Assessment of Quality Control Parameters of Two Brands (Siglita™, Janvia™) of Sitagliptin Tablets Available in Bangladesh

Submitted By

Hossain Al Mahmud

ID: 2009-3-70-036

Department of Pharmacy

East West University

Aftabnagar, Dhaka, Bangladesh

Assessment of Quality Control Parameters of Two Brands (Siglita™, Janvia™) of Sitagliptin Tablets Available in Bangladesh

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

Submitted By

Hossain Al Mahmud

ID: 2009-3-70-036

Department of Pharmacy

East West University

Aftabnagar, Dhaka, Bangladesh

Certificate

This is certify that the thesis paper entitled "Assessment of Quality Control Parameters of two Brands (Siglita™, Janvia™) of Sitagliptin 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 **Hossain Al Mahmud, ID: 2009-3-70-036.**

_____

Dr. Chowdhury Faiz Hossain

Professor and Chairperson

Department of Pharmacy

East West University

Aftabnagar, Dhaka

Bangladesh

Certificate

This is certify that the thesis paper "Assessment of Quality Control Parameters of two Brands (Siglita™, Janvia™) of Sitagliptin 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 **Hossain Al Mahmud, ID: 2009-3-70-036** under my supervision and guidance and no part of this dissertation has been or is being submitted elsewhere for the award of any Degree/Diploma.

_____

Ms. Nigar Sultana Tithi

Lecturer & Supervisor

Department of Pharmacy

East West University

Aftabnagar, Dhaka

Bangladesh

ACKNOWLEDGEMENT

I, **Hossain Al Mahmud**, a student of the Department of Pharmacy in East West University at Aftabnagar in Dhaka cordially give my thanks to the Almighty Allah (SWT) for successfully completing my project.

I cordially thank my Research Supervisor Ms. Nigar Sultana Tithi, Lecturer of the Department of Pharmacy in East West University for overseeing my project work with their utmost effectiveness.

I am indebted to Dr. Chowdhury Faiz Hossain, the Chairperson of the Department of Pharmacy in East West University for his kind support and the permission to use the facilities available at Department of Pharmacy, East West University, as well as for his encouragement to carry out the research.

I also give my thanks to the Laboratory Officers of the Department of Pharmacy in East West University for guiding and helping me with their utmost abilities throughout my project.

I also wish to express my humble regards to the Entire Faculty Panel of the Department of Pharmacy in East West University for providing me with moral as well as educational support behind my research.

Finally, I would also like to thank to my Family and Friends specially Tamanna Tuj Jhuhura and Tasdik Farooq for giving me moral support behind my project.

TABLE OF CONTENTS

LIST OF TABLE

LIST OF FIGURES

LIST OF EQUATIONS

LIST OF ACRONYMS

ACRONYMS	EXPANSIONS
U.S. FDA	United States Food & Drug Administration
IDDM	Insulin Dependent Diabetes Mellitus
STD	Standard
ADME	Absorption, Distribution, Metabolism & Elimination
NIDDM	Non – Insulin Dependent Diabetes Mellitus

ABSTRACT

Assessment of Quality Control Parameters is always a better way for the understanding of the quality of local brands. Thus, the purpose of this research work was to determine the physical quality control parameter of two brands (Janvia™ 50 and Siglita™ 50) of Sitagliptin tablets which is used for the treatment of type II diabetes. Thirty eight tablets from each brand were taken from the local market and the quality control parameters including weight variation, hardness, friability, disintegration test, dissolution test were determined. In weight variation test of Siglita™ 50 tablets, the average weight was 0.1886 gm and the weight variation ranged from +3.833% to −3.088%. Janvia™ 50 tablets had the average weight of 0.2246 gm and the weight variation ranged from +3.778% to -1.282%. All the tablets of Siglita™ 50 and Janvia™ 50 showed a percentage weight variation within the range of ±5% specified in the USP. In friability test, friability of Siglita™ 50 tablet was 0.8%. The friability of Janvia ™ 50 was 0.53%. All the tablets of both brands Siglita™ 50 and Janvia™ 50 have met the USP specification and passed the friability test. In this research study, the average hardness of Siglita™ 50 and Janvia ™ 50 were 1.835 kg/cm and 2.465 kg/cm respectively. Hardness of tablets of both brands was below the acceptance range but these tablets met the acceptance range in friability test. Less hardness can cause breakdown of tablets during use and transport. The disintegration time of six tablets of Siglita™ 50 and Janvia™ 50 were obtained as 1 min 12.17 sec and 1 min 37.83 sec respectively and met the specification of USP. In comparative study on dissolution profile of innovator brand (Januvia) and local brands of Sitagliptin, the difference factor (f_1) was found 2.992% for Siglita™ 50 and for Janvia™ 50 it was 2.536%. In case of similarity factor (f_2) the values were 67.676% and 65.695% for Siglita™ 50 and Janvia™ 50 respectively. These values ensure pharmaceutical equivalence of the two products.

Keywords: Diabetes, Sitagliptin, Dissolution test, Disintegration test, Friability test, Weight variation test, Similarity factor, Difference factor.

CHAPTER: 1

Introduction

Chapter 1: Introduction

1.1 Diabetes

Diabetes is the condition in which the body does not properly process food for use as energy. Most of the food we eat is turned into glucose, or sugar, for our bodies to use for energy. The pancreas, an organ that lies near the stomach, makes a hormone called insulin to help glucose get into the cells of our bodies. When you have diabetes, your body either doesn't make enough insulin or can't use its own insulin as well as it should. This causes sugars to build up in your blood. This is why many people refer to diabetes as "sugar." Diabetes can cause serious health complications including heart disease, blindness, kidney failure, and lower-extremity amputations. Diabetes is the seventh leading cause of death in the world, (Kelly, 2001).

1.1.1 Types of diabetes:

The elevated blood glucose associated with diabetes mellitus results from absent or inadequate pancreatic insulin secretion, with or without concurrent impairment of insulin action. The disease states underlying the diagnosis of diabetes mellitus are now classified into four categories: type-I (insulin dependent diabetes), type-2 (noninsulin dependent diabetes), type-3 (others) and type-4 (gestational diabetes mellitus), (Katzung, Masters and Trevor, 2010).

1.1.1.1 Type1

Type I diabetes, previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes, and may account for 5 percent to 10 percent of all diagnosed cases of diabetes. Risk factors are less well defined for Type 1 diabetes than for Type 2 diabetes, but autoimmune, genetic, and environmental factors are involved in the development of this type of diabetes, (National Institute for Health and Clinical Excellence, 2006).

Cause

In the postabsorptive period of a normal individual, low, basal levels of circulating insulin are maintained through constant β cell secretion. This suppresses lipolysis, proteolysis, and glycogenolysis. A burst of insulin secretion occurs within two minutes after ingesting a meal, in response to transient increases in the levels of circulating glucose and amino acids. This lasts for

up to fifteen minutes, and is followed by the postprandial secretion of insulin. However, having virtually no functional β-cells, the Type 1 diabetic can neither maintain a basal secretion level of insulin nor respond to variations in circulating fuels. The development and progression of neuropathy, nephropathy and retinopathy are directly related to the extent of glycemic control, (Lippincott's illustrated review, 2006).

1.1.1.2 Type 2

Type II diabetes was previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes. Type 2 diabetes may account for about 90 percent to 95 percent of all diagnosed cases of diabetes. Risk factors for Type 2 diabetes include older age, obesity, and family history of diabetes, prior history of gestational diabetes, impaired glucose tolerance, physical inactivity, and race/ethnicity. African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans and Pacific Islanders are at particularly high risk for type 2 diabetes .Gestational diabetes develops in 2 percent to 5 percent of all pregnancies but usually disappears when a pregnancy is over. Gestational diabetes occurs more frequently in African Americans. Hispanic/Latino Americans, American Indians, and people with a family history of diabetes are more vulnerable than in other groups. Obesity is also associated with higher risk. Women who have had gestational diabetes are at increased risk for later developing Type 2 diabetes. In some studies, nearly 40 percent of women with a history of gestational diabetes developed diabetes in the future, (National Institute for Health and Clinical Excellence, 2006).

Cause

In non insulin dependent diabetes mellitus the pancreas retains some beta cell function, but variable insulin secretion is insufficient to maintain glucose homeostasis. The beta cell mass may become gradually reduced in type-2 diabetes. In contrast to patients with type-1, those with type-2 diabetes are often obese. Type-2 diabetes is frequently accompanied by the lack of sensitivity of target organs to either endogenous or exogenous insulin. This resistance to insulin is considered to be a major causation of this type of diabetes, which is sometimes referred to as "metabolic syndrome", (Lippincott's illustrated review, and 2006).

1.1.1.3 Other specific types of diabetes

Result from specific genetic syndromes, surgery, drugs, malnutrition, infections, and other illnesses. Such types of diabetes may account for 1 percent to 2 percent of all diagnosed cases of diabetes, (National Institute for Health and Clinical Excellence, 2006).

