In-vitro Comparative Dissolution Study of Different Brands (Alcet, Lecet, Clarigen, Lozin) of Levocetirizine Dihydrochloride, Available in Bangladesh, With Respect to Purotrol.

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

Submitted by

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Declaration by the Candidate

I, Samiha Tamanna, hereby declare that the dissertation entitled **"In-vitro Comparative Dissolution Study of Different Brands (Alcet, Lecet, Clarigen, Lozin) of Levocetirizine Dihydrochloride, Available In Bangladesh, With Respect To Purotrol"** 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 Tirtha Nandi, Lecturer, 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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Certificate by the Supervisor

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Endorsement by the Chairperson

This is to certify that the thesis entitled **"In-vitro Comparative Dissolution Study of Different Brands (Alcet, Lecet, Clarigen, Lozin) of Levocetirizine Dihydrochloride, Available In Bangladesh, With Respect To Purotrol"** 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 Samiha Tamanna, ID: 2014-1-70-042, during the period 2017 of her research in the Department of Pharmacy, East West University.

Dr. Chowdhury Faiz Hossain

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Dedication

This research paper is dedicated to my beloved Parents and my family members

Abstract

The aim of the present study was to evaluate and compare dissolution pattern of locally branded drug products of Levocetirizine 2HCl available in Bangladesh with the brand of Levocetirizine 2HCl (Purotrol) marketed by Square pharmaceutical company. Purotrol is one of the most used drug of Levocetirizine 2HCl. Branded drugs are expensive than locally marketed drug. Substitution of drugs is very essential for the people of under developing country. Four different brands of Levocetirizine 2HCl tablets which are available in Bangladesh like Alcet, Seasonix, Lozin, Clarigen, and Lecet etc. with respect to purotrol were collected from a reputed pharmacy store. Two tablets from each of the brands were used for the *in-vitro* dissolution study. Cumulative drug release was measured up to 30 minutes for all the brands. All the brands were compared with Purotrol. Differential factor, f1 and similarity factor, f2 were determined. Significant difference was observed during *in-vitro* drug release pattern of local brands with respect to purotrol
.Here it was found the values of *f*1 are 26.08, 15.52, and 25.11 so it is not acceptable. Only Lozin has f1 value less than 15 i.e. (13.7) therefore that is accepted. And the similarity factor it was seen that the values of *f*2 are 30.77, 44.79, 15.52 and 25.11, so it is also not acceptable. In conclusion, further investigations are needed to evaluate better dissolution study.

Keyword: Levocetirizine 2HCl, Generic brand, % Release, Comparative dissolution, *In-vitro* drug dissolution study

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List of abbreviation

H_2 BLOCKER	Histamine Two Receptor Blocker
LCTZ / LEV	Levocetirizine
IP	Indian Pharmacopeia
ADRs	Adverse Drug Reactions
IR	Immediate Release
BCS	Biopharmaceutical Classification system
IVIVC	In Vivo-In Vitro Correlation
API	Active pharmaceutical Ingredient
FDA	Food and Drug Administration
HDC	Histidine decarboxylase
HMT	Histamine methyltransferase
DAO	Diamine oxidase
MAO	Monoamine oxidase

Chapter One

INTRODUCTION

Introduction

1.1 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).

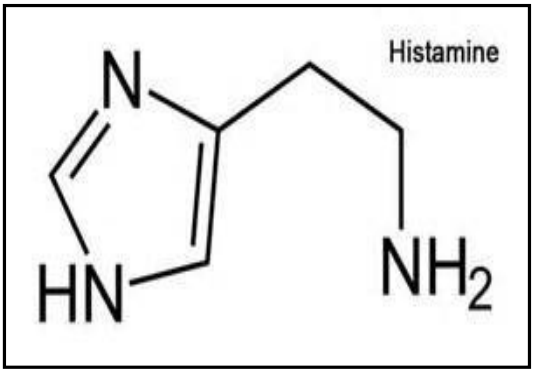

Figure 1.1: Histamine (Goodman & Gillman, 2008)

1.2 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) until the). 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).

1.3.1 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).

1.3.2 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).

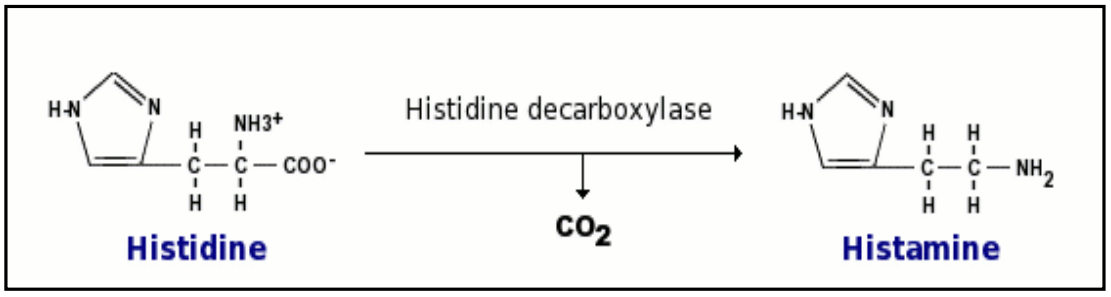

Figure 1.2: Histamine Synthesis (Anon, 2017)

