Assessment of the Quality Control Parameters of Fixocard 50® & Amloten 50® Tablets Available in Bangladesh

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

Submitted By

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Declaration By The Candidate

I, Tarikul Islam Pavel, hereby declare that this dissertation, entitled "Assessment of the Quality Control Parameters of Fixocard 50® & Amloten 50® Tablets Available in Bangladesh" submitted to the Department of Pharmacy, East West University, in the partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Honors) is a genuine & authentic research work carried out by me. The contents of this dissertation, in full or in parts, have not been submitted to any other institute or University for the award of any degree or Diploma of Fellowship.

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This is to certify that the dissertation, entitled "Assessment of the Quality Control Parameters of Fixocard 50® & Amloten 50® Tablets Available in Bangladesh" is a bona fide research work done by Tarikul Islam Pavel (ID: 2011-3-70-028), in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy under my supervision and guidance.

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Dedication

This Research Paper Is Dedicated to My Beloved Parents, Who Are My Biggest Inspirations….

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Abstract

Hypertension is associated with increased risk of cardiovascular diseases. Having hypertension for short amounts of time is normal. However, when blood pressure stays high for most of the time, it can cause serious health problems. There are lots of classes of drugs are available for treatment including single and combination therapy. The rationale for combination therapy relates to the concept that antihypertensive efficacy may be enhanced when two classes of agents are combined as well as enhances tolerability, antagonize some of the adverse effects of the second drug, simplifies the treatment regimen, prevents treatment failures that might result from missed doses. The major objective of this study was to perform a qualitative evaluation of two commercially available brands (Fixocard 50® and Amloten 50®) of combined Atenolol (50mg) and Amlodipine (5mg) tablets marketed by local pharmaceutical companies in Bangladesh. All four batches of products met the quality specification specified in USP or BP in the weight variation, thickness, disintegration and dissolution. Two batches of products didn't meet the specification of dissolution based on single tablets but based on average dissolution those tablets met the dissolution specification. Only one batch out of total batches didn't meet the minimum specification of hardness test that should be at least 4 kg. Disqualification of this hardness test may results potential loss of products as they are not capable to overcome mechanical shock & pressure during manufacture, transport & handling process. Due to technical issue friability study couldn't carry out. Conducting further study is necessary regarding the quality control parameters as these products are now becoming a potential choice of drugs for hypertension control.

Keywords: Quality control, hypertension, Atenolol, Amlodipine, weight variation, disintegration, dissolution, potency.

CHAPTER 1: INTRODUCTION

Introduction

1.1 Overview

Obtaining quality and maintaining quality products is important to make certain that each medicine reaching a patient is safe, effective, and of standard quality. Globalization of the pharmaceutical industry has the potential to rapidly spread poor-quality medicines worldwide before adequate detection and intervention are possible. There are two main categories of poor-quality medicines: substandard and counterfeit. Substandard products arise as a result of lack of expertise, poor manufacturing practices, or insufficient infrastructure, whereas counterfeits are the 'products' of criminals. Counterfeits may contain no active ingredient, incorrect ingredients, or toxins. The amount of active ingredient does not provide sufficient information to accurately determine if a medicine is counterfeit; inspection of the packaging is also required as mislabelling is a key part of the definition and counterfeits with fake packaging but the correct amount of active ingredient have been described (Caudron *et al*, 2008).

Hypertension is recognized as a major contributor to the disease burden globally. Hypertension and its complications account for an estimated 9.4 million deaths every year. It has become a significant problem in many developing countries undergoing epidemiological transition. A meta-analysis covering studies up to 1994 reported a prevalence of 11.3% in the adult population of Bangladesh. Most recent studies showed that approximately 20% of adult and 40–65% of elderly people suffer from Hypertension. Bangladesh Non-communicable Disease (NCD) Risk Factor Survey 2010 was carried out by Bangladesh Society of Medicine in collaboration with Directorate General of Health Services and World Health Organization from November 2009 to April 2010 by using WHOSTEP wise Surveillance approach in adults aged < 25 years. According to the survey, prevalence of HTN is 17.9% in general, 18.5% in men and 17.3% in women (Moniruzzaman *et al*, 2013).

Considering the vast scale of the global pharmaceutical industry and the incidence of potentially fatal diseases, any amount of poor-quality medicine is unacceptable because it increases morbidity and mortality. Some substandard drugs contain more active ingredient than stated and this may increase the prevalence of adverse effects (Taylor *et al*, 2001).

Thus, strengthening drug regulatory authorities (DRAs), improving quality of production, and facilitating the availability of good-quality anti-hypertensive are likely to be key factors in improving drug quality. There is an urgent need for data of sufficient sample size with random sampling design to reliably estimate the prevalence of poor-quality medicines (Newton *et al*, 2010).

Quality control is an essential operation of the pharmaceutical industry. Drugs must be marketed as safe and therapeutically active formulations whose performance is consistent and predictable. New and better medicinal agents are being produced at an accelerated rate. At the same time more exacting and sophisticated analytical methods are being developed for their evaluation. So, Quality control methods of assessment are useful to monitor quality characteristics of various marketed brands and product consistency of batch to batch drug release. In addition, drugs that having three or more generic brand must be assessed and monitored to ensure its interchangeability with innovator brand (Jim Heaphy, 2007).

The latest National Institute for Health and Clinical Excellence guideline advocates a calcium-channel blocker as step 1 antihypertensive treatment to people aged > 55 years and an ACE inhibitor or a low-cost angiotensin-II receptor blocker for the younger people. Calcium-channel blockers and beta-blockers have been found to be the most commonly prescribed antihypertensive drugs in Bangladesh. So, a product that is a combination of these blockers can be very helpful not only for the patient but also for treating the disease. Now-a-days, a product which is a combination of atenolol (beta-blocker) & amlodipine (calcium channel blocker) are widely prescribed for most of the hypertensive patient. It has the advantage of maintaining the blood pressure by functioning in two mechanisms. Thus it becomes a choice of drug for most of the physicians in recent times. This attracts most of the pharmaceutical company and now there are several brands available in Bangladesh pharma market (Monwarul *et al*, 2012).

1.2 Blood Pressure

Blood pressure is the force of blood pushing against the walls of the arteries as the heart pumps blood. High blood pressure, sometimes called hypertension, happens when this force is too high. Health care workers check blood pressure readings the same way for children, teens, and adults. They use a gauge, stethoscope or electronic sensor, and a blood pressure cuff. (NHLBI, 2012)

Blood pressure (BP) is the pressure exerted by circulating blood upon the walls of blood vessels.

◎ Blood Pressure = Cardiac Output x Peripheral Vascular Resistance (PVR)

◎ Cardiac Output = Stroke Volume × Heart rate

Measuring Blood Pressure

With this following way, blood pressure is measured:

- **Systolic Pressure:** blood pressure when the heart beats while pumping blood
- **Diastolic Pressure:** blood pressure when the heart is at rest between beats

Health care workers write blood pressure numbers with the systolic number above the diastolic number.

1.2.1 Normal Blood Pressure

Normal blood pressure for adults is defined as a systolic pressure below 120 mmHg and a diastolic pressure below 80 mmHg. It is normal for blood pressures to change when you sleep, wake up, or are excited or nervous. When you are active, it is normal for your blood pressure to increase. However, once the activity stops, your blood pressure returns to your normal baseline range.

Blood pressure normally rises with age and body size. Newborn babies often have very low blood pressure numbers that are considered normal for babies, while older teens have numbers similar to adults.

1.2.2 Classification of Blood Pressure

Abnormal increases in blood pressure are defined as having blood pressures higher than 120/80 mmHg. The following table outlines and defines high blood pressure severity levels.

Table 1.1: Classification of High Blood Pressure in Adults

Stages	Systolic		Diastolic
Prehypertension	120–139	And	80–89
High blood pressure Stage 1	140–159	And	90–99
High blood pressure Stage 2	160 or higher	And	100 or higher

(Lippincott *et al*, 2009: p-225-226)

The ranges in the table are blood pressure guides for adults who do not have any short-term serious illnesses. People with diabetes or chronic kidney disease should keep their blood pressure below 130/80 mmHg.

Although blood pressure increases seen in prehypertension are less than those used to diagnose high blood pressure, prehypertension can progress to high blood pressure and should be taken seriously. Over time, consistently high blood pressure weakens and damages your blood vessels, which can lead to complications (Lewington *et al*, 2002).

1.2.3 Types of High Blood Pressure

There are two main types of high blood pressure: primary and secondary high blood pressure.

Primary High Blood Pressure

Primary, or essential, high blood pressure is the most common type of high blood pressure. This type of high blood pressure tends to develop over years as a person ages.

Secondary High Blood Pressure

Secondary high blood pressure is caused by another medical condition or use of certain medicines. This type usually resolves after the cause is treated or removed.

1.3 Hypertension

Hypertension or high blood pressure, sometimes called arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated. Blood pressure is summarized by two measurements, systolic and diastolic, which depend on whether the heart muscle is contracting (systole) or relaxed between beats (diastole). This equals the maximum and minimum pressure, respectively. (Wikipedia, 2016)

High blood pressure is a common disease in which blood flows through blood vessels (arteries) at higher than normal pressures.

1.3.1 Symptoms of Hypertension

There is no guarantee that a person with hypertension will present any symptoms of the condition. About 33% of people actually do not know that they have high blood pressure, and this ignorance can last for years. For this reason, it is advisable to undergo periodic blood pressure screenings even when no symptoms are present. Extremely high blood pressure may lead to some symptoms, however, and these include:

- Severe headaches
- Fatigue or confusion
- Dizziness
- Nausea
- Problems with vision
- Chest pains
- Breathing problems
- Irregular heartbeat
- Blood in the urine. (Medicalnewstoday, 2016)

1.3.2 Causes of hypertension

1.3.2.1 Primary hypertension

Primary (essential) hypertension is the most common form of hypertension, accounting for 90–95% of all cases of hypertension.

- In almost all contemporary societies, blood pressure rises with aging and the risk of becoming hypertensive in later life is considerable. Hypertension results from a complex interaction of genes and environmental factors
- Insulin resistance, which is common in obesity and is a component of syndrome X (or the metabolic syndrome), is also thought to contribute to hypertension.
- Recent studies have also implicated events in early life (for example low birth weight, maternal smoking and lack of breast feeding) as risk factors for adult essential hypertension,
- Hypertension has also been associated with depression (Meng *et al*, 2012).

1.3.2.2 Secondary hypertension

Secondary hypertension results from an identifiable cause.

- Renal disease is the most common secondary cause of hypertension.
- Hypertension can also be caused by endocrine conditions, such as Cushing's syndrome, hyperthyroidism, hypothyroidism, Conn's syndrome or hyper aldosteronism, hyperparathyroidism.
- Other causes of secondary hypertension include obesity, sleep apnea, pregnancy, coarctation of the aorta, excessive liquorice consumption and certain prescription medicines, herbal remedies and illegal drugs (Grossman *et al*, 2012)

1.3.3 Treatment Strategies of Hypertension

The goal of antihypertensive therapy is to reduce cardiovascular adrenal morbidity and mortality. The relationship between blood pressure and the risk of cardiovascular events is continuous and thus lowering of even moderately elevated blood pressure significantly reduces cardiovascular disease. (Lippincott *et al*, 2009).

Prehypertension: Recognizes this relationship and emphasizes the need for decreasing blood pressure in the general population by education and the adoption of blood pressure lowering behaviors. For most patients, the blood pressure goal when treating hypertension is a systolic blood pressure of less than 140 mm Hg and a diastolic blood pressure of less than 90 mmHg (Lippincott *et al*, 2009).

Mild hypertension: Sometimes can be controlled with mono therapy, but most patients require more than one drug to achieve blood pressure control. Current recommendations are to initiate therapy with thiazide diuretic, ACE inhibitor, angiotensin receptor blocker (ARB), or calcium channel blocker. If blood pressure is inadequately controlled, a second drug should be added, with the selection based on minimizing the adverse effects of the combined regimen and achieving goal blood pressure. (Lippincott *et al*, 2009).

Stage II Patients with systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 100 mm Hg (or systolic blood pressure greater than 20 mm Hg above goal or diastolic blood pressure more than 10 mm Hg above goal) should be started on two antihypertensive simultaneously (Lippincott *et al*, 2009).

1.3.4 Management of Hypertension

1.3.4.1 Non-pharmacologic Treatment

Several lifestyle interventions have been shown to reduce blood pressure. Apart from contributing to the treatment of hypertension, these strategies are beneficial in managing most of the other cardiovascular risk factors. In patients with hypertension that is no more severe than stage 1 and is not associated with evidence of abnormal cardiovascular findings or other cardiovascular risks, 6 to 12 months of lifestyle changes can be attempted in the hope that they may be sufficiently effective to make it unnecessary to use medicines. However, it may be prudent to start treatment with drugs sooner if it is clear that the blood pressure is not responding to the lifestyle methods or if other risk factors appear. Also, in practice settings where patients have logistical difficulties in making regular clinic visits, it might be most practical to start drug therapy early. In genera l, lifestyle changes should be regarded as a complement to drug therapy rather than an alternative.

I. Weight loss: In patients who are overweight or obese, weight loss is helpful in treating hypertension, diabetes, and lipid disorders. Substituting fresh fruits and vegetable s for more traditional diets may have benefits beyond weigh t loss. Unfortunately, these diets can be

relatively expensive and inconvenient for patients, and can work only if patients are provided with a strong support system. Even modest weight loss can be helpful.

II. Salt reduction: High -salt diets are common in many communities. Reduction of salt intake is recommended because it can reduce blood pressure and decrease the need for medications in patients who are "salt sensitive," which may be a fairly common finding in black communities. Often, patients are unaware that there is a large amount of salt in foods such as bread, canned goods, fast foods, pickles, soups, and processed meats. This intake can be difficult to change because salty foods are often part of the traditional diets found in many cultures. A related problem is that many people eat diets that are low in potassium, and they should be taught about available sources of dietary potassium.

III. Exercise: Regular aerobic exercise can help reduce blood pressure, but opportunities to follow a structured exercise regimen are often limited. Still, patients should be encouraged to walk, use bicycles, climb stairs, and pursue means of integrating physical activity into their daily routines.

IV. Alcohol consumption: Up to 2 drinks a day can be helpful in protecting against cardiovascular events, but greater amounts of alcohol can raise blood pressure and should therefore be discouraged. In women, alcohol should be limited to 1 drink a day.

V. Cigarette smoking: Stopping smoking will not reduce blood pressure, but since smoking by itself is such a major cardiovascular risk factor, patients must be strongly urged to discontinue this habit. Patients should be warned that stopping smoking may be associated with a modest increase in body weight.

1.3.4.1 Drug used to treat Hypertension

I. Starting treatment: Treatment with drugs should be started in patients with blood pressures >140/90 mm Hg in whom life style treatments have not been effective.

In patients with stage 2 hypertension (blood pressure ≥ 160/10 0 mm Hg), drug treatment should be started immediately after diagnosis, usually with a 2-drug combination, without waiting to see

the effect s of lifestyle changes. Drug treatment can also be started immediately in all hypertensive patients in whom, for logistical or other practical reasons, the practitioner believes it is necessary to achieve more rapid control of blood pressure. The presence of other cardiovascular risk fact ors should also accelerate the start of hypertension treatment.

II. For patients older than 80 years, the suggested threshold for starting treatment is at levels ≥ 150/90 mm Hg. Thus, the target of treatment should be <140/90 mm Hg for most patients but <150/90 mm Hg for older patients (unless these patients have chronic kidney disease or diabetes, when <140/90 mm Hg can be considered).

III. The treatment regimen:

- Most patients will require more than one drug to achieve control of their blood pressure.
- In genera l, increase the dose of drugs or add new drugs at approximately 2- to 3-week interval s. This frequency can be faster or slower depending on the judgment of the practitioner. In genera l, the initial doses of drugs chosen should be at least half of the maxi mum dose so that only one dose adjustment is required thereafter. It is generally anticipated that most patients should reach an effective treatment regimen, whether 1, 2, or 3 drugs, within 6 to 8 weeks.
- If the untreated blood pressure is at least 20/10 mm Hg above the target blood pressure, consider starting treatment immediately with 2 drugs.

IV. Choice of Drugs:

- This should be influenced by the age, ethnicity/race, and other clinical characteristic s of the patient.
- The choice of drugs will also be influenced by other conditions (eg, diabetes and coronary disease) associated with the hypertension. Pregnancy also influences drug choice.
- Long-acting drugs that need to be taken only once daily are preferred to short-acting drugs that require multiple doses because patients are more likely to follow a simple treatment regimen. For the same reason, when more than one drug is prescribed, the use of a combination product with two appropriate medications in a single tablet can simplify

treatment for patients, although these products can sometimes be more expensive than individual drugs. Once –daily drugs can be taken at any time during the day, most usually either in the morning or in the evening before sleep. If multiple drugs are needed, it is possible to divide them between the morning and the evening.