1.1.2 The symptoms of diabetes

People who think they might have diabetes must visit a physician for diagnosis. They might have SOME or NONE of the following symptoms:

•Frequent urination

•Excessive thirst

•Unexplained weight loss

•Extreme hunger 1

•Sudden vision changes

•Tingling or numbness in hands or feet

•Feeling very tired much of the time

•Very dry skin

•Sores that is slow to heal

•More infections than usual Nausea, vomiting, or stomach pains may accompany some of these symptoms in the abrupt onset of insulin-dependent diabetes, now called Type 1 diabetes,(Kelly, 2001).

1.1.3 Treatment

The major components of the treatment of diabetes are:

1. Diet (combined with exercise if possible)

2. Oral hypoglycemic therapy

3. Insulin treatment.

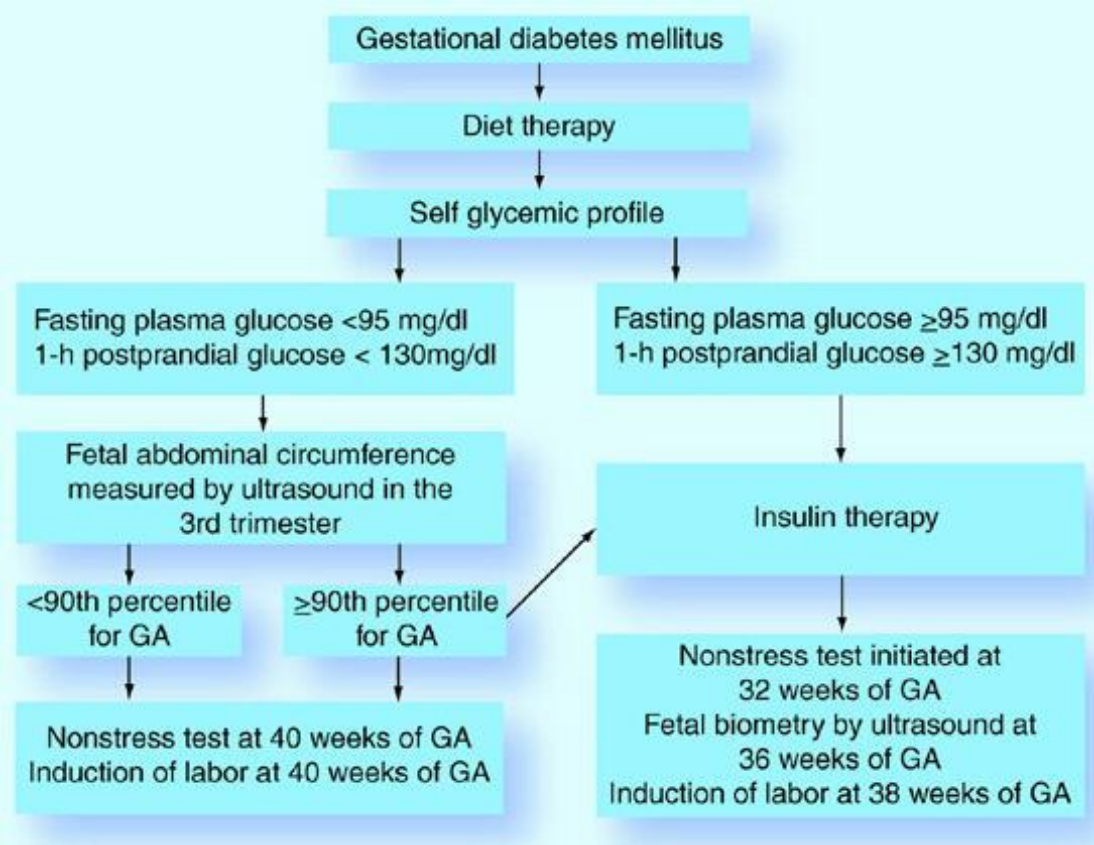

Fig 1.1: Flow chart of treatment of diabetes

Drug therapy should also be considered at this stage in the presence of marked hyperglycemia or when the condition is associated with infection or other inter-current illnesses. Otherwise contraindications are present. The choice between BG and SU may also depend on the degree of hyperglycemia, (Muller, 2004).

1.1.3.1 Dietary treatment should aim at:

- ensuring weight control
- providing nutritional requirements
- allowing good glycemic control with blood glucose levels as close to normal as
- possible

- correcting any associated blood lipid abnormalities
- ensuring consistency and compatibility with other forms of treatment if used, for
- Example oral agents or insulin,(Muller,2004)

1.1.3.2 The following principles are recommended as dietary guidelines for people with diabetes:

- Dietary fat should provide 25-35% of total intake of calories but saturated fat intake should not exceed 10% of total energy. Cholesterol consumption should be restricted and limited to 300 mg or less daily.
- Protein intake can range between 10-15% total energy (0.8-1 g/kg of desirable body weight). Requirements increase for children and during pregnancy. Protein should be derived from both animal and vegetable sources.
- Carbohydrates provide 50-60% of total caloric content of the diet. Although it has been traditionally recommended that carbohydrates should be complex and high in fibre, more emphasis should be placed on the total amount of carbohydrates consumed than the source of carbohydrate. Excessive salt intake is to be avoided. It should be particularly restricted in people with hypertension and those with nephropathy.
- Artificial sweeteners are to be used in moderation. Nutritive sweeteners (sorbital and fructose) should be restricted.
- The same precautions regarding alcohol intake that apply to the non diabetic population also apply to people with diabetes. Additionally, however, alcohol tends to increase the risk of hypoglycemia in those taking anti-diabetic drugs and should be particularly avoided in those with lipid abnormalities and patients with neuropathy.
- Except in special conditions like pregnancy and lactation, routine vitamin and mineral supplementation is generally not needed in people with a well balanced diet. There is, at present, no definite evidence to confirm that such treatment has any benefits, (Dr Alwan, 1994).

1.1.3.3 Drug treatment

Oral hypoglycemic drugs (OHD) are considered only after a regimen of dietary treatment combined with exercise has failed to achieve the therapy targets set. There are two major groups

of OHD: sulphonylureas (SUs) and biguanides (BGs). SU act by stimulating insulin release from the beta cells and also by promoting its action through extrapancreatic mechanisms. BG exerts their action by decreasing gluconeogenesis and by increasing the peripheral utilization of glucose. Several SU preparations are marketed in countries of the Eastern Mediterranean Region. However, this group of drugs may be represented by glibenclamide or tolbutamide. SUs can cause hypoglycemia and their use should therefore be closely monitored in the elderly and in those with nephropathy. Tolbutamide is a short-acting SU and may be selected in patients with renal impairment. Glibenclamide may be given in an initial dose of 1.25-2.5 mg which can be increased up to a maximum daily dose of 15 mg. For tolbutamide, the initial daily dose is *0.5* g which can be increased, if necessary, to 1.5 g in divided doses. Metformin is the only BG preparation now marketed in most Eastern Mediterranean Region countries. Metformin is primarily used in the obese not responding to dietary therapy. The starting dose is 500-850 mg with or after food, once daily, which can be increased to 500 mg tds or 850 mg bd. Because of the risk of lactic acidosis, it is contraindicated in:

- patients with impaired renal function
- elderly people above the age of 70 years
- Patients with heart failure, hepatic impairment, or predisposition to lactic acidosis.
- For the same reason, treatment with metformin should be discontinued during surgery,
- Severe infections and intercurrent illnesses.
- SU may be combined with metformin when therapy targets are not achieved with either
- Drug alone.
- Both SUs and BGs should not be used during pregnancy or breast-feeding.
- Patients with heart failure, hepatic impairment, or predisposition to lactic acidosis.

For the same reason, treatment with metformin should be discontinued during surgery, severe infections and intercurrent illnesses. SU may be combined with metformin when therapy targets are not achieved with either drug alone. Both SUs and BGs should not be used during pregnancy or breast-feeding. Some traditional and herbal therapies may be shown to lower blood glucose levels, but their long-term efficacy and safety have not been studied and they are therefore not recommended.

In people with NIDDM, insulin is indicated in the following situations:

- when diet and oral hypoglycemic drugs fail to control hyperglycemia and achieve
- therapy targets;
- diabetes during pregnancy when diet alone is inadequate;
- when oral hypoglycemic drugs are contraindicated;
- During stressful conditions such as infection and surgery.
- Further guidelines on insulin treatment are included in the section on the management of IDDM, (Drucker, et al., 2006).

1.2 INN System

A vital reference for pharmaceutical preparations is the system of International Nonproprietary Names (INN) for Pharmaceutical Substances. The existence of an international nomenclature for pharmaceutical substances in the form of an INN is important for the precise and unambiguous identification, safe prescribing and delivery of drugs to patients as well as to promote communication and exchange of information between health specialists and scientists throughout the world.

By the same token, in order to ensure the unimpeded use of INNs in international practice the nomenclature must be free from any legal constraints. Consequently, in contrast to a proprietary (brand) name, which is given to a preparation containing one or several active ingredients, produced in a particular pharmaceutical form and dose and which belongs to the manufacturer (or trademark owner), an INN identifies the actual active pharmaceutical substance under a single internationally recognized nonproprietary (generic) name.

