Comparative Evaluation of Marketed Linagliptin Tablets in Bangladesh

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

School of Pharmacy
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Declaration

It is hereby declared that

1. This thesis work is my original work, and I have done this whole work to complete my Bachelor of Pharmacy degree.
2. The whole writing involves the writings with proper citation and referencing expect this it does not contain any third party's writing.
3. This thesis is not accepted by any other institution or university.
4. I have acknowledged all the sources that I used during this work.

Student's Full Name & Signature:

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Approval

This thesis project named "Comparative Evaluation of Marketed Linagliptin Tablets in Bangladesh" submitted by Muskan Agarwala (ID:20346013) of Summer, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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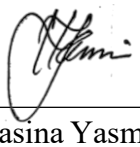

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Ethics Statement

This project study does not include any kind of human or animal trial.

Abstract

Linagliptin is often regarded as a primary treatment option for type 2 diabetes and has shown stronger inhibitory effects compared to other DPP-4 inhibitors. This study involves the comparative analysis of some key pharmaceutical parameters such as disintegration, friability, hardness, dissolution, and potency of linagliptin tablets of five different brands in Bangladesh. The analysis showed that all the brands maintain compliance with the friability test results with a little variation in their hardness and disintegration time. Brand A showed the highest dissolution rate on the other hand Brand D showed the lowest potency which is below the criteria. Although Brand A is a leading brand, the disintegration time was comparatively high than other brands. The evaluation from the analysis highlights the importance of continuous monitoring of quality control parameters in ensuring therapeutic efficacy and patient safety in different brands of linagliptin.

Keywords: Linagliptin, Disintegration, Friability, Hardness, Dissolution, Potency.

Dedication

Dedicated to all diabetic patients, my family and my respected faculty members.

Acknowledgement

First, I want to thank Almighty for giving me the opportunity, strength and guidance throughout my whole journey.

Without the guidance of my supervisor Dr. Hasina Yasmin, it was impossible for me to finish my work. With her tremendous knowledge she guided me in every single step. I want to express my heartfelt gratitude to my supervisor Dr. Hasina Yasmin ma'am because without her patience and guidance I cannot be able to work on this crucial topic. Her guidance and motivation helped me to work on my project also it was a great privilege and honor for me to work under her supervision and guidance.

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List of Acronyms

API – Active Pharmaceutical Ingredient

DPP-4 – Dipeptidyl Peptidase-4

FPG – Fasting Plasma Glucose

GLP-1 – Glucagon-like Peptide-1

GIP – Glucose-dependent Insulinotropic Polypeptide

HPLC – High-Performance Liquid Chromatography

ICR – In Vitro Comparative Release

INN – International Nonproprietary Name

PK – Pharmacokinetics

PD – Pharmacodynamics

HbA1C – Hemoglobin A1C (or Glycated Hemoglobin)

OGTT – Oral Glucose Tolerance Test

SGLT2 – Sodium-Glucose Cotransporter-2

USP – United States Pharmacopeia

UV – Ultraviolet Spectroscopy

WHO – World Health Organization

Chapter 1

Introduction

1.1 Diabetes

Diabetes mellitus, a disease of elevated blood sugar level in body which is a metabolic disease. Nowadays, diabetes is the most common disease in the world. It happens mainly due to two reasons either the body doesn't make enough insulin, or the cells don't react to it correctly. The pancreatic islets of Langerhans include two types of endocrine cells, among them alpha cells, which releases glucagon on the other hand, beta cells, secretes insulin that is responsible for controlling blood sugar levels.

1.2 Epidemiology of Diabetes

In today's advanced world diabetes has become a very dangerous threat for the people living worldwide. In global scenario, 1 in every 11 adults are now suffering from diabetes. The global prevalence of diabetes is growing faster than imagination. In Europe, Australia, and the Middle East, rates grow 2%–5% annually and rates increased 2% year in most US age and ethnic groups (Sapra & Bhandari, 2023). According to the International Diabetes Federation, 1 in 11 20-79-year-olds had diabetes in 2015 but by 2040, low-to-middle-income persons will have the higher chance for diabetes rising from 415 to 642 million. Blacks, Native Americans, Pima Indians, and Hispanics had 2–6 times more prone to diabetes than Whites (Sapra & Bhandari, 2023). Due to ethnicity the environment factor may affects the chance of developing diabetes for example Pima Indians in Mexico had a lower risk of diabetes than those in the US (Sapra & Bhandari, 2023). Bangladesh is a developing country and along with development it also needs to deal with the prevalence of diabetes. In Bangladesh, the International Centre for

Diarrheal condition Research reported about 7.1 million cases of diabetes, 3.7 million undiagnosed cases, and 129,000 fatalities from the condition in 2015.According to published studies, 2.21% to 35% of Bangladeshi people are now suffering from diabetes (Akhtar et al., 2020).

1.3 Classification

Diabetes mellitus (DM) is classified into several types includes,

- Type 1 diabetes
- Type 2 diabetes
- Gestational diabetes
- Newborn diabetes
- Maturity-onset diabetes of the young (MODY) and
- Secondary causes resulting from endocrinopathies, steroid use etc.

Type 1 and Type 2 diabetes mellitus are the most common types of diabetes. The main cause of these two types of diabetes is faulty insulin production and inability of insulin to work, respectively. Type 2 diabetes is most prevalent in middle-aged and older adults who have chronic hyperglycemia because of poor dietary and lifestyle choices. On the other hand, Type 2 diabetes is expected in children or teenagers. Gestational diabetes is a special type of diabetes that is seen to be prevalent during pregnancy. Furthermore, several types of endocrine disorder influence the glucose level in the body which ultimately causes imbalance in glucose level of body.

1.4 Pathophysiology

The causes of type 1 and type 2 diabetes are not the same, they have differences in causes, presentations, and therapies of each type (Sapra & Bhandari, 2023). In diabetes mellitus, either insulin doesn't function at all or acts poorly which is known as insulin resistance and ultimately blood sugar level raises. In type 1 diabetes, loss of beta cells in the pancreas occurs which are autoimmune mediated. Much evidence of autoimmune damage is found in body fluids and tissues such as islet cell autoantibodies (ICAs) autoantibodies to insulin (IAAs), autoantibodies to glutamic acid decarboxylase (GAD65), autoantibodies to the tyrosine phosphatases IA-2 and IA-2ß (Paliika, 2002). As a result of this destruction the beta cells present in the body get destroyed and cannot be able to produce insulin or less amount of insulin is produced than usual need. Despite this factor genetic factor is responsible for the occurrence of Type 1 diabetes, HLA (Human leukocyte antigen) on chromosome 6 is closely connected to Type 1 diabetes mellitus, which conferring 60% of genetic risk. Over 15 possible loci of gene, found on chromosomes 2 and 11, have been uncovered. HLA molecules may transport islet cell autoantigen-responsive antigens to T-helper cells. This immune reaction destroys the islet of Langerhans insulin-producing cells using autoantibodies and T lymphocytes (Paliika, 2002). Environment is also playing key factor in the Type 1 diabetic patient.

