EVALUATION OF PHOTO-DEGRADATION OF ALATROL®(CETIRIZINE HYDROCHLORIDE) UNDER DIFFERENT EXTREME LIGHTING CONDITION :AN UV ANALYSIS

Submitted by:

Shirajum Monira

ID:2014-1-70-005

Department of Pharmacy

East West University, Dhaka.

Research Supervisor:

Md.Anisur Rahman

Assistant Professor

East West University,Dhaka.

"A dissertation submitted to the Department of Pharmacy,East West University,Bangladesh ,in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy"

Declaration by the Candidate

I, Shirajum Monira, hereby declare that the dissertation entitled***" Evaluation of Photo-degradation of Alatrol***® (**Cetirizine Hydrochloride**) **Under different Extreme lighting Condition: An UV Analysis"** submitted by me to the Department of Pharmacy, East West University, in the partial fulfillment of the requirement for the award of the degree Bachelor of Pharmacy, work carried out by me during the year 2017 of my research in the Department of Pharmacy, East West University, under the supervision and guidance of , Md.Anisur sRahman ,Assistant Professor, Department of Pharmacy, East West University. The thesis paper has not formed the basis for the award of any other degree/diploma/fellowship or other similar title to any candidate of any university.

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Shirajum Monira

ID: 2014-1-70-005

Department of Pharmacy

East West University, Dhaka

Certificate by the Supervisor

This is to certify that the thesis entitled***" Evaluation of Photo-degradation of Alatrol®*** (**Cetirizine Hydrochloride**) **Under different Extreme lighting Condition: An UV Analysis"** submitted to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the award of the degree Bachelor of Pharmacy, was carried out by Shirajum Monira, ID: 2014-1-70-005, during 2017 of her research in the Department of Pharmacy, East West University, under the supervision and guidance of me. The thesis has not formed the basis for the award of any other degree/diploma/fellowship or other similar title to any candidate of any university.

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Supervisor

Md.Anisur Rahman

Assistant Professor

Department of Pharmacy

East West University, Dhaka.

Endorsement by the Chairperson

This is to certify that the thesis entitled ***" Evaluation of Photo-degradation of Alatrol®*** (**Cetirizine Hydrochloride**) **Under different Extreme lighting Condition: An UV Analysis"** submitted to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the award of the degree Bachelor of Pharmacy, was carried out by Shirajum Monira, ID: 2014-1-70-005, during the period 2017 of her research in the Department of Pharmacy, East West University.

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Dr. Chowdhury Faiz Hossain

Chairperson & Professor

Department of Pharmacy

East West University, Dhaka

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DEDICATION

This research paper is dedicated to my beloved parents, who are my biggest inspirations.

ABSTRACT

This work was aimed for the determination of photo-degradation of Cetirizine Hydrochloride. The objective of this study was to determine the effect on Cetirizine Hydrochloride under various extreme lighting conditions which comprised of sunlight, incandescent bulbs of 25watt & 40watt bulb. In normal lighting condition degradation of cetirizine hydrochloride was not reported. Under different extreme lighting conditions potency ceased differently with a percent deviation of 3.67% (1.54%) , 9.34% (2.53%) and 16.58% (3.09 %) respectively for 25 watt,40 watt and direct sunlight respectively. So it can be said that the Alatrol® containing Cetirizine Hydrochloride 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: Alatrol®, Cetirizine Hydrochloride, Photolytic Degradations, Potency.

CHAPTER ONE

INTRODUCTION

1.Introduction

Cetirizine Hydrochloride is a prescription antihistamine that is classified as a category B medication. This means it is not expected to be harmful to an unborn baby. It is generally less sedating than older antihistamines and therefore may be a good option for pregnant women. It is used for the symptomatic treatment Allergic rhinitis, Perennial allergic rhinitis, Chronic idiopathic urticarial and Hay fever.

(Drugs.com,2017)

Number of drugs introduced into the market is increasing every year.These drugs may be either new entities or partial structural modification of the existing one.Very often there is a time lage from the date of introduction of a drug into the market to date of its inclusion in pharmacopoeias.

This happens because of the possible uncertainties in the continuous and wider usage of these dr ugs, reports of new toxicities (resulting in theirwithdrawal from the market), development of pati ent resistance and introduction of better drugs by competitors.Under these conditions, standards and analytical procedures for these drugs may not be available in the pharmacopoeias. It becomes necessary, therefore to develop newer analytical methods for such drugs. Analyticalmet hods play a vital role in new drug development preformulation and formulation studies,stability studies, quality control testing and in quality assurance programmes. Analytical testing of a pharmaceutical product is necessary to ensure its stability, safety and efficacy.Suchte sting needs an analytical method with reliable result adequate for intended purpose.

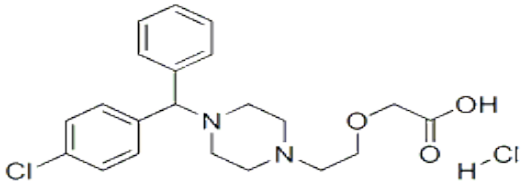

Figure : Chemical structure Cetirizine Hydrochloride

(Drugs.com,2017)

1.1 Stability:

Drug stability means the ability of the pharmaceutical dosage form to maintain the physical, chemical, therapeutic and microbial properties during the time of storage and usage by the patient. It is measured by the rate of changes that take place in the pharmaceutical dosage forms. There are some factors that affect the drug stability include temperature condition, moisture, light , microbes , packaging materials,transportation,components of drug composition and the nature of the active ingredients.

(NCBI,1979)

1.2 Photolytic Degradation:

Photolysis is the process by which light sensitive drugs or excipients molecules are chemically degraded by light,room light,or sunlight.Ultraviolet light has the more harmful radiation that affects the drugs.Shorter wavelengths are more damaging than longer wavelengths.The energy from the light radiation must be absorbed by the molecules before a photolytic reaction can occur.

Two ways in which photolysis can occur.

- ✓ One is ,the light energy must be sufficient to activate the energy .
- ✓ Another is,light energy which is absorbed by molecules is passed on to other which allows degradation to take place.

After initiating the energy ,several reactions can take place like oxidation,polymerization,or ring rearrangement.Followed by the reaction light energy may be converted to thermal energy.The photolytic reactionmay produce catalyst for the thermal reaction.

(NCBI,1979)

1.3 Histamine

The biogenic amine, histamine, is a major mediator of inflammation, anaphylaxis, and gastric acid secretion; in addition, histamine plays a role in neurotransmission. Histamine is a hydrophilic molecule consisting of an imidazole ring and an amino group connected by an ethylene group, biosynthesized from histidine by decarboxylation. The 4 histamine receptors, all GPCRs, can be differentially activated by analogs of histamine and inhibited by specific antagonists. (Goodman, Gilman and Brunton, 2008).

Histamine, is an amine that is produced as part of a local immune response to cause inflammation. It also performs several important functions in the bowel and acts as a neurotransmitter or chemical messenger that carries signals from one nerve to another.

Histamine is secreted by basophils and mast cells as part of a local immune response to the presence of invading bodies. The basophils and mast cells are found in nearby connective tissue. This histamine release causes capillaries to become more permeable to white blood cells and other proteins, which proceed to target and attack foreign bodies in the affected tissue. Aside from humans, histamine is found in virtually all animals. Histamine increases the permeability of the capillaries to white blood cells and other proteins, in order to allow them to engage foreign invaders in the affected tissues. (Mandal, 2014).

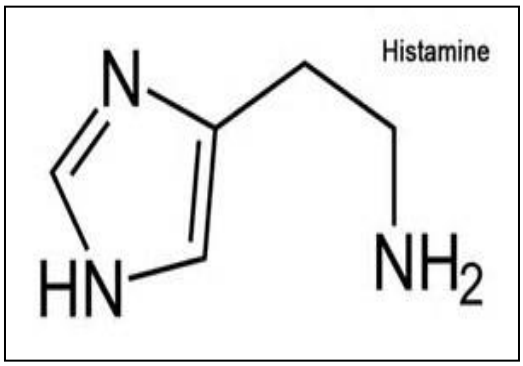

Figure 1.1: Histamine (Goodman & Gillman, 2008)

1.4 History

The history of histamine (β-aminoethylimidazole) parallels that of acetylcholine (ACh). Both were chemically synthesized before their biological significance was recognized; they were first detected as uterine stimulants in, and isolated from, extracts of ergot, where they proved to be contaminants derived from bacterial action (Dale, 1910).

Dale and Laidlaw subjected histamine to intensive pharmacological study discovering that it stimulated a host of smooth muscles and had an intense vasodepressor action. Importantly, they observed that when a sensitized animal was injected with a normally inert protein, the immediate responses closely resembled those of poisoning by histamine. These observations anticipated by many years the finding that endogenous histamine contributes to immediate hypersensitivity reactions and to responses to cellular injury. Best and colleagues (1927) isolated histamine from fresh samples of liver and lung, thereby establishing it as a natural constituent of mammalian tissues, hence the name *histamine* after the Greek word for tissue, *histos*. The presence of histamine in tissue extracts delayed the acceptance of the discovery of some peptide and protein hormones (e.g., gastrin). Technology for separating the naturally occurring substances was sufficiently advanced.

Lewis and colleagues proposed that a substance with the properties of histamine ("H substance") was liberated from the cells of the skin by injurious stimuli, including the reaction of antigen with antibody. We now know that endogenous histamine plays a role in the immediate allergic response and is an important regulator of gastric acid secretion. More recently, a role for histamine as a modulator of neurotransmitter release in the central and peripheral nervous systems has emerged. (Goodman, Gilman and Brunton, 2008).

1.5.1 Distribution

Histamine is widely distributed in animal kingdom and can be found in many venom, plant and bacteria. Almost all mammalian tissues contain histamine. In cerebrospinal fluid amount of histamine is high meanwhile in plasma and other body fluid it is low in concentration.

Concentration of histamine is particularly high in body parts like skin, bronchial mucosa, and intestinal mucosa. (Goodman, Gilman and Brunton, 2008).

1.5.2 Synthesis

Histamine is synthesized from the decarboxylation of amino acid histidine by the enzyme L-histidine decarboxylase.Usually histidine is found in almost every human tissue. Mast cells and basophils synthesize histamine and store them in secretory granules.

(Goodman, Gilman and Brunton, 2008).