The INN system has been developed by WHO and is regulated with the aim of protecting the generic name of a pharmaceutical substance from infringement of property rights to guarantee international availability. It is thus possible to systematize the nomenclature of pharmaceutical preparations registered under numerous proprietary (brand) names and produced by different pharmaceutical firms in various countries of the world using a single criterion – the presence in the preparation of a specific active substance(s), (Sashkova, et al., 1990).

1.3 Sitagliptin

Type II diabetes is the most common form of the disease, accounting for about 90% to 95 % of all diagnosed cases of diabetes. In type 2 diabetes, the body does not produce enough insulin or the cells ignore the insulin. Over time, high blood sugar levels can increase the risk for serious complications, including heart disease, blindness, nerve damage and kidney damage. Any new oral hypoglycemic drug that can increase the control of blood glucose with fewer adverse effects in patients with diabetes may be welcomed. Sitagliptin is the first and only prescription medication in a new class of oral antihyperglycemic agents, which enhance the body's own ability to lower blood glucose when it is elevated, (Stulc T, 2010).

1.3.1 Basis of discovery of Sitagliptin

Tight glycemic control is considered to be important in the therapy of type 2 diabetes mellitus (T2DM), but treatment with a single agent is not sufficient to achieve this for the majority of patients. So, there is a need for new antidiabetic agents with favorable side-effect profiles to use in combination therapy.

Advances in the understanding of the actions of endogenous glucoregulatory peptide hormones, known as incretins, have identified new therapeutic targets for T2DM. Two incretins — glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP1) — potentiate glucose-dependent insulin secretion from islet β-cells by activating specific G-protein-coupled receptors. GLP1 also inhibits glucagon secretion and gastric emptying and induces a feeling of satiety, which leads to weight loss in the majority of treated subjects. As incretin receptor activation is only coupled to stimulation of insulin secretion in the presence of elevated blood glucose, therapies that are based on potentiating endogenous incretin action should have a low risk of hypoglycemia, which is a problem with several current therapies, such as the sulphonylureas, (Drucker, 2006).

However, although native GLP1 (7–36) amide effectively lowers blood glucose, it is rapidly degraded by the ubiquitous serine protease dipeptidyl peptidase-4 (DPP4). One approach to combat this problem has been the development of long-acting degradation-resistant peptides that are subcutaneously injected. Exenatide a peptidic GLP1 receptor agonist was approved by the

FDA for T2DM. An alternative strategy has focused on the inhibition of the proteolytic activity of DPP4 to prevent the degradation of GLP1 and GIP, (Drucker, 2006).

DPP4 is a complex molecule that exists as a membrane-spanning cell-anchored protein that is expressed on many cell types, and as a soluble form in the circulation; both forms have proteolytic activity. Several lines of evidence have suggested that DPP4 is essential for the control of GLP1 bioactivity and glucose homeostasis. Importantly, small-molecule inhibitors of DPP4 prevented the N-terminal degradation of GLP1, and lowered blood glucose in preclinical studies. Complementary experiments indicated that mice with a targeted disruption of the DPP4 gene had increased plasma levels of GLP1 and GIP, enhanced glucose-stimulated insulin secretion and reduced glycemic excursion following oral glucose challenge. Proof-of-concept for the efficacy of DPP4 inhibitors as antidiabetic agents in humans was then reported using NVP DPP728, a first-generation small-molecule DPP4 inhibitor, which further encouraged the discovery and development of such agents, including Sitagliptin, (Decon & Carolyn, 2004).

1.3.2 History of Sitagliptin

In October 2006, the U.S. Food and Drug Administration (FDA) approved Sitagliptin as monotherapy and as add-on therapy to either of two other types of oral diabetes medications, Metformin or thiazolidinediones to improve blood glucose control in patients with type 2 diabetes when diet and exercise are not enough, (Daniel, Chris & Peter, 2007).

In March, 2007 it was approved in European Union. Sitagliptin is currently approved in 42 countries. The recommended dose of Sitagliptin is 100 mg once daily. It may be taken with or without food. In April, 2007 FDA approved the combination product of Sitagliptin and metformin for type 2 diabetes, (Badyal & Kaur, 2008).

1.3.3 Chemistry of Sitagliptin

Figure 1.2: Chemical Structure of Sitagliptin

Sitagliptin is available as Sitagliptin monophosphate monohydrate. The IUPAC name of Sitagliptin is (*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine. It has a molecular weight of 407.313619 and its molecular formula is C16H15F6N5O, (Kelly, 2007).

1.3.4 Indications of Sitagliptin

The use of Sitagliptin is approved in the following medical conditions.

1. To improve glycemic control in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
2. To improve glycemic control in combination with a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone does not provide adequate glycemic control and when metformin is inappropriate due to contraindication or intolerance.
3. To improve glycemic control in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycemic control.
4. For patients with type 2 diabetes in whom the use of a thiazolidinedione is appropriate, Sitagliptin is indicated.
5. In combination with the thiazolidinedione when diet and exercise plus the thiazolidinedione agonist alone does not provide adequate glycemic control.

Sitagliptin may be preferable to a thiazolidinedione for the people of-

a. In whom further weight gain would cause or exacerbate psychological or medical problems associated with high body weight.
b. In whom a thiazolidinedione is contraindicated.
c. Who have previously had a poor response to or were intolerant of thiazolidinedione therapy, (Gadsby, 2009).

1.3.5 Dose of Sitagliptin

The usual recommended dose of Sitagliptin is 100 mg per day. However, the agent is available in three strengths to allow for lower dosing in patients with moderate to severe renal impairment. A

dose of 50 mg/day is recommended in patients with a creatinine clearance (CrCl) ≥ 30 to < 50 ml/min. A dose of 25 mg/day is recommended for patients with a CrCl < 30 ml/min. The Sitagliptin-Metformin combination should be taken twice daily with meals and titrated slowly to minimize potential gastrointestinal side effects associated with Metformin, (White, 2008).

1.3.6 Pharmacokinetics of Sitagliptin

Sitagliptin is rapidly absorbed (peak concentration at 1-4 hours) after oral administration and has a high oral bioavailability. The average volume of distribution (Vd) at steady state is 198 l after a single dose of Sitagliptin. Sitagliptin is moderately bound to plasma proteins (bound fraction = 38%). Sitagliptin is primarily excreted in an unchanged form in the urine (79%) via active tubular secretion. The t1/2 of Sitagliptin was 12.4 hours after a single 100-mg dose. A relatively small fraction of Sitagliptin undergoes hepatic metabolism primarily via cytochromes P450 3A4 and 2C8. Because Sitagliptin is primarily eliminated unchanged via renal excretion, dosage adjustments are required for patients with moderate to severe renal impairment. A dose of 50 mg/day is recommended in patients with a creatinine clearance (CrCl) ≥ 30 to < 50 ml/min. A dose of 25 mg/day is recommended for patients with a CrCl < 30 ml/min or in patients with end-stage renal disease requiring dialysis, (White, 2008).

1.3.7 Mechanism of Action

Sitagliptin prolongs the activity of proteins that increase the release of insulin after blood sugar rises, such as after a meal. Sitagliptin is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4), which metabolizes the naturally occurring incretion hormones glucagon-like peptide-1(GLP-1) and glucose dependent insulinotropic polypeptide (GIP) resulting in enhanced glucose-dependent insulin secretion from the pancreas and decreased hepatic glucose production. Since GLP-1enhances insulin secretion in the presence of raised blood glucose levels, inhibiting DPP-IV activity will increase and prolong the action of GLP-1 by reducing its rate of inactivation in plasma (3). Sitagliptin reduces hemoglobin A1C (HbA1c), fasting and postprandial glucose by glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion. GLP-1 has other widespread effects including delaying gastric emptying, significantly reducing glucagon levels and possible central effects on the appetite.