Figure 1: Pathophysiology of Type 1 Diabetes (Healthcare, 2013)

According to the most widely acceptable theory, type II diabetes is characterized by elevated glucose and insulin levels because the body must secrete more insulin to overcome the block caused by less responsive insulin-sensitive insulin receptors and cell metabolic processes (Pories & Albrecht, 2001).It accounts for 90% of diabetes cases which are more frequent than type 1. Type 1 diabetes is triggered by genetic factors in the human body, family history and other heath related problems but Type 2 diabetes is mainly influenced by hereditary, age, environment, insulin resistance and unhealthy lifestyle. Maturity onset diabetes is a non-insulin dependent diabetes and transmitted by autosomal dominant (Sapra & Bhandari, 2023). Diabetes occurs in fewer than 15% of obese people, although 60–80% of type 2 diabetics are fat which indicates that weight loss and exercise reduce clinical symptoms of diabetes. Gestational diabetes mellitus pathophysiology is unknown, but the possible reasons may include family history, obesity, before pregnancy problems. Pre-existing diabetes mellitus has a poorer prognosis for the fetus and must be detected as soon as possible (Paliika, 2002).

Figure 2:Pathophysiology of Type 2 Diabetes (Healthcare, 2013)

Type 1 diabetes causes a reduction of blood glucose level very fast. On the other hand, type 2 diabetic patients experience extremely high levels of glucose in bloodstream and are mostly associated with the traditional symptoms of diabetes, such as polyuria, polydipsia, and polyphagia. In type 1 diabetic patient weight loss is very common but for type 2 diabetic

patients if it remains untreated for longer period then sudden weight loss is noticed. Other common symptoms of unidentified diabetes include bodily discomfort, restlessness, and unexplained weight loss (Ramachandran, 2014).

1.5 Signs and Symptoms of Diabetes

Though diabetes remains asymptomatic in different stages of its progression but there are different types of signs and symptoms that are common in diabetic patients, but it may vary to person to person due to human physiology. The most common signs are symptoms are given below:

- Fast weight loss
- Frequent feeling of fatigue
- Dry mouth
- Numbness, pain on feet
- Decreased vision
- Itching and irritation
- Presence of velvety dark patches of the neck, arm pit
- Frequent urination

If fatigue, restlessness, body pain and weight loss are noticed for a long period of time then it indicates undetected diabetes. Sometimes the symptoms are very mild, or it is developing in the body very slowly so that it is very hard to diagnose them.

1.6 Diagnosis Test

There is different diagnosis tests are available for detecting diabetes in patients. They are Fasting blood glucose level test, oral glucose tolerance test (OGTT), A1C test and random

blood sugar test. These tests are done when the classic symptoms of diabetes along with high blood glucose level are observed.

1.6.1 Fasting Glucose Level Test

Fasting blood glucose test is a blood test where the blood glucose level of the patient is measured when patient did not take any food and drink anything for at least 8 hours period. This test is usually done in the morning before breakfast. In this test, blood is collected from the vein of the patient and RBC is removed from the blood sample and glucose level is detected in the plasma only. Plasma level of 200 mg/dl or greater than that indicates diabetes in patients (P et al., 2012).

1.6.2 Oral Glucose Tolerance Test

During an oral glucose tolerance test (OGTT), the patient's body is evaluated to see how it processes glucose. There was a requirement that the patient fast for a period of eight to fourteen hours before this. At the beginning of the test, a blood sample is collected at zero time. If a glucose solution is given to the patient, it is consumed within five minutes of the administration of the solution. To determine the glucose levels, blood is drawn at regular intervals. The presence of a plasma glucose level that is at least 2000 mg/L two hours after the consumption of the syrup and at one other time during the two-hour test period is sufficient to validate the diagnosis of diabetes (P et al., 2012).

1.6.3 A1C Test

The A1C test measures the average glucose level in a patient's body over 3 months. This test does not have any restrictions on eating and drinking. There are other names for this test these are hemoglobin A1C, HbA1C glycated hemoglobin.

1.6.4 Random Blood Sugar Test

Random plasma glucose test is mainly conducted to check diabetes in patient when patient having symptoms of diabetes, and he want to test immediately. This test does not include any criteria one can do this test anytime.

1.7 Treatment

Treatment of type 1 diabetes involves lifestyle modifications, for example healthy diet and exercise. People who have type 1 diabetes need to take insulin injections and regular glucose level monitoring in their body. Losing weight, eating well, and exercising are also needed to treat type 2 diabetes. Few people who have type 2 diabetes can control their glucose levels by maintaining diet and exercise, but most of them need medication and insulin. People with type 2 diabetes taking diabetic medication must measure their blood glucose daily or several times a day. There are different classes of antidiabetic drug that are used to treat diabetes. They are given with examples in table below:

Table 1:Classification of Anti-Diabetic drug

No.	Types of anti-diabetic drugs	Examples
1	Sulfonylureas	Glipizide, Gliclazide, Glimepiride
2	Meglitinides	Nateglinide
3	Biguanides	Metformin
4	Thiazolidinediones	Rosiglitazone
5	Alpha-glucosidase inhibitors	Acarbose
6	DPP-4 inhibitors	Linagliptin, Saxagliptin, Sitagliptin
7	SGLT2 inhibitors	Canagliflozin, Empagliflozin

Also, there are different types of insulin injection that are available in the market for the treatment of diabetes. They include,

- Rapid acting
- Short acting
- Intermediate acting and
- Long acting.

Already mixed insulin combinations are also available in the market. Concentrated insulins are offered for individuals requiring high insulin dosages for controlling glucose level. For those who cannot or do not want to take insulin injections, inhaled insulin is available (Erika, 2023).

1.8 DPP-4 Inhibitors

Among all the classes of anti-diabetic drug one of the special classes of drug is DPP-4 inhibitors. Dipeptidyl peptidase-4 (DPP 4) inhibitors, Due to their unique mode of action and safety profile, these medicines have become essential diabetic treatments nowadays. DPP-4 inhibitors manage hyperglycemia without the danger of hypoglycemia associated with other diabetes medications by improving the body's blood glucose regulation. This drug acts as a useful alternative for Type 2 diabetes individuals who cannot manage their glucose levels with

lifestyle changes and other oral antidiabetics. Their once-daily oral delivery, fewer side effects, and little risk of weight gain or hypoglycemia make them appealing to many patients. By the combination of DPP-4 inhibitors with other diabetic drugs like metformin improves its efficacy (Erika, 2023). The examples of DPP-4 inhibitors include saxagliptin, sitagliptin, linagliptin etc.