- The choice of drugs will further be influenced by their availability and afford ability. In many cases, it is necessary to use whichever drugs have been provided by government or other agencies. For this reason, we will only make recommendations for drug classes, not individual agents, recognizing that there may be a limited select ion of drugs that can be prescribed by a practitioner. Even among generic drugs there can be a wide variation in cost.

1.3.5 Classification of antihypertensive drug and their mechanism with example

Class	Mechanism	Drug
Diuretics	Diuretics help the body get rid of excess sodium (salt) and water and help control blood pressure. They are often used in combination with additional prescription therapies.	Chlorothiazide Spironolactone Triamterene Chlorthalidone Furosemide Hydrochlorothiazide
Beta-blockers	Beta-blockers reduce the heart rate, the heart's workload and the heart's output of blood, which lowers blood pressure.	Metoprolol Carvedilol Labetalol Propranolol Timolol
ACE inhibitors	ACE stands for Angiotensin Converting Enzyme. ACE inhibitors help the body produce less angiotensin, which helps the blood vessels relax and open up, which, in turn, lowers blood pressure.	Captopril Enalapril Fosinopril Lisinopril Quinapril Ramipril

Angiotensin II Receptor Blockers	ARBs block the receptors so the angiotensin fails to constrict the blood vessel. This means blood vessels stay open and blood pressure is reduced.	Irbesartan Losartan Olmesartan Telmisartan Valsartan
Calcium channel blockers	This drug prevents calcium from entering the smooth muscle cells of the heart and arteries. When calcium enters these cells, it causes a stronger and harder contraction, so by decreasing the calcium, the hearts' contraction is not as forceful. Calcium channel blockers relax and open up narrowed blood vessels, reduce heart rate and lower blood pressure.	Nifedipine Nisoldipine Verapamil Amlodipine Diltiazem Felodipine Isradipine Nicardipine
Vasodilators	Blood vessel dilators, or vasodilators, can cause the muscle in the walls of the blood vessels (especially the arterioles) to relax, allowing the vessel to dilate (widen). This allows blood to flow through better.	Hydralazine Minoxidil

1.3.6 Drug Combination

Recent clinical trials have provided data on mortality and morbidity outcomes with respect to different combination therapies for hypertension. The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) was a prospective, randomized, open-label, blinded end point trial in which 19,257 hypertensive adults aged 40 to 79 years with ≥3 other cardiovascular risk factors received either the calcium channel blocker (CCB) amlodipine plus the angiotensin-converting enzyme (ACE) inhibitor perindopril if necessary or the β-blocker atenolol with the thiazide diuretic bendroflumethiazide added if necessary to lower BP. (ASCOT-BPLA incorporated a 2 × 2 factorial design in which patients with moderately elevated

cholesterol received placebo or atorvastatin; the lipid-lowering component was discontinued early because of the significant benefit of atorvastatin.)

The BP component of ASCOT-BPLA was stopped prematurely after 5.5 years of median follow-up because there was significantly less risk of secondary end points, including nonfatal MI, total cardiovascular end points, all-cause mortality, stroke, and heart failure in patients treated with amlodipine/perindopril compared with those treated with atenolol/bendroflumethiazide. There was also a nonsignificant trend toward reduced risk for the primary end point (nonfatal and fatal MI) favoring amlodipine/perindopril treatment. A subsequent analysis, adjusting for mean BP level, demonstrated reductions of 13% and 17% respectively, in risks for the primary end point and stroke.

Another major trial of combination antihypertensive therapy is under way, with cardiovascular mortality and morbidity as the primary outcome. The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET).is designed to test whether the angiotensin II receptor blocker (ARB) Telmisartan, the ACE inhibitor Ramipril, or the combination confers cardioprotection independent of BP lowering in high-risk patients whose BP is well-controlled. ONTARGET has enrolled 25,620 high-risk patients (mean age, 66.9 years) with either a history of cardiovascular disease (coronary artery disease, peripheral arterial disease, or cerebrovascular disease) or diabetes with documented end-organ damage. The primary end point of ONTARGET is a composite of cardiovascular death, nonfatal MI, stroke, or hospitalization for heart failure. Patient follow-up is planned for 3.5 to 5.5 years. At randomization, 68.3% of the study population had hypertension, and mean BP was 134/77 mm Hg. Results are anticipated in 2008 (Bauman *et al*, 2013).

1.4 Amlodipine

Amlodipine is used alone or in combination with other medications to treat high blood pressure and chest pain (angina). Amlodipine is in a class of medications called calcium channel blockers. It lowers blood pressure by relaxing the blood vessels so the heart does not have to pump as hard. It controls chest pain by increasing the supply of blood to the heart. If taken regularly, amlodipine controls chest pain, but it does not stop chest pain once it starts (NLM, 2014).

1.4.1 Invention

Amlodipine was discovered by a research team lead by Simon Campbell and developed by the Pfizer Corporation. Amlodipine was introduced in the US in 1992. Just two years after its discovery in 1994 the sale of amlodipine achieved a plateau of 2,000,000 new prescriptions per year (Richard F. Davies *et al*, 2005). The amlodipine has the longest half-life and the greatest bioavailability among all chemical abstract service for chemical information (CAs).This profile of amlodipine makes it suitable for convenient once-daily administration (NDA, 2007).

1.4.2 Chemistry

- Molecular Formula: $C_{20}H_{25}ClN_2O_5$
- Molecular Weight: 408.876 Da
- IUPAC Name: 3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate
- Protein binding: 97.5%
- Metabolism: Hepatic

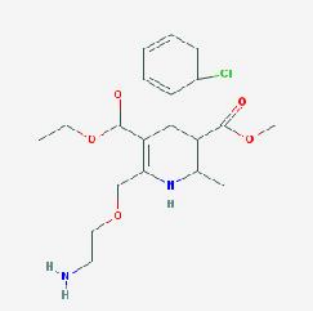

Fig 1.1: Molecular Structure of Amlodipine

1.4.3 Mechanism of Action of Amlodipine

Inhibition of the influx of calcium through slow channels in the vascular smooth muscles and myocardial tissue during depolarization. This results in systemic and coronary artery vasodilation, decreased myocardial contractility, and sinoatrial (SA) and atrioventricular (AV) nodal depression.

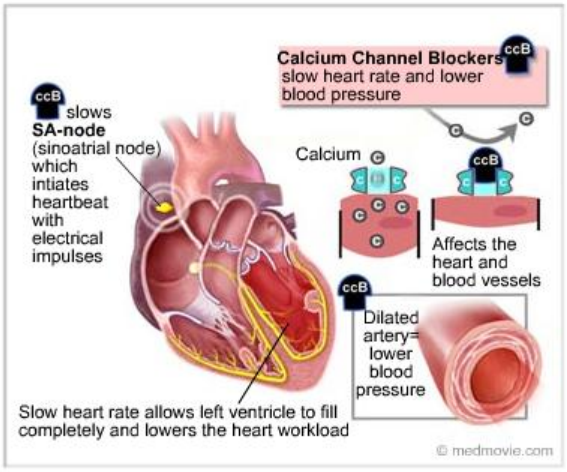

Fig 1.2: Mechanism of Action of Amlodipine

1.5 Atenolol

Atenolol is a selective β1 receptor antagonist (2^{nd} generation), a drug belonging to the group of beta blockers (sometimes written β-blockers), a class of drugs used primarily in cardiovascular diseases. Introduced in 1976, atenolol was developed as a replacement for propranolol in the treatment of hypertension. It works by slowing down the heart and reducing its workload. Unlike propranolol, atenolol does not pass through the blood–brain barrier thus avoiding various central nervous system side effects (Agon *et al*, 1991).

1.5.1 Invention

Atenolol was discovered by Imperical chemaical industries (ICI) in 1976, whilst searching for a specific Beta-1 cardioselective adrenoreceptor blocking agent. Though ICI's research was invaluable, atenolol may be seen as a drug evolved from the series of research being conducted into beta receptors during the late nineteen fifties. The first development of a chemical that acted to inhibit beta receptors was discovered by Slater and co-workers at Lilly in 1958. However the compound 3, 4-dichloro isoproterenol only acted as a partial agonist that produced marked stimulation of cardiac beta receptors before inhibition. These inferences obviously contradicted the whole objective of their research, the milestone in the treatment of hypertension and angina came from a Scottish pharmacologist, Sir James Whyte Black (1924) (Ntlworld, 2004).

Atenolol soon followed in 1976, becoming the third best-selling drug in the world. Despite many companies having introduced the drug commercially, Atenolol began as the research molecule of ICI pharmaceuticals and is one of its major success stories till this day (Ntlworld, 2004).

1.5.2 Chemistry

- Molecular Formula: $C_{14}H_{22}N_2O_3$
- Molecular Weight: 266.3361 Da
- IUPAC Name: 2-(4-{2-hydroxy-3-[(propan-2-yl)amino]propoxy}phenyl)acetamide
- Protein binding: 6-16%
- Metabolism: Hepatic

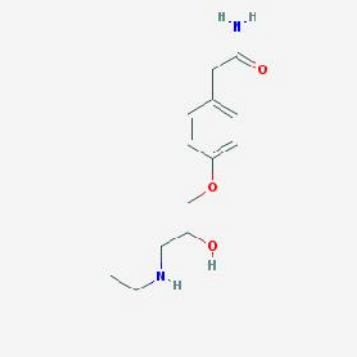

Fig 1.3: Molecular Structure of Atenolol

1.5.3 Mechanism of Action of Atenolol

Atenolol competes with sympathomimetic neurotransmitters such as catecholamines for binding at β1 adrenergic receptors in the heart and vascular smooth muscle, inhibiting sympathetic stimulation. This results in a reduction in resting heart rate, cardiac output, systolic and diastolic blood pressure, and reflex orthostatic hypotension. Higher doses of atenolol also competitively block β2 adrenergic responses in the bronchial and vascular smooth muscles. (Lippincott *et al*, 2011)

Beta-blockers bind to beta-adrenoceptors located in cardiac nodal tissue, the conducting system, and contracting myocytes. The heart has both β1 and β2 adrenoceptors, although the predominant receptor type in number and function is β1. These receptors primarily bind norepinephrine that is released from sympathetic adrenergic nerves. Additionally, they bind norepinephrine and epinephrine that circulate in the blood. Beta-blockers prevent the normal ligand (norepinephrine or epinephrine) from binding to the beta-adrenoceptor by competing for the binding site.

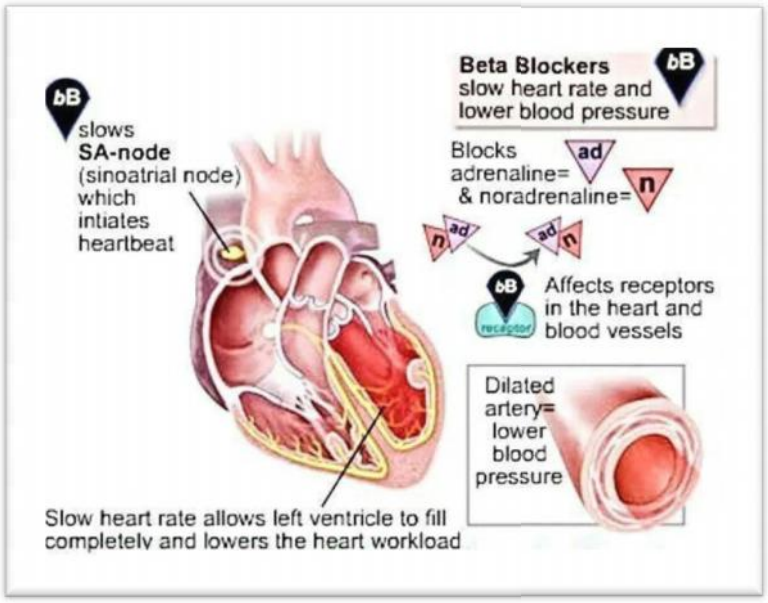

Figure 1.4: Atenolol (beta blocker) mechanism (Lippincott *et al*, 2011)

1.6 Amlodipine and Atenolol Combination

Fixed-dose combination of antihypertensive drugs can simplify dosing regimens, improve compliance, improve hypertension control, decrease dose-dependent side effects and reduce cost as the first-line treatment of hypertension (Prisant, 2002). These potential advantages make it recommendable for the combination antihypertensive therapy to be used as initial treatment, particularly in patients with target-organ damage or more severe initial hypertension (Moser and

Black, 1998). Calcium antagonists are vasodilatory and tend to increase plasma renin, therefore combination with a β-blocker is theoretically sound. Amlodipine, with its intrinsically long half-life alone or together with β-blocker, is likely to produce superior ischaemia reduction in clinical practice when patients frequently forget to take medication or take doses irregularly (Deanfield *et al*., 2002). Another study found that adding amlodipine to atenolol produced a significant reduction in blood pressure when compared with placebo in patients whose blood pressure was not controlled by atenolol alone (Mettimano *et al*., 2000). The reduction of side-effects, obtained by adding a dihydropyridine derivate to a β-blocker, confirms the effectiveness of this combination (Mettimano *et al*., 2000). It is clearly demonstrated that the combination of atenolol and amlodipine is synergistic in lowering and stabilizing BP and this synergism is highest when the dose proportion of the two drugs is 10: 1 (Li-Ping *et al*., 2005).

1.6.1 Pharmacokinetics of atenolol and amlodipine

Terms	Amlodipine	Atenolol
Absorption	Plasma levels peak 6-12 hr after oral admin. Absolute bioavailability is estimated to be 64-90%	Bioavailability: 50–60% (oral) Onset: 1 hour following oral administration. Within 5 minutes following IV administration. Duration: At least 24 hours following oral administration. About 12 hours following IV administration.
Distribution	93% bound to plasma proteins	Extent: Well distributed into most tissues and fluids except brain and CSF. Readily crosses the placenta, has been detected in cord blood. Plasma Protein Binding: Approximately 6–16%.
Elimination	90% metabolites hepatically. 60% of the metabolites are removed in the urine; elimination from the plasma is biphasic with terminal half-life of about 30-50 hr.	Metabolism: Little or no hepatic metabolism. 40–50% excreted unchanged in urine following oral administration. Half-life: 6–7 hours.

1.6.2 Dosage and Administration

Oral

Indication: Chronic stable angina, Hypertension

Adult: Per tablet contains atenolol 25 or 50 mg and amlodipine (as besylate) 5 mg: 1 tab once daily, may increase to 2 tablets daily if needed.

Elderly: Per tablet contains atenolol 25 mg and amlodipine (besylate) 5 mg: Initiate with 1 tablet daily.

Renal impairment: Per tablet contains atenolol 25 mg and amlodipine (besylate) 5 mg: Initiate with 1 tablet daily. (Drugsupdate, 2016)

1.6.3 Uses of combination of atenolol and amlodipine

Patients with

- Post MI
- Essential hypertension
- Angina pectoris & hypertension as co-existing diseases
- Refractory angina pectoris where nitrate therapy has failed.

1.6.4 Side Effects of combination of atenolol and amlodipine

❖ Drowsiness	❖ Dizziness
❖ Bradycardia	❖ Dyspnoea
❖ Chest pain	❖ Breathlessness
❖ Palpitations	❖ Dyspepsia
❖ Headache	❖ Fatigue
❖ Hypotension	❖ Cold Extremities
❖ Flushing	❖ Muscle Cramps
❖ Oedema	❖ Hypersensitivity Reactions

1.6.5 Precautions of combination of atenolol and amlodipine

Over dosage may cause hypotension and less commonly, congestive cardiac failure. Unabsorbed drug may be removed by gastric lavage or use of activated charcoal. Symptomatic treatment may be administered (Drugsupdate, 2016).

Excessive fall of BP may occur in elderly patients. Caution in patients with chronic obstructive pulmonary disease (COPD), thyrotoxicosis, congestive failure, hepatic & renal impairment. Caution in diabetic patients as beta-blockers may mask tachycardia occurring with hypoglycemia. Withdrawal should be gradual. Safety and efficacy have not been established in children. (Drugsupdate, 2016)

1.6.6 Contraindications

- Cardiogenic shock
- Overt congestive failure
- Poor left ventricular function
- Pregnancy
- Lactation
- Hypotension
- Sinus bradycardia
- Second & third degrees of heart block
- Hypersensitivity (Drugsupdate, 2016)

1.6.7 Drug Interactions

Additive effect when used with catecholamine depleting drugs; monitor for hypotension and/or marked bradycardia. If used with clonidine, clonidine withdrawal should occur a few days after withdrawal of the beta-blocker to prevent rebound hypertension, if replacing clonidine by beta-blocker beta-blocker should be introduced only after clonidine administration has stopped for several days. Concurrent use with prostaglandin synthase inhibiting drugs (e.g. indomethacin) may reduce the hypotensive effects of beta-blockers (Drugsupdate, 2016).

1.7 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 customers' need and expectation. 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). The quality, for a product or service, has two features, both of which together make for an appropriate definition of the term. The first relates to the features and attributes of the product or service. The second feature concerns the absence of deficiencies in the product (Mazumder *et al*., 2011).

