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

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

DECLARATION BY THE CANDIDATE

I, Roksana Parvin, hereby declare that the dissertation entitled "Reproducibility Study Of the Efficiency Of Coating on Preventing Photolytic Degradation of Presonil® (Metoprolol Tartrate) Tablets", submitted by me to the Department of Pharmacy, East West University, in the partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Honors) with original research work carried out by me under the supervision and guidance of Mohammed Faisal Bin Karim**,** 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 Of the Efficiency Of Coating on Preventing Photolytic Degradation of Presonil® (Metoprolol Tartrate) Tablets" submitted to the department of pharmacy, East West University in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy was carried out by Roksana Parvin (ID: 2011-3-70-042) 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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ENDORSMENT BY THE CHAIRPERSON

This is to certified that the dissertation entitle "Reproducibility Study Of the Efficiency Of Coating on Preventing Photolytic Degradation of Presonil® (Metoprolol Tartrate) Tablets" is a bonafide research work done by Roksana Parvin (ID: 2011-3-70-042) under our guidance and supervision of Mohammed Faisal Bin Karim, Lecturer, Department of Pharmacy, East West University, Dhaka.

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ABSTRACT

This work was aimed for the determination of photolytic degradation of Presonil® (metoprolol tartrate). It was also done to determine the reproducibility of results of the previous research project on photolytic degradation of metoprolol tartrate in various lighting conditions (control, sunlight, normal room light, 25watt & 40watt bulb). A group of tablets were kept in dark as control to compare the results. Besides, physical tests were performed for evaluation of color change, weight variation, thickness and hardness of Presonil® tablets from same batch according to the specification of USP. A very insignificant fluctuation in result was observed, with standard deviation ±0.0007%, ±0.02% & ±0.013% for weight variation, hardness & thickness test respectively. But in various lighting condition like 25watt bulb, 40watt bulb, direct sunlight and normal room light the concentration of metoprolol tartrate were decreased gradually with percent deviation 10.41%, 11.24%, 6.99% and 13.25% respectively. So it can be suggest that the Presonil® containing metoprolol tartrate is light sensitive and coating alone is not sufficient to protect the drug from light. So that package should be opaque thus light cannot pass through the package.

Keywords: Presonil®, Metoprolol Tartrate, Photolytic Degradations, Batch, Weight variation, Hardness, Thickness, Potency, USP.

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Chapter One

INTRODUCTION

The objective of the research project was to determine the reproducibility of results of the previous research project on photolytic degradation of metoprolol tartrate and also the film coating efficiency to prevent this degradation of photosensitive drug. In this research, photosensitivity of metoprolol tartrate will be determined as same various lightening conditions (control, sunlight, normal light, 25watt bulb and 40watt bulb condition) as previous. For this purpose, an available brand is chosen i.e. Presonil® from Incepta pharmaceutical Ltd. for determining whether it is photosensitive or not.

1.1 Beta blockers

1.1.1 Definition (Kar, 2007)

Beta blocker is a type of drug that also known as β-blockers or beta adrenergic receptor antagonists. The major target of this drug is beta receptor and it antagonizes the beta receptor. 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. Beta blockers interfere the binding with the epinephrine receptor. They are particularly used for the management of cardiac arrhythmias, myocardial infarction, angina pectoris and hypertension.

1.1.2 Mode of action of beta blocker (β- Blocker drug info, 2015)

Beta blocker or beta adrenergic receptor works by blocking the endogenous catecholamines or neurotransmitters norepinephrine and epinephrine action from binding to receptors. 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.

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.

1.2 Metoprolol Tratrate

1.2.1 Structural Formula of Metoprolol tartrate:

Metoprolol tartrate is a selective beta1-adrenoreceptor blocking agent. The chemical name of Metoprolol tartrate is (±)-1-(isopropylamino)-3-[p-2-methoxyethyl) phenoxy]-2-propanol (2:1) dextro-tartrate salt. (Metoprolol Tartrate film coated tablet, 2015)

The structural formula is:

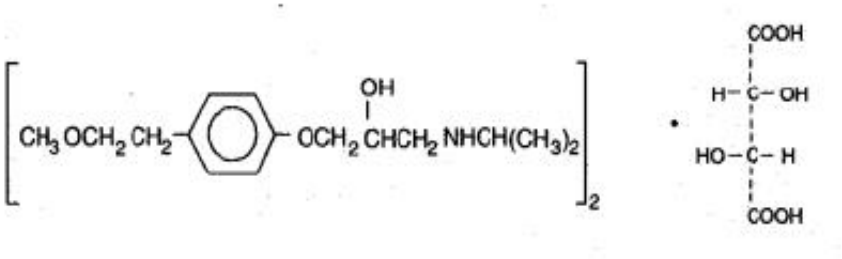

Figure 1.1: Molecular structure of metoprolol tartrate (Metoprolol Tartrate film coated tablet, 2015)

1.2.2 Physical characteristics of Metoprolol tartrate:

Physical characteristics of Metoprolol tartrate USP are given below

- White in color
- Practically odorless
- Crystalline powder
- Molecular weight : 684.82 g/mole
- Solubility: very soluble in water, freely soluble in methylene chloride, in chloroform, and in alcohol, slightly soluble in acetone and insoluble in ether. (Metoprolol Tartrate film coated tablet, 2011)

1.3 Pharmacological Properties of Metoprolol Tartrate

1.3.1 Phrmacodynamic properties (Drugs.com, 2015)

Metoprolol selectively binds with the beta 1 receptor which is demonstrated by the following:

- In healthy subjects, Metoprolol Tartrate does not reverse the beta 2 mediated vesodilating effects of epinephrine
- In asthmatic patients, FEV_1 and FVC are significantly reduced by Metoprolol than non selective beta blockers at equal dose.

No intrinsic sympathmimetic activity is shown by Metoprolol. It provides membrane stabilizing activity at higher dose than required for beta blocking activity. Metoprolol also slows the sinus rate and reduces the AV nodal conduction.

Metoprolol shows beta blocking activity 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. A linear relationship is seen between the log of plasma level and reduction of exercise heart rate. But the antihypertensive activity of Metoprolol is not related to plasma levels. (Drugs.com, 2015)

Metoprolol Tartrate decreases the heart rate, systolic blood pressure and cardiac output in patient with myocardial infarction. It does not change the stroke volume, diastolic blood pressure and pulmonary artery end diastolic pressure. Plasma concentration of Metoprolol in patients with angina pectoris shows a linear relationship with the oral dose within the range of 50-400 mg.

1.3.2 Pharmacokinetic properties (Drugs.com, 2015)

- **Absorption:** Oral bioavailability of Metoprolol is about 50% as pre-systemic metabolism occurs which can be stopped with the increase of the dose.
- **Distribution:** Volume of distribution of Metoprolol is 3.2 to 5.6 L/kg. About 10% of Metoprolol in plasma 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 a racemic mixture of R- and S- enantiomer and after administration it shows stereoselective metabolism. This metabolism is dependent on oxidation phenotype. Metoprolol Tartrate is primarily metabolized by the CYP2D6 which is absent in about 8% Caucasians and about 2% of most other populations (poor metabolizers). People having 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 in poor metabolizers it may be 7-9 hours. 5% of oral dose and 10% of intravenous dose are excreted through urine as unchanged state in normal subjects. In poor metabolizers, the excreted unchanged amount of drug increase to 30% of oral dose and 40% of intravenous dose.

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

- **Geriatric patients:** The geriatric population shows slightly higher plasma concentration of Metoprolol because of the decreasing metabolism of the drug in elderly population *and* decreasing 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:** The elimination half life of Metoprolol becomes prolonged in patients with hepatic impairment as this drug is primarily eliminated by hepatic metabolism.

1.4 Clinical Particulars of Metoprolol Tartrate

1.4.1 Indications (Metoprolol Tartrate tablets BP, 2011)

In the management of:

1. Hypertension
2. Angina pectoris
3. Cardiac arrhythmias
4. Myocardial infractions

5. Prophylaxis of migraine.

1.4.2 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

Dose for 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).

Dose for 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.

Dose for Children*:* Not recommended for children.

1.4.3 Side Effects (Metoprolol Tartrate tablets BP, 2011)

Undesirable effects are for the majority dose dependent. The frequency and severity are most pronounced in the early phase of treatment and decline during continued treatment.

Table 1.1: Side Effects of Metoprolol Tartrate(Metoprolol Tartrate tablets BP, 2011)

Disorders	**Side Effects**			
	Common	**Rare**	**Very rare**	**Not Known**
Blood & lymphatic system disorders			thrombocytopenia	
Psychiatric disorders		depression, nightmares	personality disorder, hallucinations	
Nervous system disorders	dizziness, headache	somnolence or insomnia, paraesthesia		
Eye disorders			visual disturbance (e.g. blurred vision)	
Ear and labyrinth disorders			Tinnitus, deafness	
Cardiac disorders	bradycardia	heart failure, cardiac arrhythmias	cardiac conduction disorders,	increase in intermittent claudication

Vascular disorders	orthostatic hypotension	oedema, Raynaud's phenomenon	peripheral circulatory disorders	
Respiratory disorders	exertional dyspnoea	bronchospasm	rhinitis	
Gastrointestinal disorders	Nausea vomiting & abdominal pain	diarrhoea or constipation	dry mouth	retroperitoneal fibrosis
Skin tissue disorders		skin rash	photosensitivity, hyperhydrosis, alopecia,	
Reproductive system and breast disorders			disturbances of libido and potency	Peyronie's disease

1.4.4 Contraindications (Metoprolol Tartrate tablets BP, 2011)

The major contraindication is if the patients have hypersensitivity to metoprolol, related derivatives, any of the ingredients in the tablets or to any other beta-blockers.

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

1.4.5 **Drug Interaction** (Metoprolol Tartrate tablets BP, 2011)

- Anaesthetic drugs may attenuate reflex tachycardia and increase the risk of hypotension. Metoprolol therapy should be reported to the anaesthetist before the administration of a general anaesthetic.
- It may be necessary to adjust the dose of the hypoglycaemic agent in insulin-dependent diabetes. Beta-adrenergic blockade may prevent the appearance of signs of hypoglycaemia (tachycardia).
- Digitalis glycosides in association with beta-blockers may increase auriculo-ventricular conduction time.
- When metoprolol is administered together with prazosin for the first time it may produce a first dose hypotensive effect.
- Like all beta-blockers, metoprolol should not be given in combination with calcium channel blockers i.e. verapamil and to a lesser extent diltiazem since this may cause bradycardia, hypotension, heart failure and asystole and may increase auriculo-ventricular conduction time. Calcium channel blockers (such as dihydropyridine derivatives e.g. nifedipine) should not be given in combination with metoprolol because of the increased risk of hypotension and heart failure.
- NSAIDs (especially indometacin) may reduce the antihypertensive effects of beta-blockers possibly by inhibiting renal prostaglandin synthesis
- The effect of adrenaline (epinephrine) in the treatment of anaphylactic reactions may be weakened in patients receiving beta blockers.
- Metoprolol may impair the elimination of lidocaine.
- Cocaine may inhibit the therapeutic effects of beta-blockers and increase the risk of hypertension, excessive bradycardia, and possibly heart block.
- Concurrent use of estrogens may decrease the antihypertensive effect of beta-blockers because estrogen-induced fluid retention may lead to increased blood pressure.
- Concurrent use of aldesleukin may result in an enhanced hypotensive effect.
- Concurrent use of alprostadil may result in an enhanced hypotensive effect.
- Concomitant use with anxiolytics and hypnotics may result in an enhanced hypotensive effect.

- Concomitant use with corticosteroids may result in hypotensive effect.

1.4.6 Adverse reactions (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.

1.4.7 Pregnancy & Lactation (Metoprolol Tartrate film coated tablet, 2011)

Pregnancy:

It is recommended that metoprolol should not be administered during pregnancy or lactation due to possible risk to the foetus/infant. Once metoprolol is given, special attention should be paid to the foetus, 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 foetal 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 foetal death and premature birth. Beta blockers have been reported to cause

bradycardia in the foetus 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.

1.4.8 Precautions (Metoprolol Tartrate film coated tablet, 2011)

- Assure the conformation that the patient are allergic to it; or to other beta-blockers (such as atenolol, propranolol); or have any other allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems.
- Assure that the patient have heart rhythm problems, breathing problems (such as asthma, chronic bronchitis, emphysema), liver disease, serious allergic reactions, blood circulation problems, mental/mood disorders (such as depression) or not.
- If patient have diabetes, this product may prevent the fast/pounding heartbeat that they usually feel when blood sugar level falls too low (hypoglycemia).
- Before having surgery
- This drug may make dizzy or drowsy feeling. So do not drive and limit alcoholic beverages.
- During pregnancy, this medication should be used only when clearly needed. It may harm an unborn baby.
- This drug passes into breast milk. So before breast-feeding have to assure about that.

1.4.9 Overdose (Metoprolol Tartrate film coated tablet, 2011)

Poisoning due to an overdose of metoprolol may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness, coma, nausea, vomiting, cyanosis, hypoglycaemia and hyperkalaemia. The first manifestations usually appear 20 minutes to 2 hours after drug ingestion.

