Evaluation of Pharmaceutical Equivalence of Two Different Brands (Limaryl and Dactus) of Glimepiride Tablets (2mg) Available in Bangladesh

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A thesis report, submitted to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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Declaration by the Research Candidate

I, **Bibi Moriom Tuli**, hereby declare that the dissertation entitled "Evaluation of Pharmaceutical Equivalence of Two Different Brands (Limaryl and Dactus) of Glimepiride Tablets (2 mg) Available in Bangladesh" submitted to the Department of Pharmacy, East West University, in the partial fulfillment of the requirement for the award of the degree Bachelor of Pharmacy is a bonafied record of original research work carried out by me, under the supervision and guidance of **Ms. Nigar Sultana Tithi**, Senior Lecturer, Department of Pharmacy, East West University and the dissertation has not formed the basis for the award of any other degree/diploma/fellowship or other similar title to any candidate of any university.

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Certificate by the Supervisor

This is to certify that the dissertation entitled "Evaluation of Pharmaceutical Equivalence of Two Different Brands (Limaryl and Dactus) of Glimepiride Tablets (2 mg) Available in Bangladesh" submitted to the Department of Pharmacy, East West University, Dhaka, in partial fulfillment of the requirements for the Degree of Bachelor of Pharmacy, was carried out by Bibi Moriom Tuli, ID: 2011-1-70-059 under my supervision and no part of this dissertation has been or is being submitted elsewhere for the award of any Degree/Diploma.

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Endorsement by the Chairperson

This is to certify that the thesis entitled "Evaluation of Pharmaceutical Equivalence of Two Different Brands (Limaryl and Dactus) of Glimepiride Tablets (2 mg) Available in Bangladesh" submitted to the Department of Pharmacy, East West University, Aftabnagar, Dhaka-1219 in partial fulfillment of the requirement for the degree of Bachelor of pharmacy was carried out by Bibi Moriom Tuli, ID# 2011-1-70-059.

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This Research Paper is

Dedicated

To

My Beloved Parents

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF EQUATIONS

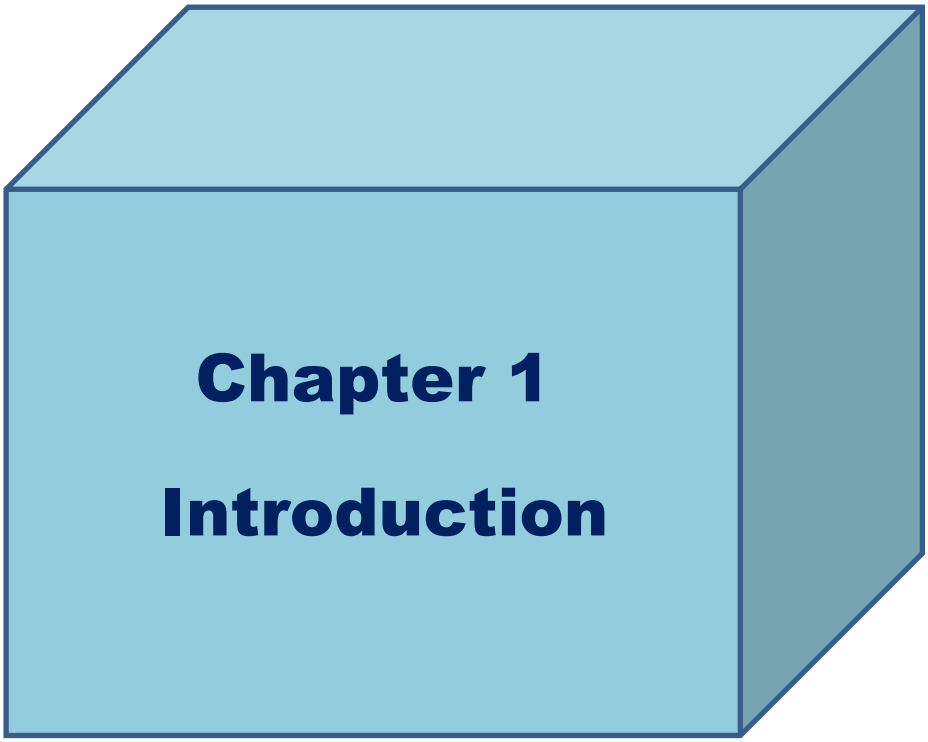
LIST OF ACRONYMS

ACRONYMS	EXPANSIONS
IDDM	Insulin Dependent Diabetes Mellitus
NIDDM	Non-insulin Dependent Diabetes Mellitus
GDM	Gestational Diabetes Mellitus
MODY	Maturity-Onset Diabetes of the Young
DM	Diabetes Mellitus
SUR1	Sulfonylurea Receptor 1
HBA1c	Glycosylated HB
FPG	Fasting Plasma Glucose
IFG	Impaired Fasting Glucose
OGTT	Oral Glucose Tolerance Testing
ADME	Absorption, Distribution, Metabolism & Elimination
AUC	Area Under the Curve
VD	Volume of Distribution
CL	Clearance
NSAID	Non-steroidal Anti-inflammatory Drugs
t.i.d	Three Times a Day
UV-VIS	Ultraviolet-visible spectrophotometry
WHO	WHO World Health Organization
USP	United States Pharmacopeia
BP	British Pharmacopeia
FDA	Food and Drug Administration

Abstract

An important aspect of the development of any pharmaceutical product is to maintain the quality standards of the product. This research work is aimed to investigate the pharmaceutical equivalence of two different brands of glimepiride (2mg) tablets available in the Bangladeshi market. In this study tablets of two batches of each brand (Limaryl and Dactus) were collected from local market. Quality control tests were performed for evaluation of hardness, thickness, weight variation, disintegration time, dissolution and potency of the tablets from each brand according to the specification of USP and BP. All the batches showed weight variation within the range of ±10% and thickness test was within acceptance limit in accordance of USP (±5%) . Hardness value of these two brands is within 2 kg, which is lower than standard range specified by USP (4kg). Less hardness may cause breakage of tablets during storage and transportation. Disintegration time of all the batches was within acceptance range of 15 minutes. All the batches had dissolution rate below the range and did not fulfill the specification. According to the BP and USP the acceptance level of percent potency of active drug lies from 100 ± 10% or 90-110%.These two brands had the percent potency greater than the range. So, more batches of these two brands should be required to carry out the dissolution and potency test according to BP and USP. Friability test could not be carried out due to some mechanical defect in the instrument. So further research study should be convey on these two brands to check whether they meet the specification or not.

Keywords: Diabetes, Glimepiride, Weight variation test,Hardness test, Thickness test, Disintegration test, Dissolution test, Assay.


Chapter 1
Introduction

Chapter 1: Introduction

1.1 Diabetes

Diabetes is a long-term condition that causes high blood sugar levels. Diabetes referred as diabetes mellitus, which is a group of metabolic diseases in which the person has high blood glucose (blood sugar), either because insulin production is inadequate, or the body's cells do not respond properly to insulin, or both. Patients with high blood sugar will typically experience polyuria (frequent urination), they will become increasingly thirsty (polydipsia) and hungry (polyphagia).

Diabetes mellitus is a chronic disease associated with abnormally high levels of the sugar glucose in the blood. Diabetes is due to one of two mechanisms,

- ✓ Inadequate production of insulin (which is made by the pancreas and lowers blood glucose), or
- ✓ Inadequate sensitivity of cells to the action of insulin. (Mycek *et al.*, 1997)

1.1.1 Types of Diabetes

There are three different types of diabetes,

1. Type 1 Diabetes (Insulin dependent diabetes mellitus, IDDM)
2. Type 2 Diabetes (Non-insulin dependent diabetes mellitus, NIDDM)
3. Gestational Diabetes

Other types of diabetes is Maturity-onset diabetes of the young (MODY) includes several forms of diabetes with monogenetic defects of beta-cell function (impaired insulin secretion), usually manifesting as mild hyperglycaemia at a young age, and usually inherited in an autosomal-dominant manner. (Katzung *et al.*, 2010).

1.1.1.1 Type 1Diabetes Mellitus

Type 1 diabetes is a lifelong (chronic) disease in which there is a high level of sugar (glucose) in the blood. In Type 1 diabetes, the body's immune system attacks and destroys the cells that produce insulin. More than 90% of the insulin -producing cells of the pancreas are permanently destroyed. So insulin is not produce and increase glucose levels, which can seriously damage the body's organs.

Type 1 diabetes is often known as insulin-dependent diabetes. Sometimes known as juvenile diabetes or early-onset diabetes because it usually develops before the age of 40, often during the teenage years.

Type 1 diabetes accounts for 5 to 10 out of 100 people who have diabetes. In type 1 diabetes, the body's immune system destroys the cells that release insulin, eventually eliminating insulin production from the body. Without insulin, cells cannot absorb sugar (glucose), which they need to produce energy. (WebMD, 2015)

Patients with type 1 diabetes mellitus (DM) require lifelong insulin therapy. Most require 2 or more injections of insulin daily, with doses adjusted on the basis of self-monitoring of blood glucose levels. (Medscape.com, 2015)

Risk Factors of Type 1 Diabetes Mellitus

- **Genetics:** The presence of certain genes indicates an increased risk of developing type 1 diabetes
- **Family history**: Anyone with a parent or sibling with type 1 diabetes has a slightly increased risk of developing the condition.
- **Age:** Although type 1 diabetes can appear at any age, it appears at two noticeable peaks. The first peak occurs in children between 4 and 7 years old, and the second is in children between 10 and 14 years old.
- Being born with jaundice
- Exposure to certain viruses, such as the Epstein-Barr virus, Coxsackie virus, mumps virus and cytomegalovirus
- Early exposure to cow's milk
- Low vitamin D levels
- Drinking water that contains nitrates
- Having a mother who had preeclampsia during pregnancy. (Mayoclinic, 2015)

Management of Type 1 Diabetes Mellitus

Insulin therapy for most patients with type 1 diabetes:

Insulin therapy for most patients with type 1 diabetes:
• Treat with multiple-dose insulin injections (3-4 injections/day of basal and prandial insulin) or continuous subcutaneous insulin infusion.
• Match prandial insulin dose to carbohydrate intake, premeal blood glucose, andanticipated activity.
• Use insulin analogs to reduce risk of hypoglycemia.
Metformin + insulin
• Reduces insulin requirements and improves metabolic control in obese/overweight subjects with poor glycemic control

Types of Insulin

Insulin acts to reduce the level of glucose into the blood. When glucose is at its lowest level, the effect of the insulin have reached its 'peak' level. People's need for insulin varies according to their body's reaction to insulin (which differs from person to person) as well as their lifestyle, including their exercise and eating patterns.(Joslin.org, 2015)

Table 1.1: Classification of Insulin

Fast Acting Insulin	Fast acting insulins are clear in appearance. These insulins: • Are very fast acting start working from 1 to 20 minutes • Peak approximately one hour later • Last from 3 to 5 hours. .
Short Acting Insulin	Short acting insulins are clear in appearance. These insulins: • Begin to lower blood glucose levels within half an hour. so injection should be given half an hour before eating • Peak effect at 2 to 4 hours

	• Last for 6 to 8 hours.
Intermediate Acting Insulin	Intermediate acting insulins are cloudy in appearance. They have either protamine or zinc added to delay their action. These insulins: • Begin to work about 1 1/2 hours after injecting • Peak at 4 to 12 hours • Last for 16 to 24 hours. Before injecting this type of insulin, The leaflet should be check inside the pack for instructions on how to prepare the insulin.
Mixed Insulin	Mixed insulins are cloudy in appearance. They contain pre-mixed combinations of either a fast acting or a short acting insulin and intermediate acting insulin, making it easier by giving two types of insulin in one injection. If the insulin is '30/70' then it contains 30% fast acting and 70% intermediate acting insulin. '50/50' is 50% of each. This insulin can be taken before a meal to meet the increase in blood glucose levels and provide a stable level of insulin for some hours after the meal. Before injecting this type of insulin, check the leaflet inside the pack for instructions on how to prepare the insulin.
Long Acting Insulin	Long acting insulins are clear in appearance. They typically have no pronounced peak and last for up to 24 hours.

(Joslin.org, 2015)

1.1.1.2 Type 2Diabetes Mellitus

Type 2 diabetes, also called adult-onset diabetes, can affect people at any age, even children. Type 2 diabetes develops most often in middle-aged and older people. People who are overweight and inactive are also more likely to develop type 2 diabetes.

Type 2 diabetes mellitus, a disorder of impaired insulin secretion and insulin resistance. It usually begins with insulin resistance a condition that occurs when fat, muscle, and liver cells do not use insulin to carry glucose into the body's cells to use for energy. As a result, the body needs more insulin to help glucose enter cells. At first, the pancreas keeps up with the added demand by making more insulin. But the pancreas doesn't make

enough insulin when blood sugar levels increase, such as after meals. If pancreas can no longer produce enough insulin, then a person will need to treat type 2 diabetes. (Mycek *et al.,* 1997)

Risk Factors for Type 2 Diabetes Mellitus

People type 2 diabetes are more likely to have the following risk factors:

- Physically inactive
- Impaired glucose tolerance
- Parent or sibling with diabetes
- Family background
- Obesity
- History of giving birth to a baby weighing more than 9 pounds
- History of gestational diabetes
- Poor nutrition during pregnancy
- High blood pressure 140/90 or above or being treated for high blood pressure
- High-density lipoprotein (HDL), or good cholesterol below 35 milligrams per deciliter (mg/dl), or a triglyceride level above 250 mg/dl
- Polycystic ovary syndrome (Tidy, 2015)

Managing of Type 2 Diabetes

- Using diabetes medicines
- Making healthy food choices
- Being physically active
- Blood pressure levels should be Control
- Cholesterol level should be control (Tidy, 2015)

1.1.1.3 Gestational Diabetes

Gestational diabetes mellitus (GDM) is a condition that develops during pregnancy when the body is not able to make enough insulin. The lack of insulin causes the blood glucose level to become higher than normal. Gestational diabetes affects between 2 and 10 percent of women during pregnancy.

It is important to recognize and treat gestational diabetes as soon as possible to minimize the risk of complications to mother and baby. In addition, it is essential for women with a

history of gestational diabetes to be tested for diabetes after pregnancy because of an increased risk of developing type 2 diabetes in the years following delivery.

Pregnant women make hormones that can lead to insulin resistance. All women have insulin resistance late in their pregnancy. If the pancreas doesn't make enough insulin during pregnancy, a woman develops gestational diabetes.

Overweight or obese women have a higher chance of gestational diabetes. Also, gaining too much weight during pregnancy may increase chance of developing gestational diabetes.

Gestational diabetes most often goes away after the baby is born. However, a woman who has had gestational diabetes is more likely to develop type 2 diabetes later in life. Babies born to mothers who had gestational diabetes are also more likely to develop obesity and type 2 diabetes. (Mycek *et al.*, 1997)

Risk Factors of Gestational Diabetes

- A history of gestational diabetes in a previous pregnancy
- Obesity
- Glucose (sugar) in urine
- A strong family history of diabetes
- History of giving birth big babies (over 9 pounds)
- High blood pressure
- Excess amniotic fluid (called polyhydramnios)
- History of unexplained miscarriage or stillbirth
- Personal history of gestational diabetes
- Being African American, Hispanic, American Indian, Alaska Native, Native Hawaiian, or Pacific Islander(Muller, 2004)

Managing Gestational Diabetes

- ✓ monitoring blood glucose levels
- ✓ adopting a healthy eating pattern
- ✓ physical activity.
- ✓ For some women insulin injections maybe required to help manage their gestational diabetes.
- ✓ Blood sugar monitoring (Muller, 2004)

1.1.1.4 Maturity-Onset Diabetes of the Young (MODY)

It includes several forms of diabetes with monogenetic defects of beta-cell function (impaired insulin secretion), usually manifesting as mild hyperglycaemia at a young age, and usually inherited in an autosomal-dominant manner. (Tidy, 2015)

1.1.2 Signs and Symptoms of Diabetes

The signs and symptoms of diabetes are,

- The early symptoms of untreated diabetes is the elevated blood sugar levels, and loss of glucose in the urine. High amounts of glucose in the urine can cause increased urine output and lead to dehydration. Dehydration causes increased thirst and water consumption
- The inability of insulin to perform normally has effects on protein, fat and carbohydrate metabolism. Insulin is an anabolic hormone, that encourages storage of fat and protein.
- Being very thirsty
- Often Urinating
- Feeling hungry
- Feeling tired
- Losing weight without trying
- Sores that heal slowly
- Dry, itchy skin
- Feelings of pins and needles in the feet
- Losing feeling in the feet
- Blurry eyesight(Diabetes.niddk.nih.gov, 2015)

1.1.3 Causes of diabetes

1.1.3.1 Causes of Type 1 Diabetes

Type 1 diabetes is caused by the immune system destroying the cells in the pancreas that make insulin. This causes diabetes by leaving the body without enough insulin to function normally. This is called an autoimmune reaction, or autoimmune cause, because the body is attacking itself.