1.8 Quality Control

The term quality control refers to the sum of all procedures undertaken to ensure the identity and purity of a particular pharmaceutical. Such procedures may range from the performance of simple chemical experiments which determine the identity and screening for the presence of particular pharmaceutical substance, to more complicated requirements of pharmacopoeial monographs. Activities extend to the area of quality control laboratories (good laboratory management practices, models, e.g. for certificate of analysis and lists of laboratory equipment, and an external assessment scheme (WHO, 2016).

The term quality control comprises of two words quality and control. Control is a universal regulatory process. The process through which we establish and meet standards is called Quality 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 (Lachman, 2008). 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. 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 and 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). There are eight dimensions of quality. They are critically important for organizational success. (Mazumder *et al*., 2011)

They are:

1. Performance: Primary operating characteristics of product.

2. Features: Additions to a product basic functioning features.

3. Reliability: Probability of not malfunctioning during specified period.

4. Conformance: The degree to which a products design and operating characteristics meet established criteria.

5. Durability: A measure of product life.

6. Serviceability: The speed and ease of repair.

7. Aesthetics: Looks, feel, tastes and smells of a product.

8. Perceived quality: As seen by a customer (Mazumder *et al*., 2011).

1.9 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 (Mazumder *et al*., 2011).

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 *et al.*, 2008).

1.10 Quality Assurance

Design, development and implementation of quality assurance are 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 (Mazumder *et al*., 2011).

1.11 Importance of Quality

Quality is important in pharmaceutical industry due to the following reasons:

- Production of Therapeutically Active & Safe Drugs

For a drug to be safe and therapeutically active it is essential that it meets its specified quality. A drug deviated from its quality can be therapeutically inactive and toxic. Therefore, for during the production of drugs utmost care should be taken care of the quality for patient safety. (WHO, 2007)

- Prosperity and Survival as a Competitive Industry

Quality is the primary objective for prosperity and survival of a pharmaceutical industry. Quality pharmaceutical products are prerequisite to customer satisfaction and subsequent profit which is important for the industry to prosper. (Quality assurance of Pharmaceuticals, 2007).

- To Gain Maximum Profit

Quality product is a tool for gaining profit. Products of poor quality yields negative customer feedback and as a result profitability decreases. On the contrary, high quality products yield positive customer feedback. Satisfied customers results in increased profitability for the company. (Quality assurance of pharmaceuticals, 2007)

- Marketing Tool

Quality of the products can also serve as a strong marketing tool for the pharmaceutical industry. (Quality assurance of pharmaceuticals, 2007)

1.12 Quality control parameters of solid dosage form

Most preferable dosage form in pharmaceutical, to clinician and physician and most importantly to patients is tablet. Tablets give good patient compliance. The physiochemical properties of this combination tablets were assessed through the evaluation of uniformity of tablet weight,

thickness test, hardness test, friability test, disintegration test, dissolution test and potency test according to the standard method (Shohin *et al*, 2011). Generally there are two types of tests:

i. Compendial tests &

ii. Non-compendial tests

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

They are also known as official tests. They include

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

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

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

1.12.1 Weight variation

Weight variation test is done to check the uniformity of the tablets. Some tablet fails to maintain uniformity, some are properly uniformed. There are several reasons that the weight of tablets varies batch to batch (Shohin *et al*, 2011).

Tablet weight variation may be caused by

1. Distribution at Hoover caused the vibration. So, small granule pushed, large granules will come out first, because there is a process of consolidation. Therefore, needs to be put a uniform granule size. So, before the compressing process begins better evaluation the particle size distribution first.

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

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

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

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

6. Poor flow properties

7. If any improper adjustment of the die cavity (Shohin *et al*, 2011).

1.12.2 Hardness test

Hardness test is done to determine the need for pressure adjustment on the tableting machine. Hardness has to maintain to withstand mechanical shocks for handling in manufacturing, packing and shipping. There are different types of hardness tester are present like Monsanto tester, Strong-cobb-tester, Pfizer tester, Schleuinger tester and Erweka (Shohin *et al*, 2011).

Hardness can affect the disintegration. So if the tablet is too hard, it may not disintegrate in the required period of time. And if the tablet is too soft, it will not withstand the handling during subsequent processing such as coating or packaging. Hardness value differ with the instrument used allowed values 8-12 Kg. Tablet hardness usually affects drug dissolution and release, and it may affect bioavailability (Lachman *et al*, 2011).

Factor affecting the hardness of tablets,

1. Compression of the tablet and compressive force.

2. Amount of binder, more binder more hardness.

3. Method of granulation in preparing the tablet (wet method gives more hardness than dry method; slugging method gives the best hardness) (Shohin *et al*, 2011).

1.12.3 Thickness test

The thickness of tablet controlled carefully from the production run. Thickness can vary with no change in weight because of difference in the density of the granulation and the pressure applied to the tablets as well as the speed of tablet compression. Tablets thickness is determined with a caliper or thickness gauge that measures the thickness in millimeters (Lachman *et al*, 2011).

If the tablets are thicker than a specified given number no longer may be contained in the volume of a given size bottles. Tablet thickness also becomes an important characteristic in counting tablet using filling equipment. Some filling equipment uses the uniform thickness of the tablet as a counting mechanism. If thickness varies a lot, the result will have variation in count. Other pieces of filling equipment can malfunctioning because of variation in tablet thickness, since tablet above specified thickness may cause wedging of tablets in previously adjusted depth of the counting slots (Lachman *et al*, 2011).

1.12.4 Friability test

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 (Lachman *et al*, 2011).

1.12.5 Disintegration test

Disintegration is a measure of the quality tablets. The disintegration test is performed to find out the time it takes for a solid oral dosage form like a tablet or capsule to completely disintegrate. The time of disintegration is a measure of the quality. This is because, for example, if the disintegration time is too high; it means that the tablet is too highly compressed or it may imply several other reasons. And also if the disintegration time is not uniform in a set of tablet being analyzed, it indicates batch inconsistency and lack of batch uniformity (Lachman *et al*, 2011).

1.12.6 Dissolution test

Dissolution testing is used to formulate the drug dosage form and to develop quality control specifications for its manufacturing process. In-vitro dissolution test is a critical test that has to correlate with in-vivo clinical studies and which could require specific method developments. In Vitro dissolution testing is used to assess batch to batch consistency and detect deviations of manufacturing, to identify critical manufacturing variables like binder effects, mixing effects, granulation Procedure, Coating Parameters, to assess excipients role in different dosage forms (Lachman *et al*, 2011).

There is some other purpose of in vitro dissolution study. These are:

1. During product development, selecting formulations for further development.

2. During end-product quality control, determining whether each batch meets predetermined in vitro release criteria.

3. During stability studies, determining whether in vitro release rate changes with product age.

4. During the market lifetime, determining whether variations affect in vitro release (Shohin *et al*, 2011).

Factor affecting dissolution of tablet:

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.

- Excipients and additives: Most solid dosage forms incorporate more than one excipient for various purposes together with the active ingredient in the formulation. The dissolution rate of a pure drug can be altered significantly when mixed with various adjuncts. These adjuncts include diluents, binders, lubricants, granulating agents, disintegrants, and so on.
- Granulating agent and binder: Binder and granulating agent incorporated in tablet formulation and other solid dosage forms can markedly influence the dissolution characteristics of the drug from the dosage form.

- Disintegrating Agents: Several reports have been published in the literature demonstrating the effect of various disintegrating agents on the dissolution rate of tablets. It must be noted that the type and amount of disintegrating agent employed in the formulation significantly controls the overall rate of dissolution of the dosage form.
- Lubricants: 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 quantity of the lubricant added can affect the dissolution rate.
- Surfactant: 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 (Shohin *et al*, 2011).

1.12.7 Potency test

Potency is the strength of a dosage form. Potency determination is the chemical characteristic of a dosage form. Potency tests are assay to estimate the quality and quantity of active ingredient in the drug. Quantitative tests such as chemical, physical, pharmacological, biological or microbiological means yield the strength or potency of the drug substance. To assure uniformity, weight variation test is not sufficient. It is to determine the amount of a substance or the presence of a substance. It is actually determine purity of a drug or drug dosage form. The test method and the acceptable limits are specified in the pharmacopoeias. Specified number of dosage units should be taken for analysis. Larger or smaller quantities from specified weight can be taken if the measurements are adjusted with equivalent accuracy and provided that any subsequent steps like dilutions are adjusted consequently to yield concentrations equivalent to those specified. Once the result is generated it is related to the amount of active ingredient per tablet by multiplying the result with the average tablet weight and dividing by the weight of portion taken for the assay. Impurity in the active ingredient or any weight variation may interact with the potency result of the drug. If a drug fails in potency test the patient may suffer under or over medication (Lachman *et al*, 2011).

Significance of the study

Hypertension is one of the most common diseases in our country. This is a kind of disease that cannot be easily cured but it can be controlled. Because of having a good number of pharmaceutical companies, our Pharmaceutical market has a good competition. They launch numerous products on different diseases. And hypertension in respect of our country is one of the fields where every pharmaceutical has several products whether it is single drug product or combined drug product. That's why it is necessary to carry out a comparative study of the quality control parameters of different brands that are available in Bangladesh for the appropriate quality evaluation, therapeutic efficacy and safety of the tablets. It is because quality of the pharmaceutical product is uppermost important and they must be marketed as safe and therapeutically active formulation whose performance is consistent and not cause any kind of worse effect (Shohin *et al*, 2011).

The evaluation of quality control parameters (weight variation, hardness, thickness, disintegration, dissolution, potency determination) of the pharmaceutical product that are available in market is important ensure their quality. It also gives us an indirect idea about its bio-availability. The combination of atenolol (50mg) and amlodipine (5mg) is such a product which is increasing day by day in term of its use. The combination of atenolol (50mg) and amlodipine (5mg) is released by most of the pharmaceutical company under their cardiovascular management. At present there are many brands available of different pharmaceutical company in market. So, it is very important to evaluate the quality control parameters like weight variation, hardness, thickness, disintegration test, dissolution test, potency test of different brands and also to compare them with each other to find out an idea about which one is better in terms of quality as well as safety and which shows variation from the specification.

Aims and objectives of the study

The aim of this research paper were,

- To determine the quality control parameters of various brands (Fixocard 50® and Amloten 50®) of atenolol (50mg) and amlodipine (5mg) combination
- To determine the potency and dissolution of selected brands.
- To make a comparison on different quality control parameters between brand to brand

CHAPTER 2: LITEREATURE REVIEW

Literature Review

2.1 Simultaneous UV spectrophotometric methods for estimation of atenolol and amlodipine besylate in combined tablet dosage form

Two simple, rapid, accurate, precise, cost effective, and reproducible UV spectroscopic methods have been developed for the simultaneous estimation of atenolol and amlodipine besylate in bulk and combined tablet dosage form. The first method is based upon the simultaneous equation and second upon the determination of Q value. Atenolol and amlodipine have absorption maxima at 224.4 and 238.2 nm respectively. Beer's law obeyed in concentration range of 2-24 µg/ml and 2-34 µg/ml for ATN and AMN respectively. The method of Q analysis is based on measurement of absorptivity at 224.4 nm and at iso-isorptive point 232.2 nm. The recovery studies from tablet are indicative of accuracy of method and are found in between 99.87-101.43 % at three different levels of standard additions. Precision studies showed satisfactory results. A novel approach to use 0.02% SLS as solvent is proved to be beneficial with respect to cost, stability and avoidance of organic solvent (Sandip *et al*, 2010).

2.2 Formulation development and in-vitro evaluation of orally disintegrating tablets of amlodipine besylate

An attempt has been made for the development of orally disintegrating tablets of amlodipine besylate prepared by direct compression method by using super disintegrants like cross povidone, cross caramellose sodium and sodium starch glycolate. Effect of different super disintegrants on disintegration behaviour of tablets was evaluated. All the formulations were evaluated for pre compression, post compression parameters and in-vitro dissolution. Wetting time of formulations containing cross carmellose sodium was least and tablets showed fast disintegration. Of the nine formulations studied 9th showed short dispersion time with maximum drug release 99.59% in 20 minutes. Combinations of super disintegrants were found to be better in the formulation of fast dissolving tablets of amlodipine besylate rather than using alone (Bharathi *et al*, 2012).

2.3 Simultaneous estimation of atenolol and amlodipine besylate in tablets formulation by Vierodt's method using UV spectrophotometry

A UV- spectrophotometric method has been developed for the simultaneous estimation of atenolol and amlodipine besylate in tablet dosage forms using 0.1N hydrochloric acid (pH 1.2). The method is based on simultaneous equation or Vieordt's method. The valus for atenolol and amlodipine besylate were found to be 224.6 nm and 239.6 nm respectively. The system obey Beer's law in the range of 4-28 µg/ml and 4-32 µg/ml with correlation coefficient of 0.9991 and 0.9932 for atenolol and amlodipine besylate respectively. Intraday and interday precision were found to be 0.08577-1.4682, 0.1080-1.71138, 0.2525-1.6080 and 0.2599-1.3906 respectively. The developed method can be successfully employed for the assay of atenolol and amlodipine besylate in different formulations (Girdhari *et al*, 2012).

2.4 Assessment of pharmaceutical quality control and equivalence of various brands of amlodipine besylate (5 mg) tablets available in the pakistani market under biowaiver conditions.

The dissolution profiles of amlodipine besylate tablets under biowaiver condition were evaluated in four different media (distill water, buffer pH 1.2, buffer pH 4.5 and buffer 6.8) using US Pharmacopoeia dissolution apparatus II. Among them dissolution either single point or multiple point including release profile comparison is the most important tool. Quality control tests were satisfactory and within the limits for all amlodipine besylate brands. The results obtained for disintegration test, assay, hardness and friability were less than 15 minutes, 98.96-100.76 %, 1.53-8.77 kg/cm^2 and less than 1% respectively. The physico-chemical characteristics of the five generic brands tested were comparable with the innovator brand. They were all within the BP limits as specified for immediate release dosage forms; these assure pharmaceutical equivalence of generics tested with the innovator. The evaluated drugs were "very rapidly dissolving" because the active pharmaceutical ingredient release at time point 15 min was more than 85% so no statistical treatment is required hence are considered to be in- vitro equivalent without in - vivo evaluation. The percent relative standard deviation (% RSD) for all time points fulfills all requirements (≤ 20% for 15 min, ≤ 10% for other time points), so results are valid. Under the

biowaiver conditions, all the generics are interchangeable with the innovator; they are therapeutically equivalent. The generic substitutions for the innovator are appropriate despite the high price differential (Mahwish *et al*, 2014).

2.5 Biowaiver Studies of Atenolol Tablets (100mg) - An Alternative to In Vivo Bioequivalence Studies.

Four brands of atenolol 100 mg tablets have been evaluated using some quality control parameters, such as weight variation, hardness, content assay, disintegration and dissolution test. In vitro dissolution testing can be used in some cases not only to determine the quality of the pharmaceutical products but also to demonstrate bioequivalence to the generic product. Similarity factor (f2) and Difference Factor (f1) were used to assess bioequivalency among four products. The FDA recommended dissolution medium for atenolol is 0.1N HCl but it shows a good releasing pattern in water also. The dissolution profiles of Aten-4 and Aten-2 in pH 1.2 is rapid and good, only Aten -3 failed to cross the similarity factor but f1 is within limit. In pH 4.5 and 6.8 all brands fulfilled biowaiver requirements, except Aten-2 in pH 6.8 that may be due to manufacturing process difference. In the same time Aten-2 has f1 value 12 that is within the limit. Therefore, generic drugs with differing in vitro dissolution will not necessarily exhibit different in vivo performance. The results suggest that the formulation and/or the manufacturing process affect the dissolution and thus the bioavailability of the drug products. Thus the significance of the observed in-vitro differences must be confirmed by an in-vivo bioequivalence study (Usman *et al.*, 2014).

2.6 Comparative quality control evaluation of atenolol tablets marketed in Kuala Lumpur, Malaysia

The main objective of this study is to perform a comparative evaluation of the physicochemical properties of five commercially available leading brands of Atenolol tablets marketed in Kuala Lumpur. The quality control parameters of five different brands of atenolol tablets were atenolol tablet assessed included uniformity of content, uniformity of weight, friability, crushing strength,

disintegration and dissolution tests as well as content uniformity of the tablets. All the tablets were assessed for conformity with British Pharmacopoeia (BP) standards.All the five brands of the tablets passed the British Pharmacopoeia (BP) standards for weight uniformity, disintegration, friability, contents uniformity and hardness tests. The quality control parameters of all five top selling brands of atenolol tablets marketed in Kuala Lumpur analyzed passed all the BP and USP quality specifications and were physically and chemically equivalent (Dharmalingam *et al*, 2014).

