Evaluation of the Quality Control Parameters of Two Different Brands (Losucon and Dieta) of Glimepiride Tablets 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, **Samiul Islam Sikder**, hereby declare that the dissertation entitled "Evaluation of the Quality Control Parameters of Two Different Brands (Losucon and Dieta) of Glimepiride Tablets 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 the Quality Control Parameters of Two Different Brands (Losucon and Dieta) of Glimepiride Tablets 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 Samiul Islam Sikder, ID: 2011-1-70-026 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 the Quality Control Parameters of Two Different Brands (Losucon and Dieta) of Glimepiride Tablets 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 Samiul Islam Sikder, ID# 2011-1-70-026.

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This Research Paper is

Dedicated

To

My Beloved Parents

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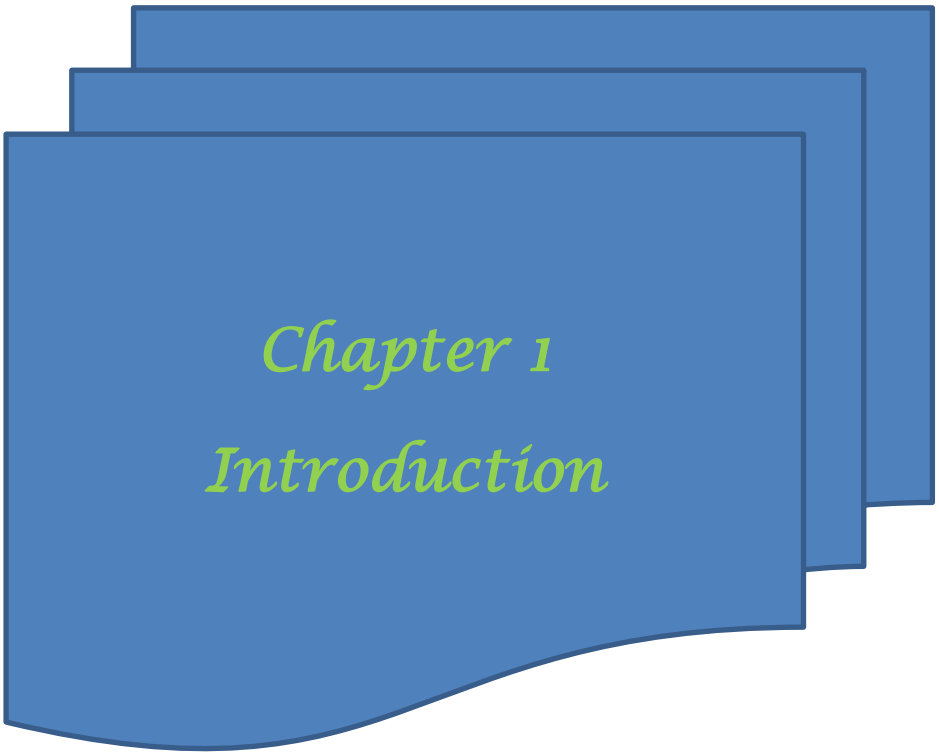
LIST OF ACRONYMS

ACRONYMS	EXPANSIONS
U.S. FDA	United States Food & Drug Administration
IDDM	Insulin Dependent Diabetes Mellitus
NIDDM	Non – Insulin Dependent Diabetes Mellitus
STD	Standard
ADME	Absorption, Distribution, Metabolism & Elimination
BP	British Pharmacopeia
USP	United States Pharmacopeia
WHO	World Health Organization
IVIVC	In vitro-in vivo correlation
BMI	Body Mass Index
GLUT2	Glucose Transporter 2
CYP2C9	Cytochrome P2C9
FDA	Food and Drug Administration

Abstract

Evaluation of the quality control parameter is always a better way for the understanding of the quality of local brands. Thus, the purpose of this research work was to determine the physical quality control parameter and the potency of two different brands (Losucon and Dieta) of glimepiride 2mg tablets (Two batches of each) which is used for the treatment of type II diabetes.According to the research study all the tablets showed a percentage weight variation within the range and meet the specification of USP. Thicknesses test of all the tablets of two different brands represents variable results but was also within acceptance range. All the tablets of these two brands had hardness lower than the standard value of 4 kg which can cause breakdown of tablets during use and transport. All the tabletsmeet the specification for disintegration time in accordance to BP. Average percent dissolution of all the batches meet the specification range. But some tablets individually were not dissolved 80% within 30 minutes. Both batches of Losucon meet the specification of potency (103.67% and 108.47%) according to BP and USP where the batches of Dieta had failed. All the test result were confirmed with the calculation of their standard deviation. As the friability study could not be performed due to some technical faults, further research for assuring the quality of drug in the local market should to be conducted.

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


Chapter 1
Introduction

Chapter 1: Introduction

1.1 Diabetes

Diabetes mellitus is commonly referred to as diabetes. Diabetes is not a single disease. Rather, it is a heterogeneous group of syndromes characterized by an elevation of blood glucose levels over a prolonged period by a relative or absolute deficiency of insulin. Insulin is a peptide hormone which is secreted from pancreatic β cells located in the islets of Langerhans. These hormones usually play an important role in regulating the metabolic activity of the body, particularly the homeostasis of blood glucose levels.

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 nonketotic hyperosmolar coma, diabetic ketoacidosis and serious long term complications include kidney failure, stroke, foot ulcers, cardiovascular disease and damage to the eyes.

Diabetes is due to either the body not responding properly to the insulin produced or the pancreas not producing enough insulin. (Clark *et al*., 2012)

1.1.1 Types of Diabetes Mellitus

There are four broad categories of diabetes mellitus,

1. Type 1 diabetes (insulin dependent diabetes mellitus)

2. Type 2 diabetes (non-insulin dependent diabetes mellitus)

3. Gestational diabetes

4. Other specific types (for example, genetic defects or medications) (Clark *et al*., 2012)

1.1.1.1 Type 1 Diabetes Mellitus

Type 1 diabetes most commonly afflicts individuals in puberty or early adulthood, but some latent forms can occur later in life. These diabetes mellitus is characterized by loss of the insulin producing beta cells of the islets of Langerhans in the pancreas, leading to insulin deficiency. Loss of β cell function is usually ascribed to autoimmune mediated processes directed against the β cell, and it may be triggered by an invasion of viruses or the action of chemical toxins. As a result of the destruction of these cells, the pancreas fails to respond to glucose, and the type 1 diabetic shows classic symptoms of insulin

deficiency (polyphagia, polydipsia, polyuria and weight loss). Exogenous insulin is requiring for type 1 diabetes to avoid the catabolic state. (Clark *et al*., 2012)

Risk Factors:

There are some medical risks associated with type 1 diabetes,

- Viral infections
- Race/ethnicity
- Geography
- Family history
- Early diet
- Other autoimmune conditions

Signs and Symptoms:

- Nausea
- Fatigue
- Polyuria
- Polydipsia
- Polyphagia
- Blurred vision
- Unexplained weight loss. (Webmd.com, 2015)

Management:

Glycemic control: The benefits of glycemic control include continued reductions in the rates of micro vascular complications, significant differences in cardiovascular events and overall mortality.

Self-monitoring: Self-monitoring allows rational adjustment in insulin doses. The patients with type 1 diabetes should learn how to self-monitor and how they record their blood glucose level with home analyzers and adjust their insulin doses accordingly. Real time continuous glucose monitors (CGMs) can be used in glycemic control. These CGMs contain subcutaneous sensor which can measure intestinal glucose levels every 1-5 minutes and can provide alarms when glucose levels are too high or too low.

Insulin therapy: A person with type 1 diabetes must rely on exogenous insulin to control hyperglycemia, avoid ketoacidosis, and maintain acceptable levels of glycosylated hemoglobin (HbA1c). Most require 2 or more injections of insulin daily, and the doses

adjusted on the basis of self-monitoring of blood glucose levels. Insulin replacement is done by giving basal insulin and a pre-prandial insulin. This basal insulin is either long acting or intermediate acting and the pre-prandial insulin is either rapid-acting or short acting.(Khardori, 2010)

1.1.1.2 Type 2 Diabetes Mellitus

Most diabetic patients have type 2 diabetes. Type 2 diabetes is influenced by genetic factors, aging, obesity, lack of physical activity, poor diet, stress, urbanization and peripheral insulin resistance, rather than by autoimmune processes or virus.

Development of type 2 diabetes is also influenced by some dietary factors. Consumption of sugar-sweetened drinks in excess is associated with an increased risk. Eating lots of white rice appears to also play a role in increasing risk. Lack of exercise is believed to cause about 7% of cases.

In the early stage of type 2 diabetes, reduced insulin sensitivity is the predominant abnormality. At this stage, these hyperglycemia can be reversed by a variety of measures and medications which improve insulin sensitivity or reduce glucose production by the liver. (Clark *et al*., 2012)

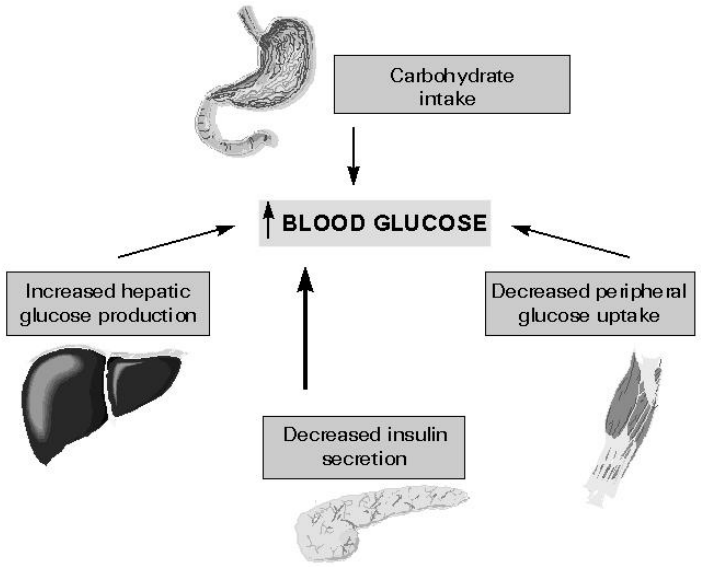


Figure 1.1: Simplified scheme for the pathophysiology of type 2 diabetes mellitus

Risk Factors:

- Obesity
- Family history

- Metabolic syndrome
- Lack of physical activity
- Impaired fasting glucose
- Impaired glucose tolerance
- Polycystic ovarian syndrome
- History of gestational diabetes
- Drug therapy (e.g., combined use of a thiazide diuretic with a beta-blocker). (Tidy, 2015)

Sign and Symptoms:

Patients with type 2 diabetes are symptomatic. Clinical manifestation include,

- Blurred vision
- Lower external paresthesias
- Yeast infections (e.g., balanitis in men)
- Classic symptoms: Polydipsia, Polyphagia, Polyuria and weight loss. (Khardori, 2010)

Management:

Patient education:

- Encouraged regular physical activity.
- A systematic patient education should be made available to all people with diabetes.
- Discuss diet and give dietary advice, taking into account other factors- e.g., hypertension, obesity and renal impairment.
- There are some suitable programs like Diabetes Education and Self-Management for Ongoing and Newly Diagnosed (DESMOND) Diabetes program.

Initial assessment and monitoring:

- Check smoking status and offer cessation advice as appropriate.
- Check height, weight, calculate BMI and also measure waist circumference which is significantly associated with cardiovascular disease.
- Glucose control: Self-monitoring of plasma glucose to a person newly diagnosed with type 2 diabetes only as an integral part of his or her self-management education. Self-monitoring should be available to those on insulin, oral glucose

lowering treatment. If blood glucose testing is unacceptable then urine glucose monitoring should be offered.

Management of glucose control:

The recommended steps for glucose control in the National Institute for Health and Care Excellence guidance are,

- Metformin
- Metformin and sulfonylurea
- Add thiazolidinedione or insulin
- Insulin, metformin and sulfonylurea
- Increase the insulin dose and intensity over time. (Tidy, 2015)

1.1.1.3 Gestational Diabetes

Gestational diabetes is a form of glucose intolerance that is diagnosed in some women during pregnancy. It occurs in about 2-10% of all pregnancies and may improve or disappear after delivery. However, approximately 5-10% of women after pregnancy with gestational diabetes are found to have diabetes mellitus, most commonly type 2 diabetes. Women who have had gestational diabetes have a 20% to 50% chance of developing diabetes in next 5-10 years. This gestational diabetes more frequently occurs among the African American, Hispanic/ Latino Americans and American Indians. It is also more common among obese women and women with a family history of diabetes.

During pregnancy gestational diabetes requires treatment to normalize maternal blood glucose level to avoid complications in infant. (Webmd.com, 2015)

Risk Factors:

- Having sugar in urine
- Family history of diabetes
- Impaired glucose tolerance
- Having too much amniotic fluid
- Being overweight prior to becoming pregnant
- Previously giving birth to a baby over 9 pounds
- Being a member of ethnic group (Black, Asian, Native American, Hispanic)

Management:

Gestational diabetes is managed by,

- Monitoring weight gain
- Controlling high blood pressure
- Monitoring blood sugar levels four times per day
- Taking insulin or an oral hypoglycemic medication
- Following specific dietary guidelines as instructed by the doctor
- Exercising after getting permission from the health care providers Monitoring urine for ketones, an acid which indicates diabetes is no under control. (Webmd.com, 2015)

1.1.1.4 Other Types

Other specific types of diabetes result from specific genetic conditions (such as maturity-onset diabetes of youth), drugs, malnutrition, surgery, infections and other illness.

