Reproducibility Study on the Efficiency of Film Coating on Preventing Photolytic Degradation of Betaloc® (Metoprolol Tartrate) Tablets

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

IN THE NAME OF ALLAH

THE MOST GRACIOUS AND MOST MERCIFUL

DEDICATION

This Research Project Is Dedicated to My Beloved Parents.

DECLARATION BY THE CANDIDATE

I, Kazi Imran Adib, hereby declare that the dissertation entitled "Reproducibility Study to Evaluate the Efficiency of Film Coating on Preventing Photolytic Degradation in Betaloc® (Metoprolol Tartrate)", submitted by me to the Department of Pharmacy, East West University, in the partial fulfilment of the requirement for the degree of Bachelor of Pharmacy with original research work carried out by me under the supervision and guidance of Md. Anisur Rahman, Senior Lecturer, Department of Pharmacy, East West University, Dhaka.

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CERTIFICATE BY THE SUPERVISOR

This is to certify that the dissertation entitled "Reproducibility Study to Evaluate the Efficiency of Film Coating on Preventing Photolytic Degradation in Betaloc® (Metoprolol Tartrate)", submitted to the Department of Pharmacy, East West University, in partial fulfilment of the requirements for the degree of Bachelor of Pharmacy was carried out by Kazi Imran Adib (ID: 2011-3-70-013) under our guidance and supervision and that no part of the research has been submitted for any other degree. We further certify that all the sources of information and laboratory facilities availed of in this connection is duly acknowledged.

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CERTIFICATE BY THE CHAIRPERSON

This is to certify that the dissertation entitled "Reproducibility Study to Evaluate the Efficiency of Film Coating on Preventing Photolytic Degradation in Betaloc® (Metoprolol Tartrate)", is a bonafide research work done by Kazi Imran Adib (ID: 2011-3-70-013) under the guidance and supervision of Md. Anisur Rahman, Senior Lecturer, and Mohammed Faisal Bin Karim (co-supervisor), Lecturer, Department of Pharmacy, East West University, Dhaka.

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Abstract

This research work was aimed to evaluate the reproducibility of the data in a study that was previously done in order to determine whether the film coating is effective to prevent the photolytic degradation of Metoprolol Tartrate which is a photosensitive drug. For this purpose, Betaloc® of Drug International Limited was chosen which was exposed in various lighting conditions (normal room light, 25watt bulb, 40watt bulb & sunlight). A group of tablet was kept in dark as control to compare the result. Physical parameters and potency of the tablets were determined. Color change, thickness, hardness, and weight variation were measured according to USP and little or no significant change was found. The standard deviation of the thickness, hardness and weight variation was ±0.0026 cm, ±0.4300 kg & ±0.0025gm respectively. Potency test was performed by UV spectroscopy at 221.5 nm wavelength showed gradual decline in potency of the tablet. In various lighting condition like 25watt bulb, 40watt bulb, direct sunlight and normal room light, the percent variation in potency was 11.48%, 12.92%, 22.62% and 16.87% respectively. So this study reveals that the Betaloc® containing metoprolol tartrate is light sensitive and coating alone is not sufficient to protect the drug from light. So that protective opaque package should be used thus light cannot pass through the package.

Keywords: Metoprolol Tartrate, Betaloc®, Potency, Light, Hardness, Thickness, Weight Variation, Photolytic Degradation.

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CHAPTER ONE

INTRODUCTION

The objective of the research project was to evaluate the reproducibility of the data in a study that was previously done in order to determine whether the film coating is effective to prevent the photolytic degradation of Metoprolol Tartrate which is a photosensitive drug. In this study, photosensitivity of metoprolol tartrate in various lightening conditions (normal light, 25watt bulb, 40watt bulb, sunlight) was determined. For this purpose, the available brand was chosen i.e. Betaloc® of Drug International Limited. In most cases this coated product are available in transparent blister packaging system in the market. Only few brands use the opaque blister packaging system due to the photosensitive report. Since there is no published data about photolytic degradation of metoprolol tartrate, a research program was operated to find whether this drug degrades in presence of light or not.

1.1 Beta blockers

1.1.1 Definition

Beta blocker is a type of drug that prevents the binding of norepinephrine and epinephrine to the beta receptors on nerves are known as beta blockers or beta adrenergic blockers. Adrenal glands as well as the nerves produce the norepinephrine and epinephrine throughout the body that serve as the neurotransmitters. These are also found in the blood. Beta receptors are found on the cells of the heart muscles, smooth muscles, arteries, kidneys, and other tissues that are part of the sympathetic nervous system especially when they are stimulated by epinephrine or adrenaline. They are particularly used for the management of cardiac arrhythmias, myocardial infarction, angina pectoris and hypertension.

There are three types of beta receptors. They are- beta$_1$ (β_1), beta$_2$ (β_2) and beta$_3$ (β_3).

- β_1- receptors are located commonly in the heart and kidneys.
- β_2- receptors are located mainly in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle.
- β_3- receptors are generally located in fat cells. (Omudhome Ogbru, 2015)

1.2 Metoprolol Tartrate

1.2.1 Structural Formula of Metprolol Tartrate

Metoprolol Tartrate tablet is a selective beta1-adrenoreceptor blocking agent. Chemical name of Metoprolol Tartrate is (±)-1-(isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol (2:1) dextro-Tartrate salt. The structural formula is given below: (Drugs.com, 2015)

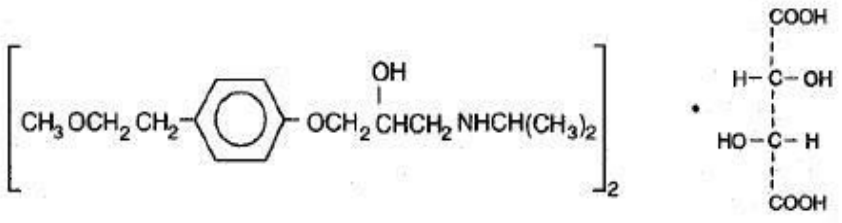

Figure 1.1: Structural formula of Metoprolol Tartrate (Drugs.com, 2015)

Physical characteristics of Metoprolol Tartrate (Drugs.com, 2015)

- White in color
- Odorless
- Crystalline powder
- Molecular weight: 684.81g
- Very soluble in water, methylene chloride, chloroform, alcohol.
- Slightly soluble in acetone and insoluble in ether.

In this research experiment conducted on sample (Brand Name: Betaloc®) which was manufactured by Drug International Limited.

1.2.2 Mechanism of action

Metoprolol Tartrate (Beta blocker) works by blocking the endogenous catecholamines or neurotransmitters norepinephrine and epinephrine action from binding to receptors. When the neurotransmitters or catecholamines are stopped binding to the receptors, it blocks adrenaline (epinephrine). This action allows the heart to relax and heart beat become slow thereby reducing the amount of blood that the heart can pump easily. Due to this action, it improves the pumping mechanism of the heart. (β- Blocker drug info, 2015)

1.2.3 Pharmacological Properties of Metoprolol Tartrate

1.2.3.1 Pharmacodynamic Properties (Drugs.com, 2015)

Metoprolol Tartrate is a cardioselective beta-adrenergic blocking agent which is demonstrated by the following:

- In healthy subjects, $Beta_2$ (β_2) mediated vesodilating effects of epinephrine are not reversed by Metoprolol Tartrate.
- In asthmatic patients, FEV1 and FVC are significantly reduced by Metoprolol than non selective beta blockers at equal dose.

Metoprolol has no intrinsic sympathomimetic activity. It provides membrane stabilizing activity at higher dose than required for beta blocking activity and also slows the sinus rate and reduces the AV nodal conduction.

Beta blocking activity is shown within 1 hour after oral administration. The duration of action is dose related. For example, after administration of single oral doses of 20, 50 and 100 mg to normal subjects the effect is reduced to 50% at 3.3, 5.0 and 6.4 hours respectively. In normal volunteers, maximum beta blockade was achieved after the infusion of drug over a 10 minute period. There is a linear relationship between the log of plasma levels and reduction of exercise heart rate. But the antihypertensive activity of Metoprolol is not related to plasma levels.

In patients with myocardial infarction Metoprolol Tartrate decrease the heart rate, systolic blood pressure and cardiac output but it does not change the stroke volume, diastolic blood pressure and pulmonary artery end diastolic pressure.

In patients with angina pectoris plasma concentration of Metoprolol shows a limear relationship with the oral dose within the range of 50-400 mg.

1.2.3.2 Pharmacokinetices Properties (Drugs.com, 2015)

Absorption: Metoprolol is readily and completely absorbed from the gastrointestinal tract. Oral bioavailability of Metoprolol is about 50% as pre-systemic metabolism occurs which can be stopped with the increase of the dose.

Distribution: Metoprolol is widely distributed across the body. Volume of distribution of Metoprolol is 3.2 to 5.6 L/kg. In plasma about 10% of Metoprolol binds with the serum albumin. It crosses the placenta and blood brain barrier. It is also found in breast milk. It does not bind with P-glycoprotein.

Metabolism: Metoprolol is extensively metabolized in the liver. After administration it shows stereoselective metabolism and it is a racemic mixture of R- and S- enantiomer. This metabolism is dependent on oxidation phenotype. Metoprolol Tartrate undergoes first-pass metabolism in the liver by CYP2D6 to inactive metabolites. CYP2D6 is absent in about 8% Caucasians and about 2% of most other populations (poor metabolizers). People those who have no CYP2D6 enzyme system shows several fold higher plasma concentration than those who have this enzyme.

Elimination: The elimination half life of Metoprolol is 3-4 hours but it may be 7-9 hours in poor metabolizers. In normal subjects, 5% of oral dose and 10% of intravenous dose are excreted through urine as unchanged state. The excreted unchanged amount of drug increases to 30% of oral dose and 40% of intravenous dose in poor metabolizers.

1.2.3.3 Pharmacokinetics in Special Population (Drugs.com, 2015)

Geriatric patients: Slightly higher plasma concentration of Metoprolol is shown in geriatric population because of the following reasons:

- Decreased metabolism of the drug in elderly population.
- Decreased hepatic blood flow.

Renal impairment: Patients with renal failure do not show significant variation in bioavailability and half life of Metoprolol than normal subjects.

Hepatic impairment: In patients with hepatic impairment, the elimination half life of Metoprolol becomes prolonged as this drug is primarily eliminated by hepatic metabolism.

1.2.4 Clinical Particulars of Metoprolol Tartrate

1.2.4.1 Indications of Metoprolol Tartrate (Metoprolol Tartrate tablets BP, 2011)

This drug is used in the management of:

- ⇨ Hypertension
- ⇨ Angina pectoris
- ⇨ Cardiac arrhythmias
- ⇨ Myocardial infractions
- ⇨ Prophylaxis of migraine.

1.2.4.2 Posology & Method of Administration (Metoprolol Tartrate tablets BP, 2011)

Posology: Following dosage regimes are used only as a guideline and should always be adjusted to the individual requirements of the patient. Dosages should be reduced where there is chance of impairment of renal or hepatic function.

Route of Administration: Oral

Adults:

- **Hypertension:** Initially 100mg daily. This may be increased, if necessary, to 200mg daily in single or divided doses. Combination therapy with a diuretic or vasodilator may also be considered to further reduce blood pressure.
- **Angina:** Usually 50-100mg two or three times daily. In general a significant improvement in exercise tolerance and reduction of anginal attacks may be expected with a dose of 50-100mg twice daily.
- **Cardiac arrhythmias:** Usually 50mg two or three times daily. If necessary the dose may be increased to 300mg daily in divided doses. Following the treatment of an acute arrhythmia with metoprolol tartrate injection, continuation therapy with metoprolol tablets should be initiated 4-6 hours later. The initial oral dose should not exceed 50mg twice daily.

- **Myocardial infarction:** In case of early intervention to achieve optimal benefits from intravenous metoprolol, given within 12 hours of the onset of chest pain. Therapy should commence with 5mg IV every 2 minutes to a maximum of 15mg total as determined by blood pressure and heart rate. The second or third dose should not be given if the systolic blood pressure is less than 90mmHg. Oral therapy should commence 15 minutes after the injection with 50mg every 6 hours for 48 hours. Patients who fail to tolerate the full IV dose should be given half of the oral dose.
- **Prophylaxis of migraine:** 100-200mg daily in divided doses (morning and evening).

Elderly: There is no evidence to suggest that dosage requirements are different in otherwise healthy elderly patients. But excessive decrease in blood pressure or pulse rate may cause the blood supply to vital organs to fall to inadequate levels. Dosage should be reduced in the elderly where there is impairment of hepatic function.

Children: Not recommended for children.

1.2.5 Pregnancy & Lactation (Metoprolol Tartrate tablets BP, 2011)

Pregnancy:

It is recommended that metoprolol should not be administered during pregnancy or lactation due to possible risk to the fetus/infant. Once metoprolol is given, special attention should be paid to the fetus, neonate and breast fed infant for any undesirable effects such as slowing of the heart rate.

Metoprolol has been used in pregnancy associated hypertension under close supervision after 20 weeks gestation. Although the drug crosses the placental barrier and no evidence of fetal abnormalities has been reported. However, there is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Beta blockers reduce placental perfusion and may cause fetal death and premature birth. Beta blockers have been reported to cause bradycardia in the fetus and the newborn child, there are also reports of hypoglycaemia and hypotension in newborn children.

Treatment with Metoprolol should be discontinued 48-72 hours before the calculated birth date. If this is not possible, the newborn child should be monitored for 24-48 hours post partum for signs and symptoms of beta blockade (e.g. cardiac and pulmonary complications).

Lactation:

The concentration of Metoprolol in breast milk is three times higher than the mother's plasma. Even though the adverse effects in the breast feeding baby would appear to be low after administration of therapeutic doses of the medicinal product breast feeding babies should be monitored for signs of beta blockade.

1.2.6 Contraindications (Metoprolol Tartrate tablets BP, 2011)

Metoprolol is contraindicated in:

1. Sick-sinus syndrome
2. Renal or hepatic failure
3. Second or third degree atrioventricular block
4. Chronic obstructive pulmonary disease
5. Bradycardia, first degree heart block, and cardiogenic shock
6. Uncontrolled heart failure
7. Metabolic acidosis
8. Myocardial infarction
9. Hypotension
10. History of bronchospasm and asthma

1.2.7 Drug Interactions (Drugs.com, 2015)

Catecholamine-depleting drugs: If Metoprolol and catecholamine depleting drugs such as respirine are administered at the same time that may give additive beta blocking effect that causes bradycardia, vertigo or postural hypotension.

Digitalis glycosides and beta blockers: Concomitant administration of digitalis glycosides and beta blocker drugs increase the risk of bradycardia as both of them lower the atrioventricular conduction and reduce the heart rate.

Calcium channel blockers: Concomitant administration of Metoprolol and calcium channel blockers may cause an additive reduction in myocardial contractility because of negative chronotropic and inotropic effect.

Hydralazine: Concomitant administration of metoprolol and hydralazine may inhibit presystemic metabolism of Metoprolol leading to increased concentrations of Metoprolol.

Alpha-adrenergic agents: Metoprolol Tartrate may potentiate the antihypertensive activity of alpha adrenergic blockers such as guanethidine, betanidine.

CYP2D6 Inhibitors: Inhibitors of the CYP2D6 enzyme increase the elimination half life of Metoprolol.

Ergot alkaloid: Concomitant administration with beta-blockers may enhance the vasoconstrictive action of ergot alkaloids.

1.2.8 Adverse Reaction (Drugs.com, 2015)

Central Nervous System: Tiredness and dizziness, mental confusion and short-term memory loss, Headache, nightmares, and insomnia.

Cardiovascular: Shortness of breath and bradycardia, cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension.

Respiratory: Wheezing (bronchospasm) and dyspnea, rhinitis.

Gastrointestinal: Diarrhea, nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn.

Hypersensitive Reactions: Pruritus or rash and very rarely, photosensitivity and worsening of psoriasis.

Miscellaneous: Peyronie's disease, musculoskeletal pain, blurred vision, and tinnitus.

1.3 Photolytic Degradation (Kumar *et al.* 2013)

Photolytic degradation is the chemical decomposition process by which light-sensitive drugs or excipient molecules are chemically decomposed by room light, extreme light, direct sunlight or other electromagnetic radiation.

1.3.1 Photolytic Condition

Exposure of drug molecules may produce photo degraded product. The rate of photo degradation depends upon the intensity of incident light and quantity of absorbed light by the drug molecule. Photolytic degradation is carried out by exposing the drug product to a combination of visible and UV light. The most commonly accepted wavelength of light is in the range of 300-800nm to cause the photolytic degradation.

CHAPTER TWO

LITERATURE REVIEW

A research group (Narendra, Srinath and Prakash Rao, 2005) worked on evaluation of the effect of formulation variables on release properties and bioadhesive strength in development of three layered buccal compact containing highly water-soluble drug metoprolol tartrate (MT). This work was done by statistical optimization technique. Based on rotatable central composite design with peripheral polymer ratio (carbopol 934P: HPMC 4KM) and core polymer ratio (HPMC 4KM: sodium alginate) the formulations were prepared. By considering bioadhesion force, percentage metoprolol tartrate release at 8 h, T50% and release exponent (n), the release profile data was subjected to curve fitting analysis to describe the release mechanism of metoprolol tartrate. The decreasing release of metoprolol tartrate was observed with an increase in both the formulation variables and as the carbopol: HPMC ratio increases the bioadhesive strength also increases.

