Evaluation of Quality Control Parameters and In Vitro Dissolution Study of Various Brands of Atenolol Available In Bangladesh

A thesis report submitted to the Department of Pharmacy, East West University, Bangladesh, in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

Submitted by

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Department of Pharmacy

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Certificate

This is certify that, `Evaluation of quality control parameters and *in vitro* dissolution study of various brands of atenolol available in Bangladesh` submitted to the Department of Pharmacy, East West University is outcome of the investigations performed by Md. Ahsanul Alam under my supervision. This is also certified that no part of this project report has been or is being submitted elsewhere for the award of any degree or diploma.

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Certificate

This is certify that, “Evaluation of quality control parameters and *in vitro* dissolution study of various brands of atenolol available in Bangladesh submitted to the Department of Pharmacy, East West University is outcome of the investigations performed by Md. Ahsanul Alam under the supervision of Arindom Pal. This is also certified that no part of this project report has been or is being submitted elsewhere for the award of any degree or diploma.

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Abstract

This research work is aimed to investigate the quality control parameters of different batches of three brands of atenolol available in the Bangladeshi market. Three batches from each brand were selected. These brands were Tenoloc, Tenoren, and Cardipro. Quality control tests were performed for evaluation of hardness, thickness, weight variation, friability, disintegration time and dissolution of the tablets from each brand. These tests were performed according to the specification of USP and BP. Hardness value and disintegration time among batches were within acceptance region. Weight variation of all batches of Tenoloc, Tenoren and Cardipro fulfilled the specification. But Percent friability of some batches fulfilled the specification and some did not. Dissolution rate of Tenoloc and Cardipro complied with specification, but dissolution rate of Tenoren did not comply with the specification described in BP.

Keywords: Quality, atenolol, Batch, Percent dissolution, Weight variation, Percent friability, USP, BP

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CHAPTER ONE

INRTODUCTION

1. Introduction

1.1. Atenolol

Beta blockers are competitive inhibitors and interfere with the action of stimulating hormones on beta-adrenergic receptors in the nervous system. Beta blockers can be subdivided into two distinct groups, known as $beta_1$ and $beta_2$. Beta $_1$ blockers mainly affect the heart; $beta_2$ blockers mainly affect receptors in bronchial tissue. Atenolol is Beta $_1$ blocker, a class of drugs used primarily in cardiovascular diseases. Atenolol is approved for controlling high blood pressure, relieving symptoms of angina, and improving survival following a heart attack.

1.2. History

Atenolol was developed by the Stuart Company which was a division of Imperial Chemical Industries (ICI). ICI was renamed Zeneca in 1992. Atenolol received approval in the United States August 19, 1981. According to drugstore.com, 90 days of generic 50 mg pills costs $17.99 in January, 2009. [1]

1.3. Chemistry

Atenolol may be defined by IUPAC nomenclature:

- 4-[2'-hydroxy-3'-[(1-methylethyl)amino] propoxy-benzeneacetamide
- Benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl) amino] propoxy][1]

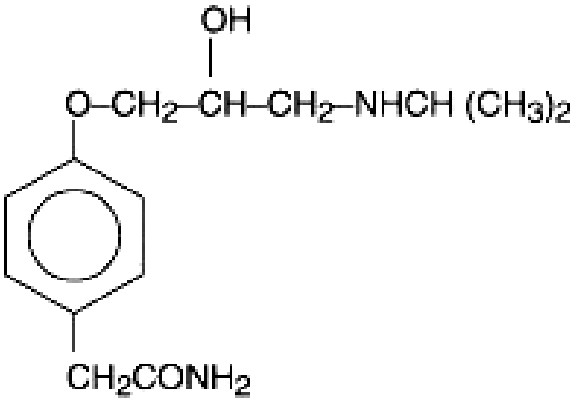

Figure: Chemical structure of atenolol

It is a hydrophilic drug, with solubility in water equal to 26.5 mg/ml at 37ºC, with chemical formula $C_{14}H_{22}N_2O_3$ and molecular mass 266.34 gram/mole for the free base form. It is freely soluble in strongly acidic solutions.[1]

1.4. Mechanism of action

Atenolol competes with sympathomimetic neurotransmitters such as catecholamines for binding at $beta_1$-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 $beta_2$-adrenergic responses in the bronchial and vascular smooth muscles.

Beta receptors are found in both the heart as well as the large airways in the chest. Atenolol blocks the stimulation of these receptors, particularly in the heart, leading to a slower heart rate and more relaxed muscle. Blockade of the beta receptors in the airways causes bronchoconstriction, or tightening of the airways, which can precipitate an asthma or COPD attack. Atenolol preferentially binds to beta receptors in the heart as opposed to in the airways. Thus, atenolol at low doses can be used safely in patients with a known history of lung disease if their blood pressure cannot to be controlled by other medications.[1]

1.5. Specific action of atenolol

Basically atenolol can reduce high blood pressure and chest pain caused by angina, and is also often administered after a heart attack to improve survival. For example:

1.5.1. High blood pressure

A blood pressure reading consists of two numbers (for example, 120/80). The top number is known as the systolic blood pressure, and the bottom number is the diastolic blood pressure. High blood pressure (hypertension) is defined as an average blood pressure higher than 140/90 with multiple blood pressure readings.

In clinical studies, atenolol has been shown to significantly lower systolic and diastolic blood pressure. The higher the dose of atenolol, the greater the drop in blood pressure is expected to be, up to an atenolol dose of 100 mg daily (at higher doses, no further blood pressure reduction is expected). By lowering blood pressure, atenolol can decrease the risks that occur with long-term high blood pressure atenolol does not, however, cure high blood pressure.[2]

1.5.2. Angina

Angina is a type of heart disease that occurs when the heart muscle is not getting enough nutrient- and oxygen-rich blood for a short period of time. The inadequate blood flow is caused by narrowed coronary arteries (the blood vessels that supply blood to the heart). Chest pain is the most common angina symptom that occurs.

Atenolol is effective at treating symptoms of angina because it decreases the workload of the heart. This, in turn, means that the heart needs less oxygen and nutrient-rich blood to function properly at any given level of effort.[2]

1.5.3. Improving survival following a heart attack

A heart attack (also known as a myocardial infarction) is a life-threatening event in which the supply of blood and oxygen to part of the heart is blocked for a long enough period of time that a portion of the heart muscle dies. When people are given atenolol after a heart attack, the risk of dying decreases by about 15%. It is not known how atenolol or other beta blockers improve survival following a heart attack.[2]

1.6. Pharmacokinetics

Absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. The elimination half-life of oralatenolol is approximately 6 to 7 hours, and there is no alteration of the kinetic profile of the drug by chronic administration. Following intravenous administration, peak plasma levels are reached within 5 minutes. Declines from peak levels are rapid during the first 7 hours; thereafter, plasma levels decay with a half-life similar to that of orally administered drug. Following oral doses of 50 mg or 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hours. When renal function is impaired, elimination of atenolol is closely related to the glomerular filtration rate; significant accumulation occurs when the creatinine clearance falls below 35 ml/min.

Atenolol is excreted unchanged in the kidneys. Elimination is dependent on the glomerular filtration rate. Atenolol is not metabolized in the liver by cytochrome P-450. With normal renal function, the serum half-life is about 8 hours. While it was originally thought and promoted that atenolol can be used once a day for isolated hypertension because the central nervous system pharmacodynamic effect persists longer, subsequent studies suggest atenolol should be dosed twice a day even for hypertension.[4]

1.7. Pharmacodynamics

In standard human pharmacological tests, beta-adrenoreceptor blocking activity of atenolol has been demonstrated by:

(1) Reduction in resting and exercise heart rate and cardiac output,

(2) Reduction of systolic and diastolic blood pressure at rest and on exercise,

(3) Inhibition of isoproterenol induced tachycardia, and

(4) Reduction in reflex orthostatic tachycardia.

A significant beta-blocking effect of atenolol, as measured by reduction of exercise tachycardia, is apparent within one hour following oral administration of a single dose. This effect is maximal at about 2 to 4 hours, and persists for at least 24 hours. Maximum reduction in exercise tachycardia occurs within 5 minutes of an intravenous dose. For both orally and intravenously administered drug, the duration of action is dose related and also bears a linear relationship to the logarithm of plasma atenolol concentration. The effect on exercise tachycardia of a single 10 mg intravenous dose is largely dissipated by 12 hours, whereas beta-blocking activity of single oral doses of 50 mg and 100 mg is still evident beyond 24 hours following administration. However, as has been shown for all beta-blocking agents, the antihypertensive effect does not appear to be related to plasma level.[4]

1.8. Undesirable effects of atenolol[5]

1.8.1. Cardiovascular: Heart failure, heart block, bradycardia, hypotension, dizziness, peripheral vasoconstriction with coldness of the extremities.

1.8.2. Eye: Visual disturbances including blurred vision, sore eyes, dry eyes (reversible on withdrawal; discontinuance of the drug should be considered if any such reaction is not otherwise explicable), conjunctivitis.

1.8.3. Gastrointestinal: Nausea, vomiting, diarrhoea, constipation and abdominal cramps, sclerosing peritonitis and retroperitoneal fibrosis.

1.8.4. General: Fatigue, headache, dry mouth, sleep disturbances of the type noted with other beta-blockers have been reported rarely.

1.8.5. Haemopoietic: Thrombocytopenia, eosinophilia and leucopenia including agranulocytosis.

1.8.6. Hepatic: After taking atenolol there may be possible of elevated liver enzymes and increased level of bilirubin.

1.8.7. Metabolic: Lupus-like syndrome. Hyperglycemia or hypoglycemia. Non-diabetic patients susceptible to hypoglycemia include those on regular dialysis, and long term patients who are nutritionally compromised or have liver disease. Atenolol may increase serum triglyceride levels.

1.8.8. Musculoskeletal, connective tissue and bone disorders: Myopathies including muscle cramps, arthralgia.

1.8.9. Nervous system: Paraesthesia, peripheral neuritis.

1.8.10. Psychiatric: Depression, psychosis, hallucinations, confusion, anxiety and nervousness.

1.8.11. Respiratory: Bronchospasm, pneumonitis, pulmonary fibrosis and pleurisy.

1.8.12. Reproductive: Impotence, Peyronie's disease;

1.8.13. Skin: Reversible alopecia, skin rashes (reversible on withdrawal; discontinuance of the drug should be considered if any such reaction is not otherwise explicable), form rash or exacerbation of psoriasis

1.8.14. Withdrawal: Sudden cessation of therapy with a beta-blocker can cause angina, myocardial infarction, ventricular arrhythmias and sudden cardiac death.

