Evaluation of the Quality Control Parameters of Two Different Brands of Sitagliptin 50 mg Tablet available in Bangladesh

SUBMITTED BY

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2009-1-70-017

Department of Pharmacy

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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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Certificate

This is certify that the thesis paper entitled “Evaluation of Quality Control Parameters of two different Brands (Sitagil® and Sliptin®) of Sitagliptin 50mg tablets available in Bangladesh” submitted to the Department of Pharmacy, East West University, Dhaka-1219, in partial fulfillment of the requirement for the Degree of Bachelor in Pharmacy, was carried out by Jannatul Hasnuva, ID: 2009-1-70-017.

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Certificate

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Abstract

The aim of this study was to evaluate the physicochemical parameters of two different market brands of Sitagliptin 50mg tablet that are from different pharmaceutical companies of Bangladesh. The drugs were obtained from the local drug shops. The tablets used were Sitagil® of Incepta pharmaceuticals Ltd; Sliptin® of Drug International Ltd & Januvia of Marc & Co. The quality control parameters including weight variation, hardness, friability, disintegration test, dissolution test were performed to evaluate the tablets and to get a comparison between these marketed products. As Sitagliptin is an INN drug it has no specific dissolution method in USP or BP. So, a dissolution method listed by USFDA (United States Food & Drug Administration) was followed. Both brands (Sitagil® and Sliptin®) were complying with the official tests. For Sitagil® hardness was 4.2-5.1kg/cm, weight variation ranged from +0.899 to 0.905%, friability was 0.166%, and disintegration time within 1.44 min. The dissolution study of Sitagil® showed similarity factor 57.7% & dissimilarity factor 3.9% in comparison to the innovator brand Januvia. For Sliptin® hardness is (5.1-5.9kg/cm), weight variation (+0.898 to0.902%), friability (0.182%), and disintegration tests within 1 minute. But dissolution study of Sliptin® could not be done due to some technical problems. Quality control parameters of tablet are useful tools for better quality of medicines. It is important for maintaining consistency in batch-to-batch manufacturing and it should be performed for every drug product. Various results were obtained from the test and compared with the specification. All the tablets met the specification and, hence, it can be concluded that the tablets of the local brands had the desired and optimum therapeutic efficacy.

Keywords: Sitagliptin, hardness, friability, disintegration, dissolution, weight variation.

Introduction: Chapter 1

1.1 Diabetes mellitus

Diabetes is a group of metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, Insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the b-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia. Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia (American diabetes association, 2012).

1.2 Classification of diabetes mellitus:

1.1.2.1 Type 1 diabetes mellitus:

Type 1 diabetes mellitus is selective B-cell destruction and severe or absolute insulin deficiency. Administration of insulin is essential in patients with type 1 diabetes. Type 1 diabetes is further subdivided into immune and idiopathic causes. The immune form is the most common form of type 1 diabetes. Although most patients are younger than 30 years of age at the time of diagnosis, the onset can occur at any age. Type 1 diabetes is found in all ethnic groups, but the highest incidence is in people from northern Europe and from Sardinia. Susceptibility appears to involve a multifactorial genetic linkage but only 10-15% of patients have a positive family history (Martha, 2007)

1.1.2.2 Type 2 diabetes mellitus:

Type 2 diabetes is characterized by tissue resistance to the action of insulin combined with a relative deficiency in insulin secretion. A given individual may have more resistance or more B-cell deficiency, and the abnormalities may be mild or severe. Although insulin is produced by the B cells in these patients, it is inadequate to overcome the resistance, and the blood glucose rises. The impaired insulin action also affects fat metabolism, resulting in increased free fatty acid flux and triglyceride levels and reciprocally low levels of high-density lipoprotein (HDL). Individuals with type 2 diabetes may not require insulin to survive, but 30% or more will benefit from insulin therapy to control the blood glucose. It is likely that 10-20% of individuals in whom type 2 diabetes was initially diagnosed actually have both type 1 and type 2 or a slowly progressing type 1, and ultimately will require full insulin replacement. Although persons with type 2 diabetes ordinarily do not develop ketosis, ketoacidosis may occur as the result of stress such as infection or use of medication that enhances resistance, eg, corticosteroids. Dehydration in untreated and poorly controlled individuals with type 2 diabetes can lead to a life-threatening condition called nonketotic hyperosmolar coma. In this condition, the blood glucose may rise to 6-20 times the normal range and an altered mental state develops or the person loses consciousness. Urgent medical care and rehydration is required. (Martha, 2007)

1.1.3 Symptoms of Diabetes

Though diabetes can produce a number of symptoms, many of its early signs can look quite similar to the symptoms of certain other health conditions. This can make it difficult to recognize this condition. But it is important to identify and treat it early, as untreated diabetes can lead to some serious health complications. Knowledge about the symptoms of this condition is immensely important for preventing such complications. The symptoms in men are explained below:

- **Excessive Thirst and Urination**: Excessive thirst and urination are considered as some of the most common symptoms. Both men and women can experience frequent urination or 'polyuria' and excessive thirst or 'polydipsia'. Frequent urination is caused

by a high level of glucose, which adversely affects the filtering capacity of the kidneys. The kidneys start to draw more water from blood, as a result of which the affected person experiences an increase in the frequency of urination. Frequent urination causes the loss of excess fluid from the body or dehydration, which manifests in increased thirst.

