg/day. All patients receiving insulin should have extensive education in the recognition and treatment of hypoglycemia. (B.WELL 2009).

Drug treatment of type -2 diabetic
The drug treatment is summarized in figure 1



[1]Metformin is the only FDA-approved oral diabetic agent for children (≥age 10); other agents may be used at the discretion of the clinician. [2]See textbook for Insulin Algorithm for Type 2 Diabetes Mellitus in Children and Adults. [3]If initial presentation with glucose ≥260 mg/dL in symptomatic patient, consider insulin or insulin analog as initial intervention, probably with dual therapy. [4]Monotherapy with sulfonylurea or metformin does not sustain A1C reductions (UKPDS study); dual therapy certainly indicated if initial glucose ≥210 mg/dL or A1C ≥9.0%. [5]These interventions should be maintained lifelong; see Medical Nutrition, Weight Loss, and Exercise Algorithms in textbook. [6]If initial dual therapy is initiated, decide on add-on therapy options within 3 months if glycemic targets are not met. [7]Sulfonylureas and metformin are the most studied and least expensive oral diabetes agents; glipizide ER and glimepiride have a lower incidence of hypoglycemia than glyburide. **Publication #45-11265.**

A. Short-Acting Insulin Secretagogues (Meglitinides)
 Lower glucose by stimulating pancreatic insulin secretion.
 Hypoglycemic risk appears to be less with meglitinides than with sulfonylureas. The average reduction in A1C is about 0.8% to 1%. They should be administered before each meal (up to 30 minutes prior).

a. Repaglinide (Prandin) is initiated at 0.5 to 2 mg with a maximum dose of 4 mg per meal (up to four meals per day or 16 mg/day).

b. Nateglinide (Starlix) dosing is 120 mg three times daily before each meal. The dose may be lowered to 60 mg per meal in patients who are near goal A1C when therapy is initiated.

B. Biguanides
It enhances insulin sensitivity of both hepatic and peripheral (muscle) tissues Reduces A1C levels by 1.5% to 2% Reduced FPG levels by 60 to 80mg/dL It reduces plasma triglycerides and LDL by 8% to 15% Modestly increases HDL (2%) It does not induce hypoglycemia when used alone Reduce the risk of total mortality and cardiovascular death.

The most common adverse effects are abdominal discomfort, stomach upset, diarrhea, anorexia, and a metallic taste, lactic acidosis.

Metformin should be discontinued 2 to 3 days prior to IV radiographic dye studies and withheld until normal renal function has been documented poststudy.

a. Metformin immediate-release is usually initiated at 500 mg twice daily with the largest meals and increased by 500 mg weekly until glycemic goals or 2,000 mg/day is achieved Metformin 850mg can be dosed once daily and then increased every1 to 2 week to a maximum of 850 mg three times daily (2,550 mg/day).

b. Metformin extended-release (Glucophage XR) can be initiated with 500 mg with the evening meal and increased by 500 mg weekly to a maximum dose of 2,000 mg/day Administration two to three times a day may help minimize GI side effects and improve glycemic control The 750-mg tablets can be titrated weekly to the maximum dose of 2,250 mg/day.

C. Thiazolidinediones (Glitazones)
 PPAR-γ agonists enhance insulin sensitivity in muscle, liver and fat tissues indirectly Reduce A1C values by about 1.5% FPG levels by about 60 to 70 mg/dL at maximal doses Monotherapy is often ineffective unless the drugs are given early in the disease course when sufficient β-cell function Pioglitazone decreases plasma triglycerides by 10% to 20%, whereas.

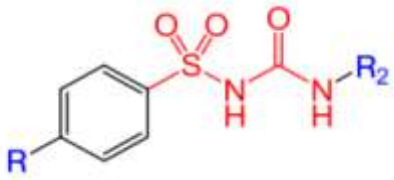
a. Rosiglitazone increase LDL by 5% to 15% Fluid retention and edema, anemia, weight gain and hepatotoxicity

b. Glitazones are contraindicated in heart failure especialy class IV.

Rosiglitazone has been associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction in several studies.

- **Pioglitazone** (Actos) is started at 15 mg once daily. The maximum dose is 45 mg/day.

 Rosiglitazone (Avandia) is initiated with 2 to 4 mg once daily.



The maximum dose is 8mg/day A dose of 4 mg twice daily can reduce A1C by 0.2% to 0.3% more than a dose of 8 mg taken once daily.

D. α-Glucosidase Inhibitors

Prevent the breakdown of sucrose and complex carbohydrates in the small intestine Reduction in the postprandial glucose concentrations (40 to 50 mg/dL) FPG levels are relatively unchanged (about 10% reduction) Reductions in A1C of 0.3% to 1%. Side effects include flatulence, bloating, abdominal discomfort and diarrhea, which can be minimized by slow dosage titration.

i. Acarbose (Precose) and **miglitol** (Glyset) are dosed similarly. Therapy is initiated with a very low dose (25 mg with one meal a day) and increased very gradually (over several months) to a maximum of 50 mg three times daily for patients weighing 60 kg or more, or 100 mg three times daily for patients above 60 kg The drugs should be taken with the first bite of the meal so that the drug is present to inhibit enzyme activity.

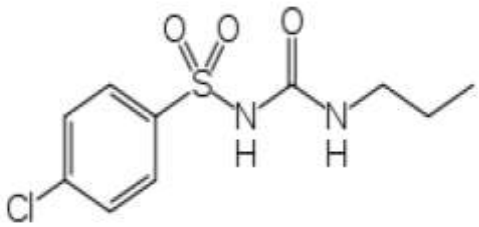
Individuals at high risk include the elderly, renal insufficiency or advanced liver disease, skip meals, exercise vigorously Weight gain is common.

Less common adverse effects include skin rash, hemolytic anemia, GI upset and cholestasis. Hyponatremia is most common with chlorpropamide but has also been reported with tolbutamide. Elderly patients who may have compromised renal or hepatic function. (B.WELL 2009).