Another research group (Liu et al., 2006) performed a research work to develop a simple, rapid and sensitive flow-injection chemiluminescence method for the determination of metoprolol tartrate. This method acts as a kind of sensitizer in the chemiluminescence emission from the redox of SO32− with Ce(IV) in acidic medium. The proposed method allows the measurement of metoprolol tartrate over the range of 1.5 × 10−8 to 7.3 × 10−6 mol/L with a detection limit of 4.7 × 10−9 mol/L (3σ), and the relative standard deviation for 7.3 × 10−7 mol/L metoprolol tartrate (n = 11) is 2.20% under the optimized conditions. The utility of this method was established by determining metoprolol tartrate in tablets and human urine sample.

In next year, Aqil et al. (Aqil et al., 2007) did a research work on high-performance reversed-phase liquid chromatographic method to quantify metoprolol tartrate (MT) in human plasma. During this methodology C_{18} column was used with acetonitrile water triethylamine with ratio 18:81:1 (v/v) as mobile phase and pinacidil monohydrate as internal standard (IS). UV absorbance was taken at 275 nm and metoprolol tartrate and internal standard were detected at retention times of 1.5 and 2.6 minutes respectively. The technique was successfully used for analysis of metoprolol tartrate in human blood plasma throughout pharmacokinetic studies.

In the same year, Ye et al. (Ye et al., 2007) did a research work in which metoprolol tartrate was diffused through plasticized isolated ethylcellulose (EC)/hydroxypropyl methylcellulose (HPMC) films prepared by solvent casting which can be used as a tool to develop spray-coated dosage forms. Due to the different hydrophilicity of the plasticizers, the permeability of the

model drug metoprolol tartrate through plasticized isolated films could be adjusted by selecting the type and amount of plasticizer in the films The release of metoprolol tartrate from coated pellets was consistent with the drug diffusion through the films which is made up of the same polymer blends. This method is useful to test isolated films for early predictions and for formulation optimization.

Again in the same year, Rahman et al. (Rahman et al., 2007) described a kinetic spectrophotometric method to evaluate Metoprolol Tartrate in commercial dosage form. In this method the drug reacts with 1-chloro-2,4-dinitro benzene (CDNB) in dimethylsulfoxide (DMSO) at 100 ± 1^{0}C. The reaction is investigated in absorbance at 420 nm and observes the change in absorbance with respect to time. After performing this experiment, the results were compared statistically and no significant difference was found between the proposed method and EI-Ries's spectrophotometric method.

In next year, Sanjay et al. (Sanjay et al., 2008) did a research work to prepare and evaluate the osmotic controlled drug delivery system of Metoprolol Tartarate that may give continous drug release for 14 to 15 hours. Before compression, the prepared granules were evaluated for flow and compression characteristics. So the prepared osmotic drug delivery system was evaluated for in vitro drug release study. The excipients employed in this study failed to alter physicochemical properties of the drug, as tested by FTIR and showed good mechanical properties (hardness and friability) and also good in vitro dissolution study profile. Stability study was carried out for one year in room temperature. The results of stability study was the statistical difference between the before and after storage of formulation in one year was very less.

In next year, a research group (Nagaich et al.,2009) worked on the buccal drug delivery system of Metoprolol tartrate were prepared by the film casting on a mercury substrate and drug release studies from in-vitro test, skin permeation studies and drug-excipients interaction analysis. The various formulations of buccal films were developed for Metoprolol Tartrate. The most satisfactory formulation had showed insignificant change in physicochemical properties, drug content, bioadhesion properties and in-vitro dissolution pattern during performing the stability studies for 2 months as per ICH guidelines Q1C.

In the same year, Tehrani et al. (Tehrani et al., 2009) represented a research work to determine Metoprolol in real sample by PVC membrane based on Metoprolol molecularly imprinted polymer (MIP) coated directly on graphite electrode. This potentiometric sensor was designed by dispersing the MIP particles in dioctylphthalate plasticizer as solvent mediator and then embedded in polyvinyl chloride matrix. Finally, the designed sensor was successfully applied as an indicator electrode to determine concentration of Metoprolol in tablets, human urine and plasma and the results were compared favorably with those obtained by HPLC technique and showed satisfactory agreements with them.

Again in the same year, Rani et al. (Rani et al., 2009) prepared Eight batches of extended release matrix tablets of Metoprolol succinate by using wet granulation technique and coating is done with hydroxyl propyl methyl cellulose and hydroxyl methyl cellulose for extended release. Then the compressed tablets were evaluated for weight variation, hardness, friability and in vitro dissolution using paddle method (USP type II) and found that all formulation showed compliance with the pharmaceutical standards.

Jasinska et al. (Jasinska et al., 2009) studied the stability of the expired Metoprolol Tartrate. Content determination was performed using HPLC method with UV detection. The proposed method was validated with regard to linearity, sensitivity, intermediate accuracy and precision. After expiring if storage of the tablet over time period, did not influence the content of the drug.

In next year, Phale et al. (Phale et al., 2010) established a stability indicating HPLC method for the analysis of Metoprolol Succinate in the presence of products generated in a stress degradation study where the drug was subjected to stress conditions of hydrolysis, oxidation, photolysis and thermal decomposition. In an alkaline medium and under thermal stress extensive degradation was found whereas in an acidic medium and under photolytic and oxidative stress minimum degradation was observed. As the method effectively separates the drugs from their degradation products, it can be used as a stability-indicating method.

Yang et al. (Yang et al., 2010) studied the stability of Metoprolol Tartrate tablets packaged in original high density polythene containers and repackaged in USP class A unit-dose blister packs. The tablets were stored at 25^0C/60% relative humidity for 52 weeks and at 40^0C/75% relative humidity for 13 weeks. The drugs were analyzed to determine the potency, dissolution,

water content, loss on drying hardness of the tablets. No differences in stability were found in both packages stored at 25^0C/60% relative humidity. The potency of the drug in both packages under either condition was same. But under 40^0C/75% relative humidity condition the repackaged tablets absorbed moisture and their weight was increased significantly.

In the same year, Rao et al. (Rao et al., 2010) prepared fast dissolving tablets of Metoprolol Tartrate to enhance the dissolution rate by sublimission method. The results concluded that fast dissolving tablets of Metoprolol Tartrate showing enhanced dissolution rate that will lead to improved bioavailability and effective therapy by using sublimation method.

After that at March, Baloglu and Senyigit (Baloglu and Senyigit, 2010) did a research on the Metoprolol Tartrate tablet with seven different polymers (carrageenan, hydroxypropylmethyl cellulose, pectin, guar gum, xanthan gum, chitosan, and ethyl cellulose). Weight variation, hardness, diameter/thickness ratio, friability, and drug content uniformity and in vitro drug release tests were studied and found that carrageenan was the best polymer in two layer matrix tablet formulation because of its better accordance to target release profile. Then accelerated stability tests were performed using carrageenan as two and three layered formulation of Metoprolol Tartrate. The tablets were kept at 25^0C/60% relative humidity and 40^0C/75% relative humidity for 6 months. After storage period physical appearance, drug content, and release characteristics were examined and no significant change were found.

Akhter et al. (Akhter et al., 2010) developed oral sustained release tablets of Metoprolol Tartrate using natural hydrophilic matrix formers (xanthan gum and tragacanth). Microcrystalline cellulose (MCC) was used as diluent. All the lubricated formulations were compressed using concave punches in compression machine. Compressed tablets were evaluated for hardness, friability, weight variation and in vitro dissolution using USP dissolution apparatus-II. The results showed that the formulation contains 30% xanthan gum and 10% gum tragacanth is the most similar to that of the reference marketed preparation.

Bharkatiya et al. (Bharkatiya et al., 2010) did a research work by preparing the matrix type transdermal patches containing metoprolol tartrate by solvent casting method employing a mercury substrate by using the combinations of EC-PVP and Eudragit RL100-PVP in different proportions. The physicochemical properties of the transdermal patches were evaluated. Based

on this test, it can be accomplished that, for the development of transdermal patches of Metoprolol tartrate Eudragit RL100-PVP are better suited than EC-PVP polymers.

In the same year, Bharkatiya et al. (Bharkatiya et al., 2010) also did a research work on niosomes. They are nonionic surfactant that has potentiality in the delivery of hydrophobic and hydrophilic drugs. Niosomes have been prepared with different surfactants. So the different batches of metoprolol tartrate niosomes were prepared by changing the surfactant concentration but keeping the cholesterol concentration constant. So the ultimate decision is niosomal formulation could be a promising drug delivery system for metoprolol tartrate.

In next year, Shalunkhe et al. (Shalunkhe et al., 2011) investigated to prepare and evaluate a floating pulsatile drug delivery system of metoprolol tartrate. They prepared floating pulsatile delivery system that consisted of three different parts: a core tablet, containing the active ingredient, an erodible outer shell and a top cover buoyant layer. Developed formulations were evaluated for their physical characteristics, drug content, in vitro disintegration time, floating time and in vivo X-ray study. The formulation showed compliance with chronotherapeutic objective of hypertension.

Dahiya et al. (Dahiya et al., 2011) prepared microspheres of a highly water soluble drug Metoprolol Tartrate by w/o/o double emulsion solvent diffusion method using ethyl cellulose polymer. A mixed solvent system of acetonitrile and dichloromethane in 1:1 ratio, liquid paraffin as a primary and span 80 as a secondary surfactant were employed. It was found that particle size and efficiency of the microspheres were enhanced with increasing drug polymer ratio but reduced with increasing stirring speed.

Shrisand et al. (Shrisand et al., 2011) prepared the bilayered buccal tablets of Metoprolol Tartrate by direct compression method using combinations of polymers (carbopol 934p along with sodium carboxy methyl cellulose, sodium alginate and hydroxy propyl methyl cellulose K4M), using mannitol as a channeling agent and ethyl cellulose as a backing layer. According to the study, the prepared buccal tablets of Metoprolol Tartrate could stay in the buccal cavity for a longer period of time, which indicate a potential use of mucoadhesive tablets of Metoprolol Tartrate for treating blood pressure.

In May, Rao et al. (Rao et al., 2011) prepared the fast dissolving tablets of metoprolol tartrate by using novel co-processed superdisintegrants consisting of crospovidone and croscarmellose sodium in the different ratios. Drug compatibility with excipients was checked by FTIR and DSC studies. Stability test were carried out by ICH guidelines for three months. It indicated that there were no significant changes in drug content and in-vitro dispersion time. From this study, the conclusion is the dissolution rate of metoprolol tartrate could be enhanced by tablets containing co-processed superdisintegrant.

Cesme et al. (Cesme et al., 2011) developed a new, simple, sensitive and accurate spectrophotometric method for the assay of Metoprolol Tartrate which is based on the complexation of drug with copper (II) [Cu (II)] at pH 6.0, using Britton-Robinson buffer solution, to produce a blue adduct. The proposed procedure has been successfully applied to the determination of this drug in its tablets.

Himabandu et al. (Himabandu et al., 2011) also did a research to improve patient compliance. So that the mouth dissolving tablets of metoporolol tartrate was an alternative to conventional oral dosage forms. The aim of the study is to prepare and evaluate Oral Disintigrating Tablets (ODT) of metoprolol tartrate by using superdisintegrants as like sodium starch glycolate, cross carmellose sodium and cross povidone and to observe the effect and efficacy of tablets.

Bagde et al. (Bagde et al., 2011) took an attempt to formulate a bi layer tablet of Metoprolol and Ramipril in which Metprolol was given in extended release layer and Ramipril was given in immediate release layer to prevent nocturnal heart attack and reduce the frequency & units dose of administration. The tablet was prepared by using dry and wet granulation technique. Hydroxylpropylmethylcellulose and sodium carboxymethylcellulose were used for the extended release of Metprolol Succinate. Then compatibility test of Metoprolol Succinate and Ramipril with the polymers was performed using FTIR method. The drugs and excipients were found to be compatible with each other. Weight variation, hardness, and in vitro dissolution studies of the tablets were also performed and found to be compliance with US pharmacopoeial standards.

Chandrashekhar et al. (Chandrashekhar et al., 2011) studied the stability test of Metoprolol succinate in distilled water, phosphate buffer and 0.1N HCl and found no degradation of the product.

Reddy et al. (Reddy et al., 2011) took an attempt to prepare a mouth dissolving tablet of Metoprolol Tartrate by direct compression method to increase patient compliance. Two different batches of tablets were prepared using the same excipients. The two superdisintegrants used in this study were Croscarmellose sodium and Sodium starch glycolate. But in one batches disintegrates were not used. Then the tablets were studied for uniformity of weight, thickness, hardness, friability, wetting time, water absorption ratio, disintegration and dissolution. From the result it has been found that the hardness, friability, disintegration time and dissolution rate of the tablets are within standard limits.

Nadenla et al. (Nadenla et al., 2011) conducted a study on the designing of sustained release pellets of Metprolol Succinate. The pellets were primarily prepared by solution technology and then a secondary coating of ethyl cellulose was given to sustain the release of drug over a period of 20 hrs. Then the pellets were evaluated for surface texture, flow properties and in vitro dissolution studies. Study found the promising result in terms of sustained release action of the drug.

Senthil et al. (Senthil et al., 2011) took an attempt to prepare orally disintegrating tablets of metoprolol tartrate by direct compression method by using different concentration of digintigrants (cross Povidone) and diluents. The mixture was examined for angle of repose, bulk density, tapped density, compressibility index. The tablet was evaluated for thickness, hardness, friability, and weight variation. Twelve formulations were prepared with cross povidone and three diluents with three different concentrations to evaluate the optimum formulation with optimum result.

In the same year, Syed et al. (Syed et al., 2011) formulated the matrix and triple layer matrix tablets of Metoprolol Tartrate by using xanthan gum as the matrix forming agent and Sodium Carboxy Methyl Cellulose as barrier layers. The prepared tablets were analyzed for hardness, friability, drug content and in-vitro drug release studies. And the result indicates that the release of drug is slower from triple layer matrix tablets. The finding of the study indicated that the matrix tablets prolonged the release, but predominantly in a first order kinetics.

In next year, Anisree et al. (Anisree et al., 2012) modified the conventional dosage form of transdermal drug delivery system. So they formulated different matrix-type transdermal films

containing metoprolol tartrate with an objective to check the effect of polymers on the release patterns. Different mixture of polymers such as polyvinyl pyrrolidone (PVP), ethyl cellulose (EC), and hydroxy propyl methyl cellulose (HPMC) were used for the films.

Agarwal et al. (Agarwal et al., 2012) prepared a delayed-onset extended-release (DOER) formulation of metoprolol tartrate on the basis of the circadian rhythm of cardiovascular diseases. This work proposes an approach to attain DOER for a hydrophilic drug by using a hydrophilic swellable polymer in press coat.

Adi et al. (Adi et al., 2012) prepared and examined intranasal delivery of metoprolol tartrate (cardioselective β1-blocker) by formulating mucoadhesive microspheres. The microspheres were prepared by ionic precipitation and chemical cross-linking method. Conclusion of the research work is the release pattern of metoprolol tartrate in nasal mucosa will attain therapeutic plasma concentration and reduce elevated blood pressure levels.

Khan et al. (Khan et al., 2012) did a research work on fabricate porous nano-particles of metoprolol tartrate by using spray-drying ammonium carbonate as pore former. Prepared nanoparticles were coated with Eudragit S100 polymer in order to prevent the release of drug in the upper GI tract. In vitro studies showed that increase in pore former made faster drug release and release kinetics proved that nano-particles follow a zero-order release mechanism.

Rasool et al. (Rasool et al., 2012) investigated the pharmacokinetics of a developed Metoprolol tablet and reference standard(Mepressor®). This metoprolol tartrate was loaded to Eudragit® FS microparticles were formulated and compressed into tablets. Physicochemical properties of the tablets were studied according to the United States Pharmacopoeia (USP) criteria and found that all the tablets met the specification. Bioequivalence test is also carried out in 28 young healthy fasting males and the results showed that the two formulations (developed formulation and reference standard) are bioequivalent.

Tagde et al. (Tagde et al., 2012) developed a bi-layer tablet of metoprolol tartrate by using disintegrant starch for the fast release layer and HPMC K grade polymers for the sustaining layer. In-vitro dissolution studies were carried out in an Indian Pharmacopoeia dissolution testing apparatus II (paddle method). The In-vitro study of this tablet indicated sustained release for metoprolol tartrate are followed zero order release and 95% drug in 24h.

Raffick et al. (Raffick et al., 2012) prepared bi layer sustained release tablet containing Metoprolol Succinate and then performed preformulation studies that includes incompatibility studies, solubility, LOD, bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. Wet granulation method using different viscosity grade of HPMC as polymers was used to prepare sustained layer of Metoprolol Succinate and immediate layer of the tablet was prepared by using super disintegrant crosscarmellose sodium by direct compression method. Then weight uniformity, hardness, friability, disintegration, drug content, in-vitro swelling studies, in-vitro dissolution study, stability studies and kinetic data analysis studies of the prepared tablets were performed. The study showed that the formulation was within acceptable limit as the drug release pattern of the tablet was closely similar to theoretical release profile.

Ancuta et al. (Ancuta et al., 2012) formulated and evaluated oral sustained drug delivery systems for metoprolol tartrate using hydrophilic polymers. The matrix tablets were prepared with different types and ratios of polymers and diluents. The matrix tablets were evaluated for mass variation, friability, hardness, thickness, swelling index, and in-vitro dissolution.The increasing amount of HPMC in the formulation led to a slow release of drug.

Shailaza et al. (Shailaza et al., 2012) formulated an orodispersible tablets of Metoprolol Tartrate with natural and synthetic superdisintegrants. Various formulations of Metoprolol Tartrate were prepared by direct compression method using different ratios of natural superdisintegrant (agar, treated agar) and synthetic superdisintegrants (sodium starch glycolate, croscarmellose sodium and crospovidone) at the concentrations ranging from 3%-12%. The formulation was found to be stable.