1.9. Contraindications

Atenolol is contra-indicated in patients with a known hypersensitivity to atenolol, severe bradycardia, second degree or third degree heart block, uncontrolled heart failure, hypotension, severe peripheral vascular disease, sick sinus syndrome, cardiogenic shock, metabolic acidosis. Although cardio selective beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers these should be avoided in patients with asthma or a history of reversible obstructive airways disease or bronchospasm unless there are compelling clinical reasons for their use.[5]

1.10. Interaction with other medicinal products and other forms of interaction:

1.10.1. Pharmacodynamic Interactions: When effects of two drugs are similar, their simultaneous use can lend to additive if not synergistic effect. For example when atenolol is used along with a non-hydropyridine calcium blocker, profound bradycardia can occur. Similarly, if two drugs with opposing effects are used together the effect of individual drug may be markedly reduced. If dopamine or dobutamine becomes necessary in a patient already on Atenolol, positive inotropic effects of these drugs may be significantly blunted by atenolol.[14]

1.10.2. Pharmacokinetic interactions: These can occur due to variety of reasons:

- If gastrointestinal absorption of a drug is reduced it is recommended to try the concomitant use of another drug,
- Change in the action of metabolizing enzymes,
- Presence of one drug changing the degree of protein binding of another drug,

- One drug affecting renal excretion (enhancing or reducing) of another drug[14]

1.10.3. Antiarrhythmics: Concurrent administration of amiodarone and atenolol causes pharmacodynamic interaction in form of conduction defects or more profound negative inotropic effect. Similar interaction may be seen with flecainide and phenytoin. Beta blockers can have pharmacokinetic interaction where by sharing the hepatic flow. Beta blockers can reduce metabolism of xylocaine by the liver, increasing its blood level leading to its toxicity. Plasma concentration of beta blocking drugs may be increased when used along with propafenon. This effect may be less common with atenolol than other beta blocking agents since excretion of atenolol is mainly renal and not hepatic.[14]

1.10.4. Calcium channel blockers like diltiazem and verapamil when used along with beta blockers, bradyarrhythmias may result. In particular sinus bradycardia/a-v block may be witnessed. Such combination can also result in marked negative ion tropism and is better avoided. However if for any reason it becomes essential to use such combination, frequent monitoring of cardiac rhythm and cardiac contractility (by echocardiography) is advisable.[14]

1.10.5. Amphetamines: Concomitant use should be avoided.[4]

1.10.6. Ampicillin: Reduces atenolol serum levels.[4]

1.10.7. Anaethetics: Enhanced hypotensive effect. Anaesthetics which cause myocardial depression, e.g. ether, halothane and enflurane should be avoided.[4]

1.10.8. Analgesics: Antihypertensive effects of beta-blockers may be impaired by non-steroidal anti-inflammatory drugs (NSAIDs), particularly indomethacin – concominant use should be avoided.[4]

1.10.9. Antacids: Reduced absorption may occur if calcium or aluminium hydroxide is administered concurrently[4].

1.10.10. Antiarrhythmics and other drugs affecting cardiac conduction: (eg, disopyramide, amiodarone, quinidine) additive negative inotropic effects on the heart, with increased risk of bradycardia, hypotension, ventricular fibrillation, heart block or asystole - concomitant use should be avoided[4].

1.10.11. Anticholinesterase agents: Increased risk of bradycardia[4].

1.10.12. Antidepressants and antipsychotics: Phenothiazines and tricyclic antidepressants and tropisetron may increase the risk of ventricular arrhythmias Enhanced hypotensive effect with monoamine oxidase inhibitors (MAOIs).[4]

1.10.13. Antidiabetics: Dosage of hypoglycaemic agents requirements may need to be increased. There may be an enhanced hypoglycaemic effect and masking of warning signs with concurrent administration of insulin and oral antidiabetic drugs. Hypoglycaemia is more likely in Type I than in Type II diabetics and may be associated with delayed recovery[4].

1.10.14. Antimalarials: Risk of bradycardia increased with mefloquine.

1.10.15. Anxiolytics and hypnotics: Enhanced hypotensive effect with benzodiazepines.

1.10.16. Cardiac glycosides: Risk of marked bradycardia and AV block[4].

1.10.17. Clonidine: Increased risk of hypertension on withdrawal.

1.10.18. Ergot alkaloids: Increased peripheral vasoconstriction.

1.10.19. Moxisylyte: Increased risk of severe postural hypotension.

1.10.20. Oestrogens and Progesterones: Oestrogens and combined oral contraceptives may antagonise the antihypertensive effect.

1.10.21. Parasympathomimetics: Increased risk of bradycardia

1.10.22. Sympathomimetics: Risk of severe hypertension and bradycardia with such agents as adrenaline, noradrenaline and ephedrine –concominant use should be avoided. Beta-blockers may also reduce the response to adrenaline in the management of anaphylaxis[4].

1.10.23. Theophylline: Atenolol antagonises bronchodilator effect: avoid concomitant use

1.10.24. Ulcer healing drugs: Carbenoxolone may antagonise the hypotensive effect.[4]

1.11. Special warnings and precautions for use of atenolol:

Care should be taken when using atenolol in patients with poor cardiac reserve. Myocardial contractility must be maintained and signs of failure controlled with digitalis and diuretics. Therapy should not be withdrawn abruptly, especially in patients with ischaemic heart disease, and replacement therapy should be considered to prevent exacerbation of angina pectoris, rebound hypertension, myocardial infarction, ventricular arrhythmias and sudden cardiac death. Treatment should not be discontinued abruptly in patients on long-term therapy, but should be discontinued over one to two weeks. If a beta-blocker is withdrawn prior to surgery it should be discontinued for at least 24 hours, if the patient is being anaesthetised. If beta-blockers are not discontinued before anaesthesia, the anaesthetist should be made aware of the beta-blocker therapy. A drug such as atropine may be given to counter increases in vagal tone. Anaesthetics causing myocardial depression such as ether, halothane and enflurane should be avoided.Beta-blockers may increase both the sensitivity towards allergens and seriousness of anaphylactic

reactions and may also reduce the response to adrenaline. They may unmask myasthenia gravis or potentiate a myasthenic condition. Patients with psoriasis should only be given beta-blockers after careful consideration, as psoriasis may be aggravated. Atenolol should be used with caution in diabetics subject to frequent episodes of hypoglycaemia. Symptoms of hypoglycaemia and of hyperthyroidism may be masked.If the use of atenolol in patients with asthma or a history of obstructive airways disease is unavoidable, the risk of inducing bronchospasm should be appreciated and appropriate precautions taken. If bronchospasm occurs, this will usually be reversed by commonly used bronchodilators such as salbutamol or isoprenaline. In patients with renal impairment or hepatic dysfunction, atenolol should be used with caution and reduction of dosage should be considered.[4]

1.12. Purpose of different quality parameter test of atenolol tablet

1.12.1. Weight variation: weight variation test is done batch to batch to check the uniformity of the tablets. Some tablet fails to maintain uniformity, some are properly uniformed. There are several reason that the weight of tablets varies batch to batch.

1.12.1.1. Tablet weight variation may be caused by[5]:

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

1.12.2. Purpose of hardness test

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

2. Hardness can affect the disintegration. So if the tablet is too hard, it may not disintegrate in the required period of time. And if the tablet is too soft, it will not withstand the handling during subsequent processing such as coating or packaging.

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

1.12.2.1 Factor affecting the hardness of tablets

1. Compression of the tablet and compressive force.

2. Amount of binder, more binder more hardness.

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

1.12.3. Purpose of friability test of tablet

Friability test is done to evaluate the ability of tablets to withstand abrasion, packaging, handling and shipping. It can also be defined as the phenomenon whereby tablet surfaces are damaged and or show evidence of lamination or breakage when subjected to mechanical shock or attrition. During manufacturing and handling, tablets are subjected to stresses from collision and tablet sliding towards one another and other solid surfaces, which can result in the removal of small fragments and particles from the tablet surface. The results will be progressive reduction in weight and change in appearance.[6]

1.12.3.1 Factor affecting friability of tablets

Tablet friability may be influenced by the moisture content of the tablet, granulation and finished tablets. A low but acceptable moisture level acts as a binder. Very dry granulations that contain only fractional percentages of moisture often produce more friable tablets than granulations containing 2-4% moisture.

1.12.4. Purpose of Disintegration test:

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

1.12.5. Purpose of dissolution test

Dissolution is a test used by the Pharmaceutical industry to characterize the dissolution properties of the active drug, the active drug's release and the dissolution from a dosage formulation. 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.

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 atenolol market lifetime, determining whether variations affect in vitro release rate.

1.12.5.1 Factor affecting dissolution of tablet[7]

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

1.12.5.1.1. 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.

1.12.5.1.2. Particle Size

Particle size of drugs contained in tablets will enhance dissolution and absorption. This can most likely be attributed to the proceduresemployed in tablet production:,that is, mixing the drug with usually hydrophilic diluents and subsequent granulation will result in a more hydrophilic surface, even for originally hydrophobic drug particles.

1.12.5.1.3. 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.

1.12.5.1.4. 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.

1.12.5.1.5. 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.

1.12.5.1.6. Interfacial tension between drug and dissolution medium

The properties of the interface between the drug and the dissolution medium can become a deciding factor as far as dissolution rate is concerned. The characteristics can be modified by the addition of agent that acts at the interface.

1.12.5.1.7. 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 when administered orally. Drugs with low solubility when incorporated with surfactants can enhance their dissolution.

CHAPTER TWO

AIMS AND OBJECTIVES OF THE STUDY

2. Aim and Objective of the study

The objective of this study was to evaluate the quality control parameters of different batches of three different brands of atenolol tablet available in the market.

Quality parameters that are mainly focused:

- Weight variation test
- Friability test
- Hardness test
- Dissolution test and
- Disintegration test

Main aim was to evaluate the physical parameters to see the batch to batch variation of atenolol tablets which are available in the market. Because when tablets are manufactured they comply with the standard quality but after they reach the market they may or may not maintain same quality after a certain period of time. This study mainly focused on whether all the batches of different brands meet all the quality parameters or not.

CHAPTER THREE

METHODS AND MATERIALS

3. Method and materials

3.1. Sample Collection

Three different types of atenolol market preparations with various batch was collected from various pharmacy shops.

3.1.1. Raw Materials

Table 3.1: Raw Materials used in the experiment including source

Materials Name	Source (Supplier Name)
Atenolol	ACI pharmaceuticals ltd.

3.1.2. Reagents

Table 3.2: Reagents used in the experiment including source

Reagents Name	Source (Supplier Name)
Hydrochloric acid	Germany
Methanol	Germany
Distilled Water	Laboratory(East West University)

3.2. Equipments & Instruments

Table 3.3: Equipments & Instruments used in the experiment including source

Serial No.	Equipments Name	Model
1	Tablet Hardness tester	VEEGO, Serial No. 54/09 05
2	Friabilator	VEEGO, Serial No. 43/03 05, Type: VPT-2D, 230 Volts, 50 Hz
3	Electronic Balance	Electronic Balance, Type: AY220, No: D432812964, Capacity: 220gm,

		Readability: 0.1 mg.
4	Tablet Dissolution Tester	PHARMA TEST Model- DT 70
5	UV-VIS Spectrophotometer	Shimadzu, Japan

Table 3.4: List of Apparatus/ Glasswares used throughout this project

Serial No.	Name	Serial No.	Name
1.	Several Plastic Containers	8.	Measuring Cylinder (1000 mL & 2000 mL)
2.	Mortar & Pastels	9.	Measuring Flask (1000 mL)
3.	Test tubes	10.	Beakers
4.	Volumetric Flasks (10 ml & 100 ml)	11.	Laboratory Mixer
5.	Micro Pipette	12.	Saptula
6.	Pipette	13.	Glass Rod
7.	Volumetric Pipette	14	Filter Papers

3.3. Figure of some instruments used in the experiment:

Figure: Dissolution tester

Figure: Tablet Friabilator

Figure: Electronic Balance

Figure: Hardness tester

3.4. Methods:

3.4.1. Hardness Test of Tablets: [16]

Tablet hardness is usually expressed as the load required crushing a tablet placed on its edge. Hardness is thus sometimes termed the tablet crushing strength. The suitability of a tablet in

regard to mechanical stability during packaging and shipment can usually be predicted on the basis of hardness. Tablet hardness, in turn, influences tablet density and porosity. It may affect tablet friability and disintegration time. It usually affects drug dissolution and release and it may affect bioavailability.

3.4.1.1. Procedure:

1. The slide scale of the hardness tester was made zero
2. One tablet was placed vertically between two jaws.
3. Force was applied with a screw thread and spring until the tablet fractured.
4. Reading in Kg was taken from the sliding scale.

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.

3.4.2 Friability Test of Tablets:

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

3.4.2.1 Procedure:

1. 10 tablets were weighted. It was considered as an initial reading
2. The tablet were placed in the section 1 of the drum of the friability tester and rotated 100 times.
3. The tablets were re-weighted. It was considered as a final reading.
4. The percent loss was calculated.
5. According to the U.S.P the tablets should not lose more than 1% of their total weight

3.4.2.2 Calculation%[15]

Percent of friability = (M1 – M2) / M1 ×100%

Where, M1 = weight of the tablets before the rotation

M2 = weight of the tablets after the rotation

3.4.3 Weight Variation Test of Tablets: [16]

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. Poor granulation flow properties, resulting in uneven die fill.
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. Differences in lower punch length, which result in different size die cavities[12].