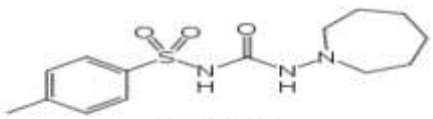
E. Sulfonylureas

They are stimulating pancreatic secretion of insulin.

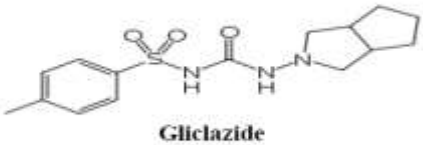
General formula of a sulfonylurea, showing the sulfonylurea backbone itself in red and the side chains that distinguish each compound in blue.



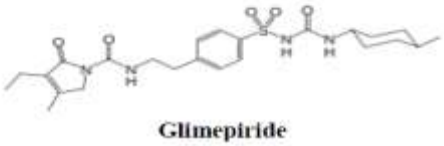
Chlorpropamide



Tolazamid



Gliclazide



Glimepiride

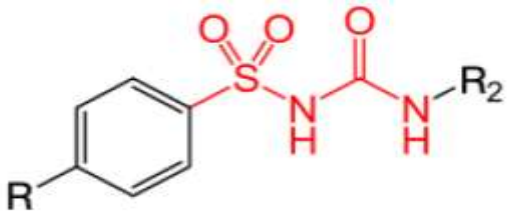
Sulfonylurea (UK: **sulphonylurea**) derivatives are a class of antidiabetic drugs that are used in the management of diabetes mellitus type 2. They act by increasing insulin release from the beta cells in the pancreas. Drugs in this class.

First generation
- Carbutamide
- Acetohexamide—No longer available in USA
- Chlorpropamide
- Tolbutamide
- Tolazamide

Second generation
- Glipizide
- Gliclazide
- Glibenclamide (Glyburide)
- Glibornuride
- Gliquidone
- Glisoxepide
- Glyclopyramide
- Glimepiride Some classify glimepiride as second-generation, while others classify it as third-generation.

Chemistry
All sulfonylureas contain a central S-phenylsulfonylurea structure (red) with a p- substituent on the phenyl ring (**R**) and various groups terminating the urea N′ end group (**R2**).

Sulfonylurea group



Sulfonylurea group

Second generation sulfonylureas have 5,64 higher risk for severe hypoglycaemia than metformin and a 6,11 higher risk than thiazolidinediones in 4 and 6 trials. (Hemmingsen B,2013).

Intensive glycaemic control with combined therapy increases the relative risk of severe hypoglycaemia by 30%. (Hemmingsen B,2011).

Weight gain
Like insulin, sulfonylureas can induce weight gain, mainly as a result of their effect to increase insulin levels. Compared with sulfonylureas, thiazolidinediones and repaglinide produced similar gains in body weight (1 to 5 kg). Metformin produced no weight gain compared with most other oral agents or placebo. (Bolen, Shari, 2007).

Other side-effects
Abdominal upset, headache and hypersensitivity reactions.

Loss of beta cells
Some diabetes experts feel that sulfonylureas as tolbutamide and glibenclamide accelerate the loss of beta cells from the pancreas and should be avoided. Relative to metformin, a greater rate of decline in beta cell function over time and therapy failure rate has been observed with sulfonylurea treatment. (Hemmingsen B,2013).

Contraindications
Sulfonylureas are contraindicated in pregnancy and lactation, type 1 diabetes, renal insufficiency for long acting products, severe liver problems and allergy to sulfonamides. Impairment of liver or kidney function increase the risk of hypoglycemia. (Triplitt CL, 2011).

Interactions
Drugs that potentiate or prolong the effects of sulfonylureas and therefore increase the risk of hypoglycemia include acetylsalicylic acid and derivatives, allopurinol, sulfonamides, and fibrates. (Dinnendahl, V, 2010).

Drugs that worsen glucose tolerance, contravening the effects of antidiabetics, include corticosteroids, isoniazide, oral contraceptives and other estrogens, sympathomimetics, andthyroid hormones. Sulfonylureas tend to interact with a wide variety of other drugs, but these interactions, as well as their clinical significance, vary from substance to substance.

Glimepride
Glimepride is indicated for the treatment of type 2 diabetes mellitus, when diet, physical exercise and weight reduction alone are not adequate.

Posology and method of administration
For oral administration
The basis for successful treatment of diabetes is a good diet, regular physical activity, as well as routine checks of blood and urine. Tablets or insulin cannot compensate if the patient does not keep to the recommended diet. (Sanofi-aventis,2013).

Posology
Dose is determined by the results of blood and urinary glucose determinations. The starting dose is 1 mg glimepiride per day. If good control is achieved this dose should be used for maintenance therapy. For the different dose regimens appropriate strengths are available.

If control is unsatisfactory the dose should be increased, based on the glycaemic control, in a stepwise manner with an interval of about 1 to 2 weeks between each step, to 2, 3 or 4 mg glimepiride per day.

A dose of more than 4 mg glimepiride per day gives better results only in exceptional cases. The maximum recommended dose is 6 mg glimepiride per day. In patients not adequately controlled with the maximum daily dose of metformin, concomitant glimepiride therapy can be initiated.

While maintaining the metformin dose, the glimepiride therapy is started with a low dose and is then titrated up depending on the desired level of metabolic control up to the maximum daily dose. The combination therapy should be initiated under close medical supervision.

In patients not adequately controlled with the maximum daily dose of Amaryl, concomitant insulin therapy can be initiated if necessary. While maintaining the glimepiride dose, insulin treatment is started at low dose and titrated up depending on the desired level of metabolic control. The combination therapy should be initiated under close medical supervision.

Normally a single daily dose of glimepiride is sufficient. It is recommended that this dose be taken shortly before or during a substantial breakfast or - if none is taken - shortly before or during the first main meal. If a dose is forgotten, this should not be corrected by increasing the next dose.