Recently, Kumar et al. (Kumar et al., 2013) prepared and evaluated a pulsatile drug delivery system of metoprolol tartrate. The prepared pulsatile delivery system consists of two different parts: a core tablet that contains the active ingredient and an erodible. On the basis of this evaluation it was found that pulsatile release formulation showed within 2hrs and in-vitro drug relrease within 8hrs where 97.8% of drug was released. The pulsatile release formulation showed compliance with chronotherapeutic objective of hypertension.

Karwa et al. (Karwa et al., 2013) investigated the compatibility of drug with the excipients in Metoprolol succincate in which carbopol was used as polymers for controlled drug release. Non-

thermal, thermal and isothermal methods were studied. The drug was found to be compatible with carbpol in non thermal and isothermal method, but thermal method showed incompatibility between the drug and carbopol.

Brahmaiah et al. (Brahmaiah et al., 2013) did a research work by preparing the floating tablets of metoprolol tartrate to increase and enhance the gastric retention and to improve the bioavailability of the drug. Metoprolol tartrate was chosen as a model drug because it is better absorbed in the stomach than the lower gastrointestinal tract. The tablets were prepared by direct compression method. The formulated tablets were evaluated for weight variation, hardness, friability, swelling index floating lag time, total floating time and dissolution rate in pH 1.2. Ultimately the result of this experiment was very satisfactory.

Mathur et al. (Mathur et al., 2013) developed metoprolol tartrate microspheres for floating pulsatile release intended for chronopharmacotherapy. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. Emulsification solvent evaporation technique was used to prepare the floating pulsatile microspheres. Result for this approach wasvery promising to use of floating pulsatile microsphere in drug delivery for site of action and time specific release of drug for chronotheraphy of hypertension.

Devi et al. (Devi et al., 2013) performed a research work to compare the effect of superdisintegrants on the melt-in-mouth property of metoprolol tartrate tablets. In the present work Melt-in-mouth tablets of metoprolol tartrate were prepared by direct compression method using superdisintegrants such as Isapgol husk, sodium starch glycolate and croscarmellose sodium. So it was concluded that sublimation method along with superdisintegrant addition was excellent method in formulation of Melt-in-mouth tablets of Metoprolol Tartrate which gives quick relief from Myocardial infarction.

In next year, Shaikh and Patil (Shaikh and Patil, 2014) did a research work to conduct the forced degradation test of Metoprolol in accordance with the ICH guideline. Acidic, basic, hydrolytic, oxidative, thermal and photolytic degradation test were studied and found that the drug was stable in acid, oxidation, thermal and photolytic stress condition and found degradation in base hydrolysis condition.

In the same year, Tomar et al. (Tomar et al., 2014) conducted formulation of an oral controlled drug delivery system for metoprolol tartrate. To evaluate the effect of the oral controlled drug delivery system formulation of metoprolol tartrate, instead of normal trial & error method, a standard experimental design was developed. A short term stability test was conducted as per ICH guidelines and it was found to be stable for long period of time.

Reddy et al. (Reddy et al., 2014) did a research work to develop a bi layer dosage form containing one immediate release drug amlodipine besylate and another extended release drug Metoprolol succinate. Crystalline cellulose, sodium starch glycolate, crosspovidone and dicalciuam phosphate were used to prepare immediate release layer. HPMC K15, sodium CMC, and carbopol were used to prepare sustained release layer. The formulation was evaluated by FTIR studies which showed that the polymers were compatible with the drug. Study also showed that the drug release pattern of Metoprolol succinate from the layer prepared by carbopol and HPMC K15 was within the USP limits.

Kumar, A.P. (Kumar, A.P., 2014) performed a work by utilizing osmotic pressure to develop an osmotically controlled drug delivery system of Metprolol. The tablet was developed by wet granulation technique. Before compression the granules were evaluated for micromeritic properties. The release of the drug was depended on the concentration of osmotic agent and swelling agent and their effect on in vitro release was studied. The result showed that 60% of the drug was released by the all formulation after 12 hrs which follow the zero order kinetics. The formulation was also evaluated for hardness and drug content studies and found to be stable.

CHAPTER THREE

MATERIALS & METHODS

3.1 MATERIALS

3.1.1 Sample Collection

For the purpose of experimentation to observe the photolytic degradation of Metoprolol Tartrate as well as to assess the coating efficiency, 700 tablets of Betaloc® (Metoprolol Tartrate 50mg) were collected from the local drug store in Dhaka as a sample. All the tablets were from the same batch (0615). Among them 300 tablets were kept light protected for control tests and the remaining 400 tablets were subjected to various lighting conditions over certain periods of time for conducting experiments to determine their potency.

3.1.2 Samples

Table 3.1: Samples used in the experiment including source (Drug International Ltd, 2015)

Sample Name	Source (Supplier Name)	Batch No.
Betaloc® Tablets	Drug International Ltd.	0615

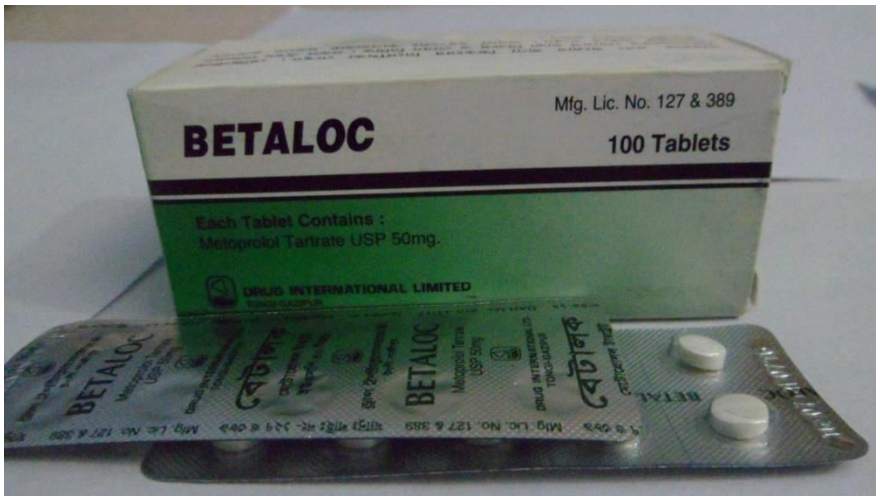

Figure 3.1: Betaloc® Tablet (Metoprolol Tartrate)

3.1.3 Reagents

Table 3.2: Reagents used in the experiment including source

Reagents Name	Source (Supplier Name)
Concentrated H_2SO_4 (98% / 36.8N)	Analar, United Kingdom
Distilled Water	Laboratory (East West University)

3.1.4 Equipments & Instruments

Table 3.3: Lists of equipments used for the experiment

Serial No.	Equipments	Source (Supplier Name)	Origin
1	UV-Spectrophotometer	Shimadzu UV1800	Japan
2	Distill Water Plant	Bibby Scientific W4000	United Kingdom
3	Electronic Balance	Shimadzu AY220	Japan
4	Hardness tester	Veego VTHT	India
5	Venire Calipers	Shanghai Tricle Brand	China

3.1.5 Images of Instruments

Some of the important instruments those were used in different tests during research work.

Figure 3.2: Shimadzu UV-1800 Double Beam Spectrophotometer and Electronic Balance [Left to right]

Figure 3.3: Hardness tester and Distilled Water Plant [Left to right]

3.1.6 Apparatus

Some technical equipment or machinery needed for a particular activity or research work. Apparatus may refer to machine, equipment and critical apparatus. Some apparatus are listed in the following table those were widely used throughout the experiments and research work.

Table 3.4: List of Apparatus used throughout this project

Serial No.	Apparatus
1	Funnel
2	Spatula
3	Beakers
4	Forceps
5	Test tubes
6	Glass Rod
7	Table Lamp
8	Pipette (5 ml)
9	Filter Papers
10	Masking Tap
11	Thermometer
12	Pipette pumper
13	Plastic Dropper
14	Test tube Holder
15	Mortar & Pestles
16	Plastic Containers
17	Aluminum foil paper
18	Electric Bulb (25 Watt & 40 Watt)
19	Volumetric Flasks (50 ml, 250ml & 1000 ml)

3.2 METHOD

3.2.1 Preparation of the solvent (0.1N H_2SO_4)

1. Lab solvent (H_2SO_4), stock solution with 98% (v/v) of strength was collected.

2. Then the concentration of the lab solvent stock solution was determined in normality where the specific gravity of solvent is 1.84.

Determination of the Concentration of the Lab Solvent (H_2SO_4) in Normality (N):

100 ml of the lab solvent stock solution contains = 98ml of H_2SO_4

100 ml of lab solvent stock solution contains = (98 x 1.84)gm of H_2SO_4

= 180.32gm of H_2SO_4

1000 ml of stock solution contains = (180.32 x 1000)/100 gm of H_2SO_4

= 1803.2gm of H_2SO_4

1000 ml of stock solution contain 49gm of H_2SO_4 = 1N of H_2SO_4

1000 ml of stock contain 1803.2gm of H_2SO_4 = (1803.2/49)N of H_2SO_4

= 36.8N of H_2SO_4

3. After the determination of the concentration of the lab solvent stock solution in Normality (N), the amount of lab solvent (36.8N H_2SO_4) stock solution required to make 1000ml of 0.1N HCL solvent was calculated as below.

Determination of the amount of 36.8N H_2SO_4 required to make 1000ml of 0.1N H_2SO_4 by using the $V_1S_1 = V_2S_2$

Where,

S_1 = Conc. of lab solvent (H_2SO_4) stock solution = 36.8N

S_2 = Final concentration of the solvent (H_2SO_4) = 0.1N

V_1 = Volume of the lab solvent (H_2SO_4) stock solution =?

V_2 = Final volume of the solvent (H_2SO_4) = 1000ml

So that,

$V_1 = (V_2S_2) / S_1$

⇨ V_1 = (1000ml x 0.1 N) / 36.8N

⇨ V_1 = 2.717ml (~ 2.72 ml of lab solvent H_2SO_4 stock solution)

4. Then 2.72ml of 36.8N H_2SO_4 was transferred from the lab solvent stock solution to a 1000ml volumetric flask which was then filled with water up to mark to make 1000ml of 0.1N H_2SO_4.

3.2.2 Determination of λ_{max} & Preparation of the Standard Curve of Metoprolol Tartrate.

1. Standards of Metoprolol Tartrate was collected from a pharmaceutical company. The potency of standard compounds was 99.5%.
2. The specific λ_{max} for Metoprolol Tartrate, at which the absorbance would be measured, was determined to be 221.5nm from the UV spectrometer by using the standard. Nine serial concentrations of the standards of Metoprolol Tartrate were prepared for the purpose of creating a standard curve.

Preparation of the stock solution for Metoprolol Tartrate using the standard :

50 mg of the standard compound, that is Metoprolol Tartrate was weighed and dissolved in 250ml of 0.1N H_2SO_4 (which is the solvent) in a 250ml volumetric flask for the 1st dilution.

Thus the concentration was calculated to be:

Concentration of 1st dilution = amount of substance added / volume
= (50 / 250) mg/ml
= 0.2 mg/ml

⇨ Then 5ml of that 0.2 mg/ml Metoprolol Tartrate solution was taken and dissolved in 50ml of 0.1N H_2SO_4. That 5ml contained 1mg of Metoprolol Tartrate.

So the concentration finally turned out to be:

Concentration of 2nd dilution = amount of substance added / volume
= (1 / 50) mg/ml
= 0.02 mg/ml

Preparation of nine serial concentrations of solution for Metoprolol Tartrate:

- ⇨ Metoprolol Tartrate had the concentration of its stock solution is 0.02 mg/ml.

- ⇨ Nine serial concentrations that were prepared for Metoprolol Tartrate were as follows 0.001 mg/ml, 0.002 mg/ml, 0.003 mg/ml, 0.004 mg/ml, 0.005 mg/ml, 0.006 mg/mi, 0.007 mg/ml, 0.008 mg/ml and 0.009 mg/ml for a final volume of 10 ml.

- ⇨ The amount of the solution that were required from the stock solution to prepare the above concentrations were calculated using $S_1V_1=S_2V_2$ formula, where S_1= initial strength or concentration, S_2= final strength or concentration, V_1= initial volume and V_2= final volume.

- ⇨ Thus the following concentrations were prepared as such for Metoprolol Tartrate as per the calculations provided below.

Table 3.5: Concentrations for preparation of Standard Curve of Metoprolol Tartrate

Sample Name	Sample no.	Concentration (mg/ml)
Metoprolol Tartrate	1	0.001
	2	0.002
	3	0.003
	4	0.004
	5	0.005
	6	0.006
	7	0.007
	8	0.008
	9	0.009

- ❖ $V_1= S_2V_2 / S_1$ = (0.001 x 10) / 0.02 = 0.5 ml of stock solution required to make 0.001 mg/ml concentration of the final solution of 10 ml (0.5 ml of stock solution + 9.5 ml of 0.1N H_2SO_4) of Metoprolol Tartrate.

- $V_1 = S_2V_2 / S_1$ = (0.002 x 10) / 0.02 = 1 ml of stock solution required to make 0.002 mg/ml concentration of the final solution of 10 ml (1 ml of stock solution + 9 ml of 0.1N H_2SO_4) of Metoprolol Tartrate.
- $V_1 = S_2V_2 / S_1$ = (0.003 x 10) / 0.02 = 1.5 ml of stock solution required to make 0.003 mg/ml concentration of the final solution of 10 ml (1.5 ml of stock solution + 8.5 ml of 0.1N H_2SO_4) of Metoprolol Tartrate.
- $V_1 = S_2V_2 / S_1$ = (0.004 x 10) / 0.02 = 2 ml of stock solution required to make 0.004 mg/ml concentration of the final solution of 10 ml (2 ml of stock solution + 8 ml of 0.1N H_2SO_4) of Metoprolol Tartrate.
- $V_1 = S_2V_2 / S_1$ = (0.005 x 10) / 0.02 = 2.5 ml of stock solution required to make 0.005 mg/ml concentration of the final solution of 10 ml (2.5 ml of stock solution + 7.5 ml of 0.1N H_2SO_4) of Metoprolol Tartrate.
- $V_1 = S_2V_2 / S_1$ = (0.006 x 10) / 0.02 = 3 ml of stock solution required to make 0.006 mg/ml concentration of the final solution of 10 ml (3 ml of stock solution + 7 ml of 0.1N H_2SO_4) of Metoprolol Tartrate.
- $V_1 = S_2V_2 / S_1$ = (0.007 x 10) / 0.02 = 3.5 ml of stock solution required to make 0.007 mg/ml concentration of the final solution of 10 ml (3.5 ml of stock solution + 6.5 ml of 0.1N H_2SO_4) of Metoprolol Tartrate.
- $V_1 = S_2V_2 / S_1$ = (0.008 x 10) / 0.02 = 4 ml of stock solution required to make 0.008 mg/ml concentration of the final solution of 10 ml (4 ml of stock solution + 6 ml of 0.1N H_2SO_4) of Metoprolol Tartrate.
- $V_1 = S_2V_2 / S_1$ = (0.009 x 10) / 0.02 = 4.5 ml of stock solution required to make 0.009 mg/ml concentration of the final solution of 10 ml (4.5 ml of stock solution + 5.5 ml of 0.1N H_2SO_4) of Metoprolol Tartrate.

3. Then the absorbance value was measured using a UV spectrophotometer against those nine serial concentrations for Metoprolol Tartrate.
4. A standard curves was plotted for Metoprolol Tartrate.
5. From this standard curve a straight line equation was obtained which was in the form of y = mx+c, where the components of the equations are described as provided below:

m = gradient value, y = absorbance values, x = concentrations and c = y-intercept.

3.2.3 Sampling, Analysis by UV-Spectrophotometry & Determination of Potency of the pharmaceutical drugs (Metoprolol Tartrate) under various lighting condition:

To determine the photo-stability of the drug (Metoprolol Tartrate) in their packaging, the tablets were subjected to various types of light exposure, which were as follows:

- ⇨ Exposure to normal lighting conditions in the room
- ⇨ Electric Bulb exposure (25 watt & 40 watt)
- ⇨ Direct Sunlight exposure

- **Exposure under Normal Lighting Condition**

1) The tablets (Betaloc®) were kept under normal lighting condition in the room for 3 months.
2) They were sampled after specific intervals like periodically after 15 days for determination their physical properties (like thickness, hardness & weight variation) and their potency.
3) On the sampling day, a piece of white paper was taken and all the details (brand name of the tablets, date of the sampling etc.) were written on top of the paper.
4) Now, 10 tablets were taken out and from this 10 tablets, 5 tablets were kept on over that white paper.
5) A photograph was taken of that paper showing the tablets with their appearances and those details.
6) Then from those 10 tablets, 5 tablets were used for physical parameter test and the rest 5 tablets for potency determination.
7) For potency determination, laboratory analysis was done by using UV spectroscopy technique:

    a. First, 5 tablets from those sampled tablets were taken.
    b. Then the total weight of those 5 tablets was noted using an analytical balance and the average weight was calculated using the formula given below:

$$\text{Average weight (in grams)} = \frac{\text{Total weight of the tablets}}{\text{Total no. of tablets}}$$

c. Then the 5 tablets were crushed by using mortar and pestle.
d. Approximately the weight of 1 tablet of crushed tablet powder was taken and dissolved it in 250 ml of the solvent (0.1N H_2SO_4) for 3 times to prepare 9 samples.
e. After that 10 ml solution was filtered and 5 ml of that filtered solution was taken and dissolved in 50ml of the solvent.
f. From then 10ml of each sample was collected and kept into 9 different test-tubes and wrapped by foil paper.
g. From test-tube the solution was poured into a cuvette and was inserted into the UV spectrophotometer to observe the absorbance value.