- **Unusual Weight Loss and Fatigue**: Unexplained weight loss can result due to the fact that the body cells fail to absorb and utilize glucose from the bloodstream effectively. The cells of the body need glucose to produce energy and so, an inability to absorb glucose can also result in unusual fatigue.
- **Increase in Appetite**: Diabetic patients experience constant hunger or an increase in appetite, if the body produces a high level of insulin in an attempt to bring down the level of blood sugar. Presence of a high level of insulin in the body can increase hunger, for which some diabetic patients can start eating more. An increase in appetite can sometimes result in weight gain. However, some of the affected individuals could lose weight in spite of eating more than usual.
- **Nerve Damage**: Nerves, especially the nerves of the peripheral nervous system can be damaged by consistently high levels of glucose. This is termed as diabetic neuropathy. Damage to the peripheral nervous system can manifest in tingling and numbness in legs, feet, hands and the fingers and toes.
- **Recurrent Infection and Slow Healing of Wounds:** A high level of blood sugar can also slow down the healing of wounds. Along with this, some men can get recurrent infections. These two are considered as the warning signs of a high level of blood sugar.
- **Vision Changes:** Blurred vision or vision changes can be a common complaint among individuals with high blood sugar level. When the level of blood sugar is consistently high, sugar can accumulate in the lens of the eye and damage the blood vessels of the retina. This condition is known as diabetic retinopathy, which if left untreated can lead to blindness.
- **Erectile Dysfunction**: Diabetes and a high level of blood glucose can slowly damage the nerves and the blood vessels of the penis. This eventually can lead to erectile dysfunction.

- **Other Symptoms**: Apart from the above mentioned symptoms, a few additional symptoms can be observed in some individuals. These symptoms include dry mouth, headaches, swollen, red and tender gums and development of dark skin patches on the neck (Bora, 2012).

1.1.4 Risk factors of diabetes

- **Obesity:** Obesity is the major type 2 diabetes risk, with millions of people throughout the world facing obesity. Almost a quarter of adults in the UK are recorded as being obese. Furthermore, the numbers continue to climb, both amongst adults and children. The number of children being diagnosed with type 2 diabetes caused by obesity is climbing everywhere. In the UK, about one in three children are classed as obese.
- **Lack of exercise & sedentary way of life:** Living a sedentary lifestyle without sufficient exercise is seriously damaging to health. Being inactive often leads to being overweight, which can lead to pre-diabetes and type 2 diabetes.
- **Unhealthy Eating Habits:** Unhealthy eating contributes largely to obesity. Too much fat, not enough fiber, and too many simple carbohydrates all contribute to a diagnosis of diabetes. Eating right is can turn the diagnosis around and reverse or prevent Type 2.
- **Family History and Genetics:** It appears that people who have family members who have been diagnosed with type 2 diabetes are at a greater risk for developing it themselves. African Americans, Hispanic-Americans and Native Americans all have a higher than normal rate of type 2 diabetes. Having a genetic disposition towards type 2 is not a guarantee of a diagnosis however. Lifestyle plays an important part in determining who gets diabetes**.**
- **High Blood Pressure and High Cholesterol:** Both of these bodily forces are risks for many diseases, one of which is type 2 diabetes.
- **History of Gestational Diabetes:** Gestational diabetes affects about 4% of all pregnant women. It begins when hormones from the placenta make the mother insulin resistant. Many women who have gestational diabetes develop type 2 diabetes years later. Their babies are also at some risk for developing diabetes later in life.
- **Increased Age:** It's a sad but true fact. The older we get, the greater our risk of type 2 diabetes. Even if an elderly person is thin, they still may be predisposed to getting

diabetes. Scientists theorize that the pancreas ages right along with us, and doesn't pump insulin as efficiently as it did when we were younger. Also, as our cells age, they become more resistant to insulin as well (Manzella, *et al,* 2010).

1.1.5 Non pharmacologic management of diabetes

These strategies are key to diabetes prevention:

- **Food**: What and how much you eat will affect your blood sugar level. Blood sugar is typically highest one to two hours after a meal.
- **Physical activity**: Physical activity moves sugar from your blood into your cells. The more active you are, the lower your blood sugar level.
- **Medication:** Any medications you take may affect your blood sugar level, sometimes requiring changes in your diabetes treatment plan.
- **Illness:** During a cold or other illness, your body will produce hormones that raise your blood sugar level.
- **Alcohol**: Alcohol and the substances you use to make mixed drinks can cause either high or low blood sugar, depending on how much you drink and whether you eat at the same time.
- **Stress**: The hormones your body may produce in response to prolonged stress may prevent insulin from working properly.

1.1.5.1 Management of Type 1 and type 2 diabetes

Type 1 diabetes is treated with insulin.

On the other hand type 2 diabetes is treated first with weight reduction, a diabetic diet, and exercise. When these measures fail to control the elevated blood sugars, oral medications are used. If oral medications are still insufficient, treatment with insulin is considered. (American diabetes association, 2012)

1.1.6.1 Classification of Type 2 diabetes drugs

1.1.6.1.1 Older Classifications and Medicines

- **Sulfonylureas:** These medications are the oldest of the oral diabetes drugs, and until 1995 they were the only drugs available for managing type 2 diabetes. Sulfonylureas stimulate the pancreas to release more insulin into the blood stream. Hypoglycemia can be a side effect of these drugs.
- **Biguanides**: These lower the production of glucose that is made in the liver. It also makes the body more sensitive to insulin. Cholesterol levels may be lowered as well. For example, Metformin.
- **Alpha-Glucosidase Inhibitors**: These delay the conversion of carbohydrates into glucose during digestion. This prevents blood glucose levels from peaking too high. For example, acarbose, miglitol
- **Thiazolidinediones**: Sensitizes muscle and fat cells to accept insulin more easily. For example, Rosiglitazone, Pioglitazone.
- **Meglitinides**: These stimulate insulin production when there is glucose present in the blood. If blood sugar is low, the drug does not work as well. For example, Repaglinide (Devis, 2006).