If a patient has a hypoglycaemic reaction on 1 mg glimepiride daily, this indicates that they can be controlled by diet alone. In the course of treatment, as an improvement in control of diabetes is associated with higher insulin sensitivity, glimepiride requirements may fall. To avoid hypoglycaemia timely dose reduction or cessation of therapy must therefore be considered. Change in dose may also be necessary, if there are changes in weight or life style of the patient, or other factors that increase the risk of hypo- or hyperglycaemia. (sanofi-aventis, 2013).

Contraindications

Glimepiride is contraindicated in patients with the following conditions:

• hypersensitivity to glimepiride, other sulfonylureas or sulfonamides

• insulin dependent diabetes, diabetic coma, ketoacidosis, severe renal or hepatic function disorders. In case of severe renal or hepatic function disorders, a change over to insulin is required. (sanofi-aventis, 2013).

Interaction with other medicinal products and other forms of interaction

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole).

Results from an in vivo interaction study reported in literature show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors. (sanofi-aventis,2013).

Undesirable effects

Blood and lymphatic system disorders
Immune system disorders
Metabolism and nutrition disorders
Eye disorders
Gastrointestinal disorders
Hepato-biliary disorders
Skin and subcutaneous tissue disorders

Pharmacokinetic properties

Absorption

The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only absorption rate is slightly diminished. Maximum serum concentrations (Cmax) are reached approx. 2.5 hours after oral intake (mean 0.3 µg/ml during multiple dosing of 4 mg daily) and there is a linear relationship between dose and both Cmax and AUC (area under the time/concentration curve).

Distribution

Glimepiride has a very low distribution volume (approx. 8.8 litres) which is roughly equal to the albumin distribution space, high protein binding (>99%) and a low clearance (approx. 48 ml/min). (sanofi-aventis, 2013).

In animals, glimepiride is excreted in milk. Glimepiride is transferred to the placenta. Passage of the blood brain barrier is low.

Biotransformation and elimination

Mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After high doses, slightly longer half-lives were noted.

After a single dose of radiolabelled glimepiride, 58% of the radioactivity was recovered in the urine, and 35% in the faeces. No unchanged substance was detected in the urine. Two metabolites - most probably resulting from hepatic metabolism (major enzyme is CYP2C9) - were identified both in urine and faeces: the hydroxy derivative and the carboxy derivative. After oral administration of glimepiride, the terminal half-lives of these metabolites were 3 to 6 and 5 to 6 hours respectively.

Table 3 summaries for drugs used in DM

No	Items & Theraputic Categories	Manufacturing Company	Manufacturing Origin	Local Agent
	Insulin Glargine			
	Recombinant Human Insulin Analogu _Long Acting			
	Natco Pharma	France	Sanofi-Aventis	Lantus 100 Iu/Ml Inj **Orginal
	Short Acting Insulin(I.V Insulin) Regular-Crystaline			
	ARRAAFAH CORP	DENMARK	NOVO NORDISK	Actrapid 100 U.I 10 Ml Inj **Orginal
	Insuli R 100 U.I 10 Ml Inj	ASIA	SYRIA	ALFURQAN PHARMA
	Insulin Bio R 100 U.I 10 Ml Inj	SEDICO Pharma	EGYPT	AL-FATH TRADING
	Insulet R 100 U.I 10 Ml Inj	Sothema	MOROCCO	BAWAM FOR DRUGS
	Jusline R 100 U.I	JULPHAR	UAE	ARD AL-GANATAIN
	Insugen R 100 U.I	Biocon	INDIA	AL-KHALIL FOR DRUGS
	Actrapid 300 Unit/ Ml 3 Ml Penfill Inj	NOVO NORDISK	DENMARK	ARRAAFAH CORP
	LONG ACTING INSULIN ZINC SUSPS			
	MONOTARD 100 UNITS/ML 10ML VIAL	NOVO NORDISK	DENMARK	ARRAAFAH CORP
	ISOPHAN INSULIN SUSP(NPH)			
	INSULATARD 100 U.I 10 ML INJ **Orginal	NOVO NORDISK	DENMARK	ARRAAFAH CORP
	INSULIN H BIO NPH 100 U.I 10 ML INJ	SEDCO PHARMA	EGYPT	AL-FATH TRADING
	INSULET N 100 U.I 10 ML INJ	SOTHEMA	MORCCO	BAWAM FOR DRUGS
	JUSLINE N 100 U.I 10 ML INJ	JULPHAR	UAE	ARD AL-GANATAIN
	INSUGEN NPH 100 U.I 10 ML INJ	BIOCON	INDIA	AL-KHALIL FOR DRUGS
	INSULATARD PENFILL 100 U.I 10 ML INJ	NOVO NORDISK	DENEMARK	ARRAAFAH CORP
	BIPHASIC ISOPHANE INSULIN			
	MIXTARD 30/70 100 U.I/ML 10 ML INJ S.C	NOVO NORDISK	DENMARK	ARRAAFAH CORP **ORGINAL
	INSULIN H MIX 100 U.I 10 ML INJ	SEDICO PHARMA	EGYPT	AL-FATH TRADING
	INSULET MIX 100 U.I 10 ML INJ	SOTHEMA	MOR0CCO	BAWAM FOR DRUDS
	JUSULINE 30/70 100 U.I 10 ML INJ	JULPHAR	UAE	ARD AL-GANATAIN
	AL-KHALIL FOR DRUGS	SYRIA	ASIA	INSULIN MIX 100 U.I 10 ML INJ
	ARRAAFAH CORP	DENMARK	NOVO NORDISK	MIXTRAD 300UNIT/ ML 3 ML PENFILL INJ