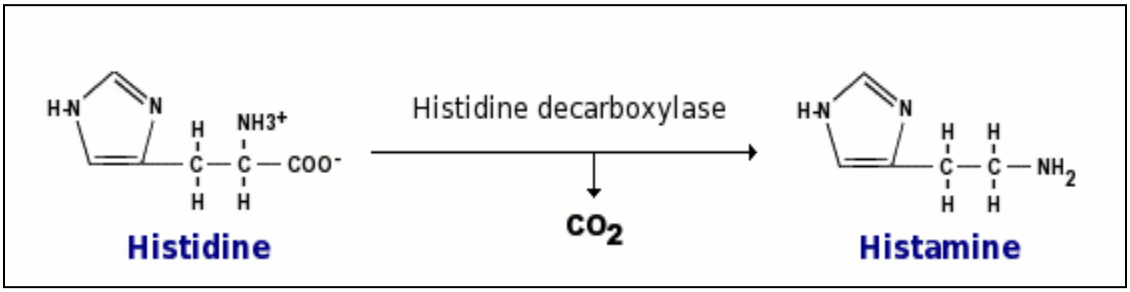

Figure 1.2: Histamine Synthesis (Anon, 2017)

1.5.3 Metabolism

Histamine is metabolized by N-methyltransferase to N-methyl histamine and imidazole acetic acid by nonspecific enzyme diamineoxidase.These metabolites have little or no activity and excreted in urine. (Goodman, Gilman and Brunton, 2008).

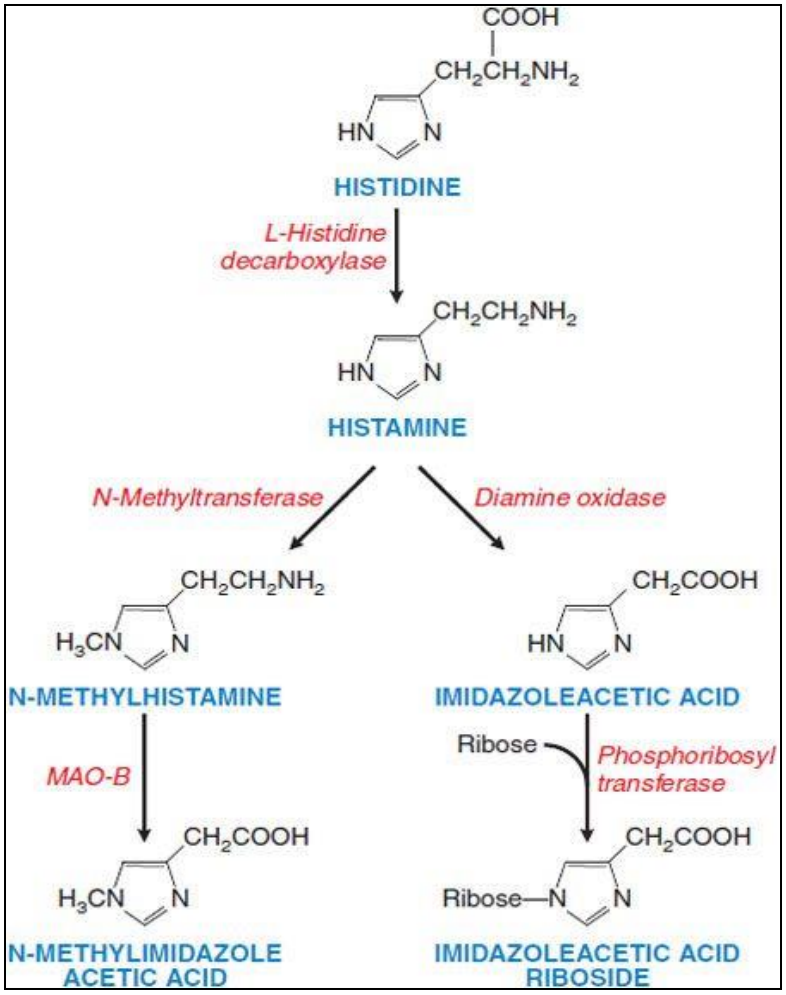

Figure 1.3: Synthesis and metabolism of histamine.(HDC - histidine decarboxylase; HMT - histamine methyltransferase; DAO - diamine oxidase; MAO - monoamine oxidase).
(Goodman, Gilman and Brunton, 2008)

1.5.4 Storage of histamine

Histamine is released by exocytosis. Histamine is mostly present in storage granules of mast cells. Tissues rich in histamine are skin, gastric and intestinal mucosa, lungs, liver and placenta. Non mast cell histamine present in brain, epidermis

(Goodman & Gilmanand Brunton,, 2008).

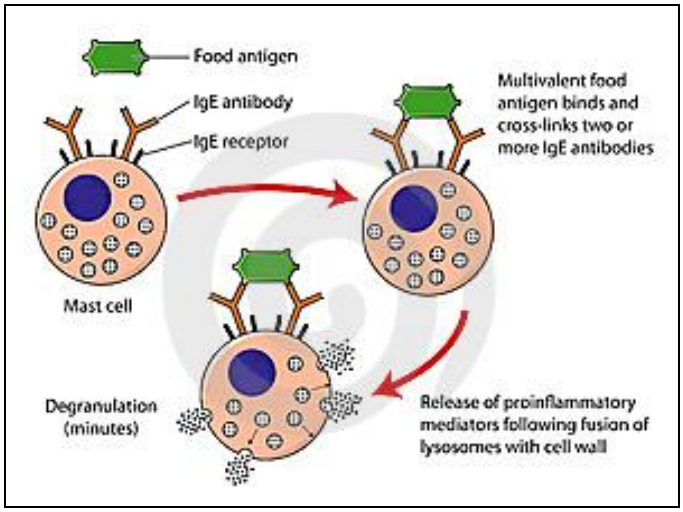

Figure 1.4: Storage and release of histamine. (Goodman & Gilmanand Brunton,, 2008)

1.6 Histamine Receptors

Four histamine receptors have been identified, all of which are G protein-coupled receptors. These different receptors are expressed on different cell types and work through different intracellular signaling mechanisms, which explains, at least at a simple level, the diverse effects of histamine in different cells and tissue.

Receptor Type	Major Tissue Locations	Major Biologic Effects
H_1	smooth muscle, endothelial cells	acute allergic responses
H_2	gastric parietal cells	secretion of gastric acid
H_3	central nervous system	modulating neurotransmission
H_4	mast cells, eosinophils, T cells, dendritic cells	regulating immune responses

Table 1.1: Types of histamine receptors. (Anon, 2017)

There are several splice variants of H_3 present in various species. Though all of the receptors are 7-transmembrane g protein coupled receptors, H_1 and H_2 are quite different from H_3 and H_4 in their activities. H_1 causes an increase in PIP2 hydrolysis, H2 stimulates gastric acid secretion, and H3 mediates feedback inhibition of histamine.

(Anon, 2017)

1.7 Functions of histamine

- **Histamine as a Neurotransmitter**: A neurotransmitter is a chemical that is passed between neurons in the nervous system. When a neuron releases molecules of a chemical neurotransmitter, it passes from what is called the "presynaptic nerve terminal" or the end of the neuron, through the "synapse" or the gap between neurons, and is finally taken up by a "receptor" area on the receiving neuron.
- **Histamine in Allergic Reactions**: There is always a small amount of histamine circulating through our body at any given time. When a foreign substance is introduced, such as the toxic chemicals of an insect bite or the oil of poison plants like poison ivy, the body releases larger amounts of histamine to the site of infection.
- **Histamine in Digestion**: Histamine plays a role in gastric secretion by helping to induce the production of acid in the stomach. In the stomach, histamine stimulates the parietal cells to produce the gastric acids required for digestion.
- **Histamine in Sleep**: The body regulates the amount of histamine in circulation and maintains a careful balance. This is most important with keeping the body awake and alert. *Antihistamines* are known to cause drowsiness and sleep.

(Ito, 2004).

- **Multiple sclerosis**: Histamine therapy for treatment of multiple sclerosis is currently being studied. The different H receptors have been known to have different effects on the treatment of this disease. The H1 and H4 receptors, in one study, have been shown to be counterproductive in the treatment of MS. The H1 and H4 receptors are thought to increase permeability in the blood-brain barrier, thus increasing infiltration of unwanted cells in the central nervous system. This can cause inflammation, and MS symptom worsening. The H2 and H3 receptors are thought to be helpful when treating MS patients.

Histamine has been shown to help with T-cell differentiation. This is important because in MS, the body's immune system attacks its own myelin sheaths on nerve cells (which causes loss of signaling function and eventual nerve degeneration). By helping T cells to differentiate, the T cells will be less likely to attack the body's own cells, and instead attack invaders.

(Jadidi-Niaragh and Mirshafiey, 2010).

- **Schizophrenia:** Metabolites of histamine are increased in the cerebrospinal fluid of people with schizophrenia, while the efficiency of H1 receptor binding sites is decreased. Many atypical antipsychotic medications have the effect of decreasing histamine production (antagonist), because its use seems to be imbalanced in people with that disorder. (Ito, 2004)
- **Protective effects**: While histamine has stimulatory effects upon neurons, it also has suppressive ones that protect against the susceptibility to convulsion, drug sensitization, denervation super sensitivity, ischemic lesions and stress. It has also been suggested that histamine controls the mechanisms by which memories and learning are forgotten.

(Alvarez, 2009)

- **Vasodilation and a fall in blood pressure:** When injected intravenously, histamine causes most blood vessels to dilate, and hence causes a fall in the blood pressure. This is a key mechanism in anaphylaxis, and is thought to be caused when histamine releases nitric oxide, endothelium-derived hyperpolarizing factors and other compounds from the endothelial cells. (Dale et al, 1910)
- **Effects on nasal mucous membrane:** Increased vascular permeability causes fluid to escape from capillaries into the tissues, which leads to the classic symptoms of an allergic reaction: a runny nose and watery eyes. Allergens can bind to IgE-loaded mast cells in the nasal cavity's mucous membranes. This can lead to three clinical responses:

  - ✓ Sneezing due to histamine-associated sensory neural stimulation.
  - ✓ Hyper-secretion from glandular tissue.

- ✓ Nasal congestion due to vascular engorgement associated with vasodilation and increased capillary permeability.