2.7 Simultaneous estimation of amlodipine besylate and atenolol in combined dosage forms marketed in pakistan by Vierodt's method using U.V. spectroscopy

Spectroscopic studies were carried out using double beam U.V spectrophotometer model JASCO. The marketed combination of atenolol and amlodipine besylate that is primol-AT 10 TAB Madley pharma and 0.1N HCL used as solvent. Then spectra of amlodipine and atenolol exhibit λmax of 239nm and 228nm resepectively. Additionaly one isoprtive point was observed at 233nm this wavelength were selected for simultaneous estimation of amlodipine and atenolol and standard calibration curves for amlodipine and atenolol were linear with correlation coefficient 0.996 and 0.993 at all selected wavelengths. This method was found to be applicable over a range of 4-24 µg/ml for amlodipine and atenolol. This method can be used as alternative for rapid and routine determination of bulk sample and tablets (Pawar *et al*, 2013).

2.8 Formulation and evaluation of fast dissolving tablets atenolol

Administration of conventional tablets of atenolol in has been reported to exhibit fluctuations in plasma drug levels, results either in manifestation of side effects or reduction in drug concentration at the receptor sites. The half-life of atenolol is 6-7 hours hence multiple doses of the drug are needed to maintain a constant plasma concentration for a good therapeutic response, and improve patient compliance, hence the objective of the study was made to develop fast dissolving tablet of atenolol. Conventional atenolol tablets available in market are not suitable where quick onset of action is required. Besides, the conventional tablets also show poor patient

compliance particularly by the geriatric and pediatric patients who experience difficulty in swallowing, and by those who are bed ridden or who are traveling and do not have an easy access of water. In this studies using polymer like AC-DI-SOL, Sodium starch glycolate and which will quickly the release of drug, increasing the bioavailability of the drug and thus decreasing the dosing frequency of the drug. The description and appearance, melting point and solubility were also performed for further characterization & it was found that all results are satisfactory. Atenolol was estimated by UV/VIS spectrophotometry in 0.1N HCl. The in vitro dissolution study was also carried out in 0.1N HCl (pH 1.2) and B7 is the best formulation among of that and it release 99.5% (Khirwadkar *et al*, 2013).

CHAPTER 3: METHODOLOGY

Methodology

3.1 Samples

40 tablets of 2 different brands of atenolol (50mg) & amlodipine (5mg) combinational tablets were collected from different pharmacy shops.

Table 3.1: Different brands along with their manufacturer names

Tablet	Manufacturer	Batch No.
Fixocard 50®	INCEPTA Pharmaceuticals Limited	16012 & 16012
Amloten 50®	ACME Laboratories Ltd.	T3235005 & T3235006

Table 3.2: Reagents and solvent

Hydrochloric Acid	**0.1N HCL**
Distilled water	Non-ionized

Table 3.3: List of Apparatus/ Glassware's used throughout this project

1. Several containers	5. Volumetric Flasks
2. Mortar & Pastels	6. Pipette
3. Measuring Cylinder	7. Beakers
4. Test tubes	8. Filter Papers

3.2 Weight variation test

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

1. Differences in lower punch length which result in different size die cavities.

2. A wide variation in granulation particle size, which result in a variation in die fill density as a function of particle size and particle size distribution at different points in the production run.

3. Poor granulation flow properties, resulting in uneven die fill (Dharmalingam *et al*, 2014).

3.2.1 Instrument: Analytical Balance (AY220, Shimadzu, Japan)

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

3.2.2 Method: Calculated average weight of 20 tablets and weighed 20 whole tablets individually. Then observed weight of individual tablets was within the range or not (USP, 2007).

3.2.3 Calculation: Percentage of weight variation was calculated by following formula (Dharmalingam *et al*, 2014).

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

3.2.4 Specification: According to the USP (2007), the individual variation from the average weights must not differ for more than two tablets than percentage listed below:

Table 3.4: Weight variation tolerance for tablets (USP, 2007)

Average weight of the tablet	Percentage of difference
130 mg or less	± 10
From 130 mg through 324 mg	± 7.5
More than 324 mg	± 5

3.3 Thickness test

3.3.1 Instrument: Vernier Calipers (Shimadzu, Japan)

Figure 3.2: Vernier Calipers (Shimadzu, Japan)

3.3.2 Method: 20 tablets were individually placed horizontally between two jaws of the calipers. The caliper scale was run to hold the tablet which gave a visual reading of tablet thickness (Dharmalingam *et al*, 2014).

3.3.3 Calculation: Thickness was calculated by using the following formula:

Thickness = Main scale reading + vernier scale reading x vernier constant ± Vernier error (Dharmalingam *et al*, 2014).

3.3.4 Specification: According to the USP (2007), tablets should have thickness about ± 5mm.

3.4 Hardness test

Tablet hardness is usually expressed as the load required crushing a tablet placed on its edge. Hardness is thus sometimes termed the tablet crushing strength. The suitability of tablet in regard to mechanical stability during packaging and shipment can usually be predicted on the basis of hardness. Tablet hardness, in turn, influences tablet density and porosity. It may affect tablet friability and disintegration time. It usually affects drug dissolution and release and it may affect bioavailability (Dharmalingam *et al*, 2014).

Figure 3.3: Hardness tester (Veego, India)

3.4.1 Instrument: Hardness tester (Veego, India)

3.4.2 Method:

- The slide scale of the hardness tester was made zero
- One tablet was placed vertically between two jaws.
- Force was applied with a screw thread and spring until the tablet fractured.
- Reading in Kg was taken from the sliding scale (Dharmalingam *et al*, 2014).

3.4.3 Measurement Units: Most materials testing are performed using the International System of Units. The Newton is the preferred unit of force as is recognized by the SI system. However the Kg can also be used. Kilogram (Kg) – The Kilogram is recognized by the SI system as the primary unit of mass (USP, 2007).

3.4.4 Specification: According to USP (2009), oral tablets normally have a hardness of 4 to 8 or 10 kg; however, hypodermic and chewable tablets are much soften (3 kg) and some sustained release tablets are much harder (10-20 kg) (USP, 2009).

3.5 Disintegration test

Disintegration is the most important step of a drug being better dissolution. The breakdown of a drug within its optimum time is the prerequisite for better absorption and consequently better therapeutic action. Disintegration time may vary considering to its disintegrator used. Higher the disintegration time required lower the dissolution rate and followed to poor absorption. So disintegration is the crucial part of a drug for therapeutic action (BP, 2009).

3.5.1 Condition:

a) Distilled water
b) 37° C temperatures to maintain body temperature (BP, 2009).

Figure 3.4: Disintegration tester

3.5.2 Instrument: Disintegration tester (Vanguard Pharmaceutical Machinery INC).

3.5.3 Method:

1. The disintegration tester was assembled.
2. Then the time and temperature was set at prescribed in specification.
3. 600ml of the distilled water was placed in each 1000ml beaker.
4. The temperature of the liquid was maintained at 37° C.
5. In each of the 6 tubes one tablet was placed.
6. The machine was then operated for the prescribed period.
7. The entire tablet was disintegrated within the prescribed time (BP, 2009).

3.5.4 Specification:

According to BP (2009), the disintegration time for uncoated tablet is 15 minutes, for coated tablet is 30 minutes and for enteric coated tablet is 60 minutes or 1 hour. (BP, 2009)

3.6 Potency Test

3.6.1 Material: Analytical balance, mortar & pestle, spatula, volumetric flask, funnel, filter paper, pipettes, pipette pumper, tablets.

3.6.2 Method: 10 tablets from each batch were weighed and ground into a fine powder. Powder equivalent to 50 mg and 5 mg of atenolol and amlodipine was transferred into 100 ml volumetric flasks and dissolved in 25 ml of 0.1 N hydrochloric (pH 1.2). The solution was sonicated for 20 mintues and was filtered through Whatman No. 40 filter paper. The residue was washed with hydrochloric acid buffer and washing were added to the filtrate. The volume was made up to the mark with 0.1N hydrochloric acid buffer. From this solution, 1 ml was pipette out into 10 ml volumetric flask and diluted up to the mark with 0.1N hydrochloric acid buffer (PH 1.2). The absolute values were measured at 223.5 nm and 237.5 nm respectively (Girdhari *et al*, 2012).

3.6.3 Calculation: Using the following formula we can measure the measure amount of the active in sample,

$$\% \text{ Potency} = \frac{A_{sample}}{A_{STD}} \times \frac{\text{Weight}_{STD}}{\text{Weight}_{sample}} \times \frac{\text{Potency}_{STD} \times \text{Dilution Factor} \times \text{Avg Wt}_{sample}}{\text{Label Claimed}} \times 100$$

3.6.4 Specification: According to BP (2009), in order to pass the potency test, tablets contain not less than 90.0% and not more than 110.0% of atenolol and amlodipine (BP, 2009).

3.7 Dissolution Test

3.7.1 Instrument: Dissolution Apparatus (LABINDIA DS 8000)

3.7.2 Condition:

Medium: 900ml 0.1N HCL

Apparatus: USP dissolution apparatus type-II

Speed: 50rpm

Temp: 37.5° C

Time: 30 min (Vuyyala, 2014)

Figure 3.5: Dissolution Tester (LABINDIA DS 8000, India)

3.7.3 Method: On the dissolution test apparatus the water tank was filled and the temp was set. Then 900 ml of 0.1N HCL was poured into one of the vessels and instrument were run till the set temp was attained. One of the tables was placed into the vessels and starts the run. Rotate the paddle at 50 revolutions per min. Run the test for 30 min. Dilution was performed wherever necessary (Vuyyala, 2014). Finally the absorbances were taken at 237.5 nm for amlodipine and at 223.5 nm for atenolol. Analysis was performed by UV-visible spectrophotometer.

3.7.4 Calculation

$$\% \text{ Dissolution} = \frac{\text{Absorbance (a)}}{\text{A}} \times \frac{\text{Dilution Factor} \times 900}{\text{tablet weight (gm)}}$$

3.7.5 Specification:

Conventional-release (or immediate-release) dosage forms

Unless otherwise specified in the individual monograph the requirements are met if the quantities of active ingredient(s) dissolved from the dosage forms tested conform to Table. Continue testing through the three levels unless the results conform at either S_1 or S_2. The quantity, Q, is the

specified amount of dissolved active ingredient expressed as a percentage of the labelled content; the 5%, 15% and 25% values in the acceptance table are percentages of the labelled content so that these values and Q are in the same terms (WHO, 2014).

Table 3.5: Acceptance criteria for Conventional-release dosage forms

Level	**Samples Tested**	**Acceptance Criteria**
S_1	6	Each value is not less than Q + 5%
S_2	6	Average value of the 12 dosage units (S1 + S2) is equal to or greater than Q and no unit is less than Q-15%
S_3	12	Average value of 24 dosage units (S1 + S2 + S3) is equal to or greater than Q; not more than 2 units are less than Q - 15%; no unit is less than Q - 25%.

(WHO, 2014)

CHAPTER 4: RESULTS

Results

4.1 Weight Variation test

Percentage of variation of 4 batches of 2 different brands of combined atenolol and amlodipine tablets are given below.

Table 4.1: Weight variation of Fixocard 50® (Batch: 16012)

Number of tablets	Weight of individual tablets (g)	Average weight (g)	Individual weight Variation (%)	Highest weight variation (%)	Lowest Weight Variation (%)
1	0.1371	0.138115	-0.7349	3.6093	-1.6037
2	0.1387		0.4236		
3	0.1373		-0.5901		
4	0.1385		0.2788		
5	0.1368		-0.9521		
6	0.1373		-0.5901		
7	0.1388		0.4960		
8	0.1382		0.0615		
9	0.1431		3.6093		
10	0.1376		-0.3729		
11	0.1369		-0.8797		
12	0.1384		0.2063		
13	0.1395		1.0028		
14	0.1371		-0.7349		
15	0.1422		2.9577		
16	0.1359		-1.6037		
17	0.1366		-1.0969		
18	0.1378		-0.2281		
19	0.1361		-1.4589		
20	0.1384		0.2063		

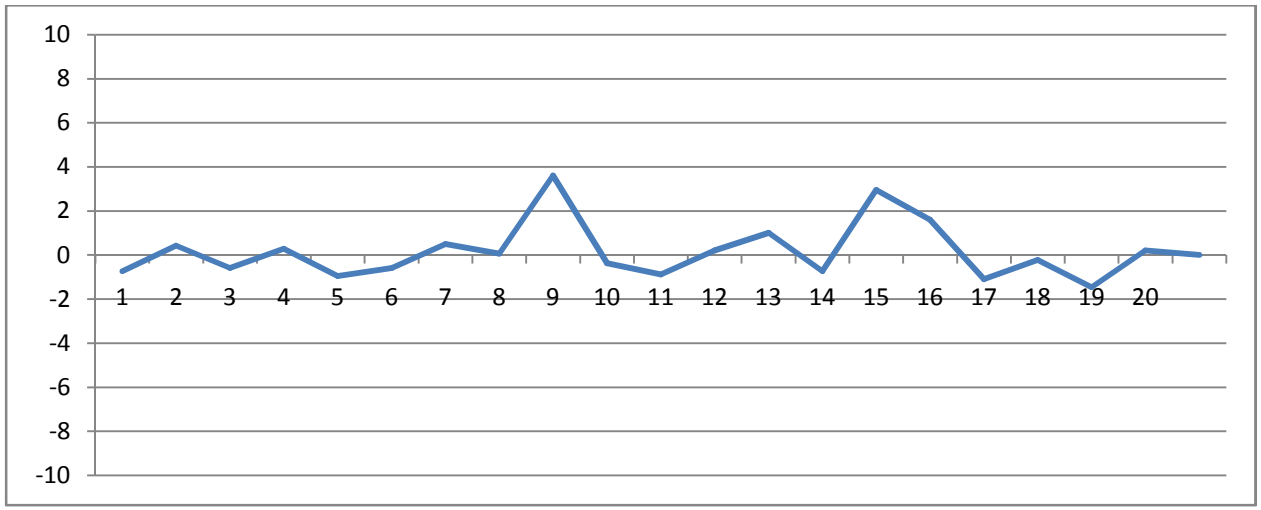

Figure 4.1: Individual weight variation of Fixocard 50® (Batch: 16012)

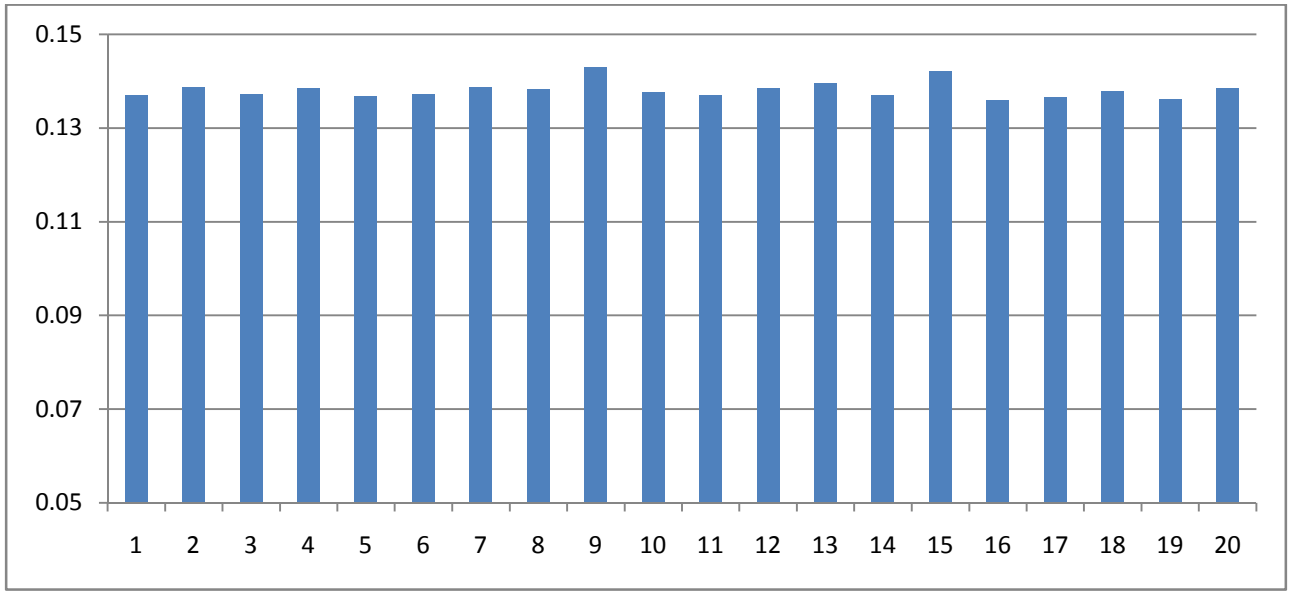

Figure 4.2: Weight of individual Tablets for Fixocard 50® (Batch: 16012)

Table 4.2: Weight variation of Fixocard 50® (Batch: 16016)