	Glibenclamide			
	Daonil 5 Mg Tab **Original	Sanofi-Aventis	France	Al-Subbary Corp
	Daonil 5 Mg Tab	Sanofi-Aventis	EGYPT	Al-Subbary Corp
	Glibenclamide 5 Mg Tab	Worckhardt	Uk	Al-Hilal Ph
	Stadoanail 5 Mg Tab	Standard	Korea	Al-Maydan
	Clamide 5 Mg Tab	Hovid	Malaysia	Al-Shefa For Importing
	Glynase 5 Mg Tab	JULPHAR	Uae	Ard Al-Gmanatain
	Glitisol 5 Mg Tab	Rimedica	Cyprus	Alawi Almehdar
	Dwabetic 5 Mg Tab	Mpi	Yemen	Mpi
	Diabecare 5 Mg Tab	Pharmacare Int Mfg	Yemen	Pharmacare
	Glicon 5 Mg Tab	Efroz	Pakistan	Al-Razi Drug Centre
	Herbal Products			
	Diabcon Tab	Himalaya Drug Co	India	Al-Mufhadal Pharma
	Gliclazide			
	Diamicron 80 Mg Tab **Original	Servier	Egypt	Arra Afah Corp
	Debacron 80 Mg Tab	Dic	Jordan	Ard Al-Ganatain
	Gliclazide 80 Mg Tab	Wockhardt	Uk	Al-Hilal Ph
	Dianormal 80 Mg Tab	Rameda	Eaypt	Apc
	Glyzide 80 Mg Tab	Julphar	UAE	Ard Al-Ganatain
	Licla 80 Mg Tab	Daewon Pharma	Korea	Al-Nedari Co.
	Emicron 80 Mg Tab	Global Pharma	UAE	Al-Nahdi Medical Co
	Gligard 80 Mg Tab	Amriya Pharma	Egypt	Apc
	Diamicron 30 Mg Mrtab	Servier	Egypt	Arra Afah Corp
	Glimepiride		**Pregnancy (Category C)**	

	Amaryl 1 Mg Tab **Original	Sanofi-Aventis	France	Al-Subbary Corp
	Glorion 1 Mg Tab	Hikma	Jordan	Ard Al-Ganatain
	Glimadel 1 Mg Tab	Delta	India	Al-Jabal For Drugs
	Sokratec 1 Mg Tab	Neo Pharma	UAE	Al-Mufhadal Pharma
	Diapred 1 Mg Tab	Sedico Pharma	Egypt	Al-Harith Corp
	Glimicip 1 Mg Tab	Cipla	India	Al-Jabal For Drugs
	Gluconorm 1 Mg Tab	Cedilla Pharma	India	Al-Jabal For Drugs
	Amaryl 2 Mg Tab **Original	Sanofi-Aventis	France	Al_Subbary Corp

	Amaryl 2 Mg Tab	Sanofi-Aventis	Egypt	Al_Subbary Corp
	Glimipride-Denk 2 Mg Tab	Denk Pharma	Germany	Al-Ghazali Trading
	Glimaryl 2 Mg Tab	Yep	Yemen	Natco Pharma
	Diabito 2 Mg Tab	Hi Pharma	Egypt	Garnada Trading Trading
	Glimcip 2 Mg Tab	Cipla	India	Al-Jabal For Drugs
	Glorion 2 Mg Tab	Hikma	Jordan	Ard Al-Ganatain
	Glemax 2 Mg Tab	Joswe Medicl	Jordan	Apc
	Diapred 2 Mg Tab	Sedico Pharma	Egypt	Al-Harith Corp
	Sokratec 2 Mg Tab	Neo Pharma	UAE	Al-Mufhadal Pharma
	Glimulin – 2 Mg Tab	Glenmark	India	Al-Garash For Trading
	Glimadel 2 Mg Tab	Delta	Egypt	Arbic Gulf
	Glirid 2 Mg Tab	Mpl	Yemen	Mpt
	Gluconorm 2 Mg Tab	Cedilla Pharma	India	Al-Jabal For Drugs
	Ampride 2 Mg Tab	Specific Shaphaco	Yemen	Specific Shaphaco
	Glimicip 2 Mg Tab	Cipla	India	Al-Jabal For Drugs
	Amaryl 3 Mg Tab **Original	Sanofi-Aventis	France	Al-Subbary Corp
	Amaryl 3 Mg Tab		Egypt	Al-Subbary Corp
	Glimipride-Denk 3 mg Tab	Denk pharma	germany	Al-ghazali Trrading
	Glemax 3 mg Tab	Joswe medical	jordan	apc
	Glorion 3 mg Tab	hikma	jordan	Ard al-ganatain
	Diapred 3 mg Tab	sedicopharma	Egypt	Al-harith corp
	Glimaryl 3 mg Tab	yep	yemen	Natco pharma
	Skoratec 3 mg Tab	Neo pharma	uae	Al-mufhadal pharma
	Glimadel 3 mg Tab	delta	egypt	Arabic gulf
	Glirid 3 mg Tab	mpi	yemen	mpi
	Glorion 4 mg Tab	hikma	jordan	Ard al-ganatain
	Glemax 4 mg Tab	Joswe medical	jordan	Apc
	Glemax 6 mg Tab	Joswe medical	jordan	Apc
	Glibenclamide = Metformin		**Pregnancy (Category B)**	

	Glucovance 500/5 mg Tab	MERCK SERONO	Germany	Ard Al-Ganatain
	Emivanz 500/5 mg Tab	GLOBAL PHARMA	UAE	Al-Nahdi Medicl Co
	Glivance 400/2.5 Tab	MARCYRL	Egypt	Al-Fath Trading Co Ltd.
	Glucovance 500/2.5 mg Tab	MERCK SERONO	Germany	Ard Al-Ganatain
	Emivanz 500/2.5 mg Tab	GLOBAL PHARMA	UAE	Al-Nahdi Medical Co
	Diformin 500/2 mg Tab	MPI	Yemen	Mpi
	Glibenclamide + Metformin			
	Amaryl M 2/500 mg Tab	Sanofi-Avrntis	France	Al-Subbary Corp
	M.O.A:> Decrease			
	Pioglitazone HCL		Pregnancy (Category C)	
	Actos 30 mg Tab	Apm	Jordan	Apc
	Glifix 30 mg Tab	Bilim	Turkey	Al-Mufhada Lpharma
	Actazon 30 mg Tab	Asia	Syria	Alfurqan Pharma
	Pioglit 30 mg Tab	Sun pharma	India	Al-Rahma Trading
	Glifix 15 mg Tab	Bilim	Turkey	Al-Mufhadal Pharma
	Actos 15 mg Tab	APM	Jordan	Apc
	Pioglit 15 mg Tab	Sun pharma	India	Al-Rahma Trading
	Rosiglitazone Maleate + Metformin		**Pregnancy (Category C)**	
	Avandamet 2/500 14 Tab **original	GSK	UK	Arra Afah Cop
	Drugs M.O.A:>			
	Repaglinide		**Pregnancy (Category C)**	
	Novonorm 0.5 mg Tab **original	Novo		Arra Afah Cop

(B Al-meri. 2014)

revealed no significant differences in pharmacokinetics, and the intraindividual variability was very low. There was no relevant accumulation.