The following triggers may also be involved:

- Viral or bacterial infection

- Chemical toxins within food
- Unidentified component causing autoimmune reaction
- Underlying genetic disposition may also be a type 1 diabetes cause.
- Genetic Susceptibility
- Autoimmune Destruction of Beta Cells. (Diabetes.co.uk, 2015)

1.1.3.2 Causes of Type 2 Diabetes

Type 2 diabetes causes are usually multifactorial - more than one diabetes cause is involved. The most overwhelming factor is a family history of type 2 diabetes.

This is the most common cause of type 2 diabetes.

There are a variety of causes for type 2 diabetes. These include:

- Obesity
- Living a sedentary lifestyle
- Increasing age
- Bad diet
- Insulin resistance
- Abnormal Glucose Production by the Liver. (Diabetes.co.uk, 2015)

1.1.4 Treatment

The major components for the treatment of diabetes are:

- Diet
- Oral hypoglycemic therapy
- Insulin treatment
- **Diabetes education:** structured education and self-management (at diagnosis and regularly reviewed and reinforced) to promote awareness.
- Healthy eating
- Regular exercise
- Life style modification
- Blood sugar monitoring
- Control of Blood pressure levels. (Thursina, 2014).

1.1.4.1 Dietary Treatment

The goal of an individualized food plan aims-

- ✓ To achieve the best possible glycemic control
- ✓ Reducing the complications arising from hyperglycemias
- ✓ Control the plasma concentrations of lipids (cholesterol and triglycerides); e,g. Correcting associated blood lipid abnormalities
- ✓ To maintain or achieve the ideal weight
- ✓ Meet the nutritional needs of the patient according to their age, sex, metabolic state, physical activity (Muller, 2004)

1.1.4.2 Drug Treatment to Reduce Blood Glucose Level

Anti-diabetic drugs are used for the management of diabetes. Anti-diabetic drugs are medicines developed to stabilize and control blood glucose levels amongst people with diabetes. The following medications are used to reduce blood glucose level.

1. **Insulin injections**

Mostly used on serious cases of diabetes.

2. **Oral antidiabetic drugs**

Suitable for most adult patients. Common types of oral antidiabetic drugs include:

a) Sulfonylureas

Sulfonylureas work by stimulating the pancreas to release more insulin and are only effective when there is some pancreatic beta-cell activity still present. They increase insulin secretion.

Sulfonylureas block ATP sensitive potassium channels in Beta cells of the islets, and reduce the potassium permeability of Beta cells. This causes depolarization of the cells, calcium entry into the cell, which causes increased insulin secretion. The insulin released reduces plasma glucose concentrations.

Sulfonylureas are widely used to treat non-insulin dependent diabetes mellitus. These drugs exert their hypoglycaemic effects by stimulating insulin secretion from the pancreatic beta-cell. Their primary mechanism of action is to close ATP-sensitive K channels in the beta-cell plasma membrane, and initiate a chain of events which results in insulin release. Recent studies have shown that the beta-cell ATP-sensitive K-channel is a

complex of two proteins: a pore-forming subunit (Kir6.2) and a drug-binding subunit (SUR1) which functions as the receptor for sulfonylureas. (Drugs.com, 2015)

Table 1.2: Classification of Sulfonylureas

1st generation	2nd generation	3rd generation
Chlorpropamide	Glipizide(Glucotrol)	
Tolbutamide	Gliclazide	
Acetohexamide	Glibenclamide,Glyburide	Glimepiride
Carbutamide	Glisoxepide	
	Gliquidone	
	Glycopyramide	

(Drugs.com, 2015)

b) Biguanides: Glucophage reduce gluconeogenesis in the liver. Metformin is an example of biguanide medicine. It lowers blood glucose mainly by decreasing the amount of sugar (glucose) that releases by the liver into the bloodstream. It also increases the sensitivity of body's cells to insulin (so more glucose is taken into cells with the same amount of insulin in the bloodstream.) Metformin has also been shown in studies to lower the risk of other complications of diabetes (such as heart attack and stroke). (Tidy, 2015)

c) Intestinal α-glucosidase inhibitors: They delay the digestion and absorption of carbohydrates; hence reduce the blood sugar elevation after a meal. For example, Acarbose.(Tidy, 2015)

d) Thiazolidinediones: It is commonly called glitazones (eg, pioglitazone), thiazolidinediones lower blood glucose by increasing the sensitivity of body's cells to insulin (so more glucose is taken into cells for the same amount of insulin in the bloodstream). They are not usually used alone, this can be taken in addition with metformin or a sulfonylurea.(Tidy, 2015)

e) Acarbose: Acarbose works by delaying the absorption of carbohydrates (which are broken down into glucose) from the gut. Therefore, it can reduce the peaks of blood glucose which may occur after meals.It can also be used in addition to other glucose-lowering tablets. However, many people develop gut-related side-effects when taking

acarbose, such as bloating, wind, and diarrhoea. Therefore, it is not used very often.(Tidy, 2015)

f) Dipeptidyl peptidase 4 inhibitors (also known as incretin enhancers): This group includes linagliptin, saxagliptin, sitagliptin and vildagliptin. Dipeptidyl peptidase-4 (DPP4) is a chemical (an enzyme) which breaks down hormones called incretins. Incretins are chemicals (hormones) which are produced by the gut (intestine) in response to food. These medicines work by reducing the blood glucose level by enhancing the effects of incretins as they prevent DPP4 from working. Addition of metformin or sulfonylurea, or both with this medicine if HbA1c level is still high. (Tidy, 2015)

1.1.5 Diagnosis

Diabetes can be diagnosed by the fasting blood glucose (sugar) test. It is very easy and convenient method. After the person has fasted overnight (at least 8 hours), a single sample of blood is taken and sent analyzed the sample in laboratory. It can also be done accurately by using a glucose meter.

Normal Fasting plasma glucose (FPG) levels are less than 100 mg per deciliter(mg/dl)

Fasting plasma glucose levels of more than 126 mg/dl on two or more tests on different days indicate diabetes. A random blood glucose test can also be used to diagnose diabetes. A blood glucose level of 200 mg/dl or higher indicates diabetes.

When fasting blood glucose stays above 100mg/dl, but in the range of 100-126mg/dl, this is known as impaired fasting glucose (IFG). While patients with IFG or prediabetes do not have the diagnosis of diabetes, this condition carries with it its own risks and concerns.

Glycosylated HB (HBA_{1c}): DM is indicated by typical symptoms and signs and confirmed by measurement of plasma glucose. Measurement after 8- to 12-h fast (FPG) or 2 h after ingestion of a concentrated glucose solution (oral glucose tolerance testing, OGTT) is best. Two-hour venous plasma glucose concentration ≥11.1 mmol/L two hours after 75 g anhydrous glucose in an oral glucose tolerance test (OGTT).

- $HBA_{1c} \geq 6.5\%$ = DM
- HBA_{1c} 5.7 to 6.4% = Prediabetes or at risk of DM

- Sometimes oral glucose tolerance testing (Drugs.com, 2015)

1.2 Glimepiride (3rd generation sulfonylurea)

Glimepiride is an oral 3rd generation sulfonylurea antidiabetic agent that contains the active ingredient Glimepiride. It is used with a proper diet and exercise program to control high blood sugar in people with type 2 diabetes. It may also be used with other diabetes medications. Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems. Proper control of diabetes may also lessen risk of a heart attack or stroke. Glimepiride belongs to the class of drugs known as sulfonylureas. It lowers blood sugar by causing the release the body's natural insulin. (MedicineNet, 2015)

It stimulates the pancreas to produce insulin and helps the body use insulin efficiently. The drug may also decrease the chances of suffering from life-threatening complications that patients with type 2 diabetes may develop.

The drug was approved by the FDA in 1995 and is manufactured by Sanofi-Aventis.

Glimepiride comes in tablet form and is usually taken once a day. It may be used alone, or in combination with insulin or another oral medication such as metformin. (Drugs.com, 2015)

1.2.1 Chemistry of Glimepiride

IUPAC Name: 3-ethyl-4-methyl-N-{2-[4-({[(4 methylcyclohexyl)carbamoyl] amino} sulfonyl)phenyl]ethyl}-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide

Chemical Formula: $C_{24}H_{34}N_4O_5S$

Molecular Weight: 490.62.

Appearance: Glimepiride, USP is a white, crystalline, odorless to practically odorless powder and is practically insoluble in water. (Drugs.com, 2015)

Structural Formula:

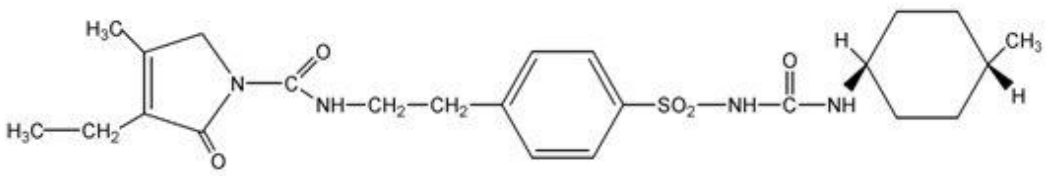


Figure 1.1: Structure of glimepiride

Synthesis of Glimepiride:

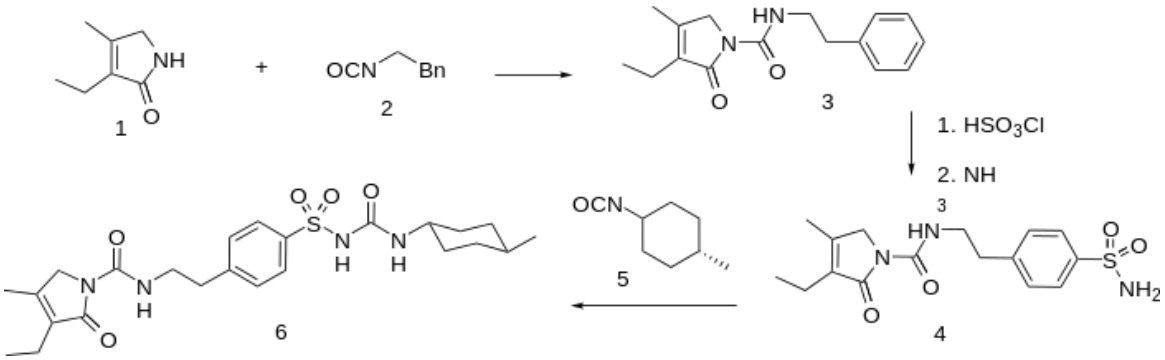


Figure 1.2: Synthesis of Glimepiride (Science24.com, 2015)

1.2.2 Mechanism of action

The mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells, and also provide glycemic control by increasing sensitivity of peripheral tissues to insulin. Glimepiride likely binds to ATP-sensitive potassium channel receptors on the pancreatic cell surface, reducing potassium conductance and causing depolarization of the membrane. Membrane depolarization stimulates calcium ion influx through voltage-sensitive calcium channels. This increase in intracellular calcium ion concentration induces the secretion of insulin. (Drugbank.ca, 2015)

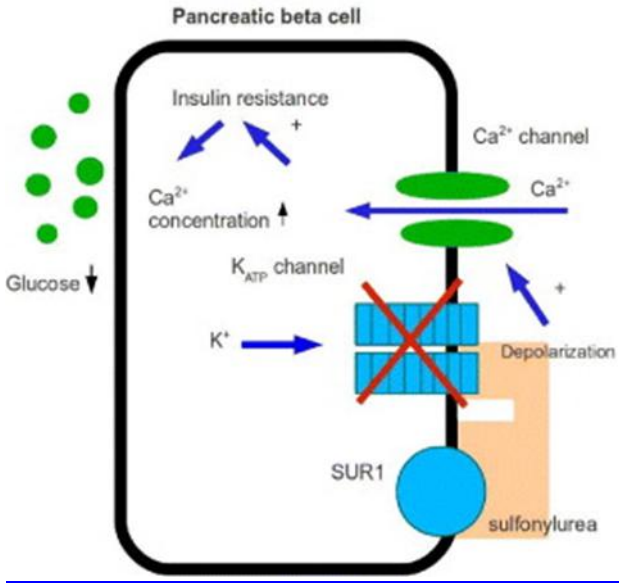


Figure 1.3: Mechanism of action of Glimepiride

1.2.3 Pharmacokinetics

Absorption

Glimepiride is completely (100%) absorbed from the GI tract following oral administration. Bioavailability is 100%. Single oral doses and multiple oral doses in patients with NIDDM have shown significant absorption of glimepiride within 1 hour after administration and peak drug levels (Cmax) at 2-3 hours.

If glimepiride given with meals, then the mean Tmax (time to reach Cmax) slightly increased (12%) and the mean Cmax and AUC (area under the curve) slightly decreased (8% and 9%, respectively).

Distribution:

The volume of distribution (VD) of glimepiride is 8.8 L (113 ml/kg), and the total body clearance (CL) is 47.8 ml/min. Protein binding is greater than 99.5%.

Metabolism:

Glimepiride is completely metabolized by oxidative biotransformation after an IV or oral dose. The major metabolites are the cyclohexylhydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 II C9 involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes.

Elimination:

About 60% is excreted in urine and about 40% in feces as metabolites.

The half-life is about 5 to 9.2 h Peak: 2 to 3 h. Duration: 24 h. (Elsevierhealth.com, 2015)

1.2.4 Indications and Clinical Use

Glimepiride is indicated for:

- It is indicated as an adjunct to proper dietary management, exercise and weight reduction to lower the blood glucose in patients with type 2 diabetes whose hyperglycemia cannot be controlled by diet and exercise alone.
- It may be used in combination with metformin when diet and exercise, and Amaryl or metformin alone do not result in adequate glycemic control.
- Glimepiride is also indicated for use in combination with insulin to lower blood glucose in patients with type 2 diabetes whose hyperglycemia cannot becontrolled

by diet and exercise in conjunction with an oral hypoglycemic agent alone. (Drugs.com, 2015)

1.2.5 Glimepiride Dosage and Administration

Recommended Dosing

- Glimepiride tablets should be administered with breakfast or the first main meal of the day.

Starting dose: The recommended starting dose of Glimepiride tablets is 1 mg or 2 mg once daily. Patients at increased risk for hypoglycemia (e.g., the elderly or patients with renal impairment) should be started on 1 mg once daily.

Maintenance dose: After reaching a daily dose of 2 mg, further dose increases can be made in increments of 1 mg or 2 mg based upon the patient's glycemic response. Up titration should not occur more frequently than every 1 to 2 weeks. A conservative titration scheme is recommended for patients at increased risk for hypoglycemia. Long-term efficacy should be monitored by measurement of HbA levels, for example, every 3 to 6 months.

- The maximum recommended dose of glimepiride is 8 mg once daily.
- Glimepiride can be used in combination with insulin. In this case, the recommended dose of glimepiride is 8 mg daily.

Dose range in patients with well controlled diabetes: The usual dose range in patients with well controlled diabetes is 1 to 4 mg glimepiride daily. Only some patients benefit from daily doses of more than 6 mg.

Distribution of doses: Timing and distribution of doses are to be decided by the physician, taking into consideration the patient's current life-style. Normally, a single daily dose of glimepiride is sufficient. This dose should be taken immediately before a substantial breakfast or- if none is taken- immediately before the first main meal. It is very important not to skip meals after taking glimepiride.

Secondary dosage adjustment: As the control of diabetes improves, insulin sensitivity is increased; therefore, glimepiride requirements may fall as treatment proceeds. To avoid an excessive reduction in blood sugar (hypoglycaemia), a timely dose reduction or cessation of glimepiride therapy must be considered. A dose adjustment must also be considered whenever the patient's weight or life-style changes, or other factors causing an

increased susceptibility to hypoglycaemia or to an excessive increase in blood sugar levels (hyperglycaemia) arise. (Drugs.com, 2015)

1.2.6 Overdose

If overdose is suspected, then one should contact local poison control center or emergency room immediately. Symptoms may include -

- Coma, confusion, fainting, fast heartbeat, lethargy, lightheadedness, seizures, severe dizziness or drowsiness, tremor, or unusual sweating.
- An over dosage of glimepiride, as with other sulfonylureas, can produce severe hypoglycemia. Mild episodes of hypoglycemia can be treated with oral glucose. Severe hypoglycemic reactions constitute medical emergencies requiring immediate treatment. Severe hypoglycemia with coma, seizure, or neurological impairment can be treated with glucagon or intravenous glucose. Continued observation and additional carbohydrate intake may be necessary because hypoglycemia may recur after apparent clinical recovery. (Dailymed, 2015)

1.2.7 Side Effects of Glimepiride

Common Side Effects of Glimepiride

Glimepiride may cause changes in blood sugar, which could cause blood sugar levels to fluctuate. Symptoms of low blood sugar may include sudden sweating, shaking, fast heartbeat, hunger, blurred vision, dizziness, or tingling in the hands or feet.