1.3.3 Metabolism

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

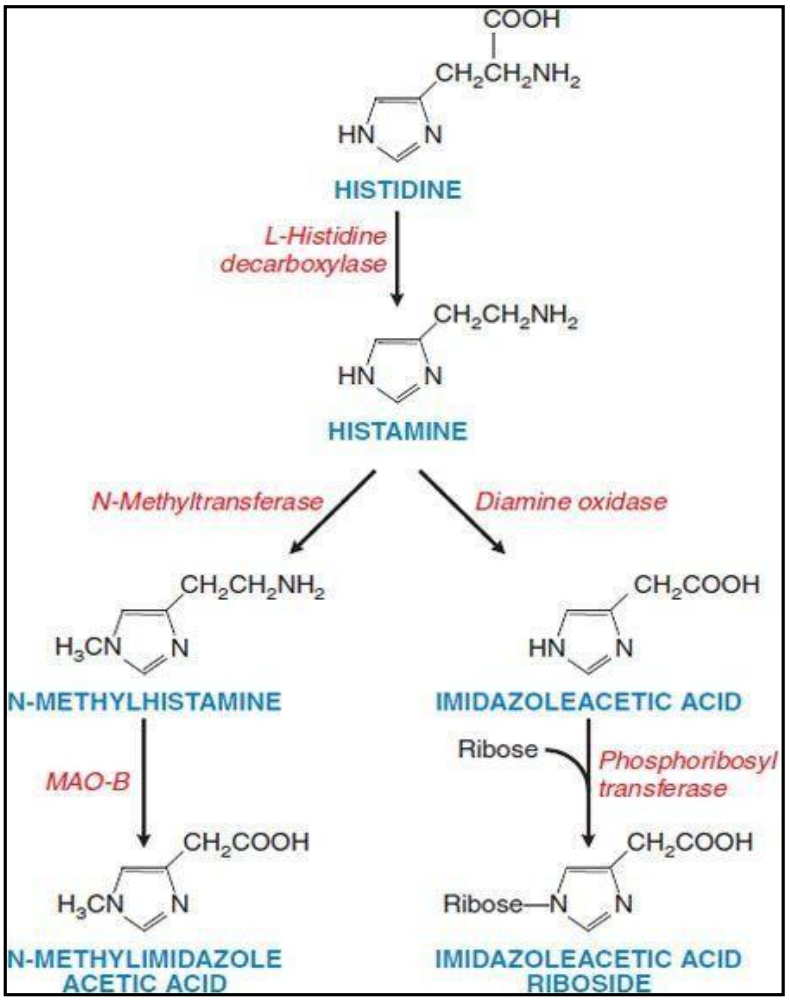

Figure 1.3: Synthesis and metabolism of histamine. (HDC - histidine decarboxylase; HMT - histamine methyltransferase; DAO - diamine oxidase; MAO - monoamine oxidase). (Goodman, Gilman and Brunton, 2008)

1.3.4 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 & Gilman, 2008).

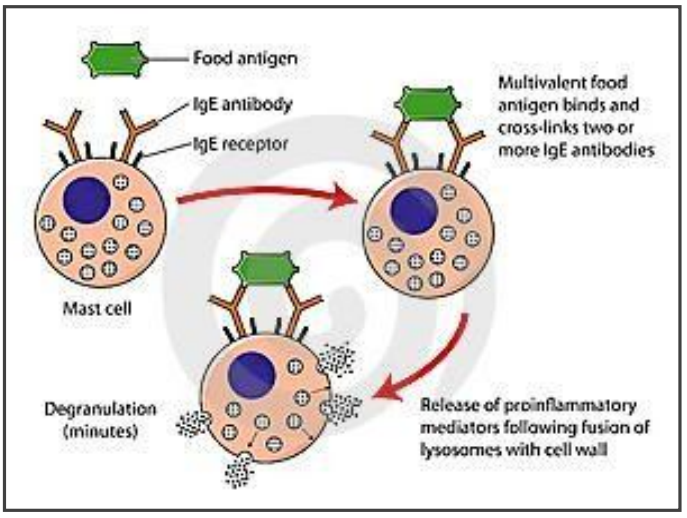

Figure 1.4: Storage and release of histamine. (Goodman & Gilman, 2008)

1.4 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)

Histamine Receptor			
Receptor	**Mechanism**	**Function**	**Antagonists**
H_1	G_q	• ileum contraction • modulate circadian cycle • itching • systemic vasodilatation • bronchoconstriction (allergy-induced asthma)	H_1-receptor antagonists • Diphenhydramine • Loratadine • Cetirizine • Fexofenadine • Clemastine
H_2	G_s $\uparrow cAMP^{2+}$	• speed up sinus rhythm • Stimulation of gastric acid secretion • Smooth muscle relaxation • Inhibit antibody synthesis, T-cell proliferation and cytokine production	H_2-receptor antagonists • Ranitidine • Cimetidine • Famotidine • Nizatidine
H_3	G_i	• Decrease Acetylcholine, Serotonin and Norepinephrine Neurotransmitter release in CNS • Presynaptic auto receptors	H_3-receptor antagonists • ABT-239 • Ciproxifan • Clobenpropit • Thioperamide
H_4	G_i	• Mediate mast cell chemotaxis.	H_4-receptor antagonists • Thioperamide • JNJ 7777120