(Alvarez, 2009)

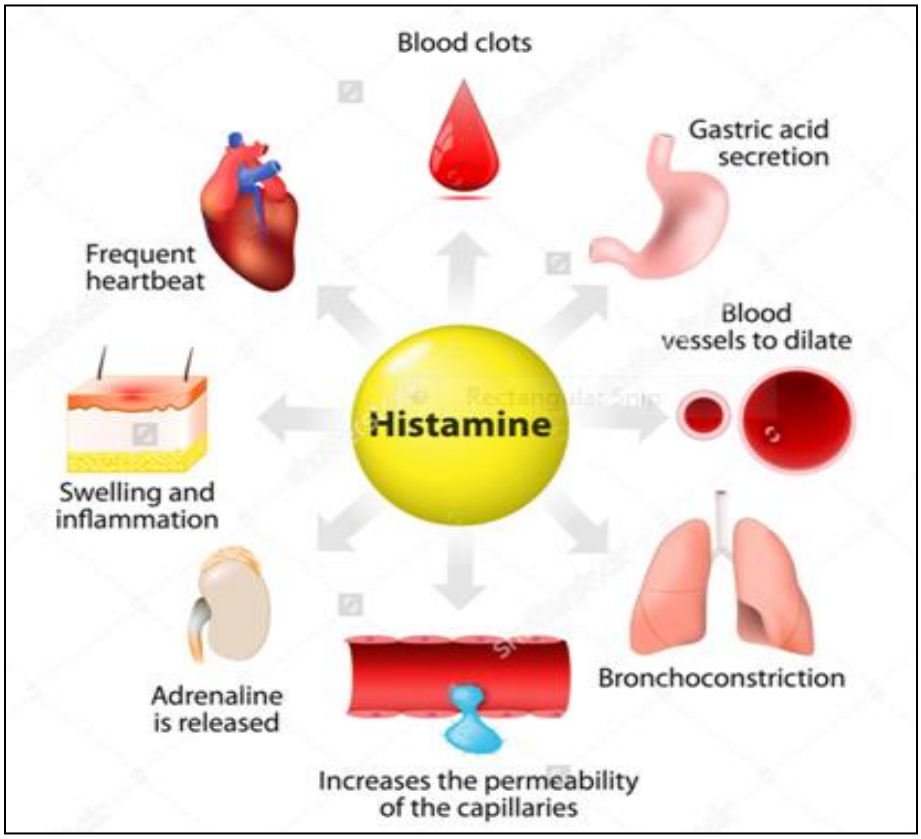

Figure 1.5 : Functions of histamine. (Alvarez, 2009).

1.8 Pharmacologic effects of histamine

Cardiovascular system

- ✓ Histamine enhances Ca2+ influx into cardiac myocytes, this leads to minor increases in heart in tropism (force of contraction) and in Chrono tropism.

Peripheral nervous endings:

- ✓ Histamine stimulates sensory nerve endings, especially those mediating pain and itching. This effect, mediated by H1 receptors, is responsible for pain and itch after an injury such as insect bite.

Bronchial smooth muscle

- ✓ Histamine causes contraction of bronchial smooth muscle, thus narrowing the airways. Asthmatic patients may be up to 1,000 times more sensitive to histamine mediated bronchoconstriction than individuals not affect by the disease.

Intestinal smooth muscle

- ✓ Histamine activation of H1 receptors produces constriction of intestinal smooth muscle, which results in increased bowel peristalsis and diarrhea.

(Kerr. M., 2016)

1.9 Mechanism of action of histamine

Histamine acts directly on the blood vessels to dilate arteries and capillaries; this action is mediated by both H 1- and H 2-receptors. Capillary dilatation may produce flushing of the face, a decrease in systemic blood pressure, and gastric gland secretion, causing an increased secretion of gastric juice of high acidity. Increased capillary permeability accompanies capillary dilatation, producing an outward passage of plasma protein and fluid into the extracellular spaces, an increase in lymph flow and protein content, and the formation of edema. In addition, histamine has a direct stimulant action on smooth muscle, producing contraction if H 1-receptors are activated, or mostly relaxation if H 2-receptors are activated. Also in humans, the stimulant

effect of histamine may cause contraction of the intestinal muscle. However, little effect is noticed on the uterus, bladder, or gallbladder. Histamine has some stimulant effect on duodenal, salivary, pancreatic, bronchial, and lacrimal glands. Histamine also can bind to H3 and H4 receptors which are involved in the CNS/PNS neurotransmitter release and immune system chemotaxis, respectively.(Ito, 2004).

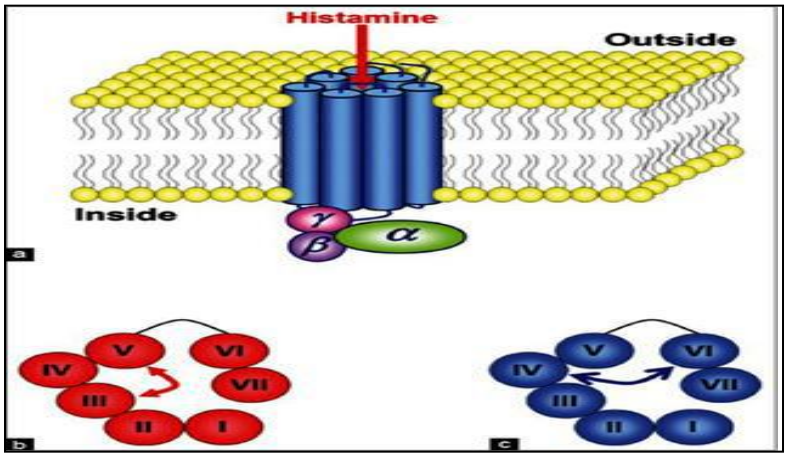

Figure 1.6: Histamine act on receptor (Ito, 2004).

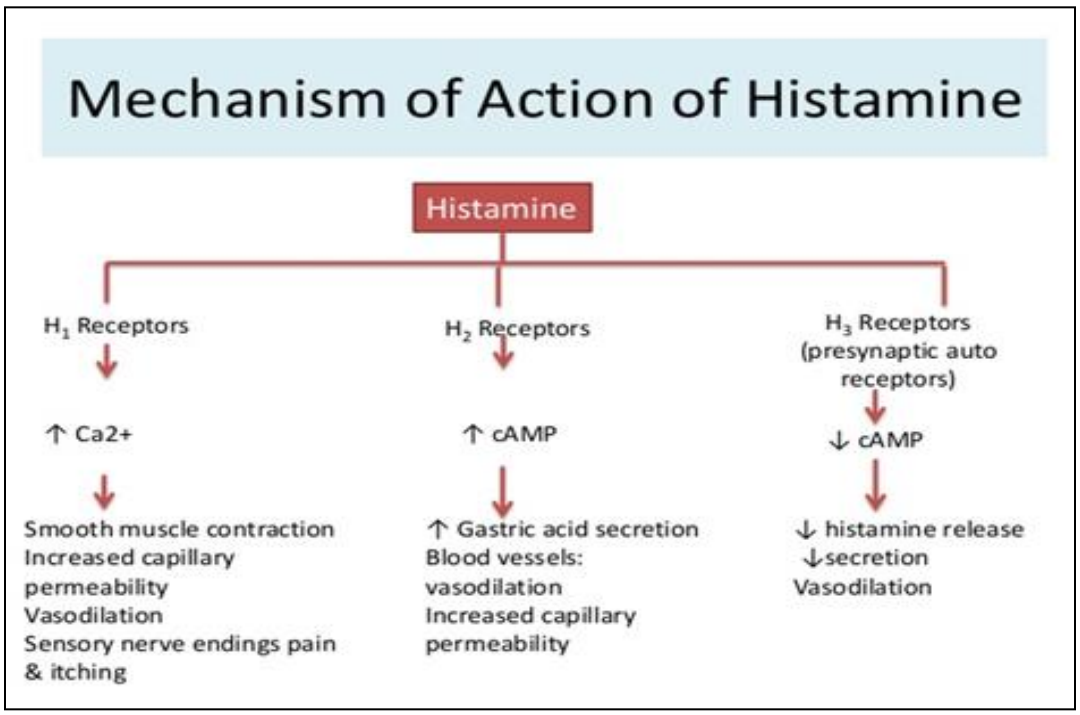

Figure 1.7: Schematic diagram of mechanism of action of histamine. (Knott, L., 2016).

1.10 Condition associated with histamine and their management

Histadelia (High histamine)

Histadelia is a disorder which is characterized by too much histamine in the blood, as opposed to histapenia in which case there is too little. It is more prominent in males.

Signs and symptoms:

- Hyperactivity
- Compulsions
- Obsessions
- Inner tensions
- Blank mind episodes
- Phobias
- Chronic depression
- Strong suicidal tendencies
- Little tolerance for pain
- Rapid metabolism
- Lean build
- Profuse sweating
- Seasonal allergies
- Frequent cold

Treatment and prevention :

The treatment of Histadelia requires great patience because six to ten weeks are often needed before the beginning of significant improvement. The treatment usually takes twelve months to complete.

Histamine Toxicity

Histamine toxicity, also known as scombroid poisoning, is a form of food poisoning. Histamine toxicity is sometimes confused with an allergic reaction to fish. As Some kinds of fish contain naturally high levels of the chemical histidine. This chemical can be converted to histamine by bacteria. In an allergic reaction, mast cells release

histamine which triggers allergy symptoms. So, if a person eats fish that has a high level of histamine, the response may resemble an allergic reaction to that food. Certain kinds of fish are more prone to cause histamine toxicity. These include tuna, mackerel, mahi-mahi, anchovy, herring, bluefish, amberjack and marlin. The most common cause of acute histamine toxicity is the result of inadequate refrigeration or spoiled fish. This causes an overgrowth of bacteria which converts histidine to high levels of histamine. Individuals who have unusually low levels of the enzyme diamine oxidase may be more susceptible to histamine toxicity.

Symptoms :

Symptoms of histamine toxicity (Scombroid poisoning) typically begin within 5 to 30 minutes after eating spoiled fish, although there are cases when symptoms are delayed for as long as two hours.

It may include:

- Flushing of the face and body
- Burning in the mouth
- Faintness
- Blurring vision
- Abdominal cramps
- Diarrhea
- Wheezing or other breathing problems
- Nausea
- Swelling of the face and tongue

Symptoms typically last a few hours or a day. In rare cases, symptoms can persist for a few days.

Treatment &Management :

Treatment for histamine toxicity depends on the severity of the symptoms. In mild cases, symptoms tend to go away in a short period of time without medication. Sometimes antihistamines can help. In severe cases, a trip to a hospital emergency room is necessary for care with IV fluids, oxygen or other medications and treatments.