3.4.3.1 Procedure:

1. 10 tablets were taken and weighed all the tablets
2. The average was taken and it was considered as the standard weight of an individual tablet
3. All the tablets were weighed individually and observed whether the individual tablets are within the range or not.

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

Average weight	Percentage difference
130 mg or less	± 10
More than 130 to 324 mg	±7.5
More than 324 mg	±5

3.4.3.2

Calculation:

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

3.4.4. Dissolution Test of Tablets: [12]

Drugs administered orally in solid dosage forms, such as tablet or capsules, must dissolve in the contents of the gastrointestinal tract before drug absorption can occur. Often the rate of drug absorption is determined by the rate of drug dissolution from the dosage form. Therefore, if it is important to achieve high peak blood levels for a drug, it will usually be important to obtain rapid drug dissolution from the dosage form.

3.4.4.1. Conditions:

- Medium: 500 ml 0.1N HCL
- Apparatus: USP Dissolution apparatus II (Paddle apparatus)
- Speed: 100 rpm
- Time: 75 minutes
- λ_{max}: 275nm
- Temperature: 37.5 C

3.4.4.2 Procedure:

1. First 0.1N HCL has been weighed properly.
2. Then 0.1N HCL has been transferred to 1000 ml volumetric flask
3. This process has been followed six times.
4. From each volumetric flask 500ml of solution has been transferred to dissolution vessel placed into the dissolution tester which is fixed to 50 rpm for 45 minutes.
5. When the dissolution tester has been ready to perform then we have to put six tablets of same brand into the vessel.
6. The same procedure has been performed three times for different batch of atenolol tablet.

7. After 45 minutes 10 ml of sample has been drawn from each vessel.
8. Finally we have to use UV spectrophotometer Absorbance of the sample has been measured by fixing the wave length at 275 nm.
9. The average of the absorbance data has been taken.
10. The above procedure has been done for standard sample also and we will get the UV absorbance data for standard sample of atenolol.

3.4.5 Disintegration test: [12]

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.

3.4.5.1. Condition:

- Distilled water
- 37^0C temperature to maintain body temperature.

3.4.5.2. Procedure:

1. The disintegration tester was assembled
2. An arbitrary figure appeared in the digital display
3. Then the time and temperature was set at prescribed in specification.
4. 600ml of the distilled water was placed in each 1000ml beaker
5. The temperature of the liquid was maintained at 35-39^{0}C
6. In each of the 6 tubes one tablet was placed
7. After placement of the tablet 6 disc was placed above the tablet.
8. The machine was then operated for the prescribed period.
9. The entire tablet was disintegrated within the prescribed time.

CHAPTER FOUR

RESULT AND DISSCUSION

4. Result and discussion

Several tests were performed to evaluate the quality control parameters of three batches of atenolol.

4.1 Weight variation test

The weight of a tablet is determined by the amount of fill placed in the die is measured by volume and not by weight and therefore depends on the granule size and the void space during its manufacturing process. With a tablet designed to contain a specific amount of drug in a specific amount of tablet formula, the weight of the tablet being made is routinely measured to help ensure that a tablet contains the proper amount of drug. All the weight variation data are represented in bar chart below

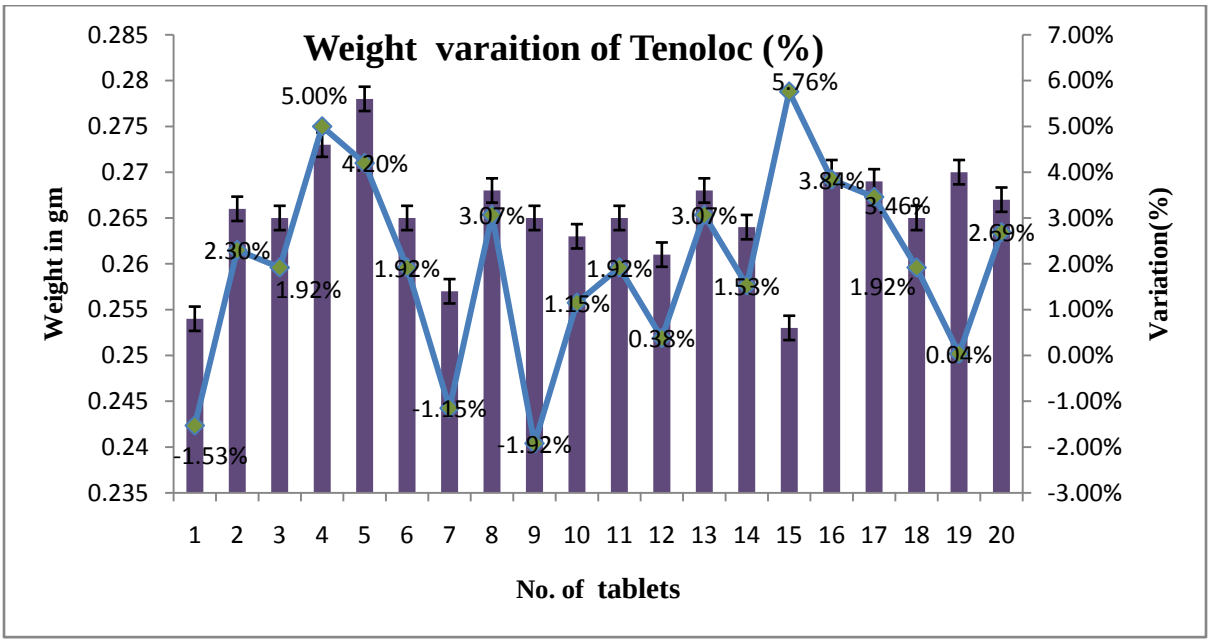

Figure 4.1: Bar chart of weight variation of Atenolol, Brand: Tenoloc, Batch no.VN1007

The graph 4.1 provides information about the individual weight of atenolol tablet and % weight variation. The bar chart is indicating individual weight of twenty tablets. The line chart is showing % weight variation. Left side of the Y axis is indicating individual weight and right side of Y axis is indicating percentage variation. According to BP all the tablets comply with all specification. No tablets exceed ± 5 % variation. That means the Batch # VN1007 of Tenoloc has passed the QC parameters.

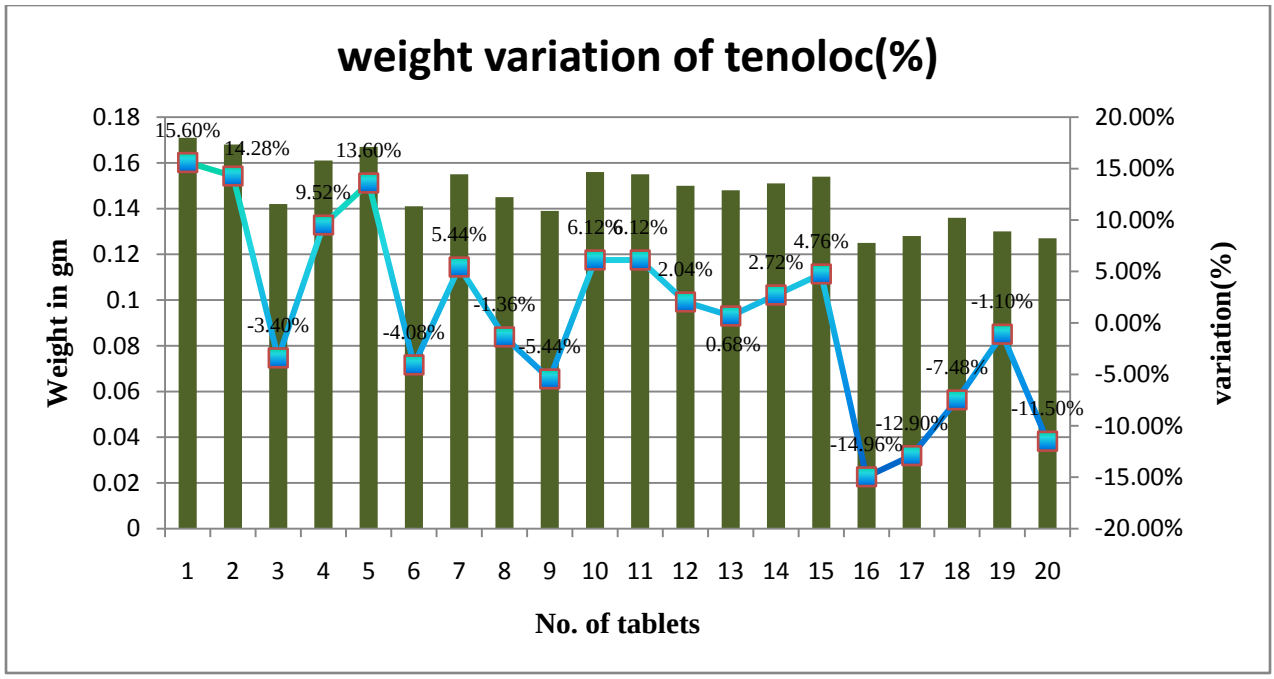

Fig 4.2: Bar chart showing weight variation of atenolol (Brand: Tenoloc, Batch: VN10011)

The graph 4.2 provides information about the individual weight of atenolol tablet and % weight variation. The bar chart is indicating individual weight of twenty tablets. The line chart is showing % weight variation. Left side of the Y axis is indicating individual weight and right side of Y axis is indicating percentage variation. According to BP maximum of the tablets did not comply with all specification. Only some tablets exceed the ± 5 % variation, that means the Batch # VN1011 of tenoloc has passed the QC parameters.

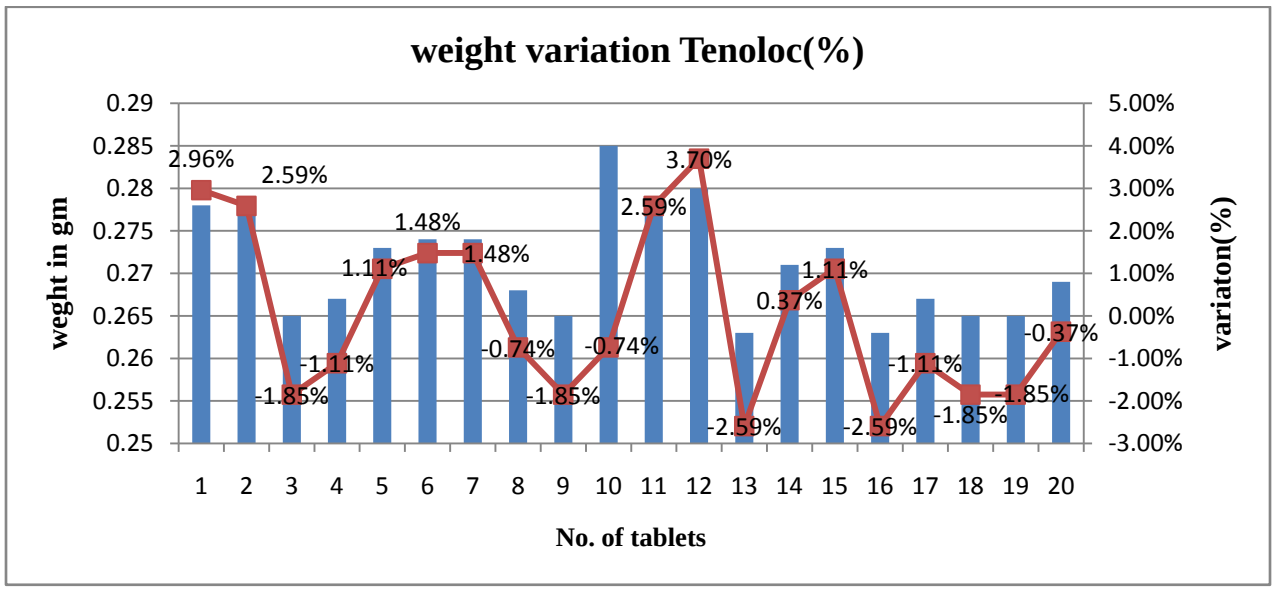

Fig 4.3: Bar chart showing weight variation of atenolol, Brand: Tenoloc, Batch:VN1007

The graph 4.3 provides information about the individual weight of atenolol tablet and % weight variation. The bar chart is indicating individual weight of twenty tablets. The line chart is showing % weight variation. Left side of the Y axis is indicating individual weight and right side of Y axis is indicating percentage variation. According to BP all the tablets comply with all specification. No tablet exceeds ± 5 % variation. That means the Batch # VN1004 of tenoloc has passed the QC parameters.