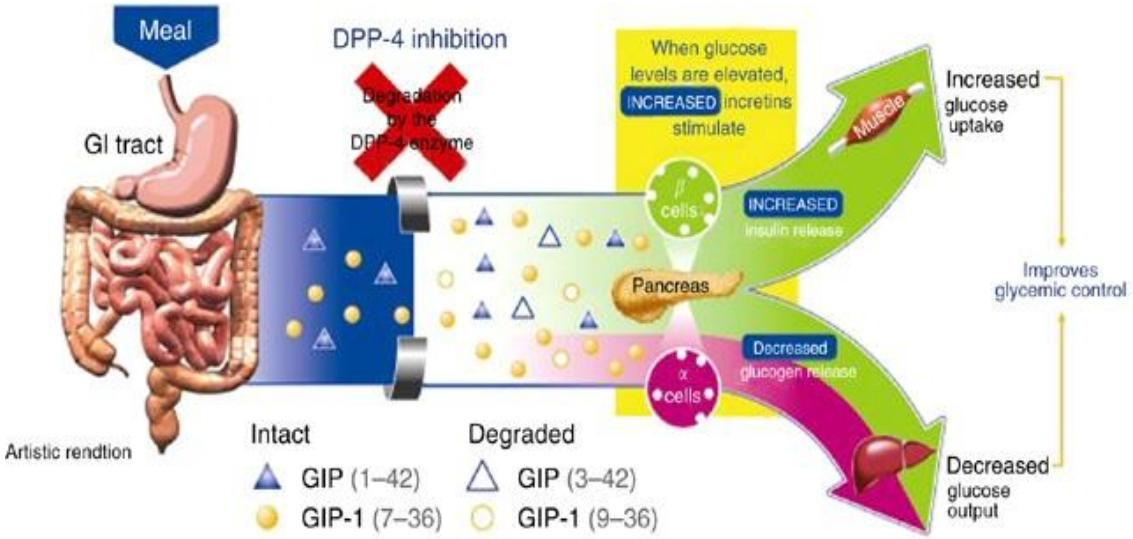

Fig 1.3: Mechanism of Action of DPP-IV inhibitor (Sitagliptin Phosphate)

(Dinesh, Badyal, et al., 1999)

1.3.8 Clinical Use

In October 2006, the U.S. Food and Drug Administration (FDA) approved Sitagliptin as monotherapy and as add-on therapy to either of two other types of oral diabetes medications, metformin or thiazolidinediones to improve blood glucose control in patients with type II diabetes when diet and exercise are not enough. In March, 2007 it was approved in European Union. Sitagliptin is currently approved in 42 countries. The recommended dose of Sitagliptin is 100 mg once daily. It may be taken with or without food. In April, 2007 FDA approved the combination product of Sitagliptin and metformin for type 2 diabetes. In clinical trials of 1-year duration, Sitagliptin improved glycemic control by reducing both fasting and postprandial glucose concentrations, leading to clinically meaningful reductions in glycosylated haemoglobin levels. Monotherapy with Sitagliptin 100mg daily decreases mean HbA1c by 0.6-0.79% (mean difference from placebo). When used in combination with metformin or pioglitazone, the mean reduction is HbA1c is 0.7% and 0.9% respectively. Sitagliptin is considered to be weight neutral and lipid Neutral, (Dobers, et al., 2001).

1.3.9 Possible explanation for "less hypoglycemic effect" of Sitagliptin

The incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released from the small intestine into the vasculature during a meal, and these incretins have a potential to release insulin from pancreatic beta cells of islets of Langerhans, affording a glucose-lowering action. However, both incretins are hurriedly degraded by the DPP-4. Inhibitors of DPP-4 (such as Sitagliptin), therefore, enhance the bioavailability of GLP-1 and GIP, and thus have been approved for better glycemic management in patients afflicted with type 2 diabetes mellitus (T2DM). GIP and GLP-1 released only during a meal, which means when blood glucose level is high. Sitagliptin is also gives its pharmacological action as DPP-4 inhibitor immediate after meal. After some times of meal GIP and GLP-1 secretion is stopped. The action of Sitagliptin is also terminated at that time, because there is no available GIP and GLP-1 and there is no need for inhibition of DDP-4 enzyme. So, Sitagliptin reduced blood glucose level immediate after a meal, when reduction of blood glucose level is mainly required for a diabetic patient. Thus Sitagliptin has less potential for hypoglycemic effect, (Balakumar & Dhanaraj, 2013).

1.3.10 Side effects of Sitagliptin

Sitagliptin is normally well tolerated medicine. Headache, sore throat, nausea, arthralgia, myalgia, rash, hives, swelling of the lips, dysphagia, and dyspnea are the common side effects of sitagliptin. Hemolysis, is a rare side effect of this drug, (Bekur, et al., 2010).

1.3.11 Adverse effects

In clinical trials, Sitagliptin demonstrated an overall incidence of side effects comparable to placebo. The most common side effects in studies were upper respiratory tract infection, stuffy or running nose, and sore (Dobers, et al., 2001).

1.3.12 Drug interactions

Sitagliptin plasma concentrations may be increased modestly (approximately 68%), with cyclosporine which is not expected to be clinically important. Digoxin plasma levels may be increased slightly (approximately 18%), no dosage adjustment is recommended. Although Sitagliptin is not as likely to cause hypoglycemia as some other oral diabetes medications, be careful while prescribing any other drug that can potentially lower blood sugar, such as: probenecid, nonsteroidal

anti-inflammatory drugs (NSAIDs), aspirin or other salicylates, sulfa drugs, a monoamine oxidase inhibitor (MAOI) or beta blockers, (Reutter, 2002).

1.3.13 Contraindications

It is a pregnancy category B drug. Because there are no adequate, well-controlled studies of Sitagliptin in pregnant women, it should be used during pregnancy only if clearly needed.

Caution should be exercised with use of Sitagliptin in nursing women. Sitagliptin can pass into breast milk and may harm a nursing baby. In children, safety and efficacy not established. Dosage adjustments are needed in patients with moderate or severe renal function impairment. In moderate renal function impairment (Ccr 30 to less than 50 mL/min) dose should be reduced to 50 mg once daily. In severe renal function impairment (Ccr less than 30 mL/min) dose sould be reduced to 25 mg once daily. Sitagliptin is also contraindicated in diabetic ketoacidosis, (Reutter, 2002).

1.4 Quality

Quality is essential for the survival and growth of any organization. Quality signifies excellence of the product or service, which is measured, based on the customer's experience with the product or service against his or her requirement. The quality of the product may be defined as "its ability to fulfill the customer's needs and expectation" (Aulton, 2002). Quality needs to be defined firstly in terms of parameters or characteristics, which vary from product to product. For example, for pharmaceutical product, parameters such as physical and chemical characteristics, medical effect, toxicity, taste and shelf life etc, (Lachman, 2008).

1.4.1 Quality of pharmaceutical product

Quality of product is the main precursor for any pharmaceutical industry to maintain its existence. In the pharmaceutical industry, the quality is a measure of the high degree of managerial, scientific and technical sophistication. Quality is always an obligatory prerequisite when we consider any product. It becomes primary when it relates to life saving products like pharmaceuticals. Although it is mandatory for the government and regulatory bodies but it is also a fact that quality of pharmaceutical product cannot be adequately controlled solely by pharmacopoeia analysis of the final product. Today quality has to be built in to the product right from its inception and rigorous

international environmental, safety and regulatory standards need to be followed. Validation had proven to be an important tool for quality management of pharmaceuticals (Aulton, 2002).

Most traditional pharmaceutical drugs are relatively simple molecules that have been found primarily through trial and error to treat the symptoms of a disease or illness. Over a period of time these molecules were perfected to ensure quality. The quality is very much related to every pharmaceutical product. Without quality pharmaceutical drug cannot be marketed or sold because it can cause many problems such as sub therapeutic or overdose.

If a drug of any brand or company does not maintain it then may cause serious problems when prescribed to the patients. The patient may suffer from the adverse effects because of its faulty quality which may sometimes prove to be fatal, (Lachman, 2008).

1.4.2 Quality Control

The term "quality control" comprises of two words quality and control. Control is a universal regulatory process. In the industry, it takes from of meeting standards. The process through which we establish and meet standards is called "control". Quality control deals with a system which accepts or rejects any activities which affect the quality and prevents Quality deficiency and imports consistency in the quality of the product or service (Marayya, 2005).

Quality is important in every product or service but it is vital in medicine as it involves life. Quality control is a concept which strives to produce a perfectly produced by a series of measure designed to prevent and eliminate errors at different stages of production. Although the responsibility for assuring product quality belongs principally to quality assurance personnel, it involves many departments and disciplines within a company. The quality of products is depending upon that of the participating constituents, some of which are sustainable and effectively controlled while others are not.

To be effective, it must be supported by a team effort. Quality must be built into a drug product during product and process design, and it is influenced by the physical plant design, space, ventilation, cleanliness, and sanitation during routine production. The product and process design begins in research and development. It also includes pre-formulation and physical, chemical, therapeutic and toxicological consideration.

Quality control ensures that a drug will have the following characteristics:

- Genuine Quality as well as good nature
- Physically and chemically pure
- It contains same amount of ingredients as mentioned on the label
- It must be in such a form that after administration it is effective
- Quality in terms of shelf life/stability
- No toxic impurities

The drug is tested for both qualities as well quantity by the quality control department. Every country will have an official pharmacopoeia which will give the standards of quality for all the medicines along with the methods to be used for quality control. Revised supplements are published periodically to stay up-to-date pertaining to drug quality, (Lachman, 2008).

1.4.3 Quality assurance

Design, development and implementation of quality assurance is the most vital function in the pharmaceutical industry. In the pharmaceutical industry, the quality is a measure of high degree of managerial, scientific and technical sophistication. Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of the product. It is the totality of arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use (Marayya and Anjuaeyulu, 2005).