1.1.6.1.2 New Classifications and Medicines

- **DPP-4 Inhibitors:** These drugs block an enzyme (DPP-4) that normally deactivates a protein (GLP-1) that keeps insulin circulating in the blood. Slowing the deactivation process helps reduce sugar production, lowering blood glucose levels.
- **Incretin Mimetics**: These mimic the action of incretin hormones which help the body make more insulin. They also slow the rate of digestion so that glucose enters the blood more slowly.
- **Byetta (exenatide)**: Byetta is an injectable medication that is used in combination with other oral diabetes medications. It is not an insulin and it does not take the place of insulin. It is used for type 2 diabetes only and cannot be given with insulin. Glucagon-

like peptide 1 (GLP-1) is a hormone that is encoded in the proglucagon gene. It is mainly produced in enteroendocrine L cells of the gut and is secreted into the blood stream when food containing fat, protein hydrolysate, and/or glucose enters the duodenum. Its particular effects on insulin and glucagon secretion have generated a flurry of research activity over the past 20 years culminating in a naturally occurring GLP-1 receptor (GLP-1R) agonist, exendin 4 (Ex-4), now being used to treat type 2 diabetes mellitus (T2DM). GLP-1 engages a specific guanine nucleotide-binding protein (G-protein) coupled receptor (GPCR) that is present in tissues other than the pancreas (brain, kidney, lung, heart, and major blood vessels). The most widely studied cell activated by GLP-1 is the insulin-secreting β cell where its defining action is augmentation of glucose-induced insulin secretion. Upon GLP-1R activation, adenylyl cyclase (AC) is activated and cAMP is generated, leading, in turn, to cAMP-dependent activation of second messenger pathways, such as the protein kinase A (PKA) and Epac pathways. As well as short-term effects of enhancing glucose-induced insulin secretion, continuous GLP-1R activation also increases insulin synthesis, β cell proliferation, and neogenesis. Although these latter effects cannot be currently monitored in humans, there are substantial improvements in glucose tolerance and increases in both first phase and plateau phase insulin secretory responses in T2DM patients treated with Ex-4. This review will focus on the effects resulting from GLP-1R activation in the pancreas.

- **Antihyperglycemic Synthetic Analogs**: These are medications that are created as synthetic versions of human substances, in this case a human hormone called amylin, which is used by the pancreas to lower blood glucose levels.
- **Symlin (pramlintide acetate):** Symlin is an injectable medication which is used with insulin for tighter blood glucose control. Symlin can increase the risk of severe hypoglycemia, therefore patients who are put on Symlin are selected carefully and monitored closely by their healthcare providers (Devis, 2006).

1.2 Sitagliptin- A new drug for Type 2 diabetes

A new oral medication called Januvia (Sitagliptin phosphate) has been approved by the U.S. Food and Drug Administration for management of Type 2 diabetes. It's the first in a new class of drugs called DPP-4 inhibitors. Januvia lowers blood sugar levels by blocking an enzyme known as dipeptidyl peptidase IV or DPP-4 (Steiner, 2012).

1.2.1 Prolongs Insulin Production

DPP-4 is responsible for breaking down the proteins that stimulate the insulin producing cells after a meal. If DPP-4 is inhibited, then the proteins can activate the release of insulin for a longer period of time, thereby lowering the glucose level in the blood (Kutoh, 2011).

1.2.2 Drug profile

a.)Chemical name: (R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine.

b.) Molecular formula: C16H15F6N5O

c.) Molecular weight: 407.314 g/mol

d.) Structure:

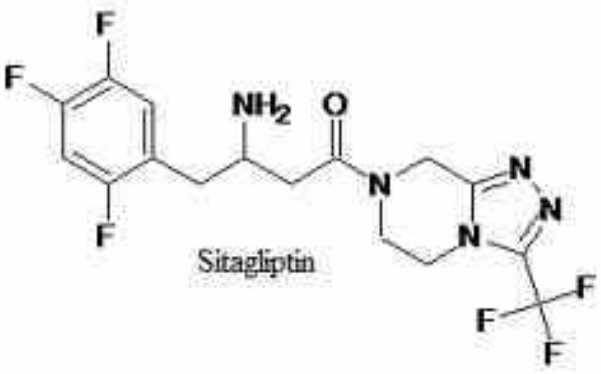

Fig 1.1 Structure of sitagliptin

e.) **Physicochemical properties:**

- Characteristics: white to off-powder
- Melting range: 198-202 degree Celsius.
- Half life: 8-14 hour
- Solubility: soluble in water and N,N-dimethyl formamide, slightly soluble in methanol
- Storage condition: Store sitagliptin at room temperature, between 68 and 77 degrees F (20 and 25 degrees C). (Steiner, 2012)

1.2.3 Mechanism of action of sitagliptin

Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by JANUVIA, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme, DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, Sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses.