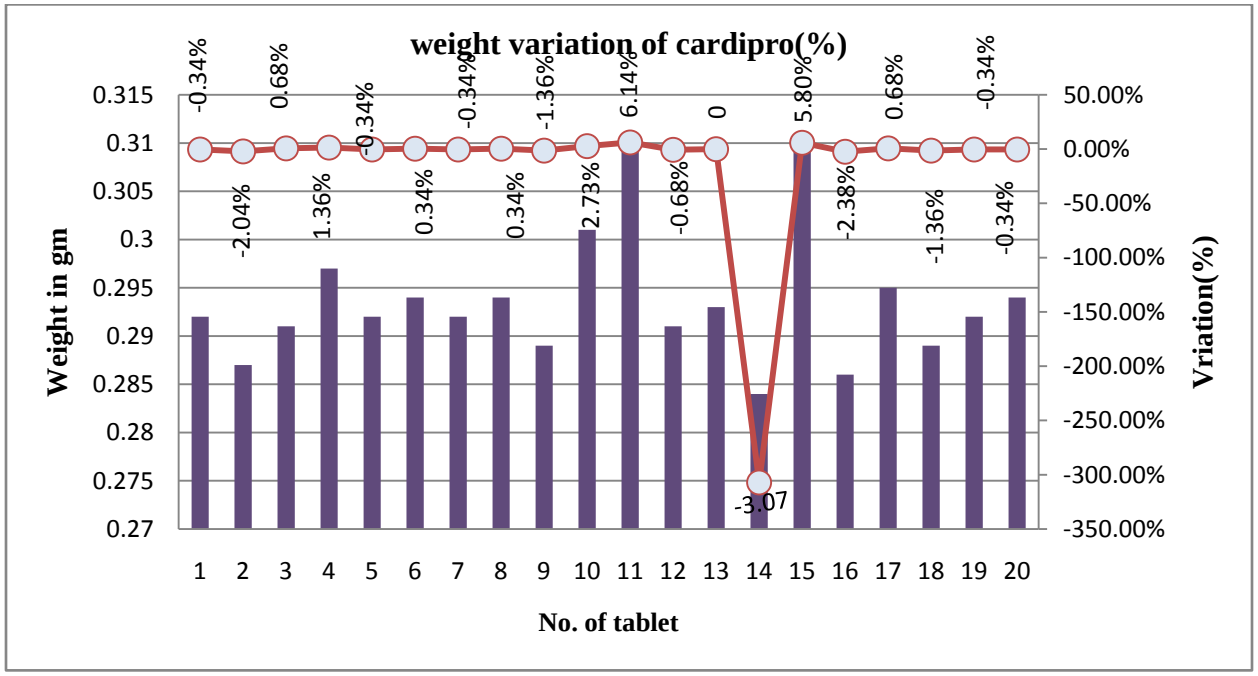

Fig 4.4: Bar chart showing weight variation of atenolol, Brand: Cardipro,batch: 9100858

The graph 4.4 provides information about the individual weight of atenolol tablet and % weight variation. The bar chart is indicating individual weight of twenty tablets. The line chart is showing % weight variation. Left side of the Y axis is indicating individual weight and right side of Y axis is indicating percentage variation. According to BP all the tablets comply with all specification. No tablet exceeds ± 5 % variation. That means the Batch #9100858 of Cardipro has passed the QC parameters.

The graph 4.5 below provides information about the individual weight of atenolol tablet and % weight variation. The bar chart is indicating individual weight of twenty tablets. The line chart is showing % weight variation. Left side of the Y axis is indicating individual weight and right side of Y axis is indicating percentage variation. According to BP all the tablets comply with all

specification. No tablet exceeds ± 5 % variation. That means the Batch#1070397 of Cardipro has passed the QC parameters.

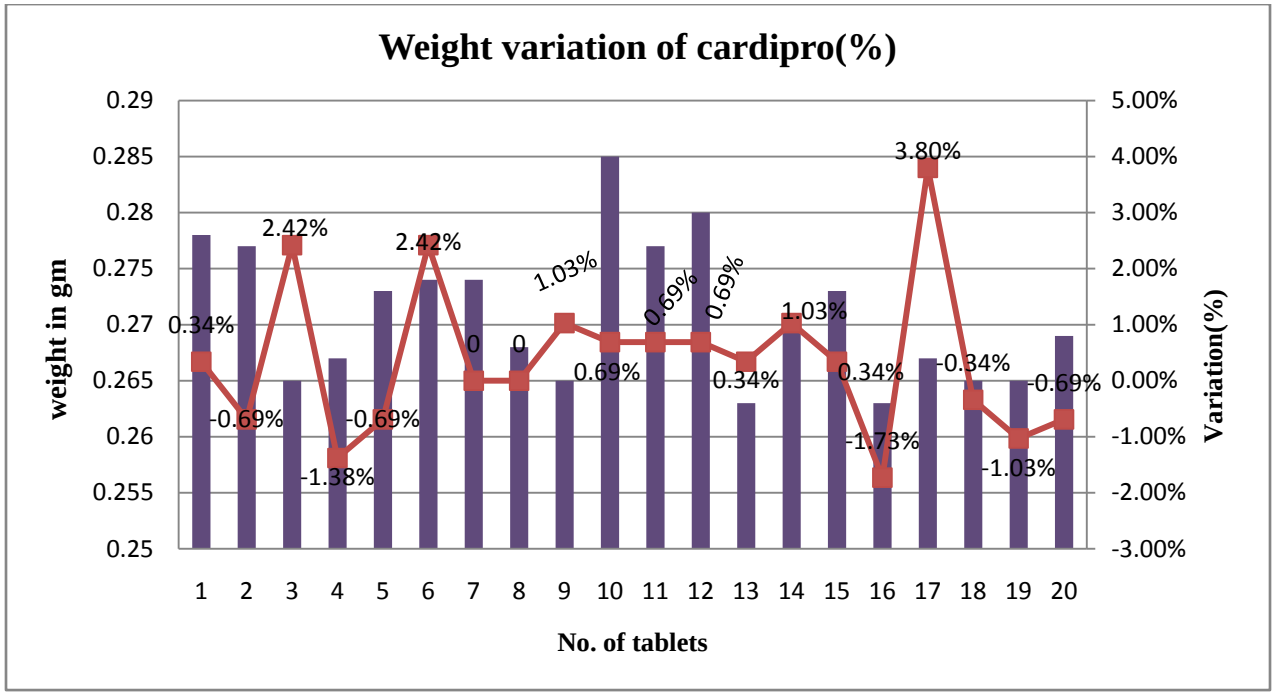

Fig 4.5: Bar chart showing weight variation of atenolol, Brand:Cardipro,Batch: 1070397

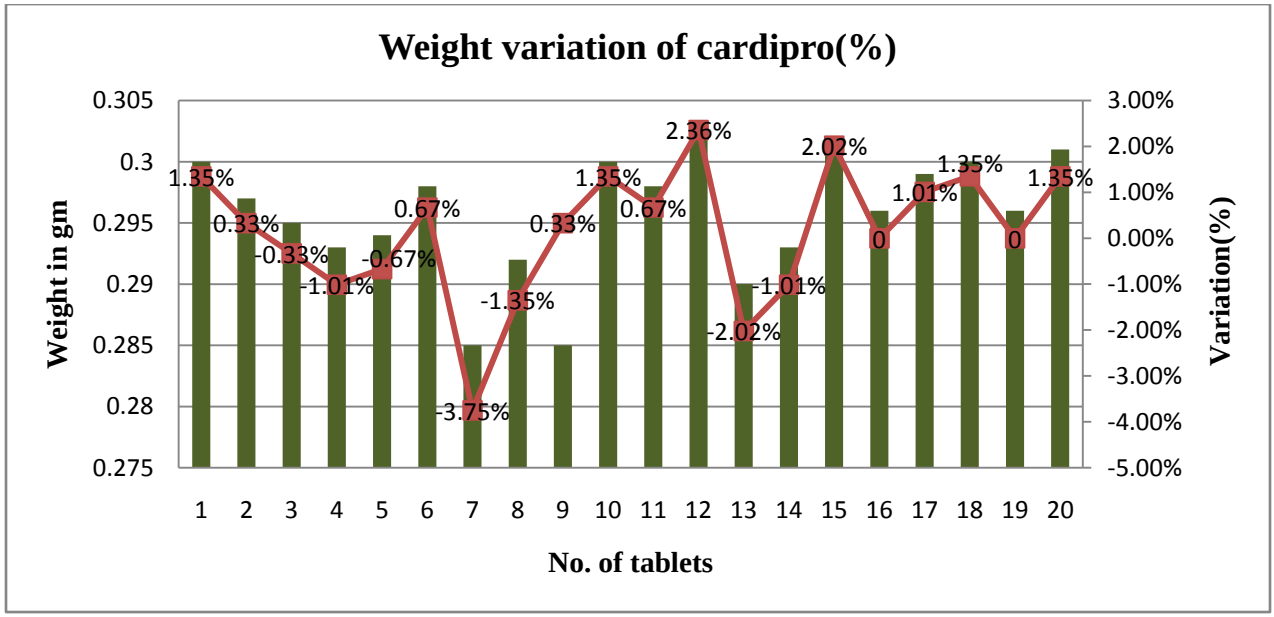

Fig 4.6: Bar chart showing weight variation of atenolol, Brand:Cardipro,Batch: 9080056

The graph4.6 provides information about the individual weight of atenolol tablet and % weight variation. The bar chart is indicating individual weight of twenty tablets. The line chart is showing % weight variation. Left side of the Y axis is indicating individual weight and right side of Y axis is indicating percentage variation. According to BP all the tablets comply with all specification. No tablet exceeds the ± 5 % variation. That means the Batch# 9080056 of Cardipro has passed the QC parameters

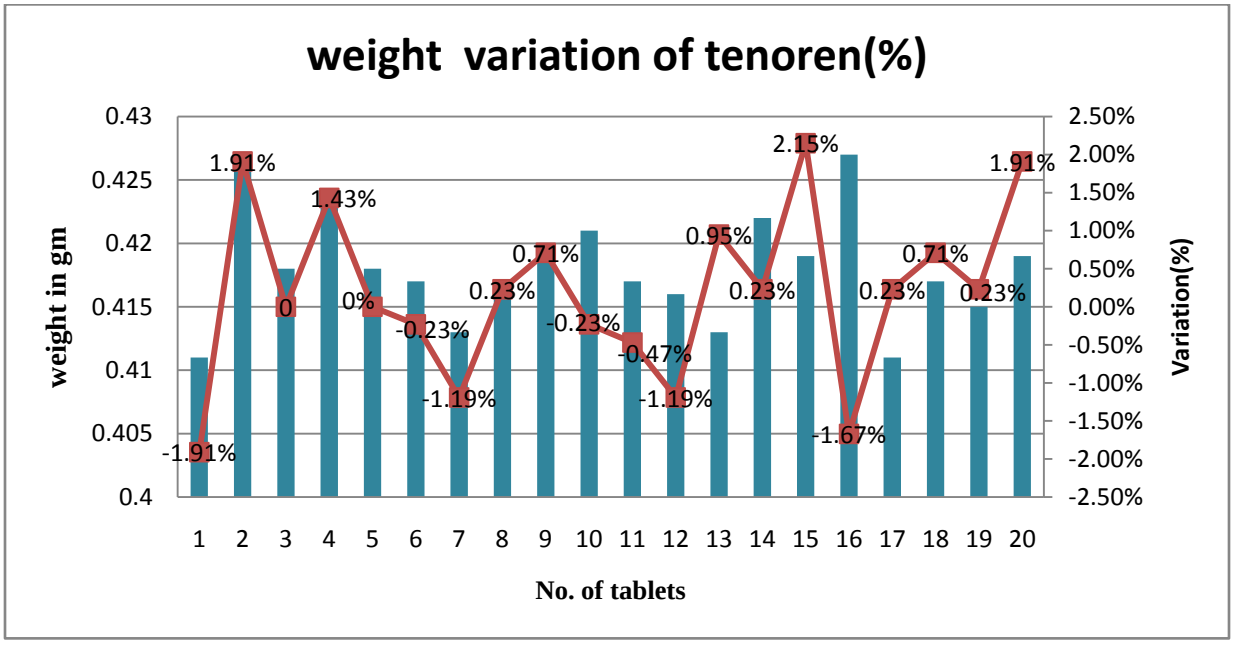

Fig 4.7: Bar chart showing weight variation of atenolol, brand:Tenoren, batch: RE41

The graph 4.7 provides information about the individual weight of atenolol tablet and % weight variation. The bar chart is indicating individual weight of twenty tablets. The line chart is showing % weight variation. Left side of the Y axis is indicating individual weight and right side of Y axis is indicating percentage variation. According to BP all the tablets comply with all specification. No tablet exceeds the ± 5 % variation. That means the Batch#RE41 of Tenoren has passed the QC parameters.