Quality control emphasizes testing of products to uncover defect, and reporting to management who make the decision to allow or deny the release, whereas quality assurance attempts to improve and stabilize production, and associated process, to avoid. Or at least minimize, issues that led to the defects in the first place. The assurance of the product quality depends on more than just proper sampling and adequate testing of various components and the finished dosage form. The prime responsibility of maintaining product quality during production rests with the manufacturing department. Removal of responsibility for manufacturing for producing a quality product can result in imperfect composition, such as ingredients missing, sub-potent or super potent addition of ingredients, or mixing of ingredient; mistakes in packaging or filing, such as product contamination, mislabeling, or deficient package; and lack of conformance to product registration. Quality assurance

personnel must establish control or checkpoint to monitor the quality of the product as it is processed and upon completion of manufacture.

Because of the increasing complexity of modern pharmaceutical manufacturing arising from a variety of unique drugs and dosage forms, complex ethical, logical and economic responsibilities have been placed on those concerned with the manufacture of modern pharmaceuticals. An awareness of these factors is the responsibilities of all those involved in the development, manufacture, control and marketing of quality products, (Lachman, 2009).

1.4.4 Quality Control process

Quality control is a process that is used to ensure a certain level of quality in a product or service. It might include whatever actions a business deems necessary to provide for the control and verification of certain characteristics of a product or service. Most often, it involves thoroughly examining and testing the quality of products or the results of services. The basic goal of this process is to ensure that the products or services that are provided meet specific requirements and characteristics, such as being dependable, satisfactory, safe and fiscally sound.

Every test or criterion that is prescribed as a standard in the pharmacopoeia is a parameter. Various parameters used in Quality Control process -

1. Weight Variation Test
2. Hardness Test
3. Friability Test
4. Disintegration Test
5. Dissolution Test (FDA, 2012)

1.4.4.1 Weight Variation Test

In tablet manufacturing, materials for direct compression tend to show high fill – weight variations as a result of poor flow properties, but coprocessed excipients, when compared with simple mixtures or parent materials, have been shown to have fewer fill-weight variation problems. The primary reason for this phenomenon is the impregnation of one particle into the matrix of another, which reduces the rough particle surfaces and creates a near-optimal size distribution, causing better flow properties, (Nachaegari & Bansal, 2004).

1.4.4.2 Hardness Test

The tablets must be hard enough to withstand mechanical stress during packaging, shipment, and handling by the consumer. Section 1216 of the USP 24 outlines a standard tablet friability test applicable to manufactured tablets. Most compounding pharmacy would not have the apparatus specified in Section 1216. However, there are several hand operated tablet hardness testers that might be useful. Examples of devices are the Strong Cobb, Pfizer, and Stokes hardness testers. The principle of measurement involves subjecting the tablet to an increasing load until the tablet breaks or fractures. The load is applied along the radial axis of the tablet. Oral tablets normally have a hardness of 4 to 8 or 10 kg; however, hypodermic and chewable tablets are much softer (3 kg) and some sustained release tablets are much harder (10 – 20 kg), (UNC, 2012).

1.4.4.3 Friability Test

Friability of tablets can be determined by using Friability Tester which subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of six inches in each revolution. Pre – weighed sample of tablets is placed in the device and were subjected to 100 revolutions. Tablets are then deducted using a soft muslin cloth and reweighed, (Mohapatra, Parikh, & Gohel, 2008).

Percentage Friability (% F) has the following formula –

$$\%F = \left(1 - \frac{W}{W_0}\right) \times 100$$

Here,

W_o = Weight of the Tablet before test

W = Weight of the tablet after test

Equation 1.1: Equation for the calculation of Percentage Friability

1.4.4.4 Disintegration Test

Disintegration test determines whether tablets and capsules disintegrate within a prescribed time when placed in an immersion fluid under prescribed experimental conditions. Disintegration is

defined as the state in which no residue of the tablet or capsule, except fragments of undissolved coating or capsule shell, remains on the screen of the test apparatus or, if any other residue remains, it consists of a soft mass having no palpably firm, unmoistened core. Disintegration apparatus consists of a circular basket-rack assembly, a suitable vessel for the immersion fluid (such as a 1L beaker), a thermostatic arrangement for maintaining the fluid at the required temperature (normally 37 ± 2 °C), and a device for raising and lowering the basket-rack in the immersion fluid at a constant frequency of 28 – 32 cycles/min through a distance of 50 – 60 mm, (WHO, 2011).

1.4.4.5 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. A dissolution test simulates the availability of active substance and allows the prediction of the time for complete release of the material from the dosage form. For an INN drug dissolution method is not available in pharmacopoeia. The FDA dissolution method for the reference listed product may be considered. Alternatively, a dissolution method development is also possible by considering some criteria or by following some process. Comparative dissolution testing, using test and reference products under a variety of test conditions, is recommended, (FDA, 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:

$$f1 = \frac{[\sum |Rt - Tt|]}{[\sum Rt]} \times 100$$

Equation 1.2: % 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.

$$f_2 = 50 \times \log \{ 1+ (1/n) \sum t=1^n (Rt - Tt)^2]^{-0.5} \times 100 \}$$

Equation 1.3: % Similarity Factor Calculation

Where,

n = the number of time points,

R = the dissolution value of the reference batch at time t, and

T = the dissolution value of the test batch at time t, (Moore & Flanner, 1996).

A specific procedure to determine difference and similarity factor is as follows:

1. Determine the dissolution profile of two products, i.e. of the test and reference products (using 12 units each).
2. For f2 calculations a minimum of three time points (excluding point zero) must be used, and only one measurement included after 85 % dissolution of both products has occurred.
3. For curves to be considered similar, f2 values should be close to 100. Generally, f2 values greater than 50 (50 to 100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test and reference products, (Moore & Flanner, 1996).

1.4.5 Factors influencing quality control parameters

1. A variety of factors concerning the formulation of a drug product can directly influence the dissolution rate of the active ingredient contained within it. Once these factors are completely characterized, we can use this information to achieve custom-tailored drug dissolution profiles.
2. Particle size of drugs contained in tablet will enhance dissolution and absorption. This can most likely be attributed to the procedures employed in tablet production that is, mixing the drug with usually hydrophilic diluents and subsequent granulation will result in a more hydrophilic surface, even for originally hydrophobic drug particles.

3. Lubricants that are commonly incorporated in the formulation of solid dosage forms fall predominantly in the class of hydrophobic compounds. Consequently, the nature, quality, and quality of the lubricant added can affect the dissolution rate and also used to reduce the friction.
4. The drugs that are practically insoluble in aqueous medium (<0.01%) are of increasing therapeutic interest, particularly due to the problems associated with their bioavailability when administered orally. Drugs with low solubility when incorporated with surfactant can enhance their dissolution.
5. Distribution at Hoover caused the vibration. So, small granule pushed, large granule will come out first, because there is a process of consolidation. Therefore, needs to be put a uniform granule size. So, before the compressing process begins better evaluation the particle size distribution first, (Gong, 2010).

1.4.5 Significance of quality control parameter

It is necessary to carry out study on the quality control parameters of Sitagliptin tablets available in Bangladesh for the appropriate quality evaluation, therapeutic efficacy, and safety of the tablets. Moreover these parameters of the tablets are also tools for understanding and maintaining brand to brand consistency during manufacturing. All of these parameters are closely related to each other and have effect on drug absorption, bioavailability, efficacy etc. Sitagliptin is used for the treatment of diabetes mellitus. The number of diabetic patient is increasing day by day. So it's a big concern now for us. Sitagliptin is available is available everywhere and people can get it in reasonable price. That's why a huge number of patients use the drug. So if the companies don't consider the quality of the drug that that can produce a very bad consequence on a large number of patients. Patient can be died even. That is why the quality of Sitagliptin should be up to the standard.

1.4.6 Aim and objectives of the study

The aim and objectives of the study were-

- To analyze different brands of Sitagliptin in terms of physical parameters like weight variation test, hardness test, friability test, disintegration test, dissolution test etc.
- To determine the dissolution profile of local brands.
- To compare dissolution profile of local brands with innovator brand.

CHAPTER: 2

Materials & Method

Chapter 2: Materials & Method

2.1 Equipments

In the characterization of Sitagliptin tablet, the following equipments were used which is listed in the table.

Table 2.1: Lists of equipments used for physical and chemical characterization of Sitagliptin phosphate tablets

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

Fig 2.1: VEEGO Tablet Friability Tester

Fig 2.2: MONSANTO Hardness Tester

Fig 2.3: GENRISTO Distill Water Plant

Fig 2.4: SHIMADZU Weighing Balance

Fig 2.5: LABINDIA Dissolution Apparatus

Fig 2.6: VANGUARD Disintegration Tester

2.2 Weight Variation Test

According to USP30/NF25, uniformity of dosage units can be demonstrated by either of two methods:

1. Content uniformity
2. Weight variation

Applicable of content uniformity or weight variation tests for tablet dosage forms from USP30: Uncoated tablets, coated tablets (film coated or others) of dose greater 25mg are applicable for weight variation test.

Uncoated tablets, coated tablets (film coated tablets or others) of dose less than 25mg are applicable for content uniformity test.

As we are working with Sitagliptin uncoated tablets of dose greater than 25mg, we will perform only weight variation test for determination the uniformity for dosage units, (Lachman, 2008).