1.9 Linagliptin

Among all the types of linagliptin is the most widely used drug in today's world for the treatment of Type 2 diabetes mellitus. This drug is a critical alternative for many patients who are having trouble in maintaining glycemic control because it provides a distinctive approach to glucose management by augmenting the body's natural capacity to regulate blood sugar levels. It is contraindicated for type I diabetes and diabetic ketoacidosis.

1.10 Chemical Structure of linagliptin

Linagliptin, for instance, has a structure that is based on xanthine (Figure 1), which may be a significant contributor to the drug's extended terminal elimination half-life (which is seen to be greater than one hundred hours).6. When compared to the much shorter half-lives of saxagliptin and sitagliptin, the extensive half-life of linagliptin may be more advantageous for individuals who occasionally fail to take their prescribed medicine dosages (Freeman, 2011).

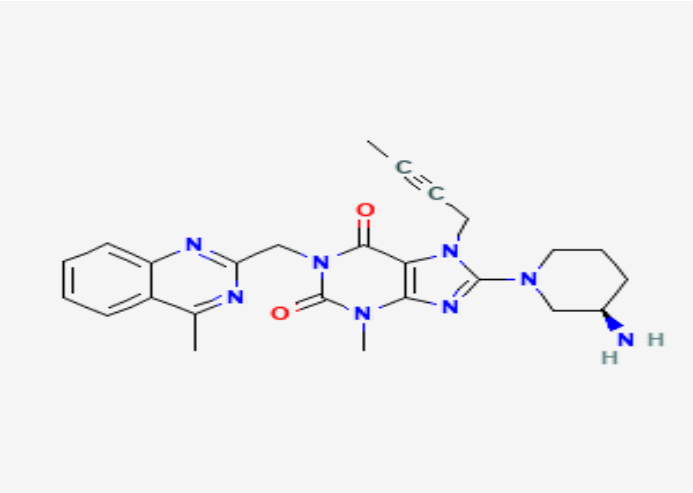

Figure 3: Linagliptin (PubChem, 2023)

1.11 Mechanism of Action of Linagliptin

Linagliptin targets on a specific enzyme in the body which is DPP-4 enzyme which is responsible for breaking down incretin hormones such as glucagon-like peptide-1(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Both hormones have a role in the natural control of glucose balance in the body and they enhance the production and release of insulin from pancreatic beta cells when blood glucose levels are not in balance. Furthermore, GLP-1 inhibits the release of glucagon from alpha-cells in the pancreas which leads to a decrease in the production of glucose in the liver. Both hormones control the release of insulin from the beta cells in the pancreas and inhibit the release of glucagon from the alpha cells, which then decreases the generation of glucose in the liver (Freeman, 2011). Linagliptin inhibits this DPP-4 enzyme and ultimately all these actions get reversed. It inhibits the breakdown of incretin in the body ultimately there will be increased amount of incretin in the body. As the amount of incretin in the body increases which causes an increase in the insulin in the human body, which in turn controls the blood sugar level in the patient's body. Linagliptin exhibits high affinity for the DPP-4 enzyme, forming a strong bond that cannot be broken.

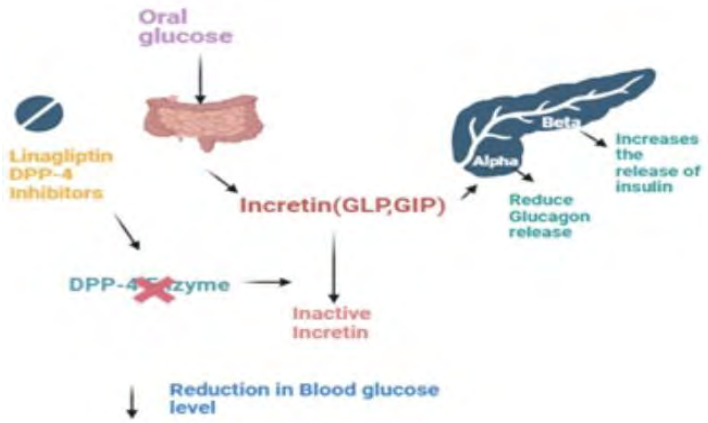

Figure 4:Mechanism of action of linagliptin

1.12 Solubility of Linagliptin

Linagliptin is not water soluble, and it can dissolve in organic solvents. It dissolves into different solvents in different percentages. Linagliptin is very well soluble in methanol but meagerly soluble in ethanol again very slightly soluble in isopropanol, alcohol. In the following table the solubility profile for linagliptin in different organic solvents is mentioned.

Table 2:Solubility profile of linagliptin (Hossain, 2019)

Name of the solvent	Solubility in mg/ml	Solubility profile
100% acetonitrile	30.53	Poor solubility
100% methanol	101.94	Excellent solubility
100% ethanol	28.86	Poor solubility
75% acetonitrile	195.28	Excellent solubility
75% methanol	271.67	Excellent solubility
75% ethanol	67.96	Poor solubility
50% acetonitrile	403.440	Excellent solubility
50% ethanol	108.97	Excellent solubility

1.13 Contraindication, Side effects, Adverse effect

1.12.1 Contraindication

Linagliptin is contraindicated to some people. There is an evidence of hypersensitivity reaction to linagliptin, such as

- Urticaria,
- Angioedema
- Bronchial hyperreactivity.

1.12.2 Adverse Effect

Linagliptin has some minor adverse effects, among them headaches and flu-like symptoms were the most common adverse events. Nausea was also seen among patients. Few patients taking linagliptin had nasopharyngitis, which has been linked to other DPP-4 inhibitors (Tella et al., 2014).

1.12.3 Side Effects

In the case of linagliptin there are no significant side effects noticed in prescribed dose. In very minor amount of patient cough, high cholesterol, pancreatis and weight gain were noticed, and these are the only side effects that were recorded in at least 2% of people who took linagliptin, which was at least two times as many people (Tella et al., 2014). Also, there may be chances of developing cardiovascular disease in patients with linagliptin.