Serious Side Effects of Glimepiride

Some side effects of glimepiride can be serious.

- Yellowing of the skin or eyes
- Dark urine
- Light-colored stools
- Pain in the upper right part of the stomach
- Diarrhea
- Fever
- Sore throat
- Unusual bruising or bleeding (Drugs.com, 2015)

1.2.8 Adverse Reactions

- ✓ Asthenia, dizziness, headache (2%).
- ✓ Nausea (1%).
- ✓ Agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia.
- ✓ Hepatic porphyria reactions and disulfiram-like reactions, hyponatremia. (Drugs.com, 2015)

1.2.9 Drug-Drug Interaction of glimepiride

The following types of medicine may interact with Glimepiride:

- ❖ ACE inhibitors, barbiturates, beta-blocker, coumarin anticoagulants, cytochrome P450 enzyme inducers, cytochrome P450 enzyme inhibitors, fibrates,glucocorticosteroids,H2 antagonists, laxatives, male sex hormones,medicines that affect the thyroid, monoamine oxidase inhibitors, nicotinic acid like medicines, oestrogens, oralantidiabetics, phenothiazines, progestogens, quinolones, salicylate, saluretics, steroids, sulphonamides, sympathicomimetics, sympatholytics, tetracyclines, thiazide diuretics. (NHS, 2015)
- ❖ The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including non-steroidal anti-inflammatory drugs(NSAID) and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monamine oxidase inhibitors, and beta adrenergic blocking agents. When these drugs are administered to a patient receiving glimepiride, the patient should be observed closely for hypoglycemia. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for loss of glycemic control.
- ❖ Coadministration of aspirin (1 g t.i.d) and glimepiride led to a 34% decrease in the mean glimepiride AUC (Area under the curve) and, therefore, a 34% increase in the mean CL/f. The mean Cmax had a decrease of 4%. Blood glucose and serum C-peptide concentrations were unaffected and no hypoglycemic symptoms were reported. Pooled data from clinical trials showed no evidence of clinically significant adverse interactions with

uncontrolled concurrent administration of aspirin and other salicylates.(Elsevierhealth.com, 2015)

1.2.10 Contraindications

Glimepiride is contraindicated in patients with the following conditions:

- ✓ Hypersensitivity to glimepiride, other sulfonylureas or sulfonamides or to any of the excipients
- ✓ Insulin dependent diabetes type-1
- ✓ Diabetic coma
- ✓ Ketoacidosis
- ✓ Severe renal or hepatic function disorders. In case of severe renal or hepatic function disorders, a changeover to insulin is required
- ✓ Pregnant or breast-feeding women. (Drugs.com, 2015)

1.2.11 Precautions

Glimepiride should not use if a patient allergic to any ingredient in this medicine. This medicine may cause drowsiness, dizziness, blurred vision, or lightheadedness.

- ➢ These effects may be worse if one take it with alcohol or certain medicines. This medicine should use with caution.
- ➢ Alcohol should not take while taking this medicine; it may increase the risk of low blood sugar. Rarely, alcohol may interact with this medicine and cause a serious reaction with symptoms such as flushing, nausea, vomiting, dizziness, or stomach pain.
- ➢ It may be difficult to control blood sugar during times of stress such as fever, infection, injury, or surgery.
- ➢ The dose of medicine should not change without checking by the doctor. This medicine may cause low blood sugar levels. Low blood sugar may cause anxious, sweaty, weak, dizzy, drowsy, or faint.
- ➢ It may also cause heart beat faster; vision change; headache, chills, or tremors; or hungry.
- ➢ Risk of low blood sugar may be increased by severe or prolonged exercise, drinking alcohol, or skipping meals.
- ➢ It may increase the risk of death from heart disease. Before you begin taking any new medicines, either prescription or over-the-counter, check with your doctor or

pharmacist. Use this medicine with caution in the elderly; they may be more sensitive to its effects, especially low blood sugar levels.

- For women: This medicine may cause harm to the fetus or newborn.
- Do not breast-feed while taking this medicine. (Drugs.com, 2015)

1.3 Quality

Quality is expressed by the ISO definition as: "The totality of features and characteristics of a product or service that bear on its ability to satisfy stated or implied needs". A product has good quality when it "complies with the requirements specified by the client".

When projected on analytical work, quality can be defined as "delivery of reliable information within an agreed span of time under agreed conditions, at agreed costs, and with necessary aftercare". The "agreed conditions" should include a specification as to the precision and accuracy of the data which is directly related to "fitness of use" and which may differ for different applications. (Fao.org, 2015)

In principle, three levels of organization of these activities can be distinguished. From the top down these levels are:

1. Quality Assurance (QA)
2. Quality Control (QC)
3. Quality Management (QM)

Every pharmaceutical product has established identity, strength, purity, and other quality characteristics designed to ensure the required levels of safety and effectiveness. For the purposes of this guidance document, the phrase achieving quality means achieving these characteristics for a product. (Fao.org, 2015)

1.3.1 Quality of Pharmaceuticals Product

Quality must be built into a product and process design and it is influenced by the

physical plant design, space, ventilation, cleanliness, and sanitation during routine production. The product and process design begins in research and development, and includes Pre-formulation and physical, chemical, therapeutic and toxicological considerations. It considers materials, in process and product control, including specifications and test for the active ingredients, the excipients and product itself, specific stability procedure for the product, freedom from microbial contamination and proper

storage of the product provide functional protection of the product against such factors as moisture, oxygen, light, volatility, and drug package Quality must be built into a product and process design and it is influenced by the physical plant interaction (Drugs.com, 2013)

Quality of pharmaceutical products and services is a vital factor in the battle to maintain sales and remain commercially viable in the fast-growing and changing market. Quality competition is as important as price competition and this trend is bound to continue. Material resources are becoming scarce and most expensive, and it is therefore economically desirable to minimize losses on scrap products by more effective quality control.

Pharmaceutical companies are challenged to find consistent, reliable, high-quality components that are manufactured with the goal of meeting their needs and the needs of patients. Quality is built in the product from the start and ensure consistent quality throughout a drug product's lifecycle. To make sure drug products maintain safety and efficacy from concept to commercialization and to reduce the total cost of ownership, packaging materials must evolve quality. (Ghulam and Shabir, 2015)

1.4 Quality Assurance

The quality assurance of pharmaceutical products is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It ensures that pharmaceutical products are of the quality required for their intended use. (WHO, 2015)

With regard to pharmaceuticals, quality assurance can be divided into major areas:

- Development
- Quality control
- Production
- Distribution and
- Inspections. (WHO, 2015)

1.5 Quality Control

Quality control is a system for verifying and maintaining a desired level of quality in a product or process, as by planning, continued inspection, and corrective action as required. (The Free Dictionary, 2015)

Quality control is an essential operation of the pharmaceutical industry. Drugs must be marketed as safe and therapeutically active formulations whose performance is consistent and predictable. New and better medicinal agents are being produced at an accelerated rate. At the same time more exacting and sophisticated analytical methods are being developed for their evaluation. (Leo, 1964)

QC usually involves:

1. Assessing the suitability of incoming components, containers, closures, labeling, in-process materials, and the finished products.
2. Evaluating the performance of the manufacturing process to ensure adherence to proper specifications and limits.
3. Determining the acceptability of each batch for release.

The suitability of drugs for their intended use is determined by:

- Their efficiency weighed against safety, according to label claim, or as promoted or publicized
- Their conformity to specifications regarding identity, purity and other characteristics.

The quality control of pharmaceutical products is a concept that covers all measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that the raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics. (WHO, 2015)

Figure 1.4: Quality control system

1.5.1 Objectives of Quality Control

Following are the important objectives of quality control:

- ✓ To establish the desired quality standards which are acceptable to the customers
- ✓ To discover flaws or variations in the raw materials and the manufacturing processes in order to ensure smooth and uninterrupted production.
- ✓ To evaluate the methods and processes of production and suggest further improvements in their functioning.
- ✓ To study and determine the extent of quality deviation in a product during the manufacturing process.
- ✓ To analyze in detail the causes responsible for such deviation.
- ✓ To undertake such steps which are helpful in achieving the desired quality of the product. (Yourarticlelibrary, 2015)

1.6 Physical Parameter

Quality control parameters are parameters or factors by which the quality of a product or dosage form is evaluated or judged. Tablets are most commonly used solid dosage forms. There is a specific set of quality control parameters to ensure the quality of tablet dosage forms. Quality parameters that are mainly focused on:

- Weight variation test
- Hardness test
- Thickness test
- Friability test
- Disintegration test and
- Dissolution test (Lachman *et al.,* 2008)

1.6.1 Weight Variation Test

Weight variation test is done batch to batch to check the uniformity of the tablets. Some tablet fails to maintain uniformity, some are properly uniformed. There are several reason that the weight of tablets varies batch to batch.

1.6.1.1 Causes of Weight Variation

1. Distribution at Hoover caused the vibration. So, small granule pushed, large granules will come out first, because there is a process of consolidation. Therefore, needs to be put

a uniform granule size. So, before the compressing process begins better evaluation the particle size distribution first.

2. If the flow of granules is not good or not free-flowing granules

3. If particle distribution is not normal, because the specific gravity is different, so that the Flow is bad.

4. If particle size distribution is not uniformed. Not too many fines and not too many granules should be used. Granules with a large particle diameter which causes the resultant tablet has a variety of unsightly weight, while too fine granules which causes unsightly flow time.

5. If lubricant or glidant less or not mixed evenly.

6. Poor flow properties

7. If any improper adjustment of the die cavity. (Vinensia.com, 2013)

1.6.1.2 Prevention of Weight Variation

- ✓ Uniform particle size distribution.
- ✓ Two different granules must have the same specific gravity/ almost the same in order to avoid variations in weight.
- ✓ To solve tablet weight variation, Excipient Aerosil or colloidal Silicon Dioxide can be added. This excipient was added to the external phase. The amount used is usually 1-2% of the total weight of the tablet. Mixing for 10-15 minutes.
- ✓ Lubricant (Magnesium Stearate) as much as 0.5% -1% can be added if needed. But, lubricant is hydrophobic, may interfere with dissolution of tablets. (Vinensia.com, 2013)

1.6.2 Hardness Test (crushing strength)

Tablet hardness testing is also called tablet breaking force testing. The tablets must be hard enough to withstand mechanical stress during packaging, shipment, and handling by the consumer. It is the load required to crush the tablet when placed on its edge.

1.6.2.1 Importance of Hardness Test

- To determine the need for pressure adjustments on the tableting machine.
- Hardness can affect the disintegration. So if the tablet is too hard, it may not disintegrate in the required period of time and if the tablet is too soft, it will not withstand the handling during subsequent processing such as coating or packaging

If the tablet hardness is too high, we first check its disintegration before rejecting the patch and if the disintegration is within time limit, we accept the patch.

If Hardness is high plus disintegration is within time then accept the batch. (Pharmainfo.net, 2015)

1.6.2.2 Advantage of Hardness Test

I. Hardness test give an idea about the amount of force which can able to fracture and it will also help to access compatibility of formulation.
II. It will also serve as a guideline in handling, packaging and storage of formulation.

1.6.2.3 Disadvantage of Hardness Test

It is unable to give idea about capping and lamination behavior of formulation especially for tablets.

1.6.2.4 Factors Affecting the Hardness

- Compression of the tablet and compressive force.
- Amount of binder. More binder à more hardness
- Method of granulation in preparing the tablet (wet method gives more hardness than direct method, Slugging method gives the best hardness). (Pharmainfo.net, 2015)

1.6.2.5 Limits

- 5 Kilograms minimum and 8 kilograms maximum.

1.6.3 Thickness Test

The thickness of tablet controlled carefully from the production run. Thickness can vary with no change in weight because of difference in the density of the granulation and the pressure applied to the tablets as well as the speed of tablet compression. Tablet thickness

is not only important in reproducing tablets identical appearance but also important for ensuring usability of packing components. Tablets thickness is determined with a caliper or thickness gauge that measures the thickness in millimeters (Lachman *et al.*, 2008).

If the tablets are thicker than a specified given number no longer may be contained in the volume of a given size bottles. Tablet thickness also becomes an important characteristic in counting tablet using filling equipment. Some filling equipment uses the uniform thickness of the tablet as a counting mechanism. If thickness varies throughout the lot, the result will have variation in count. Other pieces of filling equipment can mal functioning because of variation in tablet thickness, since tablet above specified thickness may cause wedging of tablets in previously adjusted depth of the counting slots. In general, tablet thickness is controlled within 5 percent of standard value. Tablet thickness control may be impossible unless (1) the physical properties of raw materials are closely controlled, (2) the upper and lower punch lengths are accurately and continuously standardized, (3) the granulation properties, including density, particle size, and particle size distribution are also carefully controlled . (Lachman *et al.*, 2008)

1.6.4 Friability Test

It is the tendency of tablets to powder, chip, or fragment and this can affect the elegance appearance, consumer acceptance of the tablet, and also add to tablet's weight variation or content uniformity problems. Friability is a property that is related to the hardness of the tablet.

- An instrument called friabilator is used to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping.

Figure 1.5: Friability Tester

1.6.4.1 Factor Affecting Friability of Tablets

Tablet friability may be influenced by the moisture content of the tablet, granulation and finished tablets. A low but acceptable moisture level acts as a binder. Very dry granulations that contain only fractional percentages of moisture often produce more friable tablets than granulations containing 2-4% moisture.(Anabiotec.com, 2015)

1.6.4.2 Purpose of Friability Test of Tablets

Friability test is done to evaluate the ability of tablets to withstand abrasion, packaging, handling and shipping. It can also be defined as the phenomenon whereby tablet surfaces are damaged and or show evidence of lamination or breakage when subjected to mechanical shock or attrition. During manufacturing and handling, tablets are subjected to stresses from collision and tablet sliding towards one another and other solid surfaces, which can result in the removal of small fragments and particles from the tablet surface. The results will be progressive reduction in weight and change in appearance. (Anabiotec.com, 2015)

1.6.5 Disintegration Test

Disintegration is a measure of the quality tablets. The disintegration test is performed to find out the time it takes for a solid oral dosage form like a tablet or capsule to completely disintegrate. The time of disintegration is a measure of the quality. This is because, for example, if the disintegration time is too high; it means that the tablet is too highly compressed or it may imply several other reasons. And also if the disintegration time is not uniform in a set of tablet being analyzed, it indicates batch inconsistency and lack of batch uniformity.(Lachman *et al.,* 2008)

Condition

Disintegration is consider to achieved when-

- No residues remain on the screen, or
- If there is a residue, it consist of a soft mass having no palpably firm, unmoistened core,or
- Only fragments of coating (tablets) or only fragments of shell may adhere to the lower surface of the disc.

1.6.6 Dissolution Test

Drugs administered orally in solid dosage forms, such as tablet or capsules, must dissolve in the contents of the gastrointestinal tract before drug absorption can occur. Often the rate of drug absorption is determined by the rate of drug dissolution from the dosage form. Therefore, if it is important to achieve high peak blood levels for a drug, it will usually be important to obtain rapid drug dissolution from the dosage form.

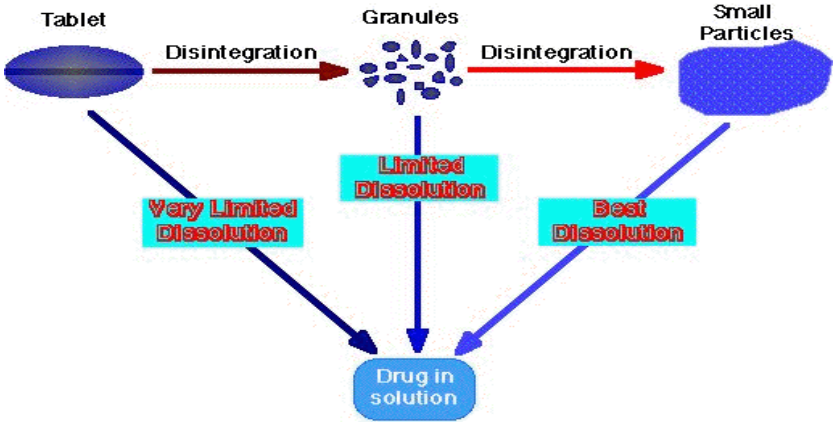


Figure 1.6: Schematic diagram of Dissolution test

1.6.6.1 Factors Affecting Dissolution Rate

1. Physicochemical Properties of Drug.

2. Drug Product Formulation Factors.

3. Processing Factors.

4. Factors Relating Dissolution Apparatus.

5. Factors Relating Dissolution Test Parameters (Lachman *et al*., 2008)

1.6.6.2 Purpose of Dissolution Study

Dissolution rate may be defined as amount of drug substance that goes in the solution per unit time under standard conditions of liquid/solid interface, temperature and solvent composition. It can be considered as a specific type of certain heterogeneous reaction in which a mass transfer results as a net effect between escape and deposition of solute molecules at a solid surface.