Table1.2: Function, mechanism and antagonists 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)

1.5 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 and Laidlaw, 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)

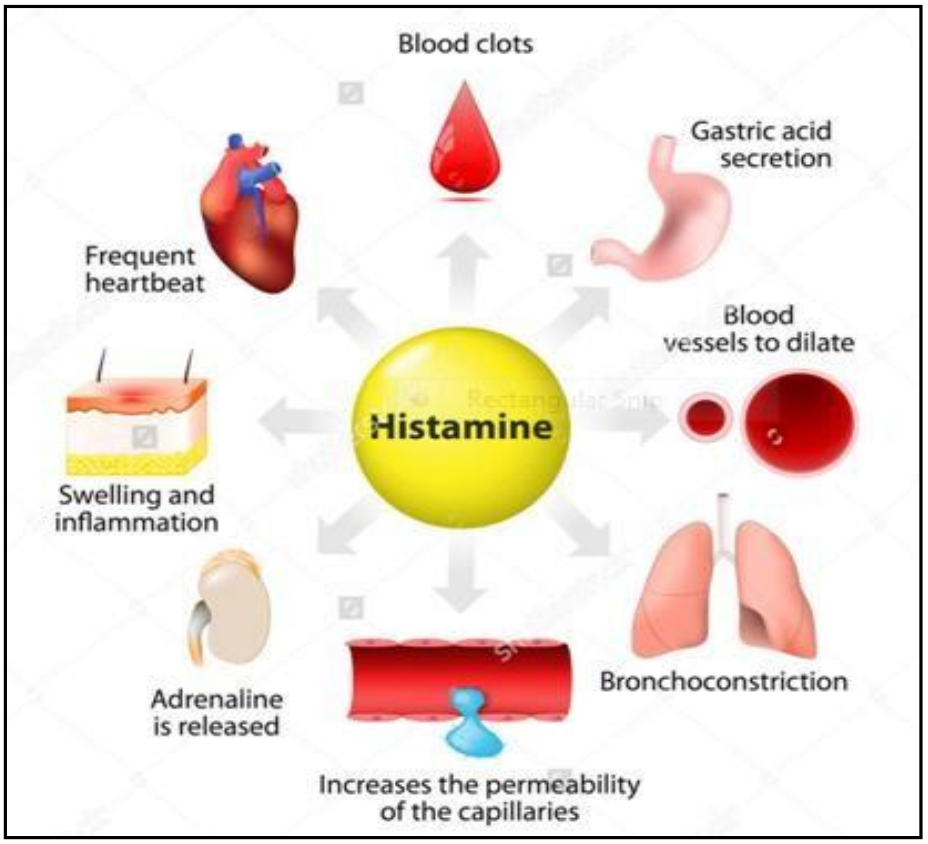

Figure1.5: Functions of histamine. (Alvarez, 2009).

1.6 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).

1.7 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).

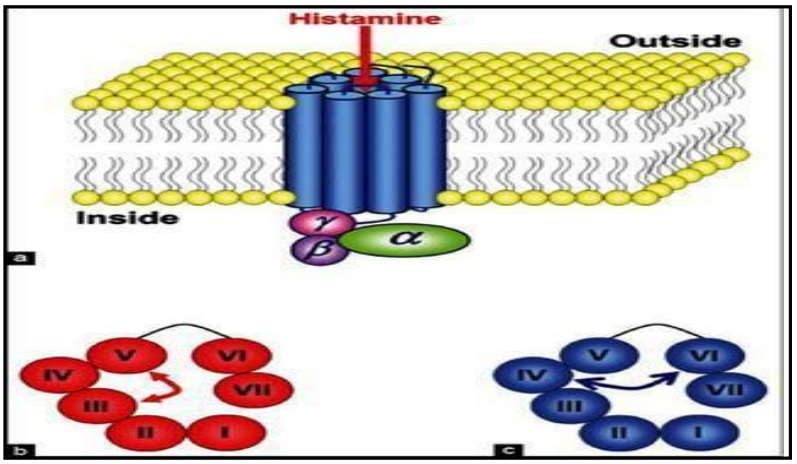

Figure 1.6: Histamine act on receptor (Ito, 2004).