These types of diabetes may account for 1% to 5% of all diagnosed case of diabetes.

1.1.2 Treatment of Diabetes Mellitus

A major factor need to consider before appropriate pharmacologic therapy is whether the patient is insulin deficient, insulin resistant or both. Treatment option can be divided into several subgroups. (Katzung *et al*., 2010)

Table 1.1: Noninsulin therapies

Subgroup	Generic Name (Brand)	Class	Route	Comments
Biguanides	Metformin	Sensitizer	Oral	Weight loss No hypoglycemia GI upset
Thiazolidinediones	Rosiglitazone Pioglitazone	Sensitizer	Oral	Weight gain Peripheral edema
Alpha glucosidase inhibitors	Acarbose Miglitol		Oral	GI upset No hypoglycemia

Sulfonylureas	Chlorpropamide Glibenclamide Glimepiride Glipizide Tolazamide Tolbutamide	Secretagogue	Oral	Hypoglycemia Weight gain
Glinides	Nateglinide Repaglinide	Secretagogue	Oral	Weight gain
Exenatide	Byetta	GLP-1 analog	Subcutaneous	Weight loss GI upset
Liraglutide	Victoza	GLP-1 analog	Subcutaneous	Weight loss Nausea
Extended release exenatide	Bydureon	GLP-1 analog	Subcutaneous	Weight loss Nausea
Pramlintide	Symlin	Incretin	Subcutaneous	Weight loss GI upset Adjunctive therapy with insulin
Dipeptidyl peptidase-4 inhibitors (DPP-4s)	Sitagliptin Saxagliptin Linagliptin	DPP-4 inhibitors	Oral	No hypoglycemia Nasopharyngitis Weight neutral
Rapid release bromocriptine	Cycloset	Other	Oral	Taken within 2 hours of awakening
SGLT-2 inhibitors	Canagliflozin Dapagliflozin	Renal glycosuria	Oral	Polyuria UTIs

(Katzung *et al*., 2010)

1.1.3 Mechanism of Action of Sulfonylureas

These agents are classified as insulin secretagogues, because the increase insulin release from the β cells of the pancreas. The primary drugs used today are the second generation drugs glyburide and glimepiride.

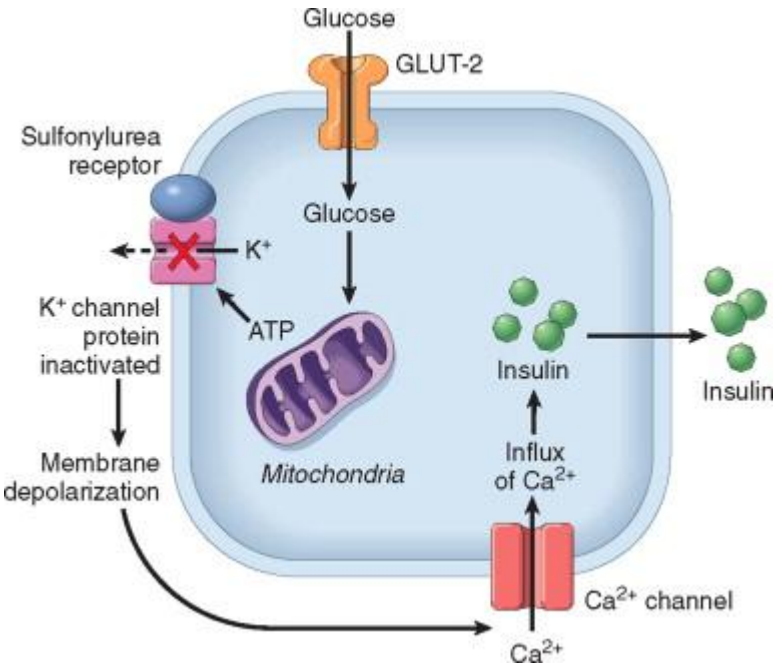


Figure 1.2: Mechanism of sulfonylurea drugs

Control of insulin release from the pancreatic beta cell by glucose and by sulfonylurea drugs. When the extracellular glucose concentration increases, more glucose enters the cell via the GLUT2 glucose transporter and leads, through metabolism, to increased intracellular ATP production with subsequent closure of ATP-dependent K+ channels, membrane depolarization, opening of voltage-gated Ca2+ channels, increased intracellular Ca2+, and insulin secretion. Sulfonylurea and other insulin secretagogues enhance insulin release by blocking ATP-dependent K+ channels and thereby triggering the events subsequent to reduced K+ influx. Drugs of sulfonylurea group include, Cholrpropamide, Glibenclamide, Glimepiride, Glipizide, Tolazamide, Tolbutamide. (Katzung *et al*., 2010)

1.2 Glimepiride

Glimepiride is used along with exercise, diet, and sometimes with other medications to treat type 2 diabetes (when the body does not use insulin normally and, for these reason the blood sugar level cannot control). Glimepiride lowers blood sugar by causing the pancreas to produce insulin and helping the body to use insulin efficiently. If the patients whose bodies produce insulin naturally, this medication will only help to lower blood sugar. Glimepiride is not used to treat type 1 diabetics or diabetic ketoacidosis (a serious condition that may occur if high blood sugar is not treated). (ASHP, 2015)

1.2.1 Chemistry

- Name: Glimepiride
- IUPAC Name: 4-ethyl-3-methyl-N-[2-[4-[(4 methylcyclohexyl) carbamoylsulfamoyl] phenyl]ethyl]-5-oxo-2H-pyrrole-1-carboxamide
- Molecular Structure:

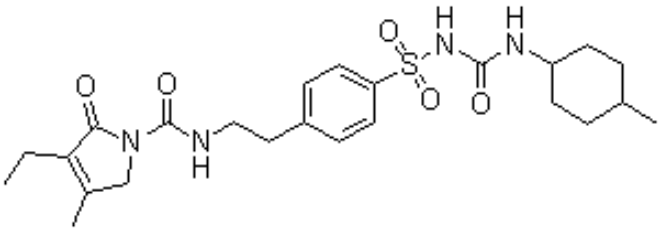


Figure 1.3: Glimepiride

- Molecular Formula: $C_{24}H_{34}N_4O_5S$
- Melting point: 212-214°C
- Average mass: 490.616 Da
- Mono isotopic mass: 490.224976 Da
- Appearance: white or almost white powder.
- Solubility: Practically slightly soluble in water, soluble in dimethylformamide, slightly soluble in methylene chloride, very slightly soluble in methanol. (Chemicalbook.com, 2010)

1.2.2 Mechanism of Action

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

1.2.3 Pharmacokinetics

Absorption:

Bioavailability: Glimepiride absorbed completely. Oral bioavailability of glimepiride is about 100%. Peak blood concentration attained within 2-3 hours. Combination of 4 mg glimepiride and 4 mg rosiglitazone is bioequivalent to the individual components administered separately even at the same dosages.

Onset: Maximum effect is given within 2-3 hours. The glucose-lowering effect is persists for 24 hours. Food increases the time to peak blood concentrations by about 12%.

Distribution:

The volume of glimepiride distribution is about 8.8 L (113 ml/kg) and plasma protein binding is about 99.5%.

Metabolism:

Glimepiride is metabolized by CYP2C9 and by cytosolic enzymes to active and inactive metabolites.

Elimination:

Metabolites are predominantly eliminated through urine (60%) and faces (40%).

Half-life:

The half-life of a single dose in healthy individuals on averages 5.3 hours. Patients with type 2 diabetes are about 9.2 hours at steady state. (Drugs.com, 2013)

1.2.4 Uses of Glimepiride

Glimepiride is used to treat a patient with type 2 diabetes who cannot control blood sugar levels by exercise and diet alone. It is used along with diet and exercise. It can be used alone or with other anti-diabetic medicines. It works by causing the pancreas to release insulin, which helps to lower blood sugar.

1.2.5 Process to Use Glimepiride

Use glimepiride as directed by a doctor. Check the label on the medicine for exact dosing instructions.

- Usually glimepiride is taken with breakfast or the first main meal of the day unless the doctor tells otherwise.
- Glimepiride works best if it is taken at the same time each day.
- Need to continue the use of glimepiride even a patient feel well. Do not miss any doses.
- If a patient miss a dose of glimepiride, need to take it as soon as possible. If it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not take 2 doses at once. (Drugs.com, 2013)

1.2.6 Dosage

Usual Adult Dose for Diabetes Type 2

- Initial dose: 1 to 2 mg orally once a day.
- Maintenance dose: 1 to 4 mg orally once a day.
- Glimepiride should be administered with breakfast or the first main meal. Maximum recommended dose is 8 mg per day.

Usual Geriatric Dose for Diabetes Type 2

- Initial dose: 1 mg orally once a day.
- Maintenance dose: 1 to 4 mg orally once a day.

Usual Pediatric Dose for Diabetes Type 2

>8 years:

- Initial dose: 1 to 2 mg orally once a day.
- Maintenance dose: 1 to 4 mg orally once a day.
- Glimepiride should be administered with breakfast or the first main meal. Maximum recommended dose is 8 mg per day.

Renal Dose Adjustments

CrCl< 30 mL/min:

- Initial dose: 1 mg orally once a day.
- Maintenance dose: 1 to 4 mg orally once a day.

Liver Dose Adjustments

After reaching a dose of 2 mg, dosage increases should be made in increments of no more than 2 mg at 1 or 2 week intervals. Glimepiride should be used with caution in patients with hepatic insufficiency.

Other Comments:

Administration advice: Glimepiride should be administered at least 4 hours prior to colesevelam to ensure that colesevelam does not reduce the absorption of glimepiride. (Drugs.com, 2013)

1.2.7 Possible Side Effects of Glimepiride

Severe allergic reactions (rash, hives, itching, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue), low blood sugar symptoms (e.g., anxiety, dizziness, drowsiness, fast heartbeat, headache, lightheadedness, tremors, unusual sweating, weakness), chest pain or irregular heartbeat, unusual bruising or bleeding, unusual tiredness or weakness, yellowing of the eyes or skin, confusion, dark urine, fainting, fever, chills, or persistent sore throat, severe or persistent blurred vision or other vision problems. (Drugs.com, 2013)

1.2.8 Overdose

If overdose is suspected the symptoms may include,

Coma, anxiety, tremor, nightmares, seizures, severe dizziness or drowsiness, confusion, fainting, shakiness, fast heartbeat, lethargy, lightheadedness, blurred vision, slurred speech, unusual sweating.

1.2.9 Contraindications

- Glimepiride tablets are contraindicated if a patients with a history of a hypersensitivity reaction to glimepiride or any of the product's ingredients.
- Patients who have developed an allergic reaction to sulfonamide derivatives may develop an allergic reaction to Glimepiride. Do not use Glimepiride in patients with a history of an allergic reaction to sulfonamide derivatives.
- If a patient have moderate to severe burns, or very high blood acid levels (acidosis) glimepiride should not be used.

- Reported hypersensitivity reactions include cutaneous eruptions with or without pruritus as well as more serious reactions (e.g. anaphylaxis, angioedema, Stevens-Johnson Syndrome, dyspnea). (Drugs.com, 2013)

1.2.10 Drug Interactions

- Drug Affecting Hepatic Microsomal Enzymes: Pharmacokinetic interaction occurs with the drugs that are CYP2C9 inducer or inhibitors, which ultimately alter the metabolism of glimepiride.
- Drug with Hyperglycemic Effects: Potential pharmacologic interaction is loss of glycemic control.
- Protein-bound Drugs: Potential pharmacokinetic interaction is increased hypoglycemic effect.

1.2.11 Storage

Glimepiride should be kept in a well closed container at 15-30°C.

1.3 Quality

The quality of a product may be defined as "its ability to fulfill the customer's needs and expectations". Quality needs to be defined firstly in terms of parameters or characteristics, which vary from product to product. For example, for a mechanical or electronic product these are performance, reliability, safety and appearance. For pharmaceutical products, parameters such as physical and chemical characteristics, medicinal effect, toxicity, taste and shelf life may be important. For a food product they will include taste, nutritional properties, texture and shelf life etc. (Waleed *et al*., 2001)

1.3.1 Quality of Pharmaceutical Products

Quality is always an imperative prerequisite when we consider any product. It becomes primary when it relates to life saving products like pharmaceuticals. Although it is mandatory from the government and regulatory bodies but it is also a fact that quality of a pharmaceutical product cannot be adequately controlled solely by pharmacopoeia analysis of the final product. Today quality has to be built in to the product right from its inception and rigorous international environmental, safety and regulatory standards need to be followed. Validation had proven to be an important tool for quality management of pharmaceuticals.