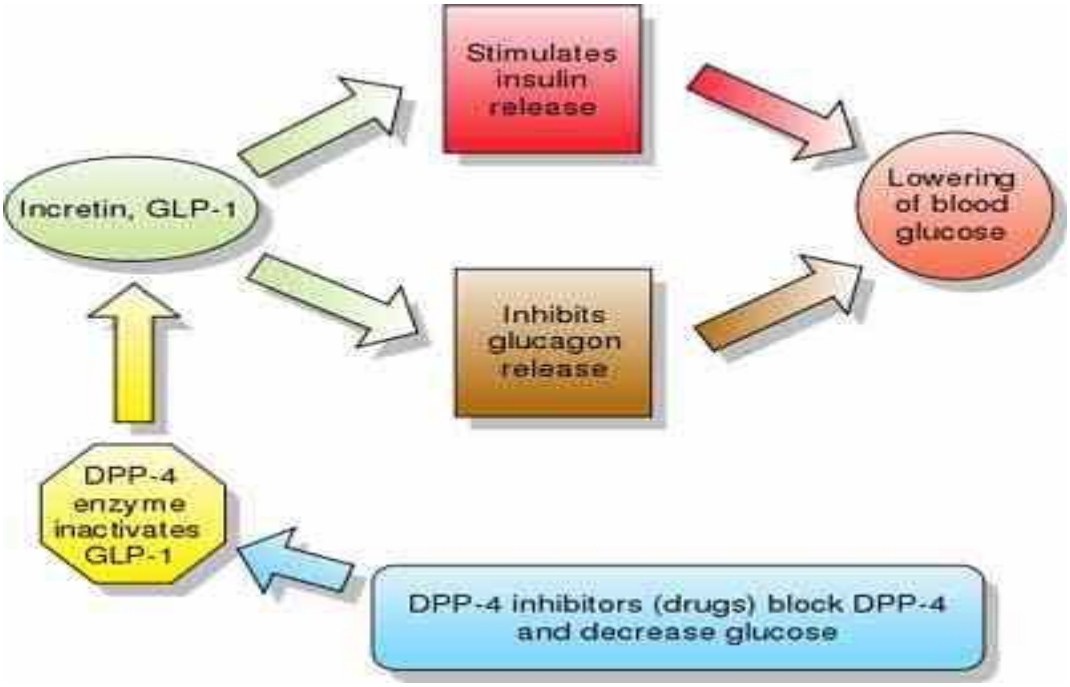

Fig 1.2: Mechanism of Sitagliptin (Steiner, 2012)

1.2.4. Indication:

Sitagliptin is approved by the FDA as an adjunct to diet and exercise to improve glycaemic control in patients with T2DM, either as a monotherapy, or in combination with metformin or a peroxisome proliferator-activated receptor-γ agonist (for example, thiazolidinediones) when the single agent does not provide adequate glycaemic control. (Medscape, 2008)

1.2.5 Contraindications:

History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema. (Medscape, 2008)

1.2.6. Dosage & Administration:

100 mg oral dose once daily or 50mg oral dose twice daily.

Dosing Modifications

Renal impairment

- CrCl >50 mL/min: Dose adjustment not necessary
- CrCl 30-50 mL/min: 50 mg PO qDay
- CrCl <30 mL/min: 25 mg PO qDay
- ESRD: 25 mg PO qDay regardless of hemodialysis

Hepatic impairment

- Mild to moderate impairment: Dose adjustment not necessary
- Severe impairment: Not studied

Take with or without food

Swallow tablet whole; do not chew, crush, or split (Medscape, 2008)

1.2.7 Adverse reactions:

Adverse reactions reported in 5% of patients treated with sitagliptin and more commonly than in patients treated with placebo are: upper respiratory tract infection, nasopharyngitis and headache. In the add-on to sulfonylurea and add-on to insulin studies, hypoglycemia was also more commonly reported in patients treated with sitagliptin compared to placebo. (Medscape, 2008)

1.3 Quality Control:

Quality control is a process employed to ensure a certain level of quality in a product or service. It may include whatever actions a business deems necessary to provide for the control and verification of certain characteristics of a product or service. The basic goal of quality control is to ensure that the products, services, or processes provided meet specific requirements and are dependable, satisfactory, and fiscally sound.

Essentially, quality control involves the examination of a product, service, or process for certain minimum levels of quality. The goal of a quality control team is to identify products or services that do not meet a company's specified standards of quality. If a problem is identified, the job of a quality control team or professional may involve stopping production temporarily. Depending on the particular service or product, as well as the type of problem identified, production or implementation may not cease entirely.

Principle of quality control study:

Principle1- Customer-Focused Organization. Organizations depend on their customers and therefore should understand current and future customer needs, meet customer requirements. Principle 2 - Leadership. Leaders establish unity of purpose, direction, and the internal environment of an organization.
Principle 3 - Involvement of People at all levels are the essence of an organization and their full involvement enables their abilities to be used for the organization's benefit. .
Principle 4 - Process Approach. A desired result is achieved more efficiently. (Riley, 2010)

1.3 Quality control parameters:

1.3.1 Weight variation test

Weight variation of tablets is measured to ensure that a tablet contains the proper amount of the drug which indicates the criteria of the tablet formulation. If weight of the active ingredient

is more than the accepted value, the patient may suffer from overmedication. On the other hand, if the determined weight is less than the accepted value, the patients will be experienced from under-medication. Weight variation test is done by electronic balance (Lachman, 2008).

1.3.2 Hardness Test:

Tablet hardness is usually expressed as the load required crushing a tablet placed on its edge. Hardness is thus sometimes termed the tablet crushing strength. The suitability of a tablet in regard to mechanical stability during packaging and shipment can usually be predicted on the basis of hardness. Tablet hardness, in turn, influences tablet density and porosity. It may affect tablet friability and disintegration time. It usually affects the drug dissolution and release and it may affect bio-availability. Harness is measured by Monsanto harness tester (Lachman, 2008).

1.3.3 Friability Test:

Friction and shock are the forces that most often cause the tablets to chip, chop or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up. Normally, when capping occurs, friability values are not calculated. A thick tablet may have less tendency to cap whereas thin tablets of large diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress (Nachaegari & Bansal, 2004).

1.3.4 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 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. Disintegration time may vary considering to its

disintegrator used. Higher the disintegration time required lower the dissolution rate and followed to poor absorption. So disintegration is the crucial part of a drug for therapeutic action (Alton, 2007).

1.3.5 Dissolution test:

Dissolution is a test used by the Pharmaceutical industry to characterize the dissolution properties of the active drug, the active drug's release and the dissolution from a dosage formulation. Drugs administered orally in solid dosage forms, such as tablet or capsules, must dissolve in the contents of the gastrointestinal tract before drug absorption can occur. Often the rate of drug absorption is determined by the rate of drug dissolution from the dosage form. Therefore, if it is important to achieve high peak blood levels of a drug, it will usually be important to obtain rapid drug dissolution from the dosage form (Lachman, 2008).

Dissolution test is carried out to determine the amount of drug released during a specific period of time by using dissolution rate apparatus. If a USP method is available for the product, then the dissolution testing should be conducted using the USP method. If the USP method is not available, then the dissolution testing can be conducted using a method recommended by the FDA (FDA- recommended method). The FDA posts a list of its recommended dissolution method. If the recommended method is inadequate for the product then one needs to develop a dissolution method. Comparative dissolution testing, using test and reference products under a variety of test conditions, is recommended (USFDA, 1997).