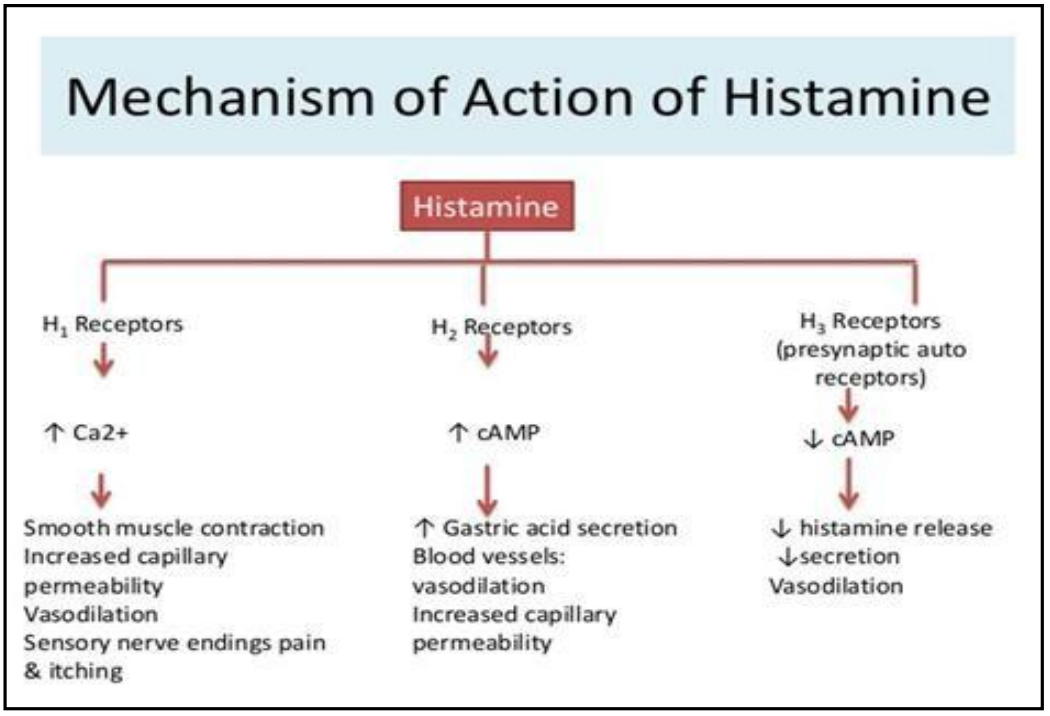

Figure 1.7: Schematic diagram of mechanism of action of histamine. (Knott, L., 2016).

1.8 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 scomorbid 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.

1.9 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)

1.10 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 allgiesand 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)

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
  - Triprolidine

- Doxepin
- Methdilazine
- Clemastine
- Azatadine

✓ 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)

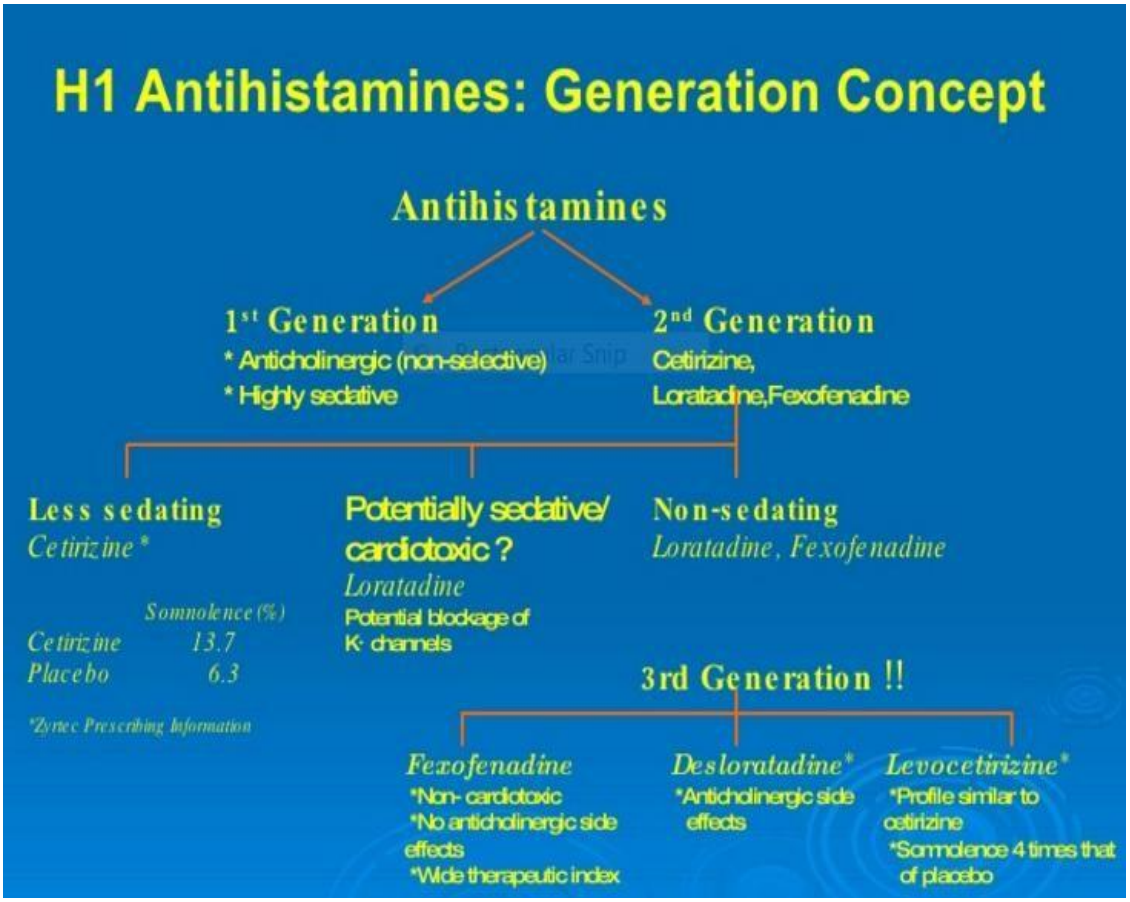

Figure 1.8: Classification of antihistamine.(Burkhart and Burkhart, 2014)

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 (eg) 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)

1.11 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)

1.12 Therapeutic Uses of antihistamine

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

✓ Drug induced parkinsonism (Pali-Schöll, Motala and Jensen-Jarolim, 2009)

1.13 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)
- Tavist (clemastine)
- Zyrtec (cetirizine)

(Simon and Simons, 2008)

1.14 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 gastric mucosa.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).