The graph 4.8 below provides information about the individual weight of atenolol tablet and % weight variation. The bar chart is indicating individual weight of twenty tablets. The line chart is showing % weight variation. Left side of the Y axis is indicating individual weight and right side of Y axis is indicating percentage variation. According to BP all the tablets comply with all

specification. No tablet exceeds the ± 5 % variation. That means the Batch# MA106 of Tenoren has passed the QC parameters.

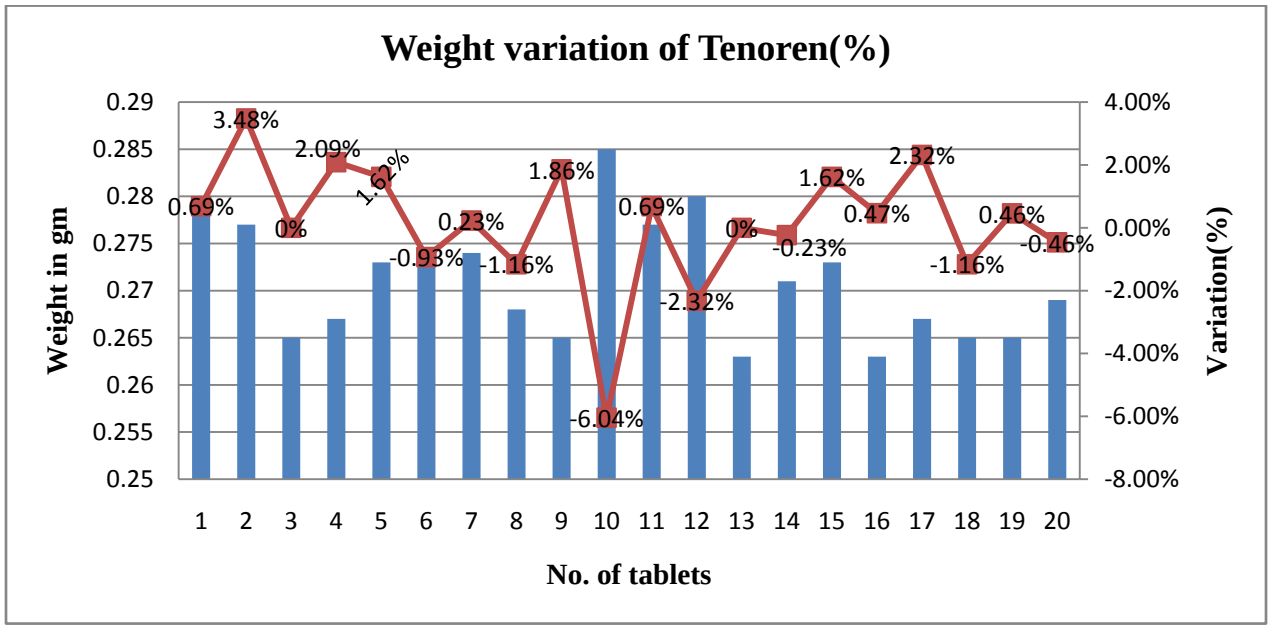

Fig 4.8: Bar chart showing weight variation of atenolol, Brand: Tenoren, batch: MA106

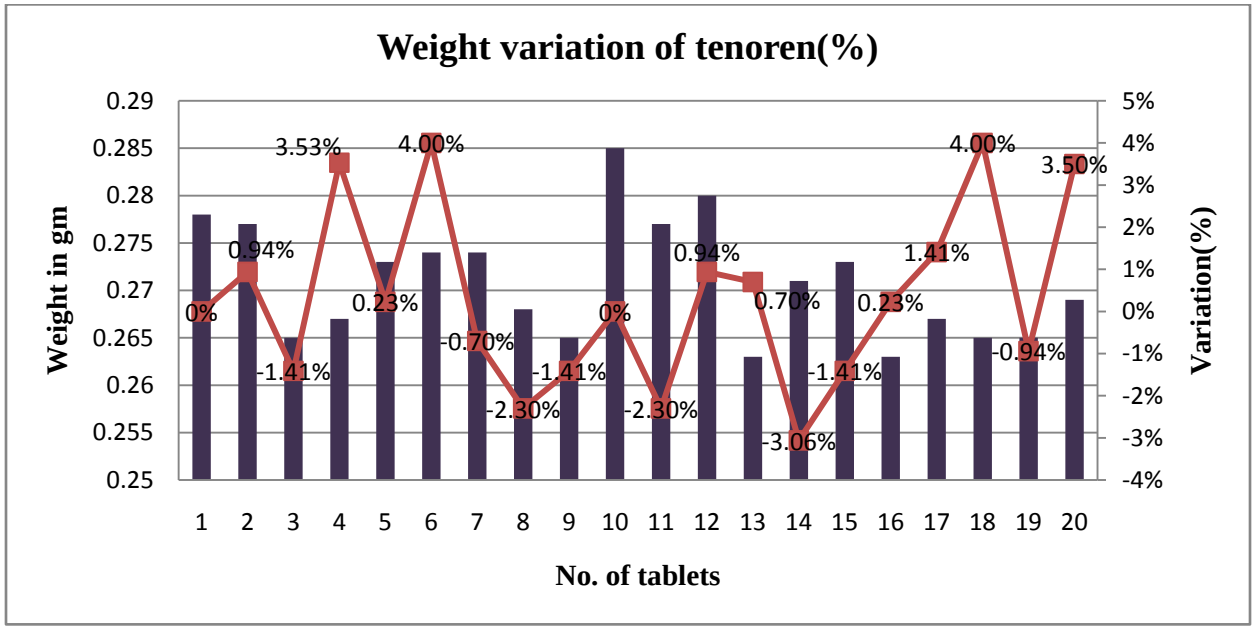

Fig 4.9: Bar chart showing weight variation of Atenolol, brand: Tenoren, Batch: RE42

The graph 4.9 provides information about the individual weight of atenolol tablet and % weight variation. The bar chart is indicating individual weight of twenty tablets. The line chart is

showing % weight variation. Left side of the Y axis is indicating individual weight and right side of Y axis is indicating percentage variation. According to BP all the tablets comply with all specification. No tablet exceeds the ± 5 % variation. That means the Batch# ME42 of Tenoren has passed the QC parameters.

4.2 Friability Testing:

Friability is the tendency of the tablet to crumble. It is important for the tablet to resist attrition. During manufacturing and handling, tablets are subjected to stresses from collision and tablet sliding towards one another and other solid surfaces, which can result in the removal of small fragments and particles from the tablet surface. Friability test is performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. The instrument used for such tests is called a friabilator.

Table 4.1: Percentage friability of atenolol (Brand name: Tenoloc)

Tab sample	Initial Weight of 10 tablets(gm)	Final weight of 10 tablet(gm)	% Friability
Batch no# VN1007	2.686	2.677	0.33%
Batch no# VN1011	1.496	0.852	43.04%
Batch no# VN1004	2.729	2.701	1.02%

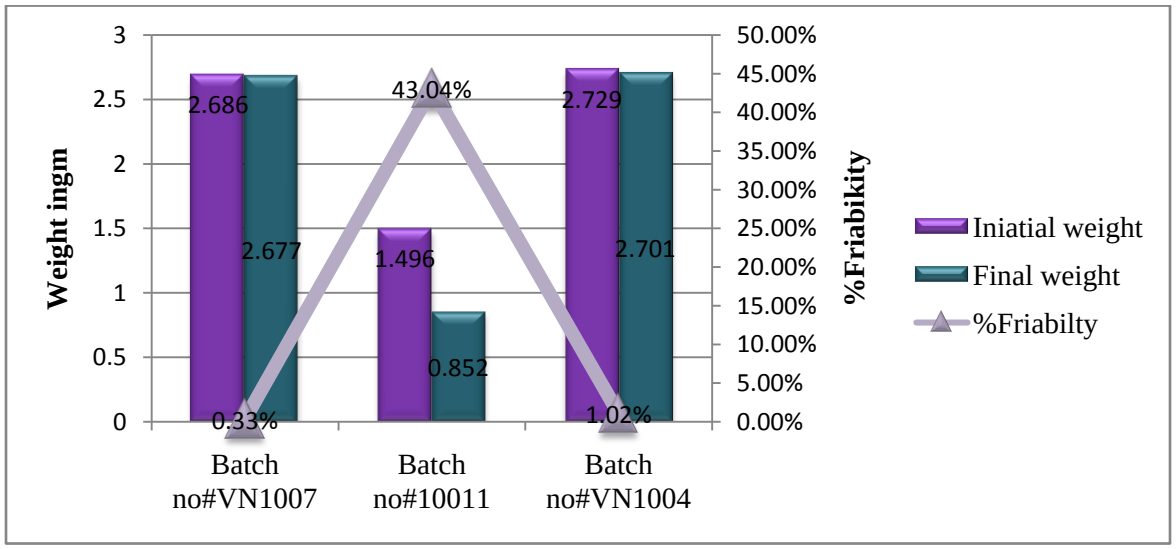

Fig 4.10: Bar chart showing percent friability of atenolol. Brand:Tenoloc

The graph 4.10 provides information about the initial and final weight of different batches of atenolol tablet and % friability variation. Left side of the Y axis is indicating weight and right side of Y axis is indicating percentage friability. The blue colored bar chart is indicating the initial weight of ten tablets. The red colored bar chart is indicating final weight ten tablets of different bathes. The line chart is showing % friability variation. According to USP Batch no# VN1004, VN1007 passed the specification but Batch no#VN1011 does not match with the specification. USP specifies that if friability study is performed with ten tablets of any batch they must not loose 1% of their initial weight.