1.11 Histamine intolerance

The actual mechanism of histamine intolerance (HIT) is under investigation but is thought to be related to a buildup of histamine. In a healthy individual, histamine is broken down on a regular basis by two enzymes: DAO and HNMT.

The mechanism of HIT is proposed to be a genetic or acquired impairment in one of these two enzymes. DAO is produced in the intestine, so if intestinal function is compromised there may not be enough DAO to degrade histamine normally. Decreased DAO (enzyme) production may be why HIT seems more common in persons with gastrointestinal disorders such as inflammatory bowel disease, IBS, celiac and SIBO. DAO activity can also be inhibited by certain medications.

Symptoms :

- Diarrhea
- Headache
- Flushing
- Rash/Urticarial (hives)/eczema
- Arrhythmia (irregular heart beat)
- Low blood pressure-due to vasodilation caused by the histamine
- Wheezing
- Runny nose
- Watery eyes
- Angioedema-swelling of face/hands/lips
- Heartburn-due to increased acid production
- Itching- typically of the skin

Treatment &Management :

Diet: A low histamine diet is the treatment of choice (food lists are below).This can be challenging if someone is already on a restricted diet such as a gluten-free or low FODMAP diet and should be done under the care of a health care practitioner so that proper nutritional intake is maintained.

Sleep**:** 7-8 hours a night helps everything.

Support**:** Health issues and dietary restrictions are stressful and challenging. Seek out support from family, community, faith organizations, online support groups, local support groups. Avoid those who provide negative interaction. Negative interactions delay healing.

Exercise**:** Any exercise is helpful. Aim for 30-60 minutes daily.

Relaxation**:** The benefits of relaxation techniques cannot be emphasized enough. Breathing exercises or progressive muscle relaxation are easy, portable and free. Yoga and meditation are great as well. Relaxation for you may also be reading, enjoying time with friends or playing music.

Medications**:** Antihistamines, topical steroids/creams, oral steroids, topical homeopathic or plant-based creams and lotions for rashes.

Supplements**:** There is little to no data on these, but the following are sometimes used. Vit C, B6, Zn, Cu, Magnesium, Mangosteen, Quercetin, DAO promoters and supplements, topical creams. Please use any supplement under the guidance of a practitioner. Supplements can have toxic side effects.

(Burkhart and Burkhart, 2014)

1.12 Antihistamine

It is a histamine antagonist that blocks different histaminic receptors. It is used for ailing allergy, gastric acid secretion and many other symptoms. Antihistamines are medicines often used to relieve symptoms of allergies, such as hay fever, hives, conjunctivitis and reactions to insect bite or stings. They're also sometimes used to motion sickness, and as a short-term treatment for insomnia. Antihistamines are drugs used to treat the symptoms of allgies and allergic rhinitis by blocking the action of histamine, a chemical released by the immune system in allergic reactions. Antihistamines are used to treat the sneezing, runny nose, and itchy eyes of allergies and allergic rhinitis, as well as allergic skin reaction and anaphylactic reactions to insect stings and certain foods. (Goodman, Gilman and Brunton, 2008)

1.13 Antihistamine classification: Antihistamines can be classified into 4 groups-

- ✓ H1 receptor antagonist
- ✓ H2 receptor antagonist
- ✓ H3 receptor antagonist
- ✓ H4 receptor antagonist

H1antihistamine: H_1 antihistamines act as inverse agonists that combine with and stabilize the inactive conformation of the H_1receptor, shifting the equilibrium toward the inactive state. H_1 antihistamines down-regulate allergic inflammation through the H_1 receptor, either directly or indirectly through nuclear factor-κB, a ubiquitous transcription factor, through which they down-regulate antigen presentation, expression of proinflammatory cytokines and cell adhesion molecules, and chemotaxis. In addition, through their effects on calcium ion channel activity, H_1 antihistamines decrease mediator release; however, this effect is only seen at high H_1-antihistamine concentrations.

- ✓ First generation H1 receptor antagonist
  - Chlorpheniramine
  - Diphenhydramine
  - Promethazine

- Hydroxyzine
- Brompheniramine

✓ Second generation H1 receptor antagonist

- Loratidine
- Cetirizine
- Rupatadine
- Terfenadine
- Emedastine
- Epinastine
- Loratadine
- Astemizol

✓ Third generation H1 receptor antagonist

- Desloratidine
- Levocetirizine
- Fexofenadine (Goodman, Gilman and Brunton, 2008)

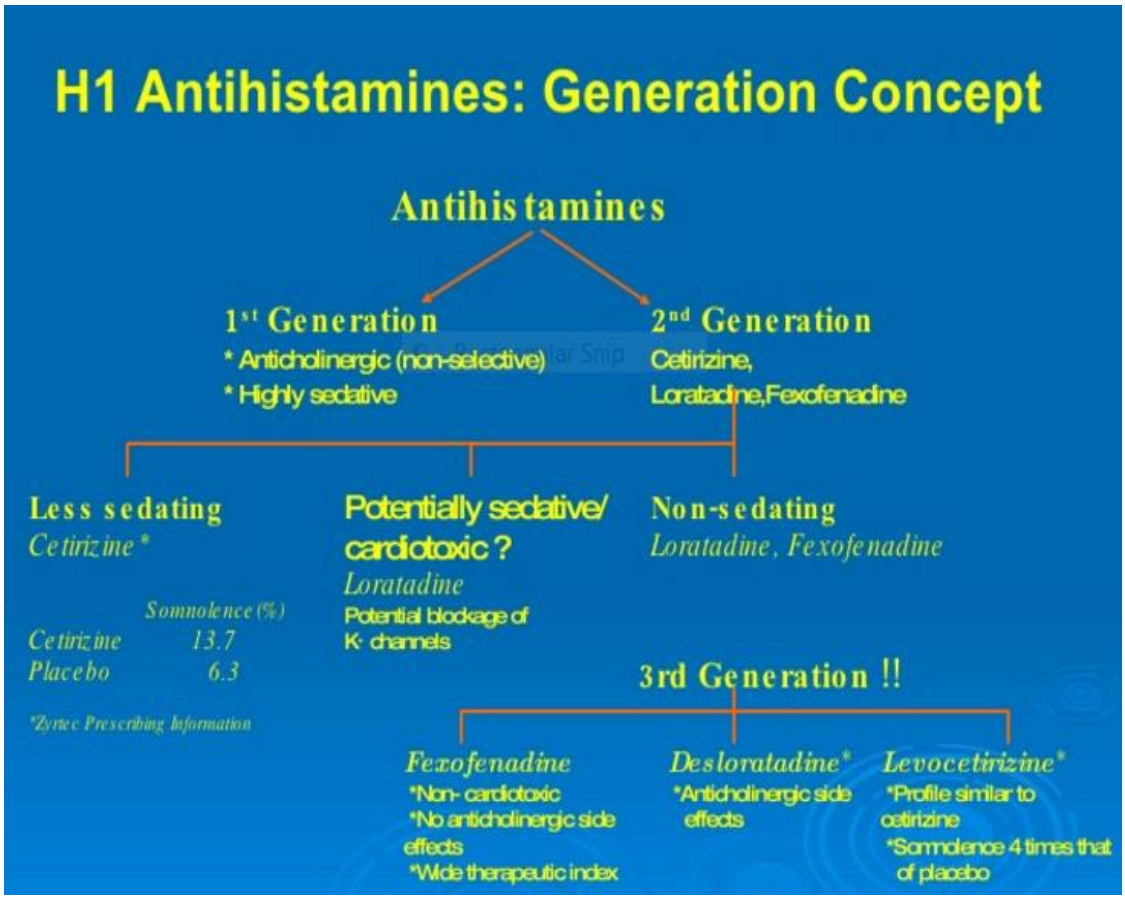

Figure 1.8: Classification of antihistamine.(Burkhart and Burkhart, 2014)

H2 anti-histamines:

H2-antihistamines, occur as inverse agonists and neutral antagonists. They act on H2 histamine receptors found mainly in the parietal cells of the gastric mucosa, which are part of the endogenous signaling pathway for gastric acid secretion. Normally, histamine acts on H2 to stimulate acid secretion; drugs that inhibit H2 signaling thus reduce the secretion of gastric acid.

H2-antihistamines are among first-line therapy to treat gastrointestinal conditions including peptic ulcers and gastro esophageal reflux disease. Some formulations are available over the counter. Most side effects are due to cross-reactivity with unintended receptors. Cimetidine (e.g) is notorious for antagonizing androgenic testosterone.

Examples:

- Cimetidine
- Famotidine
- Lafutidine
- Nizatidine
- Ranitidine
- Roxatidine
- Tiotidine

H3 anti-histamine: It is a classification of drugs used to inhibit the action of histamine at the H3 receptor. H3 receptors are primarily found in the brain and are inhibitory auto receptors located on histaminergic nerve terminals, which modulate the release of histamine. Histamine release in the brain triggers secondary release of excitatory neurotransmitters such as glutamate and acetylcholine via stimulation of H1 receptors in the cerebral cortex. Consequently, unlike the H1-antihistamines which are sedating, H3-antihistamines have stimulant and cognition-modulating effects.

Examples:

- Clobenpropit,
- ABT-239
- Ciproxifan,
- Conessine
- A-349,821
- Thioperamide (Simon and Simons, 2008)

1.14 Pharmacological action of antihistamine

Smooth muscle: It blocks the constriction of smooth muscles especially of the respiratory smooth muscle.It inhibits the vasoconstrictor effect of histamine.

Capillary permeability:H1 antagonists strongly block the capillary permeability and formation of wheal and edema caused by histamine.

Anaphylaxis and Allergy: In case of hypersensitivity autacoids like histamine is released. In human H1 antagonists effectively suppress edema and itching. Hypotension is less well antagonized. They are well used in anaphylaxis and allergy.

Central nervous system: They depress the central nervous system and bring out drowsiness. This is more evident with the first generation of H1 antagonists. So why the second generation of antihistamine emerged.