Special populations

Pharmacokinetics were similar in males and females, as well as in young and elderly (above 65 years) patients. In patients with low creatinine clearance, there was a tendency for glimepiride clearance to increase and for average serum concentrations to decrease, most probably resulting from a more rapid elimination because of lower protein binding. Renal elimination of the two metabolites was impaired. Overall no additional risk of accumulation is to be assumed in such patients.

Pharmacokinetics in five non-diabetic patients after bile duct surgery were similar to those in healthy persons. (Sanofi-aventis,2013).

Paediatric population

 A fed study investigating the pharmacokinetics, safety, and tolerability of a 1 mg single dose of glimepiride in 30 paediatric patients (4 children aged 10-12 years and 26 children aged 12-17 years) with type 2 diabetes showed mean AUC(0-last), Cmax and t1/2 similar to that previously observed in adults. (sanofi-aventis,2013).

1. TREATMENT OF COMPLICATIONS

 Retinopathy

Patients with established retinopathy should be examined by anophthalmologist at least every 6 to 12 months.

Early retinopathy may reverse with improved glycemic control. More advanced disease will not regress with improved control and may actually worsen with short-term improvements in glycemia.

 Laser photocoagulation. **(**B.WELL 2009).

 Neuropathy

Peripheral neuropathy is the most common complication in type 2 DM outpatients The feet are involved far more often than the hands. Improved glycemic control may alleviate some of the symptoms.

 Pharmacologic therapy is symptomatic and empiric, including low- dose **tricyclic antidepressants**, anticonvulsants (e.g., **gabapentin, pregabalin, carbamazepine**), **duloxetine, venlafaxine** and various analgesics, including **tramadol** and **nonsteroidal antiinflammatory drugs**.

 Nephropathy

 Glucose and blood pressure control are most important for prevention of nephropathy, and blood pressure control is most important for retarding the progression of established nephropathy.

 Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have shown efficacy in preventing the clinical progression of renal disease in patients with type 2 DM.

 Diuretics as second lines.

 Peripheral Vascular Disease and Foot Ulcer

Smoking cessation, correction of dyslipidemia, and antiplatelet therapy are important treatment strategies.

 Pentoxifylline (Trental) or **cilostazol** (Pletal) may be useful in Selected patients.

Local debridement and appropriate footwear and foot care are important in the early treatment of foot lesions.

 Topical treatments may be beneficial in more advanced lesions.

 Coronary Heart Disease
Treatment of dyslipidemia and hypertension, smoking cessation, antiplatelet therapy reduces macrovascular events. (B.WELL 2009).

 Drug use
A. Statin
Recommend goal of blood pressure of <130/80 mm Hg in patients with DM.

B. Angiotensin-converting enzyme inhibitors and **angiotensin receptor blockers** are generally recommended for initial therapy.
 Many patients require multiple agents, so diuretics, calcium channel blockers, and β-**blockers** are useful as second and third agents.

Evalution of Therapeutic Outcomes
The A1C should be measured at least twice a year Monitor symptoms such as polyuria, polydipsia, and weight gain or loss Patients receiving insulin should be questioned about the recognition of hypoglycemia at least annually Documentation of frequency of hypoglycemia and the treatment required should be recorded.

Patients with type 2 DM should have a routine urinalysis at diagnosis as the initial screening test for albuminuria Fasting lipid profiles annually if stable and at goal
❖ Regular frequency of foot exams (each visit).
❖
Ophthalmologic exams (yearly or more frequently if
❖ stable.

 Assessment for influenza and pneumococcal vaccine administration Assessment and management of other cardiovascular risk factors (e.g smoking and antiplatelet therapy).

From the previous study, and the complication of DM if it is not controlled and the importance of sulfonyl urea group for DM type2 and glimepiride as one of potent drug available in market. So, in this study formulate a new sublingual tablet for imergency cases to prevent hyperglycemia coma and of the same time to evaluate the potency of the Yemeni glimepride.

METHODOLOGY

Materials
Glimipride RS was obtained from Cipala Pharmaceuticals Ltd. Mumbai, acetonitile from alpha chemika, India; sodium di-hydrogen phosphate, phosphoric acid, and methanol obtained from Merck.

Methods
1. Chemical test
Assay test was done using HPLC method as the following:

Mobile phase preparation
Sodium di-hydrogen phosphate 0.5 gm was dissolved in 500ml distilled water, adjust the PH to 2.4 with H3PO4 and add 500 ml of Acetonitrile, mix well and filtered through 0.45µm micro membrane filter.

HPLC conditions
Column: ODS1(C18) 15* 0.45cm, flow rate: 1.0 ml/min, wavelength: 220nm, sensitivity: 1, pressure: 28 Mpa.

Preparation of standard solution
Weigh accurately equivalent to 21 mg of Glimepiride RS into 100 V.F and dissolve then dilute to volume with Acetonitrile solution 80% and mix well to get concentration at (0.21mg /ml).

Preparation of sample solution
Transfer 7 tablets (equivalent to 21 mg of Glimepiride) into 100 V.F and dilute to volume with acetonitrile solution 80% and mix well to get concentration. Sonicate for 10 minutes and filter to get (0.21 mg/ml).[14]

2. Physical test
1- **Micrometrics**: thickness and diameter of tablet are measured using micrometrics.

Procedure: measure the thickness and diameter of 10 tabs.