Table4.2: Percentage friability of atenolol (Brand name: Cardipro)

Tab sample	Initial Weight of 10 tablets	Final weight of 10 tablet	% Friability
Batch no#9100858	2.93	2.92	0.34%
Batch no# 1070397	2.898	2.88	6.2%
Batch no# 9080056	2.975	2.294	2.2%

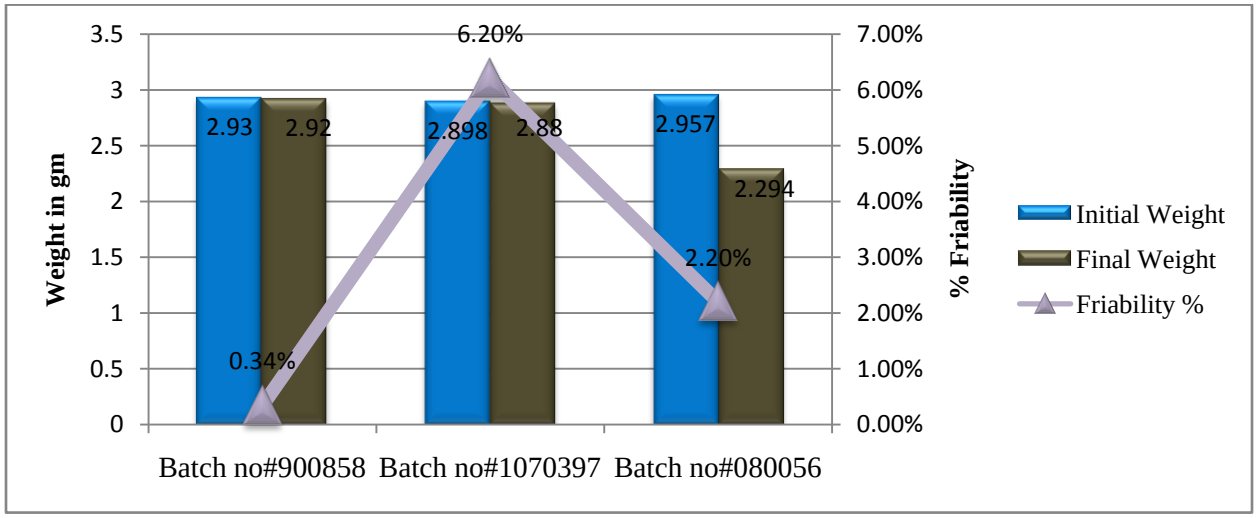

Fig 4.11: Bar chart showing percent friability of atenolol. Brand:Cardipro

The graph 4.11 provides information about the initial and final weight of different batches of atenolol tablet and % friability variation. Left side of the Y axis is indicating weight and right side of Y axis is indicating percentage friability. The blue colored bar chart is indicating the initial weight of ten tablets. The red colored bar chart is indicating final weight ten tablets of

different bathes. The line chart is showing % friability variation. According to USP Batch no# 900858, passed the specification but Batch no#1070397 and 9080056 does not match with the specification. USP specifies that if friability study is performed with ten tablets of any batch they must not lose 1% of their initial weight

Table 4.3: Percentage friability of atenolol (Brand name: Tenoren)

Tab sample	Initial Weight of 10 tablets	Final weight of 10 tablet	% Friability
Batch no# RE41	4.17	4.16	0.43%
Batch no# MA106	4.30	4.05	5.8%
Batch no# RE42	4.19	4.18	0.26%

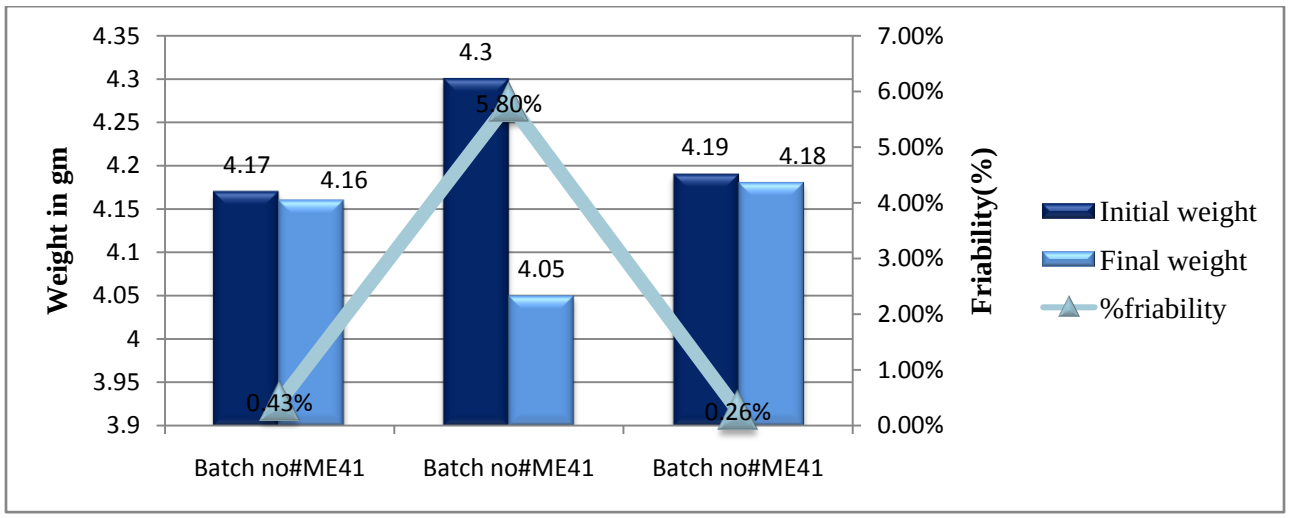

Fig 4.12: Bar chart showing percent friability of atenolol. Brand:Tenoren

The graph 3.12 provides information about the initial and final weight of different batches of atenolol tablet and % friability variation. Left side of the Y axis is indicating weight and right side of Y axis is indicating percentage friability. The blue colored bar chart is indicating the initial weight of ten tablets. The red colored bar chart is indicating final weight ten tablets of different bathes. The line chart is showing % friability variation. According to USP Batch no# RE41 and RE42, passed the specification but Batch no#MA106 does not match with the specification. USP specifies that if friability study is performed with ten tablets of any batch they must not loss 1% of their initial weight

4.3 Hardness Test:

In general, tablets should be sufficiently hard to resist breaking during normal handling, packaging and shipping, and yet soft enough to disintegrate properly after swallowing. Hardness of the tablet is controlled by (or is affected by) the degree of the pressure applied during the compression stage. The Hardness test is therefore performed to measure the degree of force required to break a tablet. The greater the pressure needed to be applied, the harder the tablet. The Hardness testers apply increasing pressure on the tablets until the tablet breaks.

In our lab VEEGO hardness tester was used, where ten tablets were randomly selected and each tablet was tested for hardness and the mean hardness, minimum and maximum values were determined.

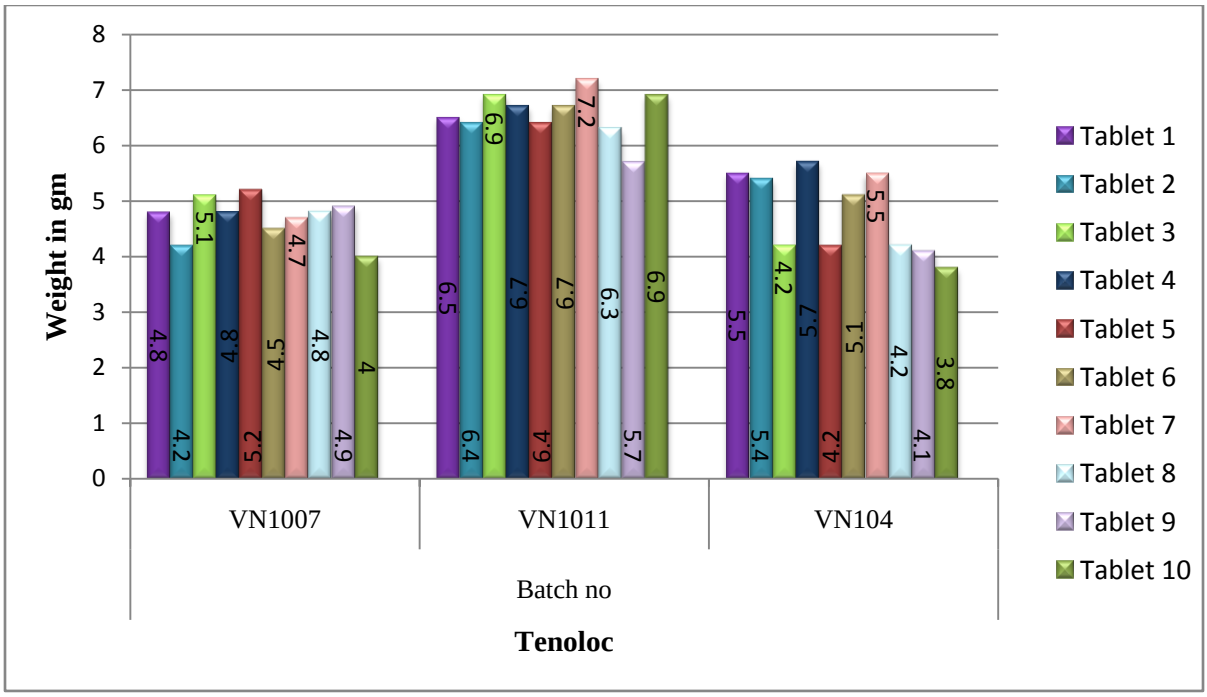

Fig 4.13: Hardness of different batches of atenolol (Tenoloc)

The graph 4.13 provides information about the hardness of ten tablets of different batches of Tenoloc. Different colored bar chart indicates the number of ten tablets of each batch and also the hardness of each ten tablet of three batches. All the tablets meet the criteria of USP standard. According to USP all the tablets passed the specification. USP specifies that hardness of any tablets must not be lower than 4 kg.

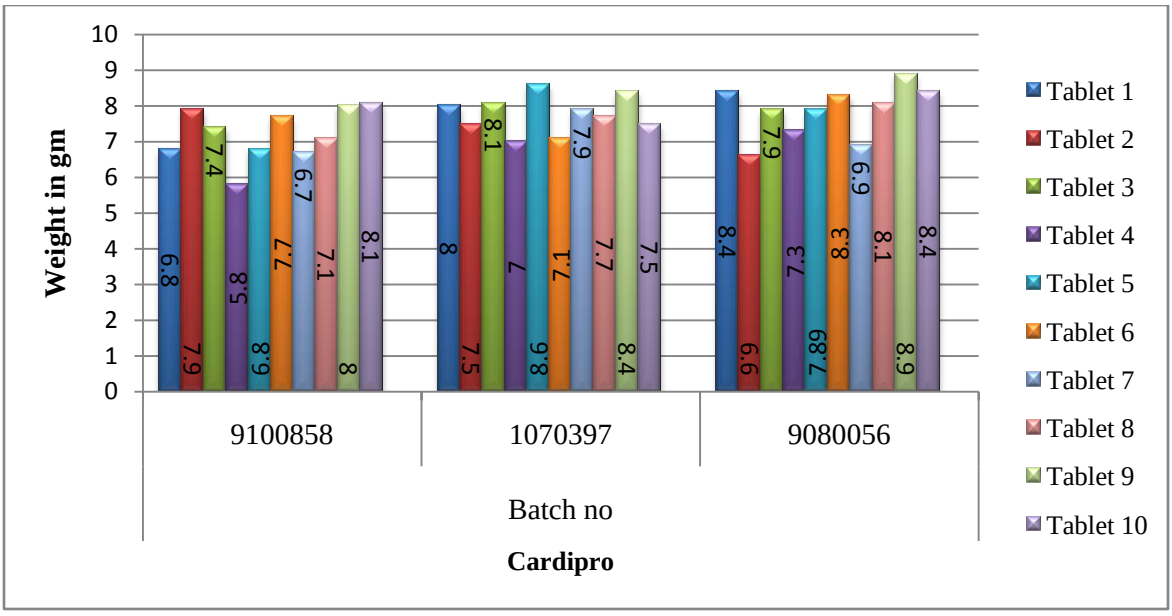

Fig 4.14: Hardness of different batches of Atenolol(Cardipro)

The graph 4.14 provides information about the hardness of ten tablets of different batches of Cardipro. Different colored bar chart indicates the number of ten tablets of each batch and also the hardness of each ten tablet of three batches. All the tablets meets the criteria of USP standard According to USP all the tablets passed the specification. USP specifies that hardness of any tablets must not be lower than 4 kg.