1.14 Pharmacokinetics

Linagliptin 5 mg is readily absorbed following oral administration, and geometric mean maximum plasma concentration values are 6–10 nmol/L after a single dosage and it takes 1.5–2.0 h to reach maximal plasma concentration. About 30% of linagliptin is bioavailable (Ceriello

& Inagaki, 2017). Food has no clinically significant influence on linagliptin absorption. After a single 5 mg intravenous dosage, steady-state volume of distribution was 1,110 L (Ceriello & Inagaki, 2017). A high apparent volume of distribution implies substantial tissue dispersion of linagliptin. Linagliptin also binds 70–80% plasma proteins concentration-dependently. Due to strong attraction of linagliptin with DPP-4 enzyme in plasma and tissues results in a long terminal half-life short accumulation half-life and non-linear PK profile. The high affinity for binding of linagliptin with DPP-4 causes non-linear relationship because when the dose increased the amount of linagliptin does not increase proportionately. Linagliptin is mostly removed unaltered by feces, with metabolism playing a small role. Th major metabolite of linagliptin known as CD 1790 which accounts for 18% of the molar linagliptin plasma exposure following a single oral 10 mg tablet which is pharmacologically inactive (Ceriello & Inagaki, 2017). The reversible binding of linagliptin to DPP-4 in the plasma and tissues indicates that a portion of the given dose is not directly available for elimination, but bile excretes most of the systemically available dose, with 12% secreted directly into the gut (Ceriello & Inagaki, 2017). In the case of hepatic or renal dysfunction, direct gastrointestinal excretion of linagliptin may offer an alternative route for drug excretion.

1.15 Pharmacodynamics

Due to the glucose-dependent enhancement of insulin release, DPP-4 inhibitors have a minimal risk of decreased blood glucose level in the body which makes them a promising option for type 2 diabetes management. Dose-dependent DPP-4 inhibition is maintained by linagliptin. Maximum glucose-lowering effectiveness is observed with DPP-4 inhibitors that inhibit DPP-437 by at least 80%. The mean maximal DPP-4 inhibition at steady state was 91–93% for all linagliptin dosages (Ceriello & Inagaki, 2017). The studied linagliptin dosages are predicted to provide maximal glucose-lowering efficacy.

1.16 Linagliptin Monotherapy and Combination Therapy

Linagliptin monotherapy is a most common therapeutic choice for people with Type 2 diabetes, It is widely used for those who have just been diagnosed or who are unable to use other antidiabetic medications due to contraindications. Linagliptin leads to an augmentation in the production of insulin and a reduction in the release of glucagon in response to glucose, which affects the regulation of blood glucose levels without inducing substantial hypoglycemia.

In a significant number of people with Type 2 diabetes, using a single medication may not be enough to reach the desired blood sugar levels. Linagliptin is frequently administered with other antidiabetic medications such as metformin, sulfonyl urea, SGLT2 inhibitors to enhance glycemic control by utilizing complementing mechanism of action.

1.17 Advantages of Linagliptin

Some desirable traits of DPP-4 inhibitors are that they can be taken by mouth once a day, they don't affect weight, and they cause fewer adverse events linked to the digestive tract. The results of clinical trials with linagliptin show that it works to lower fasting plasma glucose level (FPG) and postprandial glucose (PPG) levels when used alone or with other anti-diabetic drugs (Neumiller & Setter, 2012).All types of DPP-4 inhibitors have same mechanism of action but linagliptin has very unique chemical structure and pharmacological profile compare to other ones. Linagliptin inhibited DPP-4 activity better than vildagliptin, sitagliptin, saxagliptin, and in vitro. Additionally, linagliptin's non-linear PK profile differs from other DPP-4 inhibitors. Linagliptin also binds plasma proteins better than other DPP-4 inhibitors and has a longer terminal half-life (Ceriello & Inagaki, 2017).

1.18 Drug Interaction

Cytochrome P450 enzymes are weakly to moderately blocked by linagliptin. Since these enzymes only break down a small amount of linagliptin, it is not likely that drugs taken at the same time will change how much linagliptin a person is exposed to by blocking or starting up P450-dependent pathways (Ceriello & Inagaki, 2017). It is important to note that linagliptin has not been shown to interact clinically with widely given diabetes medicines like metformin, sulfonylureas, and glyburide. Linagliptin, works with P-glycoprotein, but it might not work as well when combined with strong P-glycoprotein inducers, like rifampicin, especially if these drugs are used for a long time. Therefore, different care is suggested in these situations.

1.19 Special Consideration

Linagliptin is age-safe and effective. Including renal impairment, Type 2 diabetics patient often have hepatic illness, including non-alcoholic fatty liver disease and cirrhosis. Even though linagliptin is mostly eliminated by the liver, hepatic impairment has no clinically significant influence on its PK, PD, or tolerability (Ceriello & Inagaki, 2017). The occurrence of mild to moderate, or severe hepatic impairment did not have impact on the single or repeated doses of linagliptin. Linagliptin is safe and effective for both men and women, and there is no evidence this has a clinically significant effect on the drug's absorption. There have not been any well-controlled studies on linagliptin in women who are pregnant or nursing, but it has been shown to cross the placenta and be found in milk from animals (Neumiller & Setter, 2012).Because of this, linagliptin should only be used during pregnancy if it is clearly needed, and women who are nursing should be very careful when taking it.

1.20 In vitro Testing of Tablets

In this article we are going to conduct some critical in-vitro testing of linagliptin tablets available in the market of Bangladesh. In vitro testing of tablets involves evaluating the properties and performance of pharmaceutical tablets outside of a living organism, in a controlled laboratory environment. These tests are crucial for ensuring the quality, safety, and efficacy of the tablets before they are approved for use in patients. Several key in vitro tests are commonly conducted on tablets such as hardness test, friability test, weight variation test, disintegration test, dissolution test, potency test, Dose uniformity test etc. Here, we are focusing on hardness test, friability test, disintegration test, dissolution test and potency test.

1.20.1 Hardness Test

The term "hardness" refers to the capacity of a tablet to endure the impact of mechanical shocks that may occur during the production, packing, and shipping processes. Between four to seven kilograms of force (kgf) is the range of hardness or crushing strength that is appropriate for tablets Sabbir et all,2019. During the research, the Tablet Hardness Tester, YD-1(Wincom, China) was used to test the level of hardness possessed by each tablet. For each of the formulations, 10 tablets of each brand were ingested, and the tablets' hardness was measured. This was done for all five brands used in this evaluation.

1.20.2 Friability Test

Tablet friability testing is an essential quality control process that is done for the purpose of determining the mechanical strength of pharmaceutical tablets. In this test, the tablet is evaluated to see whether it can survive the stresses during packaging, handling, transportation, and dispensed without disintegrating or crumbling. To ensure that the tablet retains its effectiveness and integrity until it is taken by the patient, it is important to ensure that it has

sufficient friability characteristics. The Friability tester was manufactured by Electrolab (EF2 USP) in India. After weighing each of the tablets, they were put in a friability machine and subjected to rolling at a rate of 25 revolutions per minute for a total of one hundred revolutions. After that, the tablets were cleaned of dust and weighed. As a result, the percentage of weight loss is calculated appropriately, and it needs to be kept under control within 1% (Sabbir et al.2019). The evaluation of the average data was accomplished with the use of ten tablets of linagliptin for five marketed brands.