Limits: diameter should be less than 13 mm.

2- Weight variation
Procedure
Weight 20 tablet of each drug
1) Calculate higher limit (H.L) and lower limit (L.L):
2) Average wt = total wt /20
Average wt × 5% =n
H.L = Av. Wt + n
L.L = Av. Wt - n [14]
3) Weight Variation: - for the three drugs

3- Friability
Procedure
1) Weight the tablet (w1)
2) Rotate them in the instrument for 4mint and then weight again (w2)
3) Calculate :-

$$\text{Friability} = \frac{w1-w2}{w1} \times 100$$

Limit for compressed tablet:- not more than 1%.[13]

4- Hardness
❖ **Procedure**
1) Put the tablet in specific place and fix.
2) Turn on and wait unit the fraction occurs.

3) Write the reading of scale.
4) Repeat for 10 tablet.
5) Limit is 4 – 8 kg /cm^2.[14]
6) Complete the tablet.

5- Disintegration

❖ **Procedure**

1) Put the 6 tablet in the device to test disintegration, each one tablet is placed in each basket and basket is positioned in beaker of water at 37±2 c°.
2) Move the basket up and down until complete break into particles.
3) Record time.
4) Limit uncoated tablet is 5 – 30 minutes.[14]

STATISTICAL ANALYSIS

Data were presented as means ± standard deviation (SD). A computer program (excel 2010) was used for statistical analysis. A T-test and The one-way ANOVA were performed to examine the differences among the groups. A P value of <0.05 was considered to be statistically significant.

RESULTS AND DISCUSSION

A- Chemical test

Table (1) shows the results of chemical tests for each brand of glimpride compared to the reference:

Assay	Glimaryl	Amaryl	Brand A
	104.20%	100.50%	96.60%

The assay of brand A is within the lower limit that is confirmed by presence of hardness. While the other Yemeni product Glimaryl are significant to result of reference drug Amaryl.

B- Physical test

1- Micrometrics

Table (2) shows the values of diameter and thickness for each brand of glimipride compared to the reference:

No.of tab	Glimaryl		Amaryl		Brand A	
	Diameter	Thickness	Diameter	Thickness	Diameter	Thickness
1	10.11	3.73	10.2	3.77	10.11	3.55
2	10.12	3.72	10.18	3.78	10.1	3.65
3	10.1	3.67	10.18	3.79	10.14	3.65
4	10.1	3.73	10.2	3.76	10.15	3.67
5	10.12	3.72	10.2	3.76	10.15	3.65
6	10.1	3.69	10.2	3.78	10.15	3.6
7	10.1	3.73	10.2	3.81	10.11	3.65
8	10.12	3.76	10.18	3.79	10.15	3.64
9	10.12	3.67	10.18	3.8	10.13	3.63
10	10.12	3.72	10.18	3.79	10.1	3.59
Total	101.11	37.14	101.9	37.83	101.29	36.28
Average	10.111	3.714	10.19	3.783	10.129	3.628
STD	0.00994429		0.01054093		0.0218327	

Limit of Diamiter → less than 13 mm *(pharmacopoeia, B.2009)*

The diameter of Yemeni products (Glimaryl, brand a) are significant to result of Amaryl as STD drug.

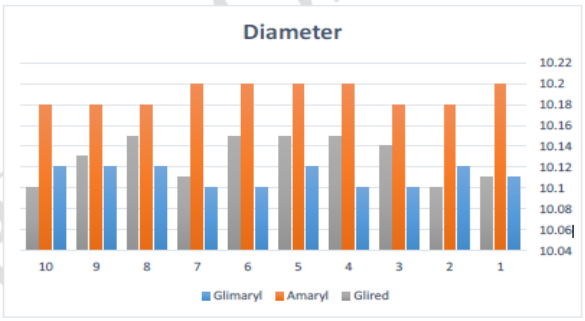


Figure 3 Diameter

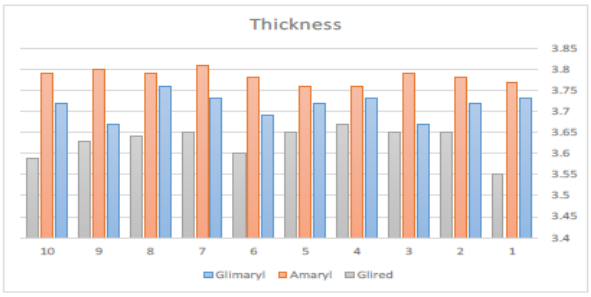


Figure 4 Thickness

2- Weight variation

Table (3) shows the results of weight variation test for each brand of glimipride tablets compared to the reference drug

No	Glimaryl		Amaryl		Brand A		
	Weight of tab	Rang	Weight of tab	Rang	Weight of tab		Rang
1	0.1676	(0.1716 – 0.1554)	0.1669	(0.1762 – 0.1596)	0.1653		(0.1697 – 0.1537)
2	0.1639		0.168		0.1634		
3	0.1644		0.1676		0.1596		
4	0.1625		0.167		0.1526	Rejected	
5	0.1636		0.1687		0.166		
6	0.1625		0.1673		0.178	Rejected	
7	0.1654		0.168		0.16		
8	0.1633		0.1688		0.1644		
9	0.162		0.1679		0.1589		
10	0.1645		0.169		0.1544		
11	0.1608		0.1672		0.1542		
12	0.1628		0.169		0.1529	Rejected	
13	0.163		0.1673		0.1623		
14	0.1641		0.1684		0.1562		
15	0.1603		0.169		0.16		
16	0.1646		0.1685		0.1773	Rejected	
17	0.163		0.1669		0.1604		
18	0.1639		0.1674		0.1566		
19	0.164		0.1678		0.177	Rejected	
20	0.1644		0.1678		0.1605		
∑	3.2706		3.3585		3.24		
Average	0.16353		0.167925		0.162		

The weight varation of brand a is within the out of limit because presence of five tablet are rejected that is confirmed by presence of the assay. While the other Yemeni product Glimaryl is the same as the reference drug Amaryl.