(Goodman, Gilman and Brunton, 2008)

1.15 Therapeutic Uses osf antihistamine

- ✓ Allergic rhinitis and common cold
- ✓ Allergic dermatitis
- ✓ urticarial
- ✓ Wasp bite
- ✓ Mild blood transfusion reaction
- ✓ Allergic conjunctivitis
- ✓ Motion sickness
- ✓ Morning sickness
- ✓ Vertigo
- ✓ Chronic Urticaria

- ✓ Drug indeced parkinsonism

(Schöll et al, 2009)

1.16 Brand names of Antihistamines

Some common antihistamines include:

- Allegra(fexofenadine)
- Astelin and Astepro (azelastine) nasal sprays
- Atarax and Vistaril (hydroxyzine)
- Benadryl (diphenhydramine)
- Chlor – Trimeton (chlorpheniramine)
- Clarinex (Desloratadine)
- Claritin and Alavert (loratadine)
- Cyproheptadine
- Dimetane (brompheniramine)
- Emadine (emedastine)eye drops
- Livostin (levocabastine) eye drops
- Optivar (azelastine)eaye drops
- Palgic (carbinoxamine)
- Xyzal (levocetirizine)
- Zyrtec (cetirizine)

(Simon and Simons, 2008)

1.17 Mode of action of antihistamine

Antihistamines are drugs that compete with histamines for their receptor sites known as H1 and H2 receptor sites. These receptor are found in tissue cells, with H1 receptors located throughout the body and H2 receptor sites found in the gastricmucosa.The majority of available antihistamines are H1 antagonists.H1 antagonist are believed to act not by opposing but preventing the physiologic action of histamine. (Goodman, Gilman and Brunton, 2009).

1.18 Antihistamine Side Effects

Common side effects of antihistamines include:

- Drowsiness or sleepiness
- Dizziness
- Dry mouth, nose, or throat
- Increased appetite and weight gain
- Upset stomach
- Thickening of mucus
- Changes in vision
- Feeling nervous, excited, or irritable

1.19 Precautions and Warnings

Children with certain medical conditions may not be able to take antihistamines. The following are absolute or relative contraindications to use of antihistamines. The significance of the contraindication will vary with the drug and dose.

- hyperthyroidism
- high blood pressure
- heart disease
- ulcers or other stomach problems
- stomach or intestinal blockage
- liver disease
- kidney disease
- bladder obstruction
- diabetes (del Cuvillo, 2008)

1.20 Absorption, metabolism and elimination of antihistamine

Absorption:

Most antihistamines show good absorption when administered via the oral route, as is demonstrated by the fact that effective plasma concentrations are reached within three hours after dosing. The good lip solubility of these molecules allows them to cross the cell membranes with ease, thereby facilitating their bioavailability.

Metabolism:

Most antihistamines are metabolized and detoxified within the liver by the group of enzymes belonging to the P450 cytochrome system. Only acrivastine, cetirizine, levocetirizine, desloratidine and fexofenadine avoid this metabolic passage through the liver. Cetirizine and levocetirizine are eliminated in urine, mainly in unaltered form, while fexofenadine is eliminate in stools.

Elimination:

Most H1 antihistamines are eliminated through the kidneys after metabolism to a lesser or greater extent. Biliary excretion is also possible, and is more extensively applicable to fexofenadine and rupatadine – the former without metabolism and the latter after extensive metabolism. In special cases in which liver or kidney function is impaired, dose adjustment may prove necessary – as in elderly patients or subjects with kidney or liver failure.

(delCuvillo, 2008)

1.21 Adverse effect of antihistamine

Cardiac toxicity: In the 1980s two H1 antagonists astemizole and terfenadine prolonged QT interval and caused polymorphic ventricular arrhythmia. Albeit cardiac toxicity is not a class effect and does not occur through H1 receptor some 1st generation generation antihistamines may be associated with prolonged QT and cardiac arrhythmia when these drugs are taken in overdoses. The 2nd generation antihistamines has not been reported with any of the above problems.

Infants: Using 1st generation antihistamines are potentially dangerous in case of infants. Albeit reports of fatal intoxication are not common and accidental homicides of infants have been reported. Sometimes over the counter cold medications can be fetal for children's and can lead them to death due to toxicities

Geriatrics: The elderly patients are too much prone to the adverse effect of 1st generation antihistamins.25% of patients older than 65 years have some cognitive impairment and histamine neurotransmission is disrupted in individuals with neurogenerativediseases.Administration of 1st generation antihistamines to this population are associated with increased of inattention,disorganizedspeech,altered consciousness and impaired function.

Pregnancy: The 1st generation antihistamines are categorized as B according to FDA.They are prescribed in pregnancy due to no evidence of teratogenicity.The main concern with these antihistamines is when they are used in large doses just before parturition they cause contraction

due to oxytocin like effect.Moreover if it is taken in large dose just before delivery the neonate may exhibit withdrawal symptom including tremulousness and irritability.

(Mayoclinic.org, 2017)

1.22 Missed Dose

If you miss a dose of this medicine, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double doses.

(Mayoclinic.org,2017)

1.23 Storage

Keep out of the reach of children. Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Keep away from freezing.

(Mayoclinic.org,2017)

1.24 Proper Use

For patients taking this medicine by mouth:

- Antihistamines can be taken with food or a glass of water or milk to lessen stomach irritation if necessary.
- If it is taken in extended-release tablet form of this medicine, the tablets should be swallowed whole.
- For patients taking dimenhydrinate or diphenhydramine for motion sickness:
- The medicine should be taken at least 30 minutes or, even better, 1 to 2 hours before you begin to travel.

For patients using the suppository form of this medicine:

- To insert suppository: Removalof the foil wrapper and then moisten of the suppository with cold water is required. Patient should lie down on his side and use his finger to push the suppository well up into the rectum. If the suppository is too soft to insert, the suppository should be chilled in the refrigerator for 30 minutes or run cold water over it before removing the foil wrapper.

For patients using the injection form of this medicine:

- If injection is given, it should be ensured to understand exactly how to give it.
- Antihistamines are used to relieve or prevent the symptoms of your medical problem. They should be taken only as directed.

(Mayoclinic.org,2017)

1.25 Dosing

The dose medicines in this class will be different for different patients.The doctor's order or the directions on the label should be followed.Thefollowing information includes only the average doses of these medicines

The amount of medicine that is taken depends on the strength of the medicine. Also, the number of doses taken on each day, the time allowed between doses, and the length of time you take the medicine depend on the medical problem for which you are using the medicine.

(Mayoclinic.org,2017)

CHAPTER TWO

LITERATURE REVIEW

2.1. Literature Review

Photosensitive drugs degrade under the exposure of normal or extreme light condition. In Bangladesh, there are different cetirizine Hydrochloride drugs available and they are marketed as different brands. From available brands one brand that is **"Alatrol®"** was chosen for determining its photosensitivity. These products are available in blister packaging system in most case in the market of Bangladesh. To find whether this drug is photosensitive or not, we operate a research program to establish a data about photolytic degradation of cetirizine Hydrochloride and for this-

A **"literature review "** was done to evaluate the previous works that were done on the cetirizine Hydrocloride. It was observed that the studies done on the Cetirizine hydrochloride were not similar to this research project.But those studies helped to find the information's that help in the research work and also helped to compare this research work with other research projects. jeast of some studies are given below :

In the year of 1991 ,a study on comparison of Central and Peripheral Effects of Cetirizine and Loratadine was done.In which a double-blind, crossover, randomized clinical pharmacological study performed on 10 healthy volunteers .The result showed that Neither drug affected subjective evaluation of central effects and cetirizine was completely devoid of electro-encephalographic (EEG) changes, whereas 10 and 40 mg loratadine induced only slight and limited EEG changes. (Pechadre et al ,1991)

A Prospective research was done on the elimination of Cetirizine in six patients with primary biliary cirrhosis.The duration of action of cetirizine was prolonged,as evidenced by significant suppression of the histamine-induced wheal and flare for 48 and 72 hours, respectively after a single dose.The result of this study concluded that Cetirizine elimination was impaired in patients with hepatic dysfunction.

(Estelle et al,1993)

A research was done for the enantioselective synthesis of cetirizine hydrochloride in which highly stereospecific chiral oxazaborolidine reduction of 4-chlorobenzene was used to establish

benzhydryl stereo center.Finally the result concluded that ,Chromium tricarbonyl also served as a stereocenter to allow stereospecific displacement of hydroxyl by amino at the benzylic stereocenter.

(Corey et al,1996)

A study was done which objective was to investigate Molecular Properties and Pharmacokinetic Behavior of Cetirizine.The ionization and lipophilicity behavior of the antihistamine (H1-receptor antagonist) Cetrizine was investigated in this study.The suggestion is offered that Cetirizine and analogous zwitterions,whose physicochemical and pharmacochemical properties differ from those of first Second-generation drugs in this class,could be considered as third-generation antihistamines.

(Pagliara et al,1998)

One year later, another research work was done which objective was to determine the efficacy and safety of cetirizine and loratadine were compared in a prospective, randomized, double-blind, longitudinal, parallel-group study of 80 children, 2 to 6 years of age, with perennial allergic rhinitis caused by house dust mites or plant pollens.It was concluded that Cetirizine and loratadine provided effective, well-tolerated relief of the symptoms of perennial allergic rhinitis in small children. Cetirizine was more effective than loratadine in inhibiting the wheal response to histamine challenge and afforded greater reductions in most individual symptoms assessed daily by the parent.

(Monge et all,1999)

A case study of Cetrizine-induced cholestasis in a 28-year-old man with no previous hepatobiliary disease after a 2-year period of taking cetirizine on a daily basis was done.The treatment of this patient included the use of ursodeoxycholic acid,as well as hydroxyzine,for symptomatic relief of pruritus.It was concluded that Cetrizine should be considered as a potential cause of drug-induced cholestasis.

(Fong et al,2000)

The aim of this study was to compare the activity of cetirizine 10 mg with that of mizolastine 10 mg *vs* placebo at 24 h after intake in healthy volunteers. This was a double-blind, randomized, placebo controlled, three-way cross-over study. This study shows that cetirizine (10 mg) suppresses skin reactivity to histamine more effectively than mizolastine (10 mg) 24 h after intake in healthy volunteers.

(Purohit et al,2002)

A study narrated a HPLC method for quantative determination of cetirizine hydrochloride using hyoscine butyl bromide. The chromatographic system and an UV detection was performed at 25 nm. The result showed that the method was rapid,sensitive and reliable and may be used in the quantitative determination of cetirizine hydrochloride.