2.2.1 Materials Required

Table 2.2: Materials required for Weight Variation Test of Sitagliptin Tablets

Materials	Company	Type	Quantity
Siglita™ 50	Square Pharmaceutical Ltd	Anti hyperglycemic agents	20 tablets
Janvia™ 50	The ACME Laboratories Ltd	Anti hyperglycemic agents	20 tablets

2.2.2 Method

1. 20 tablets were taken and weighed.
2. The average was taken and it was considered as the standard weight of an individual tablet.
3. All the tablets were weighed individually and observed whether the individual tablets are within the range or not, (British Pharmacopoeia, 2007).

N.B: The variation from the average weight in the weights not more than two tablets must not differ more than the percentage listed which is given below:

2.2.3 Acceptance limit

The tablet meet the USP test if not more than 2 tablets are out of percent limit and no tablet differs by more than 2 times the percent limit then the batch is acceptance (USP, 2007).

Table 2.3: Table of acceptance of weight variation of tablets

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

2.2.4 Calculation

$$\text{Weight variation} = \frac{\text{Tablet Weight} - \text{Average Weight}}{\text{Average Weight}} \times 100\%$$

Equation 2.1: Equation for weight variation

2.3 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 the 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.

2.3.1 Materials Required

Table 2.4: Materials required for Hardness Tests of Sitagliptin tablets

Materials	Company	Quantity
Siglita™ 50	Square Pharmaceutical Ltd	10 tablets
Janvia 50	The ACME Laboratories Ltd	10 tablets

2.3.2 Method

1. The sliding scale of hardness tester has been set off to zero.
2. The tablets have been placed vertically between the two jaws.

3. Force has been applied with the screw thread and spring until the tablets has been fractured.
4. A force of about 4-5 kg is considered to be the minimum for hardness according to The British Pharmaceutical (2 batches), (Lachman, et al., 2008).

2.4 Friability Test

It is another indicator of tablet strength. This device subjects a number of tablets to combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25rmp, dropping the tablet a distance of six inches with each revolution.

2.4.1 Materials Required

Tablet 2.5: Meterials Required for Friability Test

Materials	Company	Batch	Quantity
Siglita™ 50	Square Pharmaceutical Ltd	308001	10 tablets
Janvia™ 50	The ACME Laboratories Ltd	PQ3001	10 tablets

2.4.2 Method

1. The experience has been started by weighing 10 tablets which is considered as the initial reading.
2. All the tablets have been placed in the drum of the friability tester and rotate 100 times.
3. The percentage loss has been calculated.
4. According to BP the tablets should not lose more than 1% of their total weight. (B.P. appendix: XVII, 2003).

$$\%F=\left(1-\frac{W_0}{W}\right)\times 100$$

Here W_0= initial weight of 10 tablets

W= weight of 10 tablets after test

Equation 2.2: Equation for the Calculation of Percentage Friability Test

2.5 Disintegration Test

A process through which the tablet is breakdown into small particles or granules prior to become solution is called disintegration. In this test, time is important at which the tablets are disintegrated. BP describes the method of disintegration of coated, uncoated and enteric coated tablets individually. As Sitagliptin 50mg is coated, we followed the BP method for coated tablets.

2.5.1 Condition

Medium: 900ml distilled water

Times: 30 minutes

Temperature: $(37\pm2)^0$ C

2.5.2 Materials Required

Table 2.6: Meterials Required for Disintegration Test

Materials	Company	Quantity
Siglita™ 50	Square Pharmaceutical Ltd	6 tablets
Janvia™ 50	The ACME Laboratories Ltd	6 tablets

2.5.3 Method

Methods Disintegration Test for Sitagliptin Tablets was adopted from the procedures described by the British Pharmacopoeia (2007). For this, at first 1 tablet in each of the six tubes in basket was placed. Then, the Disintegration Apparatus was operated at 37^0C. And then disintegration time for each tablet was recorded and their average disintegration time was calculated followed by construction of a Bar diagram by using Microsoft Excel 2007. The acceptable range to pass the disintegration test is that at least 2 tablets from a batch must be between the ranges of 30 minutes or the average disintegration time the tablets from a batch must be between the ranges mentioned, (BP,2007).

2.6 Dissolution Test

Dissolution test is carried out to determine the amount of drug release during specific period of time by using dissolution rate apparatus.

2.6.1 Specifications of the test

Medium: 900ml Distilled Water

Apparatus: USP Apparatus 1 (basket)

RPM: 100

Time: 30 minutes

Lambda max: 267nm

2.6.2 Materials Required

Table 2.7: Meterials Required for Dissolution Test

Materials	Company	Quantity
Januvia	Merck & Co	12 tablets
Siglita™ 50	Square Pharmaceutical Ltd	12 tablets
Janvia™ 50	The ACME Laboratories Ltd	12 tablets

2.6.3 Method

The in vitro dissolution study is carried out using apparatus I (Basket). The Dissolution jars are cleaned with a mild detergent and then rinsed with distilled water and dry to room temperature. 900 ml of dissolution medium (Distilled Water) is transferred into the dissolution jars and are placed in the test assembly which is maintained at 37 degree Celsius which is given an allowance of 0.5 degrees Celsius. The medium is allowed to attain the set temperature. The rpm is set to 100. The test sample is introduced inside the dissolution jar and the test assembly is brought down to the Static position and the medium is stirred at 100rpm for 30 minutes. Sampling Times (minutes) are 5, 10, 15, 20 and 30. 10 ml of the samples are withdrawn using a graduated pipette and transfer it immediately to clean, dried and labeled test tubes, (FDA, 2010).

CHAPTER: 3

Results

Chapter 3: Result

3.1 Weight variation test

Table 3.1: Result of weight variation test of Siglita™ 50

Number of Tablets	Weight of tablet (gm)	Highest variation (%)	Lowest variation (%)
1	0.186		
2	0.187		
3	0.183		
4	0.189		
5	0.192		
6	0.186		
7	0.194		
8	0.186		
9	0.188		
10	0.182	+3.833	-3.088
11	0.187		
12	0.188		
13	0.184		
14	0.190		
15	0.193		
16	0.187		
17	0.195		
18	0.187		
19	0.189		
20	0.183		

Table 3.2: Result of weight variation test of Janvia™ 50

Number of Tablets	Weight of tablet (gm)	Highest variation (%)	Lowest variation (%)
1	0.198		
2	0.196		
3	0.198		
4	0.197		
5	0.203		
6	0.198		
7	0.206		
8	0.204		
9	0.203		
10	0.200	+3.778	-1.282
11	0.190		
12	0.195		
13	0.194		
14	0.202		
15	0.199		
16	0.195		
17	0.192		
18	0.195		
19	0.202		
20	0.203		

3.2 Friability Test

Tablet 3.3: Result of friability test of Siglita™ 50

Brand	Initial weight of 10 tablets (gm)	Final weight of 10 tablets (gm)	Friability (%)
Siglita™ 50	1.886gm	1.878gm	0.8

Tablet 4.2.2 Result of friability test of Janvia™ 50

Brand	Initial weight of 10 tablets (gm)	Final weight of 10 tablets (gm)	Friability (%)
Janvia 50	2.2445gm	2.2392gm	0.53

3.3 Hardness Test

Tablet 3.4: Result of Hardness test Siglita™ 50

Number of Tablets	Hardness (kg/cm)	Average(kg/cm)
1	1.9	
2	2	
3	1.75	
4	1.95	
5	1.60	1.835
6	1.75	
7	1.95	
8	1.85	
9	1.97	
10	1.65	

Tablet 3.5: Result of Hardness test Janvia™ 50

Number of Tablets	Hardness (kg/cm)	Average(kg/cm)
1	2.25	
2	2.48	
3	2.52	
4	2.47	
5	2.20	2.456
6	2.25	
7	2.75	
8	2.60	
9	2.55	
10	2.49	

3.4 Disintegration test

Tablet 3.6: Result of Disintegration test of Siglita™ 50

Brand	Sample 01	Sample 02	Sample 03	Sample 04	Sample 05	Sample 06	Mean disintegration time
Siglita™ 50	1 min 25 sec	1 min 33 sec	1 min 40 sec	1 min 42 sec	1 min 44 sec	1 min 43 sec	1 min 37.83 sec

Tablet 3.7: Result of Disintegration test of Janvia™ 50

Brand	Sample 01	Sample 02	Sample 03	Sample 04	Sample 05	Sample 06	Mean disintegration time
Janvia™ 50	1 min 11 sec	1 min 9 sec	1 min 13 sec	1 min 15 sec	1 min 11 sec	1 min 14 sec	1 min 12.17 sec

3.5 Dissolution Test

Tablet 3.8: Absorbance data of Januvia (Innovator Brand)

Serial No.	Absorbance at 5 min	Absorbance at 10 min	Absorbance at 15 min	Absorbance at 20 min	Absorbance at 30 min
1	0.271	0.290	0.296	0.288	0.257
2	0.251	0.283	0.296	0.291	0.289
3	0.267	0.300	0.314	0.300	0.291
4	0.247	0.301	0.285	0.294	0.274
5	0.263	0.301	0.292	0.289	0.302
6	0.253	0.290	0.280	0.295	0.273
7	0.246	0.258	0.259	0.255	0.256
8	0.222	0.307	0.246	0.271	0.299
9	0.231	0.253	0.246	0.249	0.274
10	0.231	0.305	0.256	0.280	0.289
11	0.242	0.291	0.261	0.290	0.301
12	0.244	0.251	0.241	0.253	0.294