Most traditional pharmaceutical drugs are relatively simple molecules that have been found primarily through trial and error to treat the symptoms of a disease or illness. Over period of time these molecules were perfected to ensure quality. The quality is very much related to every pharmaceutical product. Without quality pharmaceutical drug cannot be marketed or sold, because it can cause many problems such as sub therapeutic or over dose. Among the dosage forms of the drugs, tablet is the most suitable and famous dosage form. Tablet is mainly known for its characteristics such as easy to swallow, availability, affordability etc. so it is a big issue for the pharmaceutical industries to make and maintain quality tablets. If a drug of any brand or company is not a quality product than it also causes problems when prescribed to the patients. The patients may suffer from the adverse effects of that drug because of its faulty quality. This would not have happened if the drug was a quality product. (Aulton, 2002)

1.3.2 Quality Assurance

Quality control emphasizes testing of products to uncover defects, and reporting to management who make the decision to allow or deny the release, whereas quality assurance attempts to improve and stabilize production, and associated processes, to avoid, or at least minimize, issues that led to the defects in the first place. The assurance of product quality depends on more than just proper sampling and adequate testing of various components and the finished dosage form. Prime responsibility of maintaining product quality during production rests with the manufacturing department. Removal of responsibility from manufacturing for producing a quality product can result in imperfect composition, such as ingredients missing, subpotent or superpotent addition of ingredients, or mixing of ingredients; mistakes in packaging or filling, such as product contamination, mislabeling, or deficient package; and lack of conformance to product registration. Quality assurance personnel must establish control or checkpoints to monitor the quality of the product as it is processed and upon completion of manufacture.

Because of the increasing complexity of modern pharmaceutical manufacturing arising from a variety of unique drugs and dosage forms, complex ethical, logical and economic responsibilities have been placed on those concerned with the manufacture of modern pharmaceuticals. An awareness of these factors is the responsibility of all those involved in the development, manufacture, control, and marketing of quality products. (Lachman *et al.*, 2008)

1.3.3 Quality Control

The concept of total quality control refers to the process of striving to produce a perfect product by a series of measures requiring an organized effort by the entire company to prevent or eliminate errors at every stage in production. Although the responsibility for assuring product quality belongs principally to quality assurance personnel, it involves many departments and disciplines within a company. The quality of products is dependent upon that of the participating constituents, some of which are sustainable and effectively controlled while others are not.

If the specification does not reflect the true quality requirements, the product's quality cannot be guaranteed. For instance, the parameters for a tablet vessel should cover not only the material and dimensions but operating, environmental, safety, reliability and maintainability requirements.

To be effective, it must be supported by a team effort. Quality must be built into a drug product during 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. It also includes preformulation, physical, chemical, therapeutic and toxicological considerations. (Lachman *et al*., 2008)

1.3.4 Quality Control of Drug

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. Requirements governing the quality control of pharmaceuticals in accordance with the Canadian Food and Drugs Act are cited and discussed. (Drugs.com, 2013)

1.3.5 Importance of Quality Control Study

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)

1.3.6 Quality Parameter Test

Quality parameter tests are performed as per the pharmacopoeial standards. These tests are measure of the quality of the various dosage form of drug. Each of the pharmacopoeia like the USP, BP, IP etc each have their own set of standards and specify disintegration tests of their own. USP, European pharmacopoeia and Japanese pharmacopoeia have been harmonized by the International conference on Harmonization (ICH) and are interchangeable. (BP, 2012)

1.3.7 Quality Control Parameters of Solid Dosage Form

Most preferable dosage form in pharmaceutical, to clinician and physician and most importantly to patients is tablet. Tablets give good patient compliance. The physiochemical properties of this combination tablets were assessed through the evaluation of uniformity of tablet weight, thickness test, hardness test, friability test, disintegration test, dissolution test and potency test according to the standard method. (Shohin *et al*., 2011)

Generally there are two types of tests:

i. Compendial tests

ii. Non-compendial tests

Compendial test: Compendial tests are test methods that are described in the pharmacopoeias like United States Pharmacopeia (USP), British Pharmacopoeia (BP) etc. They are also known as official tests. They include:

- Weight variation test
- Disintegration test
- Dissolution test and
- Drug content test

Non-compendial test: These tests methods are not defined in the pharmacopeias and so that are referred as Non-compendial Tests or unofficial tests. They include:

- Friability test
- Hardness test and
- Thickness test. (Shohin *et al*., 2011)

1.3.7.1 Weight Variation Test

Tablet weight is mainly affected by factors such as tooling of the compression machine, head pressure, machine speed and flow properties of the powder. Inconsistent powder or granulate density and particle size distribution are common sources of weight variation during compression. Variation between tablet with respect to dose and weight must be reduced to a minimum. Uniformity of weight is an in process test parameter which ensures consistency of dosage units during compression. (BP, 2012)

Table 1.2:IP/BP & USP limits for tablet weight variation

IP/BP	Limit	USP
80 mg or less	± 10%	130mg or less
More than 80mg or Less than 250mg	± 7.5%	130mg to 324mg
250mg or more	± 5%	More than 324mg

(BP, 2012)

1.3.7.2 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)

1.3.7.3 Hardness Test

In this test method, the tablet is placed between two platens (jaws), one of which is attached to a load cell and the other to a motor which provides the mechanical drive. During testing, the motorized jaw drives forward pressing the tablet against the fixed jaw until such time as the tablet breaks whereupon the motorized jaw retracts and the load required to break the tablet is recorded. (Anabiotec.com, 2015)

1.3.7.4 Purpose of Hardness Test

1. To determine the need for pressure adjustment on the tableting machine

2. 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.

3. Hardness value differ with the instrument used allowed values 8-12 Kg. Tablet hardness usually affects drug dissolution and release, and it may affect bioavailability.

1.3.7.5 Factor Affecting the Hardness of Tablets

1. Compression of the tablet and compressive force.

2. Amount of binder, more binder more hardness.

3. Method of granulation in preparing the tablet (wet method gives more hardness than direct method, slugging method gives the best hardness). (Anabiotec.com, 2015)

1.3.7.6 Friability Test

Friability is the tendency for a tablet to chip, crumble or break following compression. This tendency is normally confined to uncoated tablets and surfaces during handling or subsequent storage. The basic Friability Tester comprises of a drum and a motor capable of rotating the drum at 25 rpm. The standard friability drum has an inside diameter of 287

mm and a depth of 38 mm and is fitted with a curved baffle which subjects the tablets to be tested to a drop of 156 mm. (Anabiotec.com, 2015)

1.3.7.7 Purpose of Friability Test of Tablet

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)

1.3.7.8 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.

1.3.7.9 Dissolution Test

Dissolution is the process by which a solid solute enters a solution. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. Dissolution is considered one of the most important quality control tests performed on pharmaceutical dosage forms and is now developing into a tool for predicting bioavailability, and in some cases, replacing clinical studies to determine bioequivalence. Dissolution behavior of drugs has a significant effect on their pharmacological activity. In fact, a direct relationship between in vitro dissolution rate of many drugs and their bioavailability has been demonstrated and is generally referred to as in vitro-in vivo correlation, IVIVC. (Lachman *et al.*, 2008)

1.3.7.10 Importance of Dissolution Study

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

2. Dissolution testing provides the means to evaluate critical parameters such as adequate bioavailability and provides information necessary to formulator in 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. (Lachman *et al.*, 2008)

1.3.7.11 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

1.3.7.12 Disintegration Test

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 the capsule shell gelatin is not of pharmacopoeial quality or it may imply several other reasons. And also if the disintegration time is not uniform in a set of samples being analyzed, it indicates batch inconsistency and lack of batch uniformity. (Anabiotec.com, 2015)

1.3.7.13 Purpose of Disintegration Test

Disintegration tests are performed as per the pharmacopoeial standards. 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. (Anabiotec.com, 2015)

1.3.8 Standards of the Quality

Standards are an important part in the measurement of quality of service to the people.

Pharmaceutical products can usually be tested and qualified by various Pharmacopoeias.

Current existing pronounced standards include:

- British Pharmacopoeia (BP)
- Japanese Pharmacopoeia (JP)
- European Pharmacopoeia (EP)
- United States Pharmacopoeia (USP)
- The International Pharmacopoeia (IP)

1.3.8.1 The British Pharmacopoeia

The British Pharmacopoeia (BP) is the official collection of standards for UK medicinal products and pharmaceutical substances. Produced by the British Pharmacopoeia

Commission Secretariat of the Medicines and Healthcare products Regulatory Agency, the BP makes a valuable contribution to public health by setting publicly available standards for the quality of medicines. Now used in almost 100 countries, the BP is recognized by the US FDA as an official compendium, and remains an essential reference for anyone working within pharmaceutical research and development, manufacture and quality testing worldwide.

1.3.8.2 The Japanese Pharmacopoeia

Japanese Pharmacopoeia provides the official Japanese standard for the description and quality of drug substances and products. It contains over 1,300 articles regarding: general

rules for preparations; processes and apparatus; monographs on drugs; and infrared reference spectra and ultraviolet-visible reference spectra.

1.3.8.3 The European Pharmacopoeia

The European Pharmacopoeia (Ph. Eur.) of the Council of Europe is a pharmacopoeia, listing a wide range of active substances and excipients used to prepare pharmaceutical products in Europe. It includes more than 2000 specific and general monographs, including various chemical substances, antibiotics, biological substances, vaccines for human or veterinary use, immune sera, radiopharmaceutical preparations, herbal drugs, homoeopathic preparations and homoeopathic stocks. The monographs give quality standards for all the main medicines used in Europe.

Member States of the European Pharmacopoeia must comply with these quality standards so that consumers have a guarantee for products obtained from pharmacies and other legal suppliers.

1.3.8.4 The United States Pharmacopoeia

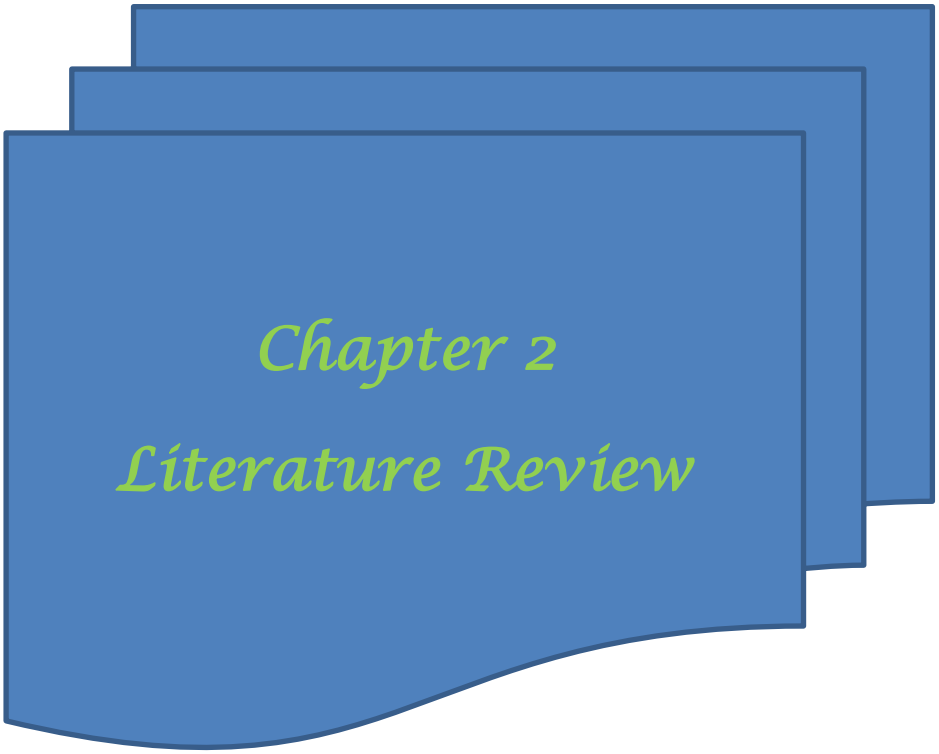
The United States Pharmacopoeia (USP) is the official pharmacopoeia of the United States. USP establishes written (documentary) and physical (reference) standards for medicines, food ingredients, dietary supplement products and ingredients. These standards are used by regulatory agencies and manufacturers to help to ensure that these products are of the appropriate identity, as well as strength, quality, purity, and consistency.

Prescription and over-the-counter medicines available in the United States must, by federal law, meet USP public standards, where such standards exist. Many other countries use the USP instead of issuing their own pharmacopeia, or to supplement their government pharmacopoeia. USP's standards are recognized and used in more than 130 countries around the globe. These standards have helped to ensure public health throughout the world for close to 200 years.

1.3.8.5 The International Pharmacopoeia

The International Pharmacopoeia (Ph. Int.) comprises a collection of quality specifications for pharmaceutical substances (active ingredients and excipients) and dosage forms together with supporting general methods of analysis, that is intended to serve as source material for reference or adaptation by any WHO Member State wishing

to establish pharmaceutical requirements. The pharmacopoeia, or any part of it, shall have legal status, whenever a national or regional authority expressly introduces it into appropriate legislation.


Chapter 2
Literature Review

CHAPTER 2: Literature Review

UV spectrophotometric method for determination of glimepiride in pharmaceutical dosage forms.

Glimepirides is an anti-diabetic drug which is used for the treatment of diabetes. In present work, a simple, sensitive, accurate and economical spectroscopic method has been developed for the estimation of glimepiride in bulk and in pharmaceutical dosage forms. An absorption maximum was found to be at 249 nm with the solvent system of chloroform. The drug follows Beer's law limits in the range of 5-30 µg/ml with correlation coefficient of 0.999732. Results of the analysis were validated for accuracy, precision, LOD were found to be satisfactory. The proposed method is simple, rapid and suitable for the routine quality control analysis. (Bhargavi *et al*., 2013)

Comparative efficacy of glimepiride and metformin in mono-therapy of type 2 diabetes mellitus: meta-analysis of randomized controlled trials.