8) Then the absorbance value was plotted into the standard curve to obtain the total amount of the drug that is present in one tablet.
9) Steps 3 to 8 were repeated again on another sampling day.

- **Under electronic bulb exposure (25W & 40W)**

1) 30 tablets were exposed to electric bulb lighting conditions for 6 hours at a stretch and 10 tablets were used as control.
2) After every 2 hours, 10 tablets were collected and wrapped up with foil paper to prevent any further exposure to the lighting condition and the temperature was noted using a thermometer.
3) The foil papers should be labeled to identify the intervals.
4) The tablets were then used for potency determination to see the effect of the exposure of bulb's lighting condition to drug ingredients.
5) For potency determination, laboratory analysis was done by using UV spectroscopy technique:

a. First, 5 tablets from those sampled tablets were taken.
b. Then the total weight of those 5 tablets was noted using an analytical balance and the average weight was calculated using the formula :

$$\text{Average weight (in grams)} = \frac{\text{Total weight of the tablets}}{\text{Total no. of tablets}}$$

c. Then the 5 tablets were crushed by using mortar and pestle. Approximately the weight of 1 tablet of crushed tablet powder was taken and dissolved it in 250 ml of the solvent (0.1N H_2SO_4) for 3 times to prepare 9 samples.
d. After that 10 ml solution was filtered and 5 ml of that filtered solution was taken and dissolved in 50ml of the solvent.
e. From then 10ml of each sample was collected and kept into 9 different test-tubes and wrapped by foil paper.
f. From test-tube the solution was poured into a cuvette and was inserted into the UV spectrophotometer to observe the absorbance value.

Table 3.6: Electric Bulb (25W & 40W) Exposed Sample List

No. of Samples	Collected Sample	Withdrawal Intervals (Hrs)	Temparature (^{0}C)
10 (Control)	10	0	30
30	10	2	30
	10	4	30
	10	6	32

6) Then the absorbance value was plotted into the standard curve to obtain the total amount of the drug that is present in one tablet.
7) Steps 5 to 6 were repeated again for another sampling hour.

8) 10 tablets were used as control and has not been exposed to any of the lighting conditions.

N.B: Same procedure (steps 1 to 8) were used to determine the potency of the tablets under both exposure of 25W and 40W lighting condition for six different days for 6 hours each.

- **Under Sunlight condition**

1) 30 tablets were kept in a Glass box and exposed to sunlight condition for 6 hours at a stretch and 10 tablets were used as control.
2) After every 2 hours, 10 tablets were collected and wrapped up with foil paper to prevent any further exposure to the lighting condition and the temperature was noted using a thermometer.
3) The foil papers should be labeled to identify the intervals.
4) The tablets were then used for potency determination to see the effect of the exposure of sunlight condition to drug ingredients.
5) For potency determination, laboratory analysis was done by using UV spectroscopy technique:

a. First, 5 tablets from those sampled tablets were taken.
b. Then the total weight of those 5 tablets was noted using an analytical balance and the average weight was calculated using the formula:

$$\text{Average weight (in grams)} = \frac{\text{Total weight of the tablets}}{\text{Total no. of tablets}}$$

c. Then the 5 tablets were crushed by using mortar and pestle.
d. Approximately the weight of 1 tablet of crushed tablet powder was taken and dissolved it in 250 ml of the solvent (0.1N H_2SO_4) for 3 times to prepare 9 samples.
e. After that 10 ml solution was filtered and 5 ml of that filtered solution was taken and dissolved in 50ml of the solvent.

f. From then 10ml of each sample was collected and kept into 9 different test-tubes and wrapped by foil paper.
g. From test-tube the solution was poured into a cuvette and was inserted into the UV spectrophotometer to observe the absorbance value.

Table 3.7: Sunlight Exposed Sample List

No. of Samples	Collected Sample	Withdrawal Intervals (Hrs)	Temparature (^{0}C)
10 (Control)	10	0	30
30	10	2	31
	10	4	31
	10	6	32

6) Then the absorbance value was plotted into the standard curve to obtain the total amount of the drug that is present in one tablet.
7) Steps 5 to 6 were repeated again for another sampling hour.
8) 10 tablets were used as control and has not been exposed to any of the lighting conditions.

N.B: Same procedure (steps 1 to 8) were used to determine the potency of the tablets under exposure of Sunlight condition for three different days for 6 hours each.

3.2.4 Determination of Physical parameters

- **Color Test**

  The color of tablets was observed to find any change in color. A digital camera was used to take the picture of the tablets for the comparative observation. In case of taking picture any kind of flash was not used or avoided. A fixed camera with fixed resolution was maintained.

- **Thickness Test**

  The thickness of tablets was measured to find the change in thickness at specific time interval. A slide calipers was used to take thickness value of tablets for the comparative observation. In case of performing the test, tablets are placed horizontally in between the fixed jaw and the moving jaw of the calipers, tighten the jaws and check the reading of main scale and vernier scale and calculate the values of each tablets.

- **Hardness Test**

  Hardness test was performed to determine the hardness of tablets. So the force will be applied during compression of tablet, greater the pressure applied the harder the tablet. Monsanto tablet hardness tester was used to measure the hardness of Betaloc®. Hardness measuring devices apply increasing pressure on the tablet until the tablet breaks (a force of about 4 kilograms is considered to be a minimum for hardness).

- **Weight Variation Test**

  Procedure

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

  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:

Table 3.8: Accepted percentage list for the weight variation test of tablets

Weight of tablet	Percentage difference
130 mg or less	±10%
More than 130 to 324 mg	±7.5%
More than 324 mg	±5%

Calculation

Following equation was used to determine % Weight Variation of tablets

$$\% \text{ Weight Variation} = (A \sim I/A) \times 100\ \%$$

Where,

I = Initial Weight of Tablet, in gram/grams (gm)

A = Average weight of Tablet, in gram/grams (gm)

CHAPTER FOUR

RESULT

4.1 Standard curve preparation

The standard was collected from Aristopharma Ltd. Its potency was 99.56%. A standard curve was made. For different concentration of Metoprolol Tartrate we found different absorption. Nine serial concentrations of the standards of Metoprolol Tartrate were prepared for the purpose of creating a standard curve.

The results are as follows:

Table 4.1: Concentration & Absorbance for Standard Curve of Metoprolol Tartrate

Concentration(mg)	Absorbance (at 221.5nm)
0.001	0.058
0.002	0.072
0.003	0.100
0.004	0.131
0.005	0.158
0.006	0.221
0.007	0.226
0.008	0.259
0.009	0.280

By plotting the absorbance against the concentration of Metoprolol Tartrate a straight line was found. From this an equation was derived where:

$$Y=29.85X+0.018$$

$$R^2=0.982$$

This equation was used to determine the concentration of Metoprolol Tartrate from different samples absorbance.

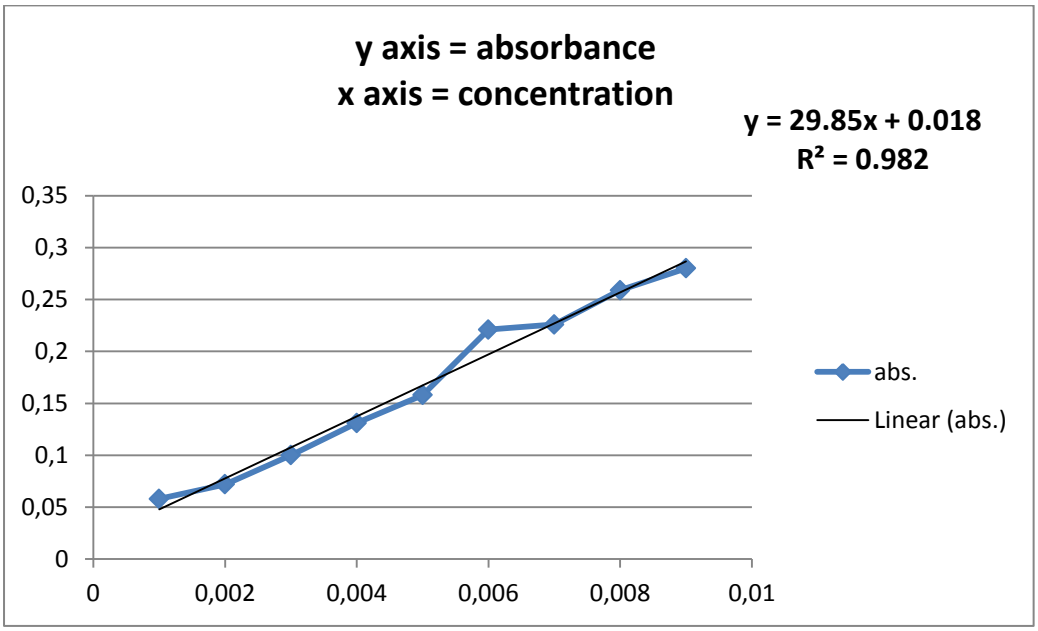

Figure 4.1: Plot showing straight line for absorbance with respect to concentration for Metoprolol Tartrate

4.2 Physical Parameters of Normal Light Exposed Samples

4.2.1 Color Test

The color of tablets was observed to find any change in color with respect to time intervals. No significant change was observed in color of the tablet. The picture of the sample tablets of different days are showed below:

Figure 4.2: Pictures of tablets after exposure to normal light with 60 days interval.

4.2.2 Weight Variation Test

Four tablet strips containing 40 tablets were exposed to normal light condition for 60 days. Weight variation test was conducted of 5 tablets of each day interval (15, 30, 45, 60 days). In experimental day, a tablet strip containing 10 tablets was taken and 5 samples were collected for the test. Weight variation test was conducted and average weight was calculated for each day. Data of these tests are given below:

Table 4.2: Weight Variation Test of Metoprolol Tartarte (Betaloc®)

Days	Average Weight for Particular Day (gm)
Initial	0.1263
15	0.1247
30	0.1249
45	0.1245
60	0.1230

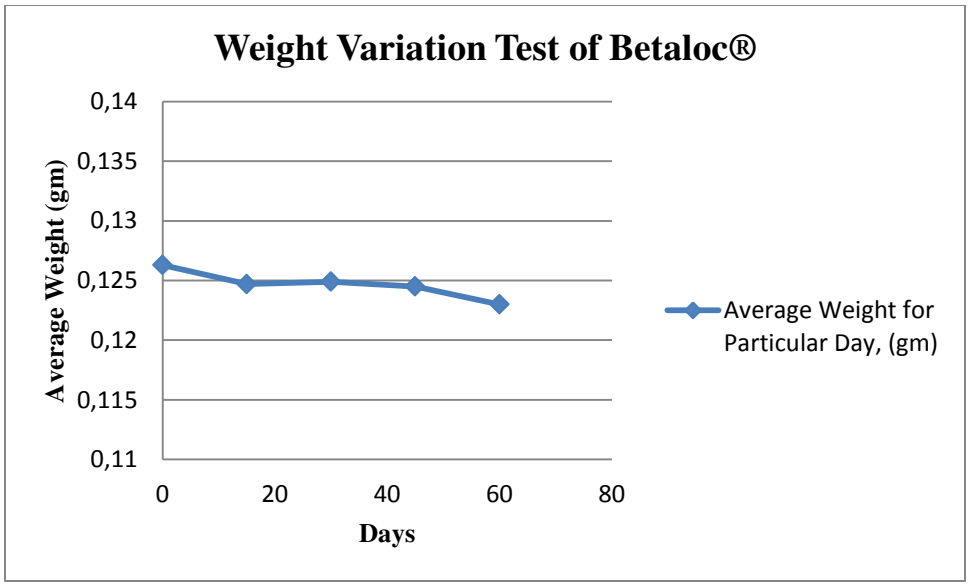

Figure 4.3: Weight variation of the sample throughout 60 days light exposure.

4.2.3 Hardness Test

Four tablet strips containing 40 tablets were exposed to normal light condition for 60 days. Hardness test was conducted of 5 tablets of each day interval (15, 30, 45, 60 days). In experimental day, a tablet strip containing 10 tablets was taken and 5 samples were collected for the test. Hardness test was conducted and average weight was calculated for each day. Data of these tests are given below:

Table 4.3: Hardness Test of Metoprolol Tartarte (Betaloc®)

Days	Average Hardness of Particular Day (Kg)
Initial	6.5
15	6.5
30	6.0
45	5.5
60	6.0

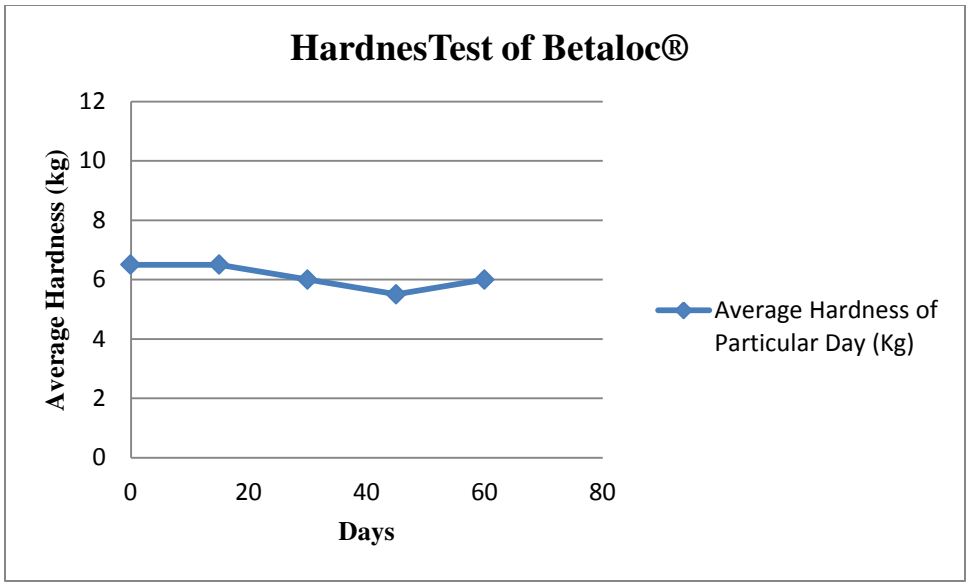

Figure 4.4: Hardness variation of the sample throughout 60 days light exposure.

4.2.4 Thickness Test

Four tablet strips containing 40 tablets were exposed to normal light condition for 60 days. Thickness test was conducted of 5 tablets of each day interval (15, 30, 45, 60 days). In experimental day, a tablet strip containing 10 tablets was taken and 5 samples were collected for the test. Thickness test was conducted and average weight was calculated for each day. Data of these tests are given below:

Table 4.4: Thickness Test of Metoprolol Tartarte (Betaloc®)

Days	Average Thickness of Particular Days (cm)
Initial	0.261
15	0.260
30	0.259
45	0.262
60	0.258

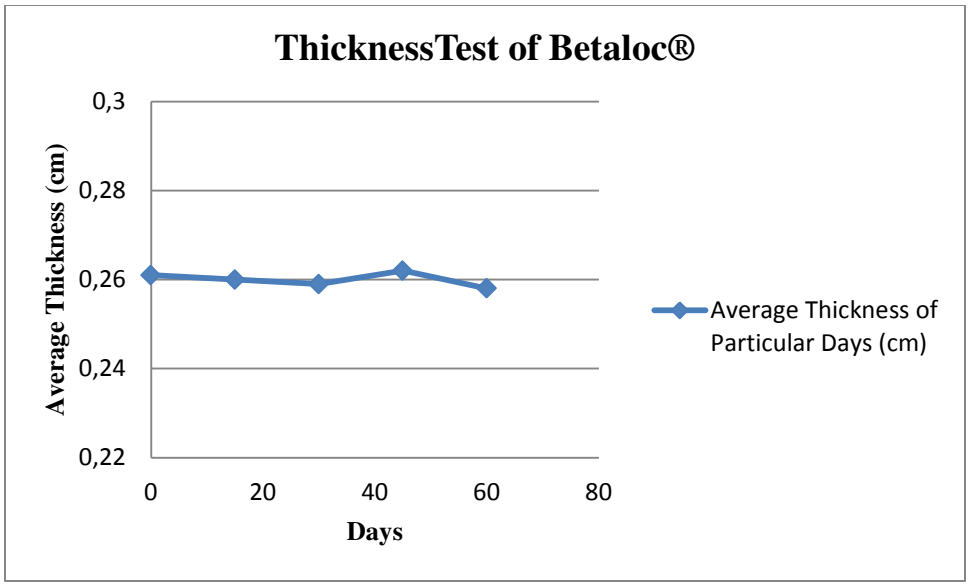

Figure 4.5: Thickness variation of sample throughout 60 days light exposure.