After ingestion of an overdose or in case of hypersensitivity, the patient should be kept under close supervision and be treated in an intensive-care ward. Artificial respiration may be required.

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

Photolytic degradation is the process by which light-sensitive drugs or excipient molecules are chemically degraded by extreme light, room light and direct sunlight.

1.5.1 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.

1.5.2 Mechanism of Photolytic Degradation

Drug products are placed and exposed under the light source

⇩

Before a photolytic degradation reaction can occur, the energy from light radiation must be absorbed by the molecules.

⇩

Degradation of drug occurs. Two ways in which photolytic degradation can occur are:

1. Light energy absorbed must sufficient to achieve activation energy.
2. Light energy absorbed by molecules is passed on to other molecules which allow degradation to take place.

⇩

When carrying out the test, the temperature should be carefully considered to allow the influence of light to be assessed independently.

⇩

After each specified time interval, the exposed drug product is collected and the physical parameter of the sample must be checked.

⇩

Finally the potency of drug must be defined by using UV spectrophotometer.

1.5.3 Photo Stability Testing of Drugs (Stability testing, 1999)

The drug product is initially tested without packaging. If unacceptable changes occur, protection is added in stages starting with the primary packaging followed by the secondary packaging (commercial packaging). Depending on the result, the packaging must be improved and/or the formulation changed. The procedure is shown as follow:

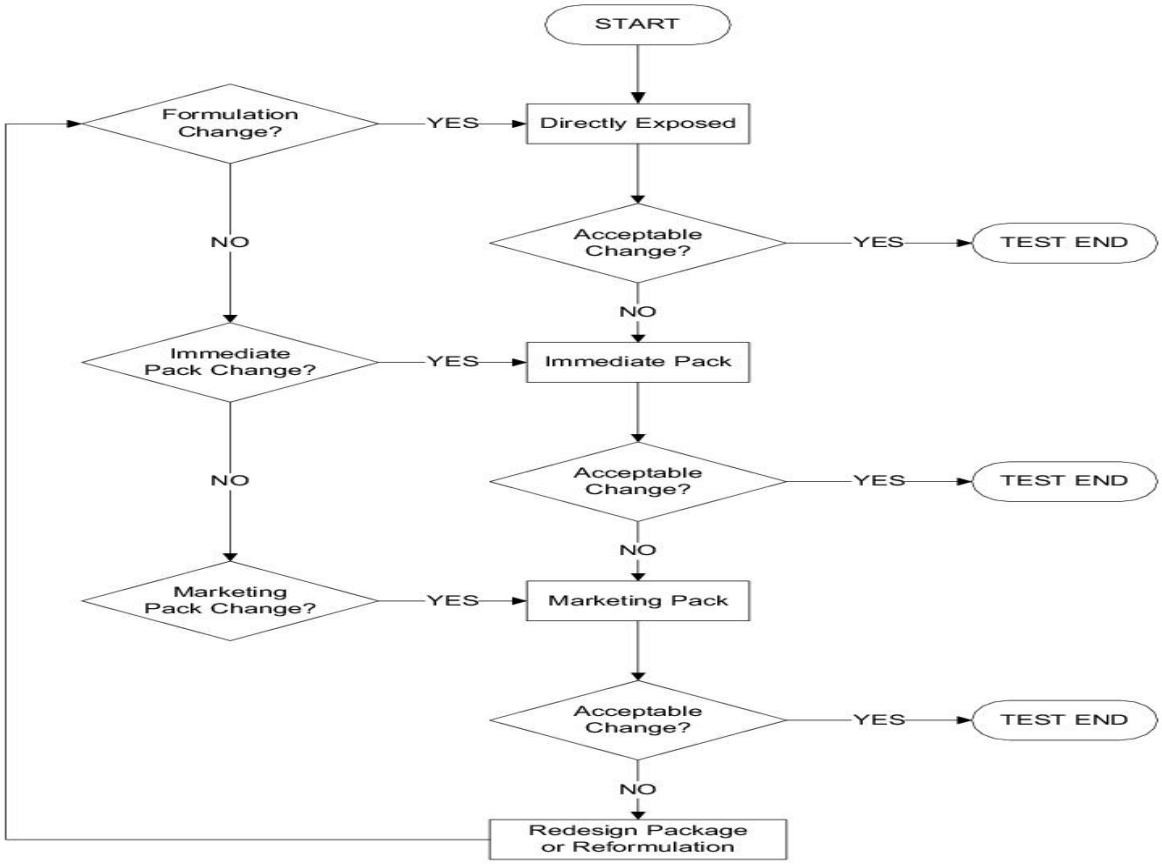

Figure 1.2: Flow chart for photo-stability testing of drug products (Stability testing, 1999)

Chapter Two

LITERATURE REVIEW

In July 1995, Ganga (Ganga *et al* 1995) and his co-scientists investigated the effect of Azone on the transdermal iontophoretic transport of metoprolol tartrate through human epidermis in vitro. Investigations were carried out to probe the mechanism of action of this enhancer and to identify whether there is any synergistic effect of this enhancer in conjugation with iontophoresis. By comparing between iontophoretic and passive transport of the drug in presence of enhancer, it was found that Azone caused increased transport of the drug through human epidermis during both process and the transport was increased 130-fold during iontophoresis compared to passive flux.

In June 1997, Polli (Polli *et al* 1997) and his research group applied three general approaches (ANOVA-base, model-independent, and model-dependent) to compare dissolution profiles of four different but bioequivalent metoprolol tartrate tablet formulations to (1) identify the advantages and disadvantages of each approach, (2) quantify the metric for comparing dissolution profiles of each method, (3) determine metric limits that are consistent with the observed bioequivalence, and (4) rationalize the observed metric limits with respect to the role of dissolution in overall metoprolol absorption. Dissolution data were collected by performing dissolution according to USP monograph method on four formulations of metoprolol tartrate tablets (Lopressor plus fast, medium, and slow dissolving test formulations). After examination, these methods suggested wide dissolution specification limits and these specifications were rationatized through an analysis of in vitro- in vivo relationships which indicated metoprolol dissolution from these formulations was not the rate-limiting steps.

In 1998, Nellore (Nellore *et al* 1998) with other researchers were studied to design a model extended-release matrix tablet formulations for metopeolol tartrate with using several grades and levels of hydroxypropyl methylcellulose and three granulation processes were evaluated by which granules for tablets were formed with comparing their forming granules quality. Using USP apparatus 2 at 50 rpm, in vitro drug release testing was performed in pH 6.8 phosphate buffer. At a fixed polymer level, drug release from the higher viscosity grades was slower as compared to lower viscosity grades which were found to be more sensitive to polymer level changes.

In January 1999, Rekhi (Rekhi *et al* 1999) with his colleagues examined the influence of critical formulation and processing variables for metoprolol tartrate extended-release matrix tablets using hydrophilic polymer hydroxypropyl methylcellulose. Analysis of variable studies (filtter ratio, polymer level, magnesium stearate level, lubricant blend time, compression force, granulations, dissolution time) indicated that change in polymer level was most significantly affect the release . Increasing dicalcium phosohate level and compression force were also affect the percent release at the later dissolution time. Three formulations having slow-, medium- and fast-releasing dissolution profiles were identified for a future bioavailability/bioequivalency study. The results of this study provided the framework for further work involving both in vivo studies and scale-up.

In 2002, Krishnaiah (Krishnaiah *et al* 2002) and his research group were work to design oral controlled drug delivery systems for highly water soluble drug using guar gum as a carrier in the form of a three-layer matrix tablet and for high water solubility, metoprolol tartrate was chosen as a model drug. Through wet granulation technique using starch paste as a binder, matrix tablets containing of guar gum were prepared. Three-layer matrix tablets of metoprolol tartrate were prepared by compressing on both sides of guar gum matrix tablet granules of metoprolol tartrate of guar gum granules as release retardant layers and both tablets were evaluated for hardness, thickness, drug content uniformity and in-vitro drug release studies by using a HPLC method. By comparing physical parameters and drug release profiles of matrix tablets and three layer guar gum matrix tablets, three layer guar gum matrix tablets showed better results than matrix tablets.

In 2006, Slegers (Slegers *et al* 2006) with his co-scientists investigated the radiostability of metoprolol tartrate aqueous solutions and the influence of the absorbed dose (0–50 kGy), dose rate (e-beam (EB) vs. gamma (γ)) and radioprotectors (pharmaceutical excipients) by HPLC-UV analyses with computer simulations. For applications such as radiosterilization to lowering the degradation of metoprolol tartrate aqueous solutions, the use of radioprotecting excipients is more promising than an increase in the dose rate.

In 2007, Ramana (Ramana *et al* 2007) and his research colleagues designed a mucoadhesive buccal drug delivery systems comtaining metoprolol tartrate with the objective of avoiding first

pass metabolism and prolonging duration of action. The mucoadhesive polymers used in formulation were Carbopol-934, hydroxypropylmethylcellulose, hydroxyethylcellulose and sodium carboxymethylcellulose and formulations were examined for physiochemical parameters such as in-vitro release studies and in-vivo placebo studies. The best mucoadhesive performance and *in vitro* drug release profile were exhibited by the tablets containing hydroxyethylcellulose and Carbopol-934 in ratio 1:2 which was more comfortable because of the absence of erosion, faster hydration rate and less viscosity of surrounding environment.

In 2007 Rahman's research group (Rahman *et al.* 2007) also described a kinetic spectrophotometric method for the determination of metoprolol tartrate in commercial dosage forms. This procedure is based on the reaction of two drugs like 1-chloro-2, 4-dinitrobenzene (CDNB) in dimethylsulfoxide (DMSO). The reaction is investigated in absorbance at 420 nm and observer hnage in absorbance with respect to time. The method has been successfully applied to check the quantity of metoprolol tartrate in commercial dosage forms. After performing this experiment the statistical comparison of the results shows that there is no significant difference between the proposed methods and El-Ries's spectrophotometric method.

Again in 2007 Aqil (Aqil *et al.* 2007) and his research team did a research work on high-performance reversed-phase liquid chromatographic method for quantification of metoprolol tartrate (MT) in human plasma. In this method 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. At the same time MT and IS were detected at retention times of 1.5 and 2.6 minutes respectively. The method was successfully used for analysis of metoprolol tartrate in human blood plasma during pharmacokinetic studies.

In 2008 Sanjay (Sanjay *et al.* 2008) with other scientists were to prepare and evaluate the osmotic controlled drug delivery system of metoprolol tartarate that provide continuous drug release for 14 to 15 hours. So the osmotic drug delivery system was evaluated for in vitro drug release study. The excipients did not alter physicochemical properties 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 2009 Nagaich's research team (Nagaich *et al.* 2009) did a research work by preparing buccal drug delivery system of Metoprolol tartrate 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 Octeber, 2009 Tehrani (Tehrani *et al.* 2009) with other scientists described the determination of 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 method and showed satisfactory agreements with them.

In 2009 Jasinska (Jasinska *et al.* 2009) and his friends were 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.

Next year in January, 2010 Yang (Yaug *et al.* 2010) and his colleagues were studied the stability of metoprolol tartrate packaged in 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. No differences in stability were found in both packages stored at 25^0C/60% relative humidity. But under 40^0C/75% relative humidity condition the repackaged tablets absorbed moisture and their weight was increased.

After that at March, 2010 Baloglu (Baloglu *et al.* 2010) with other co-scientists were studied the metoprolol tartrate with seven different polymers (carrageenan, hydroxypropylmethyl cellulose, pectin, guar gum, xanthan gum, chitosan, and ethyl cellulose). Weight variation, hardness,

thickness, friability and in vitro tests were performed and found that carrageenan was the best polymer in two layer matrix tablet formulation because of its better release profile. Then accelerated stability tests were performed using carrageenan as two and three layered formulation of metoprolol tartrate. After storage physical appearance were examined and found no change.

In June, 2010 Bharkatiya's research team (Bharkatiya *et al.* 2010) work on to prepared 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 transdermal patches were evaluated for their physicochemical properties. Based on this test, it can be concluded that Eudragit RL100-PVP are better suited than EC-PVP polymers for the development of transdermal patches of Metoprolol tartrate.

In the same year, Bharkatiya (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 2010 Akhter (Akhter *et al.* 2010) working with his co-scientists worked to develop 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.

In 2010, with a research team, Rao (Rao *et al.* 2010) was 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.

At same year Rao (Rao *et al.* 2010) prepared the fast dissolving tablets of metoprolol tartrate by direct compression method. Then the formulations were evaluated for precompressional parameters such as angle of repose, % compressibility and Hausner's ratio. From this study it is concluded that fast dissolving tablets could be prepared by direct compression method using different superdisintegrants enhanced dissolution that will lead to improved bioavailability, improved effectiveness of metoprolol tartrate.

Again in next year May, 2011 Rao (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.

In March, 2011 Dahiya (Dahiya *et al.* 2011) working with a research team, was 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.

In June, 2011 Cesme (Cesme *et al.* 2011) and his co-scientists 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.