Metformin treatment has been the most recommended mono-therapy of type 2 diabetes mellitus (T2DM) for decades but is challenged by new anti-diabetic drugs. This study conducted a meta-analysis of randomized controlled trials (RCT) comparing the efficacy of metformin and glimepiride in mono-therapy of T2DM. The result of this study suggests that metformin was not significantly better than glimepiride in glycemic control of T2DM, suggesting that glimepiride would be a good choice in the mono-therapy of T2DM. (Zhu *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)

Concurrent assay of metformin and glimepiride in tablets using RP-HPLC with wavelength programming.

A rapid assay procedure based on RP-HPLC has been developed for the simultaneous determination of metformin and glimepiride in dosage form. The HPLC determination was carried out on an Î¼Bondapak C18 (300x3.9m m) 10Î¼m with use of a flow rate of 1.0 ml/min. The programming regime was 0-5.8 min at 265 nm, 5.8-9.0 min at 230 nm and 9.0-11 min again at 265 nm. The calibration graphs were linear in the range of 400-600 and 1.6-2.4 Î¼g/ml for metformin and glimepiride respectively with correlation coefficient of 0.9999 for both. (Lad *et al*., 2003)

A simple and sensitive method for determination of glimepiride in human serum by HPLC.

A simple and sensitive high performance liquid chromatographic (HPLC) method for glimepiride determination in human serum is described. The assay involves one-step liquid-liquid extraction with dichloromethane in acidified serum. Glibenclamide is used as the internal standard. Detection is done at 228 nm and limit of quantification is less than 10 ng/mL for glimepiride. The calibration curves are linear over the concentration range tested (10–1000 ng/mL). Accuracy, precision, and stability studies are performed. This method is applied to the analysis of glimepiride serum samples of 41 Lebanese male volunteers after oral administration of a single glimepiride 3 mg tablet. Pharmacokinetic analysis of the data is done using a non-compartmental approach with WinNonlin software. (Rabbaa-Khabbaz *et al*., 2005)

Analysis of glimepiride by using derivative UV spectrophotometric method.

Glimepiride, which is a new oral anti-diabetic drug in the sulfonylurea class, was analyzed by using second order derivative UV spectrophotometry. The quantification of glimepiride in dimethylformamide was performed in the wavelength range of 245–290 nm at N=6, λ=21. The second order derivative spectra was calculated using peak to peak (λDMF=263.3–268.2 nm), peak to zero (λDMF=268.2 nm) and tangent (λ DMF=263.3–271.8 nm) method for calibration curves, the linearity range of 1.00–500.00 μg/ml by using the second order derivative UV spectrophotometric method. The developed method was applied to directly and easily to the analysis of the pharmaceutical tablet

preparations. R.S.D. was found to be 4.18% (Amaryl® tablet; 1 mg) and 2.21% (Amaryl® tablet; 2 mg). The method was completely validated and proven to be rugged. The limit of quantitation and the limit of detection were found as 1.00 and 0.4 µg/ ml, respectively. This validated derivative UV spectrophotometric method is potentially useful for a routine laboratory because of its simplicity, rapidity, sensitivity, precision and accuracy. (Altinoz and Tekeli, 2001)

Development and validation of a spectrophotometric method for quantification and dissolution studies of glimepiride in tablets.

The objective of this 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 *et al*., 2012)

Development of spectrophotometric method for dissolution and in vitro kinetic study of glimepiride tablets.

Glimepiride is a third generation sulphonylurea anti-diabetic drug. It shows low, pH dependent solubility thus is classified as class II drug according to Bio-pharmaceutics Classification Systems(BCS). The poor solubility of the drug may cause poor dissolution and unpredicted bioavailability. Scientists can ask for bio-waivers in case of Class I compounds if they are formulated as immediate release oral dosage forms. Class II drugs are also the candidates for a waiver of bioequivalence and bioavailability studies. In the present study developed dissolution medium was easy to prepare, stable over a longer period, simple and cost-effective. In vitro dissolution test was performed using 2% SLS as the medium of dissolution in USP apparatus II (paddle) at 100 rpm, for glimepiride tablet could reliably discriminate among different products. Drug release was found above 95% within 30 min. To explain the kinetics of released drug contents, various statistical models including First-order, Zero-order Higuchi’s, Hixson-Crowell’s, and

Weibull's were used. Glimepiride was best fitted to the Weibull's kinetics. Furthermore, goodness-of-fit test, the mean square error and the Akaike Information Criterion were used for selection of appropriate model; f2 test was applied for comparison of similarity between the release profiles of various trial marketed brands. (Naz *et al*., 2013)

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 sub-therapeutic 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 super disintegrantcrospovidone 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. Prepared tablets were evaluated for routine Pharmacopoeial tests. Stability studies and FT-IR studies clearly indicated that there is no drug-polymer interaction. (Chaudhuri *et al*., 2012)

A discriminating dissolution method for glimepiride polymorphs.

Glimepiride, an oral anti-diabetic drug, is practically insoluble in water and exists in two polymorphic forms, I and II, of which form II has higher solubility in water. Because the dissolution rate of drugs can depend on the crystal form, there is a need to develop discriminating dissolution methods that are sensitive to changes in polymorphic forms. In this work, a dissolution method for the assessment of 4 mg glimepiride tablets was developed and validated. The optimal dissolution conditions were 1000 mL of phosphate buffer (pH 6.8) containing 0.1% (w/v) of sodium dodecyl sulfate as the dissolution

medium and a stirring speed of 50 rpm using a paddle apparatus. The results demonstrated that all the data meet the validation acceptance criteria. Subsequently, tablets containing forms I and II of glimepiride were prepared and subjected to dissolution testing. A significant influence of polymorphism on the dissolution properties of glimepiride tablets was observed. These results suggested that the raw material used to produce glimepiride tablets must be strictly controlled because they may produce undesirable and unpredictable effects. A discriminating dissolution method for glimepiride polymorphs – Research Gate. (Bonfilio *et al*., 2012)

Development and validation of an UV derivative spectrophotometric method for determination of glimepiride in tablets.

Glimepiride is an oral antidiabetic drug widely used in treatment of type 2 diabetes. This work proposed the development and validation of a derivative UV spectrophotometric method for determination of glimepiride in tablets. The quantification of glimepiride in 5×10-3 mol L-1 NaOH was performed by using a wavelength interval of 8 nm in the range of 220-300 nm. The amplitude values obtained in the second-derivative spectra were arbitrary units of the peak height from the central zero base line to the signals obtained at 279.0, 257.5 and 256.3 nm for quantification of Amaryl® tablets 1 mg, Amaryl® tablets 2 mg and Amaryl® tablets 4 mg, respectively. The method was completely validated according to the International Conference on Harmonization (ICH) guidelines, showing accuracy, precision, selectivity, robustness and linearity. The validated method is suitable for quality control applications, since it does not use polluting reagents, it is simple and has low-cost. (Araujo *et al*., 2011)

Simple UV spectrophotometric assay of glimepirides.

The working topic of this article was that glimepirides belongs to sulfonylurea oral anti diabetic. An efficient least time consuming and simple spectrophotometric method for the assay of glimepirides has been used. The assay is based on the ultraviolet UV absorbance maxima at about 200nm wavelength of glimepirides using water as solvent. A sample of drug was dissolved in water to produce a solution containing glimepirides. Similarly, various dilutions were made. The absorbance of sample preparation was measured at 200nm against the solvent blank and the assay was determined. In our study a simple and quick assay method using U.V spectrophotometer has been used. The assay is based on measuring the absorbance of formulation of glimepirides dilutions at the wavelength of

200 nm. Fourdifferent dilutions of 50ppm, 25ppm, 12.5ppm and 6.25ppm are prepared and their percent assay is calculated. (Safila *et al.*, 2014)

Formulation and in vitro evaluation glimepiride and parecoxibmucoadhesive tablets for diabetics associated with pain and inflammation.

The main purpose of present study was to develop mucoadhesive tablets of Glimepiride and Parecoxib drugs were prepared to achieve controlled plasma level of the drug especially in diabetes mellitus patients with pain therapy. The mucoadhesive tablets were prepared by direct compression technique. The drug- excipient compatibility studies were performed by Fourier Transform Infrared spectroscopy (FTIR). Physicochemical characteristics and in vitro drug dissolution tests were performed. The in vitro drug release pattern and the dissolution data was treated with mathematical modeling Accelerated stability studies were also carried out to the optimized formulation (F-5). The FTIR studies revealed that drugs were compatible with the polymer used. The optimized formulations were found to have good physicochemical and in vitro release properties. The in vitro dissolution data was perfectly fitting to zero order and the release of drug from the formulation followed Higuchi's release. The accelerated stability studies revealed that the tablets retain their characteristics even after stressed storage conditions. From this study it was concluded that Glimepiride and Parecoxib combination mucoadhesive Tablets is a good combination for diabetics associated with pain and inflammation. (Reddy *et al*., 2011)

Studies on formulation and in vitro evaluation of glimepiride floating tablets.

Floating matrix tablets of glimepiride were developed to prolong the gastric residence time and thereby increased drug bioavailability. Diabetes condition influences the gastric emptying time which affect the absorption of the drug. Glimepiride was chosen as model drug because it has incomplete absorption due to less gastric residence time. The tablets were prepared by direct compression technique, using various grades of rate controlling polymers, Carbopol 934P either alone or in combination and other standard excipients. Tablets were evaluated for physical characteristics viz. hardness, % friability, floating capacity and content of dosage form. Tablets were evaluated for in vitro release characteristics for 8 h. In vitro drug release mechanism was evaluated by linear regression analysis. Floating matrix tablets based on the combination of polymers exhibited desired floating and prolonged drug release for 8hour. (Reichal *et al*., 2011)

A simple and convenient method for the simultaneous in vitro study of metformin and glimepiride tablets.

A simple and convenient method was developed for the simultaneous determination of metformin HCl and glimepiride in tablet dosage form of different pharmaceuticals companies. This method was validated and proved to be applicable for assay determination in intermediate and finished staged. More over a single medium dissolution of metformin HCl and glimepiride was established and the media was evaluated for comparative studies for different formulations. Reverse phase HPLC equipped with UV detector was used for the determination of metformin HCl and glimepiride. A mixture of acetonitrile and ammonium acetate buffer 0.05M pH 3.0 was used as mobile phase at flow rate of 1.0ml/min. Promocil C18 5µ 100Aº 4.6 x 100mm C18 silica column was used and detection was carried out at 270nm. Method was found to be linear over the range of 4ppm to 16ppm for glimepiride and 170ppm to 680ppm for metformin HCl. Regression co-efficient was found to be 0.9949 and 0.9864 for glimepiride and metformin HCl respectively. Dissolution was performed in 500ml 0.2% sodium lauryl sulfate at 37ºC for 45min using paddle apparatus. Dissolution of glimepiride was found to be 98.60% and 101.08% in Orinase Met1 tablet and Amaryl M tablet respectively whereas metformin was found 99.41% and 98.59% in Orinase Met 1 tablet and Amaryl M tablet. RSD for all the dissolutions was less than 2.0% after completion. (Ahmed, 2014)

Development and validation of derivative spectrophotometric method for estimation of pioglitazone HCl and glimepiride in bulk and combine dosage form.

Pioglitazone hydrochloride and Glimepiride is anti-diabetic drug. A sensitive, precise, accurate and simple first order zero crossing UV spectrophotometric method has been developed for simultaneous Estimation of Pioglitazone hydrochloride and Glimepiride in bilayer tablet dosage form. The quantification was achieved by the first-order derivative spectroscopy method at 225 nm (zero cross point of Glimepiride) for pioglitazone and 248 nm (zero cross point of Pioglitazone) for Glimepiride. Pioglitazone HCl (R2=0.9912) and Glimepiride (R2=0.9964) shows Linearity in a concentration range of 5-30µg /ml and 4-20µg/ml respectively. Procedure does not require prior separation of layers of tablet formulation. LOD values for Pioglitazone HCl and Glimepiride are found to be 0.0187µg/mL and 0.132µg/mL, respectively. LOQ values for Pioglitazone HCl and Glimepiride are found to be 0.056µg/mL and 0.40 µg/mL, respectively. The results of analysis have been validated statistically and recovery studies carried out in the range 80-

120% to confirm the accuracy of the proposed method. The relative standard deviation was found to be <2.0%. The Proposed method is recommended for routine analysis since it is rapid, simple, accurate and also sensitive and specific. (Gulve *et al*., 2013)

Significance of the Study

Today most countries worldwide have requirements for reviewing and approving pharmaceutical products or are currently working to establish them in order to ensure product quality, safety, efficacy, traceability and availability. Over the last couple of decades, significant changes have occurred in the environment of pharmaceutical regulations and these changes have required adjustments to regulatory approaches due to increased number and complexity of products, advances in science and technologies, global harmonization, etc. The pharmaceutical industry invests vast amount money and time every year to study the most used solid dosage form also known as tablets. This expense is quite reasonable when one considers the importance of tablet dosage form to the pharmaceutical industry.

Tablet dosage form has many advantageous facts such as suitability, well known, availability, affordability etc. over the other dosage forms. These facts are the main reasons for the pharmaceutical industries to vastly manufacture tablet.