1.15Antihistamine 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

1.16 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)

1.17 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 metabolization to a lesser or greater extent. Biliary excretion is also possible, and is more extensively applicable to fexofenadine and rupatadine – the former without metabolization and the latter after extensive metabolization. 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)

1.18 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 neurogenerative diseases. Administration of 1st generation antihistamines to this population are associated with increased of inattention, disorganized speech, 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)

1.19 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)

1.20 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 from freezing.(Mayoclinic.org,2017)

1.21 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: Removal of 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)

1.22 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. The following 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)

1.23.1 Levocetirizine dihydrochloride:

Levocetirizine is a third-generation non-sedative antihistamine indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitis and uncomplicated skin manifestations of chronic idiopathic urticaria. It was developed from the second-generation antihistamine cetirizine. Levocetirizine is the R- enantiomer of the cetirizine racemate. Levocetirizine is an inverse agonist that decreases activity at histamine H1 receptors. This in turn prevents the release of other allergy chemicals and increased blood supply to the area, and provides relief from the typical symptoms of hay fever. It does not prevent the actual release of histamine from mast cells. Levocetirizine was approved by the United States Food and Drug Administration on May 25, 2007 and is marketed under the brand XYZAL® by Sanofi-Aventis U.S. LLC.(Pubchem.ncbi.nlm.nih.gov, 2017)

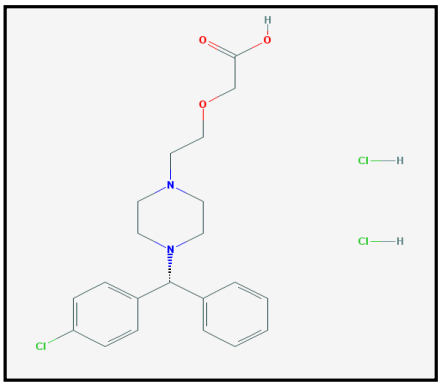

Figure1.9: Chemical Structure of Levocetirizine dihydrochloride (Pubchem.ncbi.nlm.nih.gov, 2017)

1.23.2 Synthesis of levocetirizine Dihydrochloride:

LEVO -015 and LEVO -016 added under the condition of trimethylamine and dichloromethane in the temperature of 0-5°c.and then LEVO - 017 is found. Then LEVO -019 can be found by using the catalyst of NaOH and Toluene in 120 - 130°c.Then Methane sulfonyl chloride, trimethylamine and dichloromethane in the temperature of 0-5°c aid to prepare Levo-020/Then with this LEVO-004 and Toluene in 75 to 80°c produce LEVO-021. Then from that conc. HBr, H2O in 90 to 95°c and NaOH and ethyl acetate produce Levocetirizine. And finally from that under HCl, Acetone in 0-5°c Levocetirizine Dihydrochloride is produced.