In August, 2011 Reddy (Reddy *et al.* 2011) and his research team took attempt to prepare mouth dissolving tablets of metoprolol tartrate by direct compression method to enhance patient compliance. The two superdisintegrants used in this study were Croscarmellose sodium and Sodium starch glycolate. The prepared batches of tablets were evaluated for uniformity of

weight, thickness, hardness, friability, disintegration time and dissolution study. From this experiment, it can be concluded that the hardness, friability, disintegration time and dissolution rate of prepared tablets were found to be acceptable according to standard limits.

In September, 2011 Himabindu (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.

In December, 2011 Shrisand (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 the same year Shalunkhe (Shalunkhe *et al.* 2011) was 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.

Again in 2011 Syed (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 analysed 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 2011 Senthil (Senthil *et al.* 2011) was 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 2011, Abramovic (Abramovic *et al.*2011) investigated the efficiency of the photocatalytic degradation of metoprolol tartrate (MET) in TiO_2 suspensions of Wackherr's "Oxyde de titane standard" and Degussa P25. This study was to include transformation kinetics and efficiency, identification of intermediates and reaction pathways. The photocatalytic degradation of MET with investigated range of initial concentration followed a pseudo-first order kinetics in the first stage of the reaction. It was resulting that when relatively high substrate concentrations were used, the TiO_2 Wackherr induced faster MET degradation than TiO_2 Degussa P25. It was shown that the reaction between ethanol and hydroxyl radicals ($^{\bullet}OH$) played the main role in the pholocatalytic degradation of MET. Reaction intermediates were studied in detail and a number of them were identified using LC–MS/MS (ESI+), which allowed the proposal of a tentative pathway for the photocatalytic transformation of MET as a function of the TiO_2 specimen.

Next year in April, 2012 Rasool (Rasool *et al.* 2012) was investigated the pharmacokinetics of a developed metoprolol and a reference standard (Mepressor®). This metoprolol tartrate was loaded to Eudragit® FS microparticles were formulated and compressed into tablets. From this single-dose study that the reference and test (developed) formulations met the predetermined criteria for bioequivalence in young healthy fasting male human. Thus, the two formulations can be considered bioequivalent.

In 2012, D Sojic was conducted a stydy of the degradation of thiamethoxam (THIA) and metoprolol (MET) by using UV-induced photolysis (λ= 254nm), ozonation and a combination of these methods. To find out how molecular structure of the substrate influences the rate of its

degradation, they compared these three processes for insecticide THIA and drug MET. In the degradation of THIA, the UV photolysis and the combination of UV/O_3 were found to be most effective, while the UV/O_3 process found to be most efficient in the degradation of THIA. In this study, the degradation kinetics was studied by LC-DAD and spectrophotometry

In December, 2012 Shailaza (Shailaza *et al.* 2012) was 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.

In 2012 Agarwal (Agarwal *et al.* 2012) was 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.

In 2012 Tagde (Tagde *et al.* 2012) was developed a bi-layer tablet of metoprolol tartrate by using disintegrate 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.

In 2012 Ancuta (Ancuta *et al.* 2012) was 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.

In 2012 Khan (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.

In 2012 Anisree (Anisree *et al.* 2012) was modifying 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.

In 2012 Adi (Adi *et al.* 2012) was 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.

Next year in January, 2013 Brahmaiah (Brahmaiah *et al.* 2013) was prepared 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.

In 2013, Golubovic (Golubovic *et al* 2013) used more efficient mesoporous anatase nanopowder than Degussa P25 in the degradation of relatively large pollutant molecules (>1nm in size) due to its structural and morphological properties which have been modified by varying the duration of calcinations and it synthesized by sol- gel method. Nanopowder properties have been related to the photocatalytic activity, tested in the degradation of metoprolol tartrate salt. The study has demonstrated that samples calcined for 4 and 5 hr have displayed higher photocatalytic performance than Degussa P25, whereas the sample calcined for 3 hr has shown comparable activity

In 2013, Romero (Romero *et al* 2013) was reported the pholocatalytic degradation of the metoprolol using TiO_2 suspension as catalyst. The influence of the radiation wavelength on the MET photooxidation rate was investigated by using a filter cutting out wavelengths shorter than 280nm. For evaluating noncatalytic degradation for this pharmaceutical, the effects of photolysis and adsorption were studied at different initial pH. MET adsorption onto titania was fitted to two-parameter Langmuir isotherm. From the results of adsorption, it was found that the photocatalytic degradation can occur mainly on the surface of TiO_2 the first stage photocatalytic degradation of MET by TiO_2 was followed a pseudo-first-order model. The major reaction intermediates such as 3-(propan-2-ylamino) propane-1,2-diol or 3-aminoprop-1-en-2-ol were identified by LC/MS analysis. Based on the identified intermediates, a photocatalytic degradation pathway was proposed, including the cleavage of side chain and the hydroxylation addition to the parent compounds.

In 2013, Moctezuma (Moctezuma *et al* 2013) was investigated to determin the effect of initial reactant concentration on the reaction rate and the role of the direct photolysis on the photocatalytic process by using the advance oxidation of high purity metoprolol tartate extracted from commercial medicament with TiO_2 and UV light at 365 nm. After analyzing the reactant samples by UV-Vis spectroscopy, It was resulted that metoprolol tartrate is efficiently degraded by photolysis by the hydroxylation of the aromatic ring. Kinetic studies indicated that this degradation follows a Langmuir, Hinshelwood, Hougen and Watson (LHHW) mechanism and the reaction order shifts from zero order to first order with the dropping of reactant concentration. Other additional experiments were also done which resulted in that direct photolysis plays a minor role on the photocatalytic oxidation of metoprolol tartrate. Total organic carbon (TOC) studies were also performed which showed that metoprolol tartrate is transformed to other organic intermediate reaction products before complete mineralization to CO_2. The fraction of reactant transformed into intermediate organic products and it was evaluated by a material balance using the results of analysis of the reaction samples by high performance liquid chromatography and TOC.

After that in April, 2013 Devi (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

Recently in 2013 Kumar (Kumar *et al.* 2013) was 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.

Very recently in India, Mathur (Mathur *et al.* 2013) was 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.

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

Very recently 1 February 2015, Romero (Romero *et al* 2015) used UV/H_2O_2, photo-Fenton and photocatalysis (TiO_2) to degrade metoprolol tartrate salt (MET) in aqueous solution. This study mainly investigates the variation of different parameters such as MET concentration, total organic carbon (TOC), chemical oxygen demand (COD) per accumulated energy (determined by actinometries), analyzing the performance of the different set-ups tested. The tested three

technologies resulted in nearly total MET removal while the UV/H_2O_2 technique being more efficient for MET degradation. When assessing the mineralization and the overall oxidation of the solution for a specific amount of accumulated energy (18 KJ/L), the kinetic study showed that TiO_2photolysis seems to be one step than others. By ionization / mass spectrometry, major reaction intermediates in the three processes were indentified.

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 Presonil® (metoprolol tartrate 50mg) were collected from the local drug store in Dhaka as a sample. All the tablets were from the same batch (14009). Among them 200 tablets were kept light protected for control tests and the remaining 500 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 (Incepta, 2012)

Sample Name	Source (Supplier Name)	Batch No.
Presonil® Tablets	Incepta Pharmaceutical Ltd.	14009

Figure 3.1*:* Presonil® Tablets

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	Vernier 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.

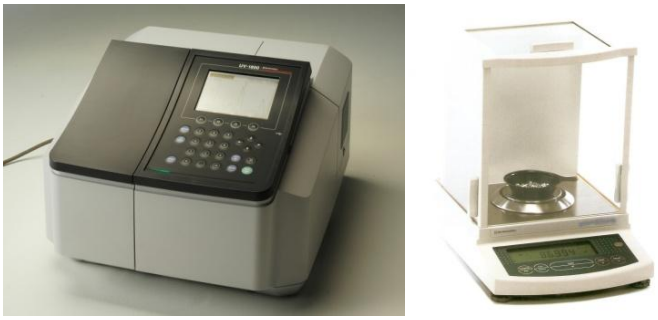

Figure 3.2: Shimadzu UV-1800 spectrophotometer and Electronic balance [Left to right]

Figure 3.3*:* Hardness tester, Distilled water plant & Vernier calipers [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 were collected from the pharmaceutical company Aristopharma Ltd. The potency of standard compounds was 99.56%.
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 that was obtained from Aristropharma Ltd.
3. 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 obtained from Aristropharma Ltd:

- 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: Concentration 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.

4. Then the absorbance value was measured using a UV spectrophotometer against those nine serial concentrations for metoprolol tartrate.
5. A standard curves was plotted for metoprolol tartrate.
6. 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:

1. Exposure under normal lighting conditions in the room
2. Under electric bulb exposure (25 watt & 40 watt)
3. Direct Sunlight exposure

1. Exposure under Normal Lighting Condition

1) The tablets (Presonil®) were kept under normal lighting condition in the room for 4 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:

$$\textbf{Average weight (g)} = \frac{\textbf{Total weight of the tablets}}{\textbf{Total no. of tablets}}$$

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 3 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 for 3 times to prepare 3 samples.
f. From then 10ml of each sample was collected and kept into 3 different test-tube and wrapped it 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.

2. 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 :

$$\textbf{Average weight (g)} = \frac{\textbf{Total weight of the tablets}}{\textbf{Total no. of tablets}}$$

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 3 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 for 3 times to prepare 3 samples.

e. From then 10ml of each sample was collected and kept into 3 different test-tube and wrapped it 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)**	
			25W	**40W**
10 (Control)	10	0	25	30
30	10	2	27	30
	10	4	27	30
	10	6	30	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 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 two different days for 6 hours each.

3. Under Sunlight condition

1) 30 tablets were kept in a Glass box and exposed to sunlight condition for 7.5 hours at a stretch.
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:

$$\textbf{Average weight (g)} = \frac{\textbf{Total weight of the tablets}}{\textbf{Total no. of tablets}}$$

    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 3 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 3 different test-tube and wrapped it 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	30
	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) Tablets were used as control has not been exposed any of lighting conditions.

3.2.4 Determination of Physical parameters:

1. 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.

2. 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.

The equation for calculation of thickness of tablet is given below:

$$\text{Thickness (cm)} = \text{Main Reading} + \left(\frac{\text{Vernier Reading}}{10} \times \text{Vernier Constant}\right)$$

3. 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 presonil®. 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).

4. Weight Variation Test

Procedure

1) 10 tablets were taken and average weight was taken and it was considered as the standard weight of an individual tablet.

2) 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

% Weight Variation = (A~I/A) ×100 %

Where,
I = Initial weight of tablet, in gram/grams (gm)
A = Average weight of tablet, in gram/grams (gm)

Chapter Four

RESULTS

4.1 Standard curve preparation

The standard was collected from Aristropharma Ltd. and tried to make a standard curve. For different concentration of metoprolol tartrate different absorption were recorded. 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 that was found in several lighting conditions.

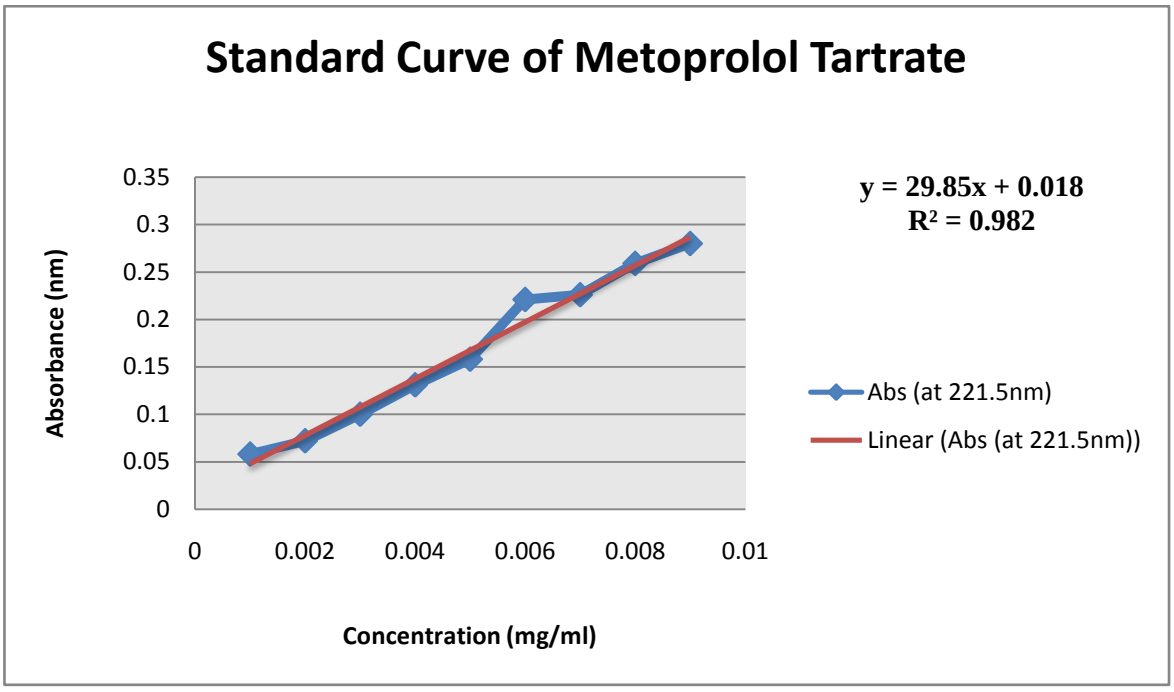

Figure 4.1: Plot showing straight line for absorbance with respect to concentration for metoprolol tartrate