(Arayne et al,2005)

In the same year, a dissolution test developed for a combination dose of cetirizine HCL for immediate release and pseudophedrine hydrochloride for extended release. For dissolution a USP apparatus 2 with a rotation of 50 rpm was used and deaerated water was used as dissolution medium. Reversed phase HPLC was used for quantification.Study concluded that the culmination was cetirizine HCl dissolved rapidly and pseudophedrine HCl was independent of dissolution conditions.

(Likar et al,2005)

The aim of this study was to explore the effects of 2 second-generation antihistamines, cetirizine and loratadine,on granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-8 (IL-8) secretions in human airway epithelial cells.It was an enzyme-linked immunosorbant assay.The observations indicate that these 2 second-generation antihistamines inhibit the release

of GM-CSF and IL-8 beyond their antagonistic histamine H1 receptor activity and may thus exert clinically relevant anti-inflammatory effects in inflammatory airway disorders.

(Cheng et al ,2006)

A research was accomplished to see the effect of cetirizine HCl in the expression of neurokinin 1(NK-1R) receptor and induced cytokine production by substance P in dermal fibrobalsts.Expression of NK1R receptor by cetirizine was detected by flow cytometry and western blotting.Cytokine and interferon gamma production was measured by ELISA. The results suggest that cetirizine may be used in the treatment of substance P induced skin inflammation.

(Liu et al,2008)

A research was accomplished to evaluate the pharmacokinetic parameters and bioavailability of a selective histamine (H1)-receptor antagonist, cetirizine hydrochloride (CTZ), following administration of a single oral dose of the drug. The properties of a test compound were compared with those of a reference product in a randomized cross-over study in 12 volunteers.It was, therefore, concluded that the two products were bioequivalent and could be used interchangeably.

(Derakhshandeh et al ,2009)

A study describes the clinical efficacy of cetirizine and levocetirizine has been studied sequentially in individual patients. Fifty chronic idiopathic urticaria patients received 10 mg of levocetirizine daily for 6 weeks. A total of 30 patients completed the study period of 6 weeks each of cetirizine and levocetirizine sequentially. In result , it was declared that the clinical efficacy of cetirizine and levocetirizine was comparable with a marginal advantage of better antipruritic effect with levocetirizine, probably at the cost of increased sedation.

(Garg et al,2009)

In the same year ,another study was done to examine whether patients who did not tolerate cetirizine due to sedation were able to tolerate levocetirizine.A retrospective chart review was completed for 471 patients seen who were prescribed levocetirizine between January 1, 2008

and June 30, 2008. When necessary, telephoned these patients for clarification. Finally it was found that out Of 50 patients, 38 were able to tolerate levocetirizine (76%).

(Tzanetos et al ,2009)

The objective of this study was Cetirizine-induced anaphylaxis which was a rare adverse drug reaction.In this study, a 30-year-old female patient was prescribed oral cetirizine 10 mg at night for the treatment of chronic idiopathic urticaria. Within 15 min of oral ingestion of cetirizine 10 mg, the patient experienced severe pruritis and urticarial eruption all over the body.In conclusion,it was confirmed that even though the safety of cetirizine has been widely established, there is an extremely rare chance of it causing anaphylaxis. Cetirizine may be used in the treatment of anaphylaxis.

(Afonso et al ,2009)

In this study, An investigation was done to determine the effect of cetirizine, on experimental viral myocarditis induced by encephalomyocarditis (EMC) virus. Cetirizine was administered orally at a dose of 1 or 10 mg/kg per day for the survival study, and 1 mg/kg for the histologic and gene expression studies, beginning on the day of viral inoculation. Finally it was suggested that cetirizine exerts its beneficial effects on viral myocarditis by suppressing expression of pro-inflammatory cytokines, genes related to cardiac remodeling in the hearts of mice.

(Akira et al , 2010)

This study was done to see the reaction between active drug substance and excipients in drug formulation process.Cetirizine was chosen as the active drug substance to evaluate the reaction with a substance having carboxylic acid moiety. The study found that the carboxylic acid cetirizine readily reacts with sorbitol and glycerol to form monoesters at a temperature as low as 40 °C.

(Yu et al,2010)

The intent of this study is to demonstrate the efficacy and safety of bilastine (20mg) compared to cetirizine hydrochloride(10mg) and placebo in patients with perennial allergic rhinitis (PAR). In this study, patients with symptomatic perennial allergic rhinitis received bilastine(20 mg),

cetirizine (10 mg), or placebo once daily for 4 weeks.The study concluded that ,No significant differences in efficacy outcomes were found between active treatments and placebo.

(Mullol et al ,2011)

A research was accomplished for the simultaneous determination of ambroxyl hydrochloride,cetirizine hydrochloride,methyl pareben,propyl paraben in liquid pharmaceutical solution.The study using reversed phase ultra-performance liquid chromatography.This method helped to separate all the compounds.Stability indicating capability was established by forced degradation experiments and separation of known and unknown degradation products.

(Trived et al,2011)

A prospective research was done to design for the evaluation of mouth dissolving tablets of cetirizine hydrochloride by using superdisintegrants.The drug and excipients were characterized using Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared (FTIR) techniques.Finally it was concluded that the tested tablets did not show any changes with respect to taste,disintegration and dissolution profiles.In conclusion ,the results of this work suggest the inclusion of Clove oil which reduces the processing charges and use of coslier taste masking agent.

(priya et al,2012)

A clinical trial was done to evaluate the efficacy of cetirizine HCl in the treatment of allergic pruritus on cats.Cetirizine HCl was administered orally at a dose of 5mg to 32 cats in every 24 hrs with allergic disease.Upon cetirizine administration no significant association between age,disease severity or cutaneous reaction pattern was found.From this study ,No adverse side effect was also reported.

(Griffin et al,2012)

A prospective study was performed to summarize the amount of data collected over 25 years of clinical use of cetirizine and compare this with data available for other SGAHs in the management of patients with allergic rhinitis (AR). By using the Pubmed database, and relevant papers published in English were selected for detailed review. The result of this study showed

that cetirizine is a commonly employed active comparator drug in AR, it is tempting to suggest that cetirizine may be a suitable benchmark in the development of novel pharmacotherapies for AR.

(Zhang et al, 2013)

This research was done for the determination of cetirizine and montelukast analysis in combined tablet dosage form.A high performance thin layer chromatography was used for this.Ethyl acetate,methanol and ammonia solution were used as mobile phase.UV detection was performed at 230nm.It was observed that the HPTLC method could be used for efficient analysis and monitoring of cetirizine and montlukast in combined tablet dosage form.

(Haghighi et al,2013)

In the same year,An enantioselective method was developed to analyze hydroxyzine and cetirizine. A dispersive liquid–liquid microextraction (DLLME) procedure was optimized to extract these analytes from liquid culture medium. The study shown to be stereoselective with predominant formation of (S)-cetirizine.

(Fortes et al,2013)

A study was done to prepare the fast disintegrating tablet of Cetirizine Hydrochloride for allergic and respiratory disorders.The tablets were evaluated for hardness, friability, weight variation, wetting time, disintegration time and uniformity of content. Finally it was found that fast disintegrating tablets of Cetirizine Hydrochloride were formulated successfully with desired characteristics which disintegrated rapidly, provide rapid onset of action, and enhance the patient convenience and compliance.

(Sharma et al,2014)

A research was done to improve encapsulation efficiency of cetirizine HCL microspheres as a model for water soluble drugs and control the release using response surface methodology.Different excipients were used and all available formulations were evaluated and morphologically characterized by scanning electron microscopy(SEM).The result showed that

the optimized cetirizine HCL microspheres exhibited a slow and controlled release over 12 hour and a improved bioavailability compared to the marketed tablets.

(El-Say et al,2014)

A study was accomplished of 27-year-old female patient with isolated angioedema on both the eye due to the administration of single dose of cetirizine(10 mg) for hemorroids with pruritus. In this study, it caused isolated bilateral angioedema of eye. Hence, possibility of cetirizine causing angioedema may be considered in the list of ADR .

(Majhee et al , 2015)

In the year of 2016,four hepatotoxicity cases resulting from cetirizine use and review of the literature was done to evaluate Cetirizine induced hepatotoxicity.It was conclude that patients with high levels of liver enzymes of unknown origin,cetirizine as well as other hepatotoxic drugs should be reconsidered.

(Coskun et al,2016)

A study was designed to assess the effect of a second generation antihistaminic (H-1 blocker) namely Cetirizine on the visual processing speed for low and high intensity stimuli in healthy human volunteers at one and three hour after Cetirizine consumption. The visual processing speed was tested on Flicker –fusion apparatus. The result showed that, Single dose 10 oral Cetirizine does not significantly alter the visual processing speed for low or high intensity stimuli at one or three hour after administration.

(Gawit et al,2017)

CHAPTER THREE

MATERIALS AND METHODS

3.1 Materials

3.1.1 Sample Collection

For the purpose of experimentation to observe the photolytic degradation of cetirizine Hydrochloride as well as to assess the coating efficiency, 500 tablets of Alatrol® (Cetrizine Hydrochloride 10mg) were collected from the local drug store in Dhaka as a sample. All the tablets were from the same batch (6M03144). Among them 200 tablets were kept light protected for control tests and the remaining 300 tablets were subjected to various lighting conditions over certain periods of time for experiments to determine their potency.

3.1.2 Sample

Table 3.1: Samples Used in the Experiment Including Source (Square, 2012)

Sample name	Source(Supplier Name)	Batch no
Alatrol 10mg tablets	Square Pharma Ltd	6M03144

Figure 3.1: Alatrol® 10mg 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.	**Equipment**	**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

3.1.5 Images of Instruments

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

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

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 H2SO4)

1. Lab solvent (H2SO4), 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 Cetirizine Hydrochloride.

1. Standards of Cetirizine Hydrochloride was collected from a pharmaceutical company. The potency of standard compounds was 99.1%.
2. The specific λ_{max} for Cetirizine Hydrochloride, at which the absorbance would be measured, was determined to be 230 nm from the UV spectrometer by using the standard. Five serial concentrations of the standards of Cetirizine Hydrochloride were prepared for the purpose of creating a standard curve.

Preparation of the stock solution for Cetirizine Hydrochloride using the standard:

10 mg of the standard compound, that is Cetirizine Hydrochloride was weighed and dissolved in 250ml of 0.1N H2SO4 (which is the solvent) in a 250ml volumetric flask.