Number of tablets	Weight of individual tablets (g)	Average weight (g)	Individual weight Variation (%)	Highest weight variation (%)	Lowest Weight Variation (%)
1	0.1393	0.138675	0.4507	2.8304	-3.0827
2	0.1376		-0.7752		
3	0.1426		2.8304		
4	0.14		0.9555		
5	0.1402		1.0997		
6	0.1382		-0.3425		
7	0.1344		-3.0827		
8	0.1402		1.0997		
9	0.1378		-0.6310		
10	0.1387		0.0180		
11	0.1374		-0.9194		
12	0.1388		0.0901		
13	0.1368		-1.3521		
14	0.1383		-0.2704		
15	0.1394		0.5228		
16	0.1389		0.1622		
17	0.1381		-0.4146		
18	0.1379		-0.5589		
19	0.1406		1.3881		
20	0.1383		-0.2704		

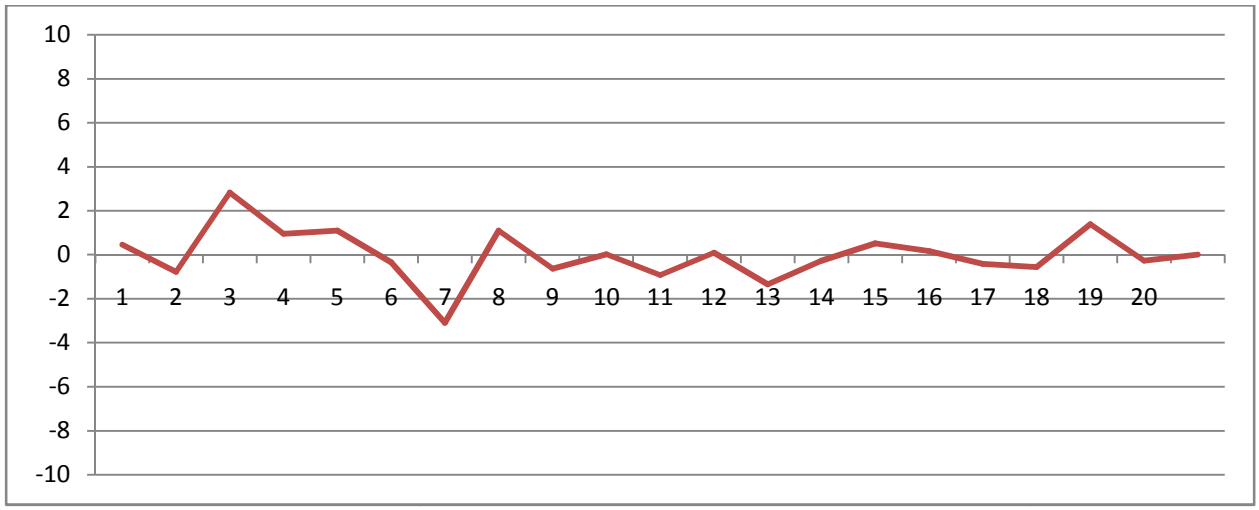

Figure 4.3: Individual weight variation of Fixocard 50® (Batch: 16016)

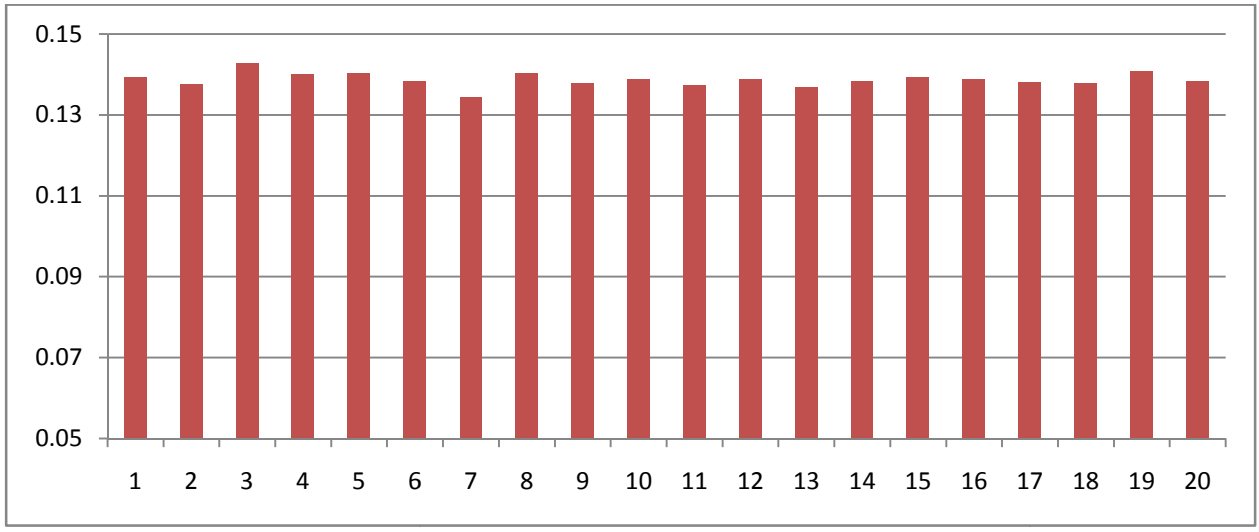

Figure 4.4: Weight of individual Tablets for Fixocard 50® (Batch: 16016)

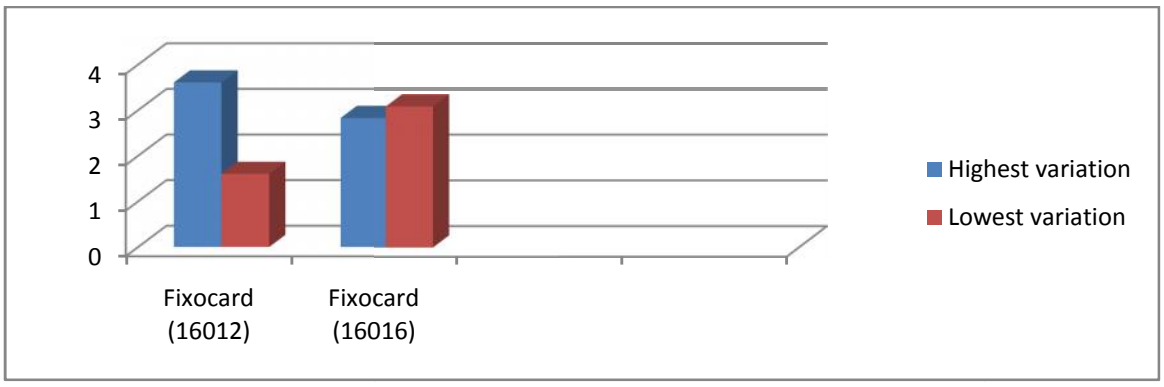

Figure 4.5: Comparison between two batches highest and lowest variations

Table 4.3: Weight variation of Amloten 50® (T3235005)

Number of tablets	Weight of individual tablets (g)	Average weight (g)	Individual weight Variation (%)	Highest weight variation (%)	Lowest Weight Variation (%)
1	0.1556	0.156605	-0.6417	4.5305	-2.6851
2	0.1561		-0.3225		
3	0.1637		4.5305		
4	0.1568		0.1245		
5	0.1609		2.7426		
6	0.1559		-0.4502		
7	0.1524		-2.6851		
8	0.157		0.2522		
9	0.1603		2.3594		
10	0.157		0.2522		
11	0.1559		-0.4502		
12	0.1564		-0.1309		
13	0.1549		-1.0887		
14	0.1563		-0.1948		
15	0.154		-1.6634		
16	0.1554		-0.7695		
17	0.1561		-0.3225		
18	0.1562		-0.2586		
19	0.1546		-1.2803		
20	0.1566		-0.0032		

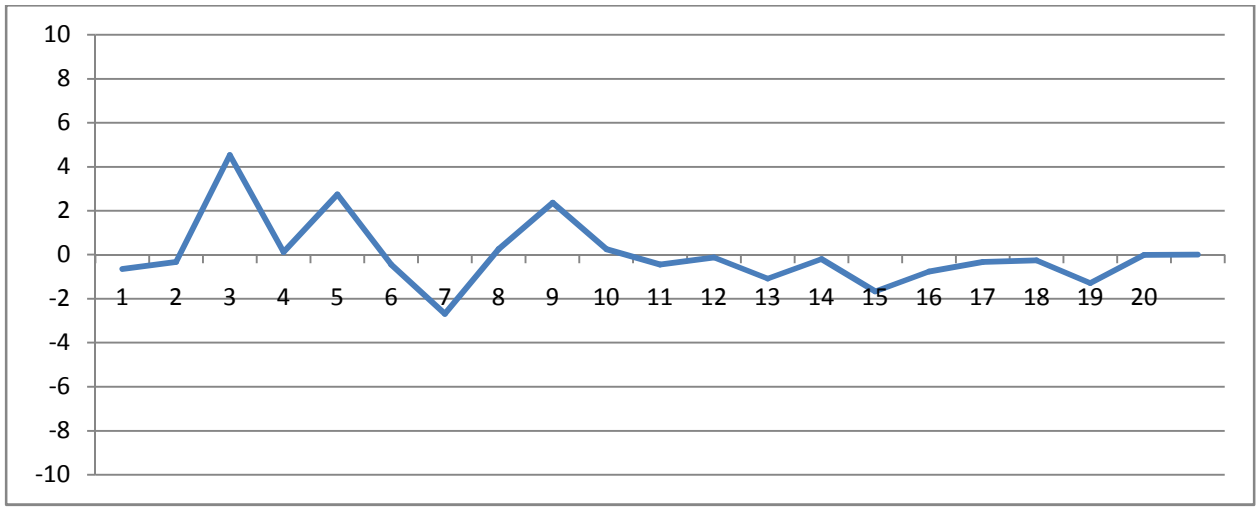

Figure 4.6: Individual weight variation of Amloten 50® (Batch: T3235005)

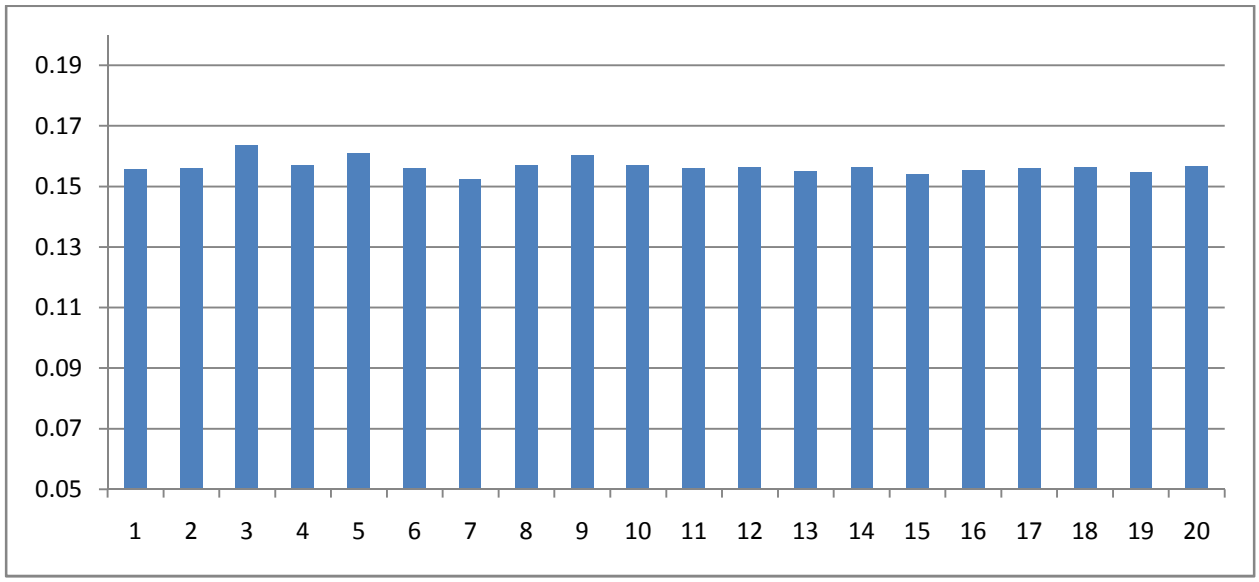

Figure 4.7: Weight of individual Tablets for Amloten 50® (Batch: T3235005)

Table 4.4: Weight variation of Amloten 50® (Batch: T3235006)

Number of tablets	Weight of individual tablets (g)	Average weight (g)	Individual weight Variation (%)	Highest weight variation (%)	Lowest Weight Variation (%)
1	0.1583	0.15776	0.3423	5.9204	-3.3976
2	0.149		5.5527		
3	0.154		-2.3834		
4	0.1671		5.9204		
5	0.1564		-0.8621		
6	0.1524		-3.3976		
7	0.162		2.6876		
8	0.16		1.4199		
9	0.156		-1.1156		
10	0.1558		-1.2424		
11	0.1568		-0.6085		
12	0.1573		-0.2916		
13	0.1553		-1.5593		
14	0.1558		-1.2424		
15	0.1549		-1.8129		
16	0.1561		-1.0522		
17	0.1544		-2.1298		
18	0.1557		-1.3058		
19	0.1569		-0.5451		
20	0.1551		-1.6861		

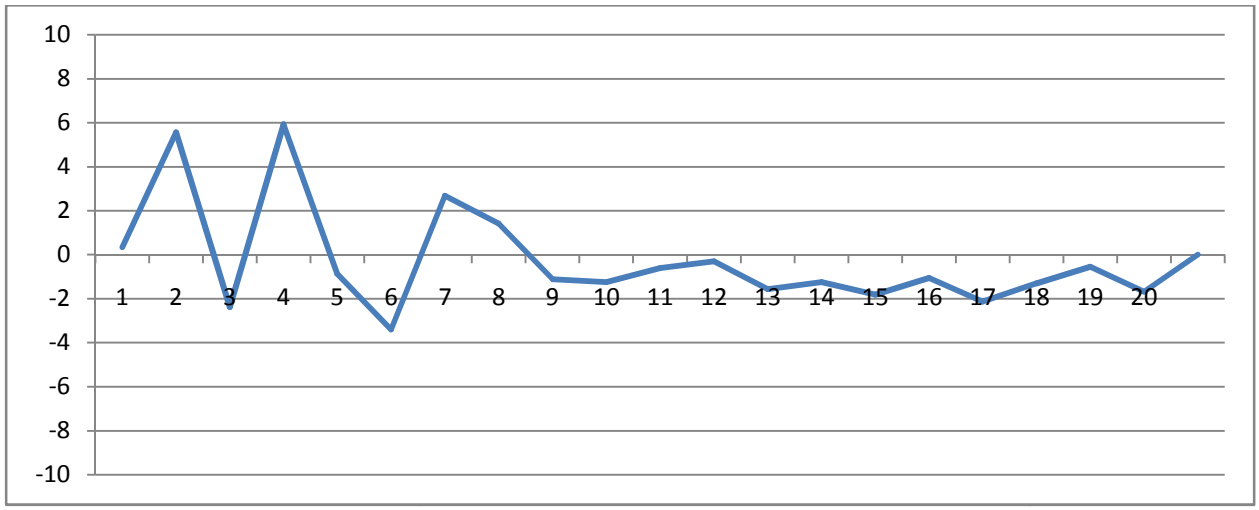

Figure 4.8: Individual weight variation of Amloten 50® (Batch: T3235006)

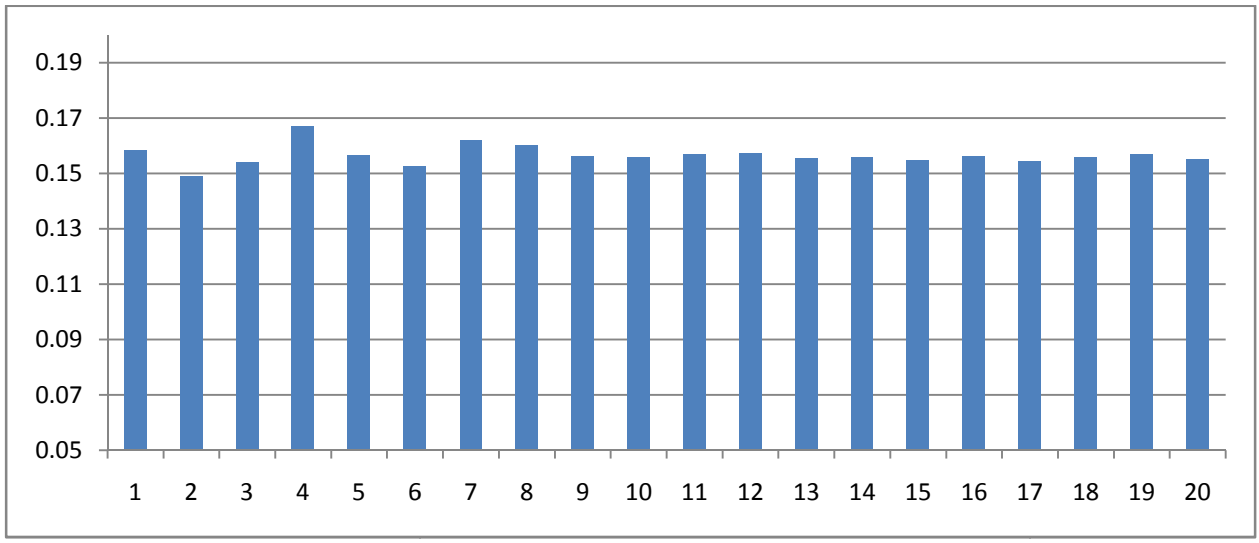

Figure 4.9: Weight of individual Tablets for Amloten 50® (Batch: T3235006)