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. Some of the pictures showing the color change are given below:

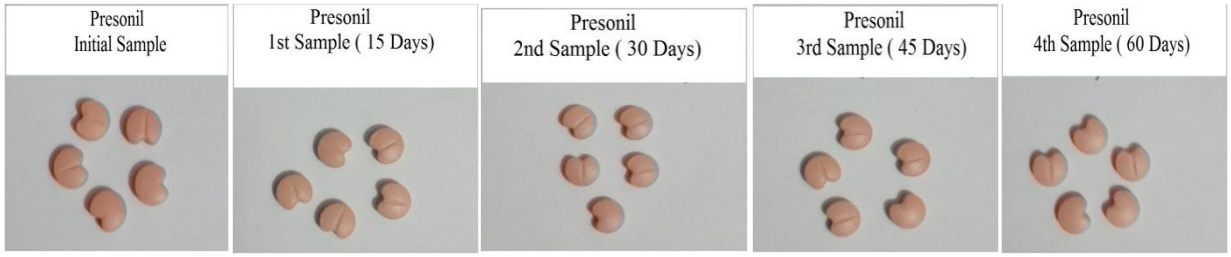

Figure 4.2: Pictures of tablets after exposure to normal light with 80 days interval

4.2.2 Weight Variation Test

Six tablet strips containing 60 tablets was exposed to normal light condition for 80 days. Weight variation test was conducted of 5 tablets of each day interval (7, 38, 52, 66, 73, 80 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 (Presonil®)

Days	Average Weight for Particular Day, I(g)	Average Weight for 60 Days Intervals, A(g)	% Weight Variation, (A-I/A)×100 %
Initial	0.1875	0.18676	-0.396
15	0.1867		0.032
30	0.1873		-0.289
45	0.1868		-0.021
60	0.1855		0.674

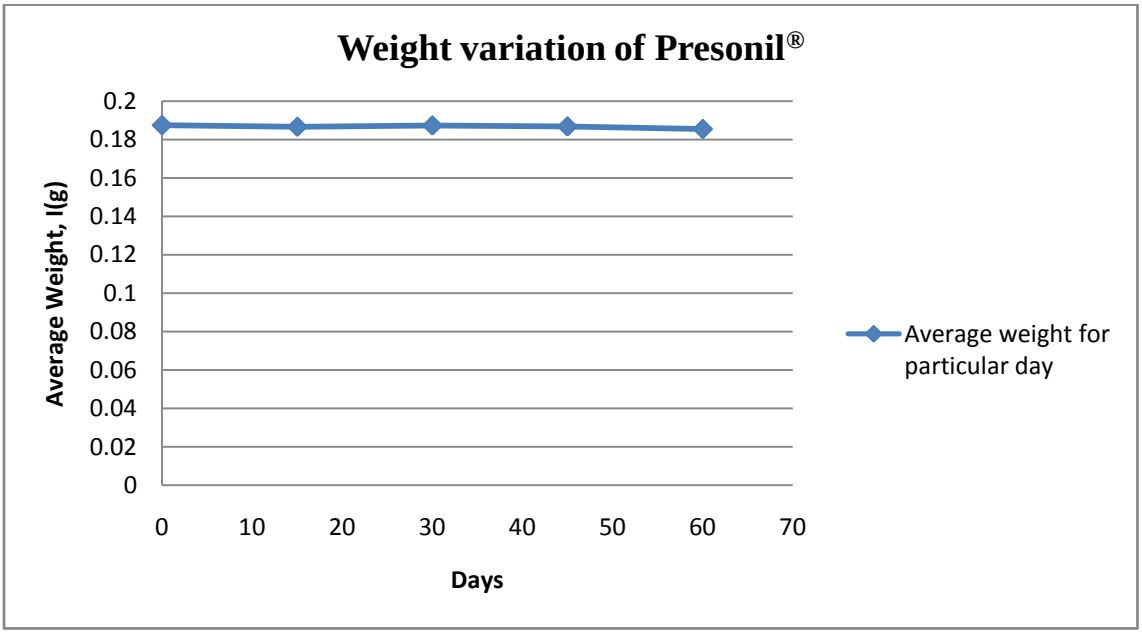

Figure 4.3: Weight variation of the sample throughout 60 days light exposure

4.2.3 Hardness Test

Six tablet strips containing 60 tablets was exposed to normal light condition for 80 days. Hardness test was conducted of 5 tablets of each day interval (7, 38, 52, 66, 73, 80 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 (Presonil®)

Days	Average Hardness of Particular Day (Kg)
Initial	6.14
15	6.12
30	6.12
45	6.08
60	6.09

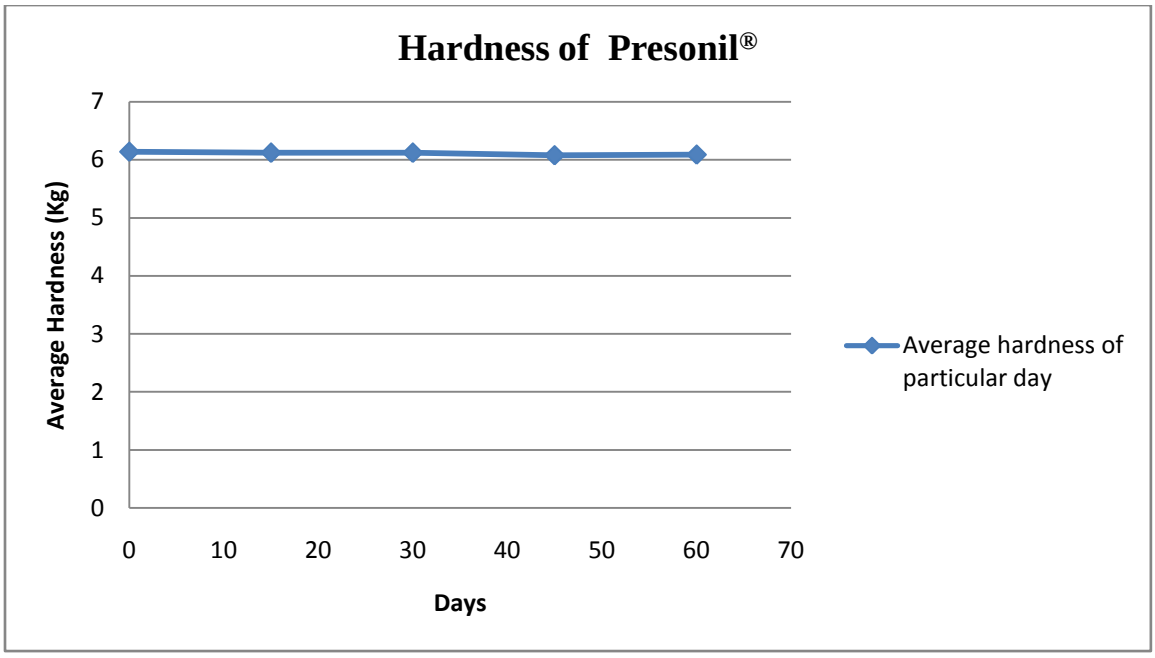

Figure 4.4: Hardness variation of the sample throughout 60 days light exposure

4.2.4 Thickness Test

Six tablet strips containing 60 tablets was exposed to normal light condition for 80 days. Thickness test was conducted of 5 tablets of each day interval (7, 38, 52, 66, 73, 80 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 (Presonil®)

Days	Average Thickness of Particular Days (cm)
Initial	0.32
15	0.35
30	0.33
45	0.35
60	0.34

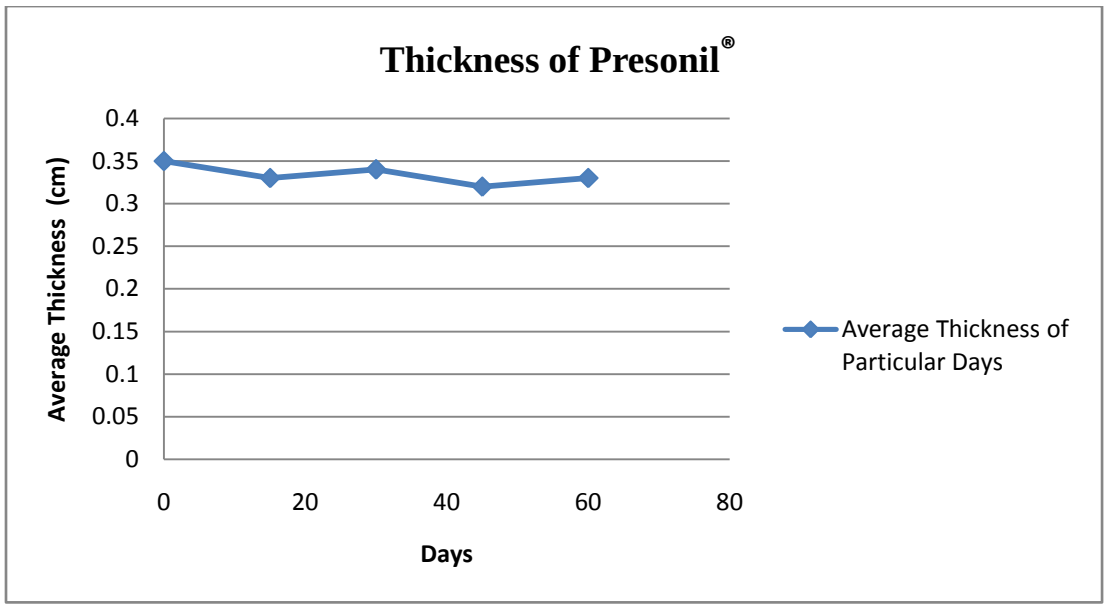

Figure 4.5*:* Thickness variation of sample throughout 60 days light exposure

4.3 Result from Potency Determination by UV- spectroscopy

4.3.1 Result from Sample that was exposed under Normal Lightening Condition

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

Table 4.5: Concentration & Absorbance of Zero Days Interval for Metoprolol Tartrate

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	0.616	0.617	0.616	0.615	50.08	50.00	100.16	100.00
	0.616	0.614						
	0.615	0.614						
	0.616	0.615	0.616	0.615	50.08	50.00	100.16	100.00
	0.615	0.614						
	0.616	0.615						
	0.615	0.613	0.616	0.614	50.08	49.92	100.16	99.84
	0.616	0.615						
	0.616	0.614						

Table 4.6: Concentration & Absorbance of 15 Days Interval for Metoprolol Tartrate

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	0.616	0.580	0.616	0.577	50.08	46.81	100.16	93.62
	0.616	0.576						
	0.615	0.576						
	0.616	0.575	0.616	0.575	50.08	46.64	100.16	93.28
	0.615	0.574						
	0.616	0.575						
	0.615	0.572	0.616	0.572	50.08	46.39	100.16	92.78
	0.616	0.572						
	0.616	0.573						

Table 4.7: Concentration & Absorbance of 30 Days Interval for Metoprolol Tartrate

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	0.616	0.534	0.616	0.534	50.08	43.21	100.16	86.49
	0.616	0.537						
	0.615	0.531						
	0.616	0.535	0.616	0.538	50.08	43.55	100.16	87.12
	0.615	0.536						
	0.616	0.542						
	0.615	0.533	0.616	0.533	50.08	43.13	100.16	86.32
	0.616	0.532						
	0.616	0.534						

Table 4.8: Concentration & Absorbance of 45 Days Interval for Metoprolol Tartrate

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	0.616	0.528	0.616	0.528	50.08	42.71	100.16	85.42
	0.616	0.528						
	0.615	0.527						
	0.616	0.543	0.616	0.527	50.08	42.63	100.16	85.26
	0.615	0.492						
	0.616	0.546						
	0.615	0.526	0.616	0.525	50.08	42.46	100.16	84.92
	0.616	0.525						
	0.616	0.524						

Table 4.9: Concentration & Absorbance of 60 Days Interval for Metoprolol Tartrate

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	0.616	0.510	0.616	0.510	50.08	41.20	100.16	82.40
	0.616	0.510						
	0.615	0.509						
	0.616	0.527	0.616	5.14	50.08	41.54	100.16	83.08
	0.615	0.489						
	0.616	0.525						
	0.615	0.505	0.616	0.507	50.08	40.95	100.16	81.90
	0.616	0.506						
	0.616	0.510						