1.20.3 Disintegration Test

The disintegration test is an essential quality control method that is used to determine the amount of time it takes for a tablet or capsule to break down into smaller pieces when it is put in a certain liquid medium under standard environment. This test assures that the drug will dissolve correctly in the gastrointestinal system, which will allow the active pharmaceutical ingredient (API) to be released and absorbed into the body in an efficient manner. This was determined by utilizing a Disintegration Testing (DT) device Wincom manufactured in China in simulated stomach fluid at a temperature of 37 degrees Celsius until there was no particle left on the basket of the system of the experimental system (Sabbir et al., 2019). The tablets are evaluated not only for their quality but also for their bioavailability and their effectiveness. Each tablet's disintegration time was measured, and the average disintegration time was calculated. In this test, we used four tablets of linagliptin of five different marketed brands.

1.20.4 Dissolution Test

The tablet dissolution test is an essential quality control process that is utilized to test the degree to which the active pharmaceutical ingredient (API) gets released from a solid dosage form, such as a tablet, into a dissolving medium over the course of time. It is a vital test which is carried out to ensure the drug's bioavailability, effectiveness, and constant performance. A

dissolving study of the sample tablets was carried out with the assistance of a Tablet dissolution tester Logan instruments Corporation, USA (Model-UDT-804). The samples tablets were placed in dissolution medium. The samples were then rotated at a speed of 100 revolutions per minute at a temperature of thirty-seven degrees Celsius with a standard deviation of half a degree Celsius (Sabbir et al., 2019). For the dissolution of marketed linagliptin we have used six tablets in six baskets for all five brands.

1.20.5 Potency Analysis

Potency testing is an essential analytical method that is used to evaluate the quantity of the active pharmaceutical ingredient (API) that is contained within a tablet. By confirming that each tablet has the appropriate amount of active pharmaceutical ingredient (API) as defined in the product formulation, this test ensures that the patient will get an effective, rational and safe treatment.

1.21 Purpose of Study

The purpose of the study is to perform in vitro analysis tests for five different famous brands available in the market of Dhaka city. As we know linagliptin is a very promising drug used for the treatment of diabetes mellites. The study will evaluate the key parameters such as hardness, friability, disintegration, dissolution and potency test and assess the consistency and effectiveness of different brands. This research will compare the performance of each brand as it enlightens their quality. This study can ensure the patient safety, therapeutic effect of drug and relevancy of the company to the regulatory standards for marketed drugs. Data collected from this research can also highlight the gap between quality control practice and regulatory compliance.

Chapter 2

Material and Methodology

2.1 List of Instruments

The table contains the name, model and origin of the instruments that are used in the project work:

Table 3:List of Instruments

Serial no.	Instrument	Model no.	Origin
1	UV-Spectrophotometer	U-2910	Japan
2	Friability tester	EF2 USP	India
3	Hardness tester	YD-1	China
4	Disintegration tester	BJ-2	China
8	Dissolution tester (8 vessel)	UDT-804	USA

Figure 5:UV spectrophotometer

Figure 6: Friability Tester

Figure 7:Hardness Tester

Figure 8: Disintegration Machine

Figure 9: Dissolution Machine (8 vessel)

2.2 List of Reagents and Chemicals

The following table contains the list of reagents and chemicals that are used during the test:

Table 4:List of Reagents and Chemicals

Serial no.	Reagent
1	0.1N HCL
2	Distilled water
3	100% methanol
4	50% methanol

2.3 List of Apparatus and Glassware

The list of apparatus with their specification that used in the project work is given in below table:

Table 5:List of Apparatus and Glassware

Serial no.	Apparatus	Specification
1	Volumetric flask	50ml,100ml,1000ml
2	Beaker	100ml,250ml,500ml, 5000ml
3	Funnel	small
4	Pipette	1ml,2ml,10ml,25ml
5	Filter paper	Whitman
6	Dropper	Small dropper
7	Pipette pump	Plastic and rubber
8	Spatula	Small

2.4 Methodology

Five different reputed brands of 5mg of Linagliptin tablet of Bangladesh were taken for the study. These five leading brands were represented using the letters A-E.

2.4.1 Friability Test

The friability test is a quality control test of tablets, and this test is conducted to determine the capability of tablets to withstand mechanical pressure and process conditions. Friability indicates the tendency of the tablets to break, crack when they are compressed. This tendency is usually available for uncoated tablets and surfaces during storage and handling conditions.

In this test, the first weight of 10 tablets from each of the brands was taken and marked as initial weight. Then they were placed in the section of the drum of friability tester. The rotation was maintained at 25 rpm for 1 minute and count was set to 100. After the rotation finished collected the tablets and again took the weight of the tablets and marked as Final weight. By using a formula, the percentage of weight loss was determined. As we know, according to the USP the percentage of weight loss should be less than 1%.

$$\text{Percentage of weight loss} = \frac{(\text{Initial weight} - \text{Final Weight})}{\text{Intial weight}} \times 100$$

For brand A,

Initial weight: 1.80 gm

After weight:1.80 gm

$$\text{Percentage of weight loss} = \left(\frac{1.80 - 1.80}{1.80}\right) \times 100$$

$$= 0\%$$

By using the same equation, calculated the percentage of weight loss for brand B, C, D, E respectively.

2.4.2 Hardness Test

Hardness test measures the hardness of the tablet by using hardness tester. If the tablet has less hardness, then it will disintegrate in the body very fast, and the therapeutic action will be fast. But if the tablet has high hardness value, then it can damage the teeth, and it will take more time to disintegrate. So, it is very important to keep the value of hardness within safe range at which it can give desired effect and maintain quality of the tablet. The test was done on 10 tablets from each of the five brands. In the hardness test the tablets are placed vertically between the two jaws of the hardness tester and the force is applied until the tablet gets cracked. The point at which the tablet gets cracked was noted in Kg and converted into Newton. The same process is repeated for all five brands once.

2.4.3 Disintegration Test

The disintegration time test is done to evaluate the time tablets take to disintegrate in the body after administration. The test was done by noting down the time a tablet takes to disintegrate in the liquid media same as our body. The disintegration tester was assembled, and 600 ml distilled water was taken in 1000ml vessel of the tester. The temperature was maintained 37°C and wait until the temperature rises to this. In 6 tubes placed 3 tablets in 3 tubes. Then the machine was started and by using a stopwatch the time taken for the tablets to disintegrate was noted down. But there are certain points that need to be considered ensuring that the tablet is completely disintegrated. They are there will be no residue present on the screen of tubes and if any residue present then it will be considered as the core coating, only fragments of coating or layers of tablets is allowed to present on the screen and the temperature was maintained to 37°C strictly to ensure the adequate environment as the body. By maintaining these points, the exact disintegration time for each five brands were noted down and compared to each other.

2.4.4 Dissolution Study

In vitro dissolution test is very important test because it can measure the percentage of release of tablets from the marketed drug sample. Dissolution test evaluates the performance of the tablet in acceptance criteria in the presence of accurate test conditions and apparatus.