The process of Quality control emphasizes testing of products to uncover defects, and reporting to management who make the decision to allow or deny the release, whereas quality assurance attempts to improve and stabilize production, and associated processes, to avoid, or at least minimize, issues that led to the defects in the first place. To maintain manufacturing of the tablet dosage form, quality parameters are necessary. Quality control parameters are the main conditions for a quality product. To improve the quality parameters the tablet manufacturing technology has undergone great improvement and experimentation. Many efforts are given to understand more clearly about the physical parameters and the factors which are considered after the tablet dosage form administered via oral route. For maintaining the standard quality, many in process quality control tests are done by the pharmaceutical industry. These tests include hardness, thickness, friability, disintegration etc. dissolution and potency tests are also done to ensure the dosage efficacy. The importance of these tests cannot be measure by any means. The main functions of these tests are to ensure uniform quality and purity of the finished dosage forms within a batch and between batches. To have a quality product, quality control tests are immensely needed. (Ulman, 2003)

Aim and Objectives of the Study

The aim and objectives of the study were-

- To analyze different brands and batches of glimepiride in terms of physical parameters like weight variation, hardness test, thickness test, disintegration test, dissolution test etc.
- To determine the potency of selected brands of glimepiride
- To assess and compare the percentage dissolution of different brands of glimepiride.

Main aim was to evaluate the physical parameters to see the batch to batch variation of glimepiride tablets which are available in the market. Because when tablets are manufactured they comply with the standard quality but after they reach the market they may or may not maintain same quality after a certain period of time.

Chapter 3

Materials & Methods

CHAPTER 3: Materials and Methods

3.1 Equipment

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

Table 3.1: Lists of equipment used for physical and chemical characterization of glimepiride tablets.

No.	Equipment	Source	Origin
1	Distill Water Plant	GENRISTO	United Kingdom
2	Electronic Balance	SHIMADZU	Japan
3	Hardness tester	MONSANTO	India
4	Disintegration Tester	VANGUARD	Japan
5	Dissolution Tester USP XXII	LABINDIA DS 8000	India
6	UV-VIS Spectroscopy	UV – 1800 SHIMADZU	Japan
7	Ultrasonic Homogenizer	HWASHIN	Korea

Fig 3.1: GENRISTO Distill Water Plant

Fig 3.2: SHIMADZU Weighing Balance

Fig 3.3: MONSANTO Hardness Tester

Fig 3.4: Vernier Calipers

Fig 3.5: LABINDIA Dissolution Apparatus

Fig 3.6: VANGUARD Disintegration Tester

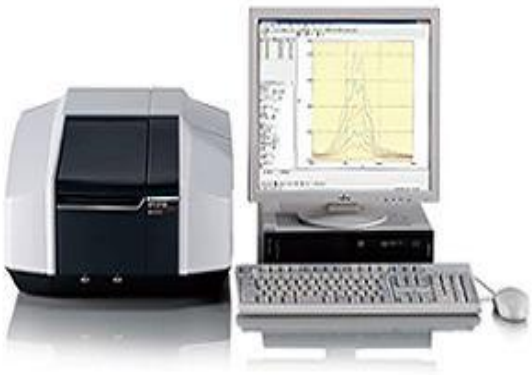


Fig 3.7: UV – 1800 SHIMADZU Spectroscopy

Fig 3.8: HWASHIN Ultrasonic Homogenizer

3.2 Sample Collection

There are almost 20 brands of glimepiride tablets available in Bangladesh and among them Losucon and Dieta (Two batches of each) are chosen for the study.

3.3 Weight Variation Test

3.3.1 Materials

Table 3.2: Name and specification of instrument required in weight variation test.

Instrument	Specification
Analytical Balance	SCALTEC SPB 31

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 3.3: Acceptance of weight variation of tablets

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

3.4 Hardness Test

3.4.1 Materials

Table 3.4: Name and specification of instrument required in Hardness test

Instrument	Specification
Hardness tester	MONSANTO Hardness Tester

3.4.2 Method

a. The test is performed for 10 tablets.

b. The sliding scale of hardness tester is set off to zero.

c. The tablets are placed vertically between the two jaws of the hardness tester.

d. Force is applied with the screw thread and spring until the tablets are fractured.

e. A force of about 4 kg is considered to be the minimum for hardness. (Allen *et al.*, 2005).

3.5 Thickness Test

3.5.1 Materials

Table 3.5: Name and specification of instrument required in thickness testing

Instrument	Specification
Vernier calipers	SHANGHAI CHINA, TRICLE Brand

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

3.6.1 Condition

Medium: 900ml distilled water

Times: 30 minutes

Temperature: (37±2)º C

3.6.2. Materials

Table 3.6: Name and specification of instrument required in disintegration test

Instrument	Specification
Disintegration tester	VANGUARD Disintegration Tester

3.6.3. Method

a. The disintegration tester is to be assembled.

b. 15 minutes of time to run the operation is set on the instrument (Revision of Monograph on tablets, 2011).

c. The temperature of water is adjusted at 37 ± 2°C.

d. 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.

e. The instrument operates at 29-30 cycles per minute.

f. In each of the 6 tubes a single tablet is to be placed and the apparatus is operated for the prescribed time.

g. All the tablets should disintegrate within the specified time.

h. 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.

i. 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

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

To prepare phosphate buffer, at first 8.0 gmNaOH was dissolved in 1000 ml 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 as 7.8 with a calibrated pH meter.For lowering the pH concentrated HCl and for increasing the pH 0.1 N NaOH was used. By this way phosphate buffer was made.

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.

3.7.4 Preparation of Standard solution

At first10 mg of glimepiride was accurately weighed and transferred to 100 ml volumetric flask. Then 20 ml of water was added andsonicated for 15 min. The volume was made up to the mark with methanol to give 100 µg/ml solution. Then the solution was made up to 2 µg/ml.

3.8. Assay

3.8.1 Materials

Table 3.7: Name and specification of instrument required for assay

Instrument	Specification
UV Spectrophotometer	UV-1800 SHIMADZU

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 100 ml volumetric flask containing some water.

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

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

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

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

g. The content of glimeperide 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

Result

CHAPTER 4: Results

4.1 Weight Variation Test

Table 4.1.: Result of weight variation test of Losucon Tablets

Tablet Number	Weight of Tablets		Weight Variation		Highest Variation		Lowest variation	
	14006	**13019**	**14006**	**13019**	**14006**	**13019**	**14006**	**13019**
1	0.0922	0.0913	-0.6679	-0.7356				
2	0.0929	0.0905	0.0861	-1.6036				
3	0.0937	0.0922	0.948	0.2446				
4	0.0919	0.0927	-0.9911	0.7882				
5	0.0921	0.0887	-0.7756	-3.5607				
6	0.0923	0.0925	-0.5602	0.5708				
7	0.0945	0.0894	1.8099	-2.7996				
8	0.0914	0.0914	-1.5298	-0.6251				
9	0.0935	0.0909	0.7326	-1.1687				
10	0.0925	0.0959	-0.3447	4.2674	1.8099	4.2674	-1.7453	-3.5607
11	0.0922	0.0920	-0.6679	0.0271				
12	0.0936	0.0923	0.8403	0.3533				
13	0.0941	0.0927	1.379	0.7882				
14	0.0932	0.0931	0.4093	1.2231				
15	0.0912	0.0912	-1.7453	-0.8426				
16	0.0939	0.0918	1.1635	-0.1902				
17	0.0916	0.0943	-1.3141	2.5278				
18	0.0928	0.0921	-0.0215	0.1359				
19	0.0931	0.0924	0.3016	0.462				
20	0.0937	0.0921	0.9480	0.1359				

Standard deviation: 0.000949 (B-14006); 0.001554 (B-13019)

Table 4.2: Result of weight variation test of Dieta Tablets

Tablet Number	Weight of Tablets		Weight Variation		Highest Variation		Lowest variation	
	14004	**14006**	**14004**	**14006**	**14004**	**14006**	**14004**	**14006**
1	0.1672	0.1711	0.1377	2.1279				
2	0.1676	0.1686	0.3773	0.6356				
3	0.1684	0.1701	0.8564	1.531				
4	0.1708	0.1625	2.2938	-3.0053				
5	0.1669	0.1675	-0.0419	-0.0208				
6	0.1677	0.1704	0.4372	1.71				
7	0.1683	0.1698	0.7965	1.3519				
8	0.1648	0.1661	-1.2996	-0.8565				
9	0.1694	0.1680	1.4553	0.2775				
10	0.1668	0.1645	-0.1018	-1.8115	2.2938	2.1279	-2.4375	-3.0053
11	0.1655	0.1701	-0.8803	1.531				
12	0.1661	0.1692	-0.521	0.9938				
13	0.1672	0.1678	0.1377	0.1581				
14	0.1678	0.1663	0.497	-0.7371				
15	0.1643	0.1672	-1.599	-0.1999				
16	0.1629	0.1654	-2.4375	-1.2743				
17	0.1638	0.1643	-1.8985	-1.9309				
18	0.1681	0.1686	0.6767	0.6356				
19	0.1692	0.1689	1.3355	0.8147				
20	0.1666	0.1643	-0.2215	-1.9309				

Standard deviation: 0.001972 (B-14004); 0.002408 (14006)

4.2 Thickness Test

Table 4.3: Result of thickness test of Losucon Tablets

Losucon-2 (14006)						
No. of tablets	**Reading of main scale**	**Reading of vernier scale**	**Vernier constant**	**Vernier error**	**Thickness of the tablet (mm)**	**Average (mm)**
1	2	6	0.1	0.05	2.65	2.685
2	2	6.5	0.1	0.05	2.70	
3	2	5.5	0.1	0.05	2.60	
4	2	7	0.1	0.05	2.75	
5	2	6.5	0.1	0.05	2.70	
6	2	7	0.1	0.05	2.75	
7	2	6.5	0.1	0.05	2.70	
8	2	5	0.1	0.05	2.55	
9	2	7	0.1	0.05	2.75	
10	2	6.5	0.1	0.05	2.70	

Losucon-2 (13019)						
No. of tablets	**Reading of main scale**	**Reading of vernier scale**	**Vernier constant**	**Vernier error**	**Thickness of the tablet (mm)**	**Average (mm)**
1	2	7	0.1	0.05	2.75	2.745
2	2	8	0.1	0.05	2.85	
3	2	6.5	0.1	0.05	2.70	
4	2	7.5	0.1	0.05	2.80	
5	2	7	0.1	0.05	2.75	
6	2	6.5	0.1	0.05	2.70	
7	2	7	0.1	0.05	2.75	
8	2	7.5	0.1	0.05	2.80	
9	2	6.5	0.1	0.05	2.70	
10	2	6	0.1	0.05	2.65	

Standard deviation: 0.066875 (B-14006); 0.059861 (B-13019).

Table 4.4: Result of thickness test of Dieta Tablets

DIETA-2 (14004)						
No. of tablets	**Reading of main scale**	**Reading of vernier scale**	**Vernier constant**	**Vernier error**	**Thickness of the tablet (mm)**	**Average (mm)**
1	2	8	0.1	0.05	2.85	2.935
2	2	8.5	0.1	0.05	2.90	
3	2	8	0.1	0.05	2.85	
4	2	9.5	0.1	0.05	3.0	
5	2	9.5	0.1	0.05	3.0	
6	2	9	0.1	0.05	2.95	
7	2	8	0.1	0.05	2.85	
8	2	8.5	0.1	0.05	2.90	
9	2	9	0.1	0.05	2.95	
10	2	9.5	0.1	0.05	3.0	

DIETA-2 (14006)						
No. of tablets	**Reading of main scale**	**Reading of vernier scale**	**Vernier constant**	**Vernier error**	**Thickness of the tablet (mm)**	**Average (mm)**
1	2	9.5	0.1	0.05	3.0	2.945
2	2	9	0.1	0.05	2.95	
3	2	9	0.1	0.05	2.95	
4	2	9.5	0.1	0.05	3.0	
5	2	8	0.1	0.05	2.85	
6	2	9	0.1	0.05	2.95	
7	2	9.5	0.1	0.05	3.0	
8	2	8.5	0.1	0.05	2.90	
9	2	8.5	0.1	0.05	2.90	
10	2	9	0.1	0.05	2.95	

Standard deviation: 0.049721 (B-14004); 0.063465 (B-14006)

4.3 Hardness Test

Table 4.5: Result of hardness test of Losucon Tablets

No. of tablets	Hardness of Tablets(kg/cm)		Average(kg/cm)	
	14006	13019	14006	13019
1	2.6	2.4	2.58	2.39
2	2.7	2.4		
3	2.5	2.5		
4	2.5	2.4		
5	2.4	2.4		
6	2.5	2.5		
7	2.5	2.4		
8	2.6	2.4		
9	2.5	2.3		
10	3.0	2.2		

Standard deviation: 0.168655 (B-14006); 0.08756 (B-13019)

Table 4.6: Result of hardness test of Dieta Tablets

No. of tablets	Hardness of Tablets(kg/cm)		Average(kg/cm)	
	14004	14006	14004	14006
1	1.9	2.0	1.87	1.96
2	2.0	1.9		
3	1.9	2.0		
4	1.9	2.1		
5	1.9	2.1		
6	1.9	2.0		
7	1.8	1.9		
8	1.7	1.8		
9	1.9	1.9		
10	1.8	1.9		