Thus the concentration was calculated to be:-

Concentration of 1st dilution = amount of substance added / volume = (10 / 250) mg/ml = 0.04 mg/ml

Preparation of five serial concentrations of solution for Cetirizine Hydrochloride:

- Cetirizine Hydrochloride had the concentration of its stock solution is 0.04 mg/ml.
- Five serial concentrations that were prepared for Cetirizine Hydrochloride were as follows 0.005 mg/ml, 0.006 mg/ml, 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 Cetirizine Hydrochloride as per the calculations provided below.

Table 3.5: Concentrations for preparation of Standard Curve of Cetirizine Hydrochloride

Sample Name	Sample no.	Concentration(mg/ml)
Cetirizine Hydrochloride	1	.005
	2	.006
	3	.007
	4	.008
	5	.009

- V1= S2V2 / S1 = (0.005 x 10) / 0.04 = 1.25 ml of stock solution required to make 0.005 mg/ml concentration of the final solution of 10 ml (1.25 ml of stock solution + 8.75 ml of 0.1N H2SO4) of Cetirizine Hydrochloride.

- V1= S2V2 / S1 = (0.006 x 10) / 0.04 = 1.5 ml of stock solution required to make 0.006 mg/ml concentration of the final solution of 10 ml (1.5 ml of stock solution + 8.5 ml of 0.1N H2SO4) of Cetirizine Hydrochloride.

- V1= S2V2 / S1 = (0.007 x 10) / 0.04 = 1.75 ml of stock solution required to make 0.007 mg/ml concentration of the final solution of 10 ml (1.75 ml of stock solution + 8.25 ml of 0.1N H2SO4) of Cetirizine Hydrochloride.

- ⇨ V1= S2V2 / S1 = (0.008 x 10) / 0.04 = 2 ml of stock solution required to make 0.008 mg/ml concentration of the final solution of 10 ml (2 ml of stock solution + 8 ml of 0.1N H2SO4) of Cetirizine Hydrochloride.

- ⇨ V1= S2V2 / S1 = (0.009 x 10) / 0.04 = 2.25ml of stock solution required to make 0.009 mg/ml concentration of the final solution of 10 ml (2.25 ml of stock solution + 7.75 ml of 0.1N H2SO4) of Cetirizine Hydrochloride.

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

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

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

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

- ⇨ Electric Bulb exposure (25 watt & 40 watt)
- ⇨ Direct Sunlight exposure

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

1) 10 tablets were exposed to electric bulb lighting conditions for 5 hours at a stretch and 10 tablets were used as control.
2) After every 5 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, 3 tablets from those sampled tablets were taken.
   b. Then the total weight of those 3 tablets was noted using an analytical balance and the average weight was calculated using the formula :

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

   c. Then the 3 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 2 ml of that filtered solution was taken and dissolved in 8 ml of solvent.

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)	Temperature (ºC)	
			25w	40w
10(Control)	10	0	26	28
10	10	5	32	35

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

N.B: Same procedure (steps 1 to 7) were used to determine the potency of the tablets under both exposure of 25W and 40W lighting condition for two different days for 5 hours each.

- **Under Sunlight condition**

1) 10 tablets were kept in a Glass box and exposed to sunlight condition for 7.5 hours at a stretch.

2) After 5 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, 3 tablets from those sampled tablets were taken.

    b. Then the total weight of those 3 tablets was noted using an analytical balance and the average weight was calculated using the formula:

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

    c. Then the 3 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 2 ml of that filtered solution was taken and dissolved in 10ml 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 (hr)	Temperature (ºC)
10(control)	10	0	27
10	10	5	36

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

CHAPTER FOUR

RESULTS

4.1 Standard curve preparation:

The standard was collected from Square pharma Ltd.and tried to make a standard curve. For different concentration of cetirizine Hydrochloride different absorption were recorded. Five serial concentration of the standards of cetirizine Hydrochloride were prepared for the purpose of creating a standard curve.

The results are as follows:

Table 4.1:Concentration & Absorption for Standard Curve of Cetirizine Hydrochloride

Concentration(mg/ml)	Absorbance(at 230nm)
0.005	0.187
0.006	0.219
0.007	0.282
0.008	0.319
0.009	0.375

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

$Y=47.6x -0.056$

$R^2=0.991$

This equation was used to determine the concentration of Cetirizine Hydrochloride from different samples absorbance that was found in several lighting conditions.

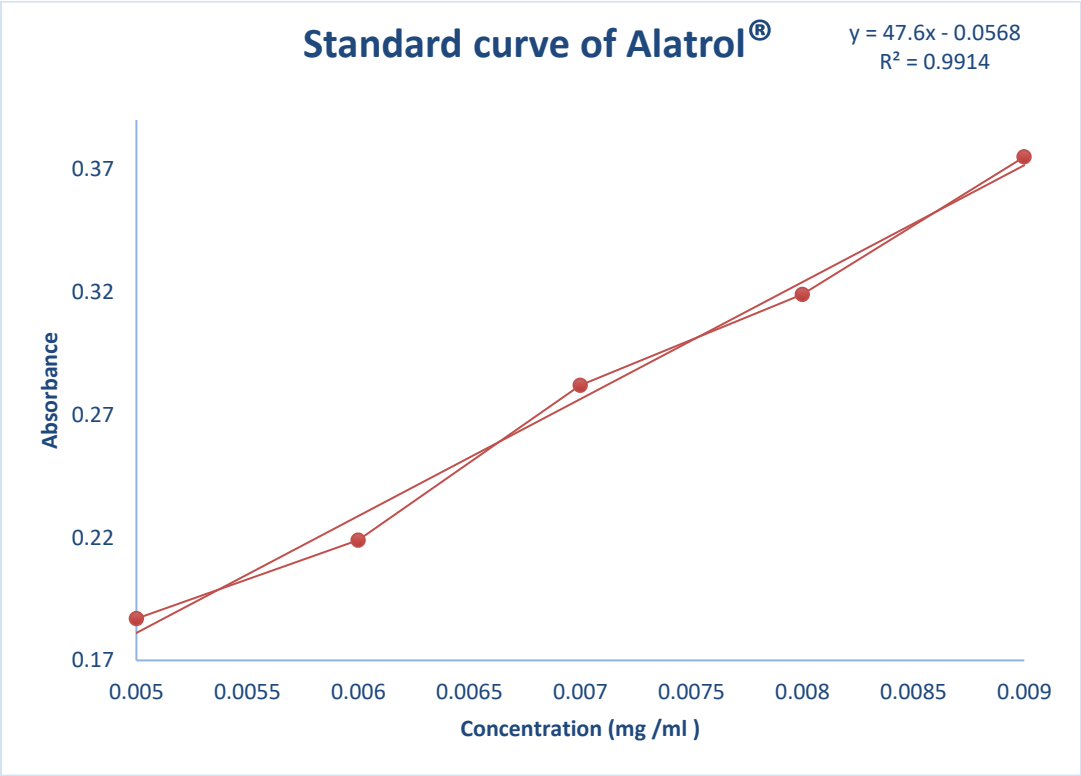

Figure 4.1: Plot showing straight line for absorbance with respect to concentration for Cetirizine Hydrochloride

4.3.2 Result of samples that were exposed under 25W bulb

In experimental day, a tablet strip containing 10 tablets was taken and 3 samples were collected for the test and observed 3 different absorbance of Cetirizine Hydrochloride for three samples exposed under the lamp (25W bulb); each for 5 hours' time interval and it was observed that the concentration of Cetrizine Hydrochloride was declined in each time interval.

Table 4.2: Concentration & Absorbance for Cetirizine Hydrochloride (Alatrol®)

Test Type	Initial Potency%	Potency after 5 hours%	Potency Decrease%	Mean Potency decrease of each formulation	Standard deviation+/- of each formulation	Mean potency decrease	Standard Deviation +/-(%)
Sample 1A	99.50	93.20	6.30	4.36	2.11	3.67	1.54
Sample 2A	99.50	94.80	4.70				
Sample 3A	99.50	97.40	2.10				
Sample 1B	99.00	93.75	5.25	3.21	1.77		
Sample 2B	99.00	97.00	2.00				
Sample 3B	99.00	96.60	2.40				
Sample 1C	99.20	94.80	4.40	3.46	0.90		
Sample 2C	99.20	96.60	2.60				
Sample 3C	99.20	95.80	3.40				

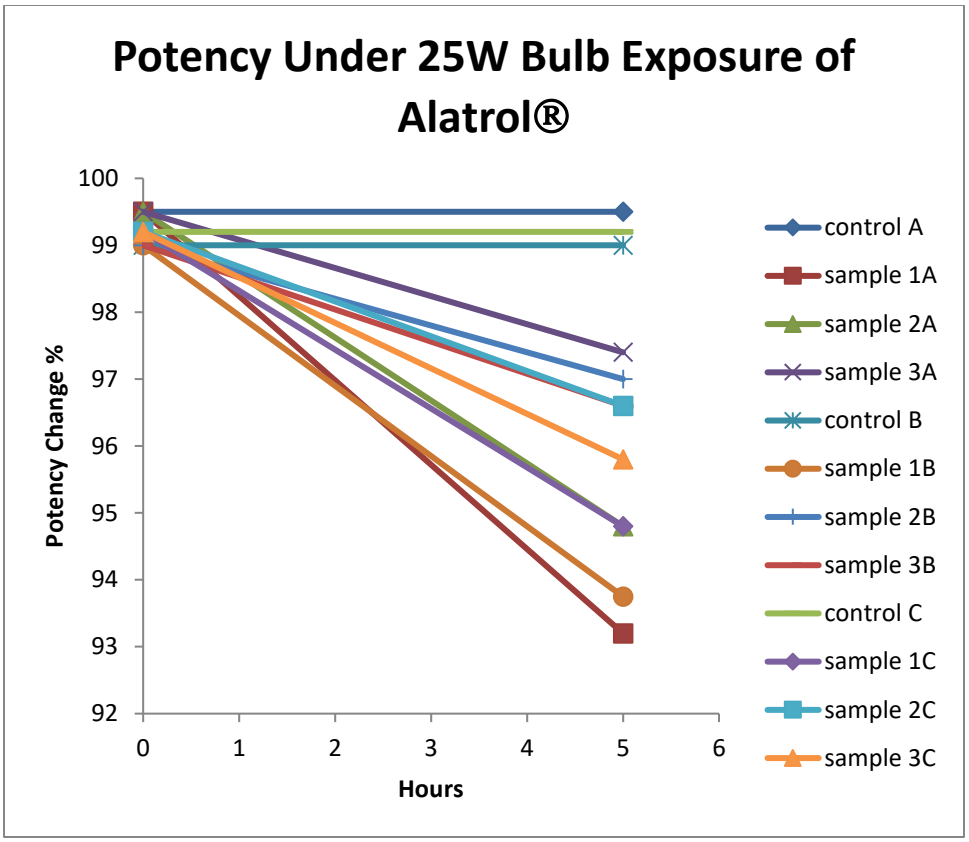

Fig 4.2: Difference in concentration after 5 hours time interval for Cetirizine Hydrochloride

4.3.3 Result of samples that were exposed under 40W bulb

In experimental day, a tablet strip containing 10 tablets was taken and 3 samples were collected for the test and observed 3 different absorbance of Cetirizine Hydrochloride for three samples exposed under the lamp (40W bulb); each for 5 hours' time interval and it was observed that the concentration of Cetirizine Hydrochloride was declined in each time interval.