2.4.4.1 Preparation of Dissolution Medium

0.1N HCL act as a standard dissolution medium for the test. For the preparation of 0.1N HCL 8.33 ml pure HCL was taken in 1000 ml volumetric flask and make it up to the mark by using distilled water.

2.4.4.2 Preparation of Standard

For the preparation of standard, the standard linagliptin was collected from Eskayef Pharmaceuticals Ltd. At first, 28mg sample was weighted and taken into 100ml of volumetric flask. To dissolve the standard, we used 0.1 N HCL and dissolved standard. Make the volume with 0.1N HCL up to the mark and mix well. Then pipette 1ml of the solution into a 50 ml volumetric flask and make it up to the mark with 0.1N HCL.

2.4.4.3 Preparation of Sample

Took 900 ml 0.1N HCL into the vessel of the dissolution machine and keep waiting for raising the temperature to 37±0.8°C. Then dropped 6 tablets of one brand into separate dissolution vessel and started the timer for 15 minutes. After 15 minutes, collected 30 ml of dissolution solution from each vessel and filtered the solution by using filter paper.

2.4.4.4 Measure Percentage of Release

For the measurement of the absorbance prepare the UV spectrophotometer. After connecting the machine set the absorbance to 296 nm. Then by using 0.1 N HCL as blank nullified the

absorbance for blank. Took the absorbance of the standard solution and note it down. Again, took the absorbance of dissolution solution of six tablets.

By using this equation calculated the percentage of release for each six tablets,

$$\text{Percentage of release} = \frac{Au}{As} X \frac{Ws}{100} X \frac{1}{50} X \frac{900}{Lc} X \frac{P}{100} X100$$

Here,

As: Absorbance of standard preparation: 0.245 nm

Ws: Weight of working standard in mg:28 mg

Lc: Label claimed of the tablet in Ing:5 mg

P: Potency Linagliptin working standard as is basis: 99.27%

For Brand A:

(Au) Absorbance for sample 6 tablets brand A:

1. 0.250 nm
2. 0.237 nm
3. 0.253 nm
4. 0.238 nm
5. 0.255 nm
6. 0.241 nm

For sample 1,

$$\text{Percentage of release} = \frac{0.250}{0.245} X \frac{28}{100} X \frac{1}{50} X \frac{900}{5} X \frac{99.27}{100} X100$$

=102.10%

For sample 2,

$$\text{Percentage of release} = \frac{0.237}{0.245} X \frac{28}{100} X \frac{1}{50} X \frac{900}{5} X \frac{99.27}{100} X100$$

=96.79%

For sample 3,

$$\text{Percentage of release} = \frac{0.253}{0.245} X \frac{28}{100} X \frac{1}{50} X \frac{900}{5} X \frac{99.27}{100} X100$$

=103.33%

For sample 4,

$$\text{Percentage of release} = \frac{0.238}{0.245} X \frac{28}{100} X \frac{1}{50} X \frac{900}{5} X \frac{99.27}{100} X100$$

=97.20%

For sample 5,

$$\text{Percentage of release} = \frac{0.255}{0.245} X \frac{28}{100} X \frac{1}{50} X \frac{900}{5} X \frac{99.27}{100} X100$$

= 104.14%

For sample 6,

$$\text{Percentage of release} = \frac{0.241}{0.245} X \frac{28}{100} X \frac{1}{50} X \frac{900}{5} X \frac{99.27}{100} X100$$

=98.45%

Mean percentage of release of brand A= $\frac{102.10+96.79+103.33+97.20+104.14+98.45}{6}$ %

=100.33%

By using the same equation, calculated the percentage of weight loss for brand B, C, D, E respectively.

2.4.5 Potency Analysis

In vitro potency test determines the amount of active pharmaceutical ingredient in a tablet. This test confirms that the tablet will contain adequate amount of API that is needed to produce claimed therapeutic effect. For potency test at first the calibration curve of standard need to produce and by using the equation from the curve the amount of API in the sample branded drug will be calculated.

2.4.5.1 Preparation of Calibration Curve

The standard for the potency test is Linagliptin standard which is collected from Eskayef pharmaceuticals Ltd. As we know linagliptin is not soluble in water. To dissolve linagliptin used 100% and 50% methanol. At first 0.1gm standard linagliptin weighted and taken in 100 ml volumetric flask. Then, put 100% methanol into volumetric flask and make it up to the mark. Now, from this stock solution prepared 20 ug/ml, 10 ug/ml, 5 ug/ml,2.5 ug/ml, 1.25 ug/ml by using serial dilution method in 50ml volumetric flask. Absorbance of the solutions were prepared by using 50% methanol as blank using UV spectrophotometer at λmax 296 nm. For each solution, the absorbance was taken 3 times. Calibration curve was prepared accordingly.

2.4.5.2 Preparation of Sample Solution

For sample took 10 tablets from each of five brands from the market and noted the average weight of the tablets. Then, by mortar & pastel crushed the tablets into fine powder and took the powder into a 50 ml volumetric flask and dissolved the powder with 100% methanol and made it up to the mark. Then, filtered the solution by using filter paper and filtered solution was stock solution. To dilute this solution used serial dilution method and made two concentrations 20 ug/ml and 10 ug/ml respectively. Repeated this dilution two times more to avoid any kind of error. Lastly, measured the absorbance by using UV spectrophotometer and during this the λmax value maintained was 296 nm. In Microsoft excel added three respective values of absorbance for each concentration and calculated the average value. Followed the same steps for other four brands and noted the data on Microsoft excel.

2.4.5.3 Determination of Linagliptin

By using equation collected from standard solution which is y= mx+c calculated the x. By using the value of x calculated the potency of tablet in percentage.

From the standard curve we got the equation

y = 0.0363x - 0.007

Here, m=0.0363

C=-0.007

For brand A,

Absorbance 1,

Absorbance at 10 ug/ml=0.353 which is the value of Y.

0.353= 0.0363x - 0.007

0.360= 0.0363x

x= 9.92 ug/ml

Average weight of tablet=0.1814 gm=181.4mg

Amount of sample taken for 10 tablets=1.814gm=1814mg

Dilution Factor (DF) = 50x50x2

$$\text{Amount of drug per tablet} = \frac{\text{concentration of drug x Dilution Factor x Average weight of tablet}}{\text{1000 x amount of sample taken}}$$

$$= \frac{9.92x50x50x2x181.4}{1000x1814}$$

=4.96 mg

$$\text{Potency} = \frac{4.96}{5}x100$$

= 99.2%

Absorbance 2,

Absorbance at 10 ug/ml=0.351 which is the value of Y.