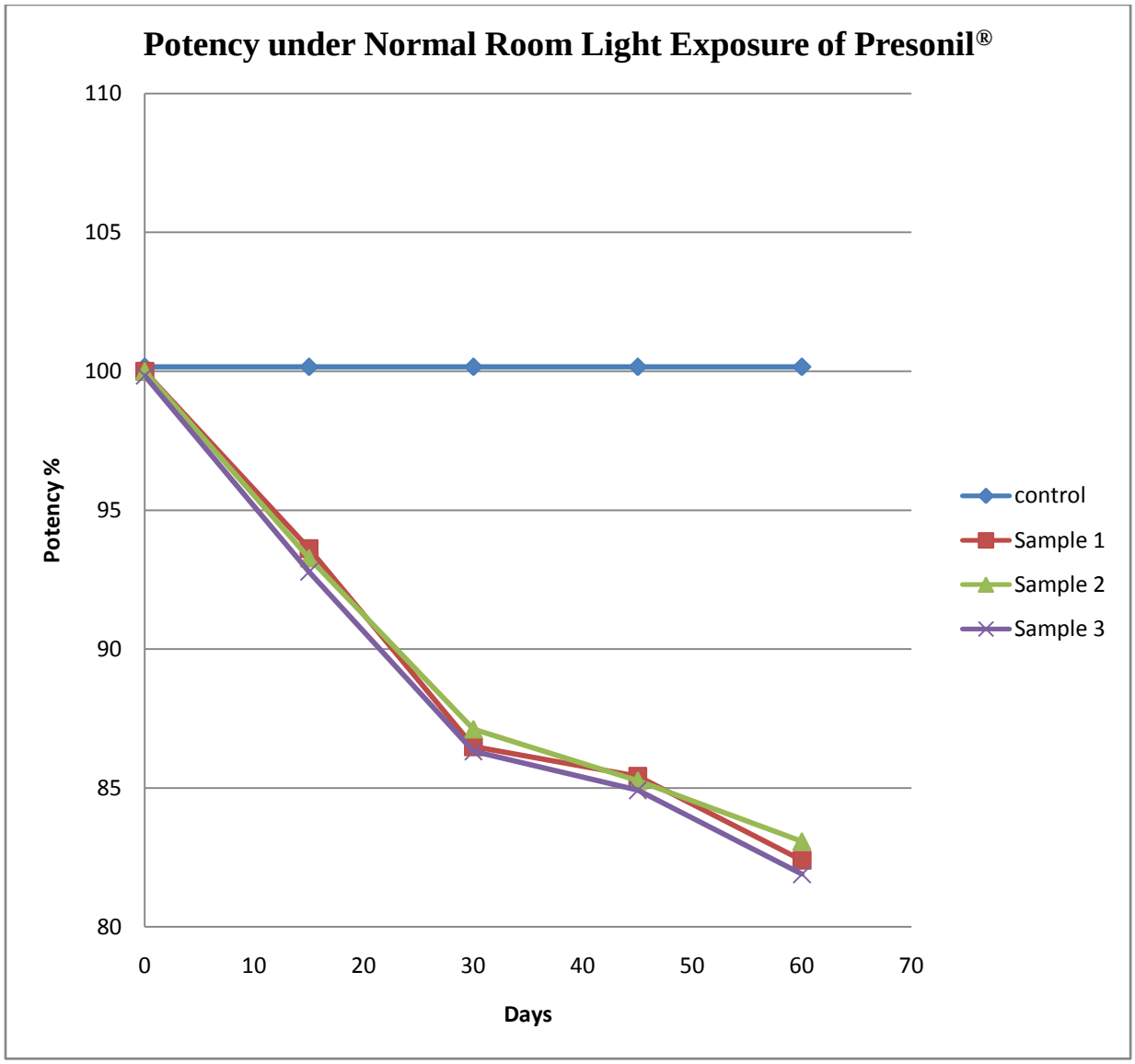

Figure 4.6: Graph showing the difference in Concentration after fixed day interval for Metaprolol Tartrate (Presonil®)

4.3.2 Result of samples that were exposed under 25W bulb

In each three experimental day, a tablet strip containing 10 tablets was taken and 5 samples were collected for the test and observed 3 different absorbance of metoprolol tartrate for three 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. The results are given below-

Table 4.10: Concentration & absorbance of Metoprolol Tartrate at Zero hour for 1st time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
Zero (Control)	0.603	0.605	49.16	98.32
	0.603			
	0.608			
	0.605	0.605	49.16	98.32
	0.604			
	0.605			
	0.604	0.605	49.16	98.32
	0.606			
	0.605			

Table 4.11: Concentration & absorbance of Metoprolol Tartrate after 2 hours for 1st time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
2	0.561	0.565	45.81	91.62
	0.565			
	0.569			
	0.562	0.562	45.56	91.12
	0.562			
	0.561			
	0.558	0.560	45.39	90.78
	0.562			
	0.560			

Table 4.12: Concentration & absorbance of Metoprolol Tartrate after 4 hours for 1st time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
4	0.545	0.548	44.38	88.76
	0.549			
	0.550			
	0.550	0.550	44.55	89.10
	0.545			
	0.555			
	0.543	0.546	44.22	88.44
	0.545			
	0.550			

Table 4.13: Concentration & absorbance of Metoprolol Tartrate after 6 hours for 1st time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
6	0.520	0.520	42.04	84.08
	0.522			
	0.518			
	0.519	0.519	41.95	83.90
	0.519			
	0.518			
	0.518	0.517	41.79	83.58
	0.515			
	0.516			

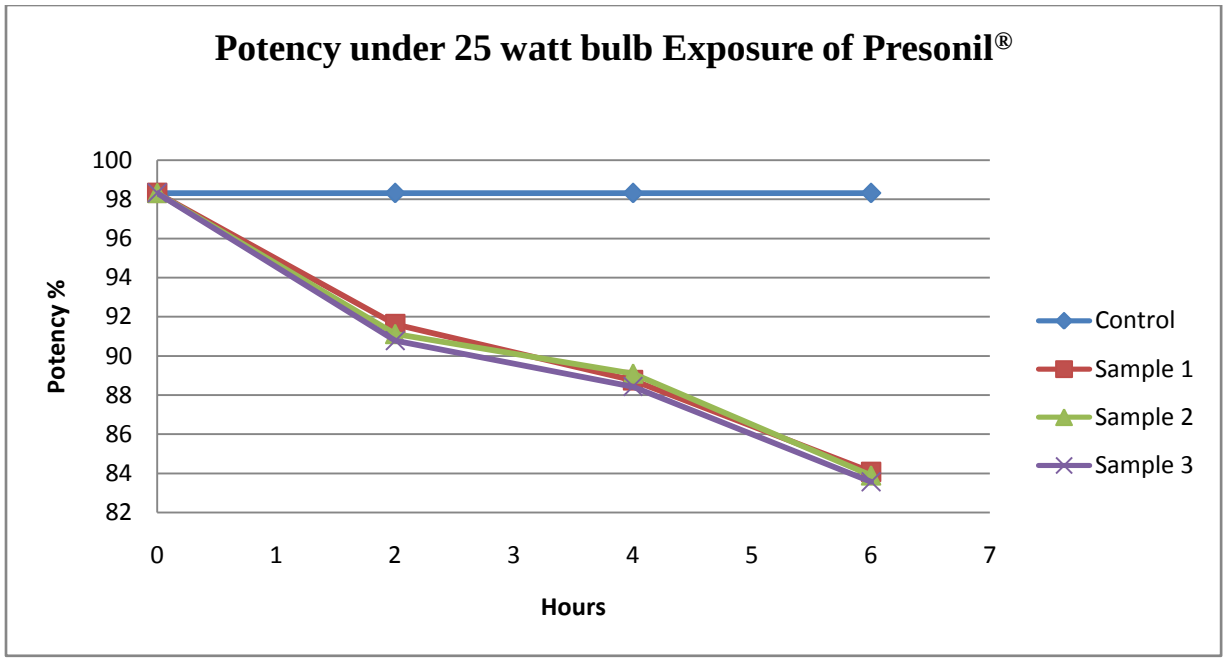

Figure 4.7: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Presonil®) for 1st time

Table 4.14: Concentration & absorbance of Metoprolol Tartrate at Zero hour for 2nd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
Zero (Control)	0.603	0.604	49.08	98.16
	0.603			
	0.606			
	0.605	0.604	49.08	98.16
	0.604			
	0.603			
	0.603	0.604	49.08	98.16
	0.606			
	0.603			

Table 4.15: Concentration & absorbance of Metoprolol Tartrate after 2 hours for 2nd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
2	0.558	0.559	45.31	90.62
	0.560			
	0.559			
	0.557	0.558	45.22	90.44
	0.558			
	0.559			
	0.562	0.562	45.56	91.12
	0.560			
	0.564			

Table 4.16: Concentration & absorbance of Metoprolol Tartrate after 4 hours for 2nd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
4	0.548	0.550	44.55	89.10
	0.552			
	0.550			
	0.557	0.549	44.47	88.94
	0.551			
	0.549			
	0.547	0.547	44.30	88.60
	0.547			
	0.546			

Table 4.17: Concentration & absorbance of Metoprolol Tartrate after 6 hours for 2nd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
6	0.521	0.521	42.13	84.26
	0.524			
	0.519			
	0.520	0.519	41.95	83.90
	0.518			
	0.519			
	0.513	0.513	41.46	82.92
	0.512			
	0.513			

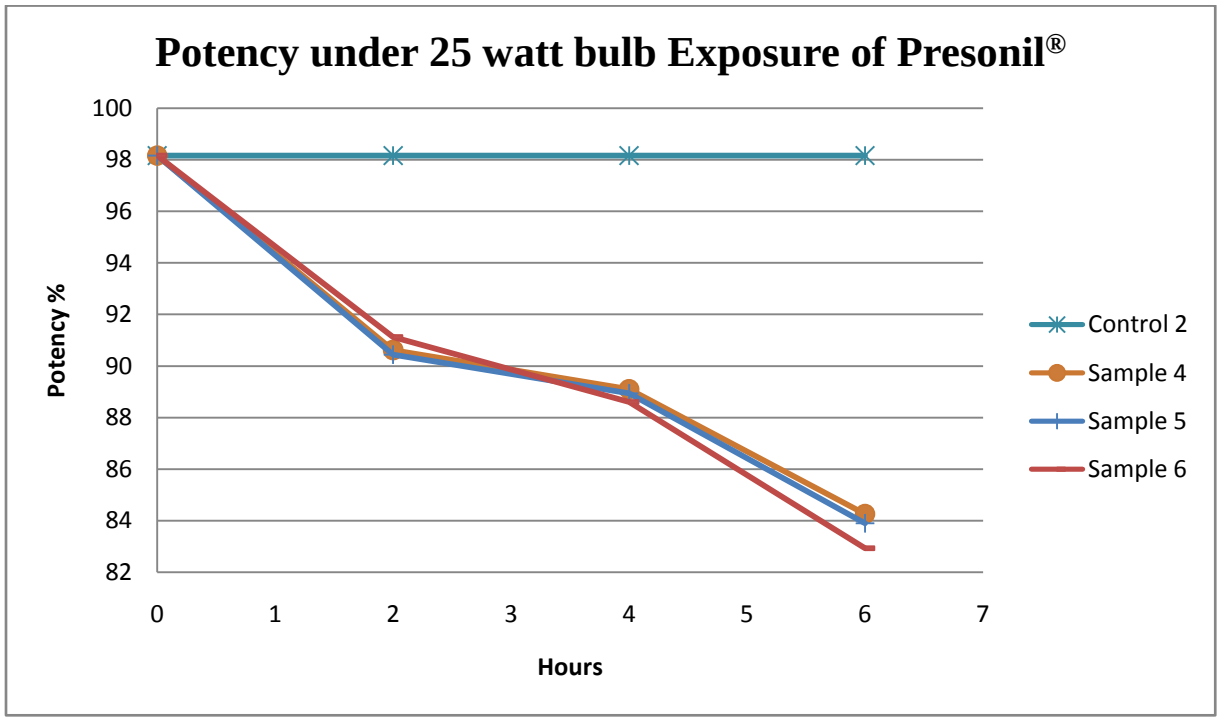

Figure 4.8: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Presonil®) for 2nd time

Table 4.18: Concentration & absorbance of Metoprolol Tartrate at Zero hour for 3rd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
Zero (Control)	0.603	0.603	48.99	97.98
	0.603			
	0.602			
	0.605	0.603	48.99	97.98
	0.604			
	0.600			
	0.604	0.603	48.99	97.98
	0.604			
	0.601			

Table 4.19: Concentration & absorbance of Metoprolol Tartrate after 2 hours for 3rd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
2	0.563	0.563	45.64	91.28
	0.565			
	0.562			
	0.564	0.565	45.81	91.62
	0.563			
	0.568			
	0.563	0.563	45.64	91.28
	0.562			
	0.563			

Table 4.20: Concentration & absorbance of Metoprolol Tartrate after 4 hours for 3rd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
4	0.545	0.548	44.39	88.78
	0.51			
	0.548			
	0.546	0.547	44.30	88.6
	0.546			
	0.548			
	0.550	0.549	44.47	88.94
	0.550			
	0.557			

Table 4.21: Concentration & absorbance of Metoprolol Tartrate after 6 hours for 3rd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
6	0.520	0.524	42.37	84.74
	0.524			
	0.528			
	0.517	0.517	41.79	83.58
	0.514			
	0.520			
	0.518	0.519	41.96	83.92
	0.516			
	0.521			