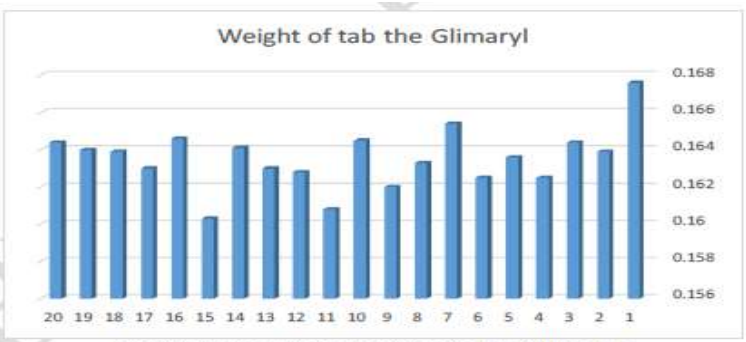


Figure 5 weight of varation to the Glimaryl

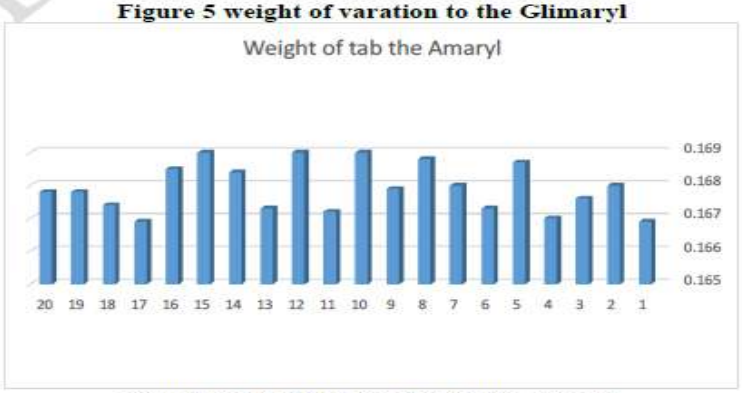


Figure 6 weight of varation to the Amaryl

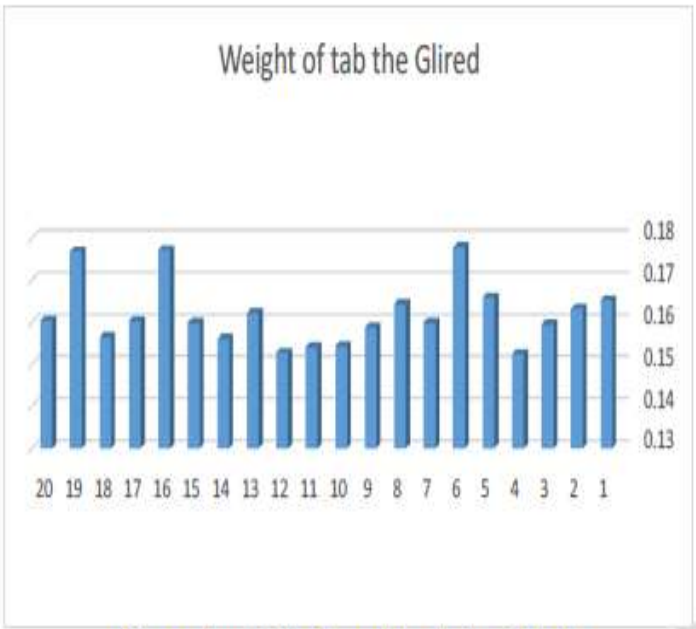


Figure 7 weight of varation to the Glired

1- Friability

Table (4) shows the results of friability test for each brand of glimipride tablets compared to the reference drug

Friability	Glimaryl	Amaryl	Brand A
	0.02%	0.02%	0.99%

The friability of brand A is within the upper limit that is confirmed by presence of weight variation and hardness. While the other Yemeni product Glimaryl is the same as the reference drug Amaryl.

2- Hardness

Table (5) shows the results of hardness test for each brand of glimipride tablets compared to the reference drug (Amaryl)

No. of	Glimaryl Result	Amaryl Result	Brand A Result
1	6.96	5.35	2.68
2	7.98	2.99	3.06
3	9.51	4.28	3.32
4	7.39	3.29	4.89
5	7.37	4.06	1.74
6	9.89	3.7	4.75
7	6.69	4.13	3.17
8	8.83	3.05	3.99
9	9.65	5.3	10.33
10	8.89	3.81	3.24
Limit 4 – 8 kg			

The hardness of the all product are rejected because it is out of limit but the Yemeni product Glimaryl is better than other Yemeni product brand a due to same as the reference drug Amaryl and the other Yemeni product Glired is height variance in result.[14]

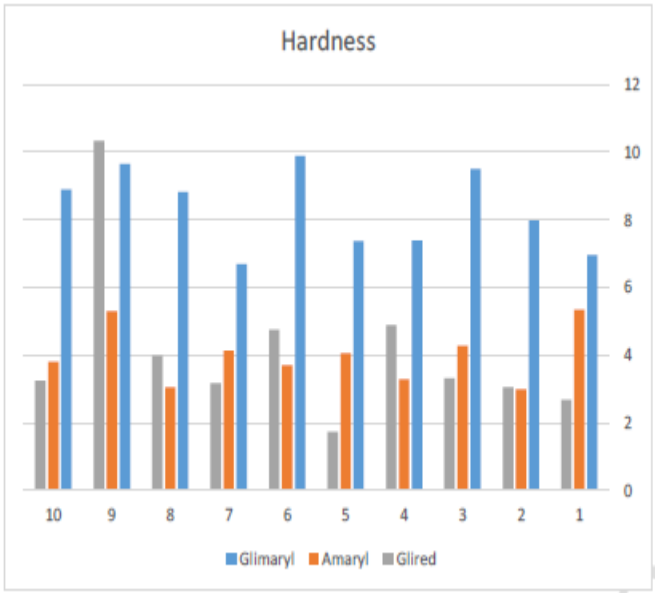


Figure 8 Hardness

3- Disintegration

Table (6) shows the results of disintegration time for each brand of glimipride tablets compared to the reference drug.