4.3 Result of Potency Determination by UV- Spectroscopy

4.3.1 Result of Samples that were exposed under Normal Lightening Condition

For our research purpose we have exposed tablets to the normal room light that were dispersed on top of the book shelf. We have collected those samples at specific intervals to determine its potency by UV-Spectroscopy. The results are given below:

Table 4.5: Concentration & Absorbance of 0 Day Interval for Metoprolol Tartrate (Betaloc®)

Time Interval (Days)	Absorbance (at 221.5nm)		Average Absorbance		Amount of Drug Present (in mg)		Potency (%)	
	Control	Sample	Control	Sample	Control	Sample	Control	Sample
Initial	0.609	0.609	0.612	0.612	49.75	49.75	99.50	99.50
	0.617	0.617						
	0.611	0.611						
	0.609	0.609	0.613	0.613	49.83	49.83	99.66	99.66
	0.618	0.618						
	0.612	0.612						
	0.617	0.617	0.611	0.611	49.66	49.66	99.33	99.33
	0.608	0.608						
	0.611	0.611						

Table 4.6: Concentration & Absorbance of 15 Days Interval for Metoprolol Tartrate (Betaloc®)

Time Interval (Days)	Absorbance (at 221.5nm)		Average Absorbance		Amount of Drug Present (in mg)		Potency (%)	
	Control	Sample	Control	Sample	Control	Sample	Control	Sample
15	0.609	0.549	0.612	0.554	49.75	44.89	99.50	89.78
	0.617	0.552						
	0.611	0.561						
	0.609	0.554	0.612	0.549	49.75	44.47	99.50	88.95
	0.617	0.547						
	0.611	0.546						
	0.609	0.553	0.612	0.550	49.75	44.56	99.50	89.11
	0.617	0.546						
	0.611	0.551						

Table 4.7: Concentration & Absorbance of 30 Days Interval for Metoprolol Tartrate (Betaloc®)

Time Interval (Days)	Absorbance (at 221.5nm)		Average Absorbance		Amount of Drug Present (in mg)		Potency (%)	
	Control	Sample	Control	Sample	Control	Sample	Control	Sample
30	0.609	0.529	0.612	0.536	49.75	43.38	99.50	86.77
	0.617	0.541						
	0.611	0.538						
	0.609	0.543	0.612	0.540	49.75	43.72	99.50	87.44
	0.617	0.539						
	0.611	0.538						
	0.609	0.537	0.612	0.534	49.75	43.22	99.50	86.43
	0.617	0.533						
	0.611	0.532						

Table 4.8: Concentration & Absorbance of 45 Days Interval for Metoprolol Tartrate (Betaloc®)

Time Interval (Days)	Absorbance (at 221.5nm)		Average Absorbance		Amount of Drug Present (in mg)		Potency (%)	
	Control	Sample	Control	Sample	Control	Sample	Control	Sample
45	0.609	0.530	0.612	0.525	49.75	42.46	99.50	84.95
	0.617	0.519						
	0.611	0.526						
	0.609	0.531	0.612	0.528	49.75	42.72	99.50	85.43
	0.617	0.527						
	0.611	0.526						
	0.609	0.533	0.612	0.530	49.75	42.88	99.50	85.77
	0.617	0525						
	0.611	0.532						

Table 4.9: Concentration & Absorbance of 60 Days Interval for Metoprolol Tartrate (Betaloc®)

Time Interval (Days)	Absorbance (at 221.5nm)		Average Absorbance		Amount of Drug Present (in mg)		Potency (%)	
	Control	Sample	Control	Sample	Control	Sample	Control	Sample
60	0.609	0.515	0.612	0.514	49.75	41.54	99.50	83.08
	0.617	0.516						
	0.611	0.511						
	0.609	0.517	0.612	0.511	49.75	41.30	99.50	82.59
	0.617	0.511						
	0.611	0.505						
	0.609	0.519	0.612	0.517	49.75	41.79	99.50	83.58
	0.617	0.520						
	0.611	0.512						

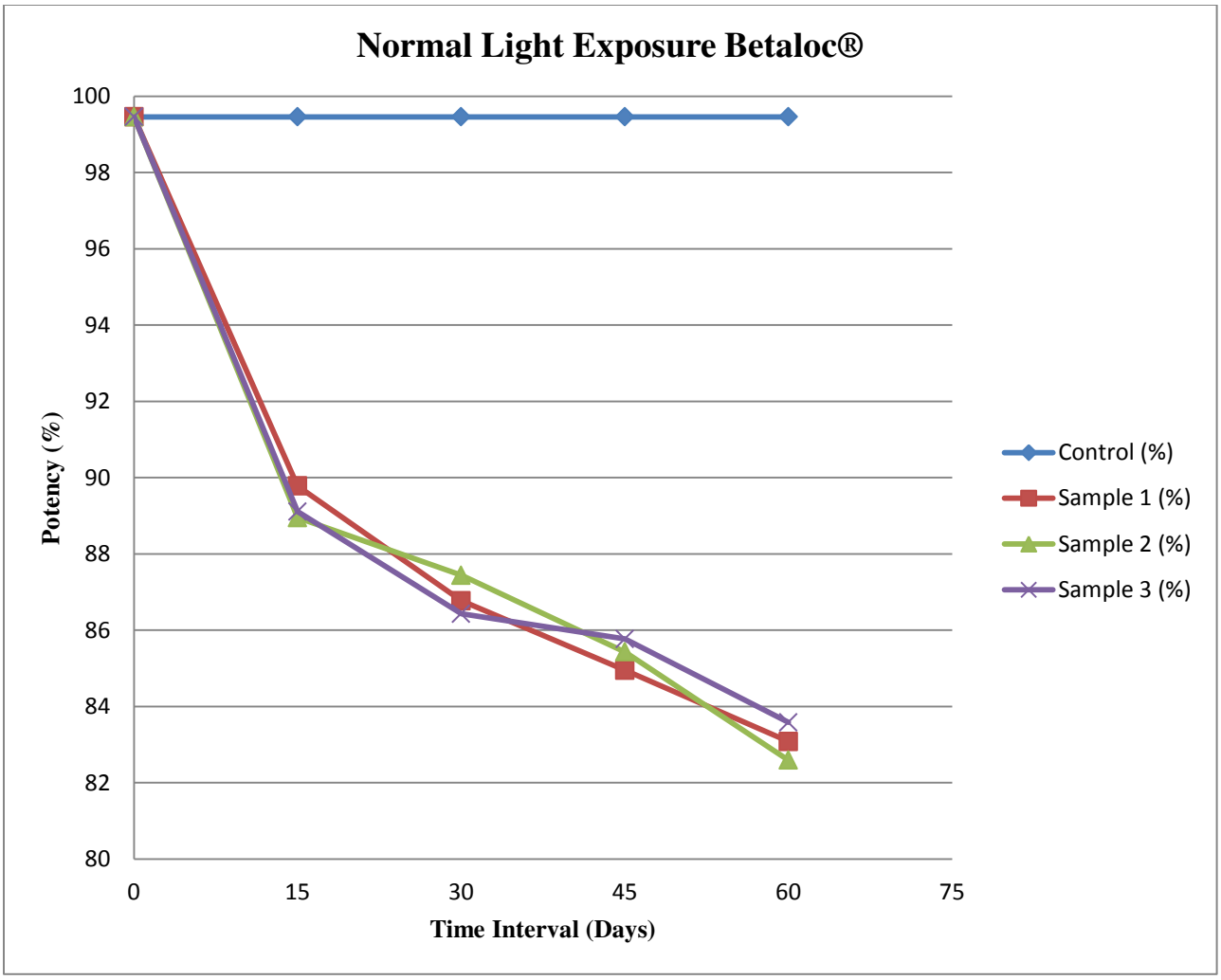

Figure 4.6: Graph showing the difference in Concentration after specific time interval for Metaprolol Tartrate (Betaloc®)

4.3.2 Result of samples that were exposed under 25W bulb

We found 27 different absorbance of Metoprolol Tartrate for twenty seven samples exposed under the lamp (25W bulb); each for 2 hours time interval and it was observed that the concentration of Metoprolol Tartrate was declined in each time interval.

Table 4.10: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 1st test under 25W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
Control	0.574	0.573	0.0186	46.48	92.83
	0.570				
	0.575				
	0.570	0.572	0.0186	46.40	92.80
	0.576				
	0.571				
	0.572	0.571	0.0185	46.35	92.68
	0.569				
	0.573				

Table 4.11: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 1st test under 25W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
2 Hour	0.531	0.532	0.0172	43.05	86.10
	0.528				
	0.537				
	0.540	0.537	0.0174	43.47	86.93
	0.533				
	0.538				
	0.520	0.528	0.0171	42.71	85.43
	0.535				
	0.529				

Table 4.12: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 1st test under 25W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
4 Hour	0.511	0.513	0.0166	41.46	82.91
	0.517				
	0.511				
	0.515	0.516	0.0167	41.71	83.42
	0.514				
	0.519				
	0.509	0.512	0.0165	41.37	82.75
	0.516				
	0.511				

Table 4.13: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 1st test under 25W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
6 Hour	0.500	0.503	0.0162	40.62	81.24
	0.511				
	0.498				
	0.499	0.499	0.0161	40.28	80.57
	0.497				
	0.501				
	0.503	0.506	0.0163	40.87	81.74
	0.507				
	0.508				

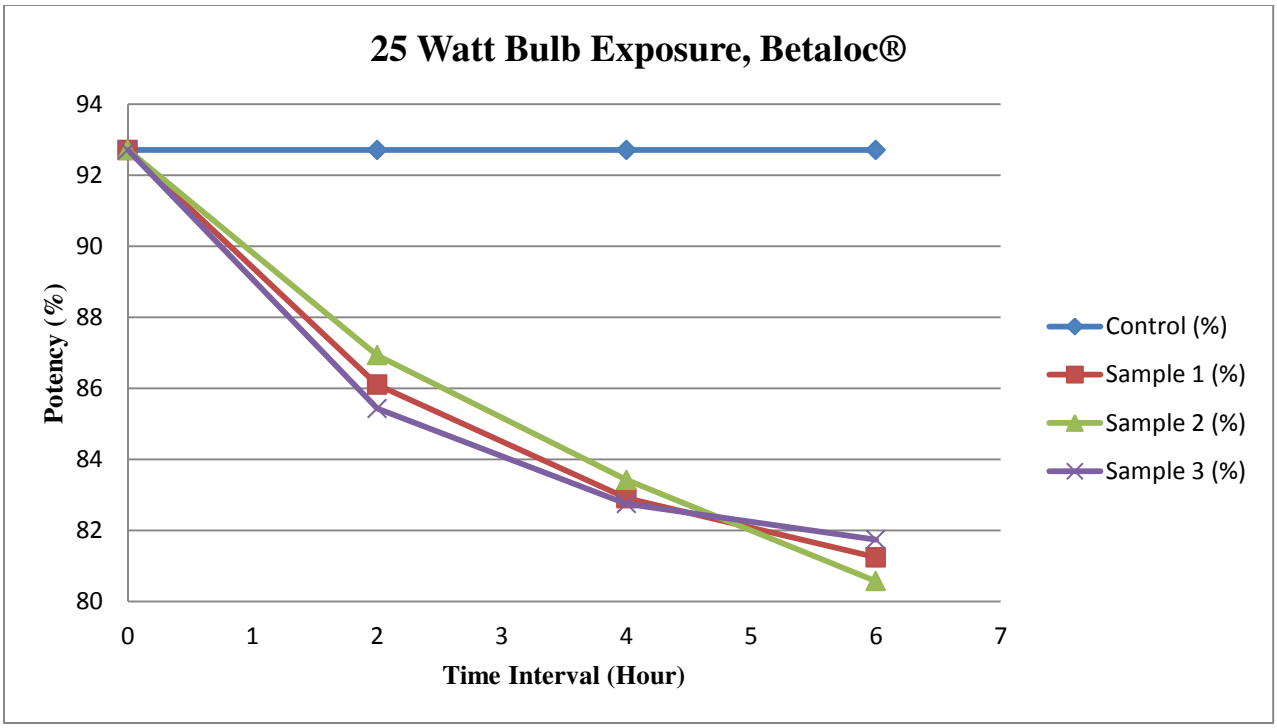

Figure 4.7: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Betaloc®) of the 1st test under 25W bulb exposure

Table 4.14: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 2nd test under 25W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
Control	0.589	0.581	0.0189	47.15	94.30
	0.578				
	0.576				
	0.579	0.580	0.0188	47.07	94.14
	0.587				
	0.575				
	0.590	0.581	0.0189	47.15	94.30
	0.579				
	0.575				

Table 4.15: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 2nd test under 25W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
2 Hour	0.529	0.532	0.0173	43.30	86.59
	0.534				
	0.533				
	0.527	0.531	0.0172	42.96	85.93
	0.535				
	0.531				
	0.539	0.536	0.0174	43.38	86.77
	0.534				
	0.536				

Table 4.16: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 2nd test under 25W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
4 Hour	0.513	0.514	0.0166	41.54	83.08
	0.515				
	0.513				
	0.514	0.517	0.0167	41.79	83.58
	0.520				
	0.516				
	0.516	0.513	0.0166	41.46	82.91
	0.510				
	0.513				

Table 4.17: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 2nd test under 25W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
6 Hour	0.501	0.501	0.0162	40.45	80.91
	0.498				
	0.508				
	0.507	0.502	0.0162	40.54	81.07
	0.497				
	0.503				
	0.499	0.505	0.0163	40.79	81.57
	0.512				
	0.503				

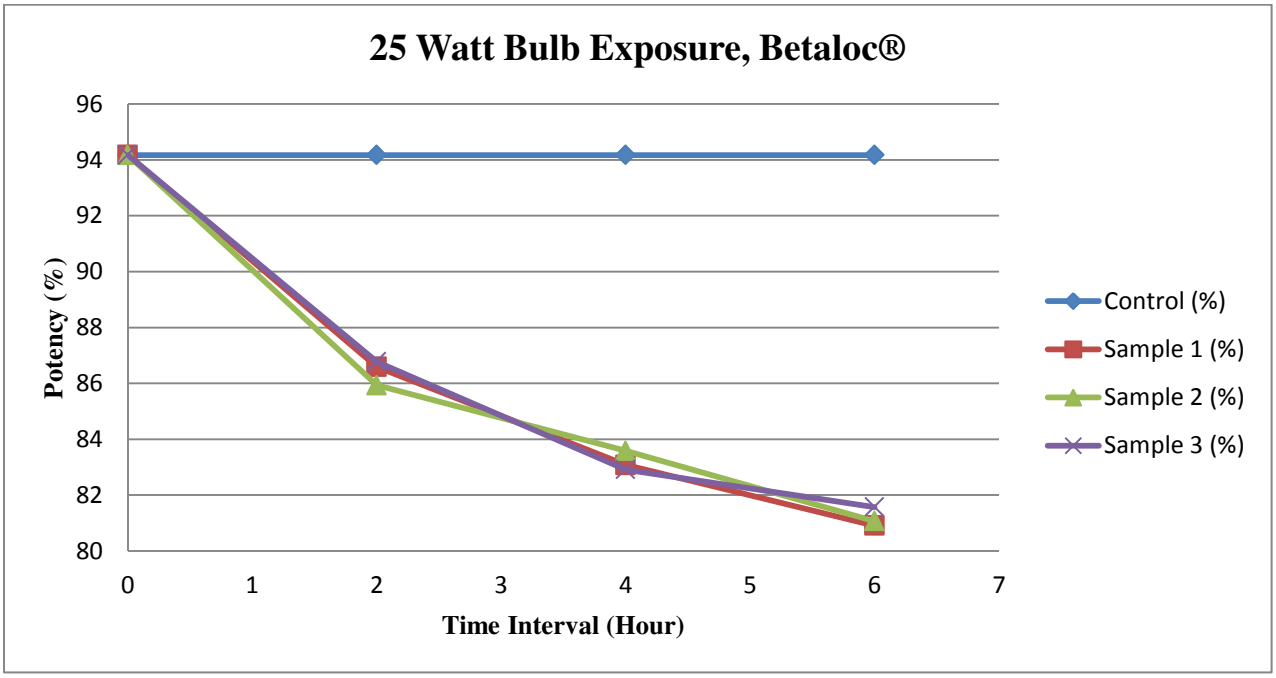

Figure 4.8: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Betaloc®) of the 2nd test under 25W bulb exposure

Table 4.18: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 3rd test under 25W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
Control	0.571	0.577	0.0187	46.82	93.63
	0.579				
	0.581				
	0.579	0.578	0.0188	46.90	93.80
	0.573				
	0.582				
	0.570	0.576	0.0187	46.73	93.47
	0.580				
	0.578				

Table 4.19: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 3rd test under 25W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
2 Hour	0.527	0.532	0.0172	42.98	85.96
	0.535				
	0.531				
	0.520	0.529	0.0171	42.77	85.54
	0.535				
	0.529				
	0.540	0.536	0.0174	43.28	86.56
	0.533				
	0.538				

Table 4.20: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 3rd test under 25W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
4 Hour	0.509	0.513	0.0165	41.43	82.86
	0.516				
	0.511				
	0.513	0.515	0.0166	41.54	83.08
	0.515				
	0.513				
	0.515	0.516	0.0167	41.63	83.26
	0.514				
	0.519				

Table 4.21: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 3rd test under 25W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
6 Hour	0.507	0.503	0.0162	40.59	81.18
	0.497				
	0.503				
	0.500	0.504	0.0163	40.52	81.04
	0.511				
	0.498				
	0.499	0.499	0.0161	40.46	80.92
	0.497				
	0.501				