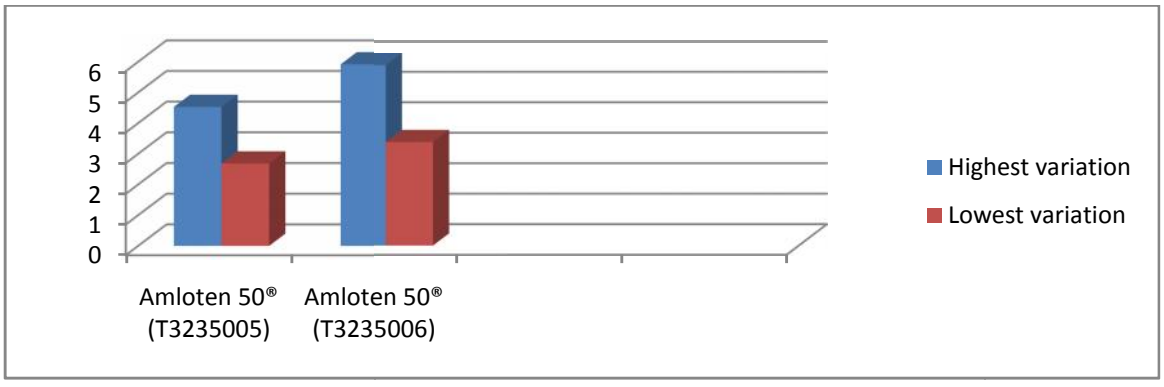

Figure 4.10: Comparison between two Amloten 50® batches highest and lowest variations

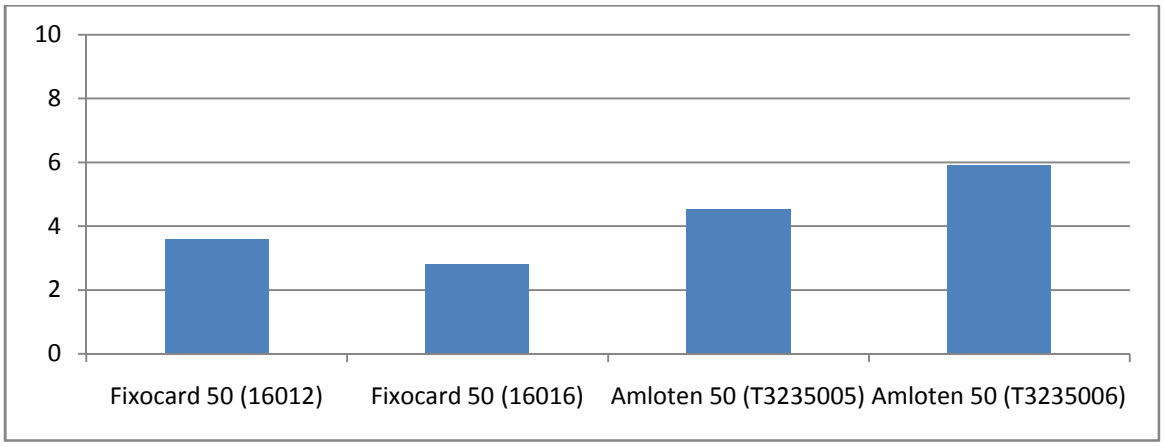

Figure 4.11: Comparison between the highest weight variations of 4 batches

4.2 Thickness test

Thickness test of 2 brands of combined atenolol and amlodipine tablets are given below.

Table 4.5: Thickness test of Fixocard 50® (Batch: 16012)

Number of tablets	Reading of main scale(mm)	Reading of Vernier scale	Vernier constant	Vernier error	Thickness (mm)	Average Thickness (mm)
1	3.5	4.5	0.1	0.05	4	4.03
2	3.5	5			4.05	
3	3.5	5			4.05	
4	3.5	5			4.05	
5	3.5	5.5			4.1	
6	3.5	5			4.05	
7	3.5	4.5			4	
8	3.5	5			4.05	
9	3.5	4.5			4	
10	3.5	4			3.95	

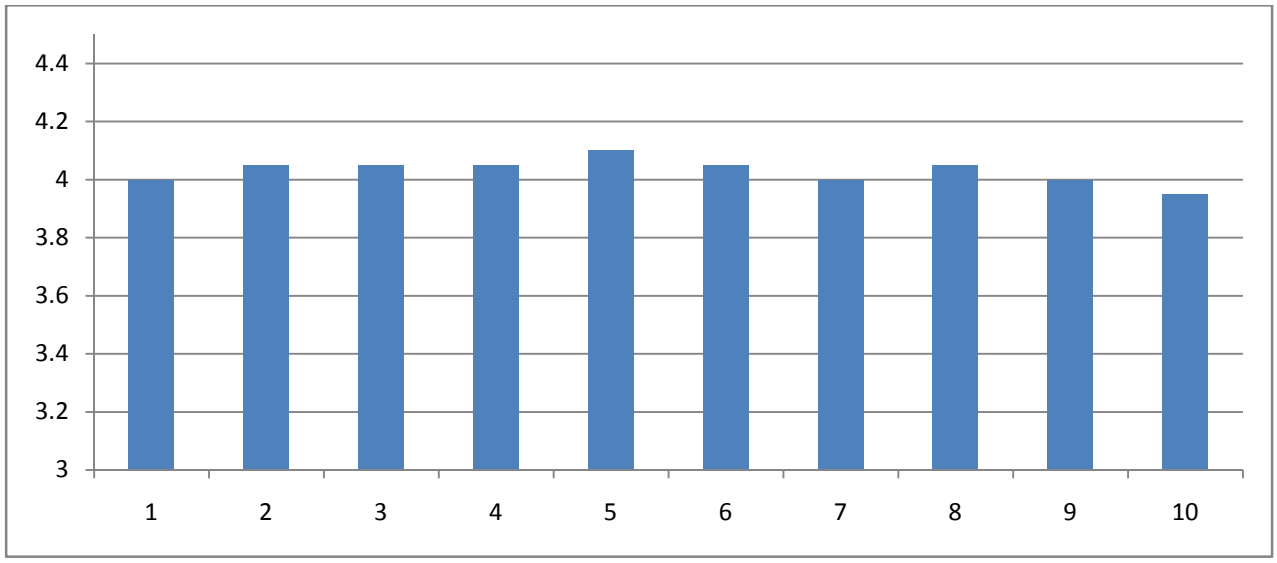

Figure 4.12: Thickness of tablets of Fixocard 50® (Batch: 16012)

Table 4.6: Thickness test of Fixocard 50® (Batch: 16016)

Number of tablets	Reading of main scale(mm)	Reading of Vernier scale	Vernier constant	Vernier error	Thickness (mm)	Average Thickness (mm)
1	3.5	5	0.1	0.05	4.05	3.969
2	3.5	4			3.95	
3	3.5	3			3.85	
4	3.5	3.5			3.9	
5	3.5	3			3.85	
6	3.5	4			3.95	
7	3.5	5			4.05	
8	3.5	5			4.05	
9	3.5	4.4			3.99	
10	3.5	5			4.05	

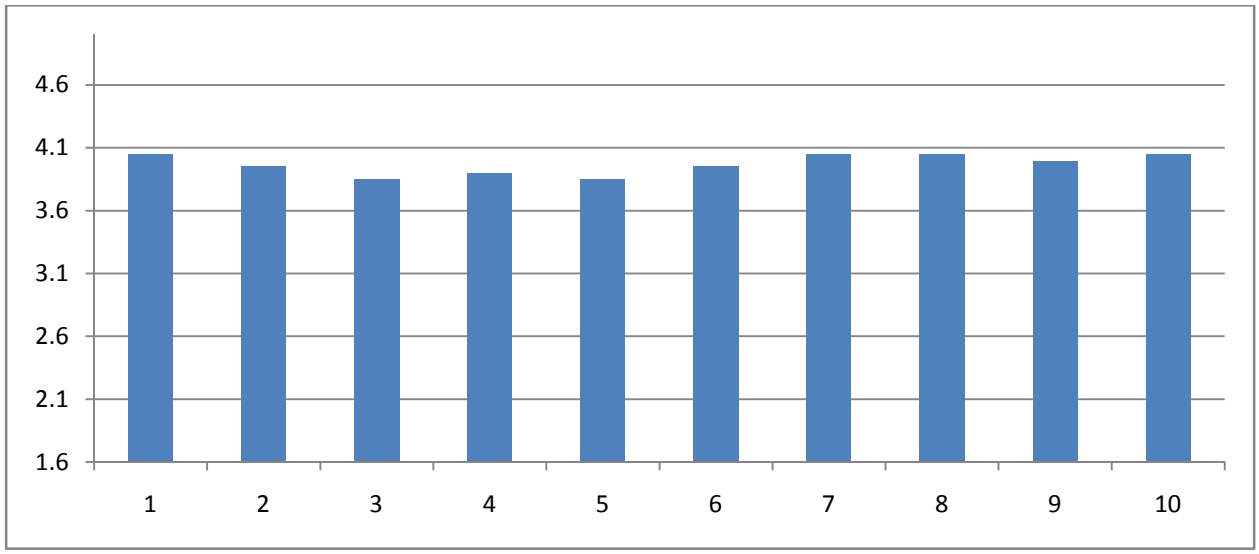

Figure 4.13: Thickness of tablets of Fixocard 50® (Batch: 16016)

Table 4.7: Thickness test of Amloten 50® (Batch: T3235005)

Number of tablets	Reading of main scale(mm)	Reading of Vernier scale	Vernier constant	Vernier error	Thickness (mm)	Average Thickness (mm)
1	3	3.5	0.1	0.05	3.4	3.415
2	3	4			3.45	
3	3	3			3.35	
4	3	3.5			3.4	
5	3	4.5			3.5	
6	3	3			3.35	
7	3	3.5			3.4	
8	3	4			3.45	
9	3	4			3.45	
10	3	3.5			3.4	

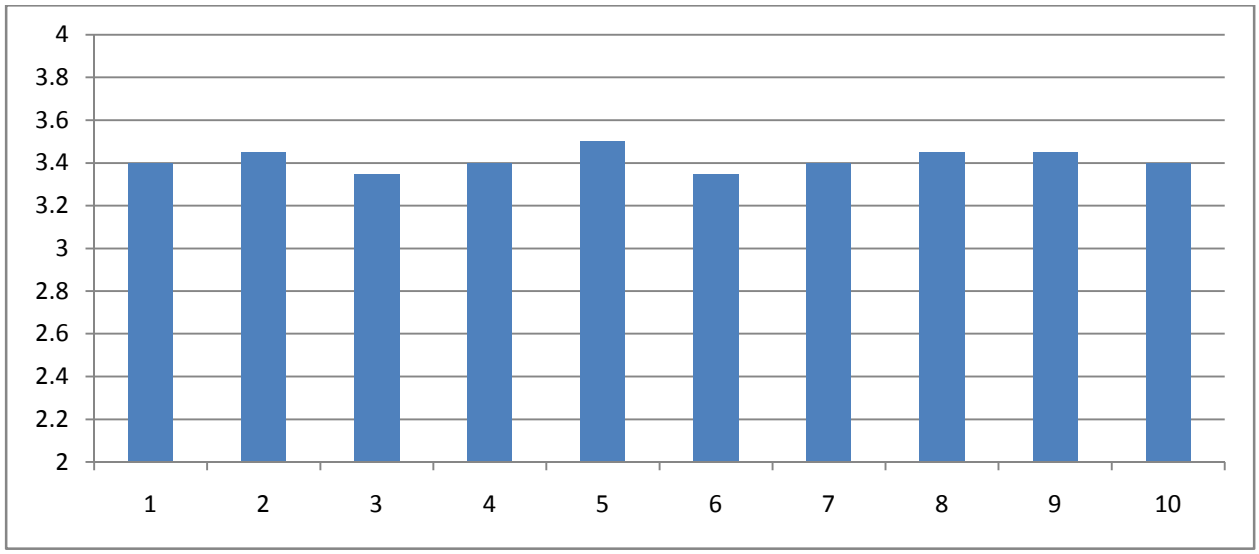

Figure 4.14: Thickness of tablets of Amloten 50® (Batch: T3235005)

Table 4.8: Thickness test of Amloten 50® (Batch: T3235006)

Number of tablets	Main scale Reading (mm)	Reading of Vernier scale	Vernier constant	Vernier error	Thickness (mm)	Average Thickness (mm)
1	3	4	0.1	0.05	3.45	3.44
2	3	3.5			3.4	
3	3	3			3.35	
4	3	4.5			3.5	
5	3	5			3.55	
6	3	3.5			3.4	
7	3	4			3.45	
8	3	3			3.35	
9	3	4.5			3.5	
10	3	4			3.45	

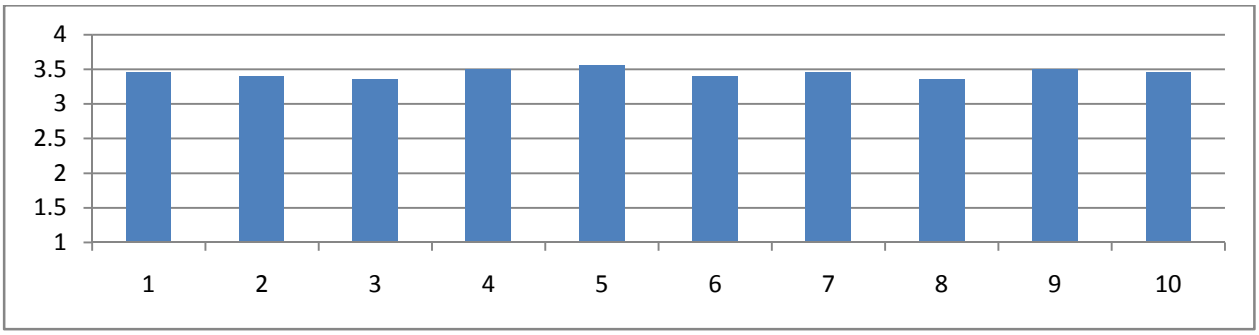

Figure 4.15: Thickness of tablets of Amloten 50® (Batch: T3235006)

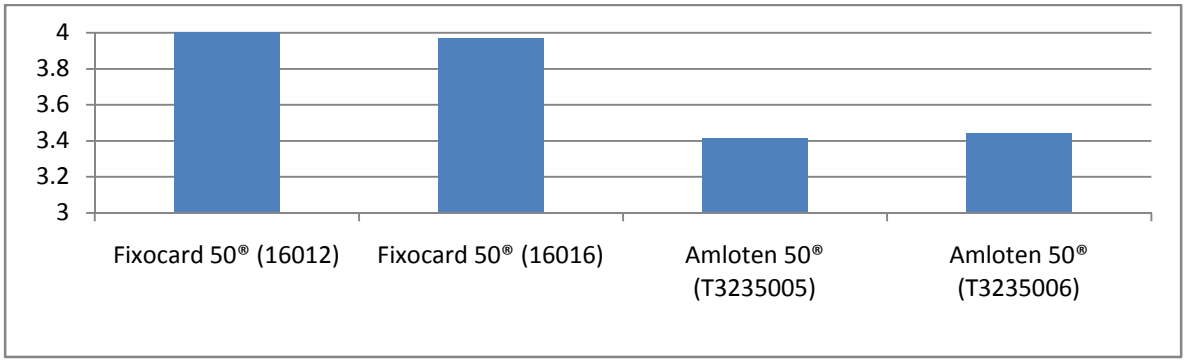

Figure 4.16: Comparison of average thickness of 4 batches

4.3 Hardness test

Hardness test of 2 brands of combined atenolol and amlodipin tablets are given below:

Table 4.9: Hardness test of Fixocard 50® (16012)

Number of tablets	Hardness (Kg)	Average (kg)
1	3.5	3.58
2	3.4	
3	3.9	
4	3.5	
5	3.8	
6	3.4	
7	3.5	
8	3.6	
9	3.5	
10	3.7	