1. Results from in-vitro dissolution rate experiments can be used to explain the observed differences in in-vivo availability.

2. Dissolution test provides the means to evaluate critical parameters such as adequate bioavailability and provides information necessary in the development of more efficacious and therapeutically optimal dosage forms.

3. Most sensitive and reliable predictors of in-vivo availability.

4. Dissolution analysis of pharmaceutical dosage forms has emerged as single most important test that will ensure quality of product.

5. It can ensure bioavailability of product between batches that meet dissolution criteria.

6. Ensure batch-to-batch quality equivalence both in-vitro and in-vivo, but also to screen formulations during product development to arrive at optimally effective products.

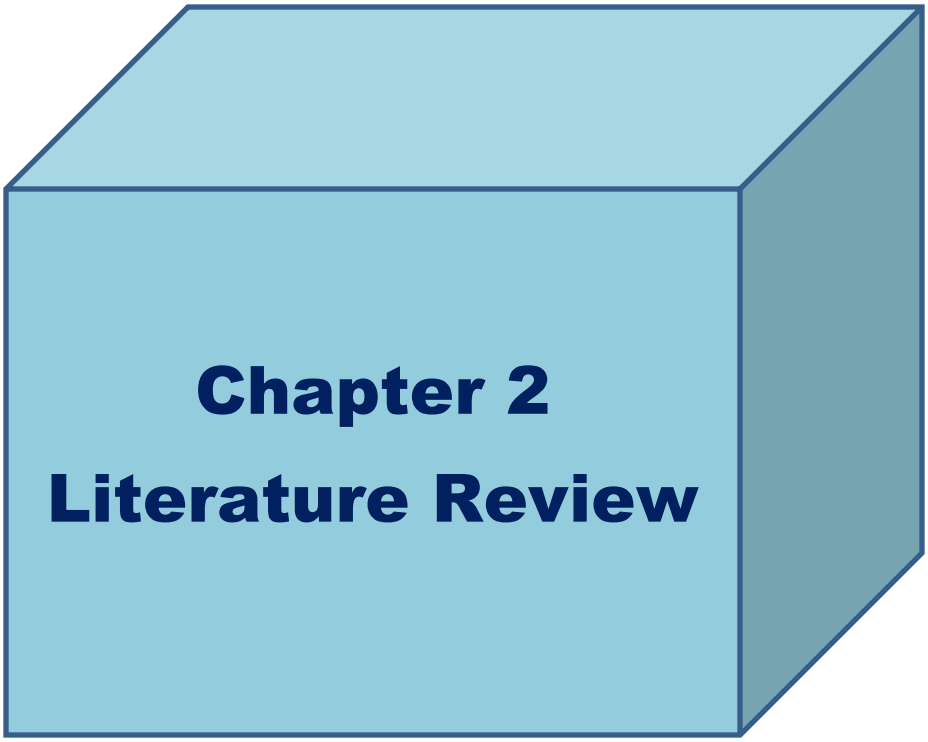
7. Physicochemical properties of model can be understood needed to mimic in-vivo environment.

8. Such models can be used to screen potential drug and their associated formulations for dissolution and absorption characteristics.

9. Serve as quality control procedures, once the form of drug and its formulation have been finalized. If hydrophobic drug than the sodium lauryl sulphate can be added into simulated fluid to solublize the drug. (Lachman *et al.*, 2008)

1.6.7 Potency

Potency referred as the concentration of the drug in a compounded preparation. Potency tests are known as quantitative tests and are designed to determine how much of a drug is in a sample. Ultraviolet-visible spectrophotometry (UV-VIS) can be employed to determine potency for single analytes in solutions. The purpose of strength, or potency, testing is to establish or verify the concentration (potency) of the drug in the compounded preparation. The United States Pharmacopeia (USP) has established that the acceptable range of most compounded preparations is typically ± 10%, or within the range of 90.0% to 110.0%. (Compoundingtoday.com, 2015)


Chapter 2
Literature Review

Chapter 2: Literature Review

Simple UV Spectrophotometric Assay of Glimepiride

Glimepride belongs to sulfonylurea oral anti diabetic. An efficient least time consuming and simple spectrophotometric method for the assay of Glimepride has been used. The assay is based on the ultraviolet UV absorbance maxima at about 200nm wavelength of Glimepride using water as solvent. A sample of drug was dissolved in water to produce a solution containing Glimepride. Similarly, various dilutions were made. The absorbance of sample preparation was measured at 200nm against the solvent blank and the assay was determined. A simple and quick assay method using U.V spectrophotometer has been used. The assay is based on measuring the absorbance of formulation of Glimepride dilutions at the wavelength of 200 nm. Four different dilutions of 50ppm, 25ppm, 12.5ppm and 6.25ppm are prepared and their percent assay is calculated. (Safila *et al*., 2014)

Surface Solid Dispersion of Glimepiride for Enhancement of Dissolution Rate

Surface solid dispersions using water-insoluble carriers like crospovidone, croscarmellose sodium, sodium starch glycolate, pre-gelatinized starch, potato starch and Avicel PH 101 were investigated to enhance the dissolution rate of the glimepiride, a poorly water insoluble drug. The effect of various carriers on dissolution profile was studied using presence absence model. The surface solid dispersion on crospovidone with drug to carrier ratio of 1:19 showed highest dissolution rate with the dissolution efficiency of 81.89% in comparison to pure drug (22.88%) and physical mixture (35.96%). The optimized dispersion was formulated into tablets by wet granulation method. These tablets, apart from fulfilling the official and other specifications, exhibited higher rates of dissolution and dissolution efficiency values. (Kiran *et al*., 2009)

Formulation and Evaluation of Sustained Release Matrix Tablets of Glimepiride Based on Combination of Hydrophilic and Hydrophobic Polymers

The objective of this study was to develop sustained release tablets of glimepiride by wet granulation method based on combination of hydrophilic and hydrophobic (Ethyl cellulose) polymers. The drug excipient mixtures were subjected to preformulation studies. The tablets were subjected to physicochemical studies, in- vitro drug release, kinetic studies and stability studies. FTIR studies shown there was no interaction between

drug and polymers. The physicochemical properties of tablets were found within the limits. Glimepiride is a first third generation sulphonyl urea agent for the treatment type II diabetes mellitus. The drug release from the optimized formulation was extended for a period of 12 hrs. The kinetic treatment showed that the release of drug follows first order models. The optimized formulations were subjected to stability studies and shown there were no significant changes in drug content, physicochemical parameters and release pattern. Results of the present study indicated the suitability of the above mentioned polymers in the preparation of sustained release formulation of glimepiride. (Hadi, 2012)

Solubility and Dissolution Enhancement of Poorly Water Soluble Glimepiride by Using Solid Dispersion Technique

Glimepiride is one of the third generation sulfonylurea used for treatment of type 2 diabetes. Poor aqueous solubility and slow dissolution rate of the glimepiride lead to irreproducible clinical response or therapeutic failure in some cases due to subtherapeutic plasma drug levels. Consequently, the rationale of this study was to improve the solubility, dissolution rate and biological performance of the drug. Solid dispersion of glimepiride in polyvinylpyrrolidone (PVP K30)with water soluble polymers were prepared by the solvent evaporation method, and then formulating solid dispersion (SDs) tablets of the best formulation of SDs. Tablet formulations were prepared by direct compression technique using superdisintegrant crospovidone in different concentrations. SDs was evaluated for FTIR, XRD, SEM, in vitro dissolution profiles. Among different formulations of SDs, SD prepared by solvent evaporation method containing drug to PVP K30 polymer in the ratio of 1:5 gives best dissolution profile, and among tablet formulations, formulations containing 5% crospovidone gives best disintegration and dissolution profiles compared with other formulations. Results showed that polyvinylpyrrolidone is a promising polymer for enhancing the solubility of glimepiride. (Chaudhuri, 2012)

Bilayer Tablet Formulation of Metformin Hydrochloride and Glimepiride: A Novel Approach to Improve Therapeutic Efficacy

The present research work was an attempt to design a formulation to improve the oral therapeutic efficacy with optimal control of plasma drug level which contains two antidiabetic drugs i.e. Metformin HCl and Glimepiride. Bilayer tablet formulation has been developed consisting of two drug containing layers which comprises Metformin

sustained release layer and an immediate release layer of Glimepiride was optimised separately and constituted in bilayer tablet, a common analytical method for quantitative combined drug estimation was employed and evaluated. Two different matrix formulations were developed, one matrix layer with hydrophilic swellable polymer and another with hydrophobic polymer as carriers for sustained drug delivery from matrices and were evaluated. Hydroxypropylmethylcellulose and Polyethylene oxide was used as polymers in order to get the sustained release profile over a period of 24 h. Tablets were evaluated for physical properties; drug content and in vitro drug release were compared with standard commercial tablets (Glimy-M). The excipients used in this formulation did not alter physicochemical properties of drug, as tested by HPLC, DSC, and FTIR. Stability of the drug release profiles at 6 months in 40◦C and 75%RH suggesting that HPMC based sustained release formulation was stable than the Polyethylene oxide sustained release formulation due to its stable and better targeting profile in terms of drug release. This formulation also exhibited the best fitted formulation into zero order kinetics and non-Fickian transport of the drug from the tablets was confirmed. Bilayer tablet prepared from optimised formula was found to be best suited method for fixed dose combination of sustained release Metformin HCl and immediate release Glimepiride. (Pattanayak and Dinda, 2011)

Glimepiride: Evidence-Based Facts, Trends, and Observations

Type 2 diabetes mellitus is characterized by insulin resistance and progressive β cell failure; therefore, β cell secretagogues are useful for achieving sufficient glycemic control. Glimepiride is a second-generation sulfonylurea that stimulates pancreatic β cells to release insulin. Additionally, is has been shown to work via several extra pancreatic mechanisms. It is administered as monotherapy in patients with type 2 diabetes mellitus in whom glycemic control is not achieved by dietary and lifestyle modifications. It can also be combined with other antihyperglycemic agents, including metformin and insulin, in patients who are not adequately controlled by sulfonylureas alone. The effective dosage range is 1 to 8 mg/day; however, there is no significant difference between 4 and 8 mg/day, but it should be used with caution in the elderly and in patients with renal or hepatic disease. In clinical studies, glimepiride was generally associated with lower risk of hypoglycemia and less weight gain compared to other sulfonylureas. Glimepiride use may be safer in patients with cardiovascular disease because of its lack of detrimental effects on ischemic preconditioning. It is effective in reducing fasting plasma glucose,

post-prandial glucose, and glycosylated hemoglobin levels and is a useful, cost-effective treatment option for managing type 2 diabetes mellitus. (Basit *et al*., 2012)

Bioequivalence Assessment of the Two Brands of Glimepiride Tablets

Glimepiride, as an antidiabetic from the group of sulfonylurea, is administered perorally in the treatment of diabetes mellitus. The aim of this study was to compare pharmacokinetic profiles and relative bioavailabilities of the two oral formulations of glimepiride, generic and innovator tablets, after a single dose of the active drug.

An oral dose of 6 mg glimepiride was given under fasting conditions to 24 healthy volunteers. A one-week washout period was applied between the two consecutive periods. The serum samples obtained before dosing, and at various time points up to 48 hours, were analyzed for glimepiride concentration using the validated high performance liquid chromatographic (HPLC) method with ultraviolet detection. Pharmacokinetic parameters representing early (maximal concentration, time to reach maximal concentration) and total exposure to glimepiride were obtained..

The point estimates of the ratios of geometric means (test/reference) of maximal concentrations and areas under the curve were 1.046 (90% confidence interval: 0.906−1.208) and 1.022 (90% confidence interval: 0.856−1.220), respectively. Transient mild hypoglycaemia, resolved spontaneously within 30−60 minutes.

Since all the parametric 90% confidence intervals for the log-transformed main variables of glimepiride were within the 0.80 and 1.25 interval, accepted as the definition of bioequivalence, and the differences in times to reach maximal concentration also did not reach statistical significance, studied tablets were considered bioequivalent.(Jovanovic *et al.,* 2006)

Design and Evaluation of Sustained Release Matrix Tablets of Glimepiride Based on Combination of Natural and Synthetic Polymers

The present research work was aimed to develop matrix tablets of Glimepiride with Aloe barbadensis miller leaves mucilage and Povidone and to study its functionality as a matrix forming agent for sustained release tablet formulations. Physicochemical properties of dried powdered mucilage of Aloe barbadensis miller mucilage and Povidone tablet blend were studied. Various formulations of Glimepiride Aloe barbadensis miller mucilage and Povidone were prepared. They found to have better satisfactory physicochemical properties with low SD values. The swelling behavior and release rate characteristics

were studied. The dissolution study proved that the dried Aloe barbadensis miller mucilage and Povidone combination can be used as a matrix forming material for making Sustained release matrix tablets. (Ahad *et al.*, 2010)

Development and Validation of ASpectrophotometric Method for Quantification and Dissolution Studies of Glimepiride in Tablets

The objective of present study was to develop and validate an analytical method for quantitative determination and dissolution studies of glimepiride in tablets. The glimepiride shows absorption maxima at 225 nm and obeyed Beer's law in the range of 6.0 – 14.0 µg/mL. The limit of detection and limit of quantitation were 0.06, and 0.17 µg/mL respectively. Percentage recovery of glimepiride for the proposed method ranged from 99.32 to 100.98% indicating no interference of the tablet excipients. It was concluded that the proposed method is simple, easy to apply, economical and used as an alternative to the existing spectrophotometric and non-spectrophotometric methods for the routine analysis of glimepiride in pharmaceutical formulations and in vitro dissolution studies. (Induri, 2012)

Analytical Method Development and Validation of Glimepiride in Bulk and Tablet Dosage Form Using UV Spectrophotometer

The main objective of the study is to develop and validate an analytical method for quantitative determination of Glimepiride in bulk tablet dosage form using UV-Visible Spectroscopy. The glimepiride shows maximum absorption at 231nm and obeys Beer's law in the range of 5-10 mg/ml. For the method development we have selected a perfect solvent system using solvent such as NaOH. Calibration curve has been plotted. The assay should be carried and percentage recovery needs to be calculated. For the validation of the analytical method developed is carried out by determining parameters like Linearity, range, LOD, LOQ, Accuracy. Precision, Ruggedness. The calibration plot did not deviate from linearity because of its low intercept value, the LOD and LOQ values were found to be 25.93mg/ml and 86.44mg/ml respectively which shows the sensitivity of the method. The ruggedness is found to be less than 2%.Thee percentage recovery was assessed using 3 different solutions of 8.0,10,12mg/ml and the results obtained were 98,101.2,and 102% respectively. The developed method was applied to the quantification of Glimepiride in tablets available in local market. It can be seen that the

result obtained by proposed method was very much similar to that of established methods. (Ranjani *et al.,* 2013)

Method development and validation of simultaneous determination of pioglitazone and glimepiride in pharmaceutical dosage form by RP-HPLC

A simple, selective, rapid, and precise reverse phase HPLC method has been developed for the simultaneous estimation of pioglitazone and glimepiride in pharmaceutical dosage form. A phenomenex Luna c18 column (4.6x150mm) was used for the separation. The mobile phase was acetonitrile: KH2PO4 buffer (60:40%v/v) (Ph6) at a flow rate of 1.5ml/min with detection at 230nm.The retention time of pioglitazone and glimepiride was 4.4 and 2.7 minutes respectively. The developed method was validated in term of accuracy, precision, specificity, system suitability, linearity, and robustness, limit of detection and limit of quantification. Linearity of pioglitazone and glimepiride were in the range of 240 to 360µg/ml and 32 to 48µg/ml respectively. The proposed method is suitable for simultaneous determination of pioglitazone and glimepiride in pharmaceutical dosage form (Boopathy et al., 2010).