Two scenarios for comparing the profiles obtained from multipoint dissolution are operative -

1. If both the test and reference product show more than 85% dissolution within 15 minutes, the profiles are considered similar (no calculation required). If not, see the next point.

2. Calculate the f2 value. If f2≥ 50, the profiles are normally regarded similar such that further *in vivo studies* are not necessary. Note that only one measurement should be considered after 85% dissolution of both products has occurred and excluding point zero.

The difference factor (f1) calculates the percent (%) difference between the two curves at each time point and is a measurement of the relative error between the two curves:

$$f_1 = \left\{ \frac{[\sum_{t=1}^{n} |R_t - T_t|]}{[\sum_{t=1}^{n} R_t]} \right\} X\ 100$$

Equation 1.1: % Difference Factor Calculation

Where, n is the number of time points, Rt is the dissolution value of the reference batch at time t, and Tt is the dissolution value of the test batch at time t, (Moore & Flanner, 1996).

The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared errors, and is a measurement of the similarity in the percentage (%) dissolution between two curves.

$$f2 = 50 \times \text{Log}\ \{[1 + (1/n)\ \Sigma\ t=1^{n}\ (Rt - Tt)^{2}]^{-0.5} \times 100\}$$

Equation 1.2: % Similarity Factor Calculation

The research is done on Quality control parameters of Sitagliptin50- an antidiabetic drug. It is an INN drug. International Nonproprietary Names (INN) facilitates the identification of pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A nonproprietary name is also known as a generic name. WHO has a constitutional mandate to "develop, establish and promote international standards with respect to biological, pharmaceutical and similar products". The World Health Organization collaborates closely with INN experts and national nomenclature committees to select a single name of worldwide acceptability for each active substance that is to be marketed as a pharmaceutical. To avoid confusion, which could jeopardize the safety of patients, trade-marks should neither be derived from INNs nor contain common stems used in INNs (WHO, 2009).

1.4 Significance of the study:

Diabetes is a global public health problem. It is a chronic disease and is now growing as an epidemic in both developed and developing countries. As in many South Asian countries, diabetes is becoming a serious health concern in Bangladesh. Between 2000 and 2008, the proportion of people suffering from diabetes increased from 4% to 7%. In 2010, the International Diabetes Federation (IDF) estimated that 5.7 million (6.1%) and 6.7 million (7.1%) of people living in Bangladesh are suffering from diabetes and impaired glucose tolerance (IGT) respectively. By 2030, that number of diabetic population is expected to rise to 11.1 million. This explosion in diabetes prevalence will place Bangladesh among the top seven countries in terms of the number of people living with diabetes in 2030 (FPMU, 2011).

In an effort to optimize glycemic control and also to reduce the burden of diabetic complications, several classes of oral hypoglycemic agents have been developed. Among them Sitagliptin is preferable. Not only is this drug the most widely prescribed anti diabetic agent in the management of type 2 diabetes, but also it has been recommended as the treatment of choice in patients with a combination of metformin.

Poor quality of Sitagliptin can cause serious trouble like health hazards and even mass death..If, available Sitagliptin tablet contains high amount of drug it may cause hypoglycemia, it cannot give effective result. Again, if it contains less amount of drug in available Sitagliptin preparation, it may cause hyperglycemia, which is life threating for diabetic patients. Poor quality Sitagliptin preparation also causes other adverse effects. So the quality control study on Sitagliptin is very essential.

With quality control, inspection is intended to prevent faulty products reaching the customer. This approach means having specially trained inspectors, rather than every individual being responsible for his or her own work. Furthermore, it is thought that inspectors may be better placed to find widespread problems across an organization (Riley, 2012).

1.5 Aim & Objective of the study:

- To analyze different brands of Sitagliptin in terms of physical parameters like hardness, friability, disintegration etc.
- To check the dissolution profile of Sitagliptin.
- To assess and compare the rates of dissolution among two different brands of Sitagliptin.
- To compare the dissolution profile with innovator brand by determining similarity & dissimilarity factor.

Chapter 2: Methods & Materials

2.1 Samples

Table 1: Samples and manufacturers name

Sample's name	Manufacturer's name
1. Januvia	1. Marc & co.
2. Sliptin	2. Drug International Ltd.
3. Sitagil	3. Incepta Pharmaceuticals Ltd.

2.2 Weight Variation Test:

Uncoated tablets and film-coated tablets formulated to contain 5% or more of the active ingredient should comply with the following test.

2.2.1 Method

Weigh 20 tablets and calculate the average mass. When weighed singly, the deviation of individual masses from the average mass should not exceed the limits given below.

Average mass of tablet	**Deviation** (%)	**Number of tablets**
less than 80 mg	±10.0	minimum 18
	±20.0	maximum 2
80 mg to 250 mg	±7.5	minimum 18
	±15.0	maximum 2

more than 250 mg	±5.0	minimum 18
	±10.0	maximum 2

If film-coated tablets fail this test it may be because of variability in the thickness (mass) of the coatings. In such a case, a test for 5.1 Uniformity of content for single-dose preparations should be applied; if the tablets meet the requirement of this test, they can be considered acceptable. (Gowen, et al., 2008)

Fig 3.1: Electronic Balance

2.2.2 Materials:

Analytical balance, Tablets

Table2: Name and specification of instrument required in weight variation test:

Instrument	**Specification**
Electronic balance	Type: AY220. NO: D432812964, Capacity: 220g, Readability: 0.1mg. Shimadzu Corporation Japan.

2.2.3 Calculation:

Weight variation= (Tablet weight- Average weight)/Average weight×100

2.3 Hardness test:

It is the load required to crush the tablet when placed on its edge.