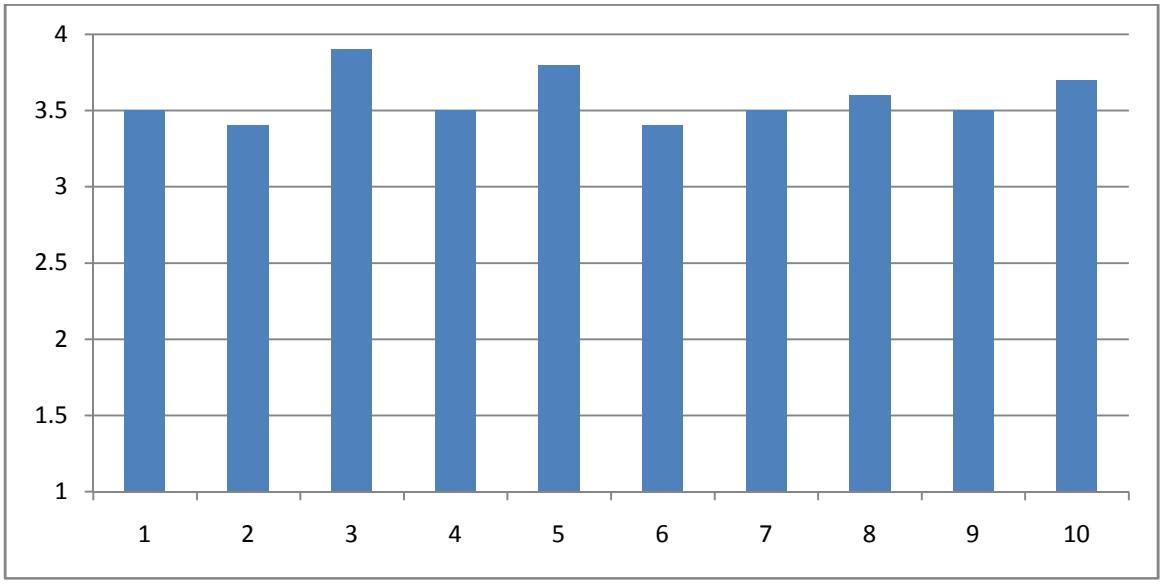

Figure 4.17: Hardness of Fixocard 50® (Batch: 16012)

Table 4.10: Hardness test of Fixocard 50® (Batch: 16016)

Number of tablets	Hardness (Kg)	Average (kg)
1	3.8	4.14
2	4.2	
3	4.1	
4	4.4	
5	3.9	
6	4.2	
7	4.4	
8	4.3	
9	4.0	
10	4.1	

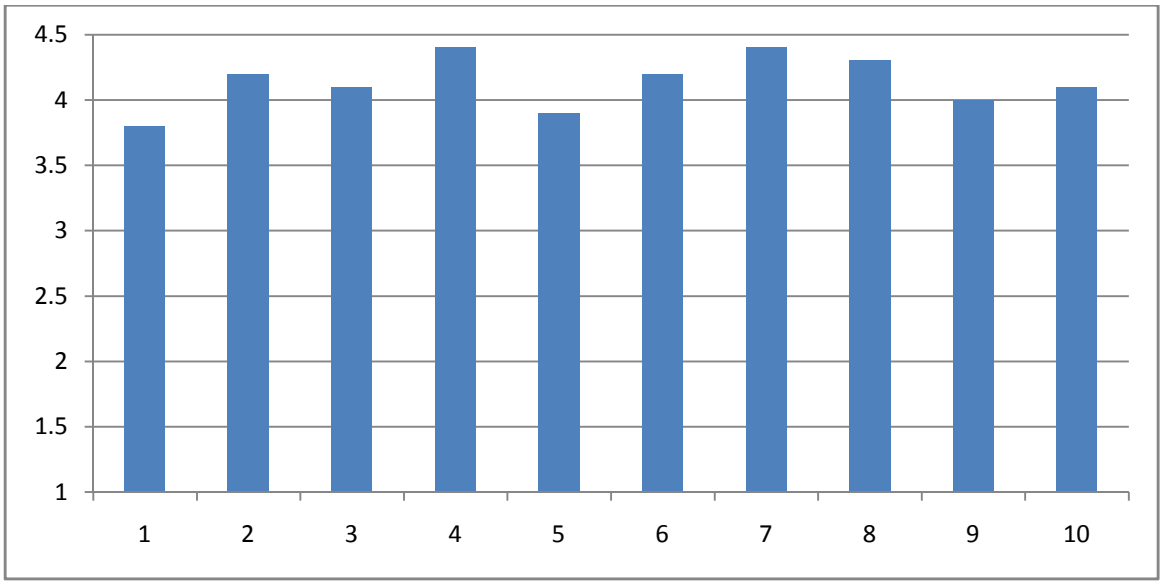

Figure 4.18: Hardness of Fixocard 50® (Batch: 16016)

Table 4.11: Hardness test of Amloten 50® (Batch: T3235005)

Number of tablets	Hardness (Kg)	Average (kg)
1	5.4	5.46
2	5.3	
3	5.5	
4	5.6	
5	5.3	
6	5.5	
7	5.2	
8	5.6	
9	5.7	
10	5.5	

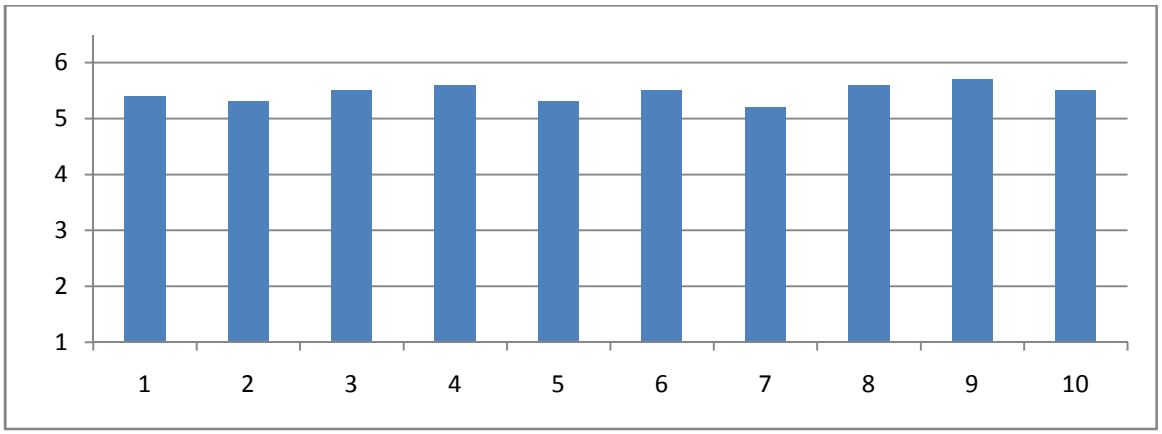

Figure 4.19: Hardness of Amloten 50® (Batch: T3235005)

Table 4.12: Hardness test of Amloten 50® (T3235006)

Number of tablets	Hardness (Kg)	Average (kg)
1	5.7	5.57
2	5.6	
3	5.5	
4	5.8	
5	5.4	
6	5.6	
7	5.5	
8	5.7	
9	5.5	
10	5.4	

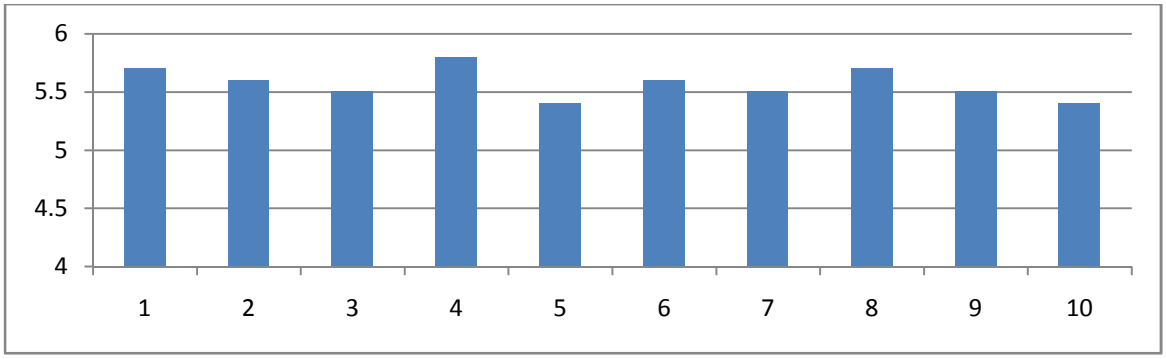

Figure 4.20: Hardness of Amloten 50® (Batch: T3235006)

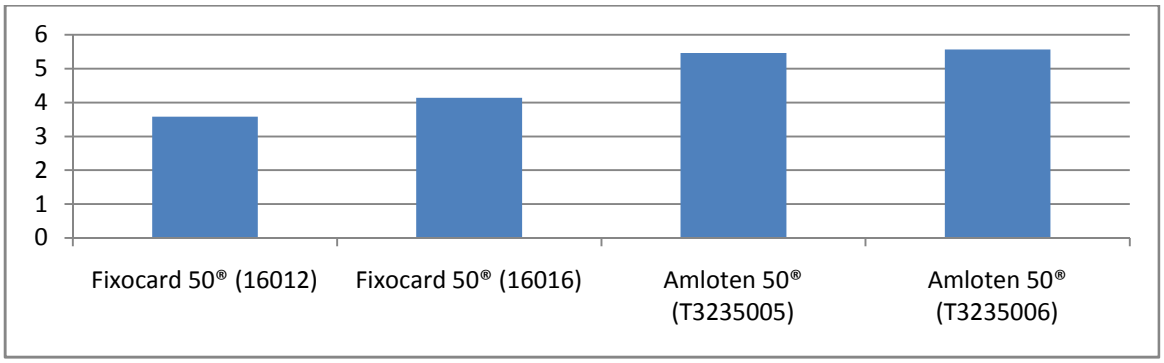

Figure 4.21: Comparison of average hardness (kg) of 4 batches

4.4 Disintegration test

Disintegration test of 2 brands of combined atenolol and amlodipine tablets are given below:

Table 4.13: Disintegration test Fixocard 50® (Batch: 16012) & Fixocard 50® (Batch: 16016)

Number of tablets	Disintegration time (min) of Fixocard 50® (16012)	Average (min)	Disintegration time (min) of Fixocard 50® (16016)	Average (min)
1	4.52	4.7667	5.35	5.635
2	4.83		5.62	
3	5.16		5.79	
4	4.96		5.83	
5	4.47		5.56	
6	4.66		5.66	

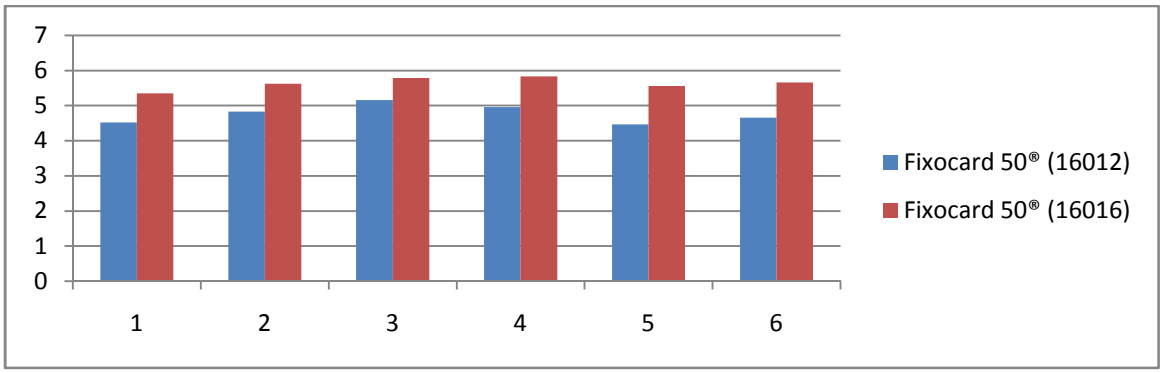

Figure 4.22: Comparison of disintegration time between two batches of Fixocard 50®

Table 4.14: Disintegration test Amloten 50® (Batch: T3235005) & Amloten 50® (Batch: T3235006)

Number of tablets	Disintegration time (min) of Amloten 50® (T3235005)	Average (min)	Disintegration time (min) of Amloten 50® (T3235006)	Average (min)
1	5.12	5.18	5.49	5.56
2	5.26		5.52	
3	4.66		5.69	
4	5.34		5.33	
5	5.28		5.64	
6	5.45		5.71	

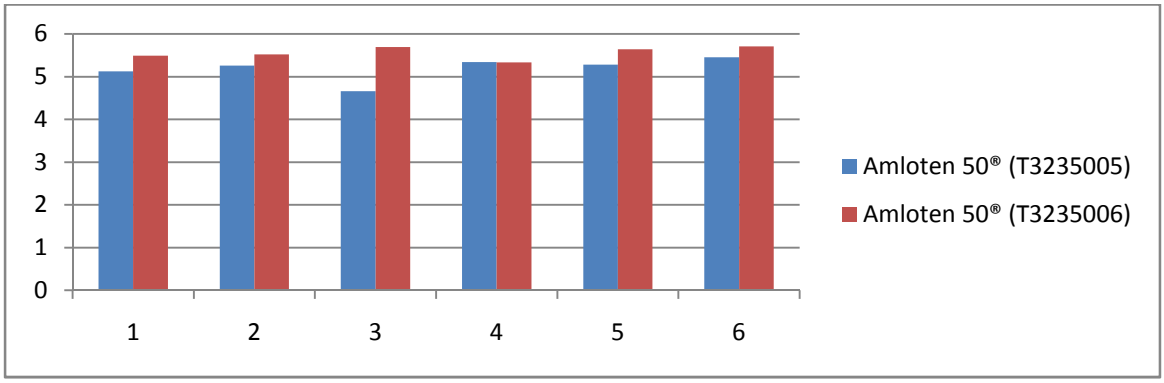

Figure 4.23: Comparison of disintegration time between two batches of Amloten 50®

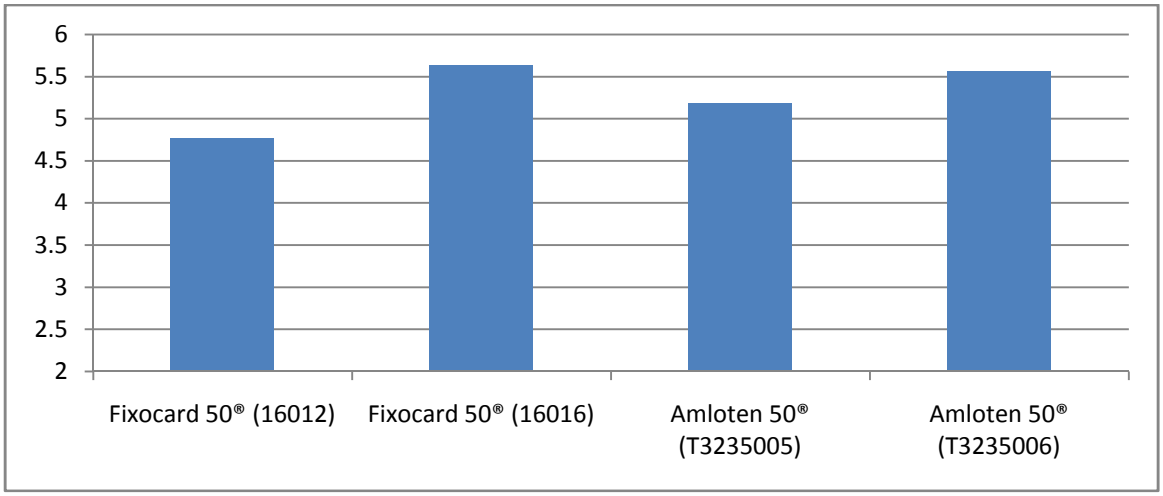

Figure 4.24: A comparison of average disintegration time among various brands

4.5 Potency test

Potency test of 2 brands of combined atenolol and amlodipine tablets are given below:

Table 4.15: Potency test of 2 brands for amlodipine

Name of brand	Concentration	Absorbance at 237.5 nm	Absorbance of pure amlodipine at 237.5 nm wavelength	% Potency
Fixocard 50® (16012)	5 µg/ml	0.765	0.520	96
Fixocard 50® (16016)		0.796		105
Amloten 50® (T3235005)		0.786		102
Amloten 50® (T3235005)		0.776		98