Significance of the study

Diabetes is a group of metabolic diseases characterized by an elevation of blood glucose levels over a prolonged period by a relative or absolute deficiency of insulin. Symptoms of high blood glucose level include increased hunger (polyphagia), thirst (polydipsia) and frequent urination (polyuria). If the symptoms left untreated, diabetes can cause many complications like acute complications include coma, diabetic ketoacidosis and serious long term complications include kidney failure, stroke, foot ulcers, cardiovascular disease and damage to the eyes. (Clark *et al*., 2012)

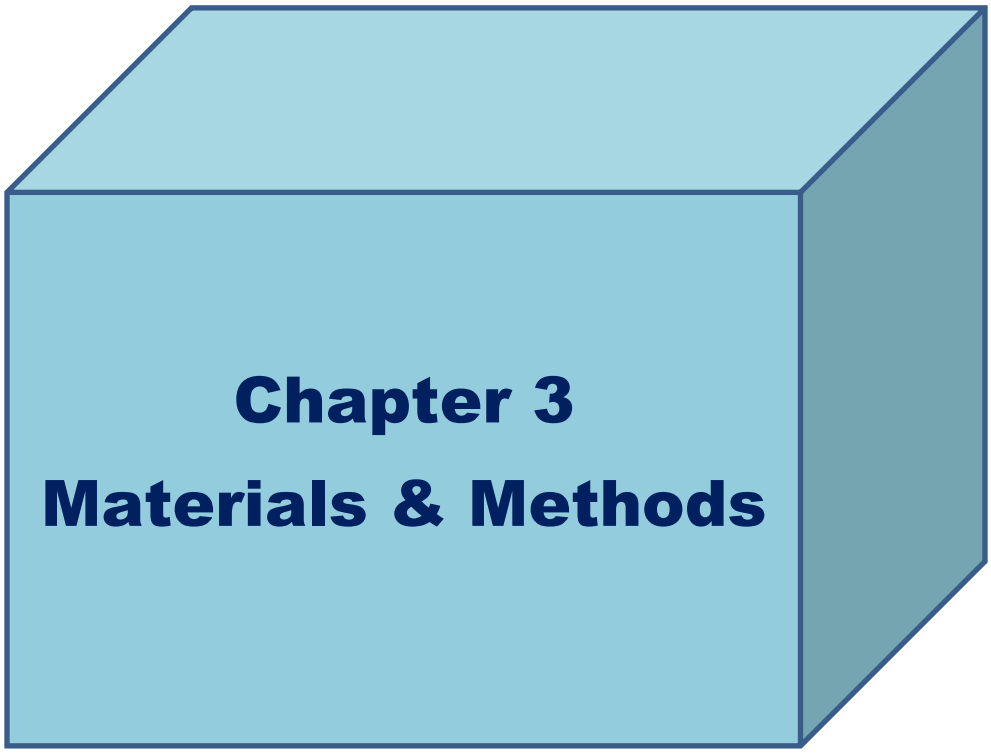
Glimepiride is an oral antidiabetic agent used along with exercise, diet, and sometimes with other medications to treat type 2 diabetes. For this research study glimepiride was choosen, because it is most commonly prescribed oral antidiabetic agent, widely available in Bangladeshi market, drug of choice for the physician. So, 4 batches of 2 different brands of glimepiride were collected and quality control parameters of these two brands should be conducted to find out whether they meet the compendium or not. If these brands meet the specification then it can be said that these brands maintain the quality.

To maintain manufacturing of the tablet dosage form, quality control parameters are necessary. Quality control parameters are the main conditions for a quality product. For maintaining quality of the product, quality control test are provided which include weight variation test, hardness test, thickness test, disintegration time, dissolution rate and potency test. These tests ensure uniform distribution, standard quality and purity of the product.

Aim and objectives of the study

The aim and objectives of the study were,

- To analyze different brands of glimepiride in terms of physical parameters like Hardness test, thickness test, friability test, weight variation, disintegration test, dissolution test etc.
- To determine the potency of selected brands of glimepiride.
- To assess and compare the rates of dissolution among different brands of glimepiride.
- Determine the batch to batch variation.


Chapter 3
Materials & Methods

Chapter 3: Materials and Methods

3.1 Sample Collection

The following 2 batches of each brands of Glimepiride tablets were chosen for the quality control parameter test.

Table 3.1: Different brands along with their manufacturer names

Tablet/Brand name	Batch no.	Company Name
LIMARYL	SCJ50	**Popular Pharmaceuticals ltd**
	SGJ43	
DACTUS	T1274017	**ACME Pharmaceuticals**
	T1274022	

Table 3.2: Solvent

NAOH	Distilled Water
KH_2PO_4	Phosphate Buffer PH 7.8

3.2 Equipment

In the characterization of glimepiride tablet, the following equipment were used which is listed in the table.

Table3.3: Lists of equipment's used for physical and chemical characterization of glimepiride tablets.

No.	Equipment	Source	Origin
1	Distill water plant	GENRISTO	United Kingdom
2	Friability tester	VEEGO	India
3	Hardness tester	MONSANTO	India
4	Disintegration tester	VANGUARD	Japan

5	Dissolution tester	LABINDIA DS 8000	India
6	UV-VIS Spectroscopy	UV-1800 SHIMADZU	Japan

Table 3.4: List of Apparatus/ Glassware's used throughout this project

Serial No.	Name	Serial No.	Name
1	Several containers	5	Measuring cylinder
2	Mortar & Pestle	6	Volumetric flasks
3	Test tubes	7	Pipette
4	Filter paper	8	Funnel, spatula

3.3 Weight Variation Test

Weight variation test is most significant because it has a relationship with content uniformity of a solid dosage forms. A small weight variation does not ensure good content uniformity between dosage units; a large weight variation precludes good content uniformity. Any of the following factors, can produce excessive tablet variations:

- Poor granulation flow properties, resulting in uneven die fill.
- A wide variation in granulation particle size, which result in a variation in die fill density as a function of particle size and particle size distribution at different points in the production run,
- Differences in lower punch length, which result in different size of die cavities (Senthil *et al.*, 2014).

3.3.1 Equipment

Table 3.5: Name and specification of instrument required in weight variation test

Instrument	Specification
Analytical Balance	SCALTEC SPB 31

Figure 3.1: Analytical Balance (AY220, Shimadzu, Japan)

3.3.2 Methods

a. The experiment is started with 20 tablets and all tablets are weighed at one time by analytical balance.

b. Then the combined weight is divided by 20 to generate an average weight.

c. Then each tablet is weighed individually and whether the individual weights are within the specified range or not is observed.

d. As per British Pharmacopoeia weight variation test procedure, individual weight is compared with the average weight.

e. The tablets meet the specification if not more than two tablets are outside the percentage limit and if no tablets differ by more than twice the percentage limit. The equation for calculation of percentage weight variation is given below:

$$\%\ of\ Weight\ Variation = \frac{Individual\ Weight - Average\ Weight}{Average\ Weight} \times 100$$

Equation 3.1: Equation of weight variation test

f. The same procedure is followed for the other brands and the results are documented.

3.3.3 Acceptance Limit

The tablet meet the USP test if not more than 2 tablets are out of percent limit and no tablet differs by more than 2 times the percent limit then the batch is accepted (USP, 2003).

Table 3.6: Acceptance of weight variation of tablets

Average Weight	Percentage Difference
130 mg or less	±10%
More than 130	±7.5%
324 mg and above	±5%

3.4 Hardness Test

Tablet hardness is usually expressed as the load required crushing a tablet placed on its edge. Hardness is thus sometimes termed the tablet crushing strength. The suitability of a tablet in regard to mechanical stability during packaging and shipment can usually be predicted on the basis of hardness. Tablet hardness, in turn, influences tablet density and porosity. It may affect tablet friability and disintegration time. It usually affects drug dissolution and release and it may affect bioavailability.

3.4.1 Materials

Table 3.7: Name and specification of materials required in hardness test

Materials	Specification
Hardness tester	Monsanto Type hardness tester

Figure 3.2: Hardness Tester

3.4.2 Method

1. The sliding scale of hardness tester has been set off to zero

2. The tablets have been placed vertically between the two jaws.

3. Force has been applied with the screw thread and spring until the tablets has been fractured.

4. A force of about 4-5 kg is considered to be the minimum for hardness according to The British Pharmacopoeia (Lachman *et al.*, 2008)

3.5 Thickness Test

3.5.1 Apparatus required for thickness test

Table 3.8: Name and specification of instrument required in thickness testing

Instrument	Specification
Vernier calipers	SHIMADZU, Japan

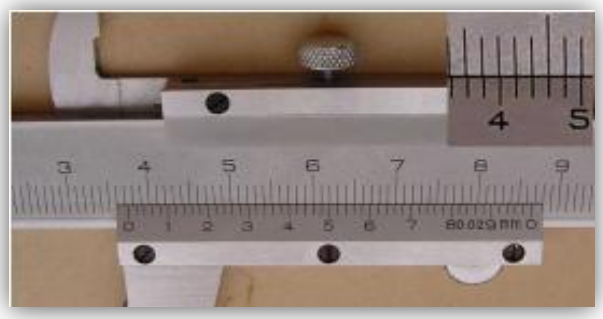


Figure 3.3: Vernier Calipers (Shimadzu, Japan)

3.5.2 Method

a. Samples of 10 tablets are taken.

b. Each tablet is placed between the two jaws of the vernier calipers on their width.

c. The screw of the slide calipers is tightened to hold the tablets.

d. The reading of the main scale and the vernier scale are noted and thickness of the tablet is measured.

Thickness = Main scale reading + (Vernier scale reading x Vernier Constant) ± Error

e. Tablet thickness should be controlled within a ± 5% variation of a standard value (Rani *et al*., 2013).

3.6 Disintegration Test

Disintegration is the most important step of a drug being better dissolution. The breakdown of a drug within its optimum time is the prerequisite for better absorption and consequently better therapeutic action. Disintegration time may vary considering to its disintegrator used. Higher the disintegration time required lower the dissolution rate and followed to poor absorption. So disintegration is the crucial part of a drug for therapeutic action (BP, 2012).

3.6.1 Condition

Medium: 900ml distilled water

Times: 30 minutes

Temperature: (37±2)0 C

3.6.2 Instrument

Disintegration tester (Vanguard Pharmaceutical Machinery INC)

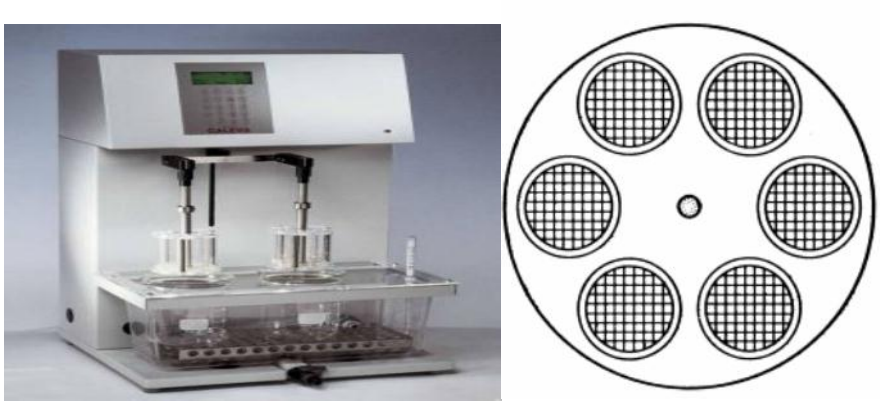


Figure 3.4: Disintegration Tester

Table 3.9: Name and specification of instrument required in disintegration test

Instrument	Specification
Disintegration tester	VANGUARD Disintegration Tester

3.6.3. Method

i. The disintegration tester is to be assembled.
ii. 15 minutes of time to run the operation is set on the instrument.
iii. The temperature of water is adjusted at 37 ± 2°C.
iv. The volume of water in the 1000 ml beaker is such that at the highest point of the upward stroke, the wire mesh remains at least 15 mm below the surface of the liquid and descends to not less than 25 mm from the bottom of the vessel on the downward stroke. About 720-750 ml of water is taken on each vessel.
v. The instrument operates at 29-30 cycles per minute.
vi. In each of the 6 tubes a single tablet is to be placed and the apparatus is operated for the prescribed time.
vii. All the tablets should disintegrate within the specified time.
viii. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the discs, if used, is a soft mass having no palpably firm core.
ix. If 1 or 2 tablets fail to disintegrate within the time specified, an additional 12 tablets are tested. If 16 out of 18 tablets do not disintegrate, the test requirements are not met (USP NF, 2006).

3.7 Dissolution Test

Drugs administered orally in solid dosage forms, such as tablet or capsules, must dissolve in the contents of the gastrointestinal tract before drug absorption can occur. Often the rate of drug absorption is determined by the rate of drug dissolution from the dosage form. Therefore, if it is important to achieve high peak blood levels for a drug, it will usually be important to obtain rapid drug dissolution from the dosage form. (Lachman *et al*., 2008).

3.7.1 Condition

- Medium: Phosphate buffer, 900 ml, pH 7.8
- Apparatus: USP apparatus-II (Paddle)
- Speed: 75 RPM
- Time: 30 minutes

 Temperature: 37±2°C (FDA, 2014)

3.7.2 Preparation of Phosphate buffer (PH 7.8)

At first 8.0 gm NaOH was dissolved in 1000 ml of distilled water that is stock solution A and 27.22 gm KH2PO4 was dissolved in 1000 ml distilled water that is stock solution B. Then we took 223 ml of stock solution A, 250 ml of stock solution B and water up to 1000 ml. Mixed them well. Adjusted the pH at 7.8 with a calibrated pH meter. For lowering the pH concentrated HCl and for increasing the pH 0.1 N NaOH was used. Thus, phosphate buffer was made.

Figure 3.5: LABINDIA Dissolution Apparatus

3.7.3 Method

It was ensured that the equipment had been calibrated within the past 6-12 months.

a. The 900 ml buffer solution was placed in each vessel of dissolution tester

b. The apparatus were assembled and was placed in the water-bath

c. The temperature of the dissolution medium was allowed to reach 37±2°C.

d. Each tablet of the preparation to be tested was allowed to sink to the bottom of each vessel before starting the rotation of the blade, taking care that no air bubbles are present on the surface of the dosage form.

e. Immediately started rotation of the paddle or basket at the rate of 75 rpm.

f. 6ml sample was withdrawn from a zone midway between the surface of the dissolution medium and the top of the rotating blad**e** or basket, not less than 10 mm below the surface and at least 10 mm from the vessel wall at the time intervals of 5, 10, 15 and 30 min from each vessel.

g. The dissolution medium was replaced instantly with a fresh buffer solution equal to the volume of dissolution medium removed with a help of a syringe of 6ml.

h. For filtration of the removed liquid as the final stage an inert filter paper was used because it does not cause significant adsorption of the active ingredient from the solution, and does not contain substances extractable by the dissolution medium that would interfere with the specified method of analysis.

i. Finally absorbance was taken of the filtered liquid at 229 nm.

$$\%Dissolved = \frac{A_{Sample} \times Wt_{standard} \times 900 \times Dilution\ Factor}{A_{Standar} \times Wt_{Sample} \times 100} \times 100$$

Equation 3.2: Equation for the calculation of % dissolved.

3.8. Potency

3.8.1 Equipment for Assay method

Table 3.10: Name and specification of instrument required for assay

Instrument	Specification
UV Spectrophotometer	UV-1800 SHIMADZU

Figure 3.6: Ultrasonic Homogenizer

3.8.2 Method

a. At first 10 tablets are weighed and powdered.

b. A quantity of powder equivalent to 2mg of glimepiride is taken in a 250 ml volumetric flask containing some water.

c. The volumetric flask is then sonicated for about 10 minutes.

d. After that the volume was made up to 100 ml.