Tablet 3.9: Absorbance data of Janvia™ 50 (Local Brand)

Serial No.	Absorbance at 5 min	Absorbance at 10 min	Absorbance at 15 min	Absorbance at 20 min	Absorbance at 30 min
1	0.303	0.282	0.285	0.289	0.296
2	0.268	0.282	0.279	0.288	0.308
3	0.236	0.265	0.255	0.266	0.258
4	0.243	0.244	0.266	0.263	0.254
5	0.249	0.267	0.284	0.273	0.291
6	0.266	0.272	0.297	0.270	0.313
7	0.271	0.285	0.284	0.276	0.292
8	0.278	0.279	0.297	0.293	0.292
9	0.273	0.275	0.283	0.291	0.281

Serial No.	Absorbance at 5 min	Absorbance at 10 min	Absorbance at 15 min	Absorbance at 20 min	Absorbance at 30 min
10	0.259	0.290	0.296	0.300	0.298
11	0.279	0.307	0.310	0.304	0.312
12	0.265	0.298	0.320	0.311	0.304

Tablet 3.10: Absorbance data of Siglita™ 50 (Local Brand)

Serial No.	Absorbance at 5 min	Absorbance at 10 min	Absorbance at 15 min	Absorbance at 20 min	Absorbance at 30 min
1	0.230	0.257	0.264	0.272	0.277
2	0.228	0.257	0.327	0.264	0.270
3	0.207	0.254	0.269	0.281	0.208
4	0.245	0.269	0.302	0.268	0.292
5	0.261	0.267	0.266	0.258	0.275
6	0.247	0.257	0.283	0.305	0.301
7	0.261	0.270	0.268	0.282	0.285
8	0.270	0.294	0.289	0.290	0.294
9	0.275	0.276	0.313	0.307	0.301
10	0.290	0.298	0.301	0.302	0.306
11	0.281	0.288	0.290	0.292	0.299
12	0.303	0.289	0.327	0.298	0.306

3.5.1 % Dissolved data

$$\% \text{ Dissolved} = \frac{a}{b} \times \frac{\text{STD wt} \times 900 \times 100}{100 \times \text{Label Claim}}$$

Equation 3.1: % Dissolved Calculation

Here, Sample Absorbance = a

Standard Absorbance, b = 0.261

Standard Weight = 6.81 mg

Label Claimed = 62.5

Table 3.11: % Dissolved of Januvia (Innovator Brand)

Serial No.	% Dissolved at 5 min	% Dissolved at 10 min	% Dissolved at 15 min	% Dissolved at 20 min	% Dissolved at 30 min
1	101.821	108.96	111.214	108.208	96.561
2	94.30	98.815	111.214	109.335	108.584
3	100.318	112.717	117.977	112.717	109.335
4	92.803	113.092	107.081	110.462	102.948
5	98.815	113.092	109.711	108.584	113.468
6	95.058	108.96	105.202	110.838	102.572
7	92.428	96.936	97.312	95.809	96.185
8	83.410	115.347	92.428	101.821	112.341
9	86.792	95.058	92.428	93.553	102.948
10	86.792	114.595	96.185	105.202	108.584
11	90.925	109.335	98.064	108.96	113.092
12	91.676	94.306	90.549	95.058	110.462
Average	**92.928**	**106.767**	**102.447**	**105.045**	**106.423**

Table 3.12: % Dissolved of Janvia™ 50 (Local Brand)

Serial No.	% Dissolved at 5 min	% Dissolved at 10 min	% Dissolved at 15 min	% Dissolved at 20 min	% Dissolved at 30 min
1	113.844	105.958	107.081	108.584	111.214
2	100.694	105.958	104.827	108.208	115.723
3	88.670	99.567	95.809	99.942	96.936
4	91.300	91.676	99.942	98.815	95.433
5	93.555	100.318	106.705	102.572	109.355
6	99.942	102.196	104.075	101.445	117.601
7	101.821	107.081	106.705	103.699	109.711
8	104.572	104.827	111.590	110.087	109.711
9	102.572	103.324	106.329	109.335	105.578
10	97.312	108.964	111.214	112.717	111.965
11	104.872	115.347	116.474	114.220	117.225
12	99.566	111.965	120.231	116.850	114.220
Average	**99.879**	**104.762**	**107.581**	**107.204**	**109.554**

Table 3.13: % Dissolved of Siglita™ 50 (Local Brand)

Serial No.	% Dissolved at 5 min	% Dissolved at 10 min	% Dissolved at 15 min	% Dissolved at 20 min	% Dissolved at 30 min
1	86.41	96.56	99.19	102.19	109.45
2	84.66	96.56	122.86	99.19	104.07
3	77.77	95.43	111.21	105.57	101.44
4	92.05	101.06	113.46	100.69	105.20
5	98.06	100.31	99.94	96.93	103.32
6	92.80	96.56	106.32	114.59	113.09
7	98.06	101.44	100.69	105.95	107.08
8	101.44	110.46	108.58	108.95	110.46
9	103.32	103.69	117.60	115.34	113.09
10	108.95	111.96	113.09	113.46	114.97
11	105.57	108.20	108.95	109.71	112.34
12	113.84	108.58	122.86	11.96	114.34
Average	**96.99**	**102.5**	**110.39**	**107**	**109.14**

3.5.2 Difference factor for Janvia™ 50 (Local Brand)

$$f1 = \frac{[\sum \ |Rt - Tt| \ ]}{[\sum \ Rt \ ]} \times 100$$

$$= \frac{|(92.28- 99.87)| + |(106.8 -104.7)| + |(102.44 –107.58)| + |(105.045 -107.24)| + |(106.43 -109.55)|}{(92.28+ 106.8+ 102.44 +105.045 +106.43)} \times 100$$

$$= \frac{|- 6.951 + 2.005 - 5.134 - 2.159 - 3.131|}{513.61} \times 100$$

$$= \frac{15.37}{513.61} \times 100$$

$$= 2.992$$

3.5.3 Similarity factor for Janvia™ 50 (Local Brand)

$f_2 = 50 \times \log \{ 1+ (1/n) \sum t=1^n (Rt - Tt)^2]^{-0.5} \times 100 \}$

$= 50 \times \log \{1+ (1/5) (-6.951)^2 + (-5.134)^2 + (-2.159)^2 + (2.005)^2 + (-3.131)^2] \times 100\}$

$= 50 \times \log \{[1+ (1/5) (48.316+4.020+26.357+4.661+9.83]^{-0.5} \times 100\}$

$= 50 \times \log \{[1+ 1/5 (93.157)]^{-0.5} \times 100\}$

$= 50 \times \log \{[1+ 18.6314]^{-0.5} \times 100\}$

$=50 \times \log \{[19.6314]^{-0.5} \times 100\}$

$= 50 \times \log (0.22569626 \times 100)$

$=50 \times \log 22.569626$

$= 50 \times 1.353524$

$= 67.6762182$

3.5.4 Difference factor for Siglita™ 50 (Local Brand)

$$f1 = \frac{[\sum |Rt - Tt|]}{[\sum Rt]} \times 100$$

$$= \frac{|(92.28- 96.99)| + |(106.8 -102.5)| + |(102.44 –110.39)| + |(105.045 -107)| + |(106.43 -109.14)|}{(92.28+ 106.8+ 102.44 +105.045 +106.43)} \times 100$$

$$= \frac{|-4.71+4.3-7.95-1.955-2.71|}{513.61} \times 100$$

$$= \frac{13.025}{513.61} \times 100$$

$=2.536$

3.5.5 Similarity factor for Janvia™ 50 (Local Brand)

$f_2 = 50 \times \log \{ 1+ (1/n) \sum t=1^n (Rt - Tt)^2]^{-0.5} \times 100 \}$

$= 50 \times \log \{1+ (1/5) (-4.71)^2 + (4.3)^2 + (-7.95)^2 + (-1.955)^2 + (-2.71)^2] \times 100\}$

$= 50 \times \log \{[1+ (1/5) (22.184+18.49+63.202+3.822+7.344)]^{-0.5} \times 100\}$

$= 50 \times \log \{[1+ 1/5 (115.042)]^{-0.5} \times 100\}$

$= 50 \times \log \{[1+ 23.008]^{-0.5} \times 100\}$

$=50 \times \log \{[24.008]^{-0.5} \times 100\}$

$= 50 \times \log (0.208476 \times 100)$

$=50 \times \log 20.8476$

$= 50 \times 1.319056$

$= 65.69528$

CHAPTER: 4

Discussion

CHAPTER 4: Discussion

4.1 Weight Variation Test

In this research study the weight variation of Siglita™ 50 tablets had the average weight of 0.1886 gm. The % weight variation ranged from +3.833% to -3.088%. Janvia 50 tablets had the average weight of 0.2246 gm. The % weight variation ranged from +3.778% to -1.282%. All the tablets of Siglita™ 50 and Janvia 50 showed a percentage weight variation within the range of ±5% and, thus it meet the specification of weight variation mentioned in the USP and pass the quality control test. (USP, 2007)