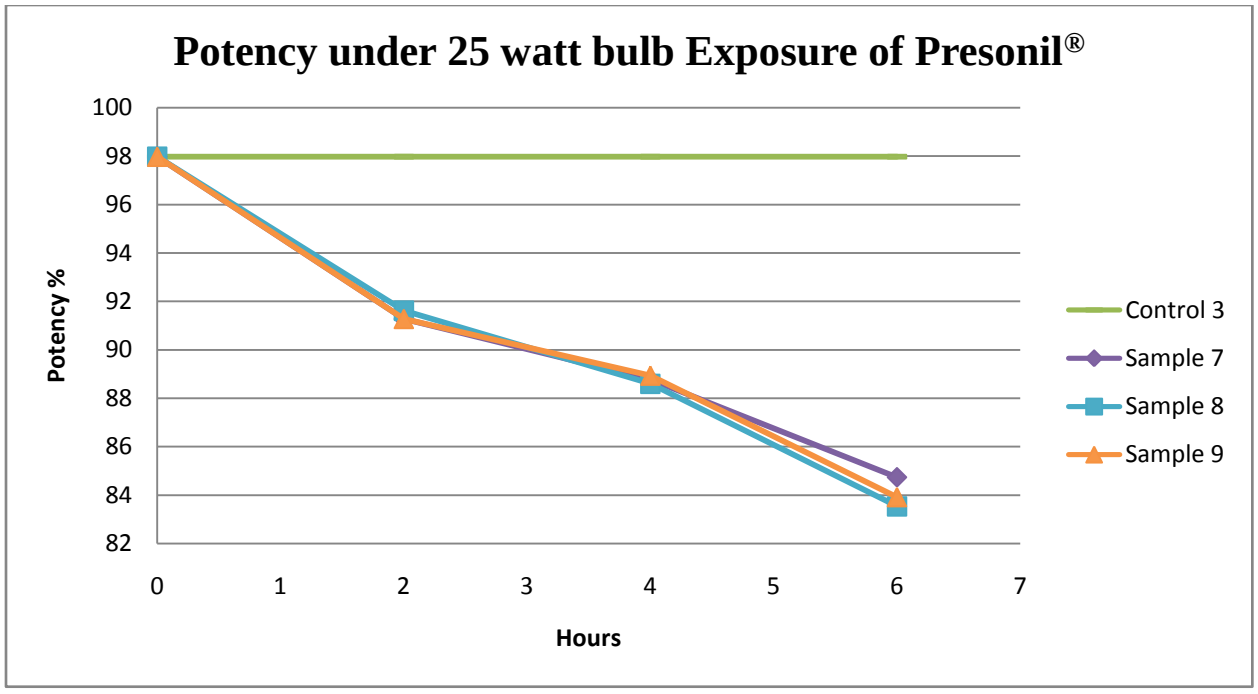

Figure 4.9: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Presonil®) for 3rd time

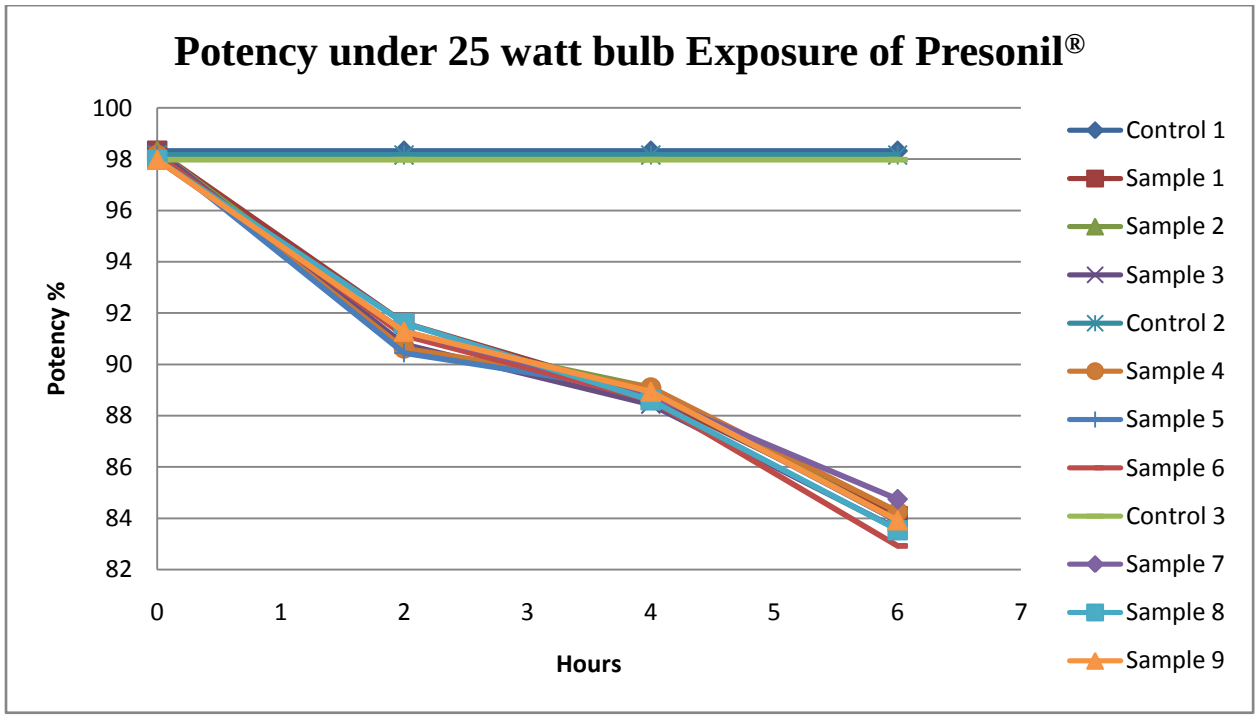

Figure 4.10: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Presonil®) for all times

4.3.3 Result of samples that were exposed under 40W bulb

In each three experimental day, a tablet strip containing 10 tablets was taken and 5 samples were collected for the test and observed 3 different absorbance of metoprolol tartrate for three 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 inter**.** The results are given below-

Table 4.22: Concentration & absorbance of Metoprolol Tartrate at Zero hour for 1st time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
Zero (Control)	0.602	0.602	48.91	97.82
	0.599			
	0.605			
	0.601	0.602	48.91	97.82
	0.604			
	0.603			
	0.602	0.602	48.91	97.82
	0.603			
	0.601			

Table 4.23: Concentration & absorbance of Metoprolol Tartrate after 2 hours for 1st time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
2	O.567	0.566	45.89	91.79
	0.565			
	0.566			
	0.567	0.567	45.98	91.96
	0.567			
	0.566			
	0.564	0.563	45.64	91.28
	0.566			
	0.559			

Table 4.24: Concentration & absorbance of Metoprolol Tartrate after 4 hours for 1st time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
4	0.545	0.545	44.13	88.26
	0.549			
	0.541			
	0.544	0.543	43.96	87.92
	0.544			
	0.541			
	0.545	0.543	43.96	87.92
	0.542			
	0.542			

Table 4.25: Concentration & absorbance of Metoprolol Tartrate after 6 hours for 1st time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
6	0.520	0.520	42.04	84.04
	0.519			
	0.520			
	0.519	0.518	41.88	83.76
	0.520			
	0.515			
	0.516	0.517	41.79	83.58
	0.515			
	0.520			

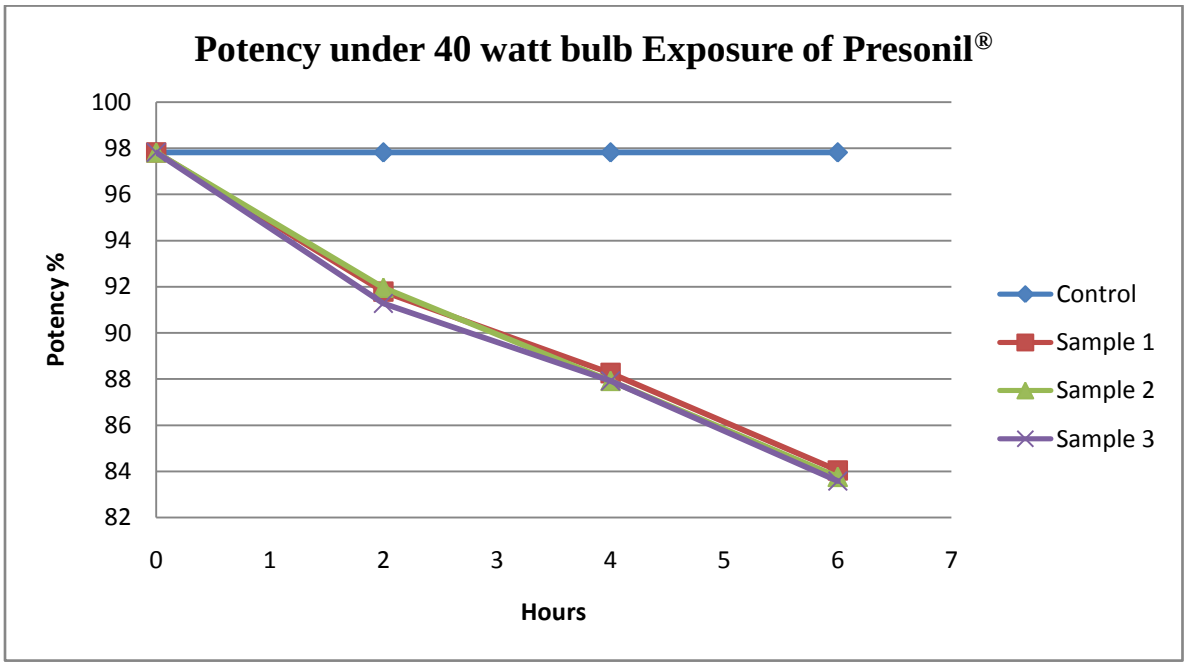

Figure 4.11: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Presonil®) for 1st time

Table 4.26: Concentration & absorbance of Metoprolol Tartrate at Zero hour for 2nd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
Zero (Control)	0.599	0.600	48.74	97.48
	0.598			
	0.603			
	0.601	0.600	48.74	97.48
	0.602			
	0.597			
	0.599	0.600	48.74	97.48
	0.600			
	0.600			

Table 4.27: Concentration & absorbance of Metoprolol Tartrate after 2 hours for 2nd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
2	0.562	0.562	45.56	91.12
	0.560			
	0.564			
	0.565	0.560	45.39	90.78
	0.557			
	0.559			
	0.561	0.563	45.64	91.28
	0.564			
	0.564			

Table 4.28: Concentration & absorbance of Metoprolol Tartrate after 4 hours for 2nd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
4	0.554	0.553	44.80	89.60
	0.553			
	0.552			
	0.549	0.549	44.72	89.44
	0.550			
	0.548			
	0.551	0.550	44.56	89.12
	0.548			
	0.551			

Table 4.29: Concentration & absorbance of Metoprolol Tartrate after 6 hours for 2nd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
6	0.522	0.522	42.21	84.42
	0.520			
	0.524			
	0.519	0.519	41.96	83.92
	0.515			
	0.523			
	0.519	0.520	42.04	84.08
	0.520			
	0.521			

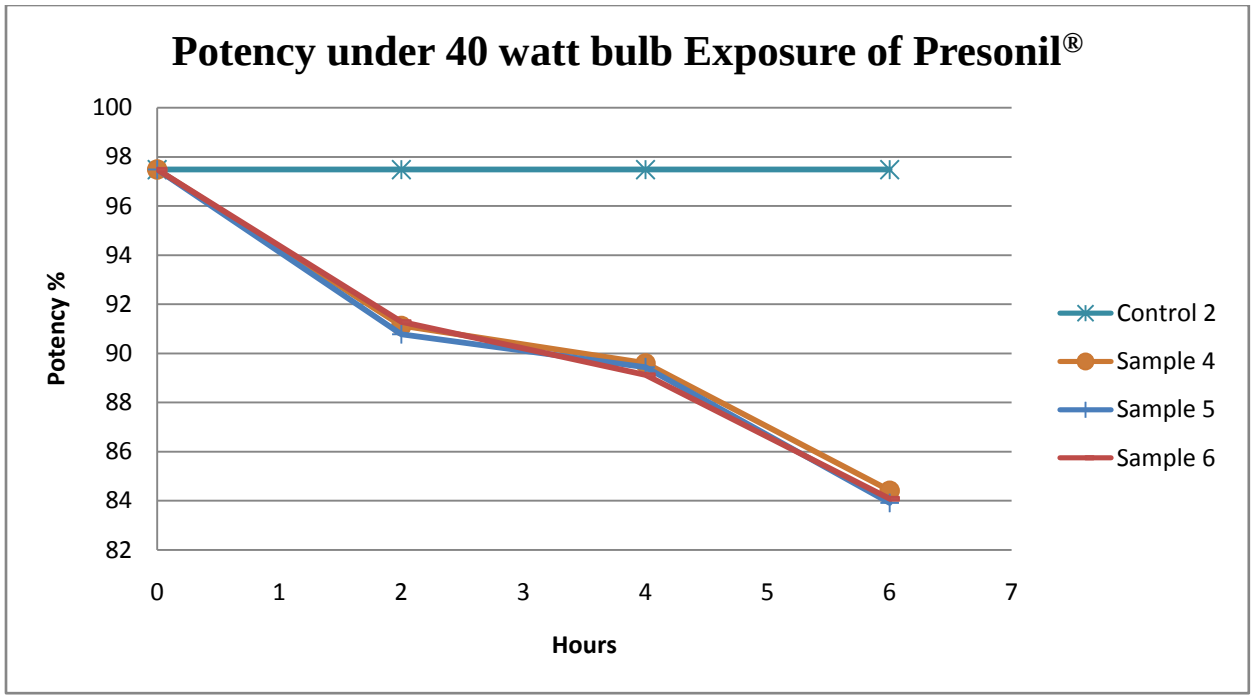

Figure 4.12: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Presonil®) for 2nd time