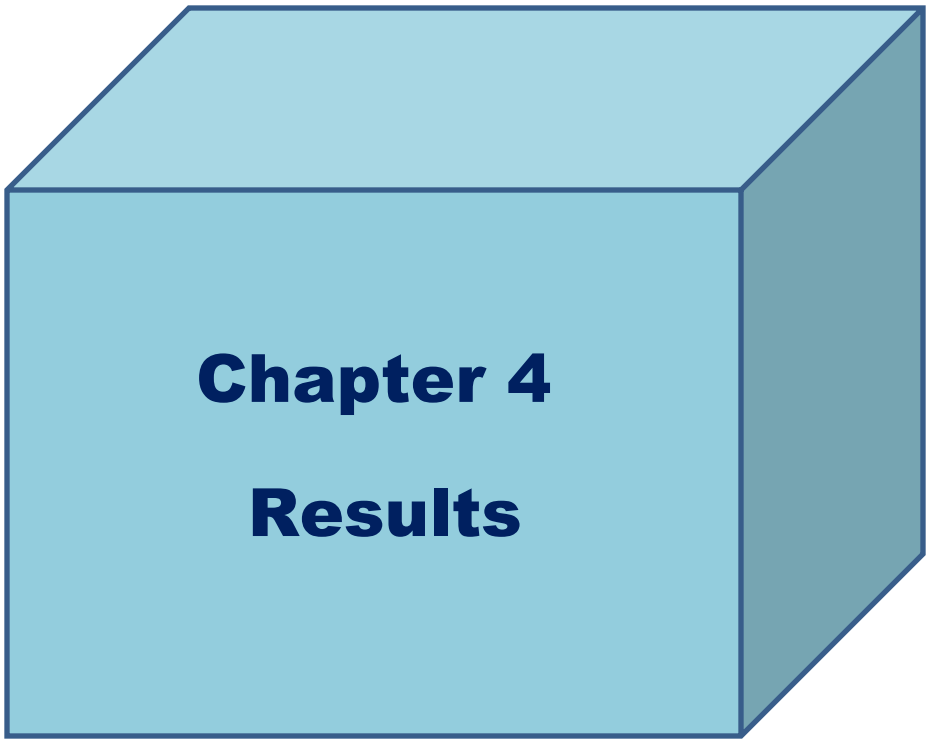
e. A concentration of 20 µg/ml was then prepared.

f. The absorbance of this solution was measured in 227 nm.

g. The content of glimepiride is calculated by the equation

$$Potency = \frac{A_{Sample}}{A_{Standard}} \times \frac{Weight_{Standard}}{Weight_{Sample}} \times \frac{Potency_{Standard} \times Dilution\ Factor \times Avg\ Wt_{Sample}}{Label\ Claimed} \times 100$$

Equation 3.3: Equation for potency determination.


Chapter 4
Results

Chapter 4: Results

4.1 Weight Variation Test

Table 4.1: Result of weight variation test of Limaryl tablets

Tablet Number	Weight of tablets		Weight Variation		Highest Variation		Lowest variation	
	SCJ 50	SGJ 43	SCJ50	SGJ43	SCJ50	SGJ43	SCJ50	SGJ43
1	0.0800	0.0806	-0.7012	1.4219				
2	0.0792	0.0790	-1.6942	-0.5914				
3	0.0814	0.0794	1.0364	-0.0880				
4	0.0784	0.0785	-2.6872	-1.2205				
5	0.0799	0.0815	-0.8254	2.5544				
6	0.0782	0.0798	-2.9355	0.4152				
7	0.0790	0.0780	-1.9425	-1.8497				
8	0.0809	0.0797	0.4158	0.2894				
9	0.0794	0.0788	-1.4460	-0.8430				
10	0.0850	0.0795	5.5048	0.0377				
11	0.0815	0.0808	1.1605	1.6735				
12	0.0799	0.0798	-0.8254	0.4152	5.5048	2.5544	-2.9355	-1.8497
13	0.0815	0.0793	1.1605	-0.2139				
14	0.0801	0.0788	-0.5771	-0.8430				
15	0.0788	0.0811	-2.1907	2.0510				
16	0.0808	0.0789	0.2916	-0.7172				
17	0.0819	0.0788	1.6570	-0.8430				
18	0.0799	0.0797	-0.8254	0.2894				
19	0.0802	0.0785	-0.4530	-1.2205				
20	0.0809	0.0788	0.4158	-0.8430				

Standard deviation: 0.001526 (Batch no.SCJ50) 0.000934 (Batch no.SGJ43)

Table 4.2: Result of weight variation test of Dactus tablets

Tablet No.	Weight of tablets		Weight Variation		Highest Variation		Lowest variation	
	T4022	**T4017**	**T4022**	**T4017**	**T4022**	**T4017**	**T4022**	**T4017**
1	0.1558	0.1401	0.9165	-6.6870				
2	0.1540	0.1516	-0.2493	0.9724				
3	0.1570	0.1544	1.6938	2.8373				
4	0.1536	0.1553	-0.5084	3.4367				
5	0.1538	0.1420	-0.3789	-5.4216				
6	0.1526	0.1391	-1.1562	-7.5263				
7	0.1536	0.1573	-0.5084	4.7688				
8	0.1516	0.1540	-1.8039	2.5709				
9	0.1528	0.1561	-1.0266	3.9696				
10	0.1551	0.1570	0.4631	4.5690				
11	0.1559	0.1418	0.9813	-5.5548	2.1472	5.1019	-1.8039	-12.082
12	0.1546	0.1554	0.1392	3.5033				
13	0.1540	0.1427	-0.2493	-4.9553				
14	0.1570	0.1561	1.6938	3.9696				
15	0.1519	0.1572	-1.6096	4.5690				
16	0.1529	0.1320	-0.9618	-12.082				
17	0.1537	0.1574	-0.4436	4.8355				
18	0.1577	0.1399	2.1472	-6.8203				
19	0.1542	0.1556	-0.1198	3.6366				
20	0.1559	0.1578	0.9813	5.1019				

Standard deviation: 0.001717 (B-T4022) &0.008264 (B-T4017)

4.2 Thickness Test

Table 4.3: Result of thickness test of Limaryl Tablets

LIMARYL 2 (SCJ50)						
Number of tablets	**Reading of main scale**	**Reading of vernier scale**	**Vernier constant**	**Vernier error**	**Thickness of tablet (mm)**	**Average (mm)**
1	2	1	0.1	0.05	2.15	2.165
2	2	1	0.1	0.05	2.15	
3	2	1	0.1	0.05	2.15	
4	2	1.5	0.1	0.05	2.20	
5	2	1	0.1	0.05	2.15	
6	2	1	0.1	0.05	2.15	
7	2	1.5	0.1	0.05	2.20	
8	2	1	0.1	0.05	2.15	
9	2	1	0.1	0.05	2.15	
10	2	1.5	0.1	0.05	2.20	

LIMARYL 2(SGJ43)						
Number of tablets	**Reading of main scale**	**Reading of vernier scale**	**Vernier constant**	**Vernier error**	**Thickness of tablet (mm)**	**Average (mm)**
1	2	1	0.1	0.05	2.15	2.16
2	2	1	0.1	0.05	2.15	
3	2	1.5	0.1	0.05	2.20	
4	2	1	0.1	0.05	2.15	
5	2	1	0.1	0.05	2.15	
6	2	1.5	0.1	0.05	2.20	
7	2	1	0.1	0.05	2.15	
8	2	1	0.1	0.05	2.15	
9	2	1	0.1	0.05	2.15	
10	2	1	0.1	0.05	2.15	

Standard deviation: 0.024152 (Batch no.SCJ50) &0.021082 (Batch no.SGJ43)

Table 4.4: Result of thickness test of Dactus Tablets

DACTUS 2 (T4022)						
Number of Tablets	**Reading of main scale**	**Reading of vernier scale**	**Vernier constant**	**Vernier error**	**Thickness of tablet (mm)**	**Average (mm)**
1	2	6	0.1	0.05	2.65	2.715
2	2	6	0.1	0.05	2.65	
3	2	5.5	0.1	0.05	2.6	
4	2	6	0.1	0.05	2.65	
5	2.5	5.5	0.1	0.05	3.1	
6	2	5.5	0.1	0.05	2.6	
7	2	5.5	0.1	0.05	2.6	
8	2	5.5	0.1	0.05	2.6	
9	2	5.5	0.1	0.05	2.6	
10	2.5	5.5	0.1	0.05	3.1	

DACTUS 2 (T4017)						
Number of tablets	**Reading of main scale**	**Reading of vernier scale**	**Vernier constant**	**Vernier error**	**Thickness of tablet (mm)**	**Average (mm)**
1	2	6.5	0.1	0.05	2.7	2.77
2	2	6.5	0.1	0.05	2.7	
3	2	7	0.1	0.05	2.75	
4	2.5	7	0.1	0.05	3.25	
5	2	6.5	0.1	0.05	2.7	
6	2	6.5	0.1	0.05	2.7	
7	2	7	0.1	0.05	2.75	
8	2	7	0.1	0.05	2.75	
9	2	6	0.1	0.05	2.65	
10	2	7	0.1	0.05	2.75	

Standard deviation: 0.204192 (B-T4022) &0.171917 (B-T4017)

4.3 Hardness Test

Table 4.5: Result of hardness test of Limaryl Tablets

Number of tablets	Hardness of tablets (kg/cm)		Average of tablets (kg/cm)	
	SCJ50	SGJ43	SCJ50	SGJ43
1	1.8	1.9	1.89	1.87
2	1.8	1.8		
3	1.9	1.8		
4	1.8	1.9		
5	1.9	1.9		
6	2	1.8		
7	1.8	1.9		
8	1.9	2		
9	2	1.9		
10	2	1.8		

Standard deviation: 0.08756 (Batch no.SCJ50) & 0.067495 (Batch no.SGJ43)

Table 4.6: Result of hardness test of Dactus Tablets

Number of tablets	Hardness of tablets (kg/cm)		Average of tablets (kg/cm)	
	T4022	T4017	T4022	T4017
1	2	2	1.89	1.93
2	2.1	1.9		
3	2	1.9		
4	1.9	1.8		
5	1.9	1.8		
6	1.8	2		
7	1.7	1.8		
8	1.7	2		
9	1.8	2.1		
10	2	2		

Standard deviation: 0.137032 (Batch no. T4022) & 0.105935 (Batch no.T4017)

4.4 Disintegration Test

Table 4.7: Result of disintegration test of Limaryl Tablets

Number of Tablets	Time (Minute)		Mean Disintegration Time	
	SCJ50 (L)	SGJ43 (L)	SCJ50 (L)	SGJ43 (L)
1	6 minute 7 seconds	6 minute 26 seconds	6 minutes 36 second	7 minutes 11 second
2	6 minute 09 seconds	6 minute 27 seconds		
3	6 minute 28 seconds	7 minute 06 seconds		
4	6 minute 47 seconds	7 minute 44 seconds		
5	7 minute 04 seconds	7 minute 54 seconds		
6	7 minute 01 seconds	7 minute 32 seconds		

Table 4.8: Result of disintegration test of Dactus Tablets

Number of Tablets	Time (Minute)		Mean Disintegration Time	
	T4017 (D)	T4022 (D)	T4017	T4022
1	1 minute 33 seconds	3 minute 42 seconds	2 minute 34 seconds	4 minute 6 seconds
2	2 minute 34 seconds	3 minute 58 seconds		
3	3 minute 55 seconds	4 minute 24 seconds		
4	2 minute 21 seconds	3 minute 49 seconds		
5	2 minute 25 seconds	4 minute 13 seconds		
6	2 minute 35 seconds	4 minute 38 seconds		

4.5 Dissolution Test

Table 4.9: Result of dissolution test of Limaryl Tablets

LIMARYL 2 (SCJ50)				
Number of Tablets	**Absorbance**	**%Dissolved**	**Average Absorbance**	**Average %Dissolved**
1	0.216	69.65	0.2518	81.207
2	0.257	82.874		
3	0.242	78.0365		
4	0.305	98.35		
5	0.220	70.942		
6	0.271	87.388		

LIMARYL 2 (SGJ43)				
Number of Tablets	**Absorbance**	**%Dissolved**	**Average Absorbance**	**Average %Dissolved**
1	0.207	66.75	0.225	72.66
2	0.217	69.97		
3	0.201	64.82		
4	0.218	70.29		
5	0.251	80.94		
6	0.258	83.19		

Table 4.10: Result of dissolution test of Dactus Tablets

DACTUS 2 (T1274022)				
Number of Tablets	**Absorbance**	**%Dissolved**	**Average Absorbance**	**Average %Dissolved**
1	0.249	80.29	0.232	74.81
2	0.238	76.75		
3	0.253	81.58		
4	0.212	68.36		
5	0.231	74.49		
6	0.209	67.39		

DACTUS 2 (T1274017)				
Number of Tablets	**Absorbance**	**%Dissolved**	**Average Absorbance**	**Average %Dissolved**
1	0.261	84.16	0.245	81.69
2	0.231	74.49		
3	0.238	76.75		
4	0.305	98.35		
5	0.225	72.55		
6	0.210	83.84		

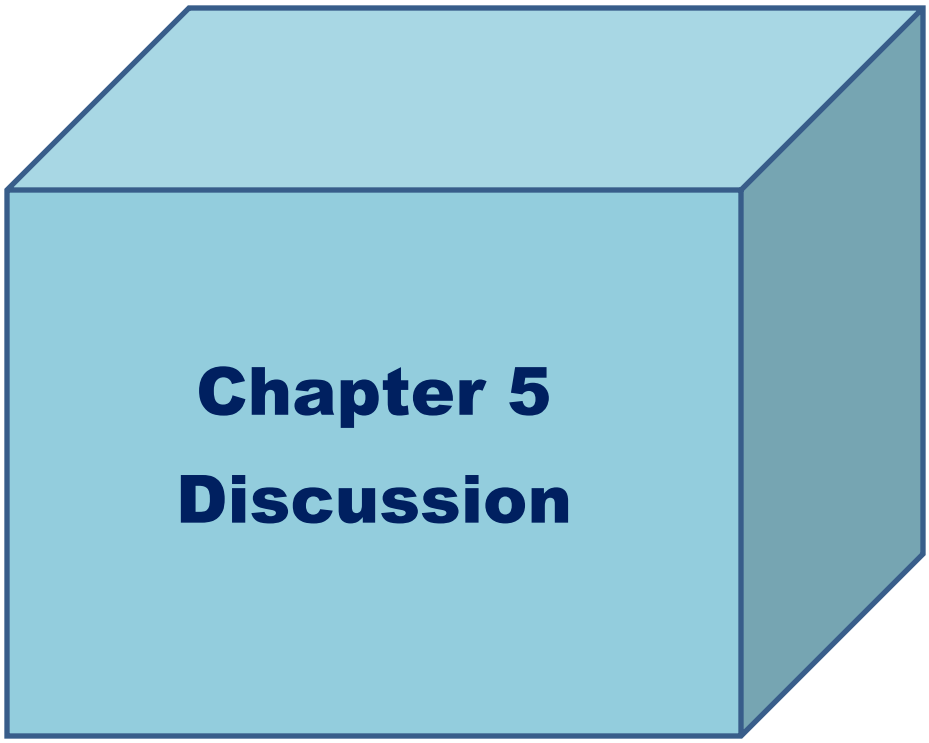
4.6 Potency Test

Table 4.11: Potency of Limaryl Tablets

Tablet Brand	Batch No.	Average weight of tablet (mg)	Absorbance of the sample	Weight of the sample (mg)	Potency (%)
LIMARYL	SGJ43	0.12378	0.496	0.125	140.11
	SCJ50	0.14912	0.433	0.148	122.32

Table 4.12: Potency of Dactus Tablets

Tablet Brand	Batch No.	Average weight of tablet (mg)	Absorbance of the sample	Weight of the sample (mg)	Potency (%)
DACTUS	T4022	0.2199	0.449	0.220	126.84
	T4017	0.2174	0.431	0.218	121.75


Chapter 5
Discussion

Chapter 5: Discussion

5.1 Weight Variation Test

According to the conducted research study, the weight variation of Limaryl tablets had the average weight of 0.080565gm (Batch no. SCJ50) and 0.07947gm (Batch no. SGJ43). The % weight variation ranged from +5.50487% to -2.935518% (Batch no.SCJ50) and +2.55442% to -1.84975% (Batch no.SGJ43). According to USP acceptance range of weight variation of tablets is ±10%. So that both batch of Limaryl meet the specification.