Standard deviation: 0.082327 (B-14004); 0.096609 (B-14006)

4.4 Disintegration Test

Table 4.7: Result of disintegration test of Losucon Tablets

Number of Tablets	Time(Minute)		Mean Disintegration Time	
	14006	**13019**	**14006**	**13019**
1	34 second	44 second	34 second	59 second
2	36 second	46 second		
3	34 second	1 minute 3 second		
4	35 second	1 minute 1 second		
5	33 second	1 minute 2 second		
6	32 second	1 minute 15 second		

Table 4.8: Result of disintegration test of Dieta Tablets

Number of Tablets	Time(Minute)		Mean Disintegration Time	
	14004	**14006**	**14004**	**14006**
1	3 minute 22 second	4 minute 56 second	5 minute 18 second	7 minute 44 second
2	4 minute 56 second	5 minute 36 second		
3	5 minute 3 second	7 minute 52 second		
4	5 minute 29 second	8 minute 2 second		
5	5 minute 59 second	8 minute 39 second		
6	6 minute 16 second	9 minute 45 second		

4.5. Dissolution Test

Table 4.9: Result of dissolution test of Losucon Tablets

Losucon-2 (14006)				
Number of Tablets	**Absorbance**	**%Dissolved**	**Average Absorbance**	**Average % Dissolved**
1	0.257	82.87	0.253	81.5%
2	0.270	87		
3	0.254	81.90		
4	0.286	92.22		
5	0.209	67.39		
6	0.241	77.71		

Losucon-2 (13019)				
Number of Tablets	**Absorbance**	**%Dissolved**	**Average Absorbance**	**Average % Dissolved**
1	0.285	91.90	0.260	83.84%
2	0.205	66.10		
3	0.279	89.96		
4	0.224	72.23		
5	0.293	94.48		
6	0.278	89.64		

Table 4.10: Result of dissolution test of Dieta Tablets

DIETA-2 (14004)				
Number of Tablets	**Absorbance**	**%Dissolved**	**Average Absorbance**	**Average % Dissolved**
1	0.286	92.22	0.262	84.48%
2	0.253	81.58		
3	0.298	96.09		
4	0.234	75.45		
5	0.273	88.03		
6	0.233	75.13		

DIETA-2 (14006)				
Number of Tablets	**Absorbance**	**%Dissolved**	**Average Absorbance**	**Average % Dissolved**
1	0.345	111.25	0.291	95.77%
2	0.232	74.81		
3	0.237	76.42		
4	0.280	90.29		
5	0.320	103.18		
6	0.335	108.02		

4.6 Potency Test

Table 4.11: Potency of Losucon Tablets

Tablet Brand	Batch	Average weight of tablet(mg)	Absorbance of the sample	Weight of the sample(mg)	Potency (%)
Losucon	14006	0.0938	0.384	0.0937	108.47
	13019	0.0927	0.367	0.0929	103.67

Table 4.12: Potency of Dieta Tablets

Tablet Brand	Batch	Average weight of tablet(mg)	Absorbance of the sample	Weight of the sample(mg)	Potency (%)
Dieta	14004	0.1669	0.414	0.1671	116.94
	14006	0.1675	0.497	0.1673	140.39

Chapter 5

Discussion

CHAPTER 5: Discussion

5.1 Weight Variation Test

According to the research study the weight variation of Losucon tablets had the average weight of 0.09282gm (Batch no. 14006) and 0.091975 gm (Batch no. 13019). The % weight variation ranged from +1.8099% to -1.7453% (Batch no. 14006) and +4.2674% to -3.5607% (Batch no. 13019) and the standard deviation were 0.000949 (Batch no.14006) and 0.001554 (Batch no. 13019).

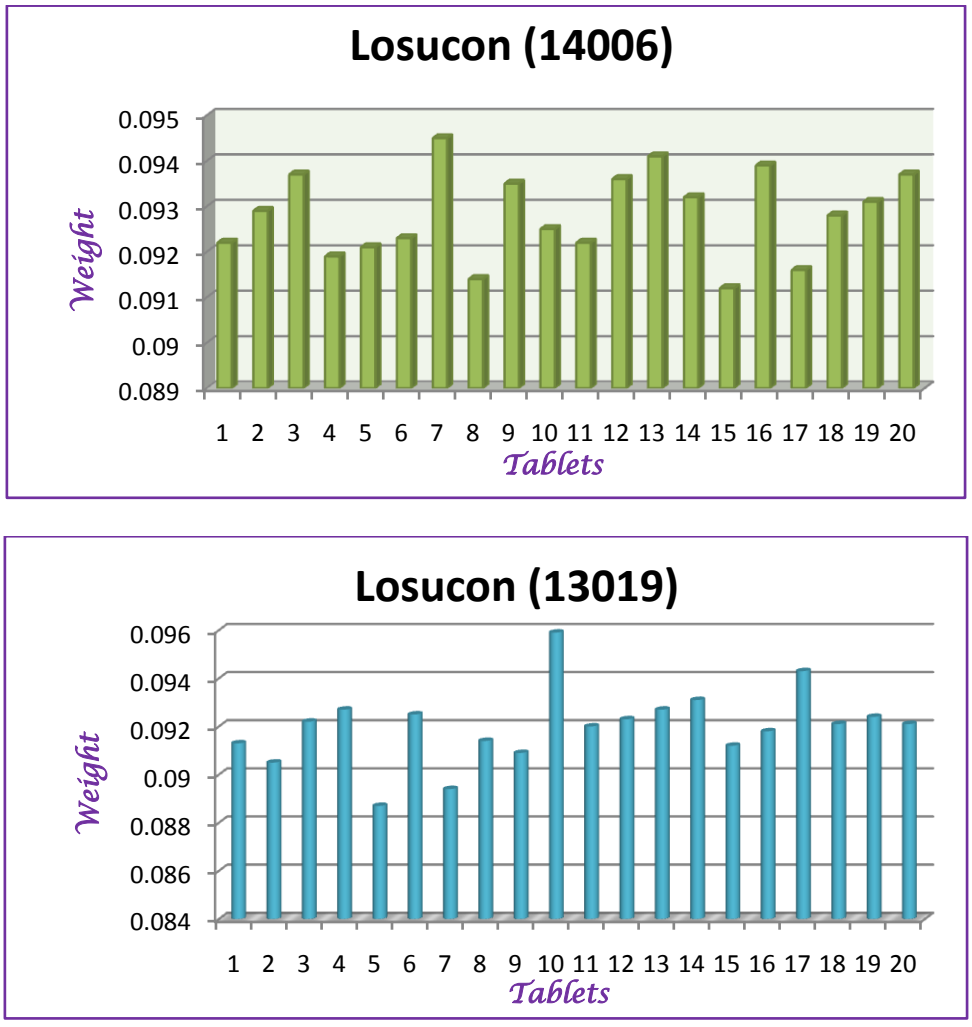


Figure 5.1: Weight variation of Losucon tablet.

According to the research study the weight variation of Losucon tablets had the average weight of 0.16697 gm (Batch no. 14004) and 0.167535 gm (Batch no. 14006). The % weight variation ranged from +2.2938% to -2.4375% (Batch no. 14004) and +2.2938% to-2.4375% (Batch no. 14006) and the standard deviation were 0.001972 (Batch no.1400) and 0.002408 (Batch no. 14006).

Figure 5.2: Weight variation of Dieta tablet.

All these tablets showed a percentage weight variation within the range of ±10% (USP, 2003) and, thus it meet the specification of weight variation and the quality control test. So the manufacturers should be more concerned to maintain the consistency of each batch during the formulation.

5.2 Thickness Test

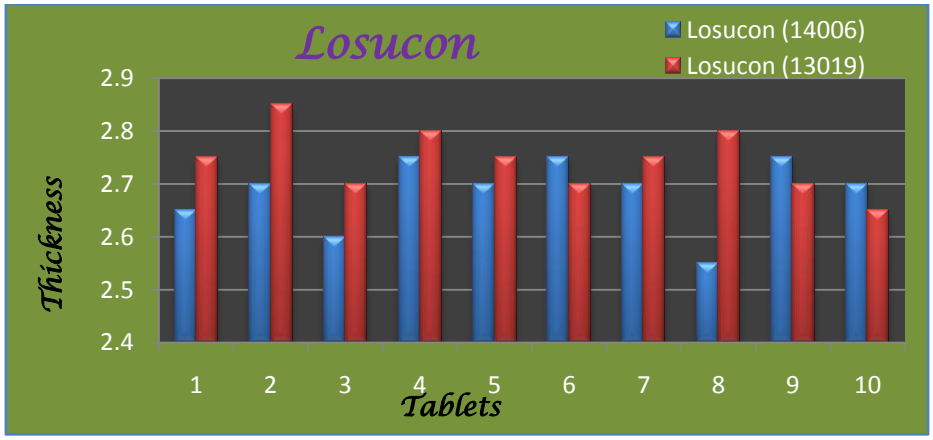


Figure 5.3: Thickness of two different batches of Losucon tablet.

According to the USP specification, the range for tablet thickness is ±5mm.The batch to batch thickness variation of Losucon tablet is consistent even the thickness of the tablets of two different batch were same and the standard deviation were 0.066875 (14006) and 0.059861(13019).

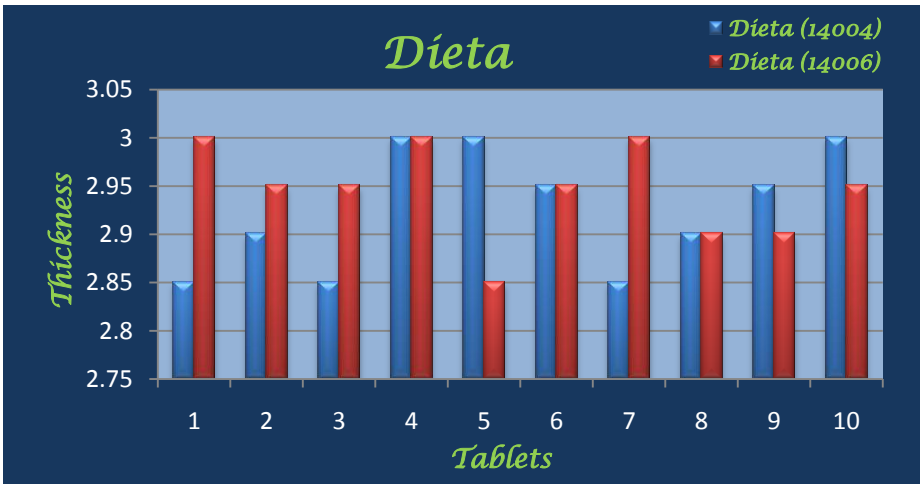


Figure 5.4: Thickness of two different batches of Dieta tablet.

The batch to batch thickness variation of Dieta tablet is consistent even the thickness of the tablets of two different batch were same and the standard deviation were 0.049721 (14004) and 0.063465 (14006).

So, it can be concluded that the formulation technique of both the Losucon and Dieta tablets are perfectly following the compendial method.

5.3 Hardness Test

In this research study, the hardness test of Losucon tablets had the range from 2.40 kg/cm to 3.00 kg/cm (Batch no. 14006) and 2.2kg/cm to 2.5 kg/cm (Batch no. 13019) and the standard deviation were 0.168655 (Batch no. 14006), 0.08756(Batch no. 13019).

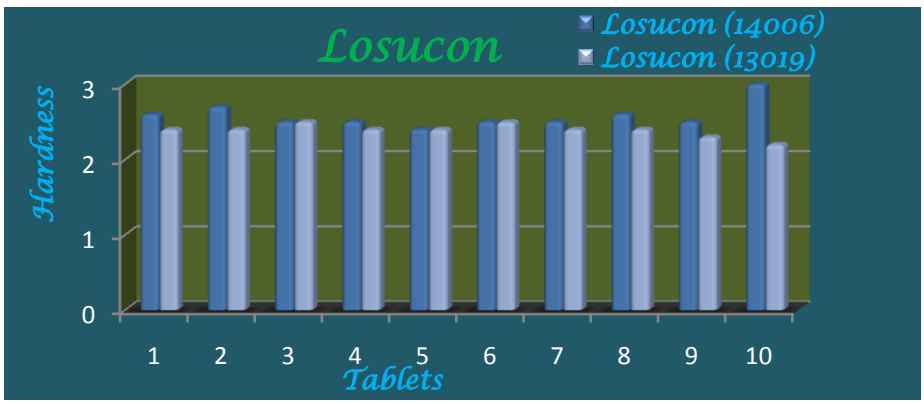


Figure 5.5: Hardness variation of two different batches of Losucon tablet.

The hardness test of Dieta tablets had the range from 1.70 kg/cm to 2.00 kg/cm (Batch no. 14004) and 1.80 kg/cm to 2.10 kg/cm (Batch no. 14006) and the standard deviation were 0.082327 (Batch no. 14006), 0.096609 (Batch no. 14006).