0.351= 0.0363x - 0.007

0.358= 0.0363x

x= 9.86 ug/ml

Average weight of tablet=0.1814 gm=181.4mg

Amount of sample taken for 10 tablets=1.814gm=1814mg

Dilution Factor (DF) = 50x50x2

$$\text{Amount of drug per tablet} = \frac{\text{concentration of drug x Dilution Factor x Average weight of tablet}}{\text{1000 x amount of sample taken}}$$

$$= \frac{9.86x50x50x2x181.4}{1000x1814}$$

=4.93mg

Potency = $\frac{4.93}{5}x100$

= 98.6%

Absorbance 3,

Absorbance at 10 ug/ml=0.378 which is the value of Y.

0.378= 0.0363x - 0.007

0.385= 0.0363x

x= 10.60 ug/ml

Average weight of tablet=0.1814 gm=181.4mg

Amount of sample taken for 10 tablets=1.814gm=1814mg

Dilution Factor (DF) = 50x50x2

$$\text{Amount of drug per tablet} = \frac{\text{concentration of drug x Dilution Factor x Average weight of tablet}}{\text{1000 x amount of sample taken}}$$

$$= \frac{10.60x50x50x2x181.4}{1000x1814}$$

=5.3 mg

Potency = $\frac{5.3}{5}x100$

= 106%

$$\text{Average} = \frac{99.2+98.6+106}{3}$$

$$=101.27\%$$

By using the same standard curve and calculation method, calculated the potency of brand B, C, D, E respectively.

Chapter 3

Result and discussion

3.1 Result

3.1.1 Friability Test

The value of friability test for five different marketed brands of linagliptin Tablets given as follows:

Table 6: Friability Test of Five brands(A-E) of Linagliptin Tablets

	A	**B**	**C**	**D**	**E**
Initial weight(gm)	1.80	1.20	0.830	1.89	1.16
Final weight(gm)	1.80	1.197	0.830	1.889	1.156
Percentage weight of loss%	0	0.25%	0	0.052%	0.345%

3.1.2 Hardness Test

The value of hardness test for five different marketed brands of linagliptin tablets given as follow and Unit is Newtons(N):

Table 7: Hardness Test of Five brands(A-E) of Linagliptin Tablets

Sample no	A	B	C	D	E
Hardness of Sample 1	59.29	162.95	54.12	78.48	66.78
Hardness of Sample 2	83.69	119.58	46.29	67.56	51.21
Hardness of Sample 3	74.68	121.54	51.56	73.49	54.37
Hardness of Sample 4	76.93	144.40	56.27	86.36	47.76
Hardness of Sample 5	65.95	145.85	43.35	88.15	57.05
Hardness of Sample 6	76.67	130.94	51.93	82.75	46.85
Hardness of Sample 7	60.57	157.60	48.88	77.74	53.85
Hardness of Sample 8	69.29	125.90	51.16	69.79	57.39
Hardness of Sample 9	74.87	120.04	26.39	82.22	53.22
Hardness of Sample 10	80.75	129.10	50.22	64.95	50.88
Mean±SD	72.27±8.23N	135.79±15.91N	42.93±9.46N	77.15±7.57N	48.84±7.67

3.1.3 Disintegration Test

The results of disintegration test for five different marketed brands linagliptin tablets are as follows:

Table 8: Disintegration Test of Five brands(A-E) of Linagliptin Tablets

Sample no	A	B	C	D	E
Disintegration time of Sample 1	28 minutes 10 second	8 minutes 2 seconds	3 minutes 38 seconds	4 minutes 8 seconds	7 minutes 30 seconds
Disintegration time of Sample 2	27 minutes 3 seconds	8 minutes 20 seconds	3 minutes 53 seconds	4 minutes 27 seconds	8 minutes 22 seconds
Disintegration time of Sample 3	28 minutes 4 seconds	8 minutes 45 seconds	3 minutes 58 seconds	4 minutes 36 seconds	8 minutes 40 seconds
Disintegration time of Sample 4	40 minutes 7 seconds	9 minutes 26 seconds	6 minutes 38 seconds	4 minutes 55 seconds	10 minutes 20 seconds
Average	30 minutes 51 seconds	8 minutes 38 seconds	4 minutes 32 seconds	4 minutes 32 seconds	8 minutes 43 seconds

3.1.4 Dissolution Test

The results for dissolution test of five marketed brands of linagliptin tablets given below:

Table 9: Dissolution Test of Five brands(A-E) of Linagliptin Tablets

Sample no.	**A**	**B**	**C**	**D**	**E**
Percentage of Release of Sample 1	102.10%	87.81%	84.95%	84.95%	81.69%
Percentage of Release of Sample 2	96.79%	93.53%	91.49%	93.94%	84.95%
Percentage of Release of Sample 3	103.33%	104.14%	92.71%	91.07%	90.67%
Percentage of Release of Sample 4	97.20%	96.39%	91.49%	91.89%	91.48%
Percentage of Release of Sample 5	104.14%	94.21%	95.97%	95.16%	82.09%
Percentage of Release of Sample 6	98.45%	97.92%	98.43%	101.70%	90.26%
Average±SD	100.33±2.92%	95.67±4.91%	92.51±4.25%	93.12±5.26%	86.86±4.09%

3.1.5 Potency Analysis

The table contains the average absorbance of linagliptin in five different concentrations that repeated for three times with its standard deviation.

Table 10: Average Absorbance and Standard Deviation of Linagliptin

Concentration	**Absorbance 1**	**Absorbance 2**	**Absorbance 3**	**Average Absorbance**	**STDEV**
1.25 ug/ml	0.036	0.030	0.048	0.038	±0.009165151
2.5 ug/ml	0.079	0.079	0.100	0.086	±0.012124356
5 ug/ml	0.185	0.158	0.198	0.174	±0.02136196
10 ug/ml	0.331	0.323	0.400	0.353	±0.042335958
20 ug/ml	0.685	0.671	0.803	0.720	±0.072507471