Table 4.5: Concentration & Absorbance for Cetrizine Hydrochloride (Alatrol®)

Test Type	Initial Potency%	Potency after 5 hours%	Potency Decrease%	Mean Potency decrease of each formulation	Standard deviation+/- of each formulation	Mean potency decrease	Standard Deviation +/-(%)
Sample 1A	100.00	94.78	5.22	8.44	3.03	9.34	2.53
Sample 2A	100.00	91.12	8.88				
Sample 3A	100.00	88.76	11.24				
Sample 1B	99.00	93.22	5.78	9.89	3.62		
Sample 2B	99.00	87.71	11.29				
Sample 3B	99.00	86.39	12.61				
Sample 1C	99.50	89.54	9.96	9.69	1.20		
Sample 2C	99.50	91.12	8.38				
Sample 3C	99.50	88.76	10.74				

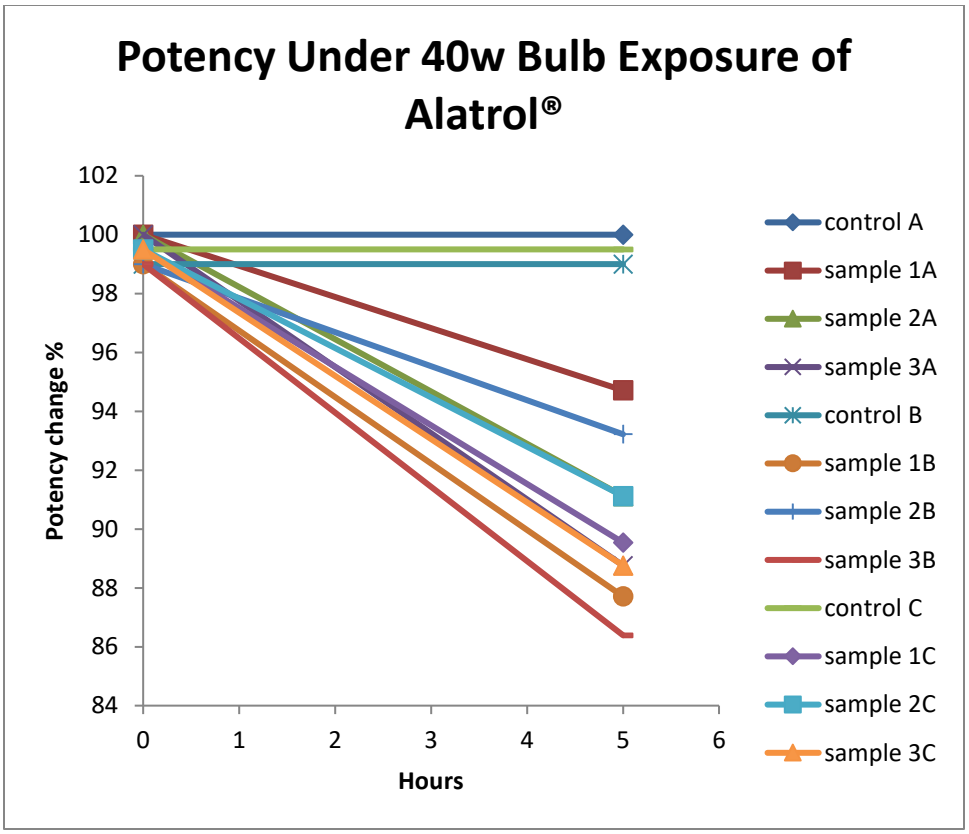

Fig 4.3: Difference in concentration after 5 hours time interval for Cetrizine Hydrochloride

4.3.4 Result of samples that were exposed under direct sunlight

In experimental day, a tablet strip containing 10 tablets was taken and 3 samples were collected for the test and observed 3 different absorbance of Cetirizine Hydrochloride for three samples exposed under the direct sunlight, each for 5 hours' time interval and it was observed that the concentration of Cetirizine Hydrochloride was declined in each time interval.

Table 4.6: Concentration & Absorbance for Cetirizine Hydrochloride (Alatrol®)

Test Type	Initial Potency%	Potency after 5 hours%	Potency Decrease%	Mean Potency decrease of each formulation	Standard deviation+/- of each formulation	Mean potency decrease	Standard Deviation +/-(%)
Sample 1A	100.00	78.51	21.49	18.86	2.92	16.58	3.09
Sample 2A	100.00	84.29	15.71				
Sample 3A	100.00	80.61	19.39				
Sample 1B	99.50	80.09	19.41	16.26	3.15		
Sample 2B	99.50	83.24	16.26				
Sample 3B	99.50	86.39	13.11				
Sample 1C	99.20	84.82	14.38	14.64	2.50		
Sample 2C	99.20	81.93	17.27				
Sample 3C	99.20	86.92	12.28				

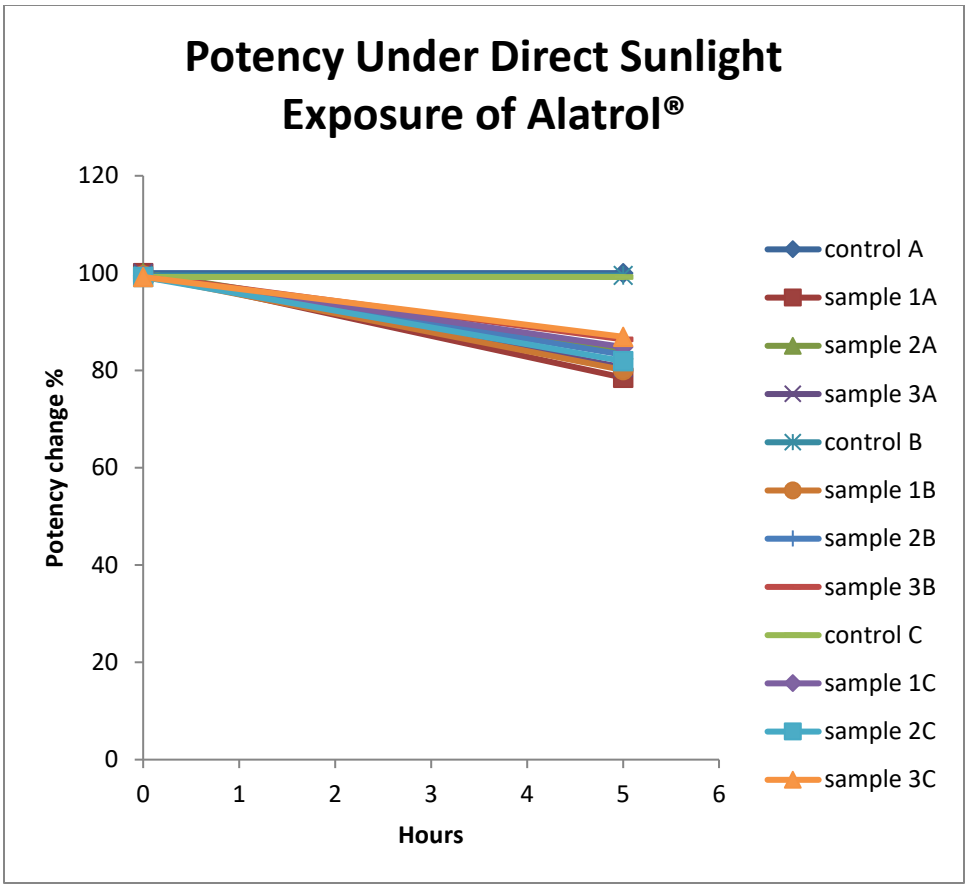

Figure 4.4: Difference in concentration after 5 hours time interval for Cetirizine Hydrochloride

CHAPTER FIVE

DISCUSSION

5.1 Discussion

Photolytic degradation refers to the breakdown or alteration of chemical structure due to the influence of light radiation or the reduction in potency in presence of light.Generally in normal lighting conditions photo degradation of cetirizine hydrochloride was not reported. We conducted this research to examine the robustness of degradation if the drug samples kept under different extreme conditions (incandescent bulbs of 25watt and 40 watt and direct sunlight) .It was found that the concentration of cetirizine Hydrochloride was decreased gradually in every ovation of light exposure. When sample tablets (Alatrol®) were kept under incandescent bulbs of 25watt and 40 watt and tested after every 5 hour light exposed, the result showed that the drug degraded under such conditions.Exposing these drug samples to direct sunlight showed the identical result.But the degradation rate of drug samples exposed to sunlight was myriad in contrast with incandescent bulb (25watt and 40watt).So under 25watt bulb, 40watt bulb and direct sunlight the concentration of cetirizine decreased were decreased gradually with percent deviation 3.67% (1.54%) , 9.34% (2.53%) and 16.58% (3.09 %) respectively.

From this research project, it can be conclude with a decision that, there should be a change in the packaging system of the cetirizine hydrochloride because we cannot fore spell whether the patient will keep the drug sample in proper storage or not. 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 to impede degradation of Alatrol®

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CHAPTER SIX

CONCLUSION

6.1. Conclusion

According to this experiment,it was observed that the concentration of cetirizine hydrochloride was decreased gradually after exposureunder extreme condition (incandescent bulb of 25watt,40watt and direct sunlight) . As there were remarkable changes in concentration/potency ,So it can say that the **Alatrol®** containing cetirizine hydrochloride is light sensitive. It means coating alone is not sufficient to protect the drug from light. Thus the package should be opaque so that light cannot pass through the package and Proper concentration should be imposed in the packaging of the drug sample to eradicate degradation and maintain stability.

CHAPTER SEVEN

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