Table3: Name and specification of instrument required in hardness test;

Instrument	Specification
Monsanto hardness tester	Veego, Serial no: 02/0305, Type:VTHT, Volts:230volts,50Hz

2.3.1 Test Methods:

The standard method used for tablet hardness testing is compression testing.

The tablet is placed between two jaws that crush the tablet. The machine measures the force applied to the tablet and detects when it fractures.

This method is used for research &development and for quality control. ((Gowen, et al., 2008)

Fig 2.2: Monsanto Hardness Tester

2.4 Friability Test:

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

Friability is a property that is related to the hardness of the tablet. An instrument called friabilator is used to evaluate the ability of the tablet to withstand abrasion in packaging, handling, and shipping. (Gowen, et al., 2008)

2.4.1 Materials:

Friability tester, electronic balance, tablets.

Table4: Name and specification of instrument required in friability test:

Instrument	Specification
Friability tester	Model: VPT-2D, Serial no:43/0305, Volts:230V, 50Hz

2.4.2 Method:

1. Initial Weigh of 10 tablet = Wo

2. Put these tablets in the friabilator and adjust the instrument at 100 rpm (i.e. = 25 rpm for 4 min)

3. Weigh the 10 tablets after test = W

4. Friability (% loss) = (1-Wo/W) ×100

It must be less than or equal to1% but if more we do not reject the tablets as this test is non-official. Perform this test using 20 tablets that were used first in the weight variation test. (Gowen, et al. 2008)

2.4.3 Limit of acceptance

Conventional compressed tablets that lose than 0.5% to 1% of their weight are generally considered acceptable (USP, 2007)

Fig 2.3: Friability Tester

2.5 Disintegration Test:

It is the time required for the tablet to break into particles, the disintegration test is a measure only of the time required under a given set of conditions for a group of tablets to disintegrate into particles.

U.S.P. method for uncoated tablets:

- Start the disintegration test on 6 tablets.
- If one or two tablets from the 6 tablets fail disintegrate completely within 30min repeat the same test on another 12 tablet. (i.e. the whole test will consume 18 tablets).
- Not less then 16 tablets disintegrate completely within the time

If more then two tablets (from the 18) fail to disintegrate, the batch must be rejected.

2.5.1 Materials:

Disintegration tester, distilled water

2.5.2. Conditions

Medium: 900ml distilled water

Time: 30 minutes

Temperature: (37±2) °C

Fig 2.4: Disintegration Tester

Table5: Name and specification of instrument required in disintegration test:

Instrument	**Specification**
Disintegration tester	Serial no: 050503375, Volts: 230volts, 50 Hz. Model: Vanguard Pharm,machiner

2.5.3 Method:

Disintegration Test for Sitagliptin® Tablets were adopted from the procedures described by the USFDA (2007). For this, at first 1 tablet in each of the six tubes in basket was placed. Then, the Disintegration Apparatus was operated at 37^{0}C. And then disintegration time for each tablet was recorded The acceptable range to pass the disintegration test is that at least 2 tablets from a batch

must be between the range of 15 to 30 min or the average disintegration time the tablets from a batch must be between the range mentioned. (Gowen, et al. 2008)

2.6 Dissolution Test:

Dissolution medium: Distilled water 900 ml.

Apparatus: Apparatus 2 (Basket Apparatus)

RPM: 100

Time: 30 min

Temperature: 37°C

Max: 267 nm

Fig 2.5: Dissolution Tester

Fig 2.6: UV Spectrophotometer

2.6.1 Materials

Dissolution tester, distilled water, UV spectrophotometer

Table 6: Name and specification of instrument required in disintegration test:

Instrument	**Specification**
Dissolution tester	Model: RCZ 6B2. Chaina
UV spectrophotometer	Model: UV – 1201 PC SHIMADZU, Japan

2.6.2 Method:

- The dissolution tester was assembled.
- Water tank was filled by the water and operating parameters were setted.
- 900 mL of the distilled water was poured into 6 vessels and run the instrument till the set temperature was attained.
- 100 mL of the medium was remained for use as the blank.
- The tablets were placed into the baskets and start run.

- During operation 6 ml of the solution from 6 vessels were transferred to 6 conical flasks and filtered with an interval of 5,10,15,20 and 30 minutes.
- After completion of the operation the absorbance of each interval was taken by using UV spectroscopy and the reading was noted.

2.6.3 Calculation:

$$\% \text{ dissolve} = \frac{\text{Sample absorbance}}{\text{STD absorbance}} \times \frac{\text{STD Wt.} \times 900 \times 100}{100 \times \text{Label claim}}$$

Here, STD (Standard) absorbance= 0.261

STD. wt. = 6.81 mg

Label claim = 62.5

Chapter 3: Result

3.1 Weight variation test

Table 3.1.1: Result of weight variation test of Sitagil®

No of tablet	Tablet weight (g)	Highest variation (%)	Lowest variation (%)
1	0.181		
2	0.179		
3	0.179		
4	0.180		
5	0.179		
6	0.179		
7	0.178		
8	0.179		
9	0.182		
10	0.168	+0.899	-0.905
11	0.177		
12	0.182		
13	0.180		
14	0.177		
15	0.177		
16	0.182		
17	0.180		
18	0.182		
19	0.181		
20	0.183		

Table 3.1.2: Result of weight variation test of Sliptin®

No of Tablets	Weight of tablet	Highest variation (%)	Lowest variation (%)
1	0.169		
2	0.162		
3	0.167		
4	0.166		
5	0.164		
6	0.169		
7	0.162		
8	0.169		
9	o.160		
10	0.163	+0.898	-0.902
11	0.168		
12	0.164		
13	0.163		
14	0.164		
15	0.161		
16	0.164		
17	0.162		
18	0.161		
19	0.163		
20	0.160		