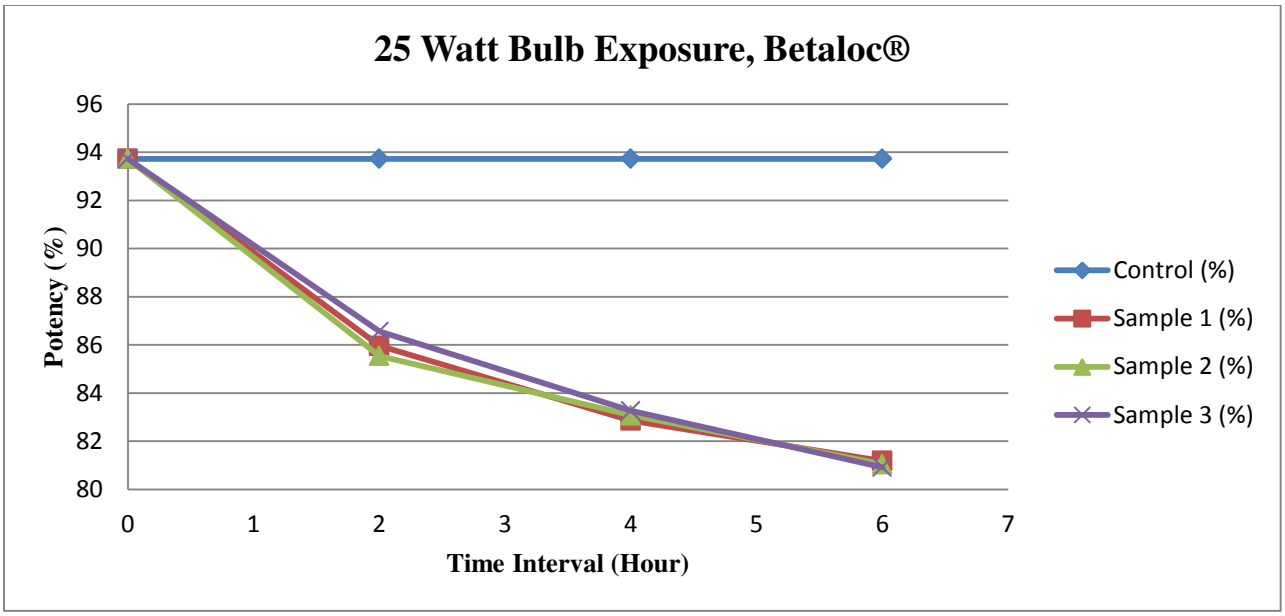

Figure 4.9: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Betaloc®) of the 3rd test under 25W bulb exposure

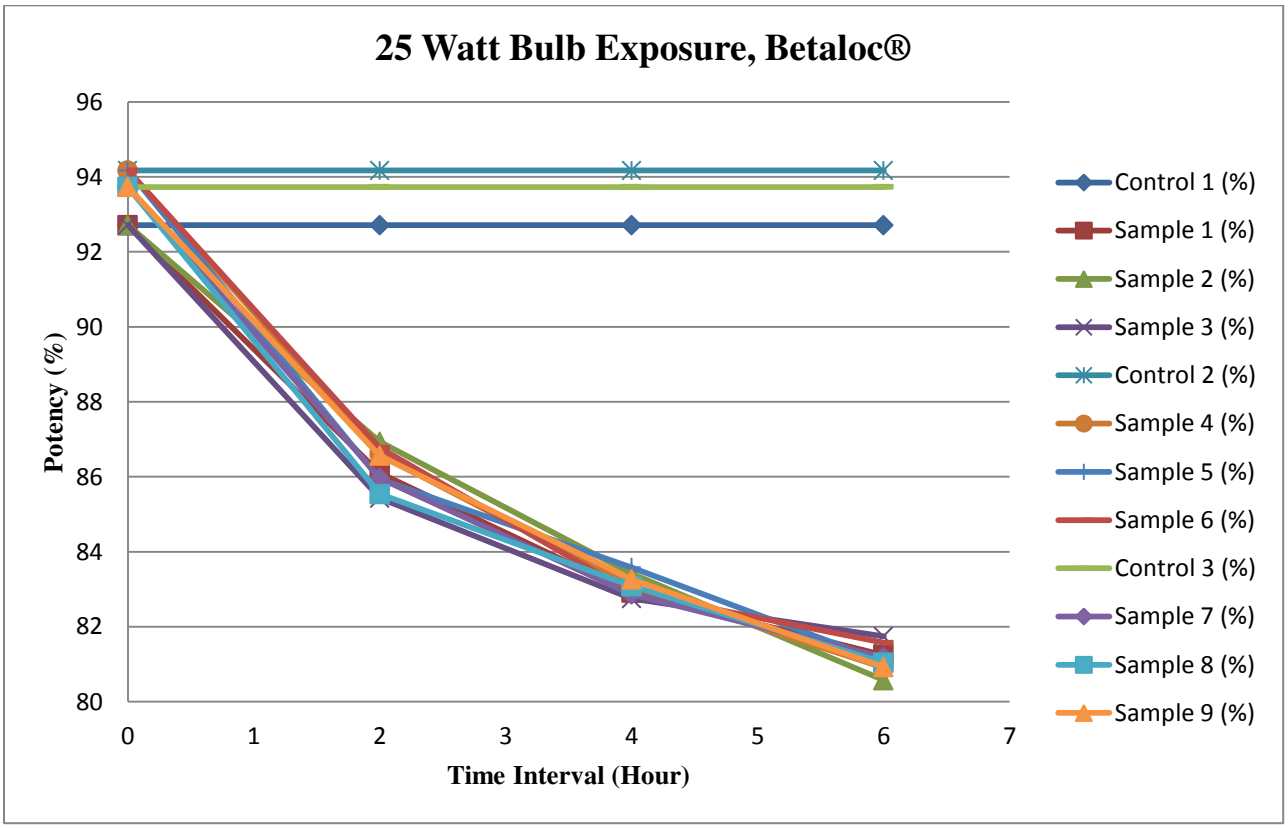

Figure 4.10: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Betaloc®) of the 1st, 2nd and 3rd test under 25W bulb exposure

4.3.3 Result of samples that were exposed under 40W bulb

We found 27 different absorbance of Metoprolol Tartrate for twenty seven samples exposed under the lamp (40W bulb); each for 2 hours time interval and it was observed that the concentration of Metoprolol Tartrate was declined in each time interval.

Table 4.22: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 1st test under 40W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
Control	0.591	0.583	0.0189	47.32	94.64
	0.576				
	0.582				
	0.581	0.585	0.0190	47.49	94.97
	0.592				
	0.579				
	0.586	0.586	0.0191	47.57	95.14
	0.580				
	0.591				

Table 4.23: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 1st test under 40W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
2 Hour	0.522	0.529	0.0171	42.80	85.59
	0.534				
	0.530				
	0.541	0.526	0.0170	42.55	85.10
	0.533				
	0.539				
	0.521	0.528	0.0171	42.71	85.43
	0.533				
	0.531				

Table 4.24: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 1st test under 40W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
4 Hour	0.513	0.509	0.0164	41.12	82.25
	0.506				
	0.508				
	0.511	0.506	0.0163	40.87	81.74
	0.507				
	0.500				
	0.503	0.508	0.0164	41.04	82.08
	0.512				
	0.509				

Table 4.25: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 1st test under 40W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
6 Hour	0.501	0.498	0.0161	40.20	80.40
	0.499				
	0.494				
	0.491	0.495	0.0160	39.95	79.90
	0.500				
	0.494				
	0.502	0.497	0.0160	40.12	80.23
	0.490				
	0.499				

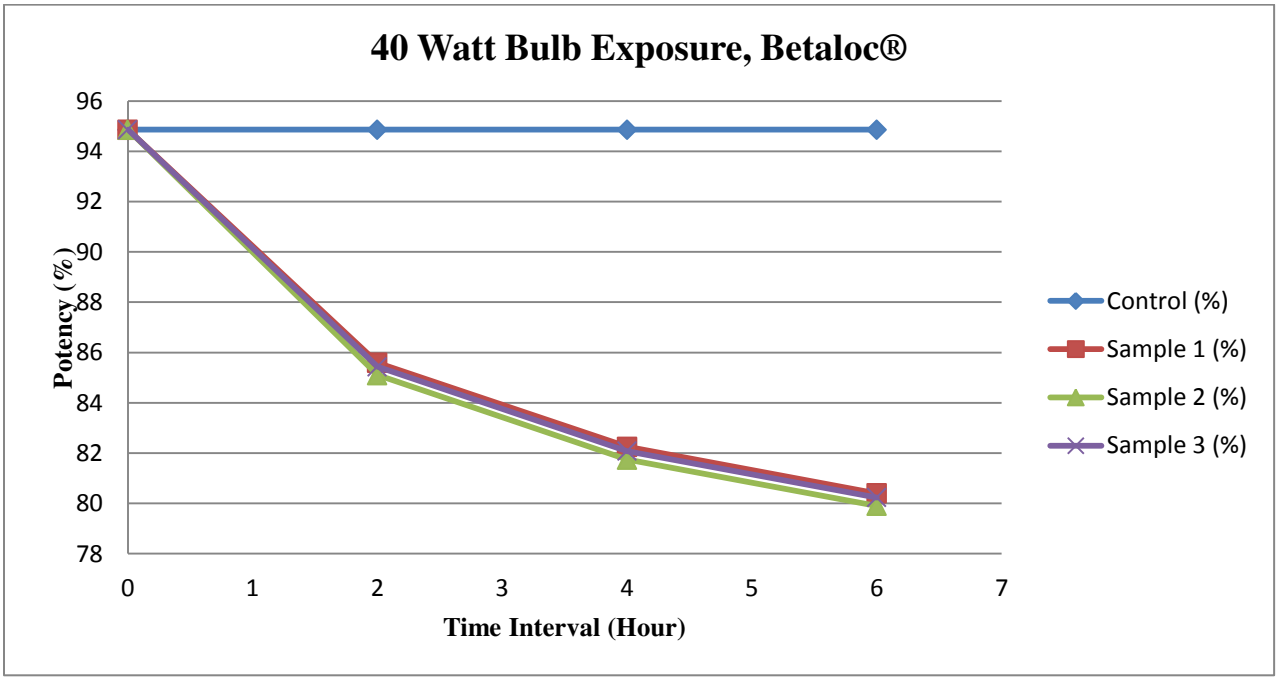

Figure 4.11: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Betaloc®) of the 1st test under 40W bulb exposure

Table 4.26: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 2nd test under 40W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
Control	0.588	0.589	0.0191	47.82	95.64
	0.591				
	0.588				
	0.587	0.591	0.0192	47.99	95.98
	0.590				
	0.596				
	0.586	0.588	0.0191	47.74	95.48
	0.593				
	0.585				

Table 4.27: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 2nd test under 40W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
2 Hour	0.539	0.527	0.0171	42.63	85.27
	0.541				
	0.534				
	0.530	0.525	0.0170	42.46	84.94
	0.520				
	0.532				
	0.521	0.528	0.0171	42.72	85.45
	0.533				
	0.531				

Table 4.28: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 2nd test under 40W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
4 Hour	0.505	0.507	0.0164	40.95	81.91
	0.512				
	0.508				
	0.500	0.504	0.0163	40.70	81.40
	0.509				
	0.507				
	0.500	0.506	0.0163	40.88	81.75
	0.511				
	0.507				

Table 4.29: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 2nd test under 40W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
6 Hour	0.499	0.494	0.0159	39.86	79.75
	0.494				
	0.491				
	0.500	0.495	0.0160	39.95	79.90
	0.494				
	0.491				
	0.499	0.496	0.0160	40.03	80.06
	0.490				
	0.503				

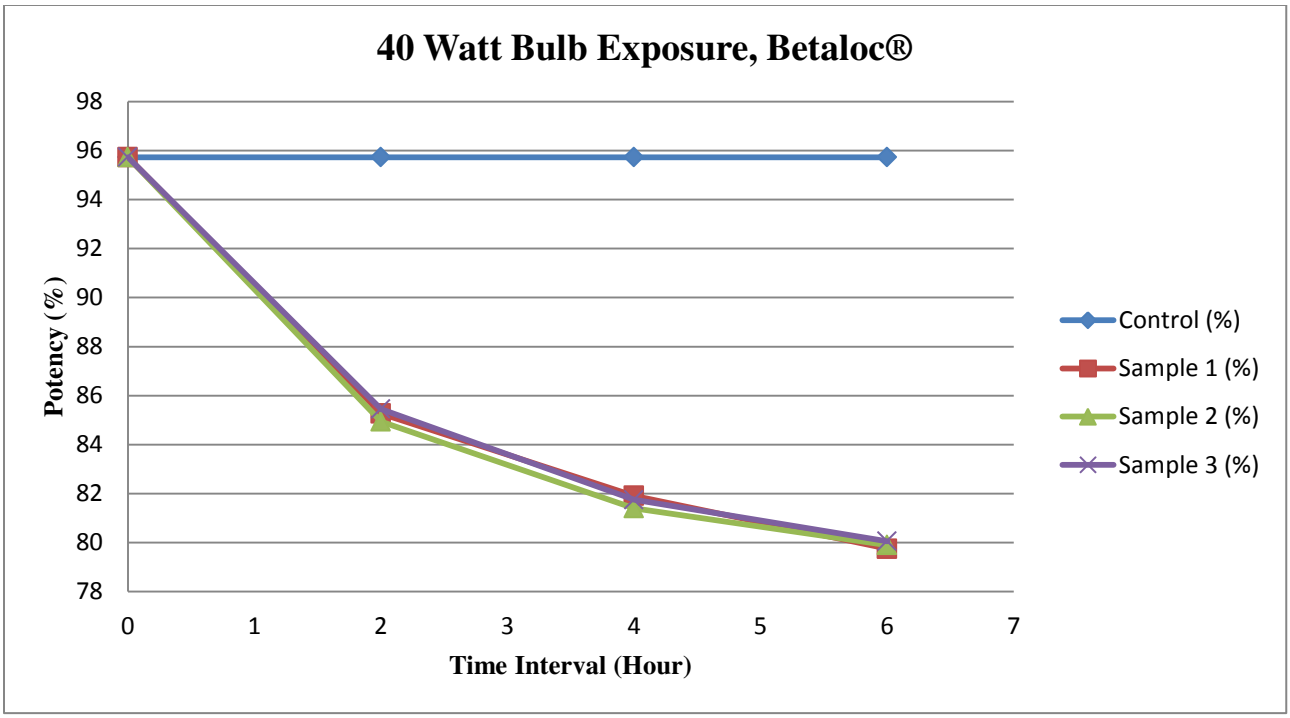

Figure 4.12: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Betaloc®) of the 2nd test under 40W bulb exposure

Table 4.30: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 3rd test under 40W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
Control	0.591	0.587	0.0191	47.65	95.31
	0.584				
	0.586				
	0.588	0.590	0.0192	47.91	95.81
	0.593				
	0.589				
	0.585	0.586	0.0190	47.57	95.14
	0.584				
	0.589				

Table 4.31: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 3rd test under 40W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
2 Hour	0.533	0.526	0.0170	42.55	85.10
	0.539				
	0.541				
	0.534	0.527	0.0170	42.63	85.26
	0.541				
	0.539				
	0.532	0.525	0.0170	42.46	84.93
	0.520				
	0.530				

Table 4.32: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 3rd test under 40W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
4 Hour	0.501	0.504	0.0163	40.70	81.40
	0.507				
	0.508				
	0.506	0.509	0.0164	41.12	82.25
	0.508				
	0.513				
	0.510	0.508	0.0164	41.07	82.10
	0.502				
	0.512				

Table 4.33: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 3rd test under 40W bulb exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
6 Hour	0.490	0.497	0.0161	40.12	80.23
	0.499				
	0.502				
	0.503	0.496	0.0160	40.03	80.06
	0.499				
	0.490				
	0.499	0.494	0.0159	39.87	79.73
	0.491				
	0.494				

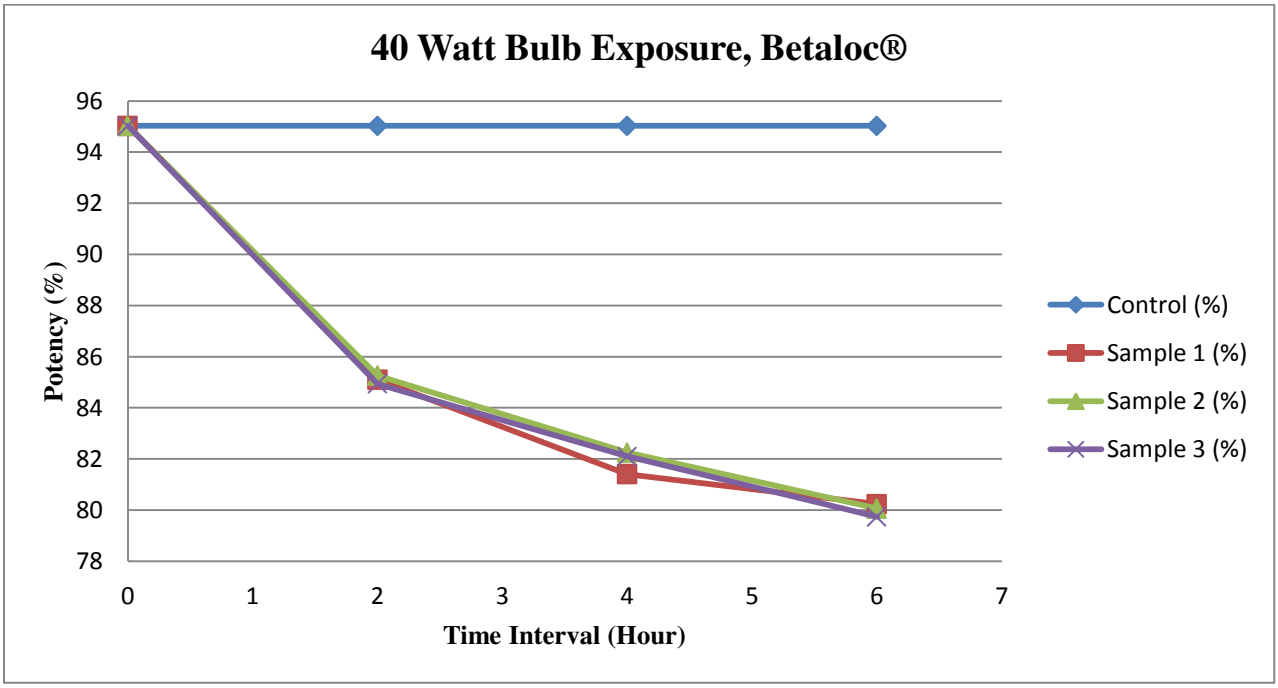

Figure 4.13: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Betaloc®) of the 3rd test under 40W bulb exposure