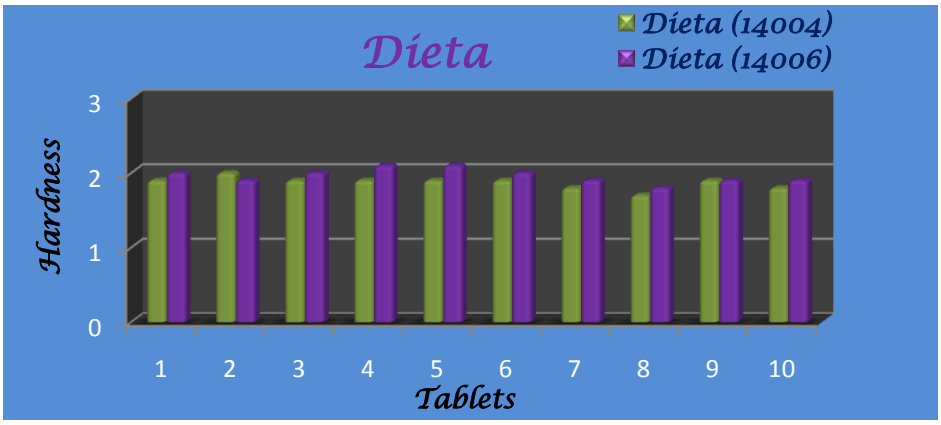


Figure 5.6: Hardness variation of two different batches of Dieta tablet.

Here, all the tablets of these two brands had hardness lower than the standard value of 4 kg which can cause breakdown of tablets during use and transport.

5.4 Disintegration Test

In this research, the disintegration time of two batch of Losucon tablets had the range from 32 sec to 36 sec (Batch no. 14006) and 44 sec to 1 min 15 sec (Batch no. 13019). On the other hand, the disintegration time of Dieta tablets are much higher. The Dieta tablets had the range from 3 min 22 sec to 6 min 16 sec (Batch no. 14004) and 4 min 56 sec to 9 min 45 sec (Batch no. 14006). According to the BP, the disintegration time for uncoated tablets should be within 15 minutes. Both the Losucon and Dieta tablets had the disintegration time that 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)

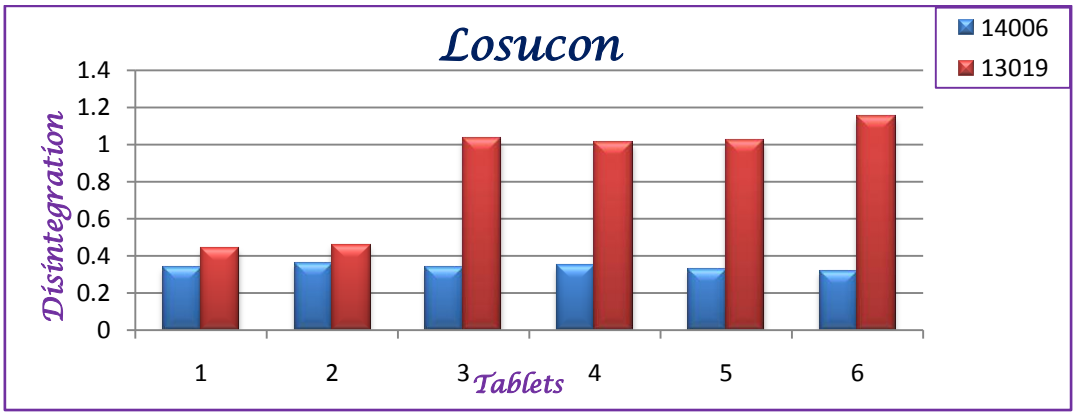


Figure 5.7: Disintegration time of two different batches of Losucon tablets.

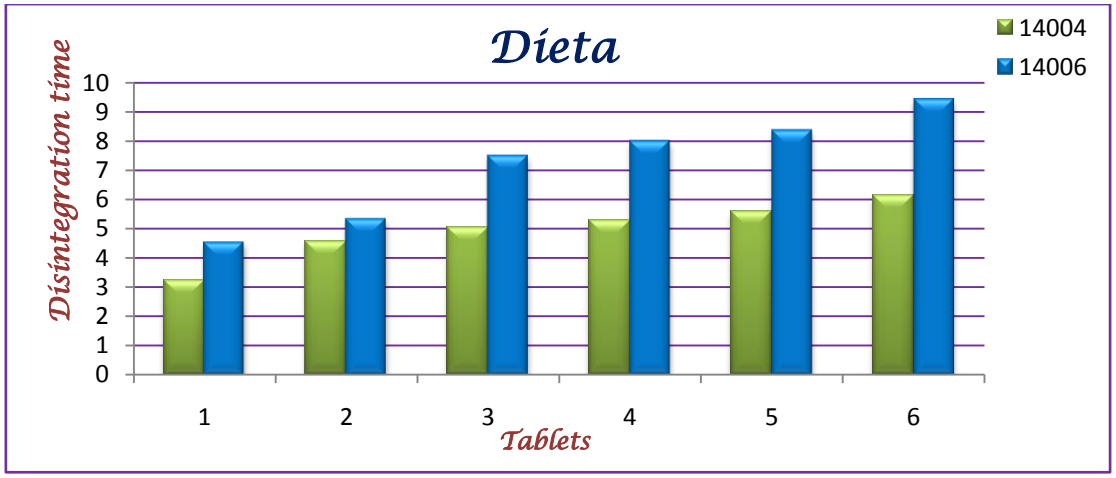


Figure 5.8: Disintegration time of two different batches of Dieta tablets.

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 meet. (USP NF, 2006)

5.5 Dissolution Test

Dissolution tests and test specification have been developed for nearly all tablet products. Therate of drug absorption in the GI tract is oftendetermined by the rate of drug dissolution from the tablets. If the attainment of high peak bloodlevels of the drug is a product objective, obtaining rapid drug dissolution from tablet is critically important. The rate of dissolution may thus be directly related to the efficacy of the drug product, as well as bioavailability differences between formulations.

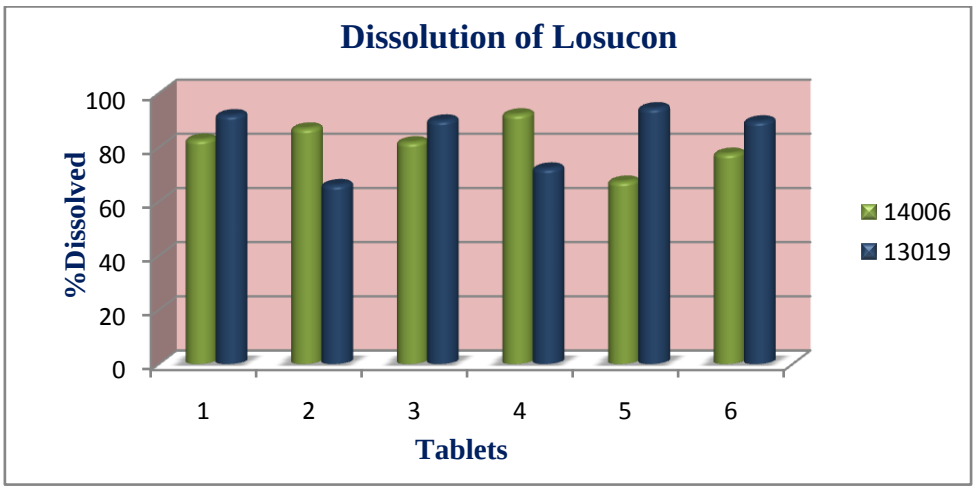


Figure 5.9: Dissolution of two different batches of Losucon tablets

Losucon tablets had the dissolution ranges from 67.39% to 92.22% (Batch no. 14006) and from 66.10% to 94.48% (Batch no. 13019) within 30 minutes. In batch no.14006 and 13019 two tablets are below the 80% dissolution.

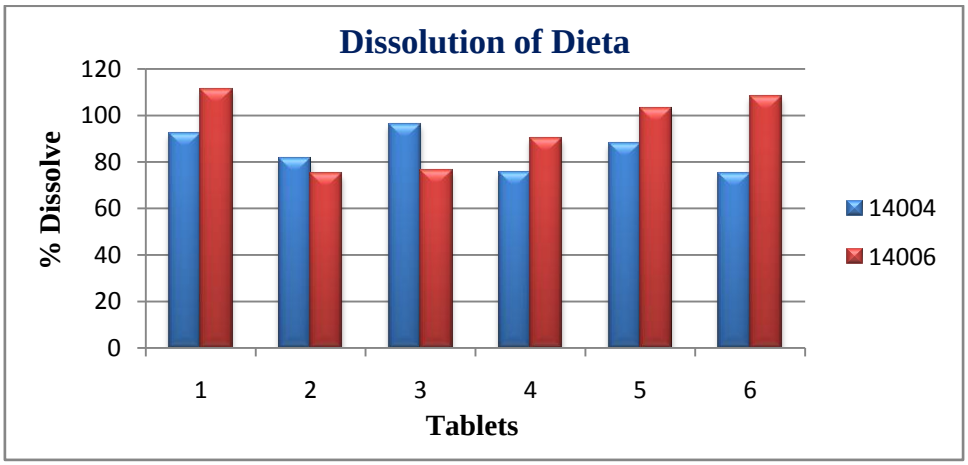


Figure 5.10: Dissolution of two different batches of Dieta tablets

The graph 5.10 provides the information that the Dieta tablets had the dissolution range from 75.13% to 96.09% (Batch no. 14004) and 74.81% to 111.25% (Batch no. 14006). In batch no. 14004 and 14006 two tablets are below the range but in batch no. 14006 three tablets are above 100%.

Here, the overall dissolution rate has failed to meet the specified range. So, 6 more tablets from each batch need to recheck the dissolution rate and if failed then 12 more tablets are tested.

5.6 Potency Test

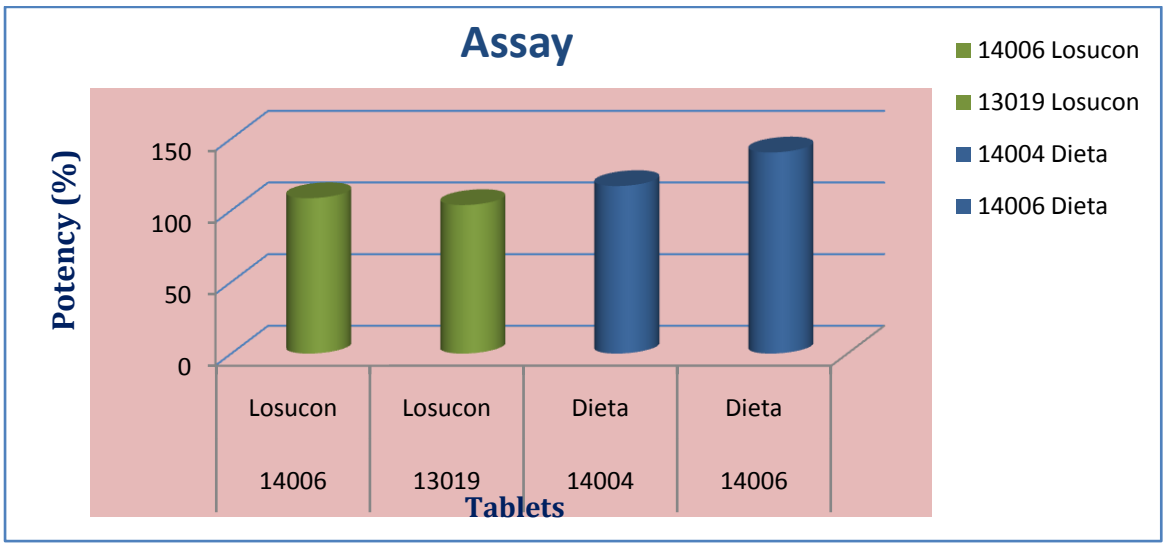
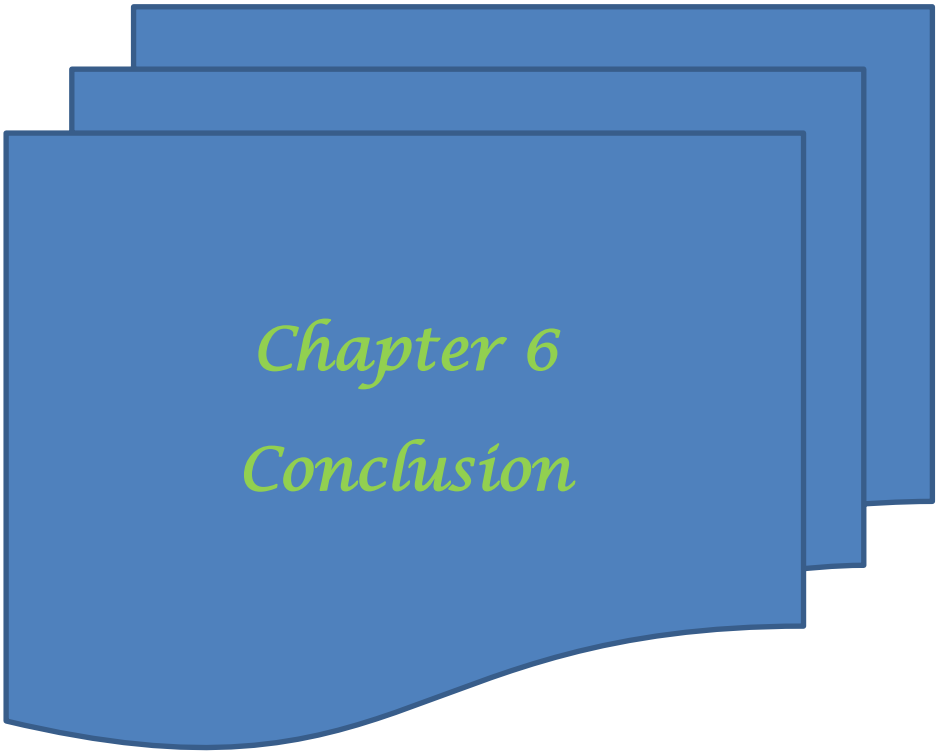