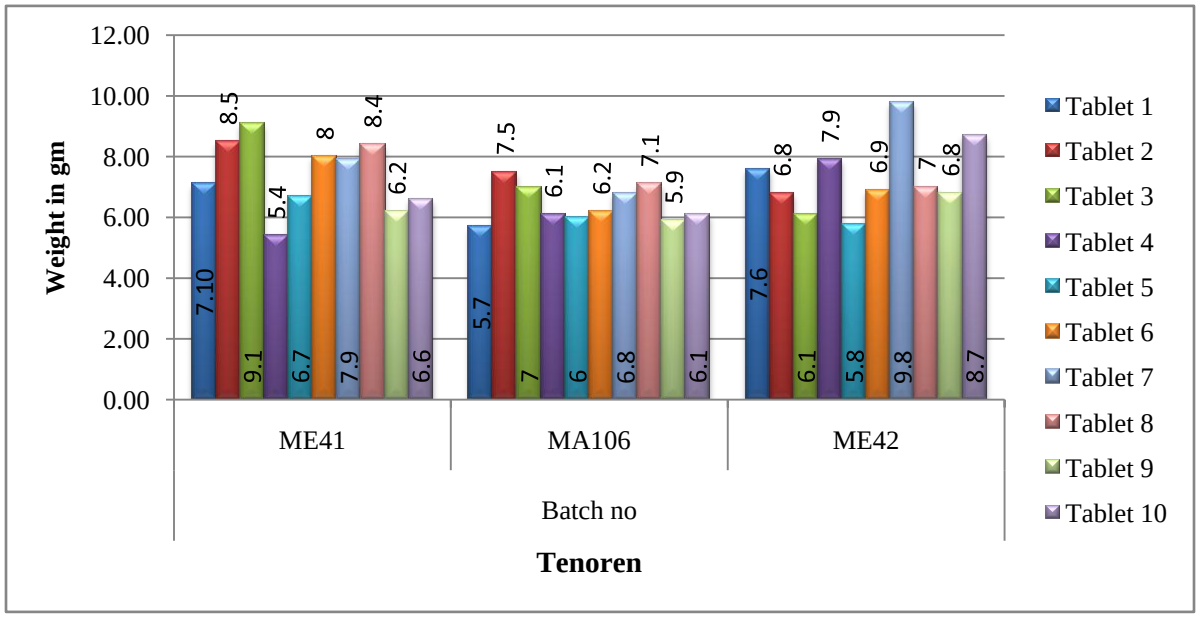

Fig 4.15: Hardness of different batches of atenolol (Tenoren)

The graph 4.15 provides information about the hardness of ten tablets of different batches of Tenoren. Different colored bar chart indicates the hardness of each ten tablet of three batches. According to USP all the tablets passed the specification. USP specifies that hardness of any tablets must not be lower than 4 kg.

4.4 Disintegration Test:

The rate of drug absorption in the acidic environment as well as the therapeutic efficacy of the drug is dependent upon the disintegration time. If the disintegration time is not perfect we cannot say that effectiveness of the drug is good.

Table 4.4: Disintegration time of atenolol tablet, brand: Tenoloc.

	Disintegration time		
Tablet sample	**Batch no.VN1007**	**Batch no.VN1011**	**Batch no.VN1004**
1	1.13 min	3.50 min	1.10 min
2	1.00 min	3.50 min	1.15 min
3	1.30 min	3.55 min	1.20 min
4	1.20 min	2.26 min	2.11 min
5	1.31min	3.40 min	2.11 min
6	1.50 min	3.50 min	2.15 min

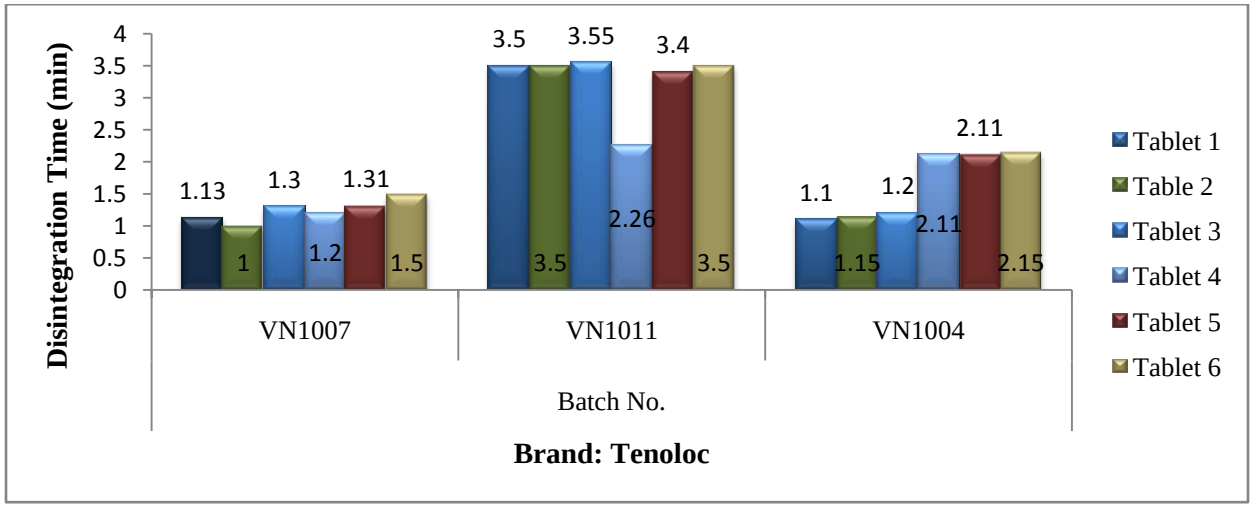

Fig 4.16: Bar chart showing the disintegration time of different batches of Tenoloc

The graph 4.16 provides information about the disintegration time of six tablets of different batches of Tenoloc. Three sets of bars is indicating disintegration time of different tablets of batch # VN1007, vn1011, and VN1004 respectively.

Table 4.5: Disintegration time of atenolol tablet,Cradipro

	Disintegration time		
Tablet sample	**Batch no. 9100858**	**Batch no. 1070397**	**Batch no. 9080056**
1	5.10 min	5.19 min	1.57 min
2	9.55 min	6.65 min	3.29 min
3	4.46 min	3.57 min	2.32 min
4	8.08 min	5.04 min	2.23 min
5	11.42 min	6.43 min	2.23 min
6	5.58 min	3.13 min	3.19 min

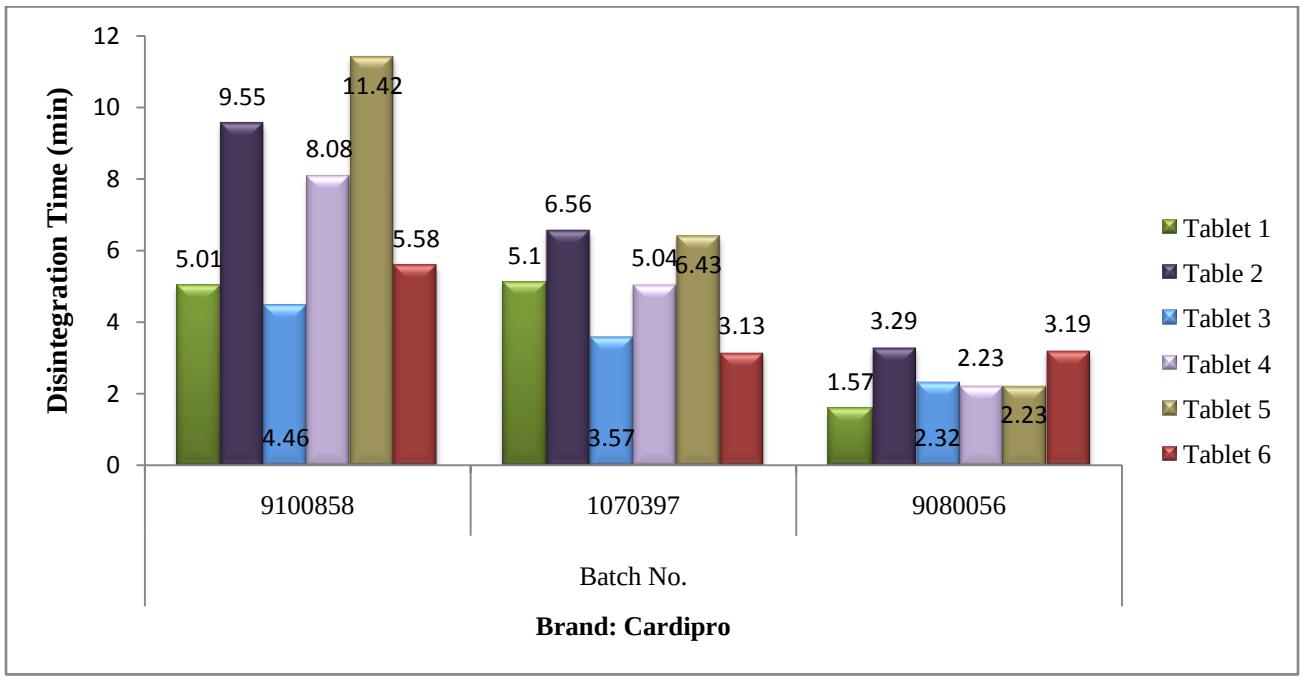

Fig 4.17: Bar chart showing the disintegration time of different batches of Cardipro

The graph 3.17 provides information about the disintegration time of six tablets of different

batches of Cardipro. Three sets of bars is indicating disintegration time of different tablets of batch # 9100858, 1070397, and 9080056 respectively.

Table 4.6: Disintegration time of atenolol tablet, Tenoren

	Disintegration time		
Tablet sample	**Batch no.RE41**	**Batch no.MA106**	**Batch no.RE42**
1	2.30 min	1.47 min	2.02 min
2	3.26 min	1.50 min	1.30 min
3	2.39 min	1.51 min	1.38 min
4	2.47 min	1.51 min	1.56 min
5	3.13 min	1.47 min	1.58 min
6	2.56 min	1.34 min	1.32 min

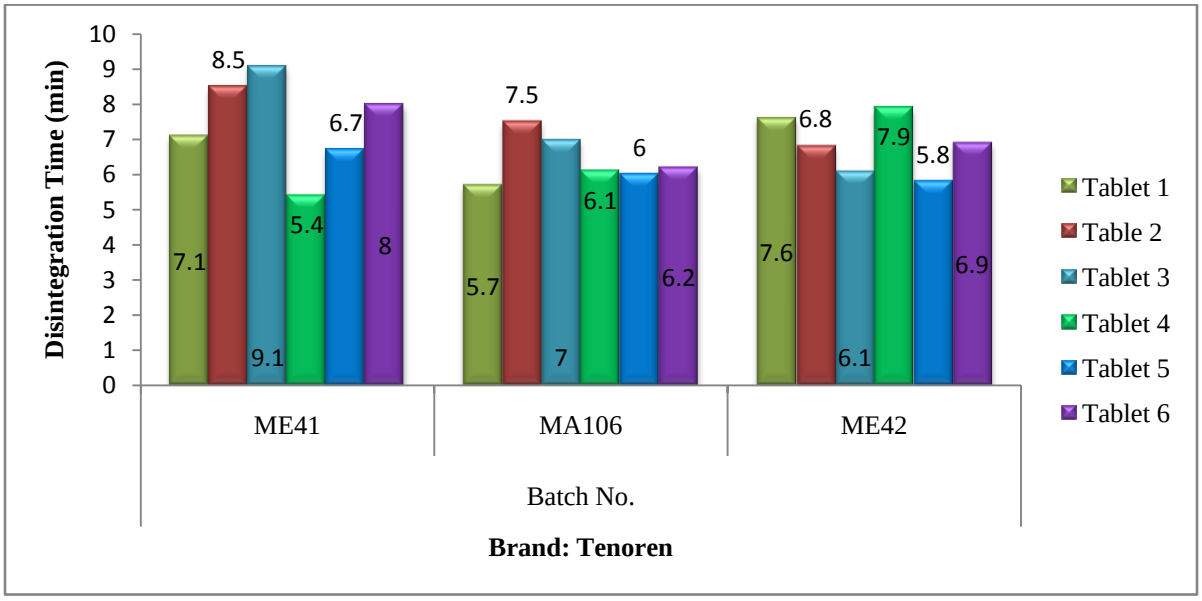

Fig 4.18: Bar chart showing the disintegration time of different batches of Tenoren

The graph 4.18 provides information about the disintegration time of six tablets of different batches of Tenoren. Three sets of bars is indicating disintegration time of different tablets of batch # RE41, RE42, and MA106 respectively.

4.5 Dissolution Test:

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

Absorbance of the Standard Atenolol:

Absorbance of standard atenolol sample was measured with UV-spectrophotometer at 275nm.