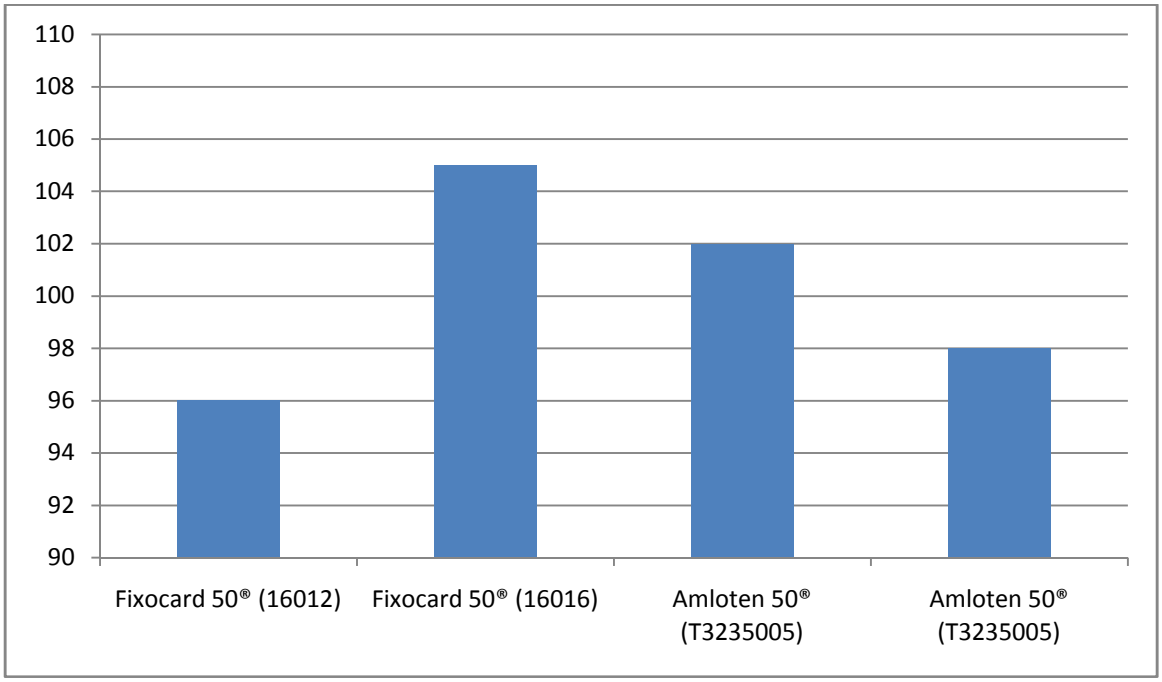

Figure 4.25: Comparison of %Potency of amlodipine among various brands

Table 4.16: Potency test of 2 brands for atenolol:

Name of brand	Concentration	Absorbance at 223.5 nm	Absorbance of pure atenolol at 223.5 nm wavelength	% Potency
Fixocard 50® (16012)	5 µg/ml	0.439	0.265	92
Fixocard 50® (16016)		0.515		99
Amloten 50® (T3235005)		0.494		96
Amloten 50® (T3235005)		0.508		98

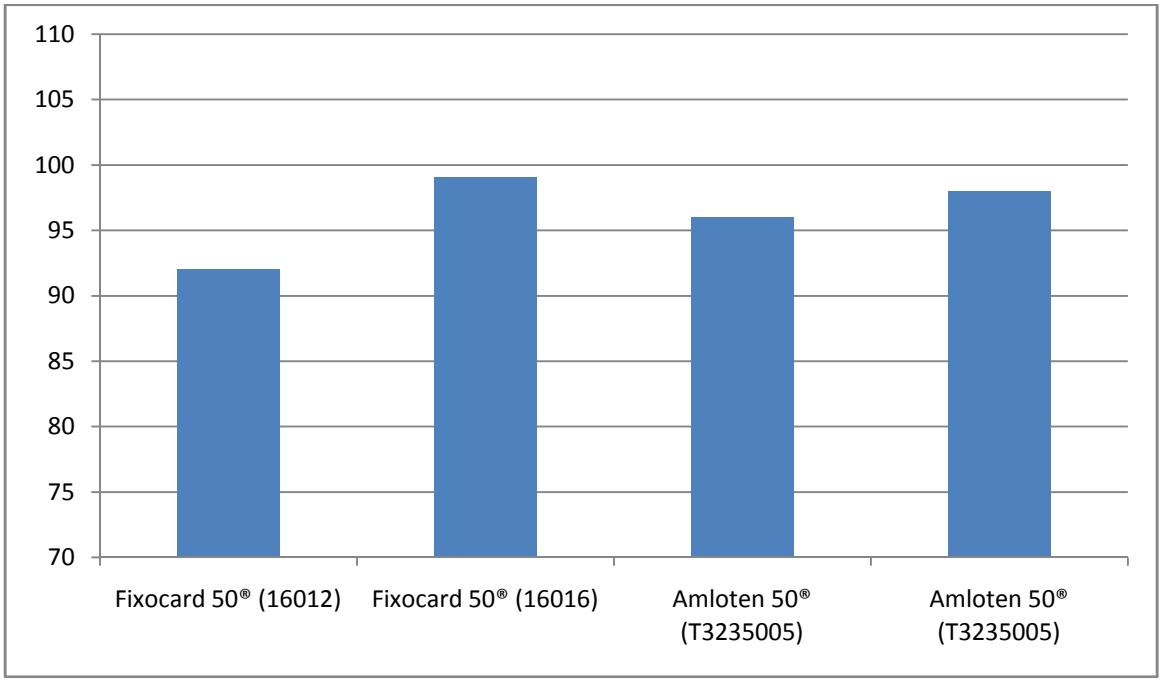

Figure 4.26: Comparison of % Potency of atenolol among various brands

4.6 Dissolution Test

Table 4.17: Dissolution test of Fixocard 50® (Batch: 16012)

Amlodipine				Atenolol			
Drug	**Absorbance (237.5 nm)**	**Conc.**	**% dissolved**	**Drug**	**Absorbance (223.5 nm)**	**Conc.**	**% dissolved**
1	0.746	5 µg/ml	93	**1**	0.222	5 µg/ml	111
2	0.743		92	**2**	0.207		103
3	0.748		93	**3**	0.212		106
4	0.754		94	**4**	0.200		100
5	0.786		98	**5**	0.204		102
6	0.778		97	**6**	0.233		116
Average			**94.5**	**Average**			**106.33**

Table 4.18: Dissolution test of Fixocard 50® (Batch: 16016)

Amlodipine				Atenolol			
Drug	**Absorbance (237.5 nm)**	**Conc.**	**% dissolved**	**Drug**	**Absorbance (223.5 nm)**	**Conc.**	**% dissolved**
1	0.780	5 µg/ml	97	**1**	0.228	5 µg/ml	114
2	0.765		95	**2**	0.184		92
3	0.777		97	**3**	0.221		110
4	0.769		96	**4**	0.189		94
5	0.754		94	**5**	0.224		112
6	0.761		95	**6**	0.199		99
Average			**95.666**	**Average**			**103.5**

Table 4.19: Dissolution test of amloten 50® (Batch: T3235005)

Amlodipine				Atenolol			
Drug	**Absorbance (237.5 nm)**	**Conc.**	**% dissolved**	**Drug**	**Absorbance (223.5 nm)**	**Conc.**	**% dissolved**
1	0.742	5 µg/ml	92	**1**	0.238	5 µg/ml	119
2	0.719		90	**2**	0.240		120
3	0.705		88	**3**	0.216		108
4	0.729		91	**4**	0.235		117
5	0.735		92	**5**	0.223		111
6	0.756		94	**6**	0.230		115
Average			**91.167**	**Average**			**115**

Table 4.20: Dissolution test of amloten 50® (Batch: T3235006)

Amlodipine				Atenolol			
Drug	**Absorbance (237.5 nm)**	**Conc.**	**% dissolved**	**Drug**	**Absorbance (223.5 nm)**	**Conc.**	**% dissolved**
1	0.784	5 µg/ml	98	**1**	0.211	5 µg/ml	105
2	0.765		95	**2**	0.226		113
3	0.770		96	**3**	0.235		117
4	0.763		95	**4**	0.221		110
5	0.760		95	**5**	0.218		109
6	0.794		99	**6**	0.229		114
Average			**96.33**	**Average**			**111.33**

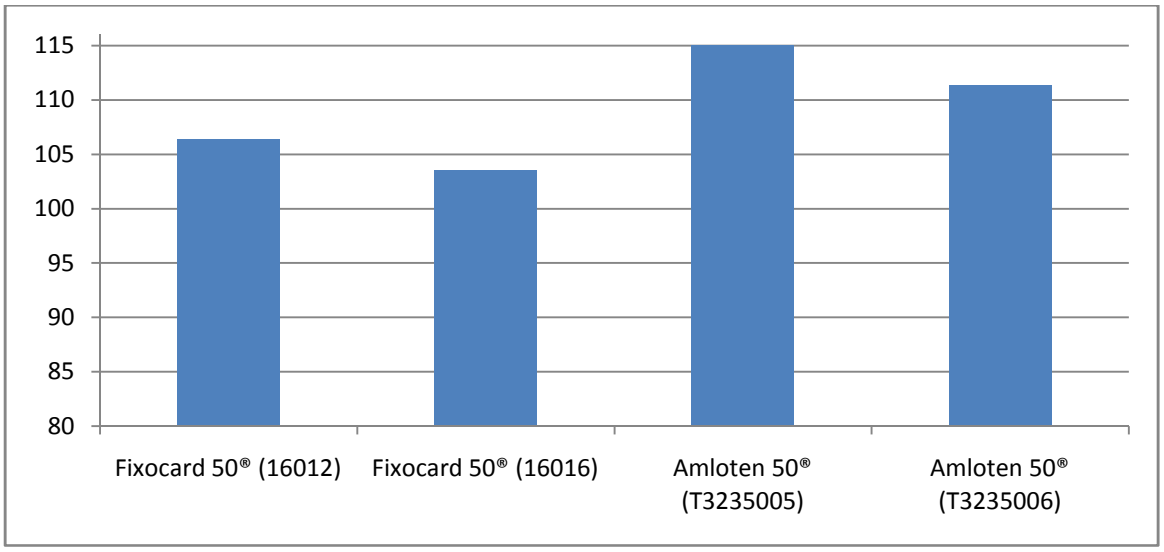

Figure 4.27: Comparison of %Dissolved of atenolol among various brands

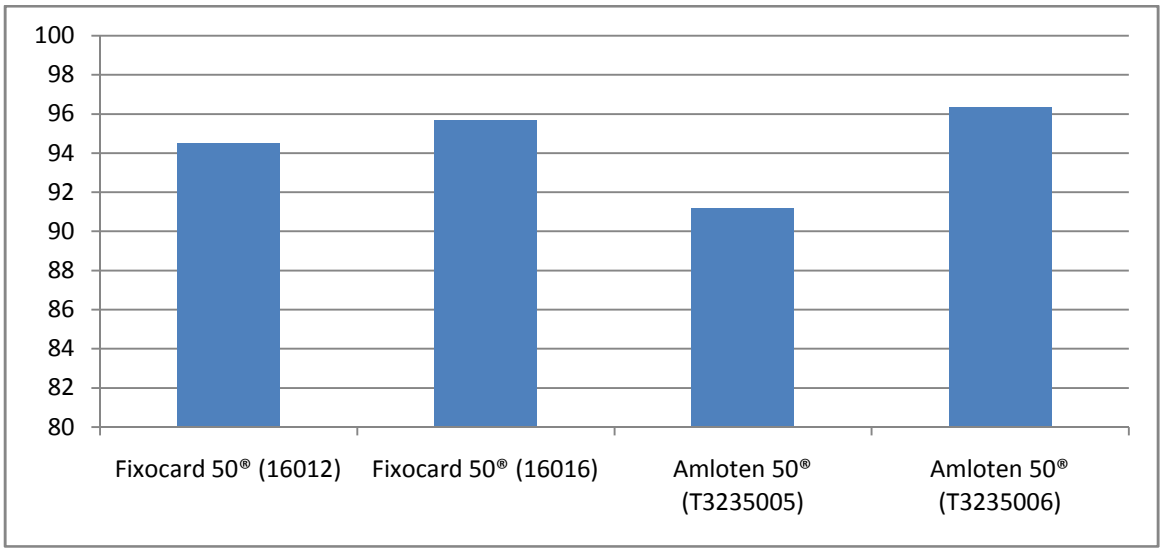

Figure 4.28: Comparison of %Dissolved of amlodipine among various brands

CHAPTER 5: DISCUSSION

Discussion

5.1 Weight variation

The percent weight variation for Fixocard 50® ranged from 3.6093% to -1.6037% (Batch no 16012) and 2.8304% to -3.0827% (Batch no 16016) for individual weight. The % weight variation for Amloten 50® ranged from 4.5305% to -0.2.6851% (Batch no. T3235005 and 5.9204% to -3.3976% (Batch no. T3235006) for individual weight. Average weights of tablets were in between 130 mg to 324 mg so, according to the USP specification, the range of weight variation is ±7.5% (USP, 2007). All 4 batches of tablets from the two brands complies with USP specification and signifies that there is uniformity in flow of powder blend which leads to uniform die fill (USP, 2007).

5.2 Thickness test

According to the USP specification, the range for tablet thickness is ±5mm. All the brands of combined atenolol and amlodipine, Fixocard 50® (Batch 16012) with an average thickness of 4.03mm, Fixocard 50® (Batch 16016) with an average thickness of 3.369mm, Amloten 50® (Batch T3235005) with an average thickness of 3.415mm, Amloten 50® (Batch T3235006) with an average thickness of 3.44mm, met the specification of USP for tablet thickness (USP, 2007).

5.3 Hardness test

According to the USP specification, the minimum tablet hardness is 4 kg (USP, 2009) and the range of hardness is 4 to 8 kg or 10 kg for oral tablets. All the batches, Fixocard 50® (Batch 16016) with an average hardness of 4.14 kg, Amloten 50® (Batch T3235005) with an average hardness of 5.46 kg, Amloten 50® (Batch T3235006) with an average hardness of 5.57 kg met the USP specification except Fixocard 50® (Batch 16012) with an average hardness of 3.58 kg. So the brand Fixocard 50® (Batch 16012) falls short on the range, none even comes close to the acceptable range (USP, 2009).

5.4 Disintegration test

According to BP limit of disintegration time for, uncoated tablet is 15 minutes (BP, 2009); coated tablet is 30 minutes enteric coated tablet is 60 minutes or 1 hour. Both Fixocard 50® and

Amloten 50® are uncoated tablets and all the bathes, Fixocard 50® (Batch 16012) with an average disintegration time of 4.77 min, Fixocard 50® (Batch 16016) with an average disintegration time of 5.64 min, Amloten 50® (Batch T3235005) with an average disintegration time of 5.19 min, Amloten 50® (Batch T3235006) with an average disintegration time of 5.56 min met the specification (BP, 2009).

5.5 Potency test

According to BP, in order to pass the potency test, tablets should not contain less than 90.0% and not more than 110.0% (BP, 2009) of atenolol and amlodipine. For atenolol all four batches; Fixocard 50® (Batch 16012) with a potency of 92%, Fixocard 50® (Batch 16016) with a potency of 98%, Amloten 50® (Batch T3235005) with a potency of 96% and Amloten 50® (Batch T3235006) with a potency of 99% met the specification. For amlodipine all four batches; Fixocard 50® (Batch 16012) with a potency of 96%, Fixocard 50® (Batch 16016) with a potency of 105%, Amloten 50® (Batch T3235005) with a potency of 102% and Amloten 50® (Batch T3235006) with a potency of 98% met the specification (BP, 2009).

5.6 Dissolution Test

According to WHO for sample of six tablets, the % release of tablet should be 85% within 30 minute (WHO, 2014). For Fixocard 50® (Batch 16012), % dissolved of amlodipine ranged from 94-100% with an average of 94.5% and atenolol ranged from 102-120% with an average of 106.33. For Fixocard 50® (Batch 16016), % dissolved of amlodipine ranged from 92-104% with an average of 95.6% and atenolol ranged from 98-114% with an average of 103.5. For Amloten 50® (Batch T3235005), % dissolved of amlodipine ranged from 90-95% with an average of 91.17% and atenolol ranged from 105-125% with an average of 115. For Amloten 50® (Batch T3235006), % dissolved of Amlodipine ranged from 92-99% with an average of 96.33% and atenolol ranged from 105-1130% with an average of 111.33.Thus all 4 batches met the specification based on average dissolution requirements. But two batches (T3235005 and 16012) didn't met specification based on single tablet (total 6 tablets per batches) dissolution specification (WHO, 2014).

CHAPTER 6: CONCLUSION

Conclusion

Atenolol and amlodipine, in combination, significantly decreased blood pressure. Combination of the two drugs results in additive antihypertensive action. Hence it is important to maintain its quality to give the specified and expected effect. In this study it was observed that the two brands of combined atenolol and amlodipine have passed most of the quality control parameter tests with the specifications described in USP and BP. In weight variation test a comparison among the two brands revealed that Fixocard 50® had the highest weight variation. In thickness test a comparison among two brands clearly shows that Amloten 50® has a more consistence thickness than Fixocard 50®. In the hardness test all batch met specification except one batch of Fixocard 50® as it had a very low hardness value. This low hardness value indicate that it was not hard enough to withstand mechanical shocks during packaging, shipping, handling and could face reasonable abuse by the consumer. In the potency test for Atenolol all batches met the specification. In dissolution test, two batches didn't meet specification based on the single tablets but met specification based on average dissolution rate. Due to some technical issue friability study was not performed. For better evaluation, further study needs to be conducted regarding the quality control parameters as these products, at present, a potential choice of drugs for controlling hypertension.

CHAPTER 7: REFERENCES

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