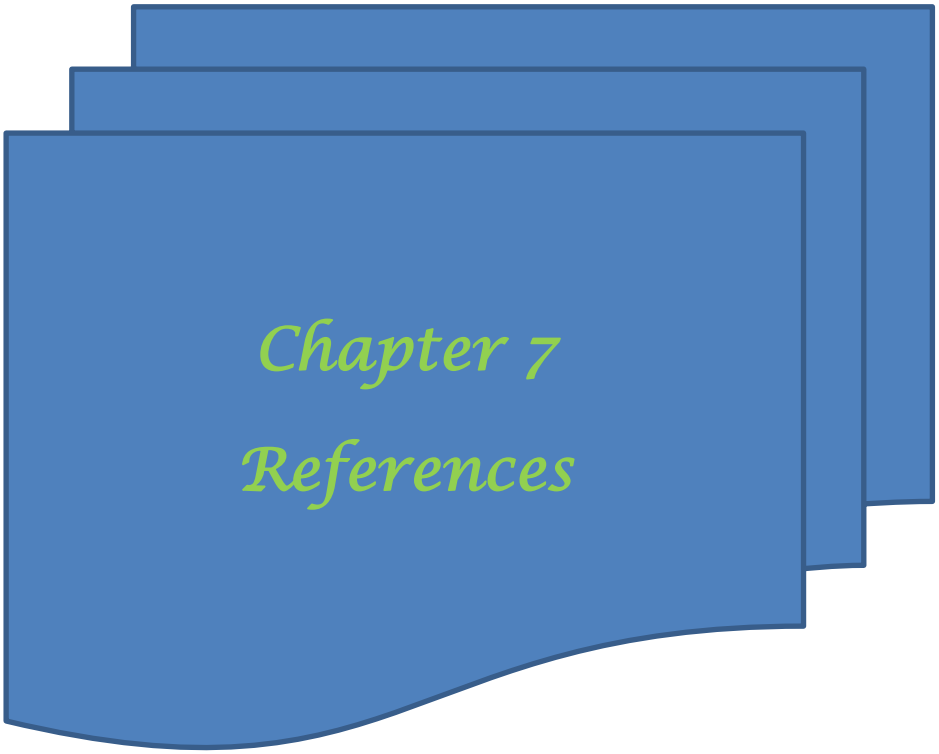
Figure 5.11: Potency value of two brands of glimepiride tablet each with two batches.

The assay of the two different brands (Losucon and Dieta) of glimepiride showed potency that ranges from 103.67 to 140.39. 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 ± 10% or 90-110%. The above graph represents that the percent potency of Losucon (13019 and 14006)is within the range and both the batch of Dieta (14004 and 14006) tablets are not within the acceptable range of BP and USP. This variation could also may result from various factors like temperature condition, storage, transportation, environmental condition of the place where the test is performed 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

In world as well as Bangladesh, patients of diabetes are increasing tremendously which is in the fourth position (FDA.gov, 2014) among fatal diseases and causes death of most people. So it is necessary to arrange more research for antidiabetic drugs. In this research study quality control parameter of two brands (Losucon and Dieta) were observed by undergoing with the process of weight variation test, hardness test, thickness test disintegration test, dissolution test and assay. The results of all tests were not within the acceptable range and as the friability test results which has an utmost importance to draw a standard concluding remark were absent due to some technical faults in those instruments so we could not firmly assure about the quality of the drugs in our local market but some of the parameters that deviate from the acceptable range may be due to the formulation error of the manufacturer or may be due to the error in the analysis. However, after performing this research it can be firmly concluded that the study reveals a promising approach to achieve appropriate quality medicine in our local market.


Chapter 7
References

CHAPTER 7: References

Ahmed, R. (2014). A simple and convenient method for the simultaneous in vitro study of metformin and glimepiride tablets.*Pakistan journal of pharmaceutical sciences*, 27(6), 1939-1943.

Allen, L., Popovich, N., Ansel, H. and Ansel, H. (2005).*Ansel's pharmaceutical dosage forms and drug delivery systems*.Philadelphia: Lippincott Williams & Wilkins, 225-256.

Altinoz, S. and Tekeli, D. (2001).Analysis of glimepiride by using derivative UV spectrophotometric method.*Journal of Pharmaceutical and Biomedical Analysis*, 24(3), 507-515.

American Society of Health-System Pharmacist, (2015). ASHP: *Glimepiride*. [Online] Available from: http://www.nlm.nih.gov/medlineplus/druginfo/meds/a696016.html [Accessed: 11th February, 2015]

Anabiotec,(2015).*Friability, hardness and disintegration testing of pharmaceuticals | Anabiotec*.Available from: http://www.anabiotec.com/testing/detail/hardness-friability-disintegration [Accessed: 17th June, 2015]

Araujo, B. M., Salgado, N. R. H. andBonfilio, R. (2011).Development and validation of an UV derivative spectrophotometric method for determination of glimepiride in tablets.*Journal of the Brazilian Chemical Society*, 22(2), ISSN: 0103-5053.

Aulton, M.E. (2002). *The science of dosage form design*. 2nd edition, London: Churchill

Livingstone,247-252.

Bhargavi, S., Suryasagar, G., Sowmya, D., Ashok, K. and Nama, S. (2013). UV Spectrophotometric Method for Determination of Glimepiride in Pharmaceutical Dosage Forms.*International Journal of Pharmaceutuical Science*, 21(2), 131-133.

Bonfilio, R., Pires, A. S., Ferreira, L., Almeida, E. A. andDoriguetto, C. A. (2012).A discriminating dissolution method for glimepiride polymorphs.*Journal of Pharmaceutical Sciences*, 101(2), 794-804.

Boopathy, D., Reddy, B., Mathew, B., Prakash, M. and Perumal, P. (2010). Method development and validation of simultaneous determination of Pioglitazone and Glimepiride in pharmaceutical dosage form by RP-HPLC. *International Journal of ChemTech Research*, 2(1), 50-53.

Brtish pharmacopoeia, (2012).*Quality parameter tests of drugs*. [Online] Available from: http://www.pharmacopoeia.co.uk/ [Accessed: 27th February, 2015]

Chaudhuri, D. M., Sonawane, O. R., Zawar, L., Nayak, S. and Bari, B. S. (2012). Solubility and dissolution enhancement of poorly water soluble glimepiride by using solid dispersion technique.*International Journal of Pharmacy and Pharmaceutical Sciences*, 4(5), ISSN: 0975-1491.

Chemicalbook.com (2010).*Glimepiride*.[Online] Available from: http://www.chemicalbook.com/ChemicalProductProperty_EN_CB8318552.htm [Accessed: 11th March, 2015]

Clark, M. A., Finkel, R., Rey, J. A., Whalen, K. and Harvey, R. A. (2012).*Lippincott's Illustrated Reviews: Pharmacology*. 5th edition, New York: Lippincott's Williams & Wilkins, 301-315.

Drugs.com (2013).*Glimepiride, Monograph of glimepiride*. [Online] Available from: http://www.drugs.com/monograph/glimepiride.html [Accessed: 21st February, 2015]

FDA.gov (2014).*Medication Guide*. [Online] Available from: http://www.fda.gov/safety/medwatch/safetyinformation/ucm167736.htm [Accessed: 23rd March, 2015].

Gulve, A. S., Tarkase, K. N., Mundhe, D. B. andHajare, P. P. (2013). Development and validation of derivative spectrophotometric method for estimation of pioglitazone HCl and glimepiride in bulk and combine dosage form. *Der PharmaChemica*, 5(3), 122-127.

Induri, M., Raju, M., Prasad Y. and Reddy K. P. (2012).Development and Validation of a Spectrophotometric Method for Quantification and Dissolution Studies of Glimepiride in Tablets.*E-Journal of Chemistry*, 9(2), 993-998.

Katzung, B.G., Masters, S.B. and Trevor, A.J. (2010).*Basic and Clinical pharmacology*. 11th edition, New York: Lange Publication. 363-372.

Khardori, R. (2010). *Diagnosis and Classification of Diabetes Mellitus*. [Online] Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2797383/ [Accessed: 5th February, 2015]

Lachman, L., Liberman, H.A. andKanig, J.L. (2008).*The Theory and Practice of Industrial Pharmacy*. 3rd edition, Bombay: Varghese publication,300-852

Lad, R. N., Bhoir, I. S. andSundaresan, M. (2003).Concurrent Assay of Metformin and Glimepiride in tablets using RP-HPLC with wavelength programming.*Indian Journal of Pharmaceutical Sciences*, 65(6), 650.

Naz, A., Ali, H., Zafar, F., Shah, N. S., Sharif, H., Siddiqui, S., Nisa, Z. andNaqvi, R. G. (2013). Development of spectrophotometric method for dissolution and in vitro kinetic study of glimepiride tablets. *Latin American Journal of Pharmacy*, 33(9), 1418-1424.

Pharusuniversity in Alexandria, (2012). *Quality control test for tablets*. [Online] Available from: http://www.scribd.com/doc/47820878/Quality-Control-Tests-Tablets-Lecture7 [Accessed: 16th February, 2015]

Rabbaa-Khabbaz, L., AbiDaoud, R., Karam-Sarkis, D., Atallah, C. and Zoghbi.A. (2005).A Simple and Sensitive Method for Determination of Glimepiride in Human Serum by HPLC.*Journal of Liquid Chromatography & Related Technologies*, 28(20), 3255-3263.

Rani, B., Dhanalakhmi, G., Manuja, P., Prathusha, M. and Meenakshi, S. (2013). Formulation and evaluation of controlled release matrix tablet of pantaprazole sodium. *International journal of inventions in pharmaceutical sciences*, 1(2320-1428), 42-52.

Reddy, D. N., Srinath, Ahad, A., Sravanthi, andKavitha, (2011). Formulation and in vitro evaluation glimepiride and parecoxibmucoadhesive tablets for diabetics associated with pain and inflammation. *Der Pharmacia Sinica*, 2(2), 101-109.

Reichal, R. C, Lakshmi, B. J. and Ravi, K. T. (2011).Studies on formulation and in vitro evaluation of Glimepiride floating tablets.*Journal of Chemical and Pharmaceutical Research*, 3(3), 159-164.

Revision of monograph on tablets, (2011).1st ed. [ebook] *World Health Organization*. Available from: http://www.who.int/medicines/publications/pharmacopoeia/Tabs-GeneralMono-rev-Final_31032011.pdf [Accessed: 17th April, 2015]

RxList, (2015).Amaryl (Glimepiride) Drug information: *Clinical Pharmacology-Prescribing Information at Rxlist*. Available from: http://www.rxlist.com/amaryl-drug/clinical-pharmacology.htm [Accessed: 26th January, 2015]

Safila, N., Hina, Q., Wardha, J. and Urooj, B. (2014).Simple UV Spectrophotometric Assay of Glimepride.*Open Science Journal of Clinical Medicine*, 2(4), 94-97.

Shohin, I.E, Ramenskaya, G.V, Vasilenko, G.F. and Davydova K.S. (2011).*Application of scientifically justified biowaiver for immediate release solid oral dosage form*.International Journal of Pharmaceutical science. 3 (1), 918-923.

Sortax, (2012).*Dissolution testing*.Available from: http://www.sotax.com/Dissolution-testing.52.0.html [Accessed: 26th February, 2015]

The United States Pharmacopeia, (2003). 26th ed. Toronto: United States Pharmacopeial Convention, Inc.

The United States Pharmacopeia: The National Formulary, (2006). 20th ed. United States Pharmacopeial Convention.

Tidy, D. (2015). Diabetes Mellitus.Information about Diabetes Mellitus (DM).Patient | Patient.co.uk.[Online] Available from: http://www.patient.co.uk/doctor/diabetes-mellitus# [Accessed: 29 May, 2015].

Ulman, K. L., Rafidison, D. P. (2003). Good Manufacturing Practice: *A Synopsis of Their Role and Rationale in Today's Pharmaceutical Marketplace*. ISSN:181-6403.

Vinensia, (2013*). Tablet weight variation and what causes it and how to deal with variation*. [Online] Available from: http://formulation.vinensia.com/2010/11/tablet-weightvariation-what-causes-it.html [Accessed: 12th February, 2015]

Waleed M.S.A.S, Zairi, M. (2001).*The role of quality in pharmaceutical care management Volume*. 11 Issue: 1 ISSN: 0960-4529. 32-39.

Webmd.com (2015).*Diabetes Mellitus*.Available from: http://www.webmd.com/diabetes/types-of-diabetes-mellitus?page=1#1 [Accessed: 3rd February, 2015]

Zhu, H., Zhu, S., Zhang, X., Guo, Y., Shi, Y., Chen, Z. and Leung, S. (2013). Comparative efficacy of glimepiride and metformin in monotherapy of type 2 diabetes mellitus: meta-analysis of randomized controlled trials. *DiabetolMetabSyndr*. [Online] Available from: http://www.dmsjournal.com [Accessed: 9th May, 2015].