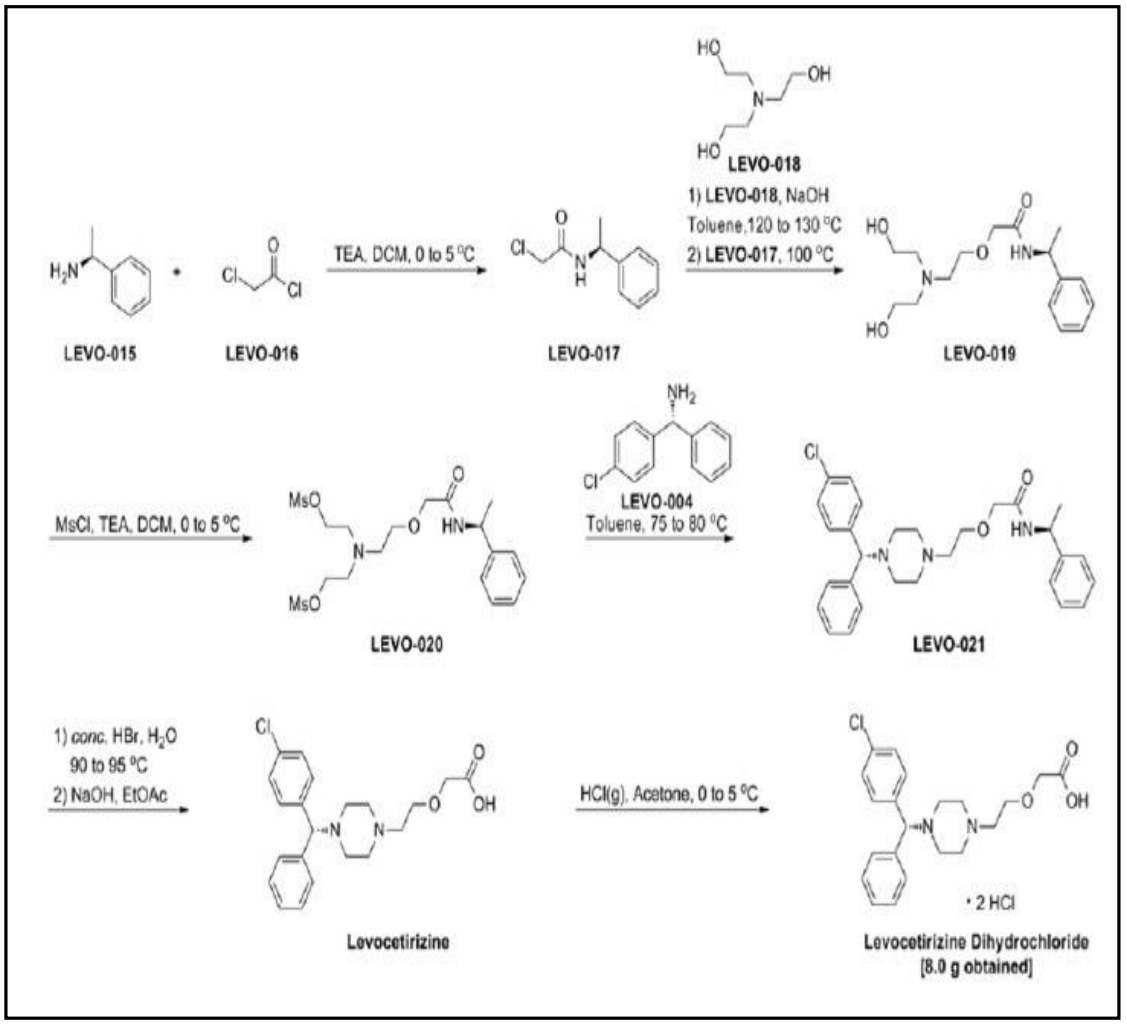

Figure1.10: Synthesis of Levocetirizine Dihydrochloride (Pharmacodia.com, 2016)

1.23.3 Mechanism of Action

The active enantiomer of cetirizine, is an anti-histamine; its principal effects are mediated via selective inhibition of H1 receptors. The antihistaminic activity of has been documented in a variety of animal and human models. In vitro binding studies revealed that has an affinity for the human H1-receptor 2-fold higher than that of cetirizine (Ki = 3 nmol/L vs. 6 mmol/L, respectively). This increased affinity has unknown clinical relevance.

Levocetirizine competes with endogenous histamine for binding at peripheral H1-receptor sites on the effector cell surface. This prevents the negative symptoms associated with histamine release and an allergic reaction. In addition, as histamine

plays an important role in angiogenesis during an allergic inflammatory reaction, blocking the action of histamine may modulate the expression of proangiogenic factors and thus may prevent angiogenesis. As a third-generation histamine H1 receptor antagonist, levocetirizine has fewer side effects than most second-generation antihistamines.

(Pharmacodia.com, 2016)

1.23.4 Pharmacokinetics of levocetirizine dihydrochloride

Levocetirizine is a third-generation, non-sedating antihistamine, developed from the second- generation antihistamine cetirizine. Biological half-life 6 to 10 hours, Metabolism Hepatic 14% CYP3A4 ,Formula C21H25ClN2O3 ,Drug classH1 antagonist, class Cetirizine, Desloratidine, Levocetirizine is an antihistamine that reduces the effects of natural chemical histamine in the body. Histamine can produce symptoms of sneezing, itching, watery eyes, and runny nose. Levocetirizine is used to treat symptoms of year-round (perennial) allergies in children who are at least 6 months old. Levocetirizine is also used to treat itching and swelling caused by chronic urticaria (hives) in adults and children who are at least 6 months old. (Knott, L. ,2016).

Absorption: It is rapidly and extensively absorbed following oral administration. In adults, peak plasma concentrations are achieved 0.9 hour after administration of the oral tablet. The accumulation ratio following daily oral administration is 1.12 with steady state achieved after 2 days. Peak concentrations are typically 270 ng/mL and 308 ng/mL following a single and a repeated 5 mg once daily dose, respectively. Food had no effect on the extent of exposure (AUC) of the tablet, but T_{max} was delayed by about 1.25 hours and Cmax was decreased by about 36% after administration with a high fat meal; therefore, can be administered with or without food.

Distribution:The mean plasma protein binding of Levocetirizine in vitro ranged from 91 to 92%, independent of concentration in the range of 90-5000 ng/mL, which includes the therapeutic plasma levels observed. Following oral dosing, the average

apparent volume of distribution is approximately 0.4 L/kg, representative of distribution in total body water.