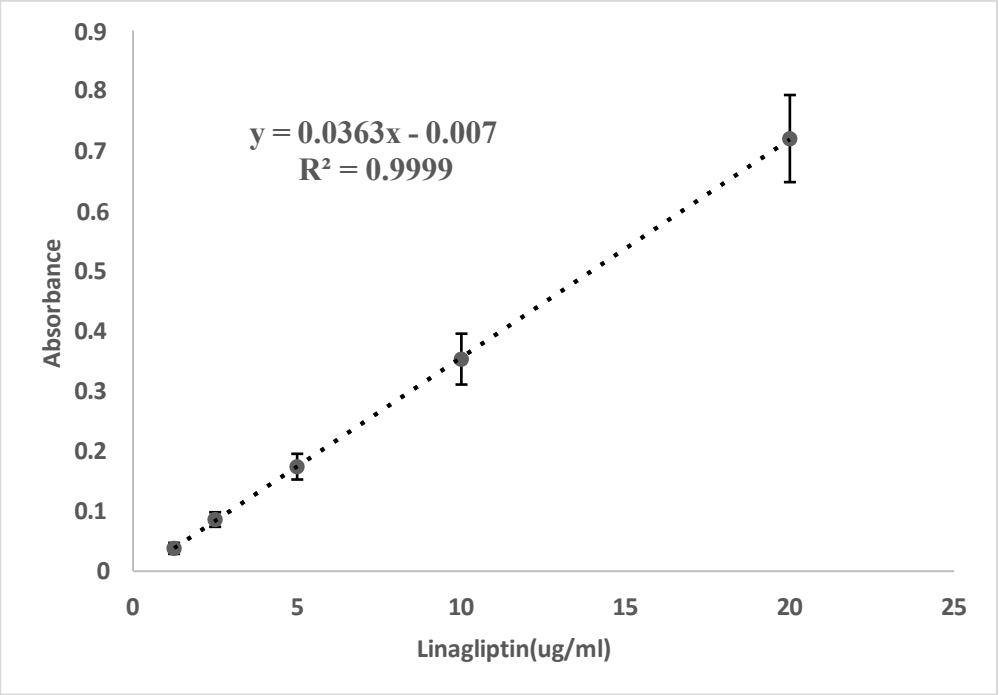

Figure 10:Calibration Curve of Linagliptin(N=3)

The following table contains results for potency analysis of market five brands of linagliptin tablets:

Table 11:Potency Analysis of Five brands(A-E) of Linagliptin Tablets

Sample no	A	B	C	D	E
Potency of sample 1	99.2%	107.7%	103.5%	81.2%	105.2%
Potency of sample 2	98.6%	103%	99.1%	95.5%	112.3%
Potency of sample 3	106%	89%	102.4%	90%	109.3%
Mean±SD	101.27±3.36	99.9±7.94%	101.67±1.87%	88.9±5.89%	108.9%±2.91%

3.2 Discussion

The value for friability test of five marketed linagliptin ranges from 0 to 0.345%. If we compare these five brands brand A and C showed very good results, which is 0 that means, there will be no loss of weight found in friability test for these two brands. These two are leading company in Bangladesh. On the other hand, brand B and E showed the highest loss of weight during analysis which is 0.25% and 0.345% respectively. Among these two brands brand B is the fast-growing company in Bangladesh and people hoping that brand B will be leading company in future Bangladesh, but E is the least growing company showed the highest loss of weight during friability testing. Brand D showed very little amount of weight loss which is 0.052%. From the overall results, there is very little difference between the percentage of weight loss of all five brands. All the brands followed the international criteria for friability testing. These five brands can withstand mechanical strength during handling, packaging and dispensing.

The results for hardness value ranges for five brands from 48.84±7.67 to 135.79±15.91N. Brand A and brand D showed very similar results which are 72.27±8.23N and 77.15±7.57N respectively. Brand A is one of the leading brands in Bangladesh and brand D is also becoming very trustable for people nowadays. In the case of brand B, the hardness value is highest which

is 135.79±15.91N. Brand B is the fast-growing company in our country but high hardness value has an impact on the rate of disintegration and dissolution. For brand C and E, they are showing close results which are 42.93±9.46N and 48.84±7.67. These two brands showed the lowest hardness value. Though low hardness value can cause serious defects in tablets such as lamination and corrosive nature. From all the evaluations, brand B showed very high hardness value which is not satisfactory. On the other hand, brand C and E showed lower hardness value, but they fall within the range for hardness test value.

It needs to be mentioned that all the tablets used for the disintegration test are film coated. The results for disintegration time for brand A is the highest which is 30 minutes 51 seconds. As the high disintegration time indicates that the tablets have slow onset of action. The second highest disintegration time is noticed for brand B and E which is 8 minutes 38 seconds and 8 minutes 42 seconds also they are almost close to each other. The disintegration time for both brands is good and accepted. For brand C and D, the lowest disintegration time is noticed which is same for both that is 4 minutes 32 seconds. The lower the disintegration time the higher the onset of action. Both the brands will have the highest onset of action compared to the other three brands. To conclude, as a leading brand the result for brand A is not satisfactory at all as it has the slowest onset of action among all the five brands.

For dissolution test results the percentage of drug release ranges from 86% to 100%. The highest percentage of drug release noticed for brand A is 100.33±2.92% or 100% with slight deviation. The result is very good, and it indicates that the drug has a very good dissolution profile. On the other hand, the result or brand B, C and D is almost close to each other which is 95.67±4.91%,92.51±4.25% and 93.12±5.26% respectively. The results for all these three brands are also satisfactory. But the lowest percentage of release 86.86±4.09% noticed for brand E which indicates that this brand has slower onset of action and is less acceptable to people.

Brand A and brand C showed a potency of 101.27±3.36 and 101.67±1.87% respectively which indicates that the tablets of this brand-maintained consistency in quality control as a leading company. Both of these brands maintained almost the same potency with little variation. In case of brand B, potency calculated 99.9±7.94% that means the tablets contained the exact amount of API with slight deviation claimed on the label. As brand B is the fast-growing brand this result is very appreciated and accepted by mass people. For brand E, the potency is 108.9%±2.91% which exceeds the amount claimed on the label. But the potency Brand D showed lowest potency among all the brands, which is 88.9±5.89%. This brand contained less amount of API than claimed on the label. To conclude, brand A and B showed very good potency that can serve its desired therapeutic effect efficiently. But for brand C and E the amount is little bit higher than claimed dose which is within pharmaceutical limit but sometimes this little amount can lead to overdose and other problems. Brand D showed lower potency that is disappointing as it is one of the leading brands in Bangladesh. This lower potency could not able exert its desired therapeutic effect to the patients and the patient's safety and efficacy will be hampered.

Chapter 4

Conclusion

The five brands of marketed linagliptin in Bangladesh were evaluated and compared based on their quality control parameters such as friability, hardness, disintegration, dissolution and potency. In vitro dissolution test and potency analysis were performed by using UV visible spectrophotometer. All the brands followed an acceptable range in friability testing. Except company A all the four companies showed satisfactory results in hardness testing. The disintegration time for all the companies showed acceptable results except brand A. In the dissolution test, all the five companies showed satisfactory results but among them brand E showed the lowest percentage. For potency analysis, only two brands showed satisfactory results. Brand C and E exceeded the amount claimed on the labels. Variability in the results can arise from various factors including sample size, technical errors, human errors etc. In conclusion, it is noticed that all the brands producing linagliptin in Bangladesh showed consistent results with little variation. As linagliptin is an INN drug, companies should take appropriate measures to maintain the quality of the drug and to ensure its safety and efficacy to the patients.

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