Concentration mg/100 ml	Absorbance (275nm)
20	0.92
10	0.46
5	0.24
4	0.20

Table 4.7: Concentration and absorbance of standard atenolol sample

Standard curve for pure (standard) atenolol sample:

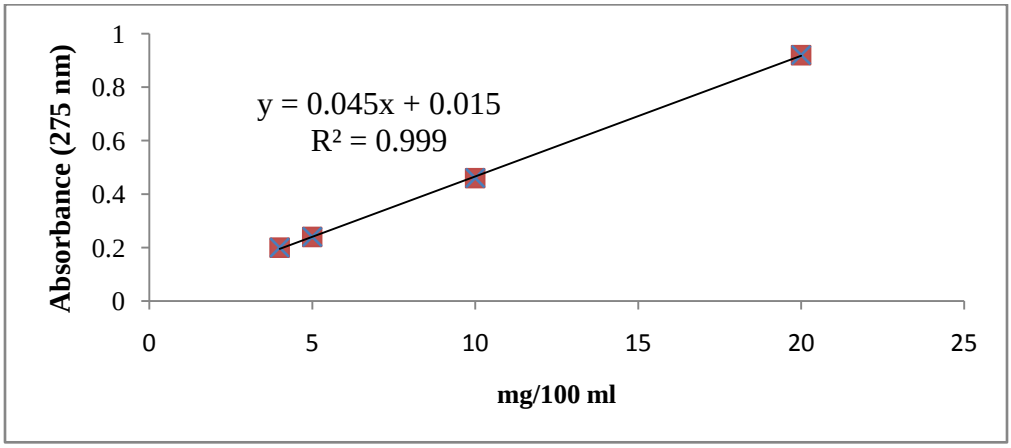

Fig 4.19: Standard curve of atenolol sample

Calculation for determination of dissolution of atenolol tablet:

$$\%\text{Dissolution} = \frac{\text{Absorbance of sample} \times \text{Total volume of the dissolution medium} \times \text{Dilution factor}}{\text{Concentration factor (mg/100ml)} \times \text{weight of the tablet}} \times 100$$

N.B: Concentration is calculated from the equation of standard curve (y= 0.0455x + 0.009)

Table 4.8: Dissolution of Atenolol Tablet, Brand name: Tenoloc (Batch No# VN1007)

Number of sample	Absorbance(275nm)	Concentration (mg/100 ml)**	% Release
1	0.198	4.06	101.44
2	0.185	3.77	94.24
3	0.203	4.17	104.21
4	0.195	3.99	99.78
5	0.205	4.21	105.32
6	0.199	4.08	102.00

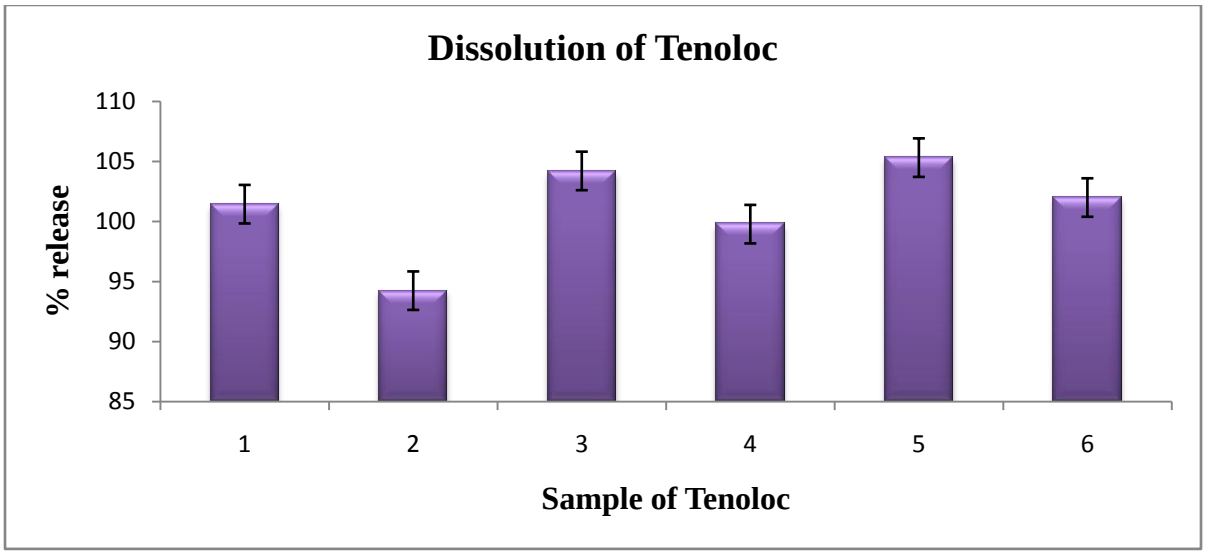

Fig 3.20: Dissolution of Tenoloc

The graph 4.20 provides information about the % dissolution of Tenoloc batch #1007. The blue colored bar chart is indicating the %dissolution of Batch #VN1007. According to BP all the

tablets passed the specification. BP specifies that after 45 minute 98-102% of the active ingredient of atenolol must dissolute into the suitable medium.

Table 4.9: Dissolution of Atenolol tablet, brand name: Cardipro (Batch No# 9080056)

Number of sample	Absorbance(275nm)	Concentration (mg/100 ml)**	% Release
1	0.198	4.06	101.44
2	0.197	4.04	100.8
3	0.204	4.19	104.77
4	0.211	4.35	108.65
5	0.191	3.90	93.68
6	0.184	3.75	102.00

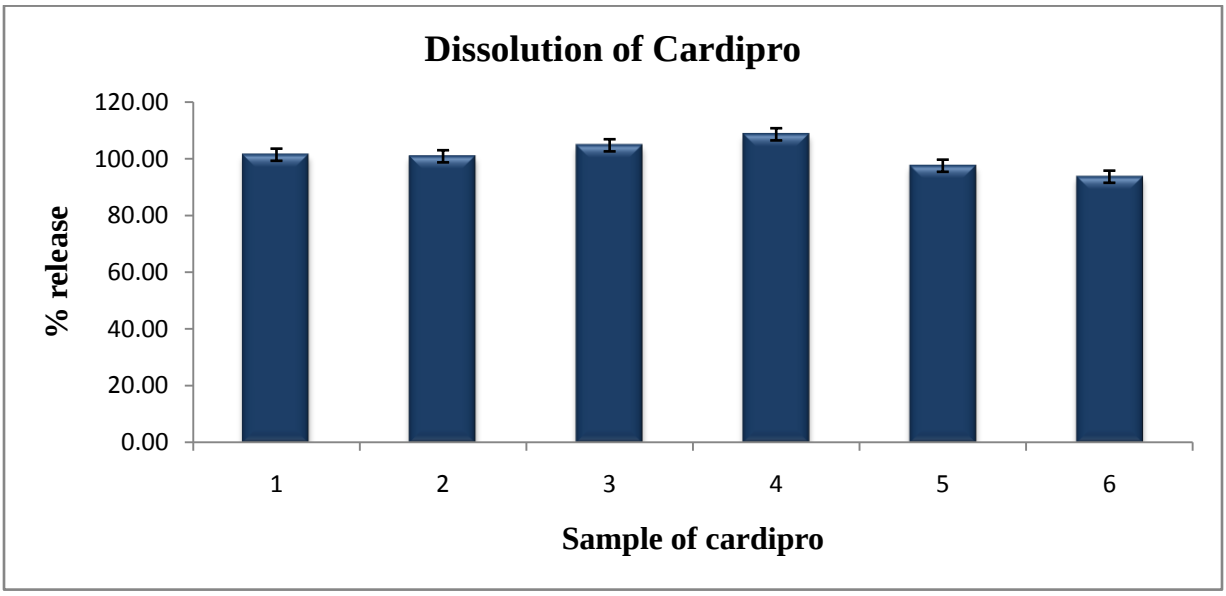

Fig 4.21: Dissolution of Cardipro, batch No# 908005

The graph 4.21 provides information about the % dissolution of Cardipro batch #9080056. The blue colored bar chart is indicating the %dissolution of Batch #9080056. According to BP all the tablets pass the specification. BP specifies that after 45 minute 98-102% of the active ingredient of atenolol must dissolute into the suitable medium.

Table 4.9: Dissolution of Atenolol Tablet, Brand name: Tenoren (Batch No# RE42)

Number of sample	Absorbance(275nm)	Concentration (mg/100 ml)**	% Release
1	0.198	3.48	87.03
2	0.197	3.26	81.49
3	0.204	3.41	85.37
4	0.211	3.04	75.94
5	0.191	3.55	88.69
6	0.184	3.68	92.02

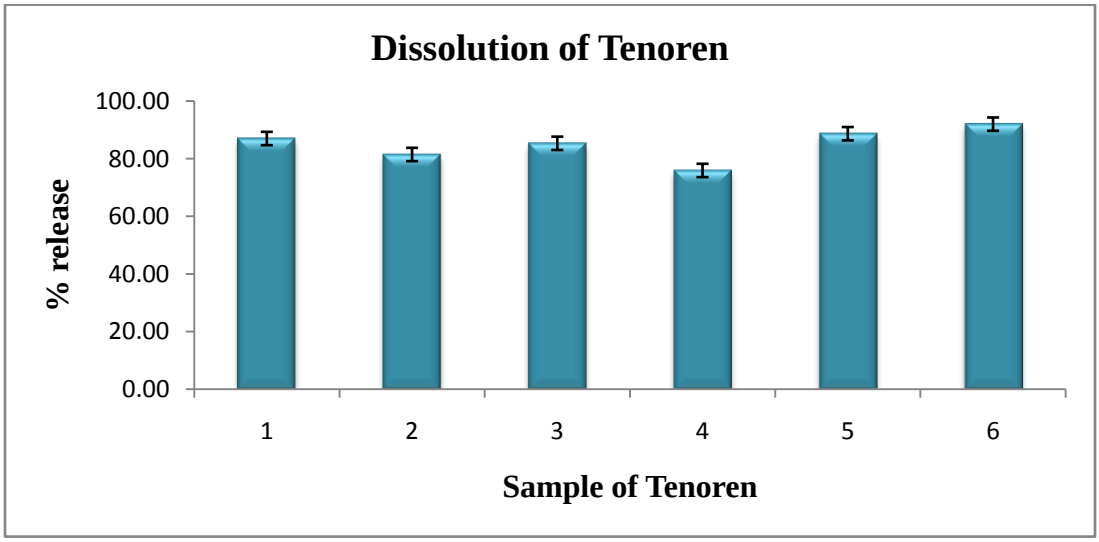

Fig 4.22: Dissolution of Tenoren, batch No# RE42

The graph 4.22 provides information about the % dissolution of Tenoren batch #9080056. The blue colored bar chart is indicating the %dissolution of Batch #RE42. According to BP all the tablets did not pass the specification. BP specifies that after 45 minute 98-102% of the active ingredient of atenolol must dissolute into the suitable medium.

CHAPTER FIVE

CONCLUSION

Chapter 5

Conclusion

In this study it was observed that maximum batches of different brands of atenolol in the quality control parameter tests have passed with the specifications described in USP and BP. For example, in weight variation test all the tablets have passed. All the three brands have passed the hardness test also. On the other hand in case of friability testing batch no# VN1004, VN1007 (Tenoloc) passed the specification but batch no#VN1011 (Tenoloc) did not comply with the specification. Also the Batch no# 900858 (Cardipro), passed the specification but Batch no#1070397 (Cardipro) and #9080056(Cardipro) did not comply with the specification. The reasons behind not passing the friability test may be inappropriate pressure applied by the punch. Disintegration time of all the tablets was satisfactory. Dissolution rate of two brands (Tenoloc and Cardipro) meet the specification according to BP. But dissolution rate of Tenoren did not match the specification according to BP. So there was a considerable variation in quality parameters within these three brands. This may occur due to formulation or processing error or may be due to deviation from proper storage conditions and various other factors. So, care should be taken during manufacturing and storage of tablets.

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