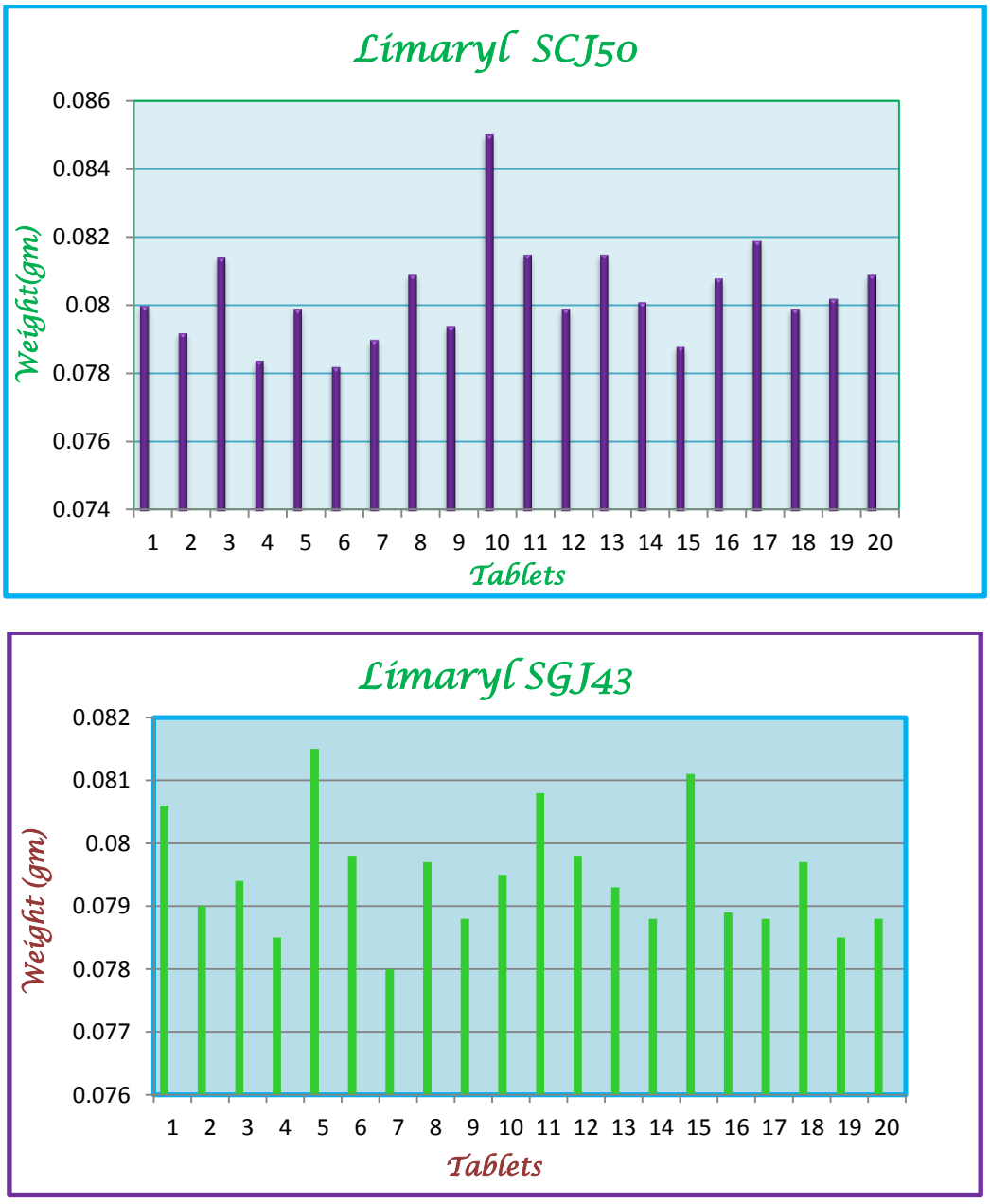


Figure 5.1: Weight variation of Limaryl tablets

Also the weight variation of Dactus tablets had the average weight of 0.154385gm (Batch no. T1274022) and 0.15014gm (Batch no. T1274017). The % weight variation ranged from +2.147229% to -1.80393% (Batch no.T4022) and +5.101905% to -12.08206% (Batch no.T1274017). According to USP acceptance limit of weight variation of tablets are ±10%. If 2 tablets deviated from the range out of 20 tablets then it is considered that the batch has passed. One tablet from batch T1274017 is deviated from the range. So, both the batch T1274022 and T1274017 meet specification and passed the weight variation test.

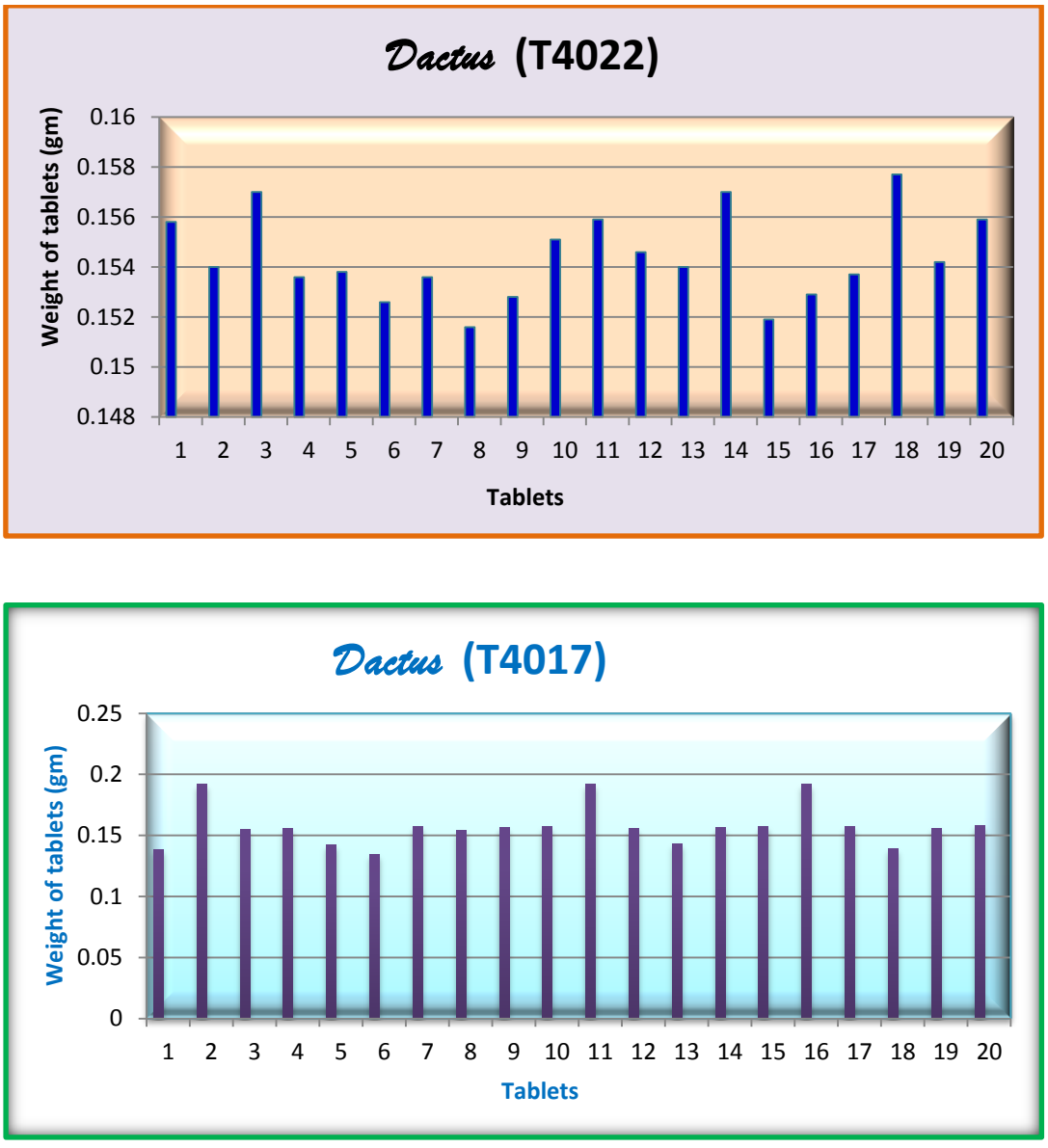


Figure 5.2: Weight variation of Dactus tablets

5.2 Thickness Test

According to the USP specification, the range for tablet thickness is ±5mm. The batch to batch thickness variation of Limaryl tablet is identical even the thickness of the tablets of two different batch were same and standard deviation was 0.024152 (Batch no. SCJ50) 0.021082 (Batch no. SGJ43).Very few tablets are not consistent, which is very minor. But each tablet is within the range. So, it can be concluded that the formulation technique is perfectly following the compendial method.

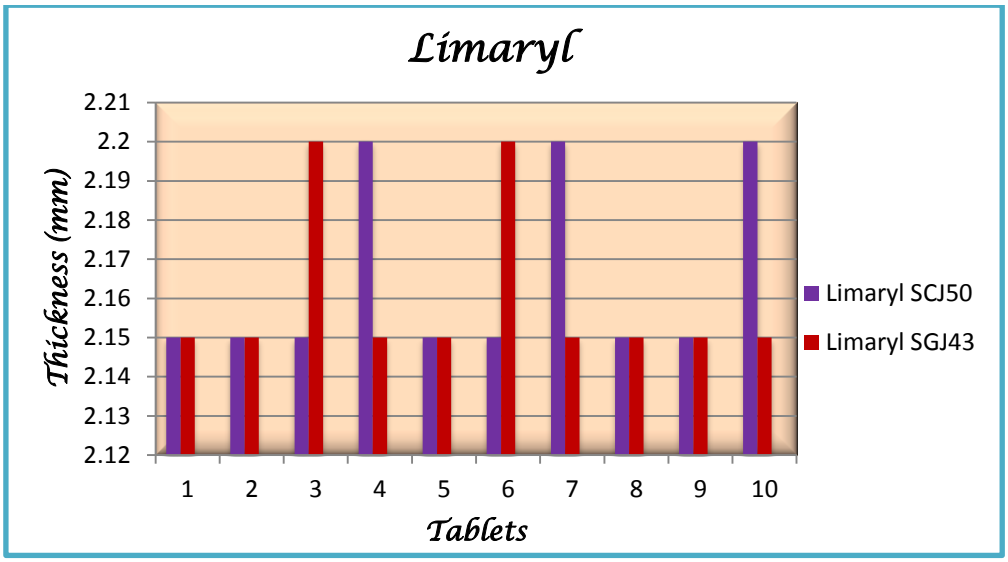


Figure 5.3: Thickness of two different batches of Limaryl tablets

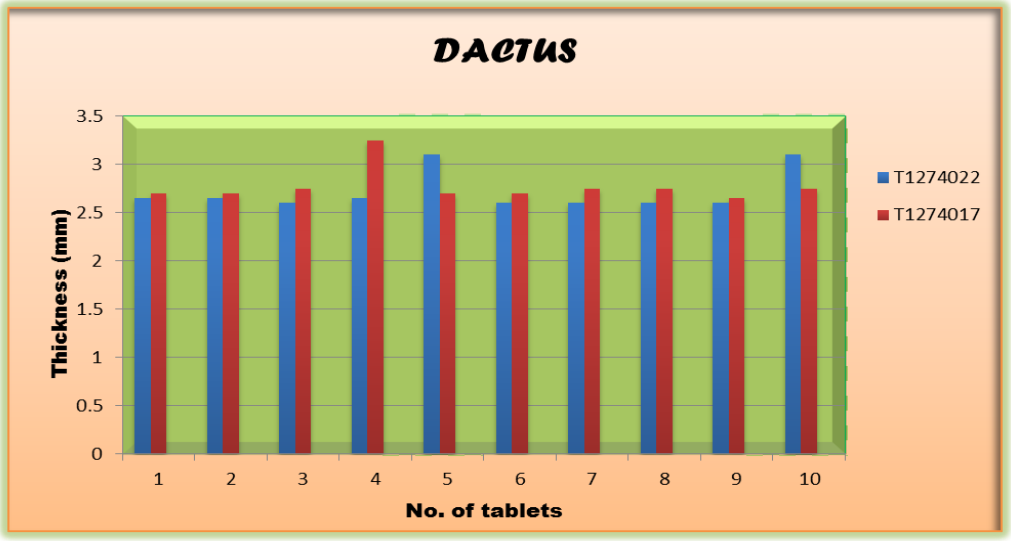


Figure 5.4: Thickness test of different batch of Dactus tablets

According to the USP specification, the range for tablet thickness is ±5mm. The batch to batch thickness variation of Dactus tablet is identical and the thickness of the tablets of two different batches was same. So, it can be concluded that the manufacturing process is accurately follow the compendial method. Tablet thickness test provides an idea about the compressive strength during compression process. Thickness was always an issue when tablets are considered. If the tablet is thicker than it cannot be swallowed by an average person. On the other hand, if the tablet is less thick then it can breakdown easily.

5.3 Hardness Test

According to the conducted research study, the hardness test of Limaryl tablets had the range from 1.8 kg/cm to 2.00 kg/cm (Batch no. SCJ50) and 1.8kg/cm to 2 kg/cm (Batch no. SGJ43)

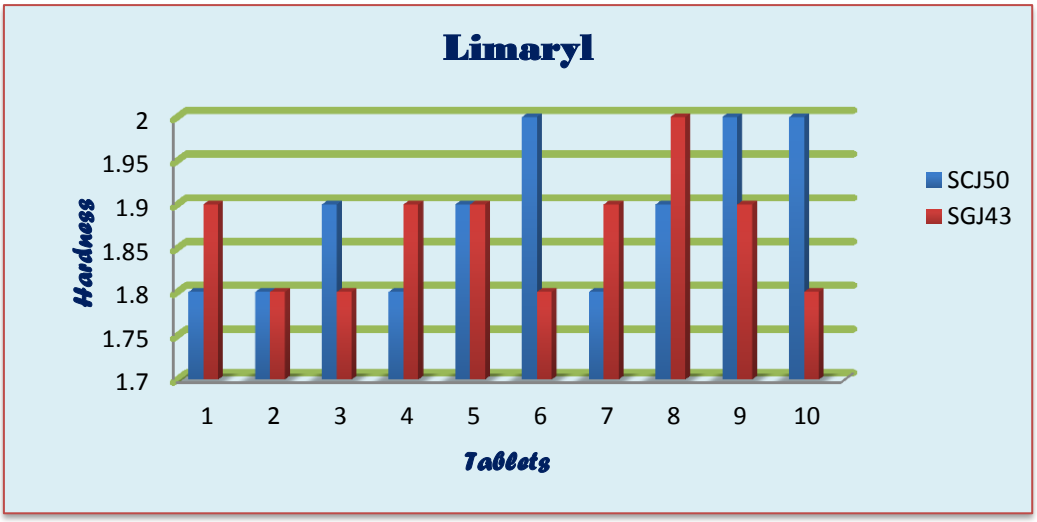


Figure 5.5: Hardness of Limryl tablets

According to the conducted research study, the hardness test of Dactus tablets had the range from 1.7 kg/cm to 2.1 kg/cm (Batch no. T4022) and 1.8kg/cm to 2.1 kg/cm (Batch no. T4017).According to BP and USP range of hardness test is 4 kg. So that all the tablets of these two brands did not fulfill the specification. If hardness is below the range than it may cause breakage during storage and transportation.

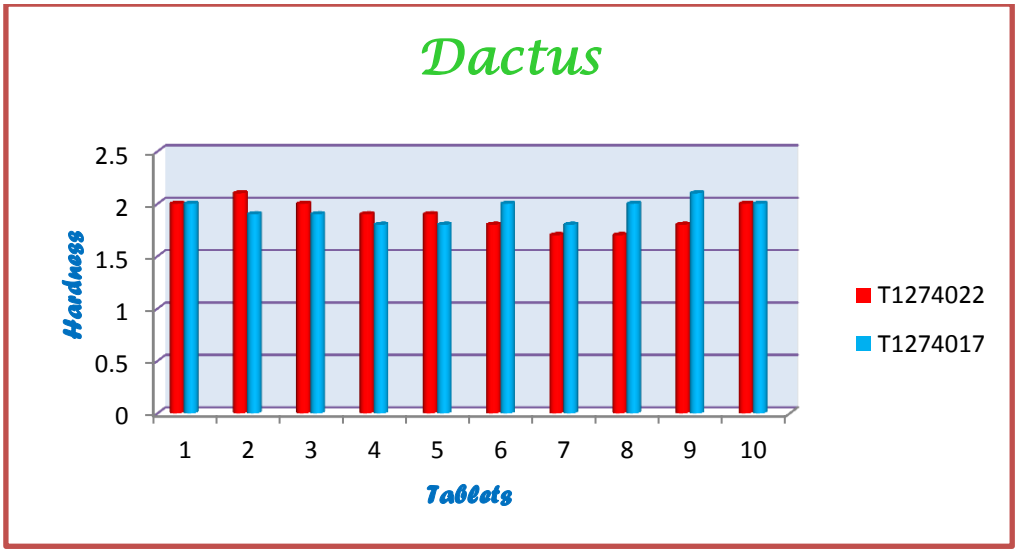


Figure 5.6: Hardness of Dactus tablets

5.4 Disintegration Test

Disintegration is the pre step of dissolution. Disintegration is a process by which the surface area of a tablet is increased by fragmentation to promote rapid release of the drug. Disintegration tests helps to measure whether a tablet has the ability to break down into particles under specified conditions or not. In this research study, the disintegration time of two batch of Limaryl tablets had the range from 6 min 7 seconds to 7 minutes 4 sec (Batch no.SCJ50) and 6 min 26 sec to 7 min 54 sec (Batch no. SGJ43). On the other hand, the disintegration time of Dactus tablets are much higher. The Dactus tablets had the range from 1 min 33 sec to 3 min 55 sec (Batch no. T4017) and 3 min 42 sec to 4 min 38 sec (Batch no. T4022).