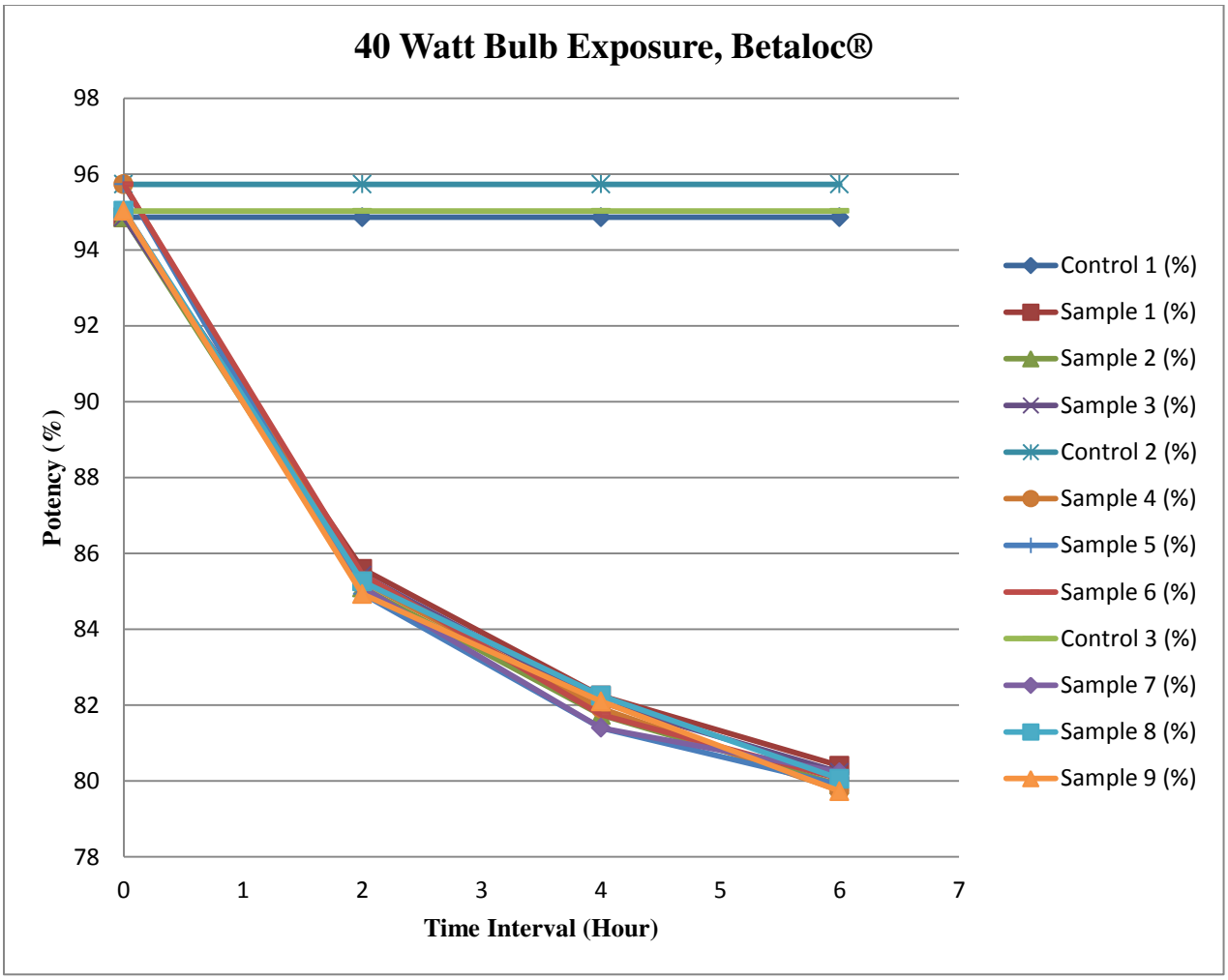

Figure 4.14: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Betaloc®) of the 1st, 2nd and 3rd test under 40W bulb exposure

4.3.4 Result of samples that were exposed under direct sunlight

We found 27 different absorbance of Metoprolol Tartrate for twenty seven samples exposed under the direct sunlight, each for 2 hours time interval and it was observed that the concentration of Metoprolol Tartrate was declined in each time interval.

Table 4.34: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 1st test under direct sunlight exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
Control	0.597	0.594	0.0193	48.24	96.48
	0.592				
	0.593				
	0.595	0.593	0.0193	48.16	96.32
	0.591				
	0.596				
	0.592	0.592	0.0192	48.07	96.15
	0.594				
	0.595				

Table 4.35: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 1st test under direct sunlight exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
2 Hour	0.502	0.497	0.0160	40.12	80.23
	0.491				
	0.498				
	0.496	0.494	0.0160	39.87	79.73
	0.493				
	0.493				
	0.494	0.498	0.0161	40.20	80.40
	0.499				
	0.501				

Table 4.36: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 1st test under direct sunlight exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
4 Hour	0.468	0.465	0.0150	37.44	74.87
	0.463				
	0.464				
	0.467	0.467	0.0150	37.60	75.20
	0.469				
	0.465				
	0.465	0.462	0.0149	37.19	74.37
	0.463				
	0.458				

Table 4.37: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 1st test under direct sunlight exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
6 Hour	0.445	0.442	0.0142	35.51	71.02
	0.440				
	0.441				
	0.451	0.444	0.0143	35.68	71.36
	0.439				
	0.442				
	0.444	0.445	0.0143	35.76	71.52
	0.449				
	0.442				

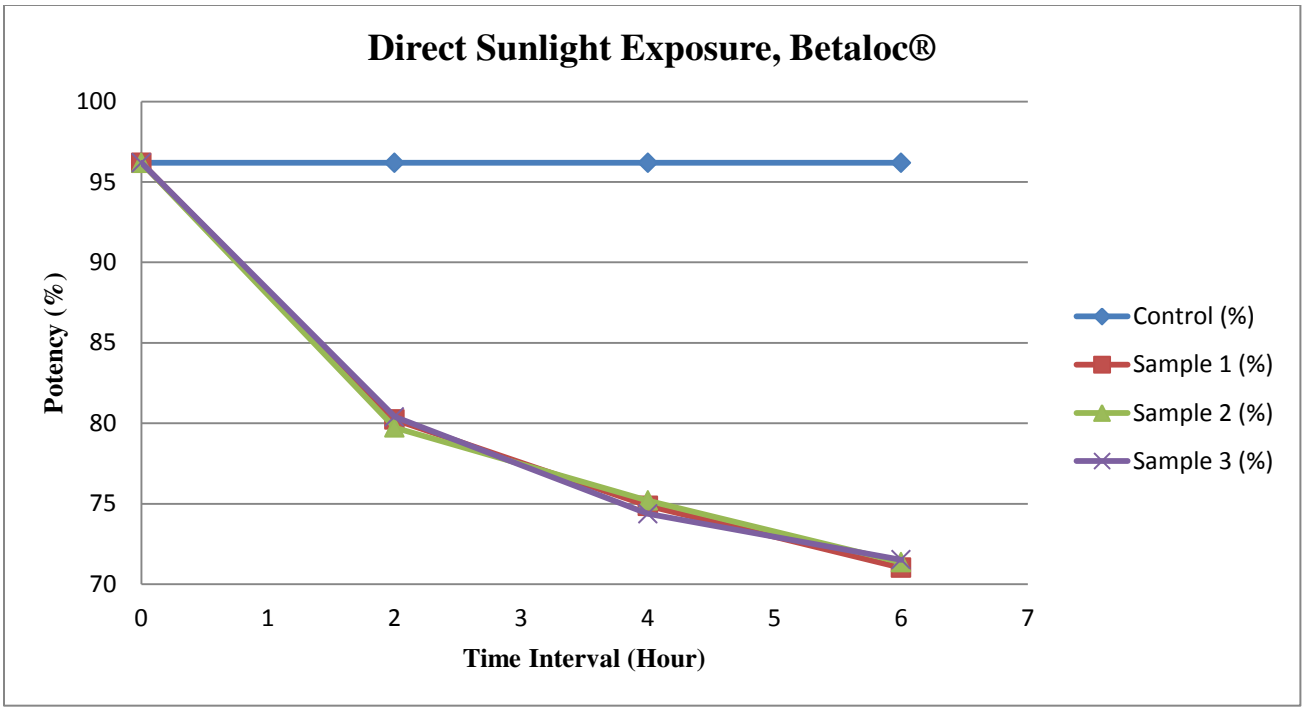

Figure 4.15: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Betaloc®) of the 1st test under direct sunlight exposure

Table 4.38: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 2nd test under direct sunlight exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
Control	0.595	0.593	0.0193	48.16	96.32
	0.591				
	0.596				
	0.587	0.591	0.0192	47.99	95.98
	0.590				
	0.596				
	0.586	0.588	0.0191	47.74	95.48
	0.593				
	0.585				

Table 4.39: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 2nd test under direct sunlight exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
2 Hour	0.502	0.496	0.0160134	40.03	80.06
	0.500				
	0.490				
	0.501	0.498	0.016080402	40.20	80.40
	0.494				
	0.499				
	0.491	0.494	0.015946398	39.87	79.73
	0.496				
	0.495				

Table 4.40: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 2nd test under direct sunlight exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
4 Hour	0.467	0.463	0.014907872	37.27	74.54
	0.460				
	0.462				
	0.461	0.464	0.014941373	37.35	74.71
	0.468				
	0.463				
	0.467	0.467	0.015041876	37.60	75.20
	0.468				
	0.466				

Table 4.41: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 2nd test under direct sunlight exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
6 Hour	0.450	0.444	0.014271356	35.68	71.36
	0.440				
	0.442				
	0.443	0.441	0.014170854	35.43	70.85
	0.440				
	0.442				
	0.449	0.447	0.014371859	35.93	71.86
	0.443				
	0.449				

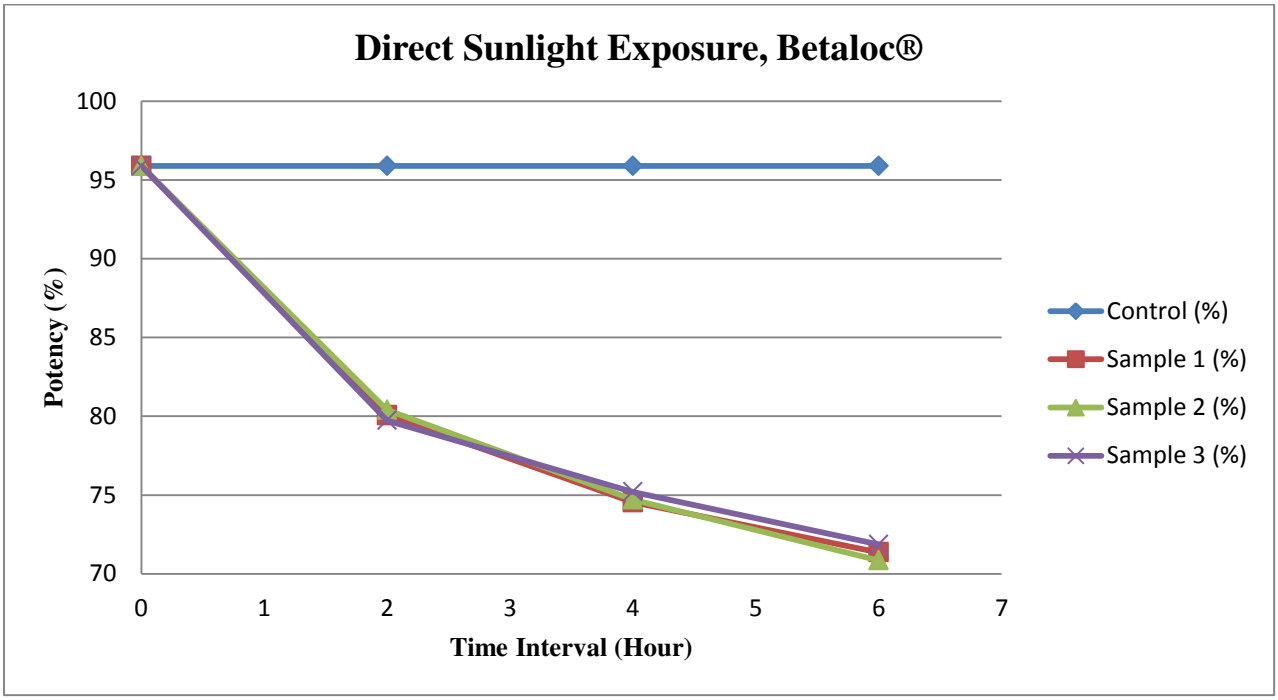

Figure 4.16: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Betaloc®) of the 2nd test under direct sunlight exposure

Table 4.42: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 3rd test under direct sunlight exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
Control	0.592	0.592	0.0192	48.07	96.15
	0.594				
	0.595				
	0.588	0.590	0.0192	47.91	95.81
	0.593				
	0.589				
	0.597	0.594	0.0193	48.24	96.48
	0.592				
	0.593				

Table 4.43: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 3rd test under direct sunlight exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
2 Hour	0.499	0.495	0.015979899	39.95	79.90
	0.494				
	0.492				
	0.498	0.493	0.015912897	39.78	79.56
	0.491				
	0.490				
	0.490	0.496	0.0160134	40.03	80.06
	0.502				
	0.500				

Table 4.44: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 3rd test under direct sunlight exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
4 Hour	0.462	0.464	0.014941373	37.35	74.71
	0.463				
	0.467				
	0.469	0.466	0.015008375	37.52	75.04
	0.465				
	0.464				
	0.467	0.465	0.014974874	37.44	74.87
	0.465				
	0.463				

Table 4.45: Concentration & absorbance for Metoprolol Tartrate (Betaloc®) of the 3rd test under direct sunlight exposure

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Diluted Concentration from Samples in mg/ml (2500 times diluted)	Amount of Drug present (in mg)	Potency (%)
6 Hour	0.439	0.441	0.014170854	35.43	70.85
	0.444				
	0.441				
	0.445	0.445	0.014304857	35.76	71.52
	0.448				
	0.443				
	0.442	0.443	0.014237855	35.60	71.19
	0.445				
	0.443				

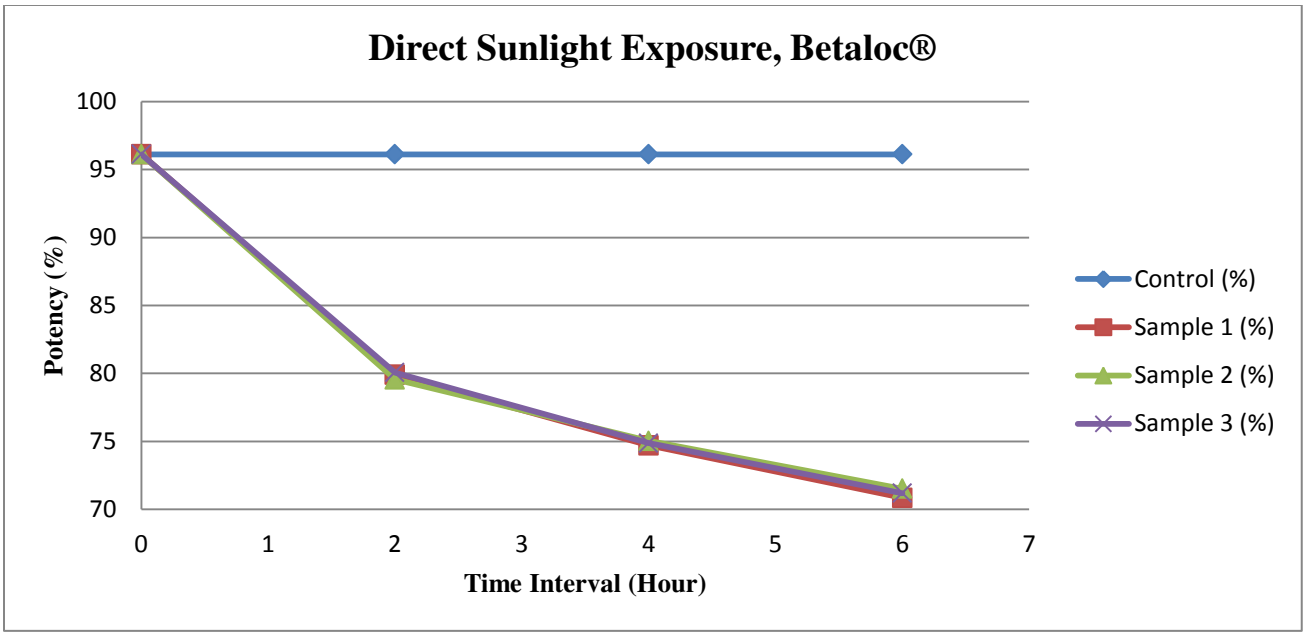

Figure 4.17: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Betaloc®) of the 3rd test under direct sunlight exposure