4.2 Friability Test

In this research study the friability test of Siglita™ 50 tablets had 0.8%. The friability % of Janvia ™ 50 tablets had 0.53%. USP specifies that if friability study is performed with ten tablets, they must not lose 1% of their initial weight. All the tablets of both brands Siglita™ 50 and Janvia ™ 50 have met the USP specification and passed the friability test. (USP, 2007)

4.3 Hardness Test

In this research study, the Hardness test of Siglita™ 50 tablets had the range from 1.60 kg/cm to 2 kg/cm. For Janvia ™ 50 the range was from 2.20kg/cm to 2.75 kg/cm. The average hardness of Siglita™ 50 and Janvia ™ 50 were 1.835 kg/cm and 2.465 kg/cm respectively. USP specifies that hardness of any tablets must not be lower than 4 kg. All tablets of both brands Siglita™ 50 and Janvia™ 50 have hardness lower than 4 kg. The hardness of tablets is usually kept lower to make it easy to disintegrate and dissolve the tablet into the body. But high hardness is more preferable for because tablets require a certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packaging, and shipping. In addition, tablets should be able to withstand reasonable abuse when in the hands of the consumer, such as bouncing about in a woman's purse in a partially filled prescription bottle. Adequate tablet hardness and resistance to powdering and friability are necessary requisites for consumer acceptance. More recently, the relationship of hardness to tablet disintegration, and perhaps more significantly, to the drug dissolution release rate, has become apparent. The monitoring of the tablet hardness is especially important for drug products

that possess real or potential bioavailability problems or that are sensitive to altered dissolution release profiles as a function of the compressive force employed. (Lachman L., 1986)

4.4 Disintegration Test

In present research the test result showed the disintegration time of six tablets of Siglita™ 50 and Janvia™ 50 obtained disintegration time of 1 min 12.17 sec and 1 min 37.83 sec respectively. All the tablets Siglita™ 50 and Janvia 50 had a disintegration time that is below the acceptable range (4 mins) and have not met the specification of USP that is all tablets must be disintegrate within 30 minutes, (USP, 2007).

4.5 Dissolution Test

In comparative study on dissolution profile, for innovator brand (Januvia) and local brand Sitagliptin (Siglita™ 50) the difference factor (f_1) value was found 2.992% and similarity factor (f_2) was 67.6762%. In case of Janvia™ 50 the difference factor (f_1) value was 2.992% and similarity factor (f_2) was 67.6762%. For both local brands difference factor (f_1) values were close to 0% and similarity factor (f_2) values were greater than 50% and less than 100%. As both difference and similarity factors were within the range, so it can be said dissolution as well as bioavailability of local brands are similar to innovator brand.

CHAPTER: 5

Conclusion

CHAPTER 5: Conclusion

In world as well as Bangladesh, patients of diabetes are increasing tremendously. It has become a big concern for the people of the world. Diabetes is a disease which causes many other fatal diseases. It is in 4th position among fatal diseases which cause most of death of people. So it is necessary to arrange more research for antidiabetic drugs. Sitagliptin is a relatively new drug used for the treatment of diabetes and recently have been widely used in clinical practice. It is used in the treatment of type II diabetes It is a Dipeptidyl peptidase 4 inhibitor (DPP- 4 inhibitor) and Sitagliptin exerts it action through degradation inhibition of endogenous glucagon-like peptides (GLP-1) and glucose-dependent insulinotropic peptides (GIP) , (Solun, Marcoviciu & Dicker, 2013).

Here quality control tests of two brands of Sitagliptin (Siglita™ 50 and Janvia™ 50) were observed. The study was undergone with weight variation test, hardness test, friability test, disintegration test and dissolution test. Results of all tests were within the acceptance range except hardness test. It was below than range. As because result of friability test was within the range, there is less possibility of breaking of tablets during transport and using. So less hardness of the tablets is not a big concern for quality. But manufacturer should consider it during development of the tablets.

There are still opportunities of study for the potency of Sitagliptin tablets. There are also scopes of studying about dissolution test in other ways.

The approach of our study was to make an assessment of quality control parameters of two brands (Siglita^{TM}, Janvia^{TM}) of Sitagliptin tablets available in Bangladesh. We found a similar quality control profile between these two brands of Sitagliptin. The study reveals a promising approach to achieve appropriate quality medicine in our local market.

CHAPTER: 6

References

Chapter 5: References

Bai G., Wang Y., Armenante, (2008). "Velocity profiles and shear strain rate variability in the USP Dissolution Testing Apparatus 2 at Different Impeller Agitation Speeds, " International Journal of Pharmaceutics, 403 (1-2), Pages 1-14.

BP. (2007). British Pharmacpoeia (2010 ed., Vol. 4). London, United kingdom: The Stationery Office on behalf of the Medicines and Healthcare Products.

Dinesh K., Badyal, Jasleen K., (1999). 'Sitagliptin: a New Class of Oral Drug for Type 2 Diabetes', JK SCIENCE, P: 97-99.

Drucker & Nauck, (2006). The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 368:1696–1705.

Dr Alwan K., (1994). 'Management of Diabetes MellitUuSs Standards of Care and Clinical Practice Guidelines', World Health Organization for Eastern Meditarranean, pp. 68-75.

Gubbi R. & Jarag R., (2010). "Formulation and characterization of sitagliptin tablet". Asian Journal of Pharmaceutical Sciences. 5 (2), 320-321.

Jane K., (2001). 'All about Diabetes', Medical News Today, vol 2, July, pp. 121-127.

Jane K., (2001). 'All about Diabetes', Medical News Today, vol 2, July, pp. 121-127

Kortejärvi H, Malkki J, (2007). "Level A In Vitro-In Vivo Correlation (IVIVC) Model with Bayesian Approach to Formulation Series". J Pharm Sci. 95 (7), Pages 1595-1605.

Mohapatra A., Parikh K., & Gohel C., (2008). Formulation, Development and Evaluation of Patient Friendly Dosage Forms of Atorvastatin, Part-I: Orally Disintegrating Tablets. Asian Journal of Pharmaceutics, 2(3), 167-171.

Muller V., (2004). 'Treatment of diabetes', American Diabetes Association, Diadetes care, pp. 45-56

Nachaegari S. & Bansa, (2004). Coprocessed Excipients for Solid Dosage Forms. Pharmaceutical Technology, 34 (4), 52-64.

Pfizer, (2012). Product Monograph: Prescribing Information. Website: http://www.pfizer.ca/en/our_products/products/monograph/219

Pfizer, (2009). Lipitor: Prescribing Information. Website: http://www.pfizer.com/ files/products/ uspi_lipitor.pdf

Salam W., Lupuleasa, D., (2009). Enhancement of solubility and dissolution rate of different forms of Atorvastatin calcium in direct compression tablet formulas . Farmacia. 52 (3), 144-148.

Salam W., Lupuleasa, D., (2009). Enhancement of solubility and dissolution rate of different forms of Atorvastatin calcium in direct compression tablet formulas . Farmacia. 52 (3), 144-148.

Sanjeev R., Sharma A., (2012). Preparation, Health Professional Information of Atorvastatin, Current Pharma Research ISSN: 1240-3642 CPR 2(4), 2012, 120-130.

Stulc T. & Sedo A., (2010). Inhibition of multifunctional dipeptidyl peptidase-IV: is there a risk of oncological and immunological adverse effects? Diabetes Res Clin Pract 88:125–131.

UNC, (2012). Evaluation of Tablets. (UNC Eshelman School of Pharmacy) Retrieved September 12, 2013, from A Website of Integrated Pharmaceutical Care Laboratory at UNC Eshelman School of Pharmacy: http://pharmlabs.unc.edu/labs/tablets/evaluation.htm

USP. (2007). United States Pharmacopoeia, 23th edition, Page: 579-583.

White R., (2008). Dipeptidyl Peptidase-IV Inhibitors: Pharmacological Profile and Clinical Use. American diabetes association, Clinical Diabetes, 26: 53-57.

World Health Organization. Guidelines on the use of international nonproprietary names (INNs) for pharmaceutical substances. WHO/PHARMS/NOM 1570 (1997).

World Health Organization. The graphic representation of chemical formulae in the publication of international nonproprietary names (INN) for pharmaceutical substances. WHO/PHARM/9.579 (1995).

World Health Organization. The use of common stems in the selection of international nonproprietary names for pharmaceutical substances. WHO/EDM/ QSM/2003.2 (2002).

Yan S., Marguet D., Dobers J, Reutter W., Fan H., (2003). Deficiency of CD26 results in a change of cytokine and immunoglobulin secretion after stimulation by pokeweed mitogen. Eur J Immunol 33:1519–1527.

Young D., Devane J. and Butler J., (1997). In Vitro-In Vivo Correlations. New York: Plenum press.