3.2 Hardness test:

Table 3.2.1: Result of Hardness test of Sitagil®

No of tablet	Hardness of tablet(kg/cm)	Average hardness (kg/cm)
1	4.9	
2	4.8	
3	4.7	
4	5	
5	4.7	4.7
6	4.8	
7	4.8	
8	4.7	
9	5.1	
10	4.2	

Table 3.2.2: Result of hardness test of Sliptin®

No of tablet	Hardness of tablet(kg/cm)	Average hardness (kg/cm)
1	5.2	
2	5.4	
3	5.4	
4	5.3	
5	5.1	5.43
6	5.9	
7	5.1	
8	5.8	
9	5.2	
10	5.9	

3.3 Friability test

Table 3.3.1: Result of friability test of Sitagil®

No of tablet	Weight of tablet(g)	Average weight of tablet(g)	% Friable
1	0.181		
2	0.179		
3	0.179		
4	0.180		
5	0.179	0.1784	0.166%
6	0.179		
7	0.178		
8	0.179		
9	0.182		
10	0.168		

Table 3.3.1: Result of friability test of Sliptin®

No of tablet	Weight of tablet(g)	Average weight of tablet(g)	% friable
1	0.169		
2	0.162		
3	0.167		
4	0.166		
5	0.164	0.1645	0.182%
6	0.169		
7	0.162		
8	0.169		
9	0.160		
10	0.163		

Table 3.4.1: Result of disintegration test of Sitagil®

No of tablet	Disintegration time(min)
1	1.25
2	1.33
3	1.40
4	1.42
5	1.44
6	1.43

Table 3.4.2: Result of disintegration test of Sliptin®

No of tablets	Disintegration time(sec)
1	54
2	59
3	56
4	57
5	58
6	59

3.5 Dissolution Test:

3.5.1 Formula of percentage dissolved

$$\% \text{ dissolve} = \frac{\text{Sample absorbance}}{\text{STD absorbance}} \times \frac{\text{STD Wt.} \times 900 \times 100}{100 \times \text{Label claim}}$$

Here, STD. absorbance= 0.261

STD. wt. = 6.81 mg

Label claim = 62.5

3.5.2 List of absorbance, % dissolved, average % dissolved of innovator brand (januvia)

For 5 minute,

Sample no.	Absorbance	% dissolved
1.	0.271	101.8 %
2.	0.251	94.3 %
3.	0.267	100 %
4.	0.247	92.8 %
5.	0.263	98.8 %
6.	0.253	95 %
7.	0.246	92.4 %
8.	0.222	83.4 %
9.	0.231	86.7 %
10.	0.231	86.7 %
11.	0.242	90.6 %
12	0.244	91.6 %
Average % dissolved (Rt) = 92.8 %		

For 10 minute,

Sample no.	Absorbance	% dissolved
1.	0.290	108.9 %
2.	0.283	106.3 %
3.	0.300	112.7 %
4.	0.301	113.0 %
5.	0.301	113.0 %
6.	0.290	108.9 %
7.	0.258	96.9 %
8.	0.307	115.3 %
9.	0.253	95 %
10.	0.305	131.5 %
11.	0.291	109.3 %
12	0.251	94.3 %
Average % dissolved (Rt) = 99.3 %		

For 15 minute,

Sample no.	Absorbance	% dissolved
1.	0.296	111.2 %
2.	0.296	111.2 %
3.	0.314	117.9 %
4.	0.285	107 %
5.	0.292	109.7 %
6.	0.280	105.2 %
7.	0.259	97.3 %
8.	0.246	92.4 %
9.	0.246	92.4 %

10.	0.256	96.1 %
11.	0.261	98.4 %
12	0.241	90.5 %
Average % dissolved (Rt) = 95.85 %		

For 20 minute,

Sample no.	Absorbance	% dissolved
1.	0.288	108.2 %
2.	0.291	109.3 %
3.	0.300	112.7 %
4.	0.294	110.4 %
5.	0.289	108.5 %
6.	0.295	110.8 %
7.	0.255	95.8 %
8.	0.271	101.8 %
9.	0.249	93.5 %
10.	0.280	105.2 %
11.	0.290	108.9 %
12	0.253	95 %
Average % dissolved (Rt) = 105 %		

For 30 minute,

Sample no.	Absorbance	% dissolved
1.	0.257	96 %
2.	0.289	108.5 %
3.	0.291	109.3 %
4.	0.274	102.9 %
5.	0.302	113.4 %
6.	0.273	102.5 %
7.	0.256	96.1 %
8.	0.299	112.3 %
9.	0.274	102.9 %
10.	0.289	108.5 %
11.	0.301	113.0 %
12	0.294	110.4 %
Average % dissolved (Rt) = 106.3 %		

3.5.3 List of absorbance, % dissolved, average % dissolved of local brand (Sitagil)

For 5 minute

Sample no.	Absorbance	% dissolved
1.	0.245	92.0 %
2.	0.253	95 %
3.	0.243	91.3 %
4.	0.238	89.4 %
5.	0.246	92.4 %
6.	0.244	91.6 %
7.	0.210	90.1 %

8.	0.259	97.3 %
9.	0.265	99.5 %
10.	0.284	107 %
11.	0.258	96.9 %
12	0.251	94.3 %
Average % dissolved (Tt) = 94.73 %		

For 10 minute

Sample no.	Absorbance	% dissolved
1.	0.259	97.3 %
2.	0.258	96.9 %
3.	0.252	94.6 %
4.	0.261	98 %
5.	0.273	102.5 %
6.	0.265	99.5 %
7.	0.251	97.3 %
8.	0.265	94.3 %
9.	0.263	99.5 %
10.	0.274	98.8 %
11.	0.273	102.9 %
12	0.270	102.5 %
Average % dissolved (Tt) = 90.5 %		