Time	Glimaryl	Amaryl	Brand A
	3.9 min	1.15 min	28 s

The results of the Yemeni glimepride showed different activity as the assay of brand a give low limit of activity with 96.6 as the limit is 90-110 so the activity may decrease with time even before the expire data whereas

the assay of other Yemeni product glimaryl give high assay 104.2% which is close to amaryl and also much better and when the other physical test confirm the result as the hardness activity of glired give big difference in hardness with brand a while the glimaryl and amaryl give good results with disintegration and hardness as well as the weight variation.

CONCLUSION

According to quality control tests of Brand A (Yemeni product) give the minimum disintegration time but the tablets was friable so the hardness test were rejected as well as the weight variation. The hardness of brand A gave significant difference with amaryl that make the product is not accepted.

The glimaryl (another Yemeni product) showed non-significant difference with amaryl and close weight and weight variation. Glimaryl can be best alternative and comparative to the amaryl. That make the Yemeni product is good product and formulation to be used.

ACKNOWLEDGMENT

The Authors are gratful to the department of Pharmacy, Faculty of medical sciences, Yemeni Jordanian University for supply of all basic requirements of this search.

REFERENCE

1. Wells B, DiPiro J, schwinghammer T. pharmacotherapy handbook 7th edition by the McGraw- hill companied, 2009.
2. Triplitt CL, Reasner CA. "Chapter 83: diabetes mellitus". In DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. Pharmacotherapy: a pathophysiologic approach (8th ed.). New York, NY: McGraw-Hill, 2011; 1274. ISBN 0-07-170354-3.
3. Davidson J. Clinical diabetes mellitus: a problem-oriented approach. Stuttgart: Thieme, 2000; 422. ISBN 0-86577-840-X.
4. Shaughnessy AF, Slawson DC. "What happened to the valid POEMs? A survey of review articles on the treatment of type 2 diabetes". BMJ, 2003; 327(7409): 266.doi:10.1136/bmj.327.7409.266. PMC 167157. PMID 12896940.
5. Hemmingsen B, Schroll JB, Lund SS, Wetterslev J, Gluud C, Vaag A, Sonne DP, Lundstrøm LH, Almdal T. "Sulphonylurea monotherapy for patients with type 2 diabetes mellitus". Cochrane Database Syst Rev., 2013; 4: CD009008. doi:10.1002/14651858.CD009008.pub2. PMID 23633364.
6. Hemmingsen, B; Lund, SS; Gluud, C; Vaag, A; Almdal, TP; Hemmingsen, C; Wetterslev, J. "Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus.". The Cochrane database of systematic reviews, Nov 11, 2013; 11: CD008143. PMID 24214280.
7. Hemmingsen, B.; Lund, S. S.; Gluud, C.; Vaag, A.; Almdal, T.; Hemmingsen, C.; Wetterslev, J. "Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials". BMJ, 24 November 2011; 343(nov24 1): d6898–d6898. doi:10.1136/bmj.d6898.
8. Bolen, Shari. "Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus". Annals of Internal Medicine, 18 September 2007; 147(6): 386. doi:10.7326/0003-4819-147-6-200709180-00178.
9. Monami, M.; Genovese, S.; Mannucci, E. "Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials". Diabetes, Obesity and Metabolism, October 2013; 15(10): 938–953. doi:10.1111/dom.12116.
10. Maedler, K; Carr, RD; Bosco, D; Zuellig, RA; Berney, T; Donath, MY. "Sulfonylurea induced beta-cell apoptosis in cultured human islets.". The Journal of clinical endocrinology and metabolism, Jan 2005; 90(1): 501–6. PMID 15483097.
11. Takahashi, A; Nagashima, K; Hamasaki, A; Kuwamura, N; Kawasaki, Y; Ikeda, H; Yamada, Y; Inagaki, N; Seino, Y. "Sulfonylurea and glinide reduce insulin content, functional expression of K(ATP) channels and accelerate apoptotic beta-cell death in the chronic phase.". Diabetes research and clinical practice, Sep 2007; 77(3): 343–50. PMID 17316868.
12. Eurich, DT; Simpson, SH; Majumdar, SR; Johnson, JA. "Secondary failure rates associated with metformin and sulfonylurea therapy for type 2 diabetes mellitus.". Pharmacotherapy, Jun 2005; 25(6): 810–6. PMID 15927899.
13. Haberfeld, H, ed. (2009). Austria-Codex (in German) (2009/2010 ed.). Vienna: Österreichischer Apothekerverlag. ISBN 3-85200-196-X.
14. Dinnendahl, V.; Fricke, U., eds. Arzneistoff-Profile (in German) 4 (23 ed.). Eschborn, Germany: Govi Pharmazeutischer Verlag, 2010. ISBN 978-3-7741-9846-3.
15. Jump up^ Greeley SA, Tucker SE, Naylor RN, Bell GI, Philipson LH. "Neonatal diabetes mellitus: a model for personalized medicine". Trends Endocrinol. Metab, 2010; 21(8): 464–doi:10.1016/j.tem.2010.03.004. PMC 2914172. PMID 20434356.
16. Janbon M, Chaptal J, Vedel A, Schaap J. "Accidents hypoglycémiques graves par un sulfamidothiodiazol (le VK 57 ou 2254 RP)". Montpellier Med, 1942; 441: 21–22.
17. Patlak M. "New weapons to combat an ancient disease: treating diabetes". FASEB J., 2002; 16(14): 1853. doi:10.1096/fj.02-0974bkt. PMID 12468446.
18. Sanofi-aventis Canada Inc. 2905 place Louis R.-Renaud. Laval, Quebec H7V 0A3. September 10, 2013.

19. Pharmacopeia, B. "British pharmacopoeia commission office. "London, UK, 2009; 2: 1078-1080.
20. Al – meri B(2014) modern drug index yemen pharmacy world group.