Table 4.30: Concentration & absorbance of Metoprolol Tartrate at Zero hour for 3rd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
Zero (Control)	0.602	0.599	48.65	97.30
	0.597			
	0.598			
	0.601	0.599	48.65	97.30
	0.601			
	0.595			
	0.598	0.599	48.65	97.30
	0.599			
	0.599			

Table 4.31: Concentration & absorbance of Metoprolol Tartrate after 2 hours for 3rd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
2	0.560	0.563	45.64	91.28
	0.562			
	0.567			
	0.565	0.566	45.89	91.78
	0.568			
	0.565			
	0.563	0.564	45.73	91.46
	0.563			
	0.562			

Table 4.32: Concentration & absorbance of Metoprolol Tartrate after 4 hours for 3rd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
4	0.546	0.548	44.38	88.76
	0.549			
	0.547			
	0.547	0.547	44.30	88.60
	0.546			
	0.547			
	0.549	0.549	44.47	88.94
	0.543			
	0.555			

Table 4.33: Concentration & absorbance of Metoprolol Tartrate after 6 hours for 3rd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
6	0.524	0.524	42.37	84.74
	0.523			
	0.525			
	0.518	0.517	41.79	83.58
	0.519			
	0.514			
	0.518	0.519	41.95	43.9
	0.519			
	0.518			

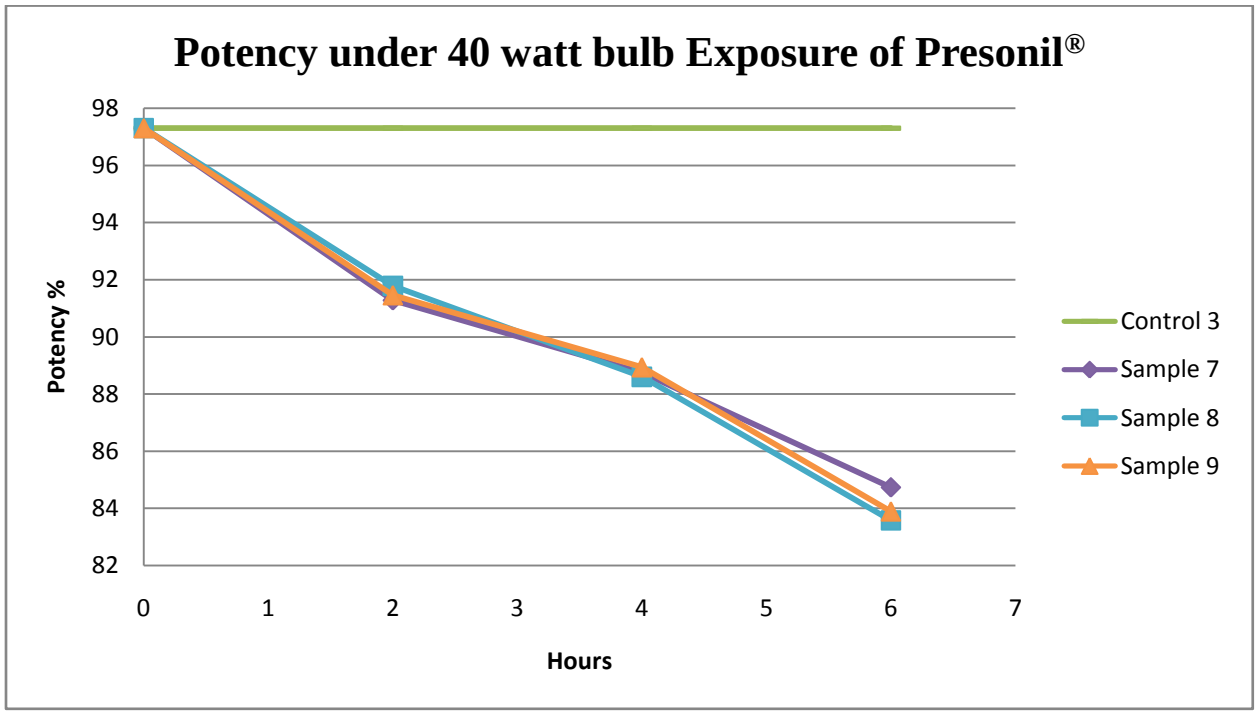

Figure 4.13: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Presonil®) for 3rd time

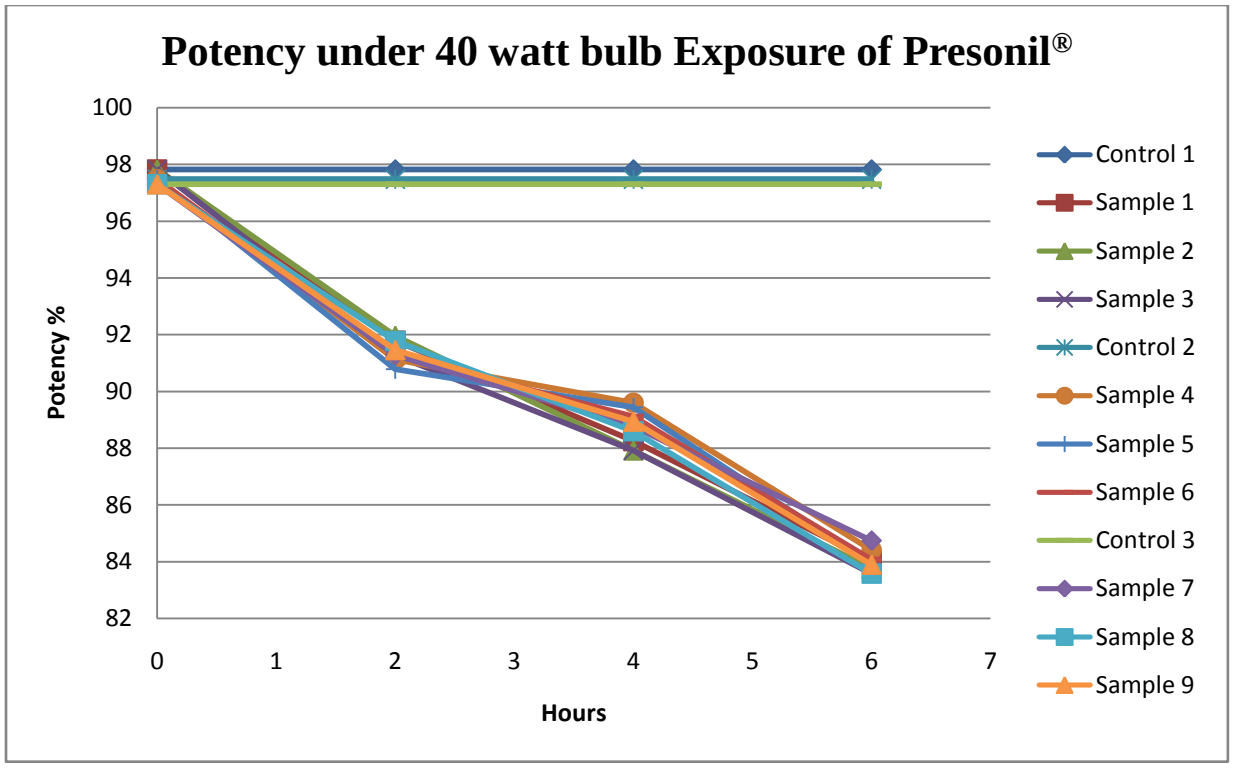

Figure 4.14: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Presonil®) for all time**s**

4.3.4 Result of samples that were exposed under direct sunlight

In experimental day, a tablet strip containing 10 tablets was taken and 5 samples were collected for the test and observed 3 different absorbance of metoprolol tartrate for three 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. The results are given bellow-

Table 4.34: Concentration & absorbance of Metoprolol Tartrate at Zero hour for 1st time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
Zero (Control)	0.605	0.597	48.49	96.98
	0.580			
	0.606			
	0.601	0.597	48.49	96.98
	0.595			
	0.595			
	0.598	0.597	48.49	96.98
	0.598			
	0.595			

Table 4.35: Concentration & absorbance of Metoprolol Tartrate after 2 hours for 1st time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
2	0.571	0.572	46.39	92.78
	0.575			
	0.570			
	0.569	0.570	46.23	92.46
	0.572			
	0.569			
	0.571	0.570	46.23	92.46
	0.569			
	0.574			

Table 4.36: Concentration & absorbance of Metoprolol Tartrate after 4 hours for 1st time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
4	0.549	0.550	44.56	89.12
	0.548			
	0.553			
	0.564	0.547	44.30	88.60
	0.564			
	0.512			
	0.549	0.548	44.38	88.76
	0.552			
	0.543			

Table 4.37: Concentration & absorbance of Metoprolol Tartrate after 6 hours for 1st time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
6	0.532	0.532	43.04	86.24
	0.533			
	0.531			
	0.535	0.534	43.21	86.42
	0.535			
	0.532			
	0.534	0.533	43.13	86.26
	0.532			
	0.533			

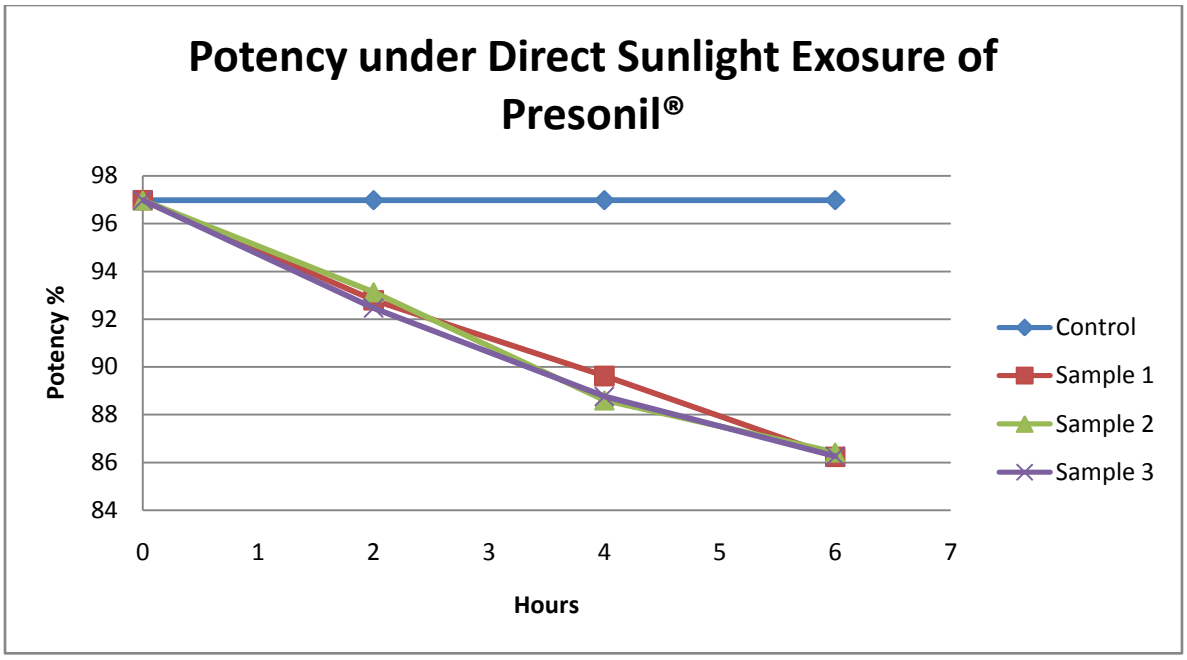

Figure 4.15: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Presonil®) for 1st time for 1st time

Table 4.38: Concentration & absorbance of Metoprolol Tartrate at Zero hour for 2nd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
Zero (Control)	0.593	0.593	48.16	96.32
	0.590			
	0.596			
	0.590	0.593	48.16	96.32
	0.595			
	0.594			
	0.590	0.593	48.16	96.32
	0.596			
	0.593			

Table 4.39: Concentration & absorbance of Metoprolol Tartrate after 2 hours for 2nd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
2	0.578	0.577	46.82	93.63
	0.579			
	0.574			
	0.574	0.574	46.57	93.14
	0.576			
	0.572			
	0.577	0.576	46.73	93.47
	0.575			
	0.576			