For 15 minute

Sample no.	Absorbance	% dissolved
1.	0.260	97.6 %
2.	0.269	101.0 %
3.	0.253	95 %
4.	0.265	99.5 %
5.	0.259	97.3 %
6.	0.255	95.8 %
7.	0.258	96.9 %
8.	0.271	101.8 %
9.	0.267	100.3 %
10.	0.273	102.5 %
11.	0.277	104 %
12	0.275	103.3 %
Average % dissolved (Tt) = 99.5 %		

For 20 minute

Sample no.	Absorbance	% dissolved
1.	0.259	97.3 %
2.	0.264	99.1 %
3.	0.263	98.8 %
4.	0.258	96.9 %
5.	0.254	95.4 %
6.	0.262	98.4 %
7.	0.263	98.8 %

8.	0.272	102.1 %
9.	0.272	102.1%
10.	0.278	104.4 %
11.	0.282	105.9 %
12	0.267	100.3 %
Average % dissolved (Tt) = 99.95 %		

For 30 minute

Sample no.	Absorbance	% dissolved
1.	0.270	101.4 %
2.	0.277	104.0 %
3.	0.272	102.1 %
4.	0.267	100.3 %
5.	0.264	99.1 %
6.	0.262	98.6 %
7.	0.264	99.1 %
8.	0.281	105.5 %
9.	0.274	102.9 %
10.	0.291	109.3 %
11.	0.289	108.5 %
12	0.284	106.7 %
Average % dissolved (Tt) = 94.90 %		

3.5.4 Dissimilarity factor

$$f_1 = \frac{[\sum | Rt - Tt |]}{[\sum Rt]} \times 100$$

$$= \frac{|(92.8- 94.73)| + |(99.3 -90. 5)| + |(95.85 – 99.5)| + |(105 -99.95)| + |(106.3 -94.90)|}{(92.8+ 99.3+ 95.85 +105 +106.3)} \times 100$$

$$= \frac{| 19.67 |}{499.25} \times 100$$

$$= 3.9$$

3.5.5 Similarity factor

$$f_2 = 50 \times \log \{ 1+ (1/n) \sum (Rt – Tt)2]^{-5} \times 100 \}$$

$$= 50 \times \log \{1+ (1/n) [|(92.8- 94.73)|^2 + |(99.3 -90. 5)|^2 + |(95.85 – 99.5)|^2 + |(105 - 99.95)|^2 + |(106.3 -94.90)|^2]^{-5} \times 100 \}$$

$$= 50 \times \log \{ [1+ (1/5) \times 249.9]^{-5} \times 100 \}$$

$$= 50 \times \log \{ [1+ 49.98]^{-5} \times 100 \}$$

$$= 50 \times \log (14.3)$$

$$= 50 \times 1.155$$

$$= 57.7$$

3.5.6 Result

The dissimilarity factor between the innovator brand januvia & local brand sitagil was 3.9% and the similarity factor was 57.7%

Chapter 4: Discussion

4.1 Weight variation test

The weight variation ranged from -0.905 to +0.899% for Sitagil®. The weight variation ranged from -0.898 to +0 .902% for two batches of Sliptin®.
All the tablets of Sitagil® and Sliptin® showed a percentage weight variation within the range of ±5% that meet the specification of USP (United States Pharmacopeia).

4.2 Hardness test:

The hardness of the tablets ranged from 4.2 to 5.1 kg/cm for Sitagil® and 5.1 to 5.9 kg/cm for Sliptin®. The average hardness of Sitagil® was 4.4 kg/cm and of Sliptin® was 5.43 kg/cm. Sitagil® and Sliptin® had hardness greater than 4kg/cm and therefore, meet the USP specification and pass the quality control parameter.

4.3 Friability test

USP specifies that if friability study is performed with 20 tablets of any batch they must not lose 1% of their initial weight. The friability was 0.166% for Sitagil® and the % friability was 0.182 for Sliptin®. All tablets of both brands Sitagil® and Sliptin® had passed the friability test.

4.4 Disintegration test

The two brands have a disintegration time that is within the range Sitagil® (51-59) second & Sliptin® within 1 minute and have met the specification of USP where a majority of the tablets have a maximum disintegration time of 30 minutes.

4.5 Dissolution test

The dissolution test is done only on Sitagil®. Due to some technical problems the dissolution profile of Sliptin® cannot be studied. In this dissolution study the similarity factor & dissimilarity factor is determined. A comparison is also done on the innovator brand Januvia® & the local Brand Sitagil®. The dissimilarity factor (f_1) value is 3.9% & the similarity factor (f_2) value is 57.7%. It should be considered that, f_1 value should be closer to 0, and f_2 value close to 100. Generally f_1 value up to 15 (0-15) and f_2 value greater than 50 (50-100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test and reference products. So the local brand Sitagil® is quite similar with the innovator brand Januvia® in terms of dissolution.

Chapter 5: Conclusion

Sitagliptin is an antidiabetic drug. Hence, it is essential that it is manufactured following Good Manufacturing Practice (GMP). As population is growing in Bangladesh, the necessities of pharmaceutical products are also increasing rapidly. Different pharmaceutical companies are manufacturing various medicines. As a result there is always a competition among the companies in the market. For this reason, quality assurance is an essential part in manufacturing medicines. Poor quality of a medicine can cause mass death and mass health hazards all over the country. Extensive study should be conducted to analyze and compare the quality in actual therapeutic effectiveness, bioavailability or bioequivalence to ensure the safety in using those drugs. In this study, it was observed that the entire brands complied with the specification. It is important that the tablets meet all the specification because all are essential for therapeutic efficacy and safety. So company needs more evaluation for their tablets. All the quality parameter met the specified range. A comparative dissolution profile has been checked with the innovator brand Januvia & Sitagil®. The dissolution profile of Sliptin® cannot be checked due to some unavoidable technical problems. Due to lack of developed assay method potency test cannot be done. According to my knowledge, not much work has been done to determine the quality control parameters of Sitagliptin in Bangladesh. So further study could be conducted regarding the quality control parameters and developing methods for the quality tests.

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