Metabolism: Itis poorly metabolized and mostly excreted. This is favourable as it is unlikely to be modified by drugs administered concomitantly. The extent of metabolism of Levocetirizine in humans is less than 14% of the dose and therefore differences resulting from genetic polymorphism or concomitant intake of hepatic drug metabolizing enzyme inhibitors are expected to be negligible. Metabolic pathways include aromatic oxidation, N- and O-dealkylation, and taurine conjugation. Dealkylation pathways are primarily mediated by CYP 3A4 while aromatic oxidation involves multiple and/or unidentified CYP isoforms

Elimination:Renal excretion, mainly tubular excretion - therefore dose adjustment may be required in patients with renal impairment. After administration of a 5 mg dose of radiolabeled oral - 85.4% was excreted in urine and 12.9% in feces (146 hours later). The plasma half-life in adult healthy subjects was about 8 to 9 hours after administration of oral tablets and oral solution, and the mean oral total body clearance for Levocetirizine was approximately 0.63 mL/kg/min. The major route of excretion of Levocetirizine and its metabolites is via urine, accounting for a mean of 85.4% of the dose. Excretion via feces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion. Renal clearance of Levocetirizine correlates with that of creatinine clearance. In patients with renal impairment the clearance of Levocetirizine is reduced.

1.23.5 SideEffects

Levocetirizine dihydrochloride is an antihistamine indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 2 years of age and older. Side effects reported with the administration of this are usually include:

- Body aches or pain
- congestion
- diarrhea

- dryness or soreness of the throat
- earache
- hoarseness
- redness or swelling in the ear
- tender, swollen glands in the neck
- voice changes

More common sideeffects

Side effects of levocetirizine can vary according to age

In adults and children ages 12 and older	**In children ages 6– 11 years**	**In children ages 1– 5 years**	**In children ages 6– 12**
• tiredness • drymouth • sorethroat • nasopharyngitis (redness and inflammation in the nose and throat)	• fever • cough • sleepiness • nosebleeds	• fever • diarrhoea • vomiting • ear infections	• diarrhea • constipation

Table 1.3: More common side effects

Serious side effects

Serious side effects and their symptoms can include the following:

Allergic reactions	**Kidney problems**	**Blurry vision**
• rash, itching • hives • swelling of lips, tongue, face, or throat	• trouble in urinating • changes in the amount of urinate • blood in urine	Different eyesight problems occur

Table 1.4: Serious side effects

1.23.6 Forms and strength of levocetirizine

Form	Strengths
Oral tablet	5 mg
Oral solution	2.5 mg/5 mL

Table 1.5: Forms and strengths of levocetirizine

1.23.7 Dosage for seasonal and year-round allergies and chronic itching

Adult dosage (ages 18–64	Child dosage (ages 12–17	Child dosage (ages 6–11	Child dosage (ages 5 years	Senior dosage (ages 65 years and older)
The typical dosage is one 5-mg tablet once per day in the evening.	The typical dosage is one 5-mg tablet once per day in the evening	The typical dosage is one half-tablet (2.5 mg) once per day in the evening.	Dosage for Levocetirizine oral tablet hasn‘t been established for Children younger than 6 years of age.	The kidneys of older adults may not work and they used to. This can cause body to process drugs more slowly. As a result, more of a drug stays in your body for a longer time. This raises your risk of side Effects.

Table 1.6: Dosage of levocetirizine

1.23.8 Special considerations

The typical dosages for people with **kidney problems** include:

Mild kidney disease	Moderate kidney disease	Severe kidney disease	End-stage kidney disease and on hemodialysis

2.5 mg once per day.	2.5 mg once every other day.	2.5 mg twice per week (taken once every 3–4 days).	Do not take this drug.

Table 1.7 : Dosage of levocetirizine for kidney patients .(Pubchem.ncbi.nlm.nih.gov, 2017)

1.24 BCS Classification

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. It allows for the prediction of in vivo pharmacokinetics of oral immediate-release (IR) drug products by classifying drug compounds into four classes based on their solubility related to dose and intestinal permeability in combination with the dissolution properties of the dosage form. The interest in this classification system stems largely from its application in early drug development and then in .The Biopharmaceutical Classification System (BCS) is one of the experimental models that measures permeability and solubility under specific conditions. The main purpose of the system was to aid in the regulation of post-approval changes, providing acceptance based on in vitro data when appropriate is available. Importantly, the system was designed around on oral drug delivery since the majority of drugs is and remains orally dosed. Waivers, permission to skip *in vivo* bioequivalence studies, are kept for drug products that meet certain requirements like solubility and permeability and that are also rapidly dissolving characters (Knott, 2016).

Class	Solubility	Permeability
I	High	High
II	High	low
III	Low	high
IV	Low	low

Table 1.8: The Bio pharmaceutics classification system

This classification is associated with a drug dissolution and absorption model, which identifies the key parameters controlling drug absorption as a set of dimensionless numbers. Levocetirizine is in the Class II as it has high solubility and low permeability (Knott, 2016).

Class I

The drugs of this class exhibit high absorption number and high dissolution number. The rate-limiting step is drug dissolution, and if dissolution is very rapid, then the gastric- emptying rate becomes the rate-determining step. These compounds are well absorbed, and their absorption rate is usually higher than the excretion rate. Examples include metoprolol, diltiazem, verapamil, and propranolol.