Table 4.40: Concentration & absorbance of Metoprolol Tartrate after 4 hours for 2nd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
4	0.555	0.555	44.97	89.94
	0.556			
	0.554			
	0.553	0.553	44.81	89.62
	0.551			
	0.555			
	0.548	0.549	44.47	88.94
	0.550			
	0.548			

Table 4.41: Concentration & absorbance of Metoprolol Tartrate after 6 hours for 2nd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
6	0.533	0.534	43.21	86.42
	0.535			
	0.534			
	0.530	0.532	43.05	86.10
	0.529			
	0.537			
	0.532	0.531	42.96	85.92
	0.530			
	0.532			

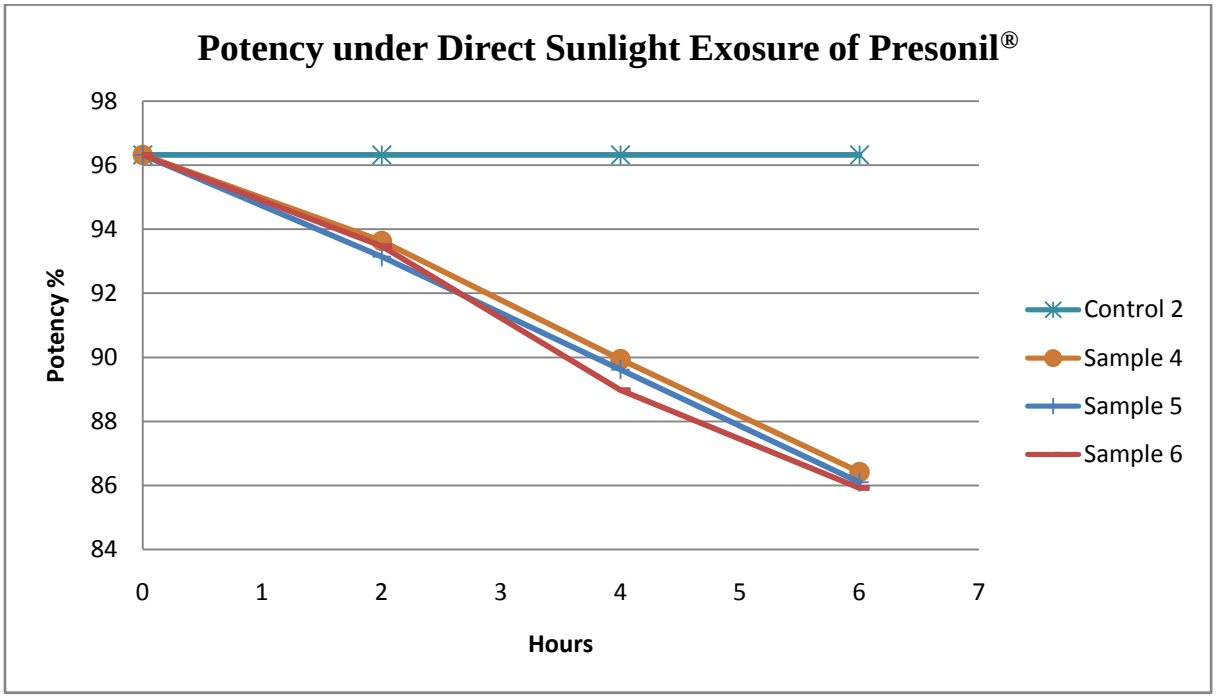

Figure 4.16: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Presonil®) for 2nd time

Table 4.42: Concentration & absorbance of Metoprolol Tartrate at Zero hour for 3rd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
Zero (Control)	0.594	0.595	48.32	96.64
	0.597			
	0.596			
	0.600	0.595	48.32	96.64
	0.593			
	0.592			
	0.591	0.595	48.32	96.64
	0.597			
	0.597			

Table 4.43: Concentration & absorbance of Metoprolol Tartrate after 2 hours for 3rd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
2	0.573	0.574	46.57	93.14
	0.576			
	0.573			
	0.570	0.571	46.31	92.62
	0.570			
	0.574			
	0.571	0.571	46.31	92.62
	0.572			
	0.571			

Table 4.44: Concentration & absorbance of Metoprolol Tartrate after 4 hours for 3rd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
4	0.554	0.553	44.80	89.6
	0.555			
	0.550			
	0.554	0.554	44.89	89.78
	0.553			
	0.554			
	0.553	0.554	44.89	89.78
	0.552			
	0.557			

Table 4.45: Concentration & absorbance of Metoprolol Tartrate after 6 hours for 3rd time

Time Interval	Absorbance (at 221.5 nm)	Average Absorbance	Amount of Drug present (in mg)	Potency (%)
6	0.534	0.535	43.29	86.58
	0.533			
	0.538			
	0.532	0.533	43.13	86.26
	0.532			
	0.535			
	0.534	0.532	43.05	86.10
	0.531			
	0.533			

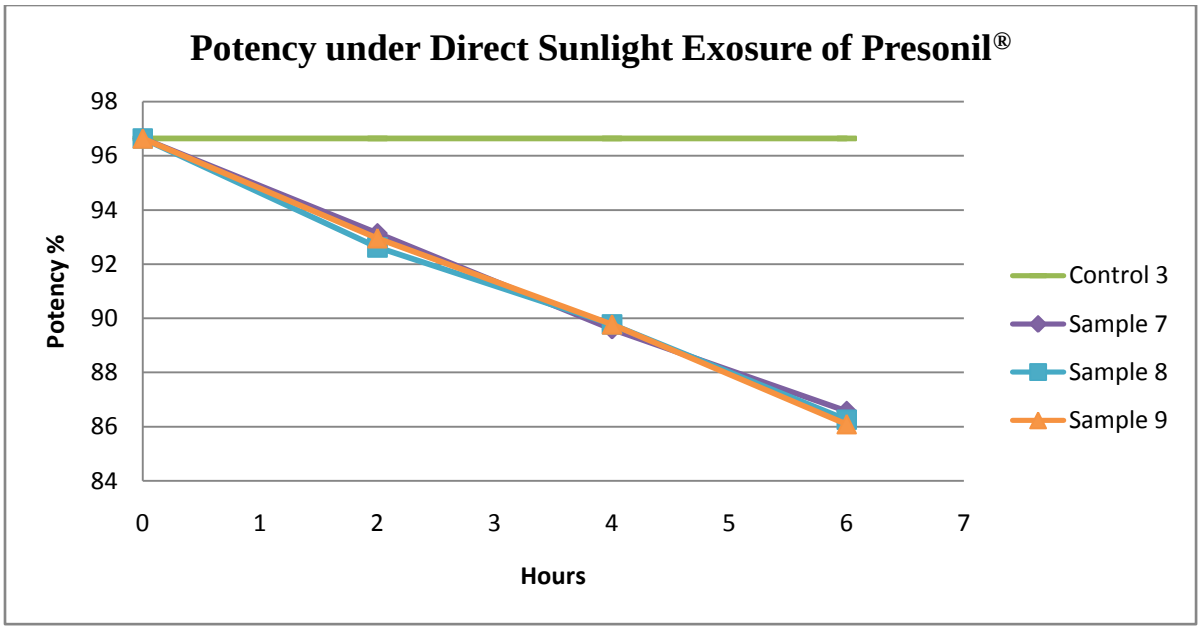

Figure 4.17: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Presonil®) for 3rd time

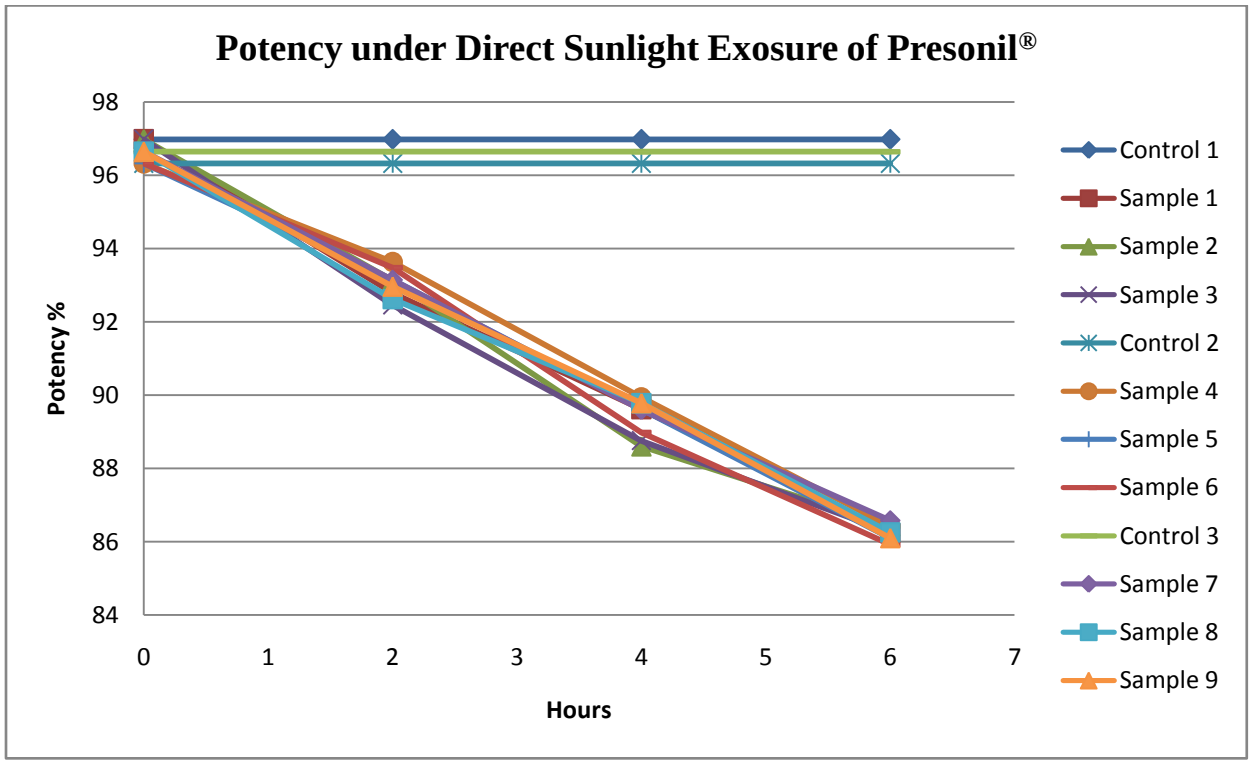

Figure 4.18: Graph showing the difference in Concentration after each 2 hour time interval for Metaprolol Tartrate (Presonil®) for all times

Chapter Five

DISCUSSIONS

In this experiment it was found that the percentage of Weight Variation of the sample tablets was within the accepted range (Weight of tablet 130 mg or less then = ±10%) with standard deviation ±0.0007%. According to U.S.P. if no more that 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit, the tablet pass the test. So, it is clear that, the light has no effect on weight of the metoprolol tartrate. Even the color of the tablets remains unchanged throughout the periodic work.

In this study it was observed that the hardness of the sample tablets was fluctuated with a very short range with standard deviation ±0.02 within the total 60 days interval works. Even the average hardness value was also very close to each others. So the hardness of metoprolol tartrate was not affected by different lighting conditions.

According to this experimental overview the thickness of the sample tablets was also very close to each other or a very insignificant fluctuation with standard deviation ±0.013 throughout periodic work. After each days interval the thickness remains constant or close to constant. So the effects of light dose not influence the thickness of metoprolol tartrate.

It was found that the concentration of metoprolol tartrate was decreased gradually in every observation of light exposure. When sample tablets (Presonil®) were kept under the electrical bulb (25 watt & 40 watt) and tested every 2 hour light exposed, it was found that the concentration of metoprolol tartrate was decreased gradually. The tablet samples which were exposed 4 hours on light had less concentration of metoprolol tartrate than the 2 hour exposed sample tablet had. Even for 6 hour exposed sample tablets had less concentration of metoprolol tartrate than 2 hour and 4 hour light exposed sample. Same results were found for direct sunlight exposed sample tablets and for the tablets which were kept on normal room light conditions. So that, in 25watt bulb, 40watt bulb, direct sunlight and normal room light the concentration of metoprolol tartrate were decreased gradually with percent deviation 10.41%, 11.24%, 6.99% and 13.25% respectively.

From this research project it can be conclude with a decision that, there should be a change in the packaging system of the metoprolol tartrate. Now in local market most of the available brand of

this drug is packaged in plastic transparent blister strip. This package should be opaque thus the light cannot pass through the package.

Chapter Six

CONCLUTION

According to this experiment it was observed that the physical parameters like weight variation, hardness, thickness have passed the USP and BP specification. But there were remarkable changes in concentration/potency of drug. The concentration of metoprolol tartrate was decreased gradually after exposure in electrical bulb light condition, direct sunlight and normal light exposure (room temperature) condition. So it indicate that the Presonil® containing metoprolol tartrate is light sensitive and the concentration/potency is decreased after light exposure. It means coating alone is not sufficient to protect the drug from light. So that package should be opaque thus light cannot pass through the package.

Chapter Seven

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