According to the BP, the disintegration time for uncoated tablets should be within 15 minutes. The disintegration time of Limaryl and Dactus tablets is within the acceptable range which clearly indicates that these tablets could satisfy the desired purpose for which it is used (15 minutes). (USP, 2003)

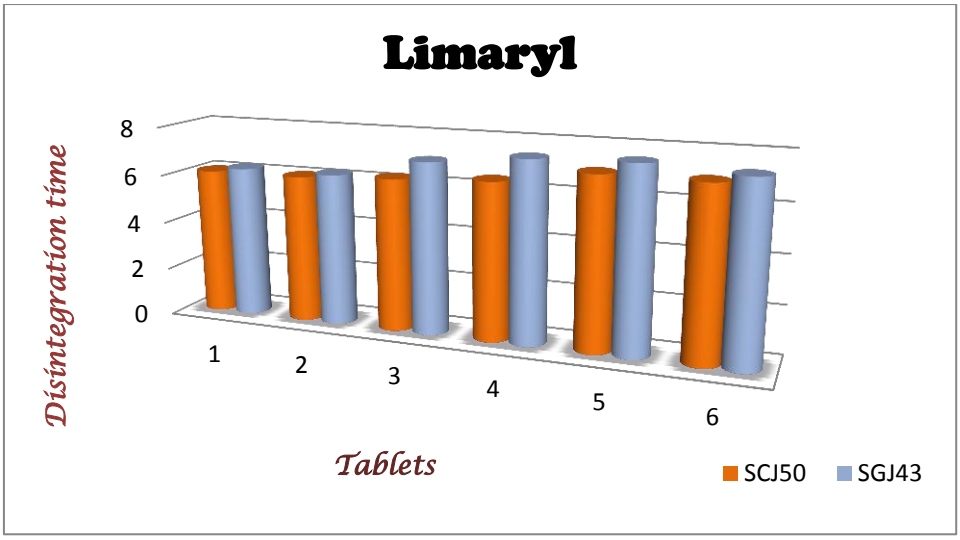


Figure 5.7: Disintegration of Limaryl tablets

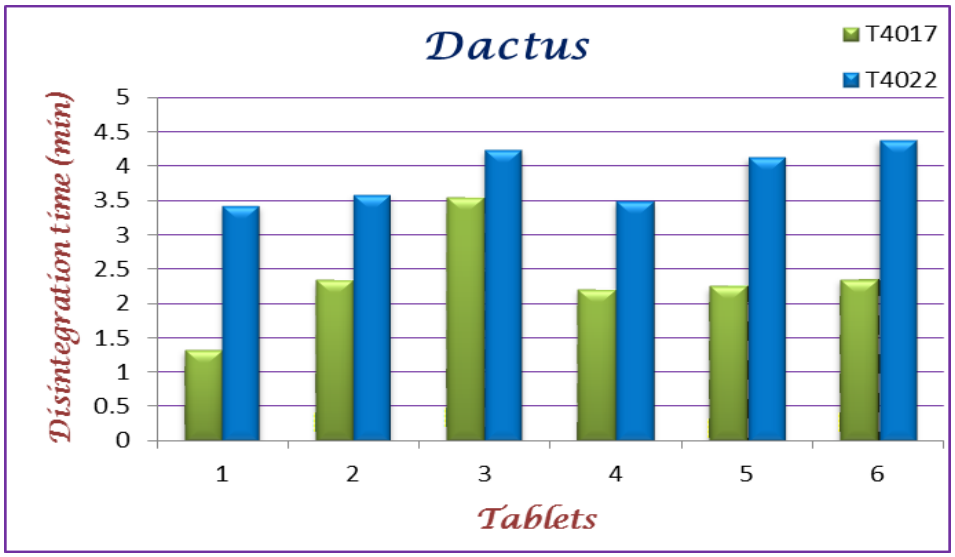


Figure 5.8: Disintegration of Dactus tablets

5.5 Dissolution Test

Dissolution test is done to determine compliance with dissolution requirements for a solid dosage form. It is considered as the rate limiting step in the sequence of steps leading to absorption of the drug into systemic circulation. Absorption is the process of transporting the drug substances from the gastrointestinal lumen into the systemic circulation. It is the first step before the distribution, metabolism and elimination (ADME) properties of drugs in the human body.

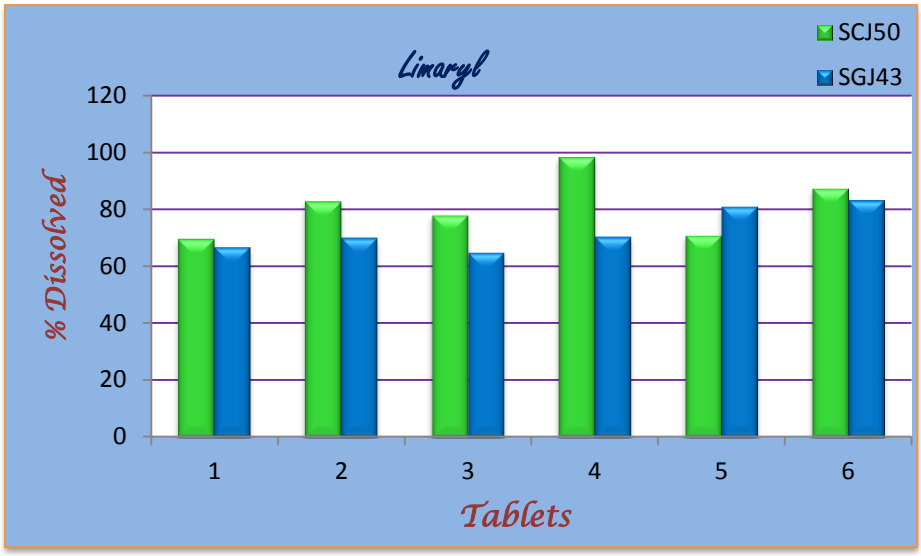


Figure 5.9: Dissolution of two different batches of Limaryl tablets

The above graph represent that Limaryl tablets had the dissolution ranges from 69.65% to 98.35% (Batch no.SCJ50) and from 64.82% to 83.19% (Batch no.SGJ43) within 30 minutes. In batch no. SCJ50 average % Dissolved is 81.207% and in batch SGJ43 average % Dissolved is 72.66%. But 3 tablets from batch no. SCJ50 and 4 tablets from batch no. SGJ43 were below the range.

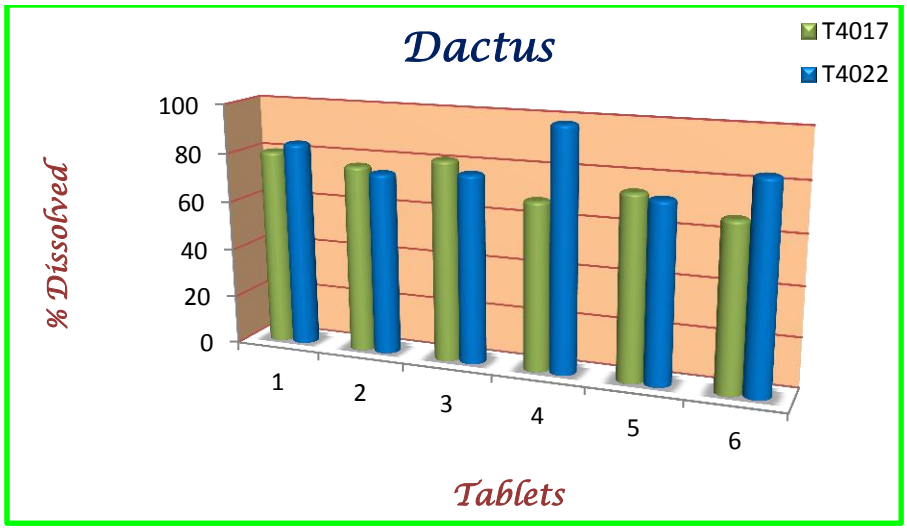


Figure 5.10: Dissolution of two different batches of Dactus tablets

DACTUS tablets had the dissolution ranges from 67.39% to 81.58% (Batch no.T1274022) and from 72.55% to 98.35% (Batch no.T1274017) within 30 minutes. In batch no.T1274022 average % Dissolved is 74.81% and in batch T1274017 average % Dissolved is 81.69%. 4 tablets from batch T1274022 and 3 tablets from batch T1274017 were lower than the range.

So that, six more tablets from each batches of two brands need to perform re-dissolution test and if the dissolution have failed to meet the specification then another 12 more tablets need to reexamine whether the dissolution is within the range or not.

5.6 Potency

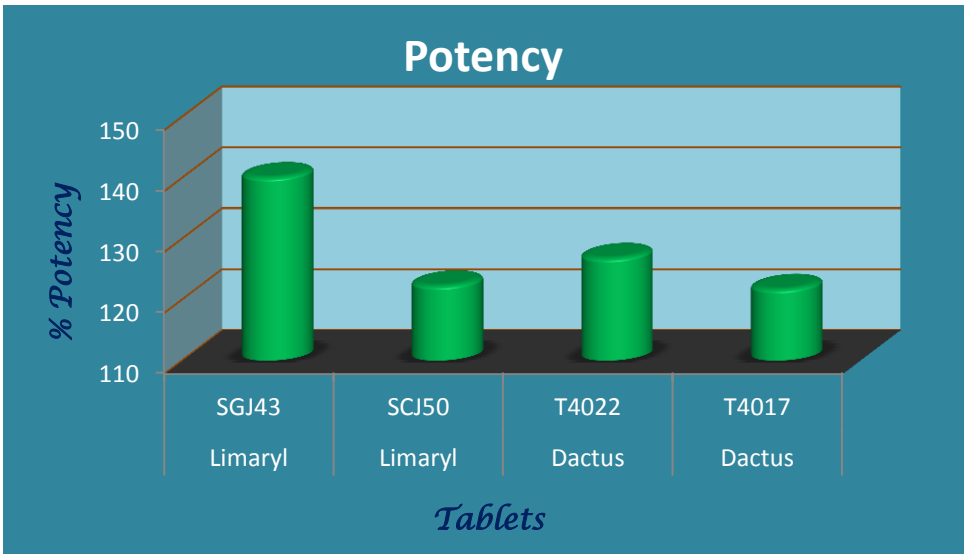
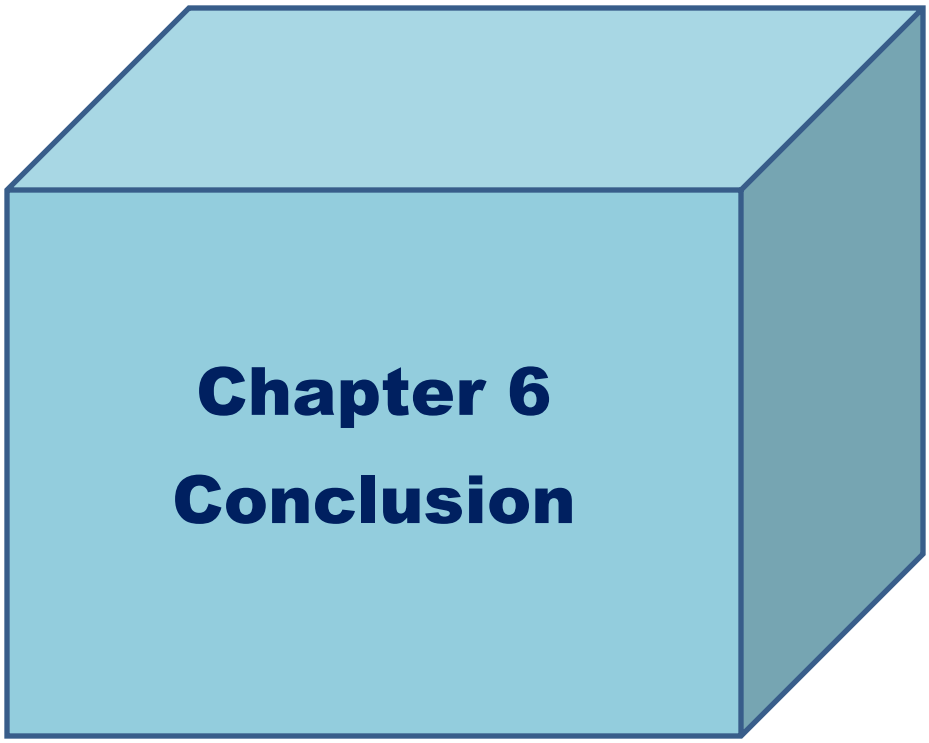


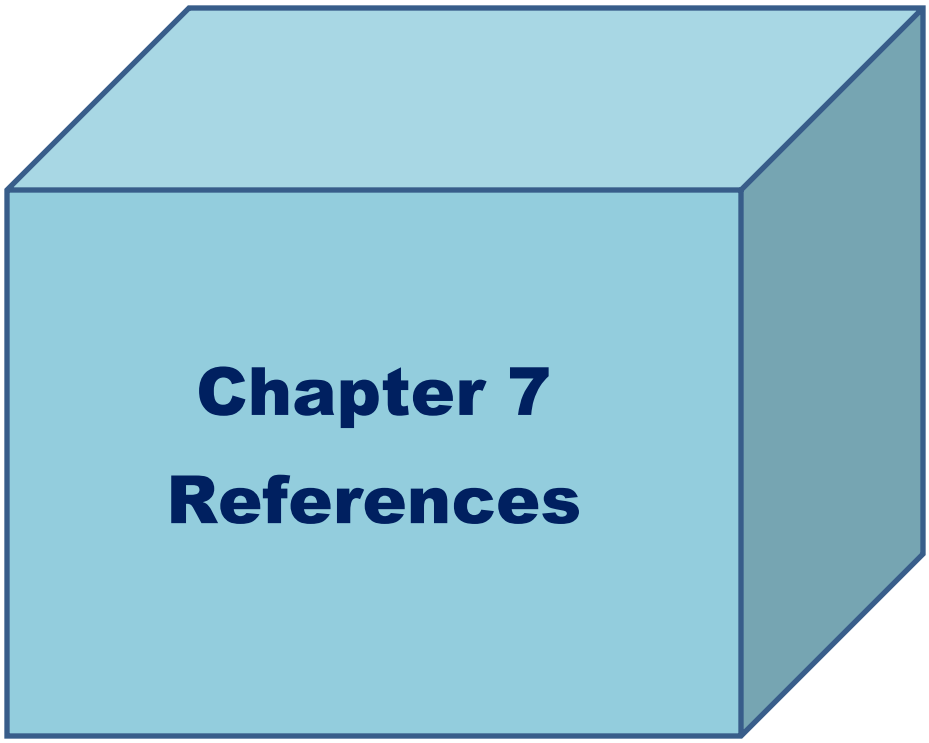
Figure 5.11: Potency value of two brands of glimepiride tablet each with two batches.

The assay of the two different brands (Limaryl and Dactus) of glimepiride showed potency that ranges from 121.75 to 140.11. But it varies from batch to batch and according to the BP and USP the acceptance level of percent potency of potent drug lies from 100 ± 5% or 95-105%. The above graph represents that the percent potency of Limaryl (SCJ43) is 140.11% which is out of the range and one batch of Limaryl(SGJ50) is 122.32.It is also out of the range and both batch of Dactus (T4022 and T4017) tablets are not within the acceptable range of BP and USP. This variation could also may result from various factors like storage, temperature condition, environmental condition of the place where the test is performed transportation, etc. As, there are many batches available in the local market we need to perform potency test with more tablets of these two brands. If that time potency test do not meet the specification only then we can say the potency of these two brands are not within the range. But all the batches of all the brands should be within the range or have to meet the criteria of the compendium (USP, 2003).


Chapter 6
Conclusion

Chapter 6: Conclusion

Diabetes is projected to become one of the world's main disablers and killers within the next twenty-five years. Immediate action is needed to stem the tide of diabetes and to introduce cost-effective treatment strategies to reverse this trend. So that more research should be conducted for anti-diabetic drugs and also quality parameters of the pharmaceutical products are very important for optimum efficacy, safety and cost effective treatment. In this research study quality control parameter of two brands (Limaryl and Dactus) were observed by undergoing with the process of weight variation test, thickness test, hardness test, disintegration test, dissolution test and potency test. It was observed that maximum batches of different brands of Limaryl and Dactus in the quality control parameter test have passed with the specifications described in USP and BP. For example, in weight variation test and thickness test all the tablets have passed and disintegration time of all the tablets was within the acceptable range. But dissolution rate of two brands did not match the specification according to BP. Hardness test and Potency test is also deviated from the acceptable range of BP and USP. This may occur due to formulation or processing error or may be due to deviation from proper storage conditions or may be for my personal error and various other factors. So, care should be taken during manufacturing and storage of tablets. As the friability study could not be performed due to some technical faults in the instrument, so there was a considerable variation in quality parameters within these two brands. So that further research should be conducted on these two brands of similar batches or different batches of glimepiride for the improvement of these brands and to fulfill all the specification.


Chapter 7
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Chapter 7: References

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