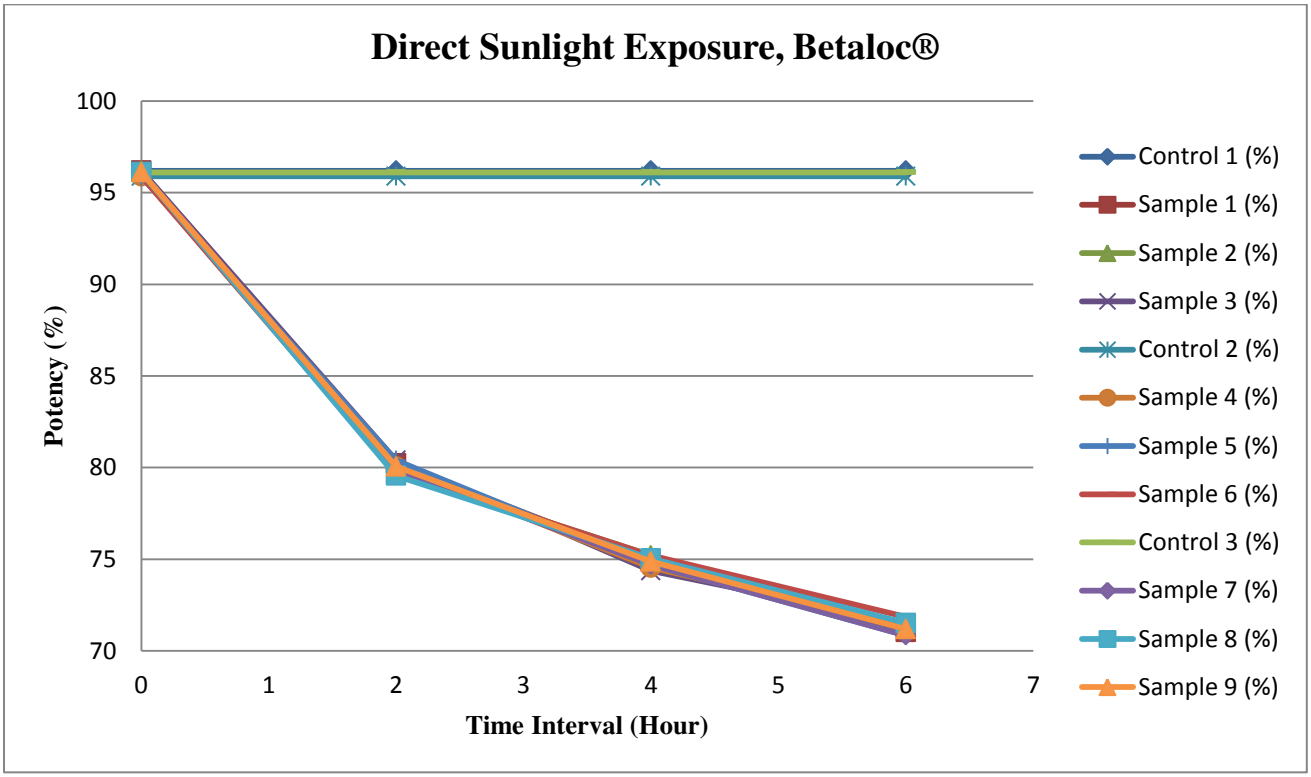

Figure 4.18: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Betaloc®) of the 1st, 2nd and 3rd test under direct sunlight exposure

CHAPTER FIVE

DISCUSSIONS

In this experiment, it was found that the measured physical parameters- color test, weight variation, hardness and thickness- did not change significantly throughout the course of the study. Average weight, hardness and also thickness of the tablets were close to each other. The standard deviation of the thickness, hardness and weight variation was ±0.0026 cm, ±0.4300 kg & ±0.0025gm respectively. So, it can be said that light has little or no effect on the color, weight, hardness and thickness of Betaloc® (Metaprolol Tartrate).

But there were remarkable changes in potencies. The potency of Betaloc® (Metaprolol Tartrate) was decreased gradually after exposure in electrical bulb light condition, direct sunlight and normal light exposure (room temperature) condition.

Each time of testing the potency of exposed sample, the potency of the control was also tested which was kept in dark and found that controlled sample retained its potency over the period of the study.

Potency test was performed by UV spectroscopy at 221.5 nm wavelength. In various lighting condition like 25watt bulb, 40watt bulb, direct sunlight and normal room light, the percent variation in potency was 11.48%, 12.92%, 22.62% and 16.87% respectively.

So from this study it is verified that only film coating of the Betaloc® containing (Metoprolol Tartrate) may not protect it from photolytic degradation since storage condition is different throughout the country. Therefore, to prevent this photolytic degradation protective opaque package should be used.

CHAPTER SIX

REFERENCES

Adi, B. D., Raj, K. K., Anil, S. K., Rajesh, K. K. & Gulam, H. M. (2012), Formulation and in vitro characterization of metoprolol tartrate loaded chitosan microspheres. *Ars Pharmaceutica,* 53(3), 13-18.

Agarwal, S., Dadarwal, S. C. & Madam, S. (2012), Formulation & evaluation of delayed-onset extended-release tablets of metoprolol tartrate using hydrophilic-swellable polymers. *Acta Pharma*, 62, 105-114.

Akhter, R., Iqbal, M., Murtaza, G. & Hanif, M. (2010), Design, Development and In-vitro Evaluation of Metoprolol Tartrate Tablets Containing Xanthan Tragacanth. *Acta Poloniae Pharmaceutica ñ Drug Research*, 67(5), 517-522.

Ancuta, C., Lupuliasa, D., Hirjau, B., Sala, M. & Saramet, G. (2012), The influence of Formulation Factors on the Release of the Metoprolol tartrate from Extend Release Tablets. *Farmacia*, 60(6), 905-914.

Anisree G.S. & Ramasami, C. (2012), Formulation of Transdermal Drug Delivery System of Metoprolol Tartrate & Evaluation. *Journal of Pharmaceutical Science and Research*, 4(10), 1939-1942.

Aqil, M., Ali, A., Ahad, A., Sultana, Y., Nazmi, A. K. & Saha, N. (2007), Validation HPLC Method for Estimation of Metoprolol in Plasma. *Acta Chromatographica*, 19, 130-139.

Bagde, S.B., Bakde, B.V., Channawar, M.A. & Chandewar, A.V. (2011), Formulation and Evaluation of Bilayer Tablet of Metprolol Succinate and Ramipril. *International Journal of Pharmacy and Pharmaceutical Sciences,* 3(4), 174-178.

Baloglu, E. & Senyigit, T. (2010), Design and Evaluation of Layered Matrix Tablet Formulations of Metoprolol Tartrate. *AAPS PharmSciTech*, 11(2), 563-573.

Beta Blockers Drug Information, (2015). [Online] Available at: http://www.rxlist.com/beta_blockers/drugs-condition.htm#What%20are%20beta-blockers [Accessed 03 May, 2015].

Bharkatiya, M., Nema, R. K. & Batnagar, M. (2010), Development and Characterization of Transdermal Patches of Metoprolol tartrate. *Asian Journal of Pharmaceutical and Clinical Research*, 3(2), 130-133.

Bharkatiya, M., Nema, R. K. & Batnagar, M. (2010), Formulation and Evaluation of Metoprolol Tartrate Entraped Niasomes. *International Journal for Chemistry and Science*, 8(4), 2055-2062.

Brahmaiah, B., Bhagat, G. P. & Gudipati, M. (2013), Formulation and Evaluation of Gastro-retentive Floating Drug Delivery System of Metoprolol Tartarte. *International Journal of Life Science Biotechnology and Pharma Research*, 2(1), 183-196.

Cesme, M., Tarinc, D. & Golcu, A. (2011), Spectrophotometric Determination of Metoprolol Tartrate in Pharmaceutical Dosage Forms on Complex Formation with Cu(II), 4, 964-975.

Chandrashekhar, R.K., Abbulu, K & Bashkar, R.R. (2011), Preformulation Parameters Characterization to Design, Development and Formulation of Metoprolol Succinate Extended Release Tablets for Oral Use. *International Journal of Pharmacy & Industrial Research,* 01 (04), 289-294.

Dahiya, S. & Gupta, O. N. (2011), Formulation and In-vitro Evaluation of Metoprolol Tartrate Microspheres. *Bulletin of Pharmaceutical Research*, 1(1), 31-38.

Devi, M., Naga, J. & Reddy, S. (2013), Design and characterization of melt-in-mouth tablets of metoprolol tartarate. *International Journal of Pharmacy and Life Science*, 4(4), 2608-2614.

Drugs.com, (2015). *Metoprolol - FDA prescribing information, side effects and uses*. [online] Available at: http://www.drugs.com/pro/Metoprolol.html [Accessed 03 May, 2015].

Himabindu, S. & Satish, D. (2011), Preparation and Evaluation of Oral Disinetegrating Tablets of Metoprolol Tartrate and Effect of Diluent on Drug Release Profile. *International Journal of Research in Pharmaceutical and Biomedical Sciences*, 2(3), 1161-1170.

Jasinska, M., Karwaski, B. & Kurczewska, U. (2009), Stability Studies of Expired tablets of Metoprolol Tartrate and Propranolol Hydrochloride. *Acta Poloniae Pharmaceutica n Drug Research,* 66(6), 697-701.

Kar, A. (2007) *Medicinal Chemistry*, 4th edition, New Age Int. Publisher, New-Delhi.

Karwa, P., Kasture, P.V. & Kimbahune, R. (2013), Application of Thermal and Isothermal Methods for Compatibility Studies of Metoprolol Succinate with Carbopol Polymers. *Indo American Journal of Pharmaceutical Research,* 3(11), 9085-9092.

Khan, M. S., Vishakante, G. D. & Shrivakumer, H. G. (2012), Porous nanoparticles of metoprolol tartrate produced by spray-drying: Development, characterization & in vitro evaluation. *Acta Pharmaceutica*, 62, 383-394.

Kumar, K. & Kumar, S. P. (2013), Forced Degradation Studies – Practical Approaches and Overview of the Regulatory Guidance of Drug Products. *International Research Journal of Pharmacy*, 4(5), 78-85.

Kumer, K. S., Kotaiah, M. R. & Rao, M. P. (2013), Formulation and Evaluation of Pulsatile Drug Delivery System of Metoprolol Tartrate. *International Journal of Pharmaceutical Research and Bioscience*, 2(5), 246-257.

Kumar, A.P. (2014), Fabrication and In-vitro Evaluation of Porous Osmotic Pump Based Controlled Drug Delivery of Metoprolol Succinate. *International Journal of Pharmacy and Pharmaceutical Sciences*, 6(2), 496-500.

Liu, H., Ren, J., Hao, Y., Ding, H., He, P. and Fang, Y. (2006). Determination of metoprolol tartrate in tablets and human urine using flow-injection chemiluminescence method. *Journal of Pharmaceutical and Biomedical Analysis*, 42(3), 384-388.

Mathur V. B., RAthor, H. D. & Shivhare, U. D. (2013), Development and Evaluation of Floating Pulsatile Microspheres of Metoprolol Tartrate Using Emulsification-Solvent Evaporation Technique. *Scholars Academic Journal of Pharmacy*, 2(5), 365-372.

Metoprolol Tartrate Tablets BP 50mg, (2011). [Online] Available at: http://www.medicines.org.uk/emc/medicine/24014/SPC#PHARMACODYNAMIC_PROPS [Accessed 03 May, 2015].

Nadenla, R.R., Mopidevi, S.L. & Chilakala, K.M. (2011), Design and in vitro Evaluation of Sustained Release Pellets of Metoprolol Succinate. *Journal of Pharmacy Research*,4(4), 1157-1160.

Nagaich, U., Choudhury, V., Sharma, P. & Yadav, A. (2009), Formulation and Development of Metoprolol Tartrate Bucco Adhesive Films. *The Journal of Pharma Research*, 1, 41-51.

Narendra, C., Srinath, M. and Prakash Rao, B. (2005). Development of three layered buccal compact containing metoprolol tartrate by statistical optimization technique. *International Journal of Pharmaceutics*, 304(1-2), 102-114.

Omudhome Ogbru, P. (2015). *Metoprolol, Lopressor, Toprol XL: Drug Facts, Side Effects and Dosing*. [online] MedicineNet. Available at: http://www.medicinenet.com/Metoprolol/article.htm [Accessed 03 May, 2015].

Phale, Mitesh, D., Hamrapurkar & Purnima, D. (2010), Optimization and Establishment of a Validated Stability-Indicating HPLC Method for Study of the Stress Degradation Behavior of Metoprolol Succinate, *Journal of AOAC International*, 93(3), 911-916.

Raffick, M.M., Mohamed, J.M., Vetriselvan, S., Vignesh, M., Selvakumar, K., Parkavi, V. & Ruby, J.J. (2012), Preparation and Evaluation of *In-vitro* Release Kinetics of Novel Bilayer Metoprolol Succinate as Sustained Release and Amlodipine Besylate as Immediate Release Tablets. *International Journal of Biological & Pharmaceutical Research*, 3(2), 285-297.

Rahman, N., Haque, S. M. & Azmi, S. N. H. (2007), Kinetic Spectrophotometric Determination of Metoprolol Tartrate in Commercial Dosage Forms. *Journal of the Chinese Chemical Society,* 54, 1511-1520.

Rani, K.R.V., Prakash, S.E.L. & Rajeswari, R.L.S. (2009), Formulation and Development of ER Metoprolol Succinate Tablets. *International Journal of PharmTech Research,* 01 (03), 634-638.

Rao, N. G. R., Thube, K. & Pentewar, R. (2010), Compression of Different Superdisintegrants in Designing of Fast Dissolving Tablets of Metoprolol Tartrate. *International Journal of Pharmaceutical Sciences and Research*, 1(4), 56-65.

Rao, N. G. R., Thube, K. & Suresh, D. K. (2010), Formulation and Evaluation of Mouth Dissolving Tablets of Metoprolol Tartrate by Sublimission Method. *International Journal of Pharma and Bio Sciences,* 1(2), 1-14.

Rao, N. G. R., Bala, S. & Patel, K. V. (2011), Design of Fast Dissolving Tablets of Metoprolol Tartrate Using Novel Co-processed Superdisintegrants. *International Journal of Pharmaceutical Sciences Review and Research,* 8(2), 147-150.

Rasool, F., Ahmed, M., Murtaza, G. & Khan, S. A. (2012), Pharmacokinetic Studies on Metoprolol – Eudragit Matrix Tablets and Bioequivalence Consideration with Mepressor®. *Tropical Journal of Pharmaceutical Research*, 11(2), 281-287.

Reddy, B.V., Navaneetha, K., Reddy, K.V.R. & Reddy, P.P. (2014), Design and Development of Bilyered Tablets of Amlodipine Besylate and Metoprolol Succinate. *World Journal of Pharmaceutical Research,* 3(4), 862-881.

Reddy, V. S., Ramesh, Y. and Parameshwar, K. (2011), Formulation and Evaluation of Mouth Dissolving Tablets of Metoprolol tartrate by new Co-processed Technique. *Research Journal of Pharmaceutical, Biological and Chemical Sciences,* 2(3), 385-389.

Sanjay, P., Mukesh, G. & Rajesh, P. (2008), Evaluation of Osmotic control Drug Delivery System of Metoprolol Tartrate. *International Bulletin of Drug Research*, 1(1), 84-93.

Salunkhe, A. K., Dias, R. J., Mali, K. K. & Mahajan, N. S. (2011), Formulation and evaluation of floating pulsatile drug delivery system of Metoprolol tartrate. *Scholars Research Library,* 3(3), 147-160.

Senthil, A., Himabandhu, S. & Rajesh. T. S. K. (2011), Development and Evaluation of Orally Disintegrant Tablets of Metoprolol Tartrate by Direct Compression Method. *International Research Journal of Pharmacy*, 2(1), 118-125.

Shailaja, T., Latha, K., & Sashibushan, P. (2012), Formulation and Evaluation of Orodispersible tablets of Metoprolol tartarte with Natural and Synthetic Superdisintegrants. *International Journal of Pharmacy and Pharmaceutical Sciences*, 4(3), 148-154.

Shikh, K. A., Patil, A. T., (2014), Stress degradation studies of Telmisartan and Metoprolol extended release tablets by a validated stability indicating reverse phase-high performance liquid chromatography method. *Drug Development and Therapeutics,* 5(2), 158-163.

Shrisand, S. B., Nagendrakumer, D. & Para, M. S. (2011), Design and Evaluation of Metoprolol Tartrate Containing Buccal Tablets. *Dhaka University Journal of Pharmacy & Science,* 10(2), 101-108.

Syed, I. A., Mangamoori, L. N. & Rao, Y. M. (2011), Formulation and Characterization of Matrix and Triple-Layer matrix tablets for Controlled Delivery of Metoprolol tartrate. *International Journal of Pharmaceutical Sciences and Drug Research,* 3(1), 23-28.

Tagde, P., Jain, N. & Pathak, A. K. (2012), Formulation and Evaluation of Bilayer Floating Tablets of Metoprolol Tartrate. *International Journal of Biomedical Research,* 3(2), 122-127.

Tehrani, M. S., Verdini, M. T., Azar, P. A. & Hussain, S. W. (2009), Molecularly Imprinted Polymer Based PVC Membrane Coated Graphite Electrode for the Determination of Metoprolol. *International Journal of Electrochemical Science*, 5, 88-104.

Tomer, S. B., Patel, D. & Parekh, N. (2014), Formulation and Evaluation of Controlled Release Tablet of Metoprolol Tartarate. *Journal of Pharmaceutical Science & Bioscientific research,* 4(1), 96-100.

Yang, Y., Gupta, A., Carlin, A., Faustino, P., Lyon, R., Ellison, C., Rothman, B. and Khan, M. (2010). Comparative stability of repackaged Metoprolol Tartrate tablets. *International Journal of Pharmaceutics*, 385(1-2), 92-97.

Ye, Z., Rombout, P., Remon, J., Vervaet, C. and Van den Mooter, G. (2007). Correlation between the permeability of metoprolol tartrate through plasticized isolated ethylcellulose/hydroxypropyl methylcellulose films and drug release from reservoir pellets. *European Journal of Pharmaceutics and Biopharmaceutics*, 67(2), 485-490.