Class II

The drugs of this class have a high absorption number but a low dissolution number. In vivo drug dissolution is then a rate-limiting step for absorption except at a very high dose number. The absorption for Class II drugs is usually slower than for Class I and occurs over a longer period of time. In vitro–in vivo correlation (IVIVC) is usually accepted for Class I and Class II drugs. The bioavailability of these products is limited by their solvation rates. Hence, a correlation between the in vivo bioavailability and the in vitro solvation can be found (7, 9, and 10). Examples include glibenclamide, phenytoin, danazol, mefenamic acid, nifedinpine, ketoprofen, naproxen, carbamazepine, and ketoconazole (Knott, 2016).

Class III

Drug permeability is the rate-limiting step for drug absorption, but the drug is solvated very quickly. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. Examples include cimetidine, ranitidine, acyclovir, neomycin B, atenolol, and captopril (Knott, 2016).

Class IV

The drugs of this class are problematic for effective oral administration. These compounds have poor bioavailability. They are usually not well absorbed through the intestinal mucosa, and a high variability is expected. Fortunately, extreme examples of Class IV compounds are the exception rather than the rule, and these are rarely developed and marketed. Nevertheless, several Class IV drugs do exist Examples include hydrochlorothiazide, taxol and furosemide (Knott,2016).

1.25 Dissolution

Dissolution is the primary quality control test to determine whether a drug product can release its active pharmaceutical ingredients in a timely manner. A dissolution test is a means of identifying and proving the availability of active drug materials in their delivered form. A dissolution test simulates the availability of active substance and allows the prediction of the time for complete release of the material from the dosage form. In the pharmaceutical industry, drug dissolution testing is routinely used to provide critical in vitro drug release information for both quality control purposes, i.e., to assess batch-to- batch consistency of solid oral dosage forms such as tablets, and drug development, i.e., to predict in vivo drug release profiles (Knott, 2016).

1.26 Factors influence dissolution from drug products

- The properties of the API,
- The quality and design of the drug product,
- The conditions under which the test is run and the coating material.

Properties of the API important to dissolution include

The solubility of the API in the dissolution medium, which is usually an aqueous buffer solution (may contain surfactants as well).Whether the API is hydrophilic or hydrophobic (ease of surface wetting). The particle size of the API. Whether the API is crystalline or amorphous in the drug product. If there are polymorphs, which polymorph is present. If a salt form is used.

Applications of Dissolution in the Pharmaceutical Industry

1. As a formulation design aid (since formulation can profoundly affect dissolution behavior)

2. As a quality control measure immediately after production for batch release

3. As a quality control measure to check performance during the shelf life

4. To predict performance under various dosing conditions (—bio relevant methods‘‘)

5. To verify that the quality of a product is not adversely affected when there is a change in excipients or manufacturing method (can sometimes be used instead of a pharmacokinetic study).

Tablets or capsules taken orally remain one of the most effective means of treatment available. The effectiveness of such dosage forms relies on the drug dissolving in the fluids of the gastrointestinal tract prior to absorption into the systemic circulation. The rate of dissolution of the tablet or capsule is therefore crucial. One of the problems facing the pharmaceutical industry is to optimize the amount of drug available to the body, i.e. its bioavailability**.** Inadequacies in bioavailability can mean that the treatment is ineffective and at worst potentially dangerous (toxic overdose).Drug release in the human body can be measured *in-vivo* by measuring the plasma or urine concentrations in the subject concerned. However, there are certain obvious impracticalities involved in employing such techniques on a routine basis. These difficulties have led to the introduction of official *in- vitro* tests which are now rigorously and comprehensively defined in the respective Pharmacopoeia. Tablet Dissolution is a standardized method for measuring the rate of drug release from a dosage form,

The principle function of the dissolution test may be summarized as follows: Optimization of therapeutic effectiveness during product development and stability assessment; routine assessment of production quality to ensure uniformity between production lots; assessment of _bioequivalence‘, that is to say, production of the same biological availability from discrete batches of products from one or different manufacturers and prediction of *in-vivo* availability, i.e. bioavailability (where applicable).

Although initially developed for oral dosage forms, the role of the dissolution test has now

Been extended to drug release studies on various other forms such as topical and transdermal systems and suppositories (Knott, 2016).

1.27 Comparative dissolution

In a dissolution test a drug product is added to media, simulating gastrointestinal fluids in a patient. At several time points the concentration of the dissolved API is determined. Drug dissolution testing is routinely used to provide critical in vitro drug release information for both drug development purposes and quality control. Dissolution testing during drug development is important to predict in vivo drug release profiles. In vitro drug dissolution data generated from dissolution testing experiments can be related to in vivo pharmacokinetic data by means of in vitro-in vivo correlations (IVIVC). A well- established predictive IVIVC model can be very helpful for drug formulation design and post-approval manufacturing changes

Levocetirizine is used in allergic rhinitis and urticarial therapy and available as several brands in the market which makes it difficult to select the safe, effective and economic one. The aim of this study is to establish similarity among the different brands of Levocetirizine tablets available in local market. Six different brands of (150 mg) were selected for the study.

A generic drug is an off-patent medication that has the same active ingredient, dose and route of administration as the original product. They are safe, effective, and cheap and thus they have many advantages from a medical and financial viewpoint as well. Since there is difficulty in the selection of generic drugs by the pharmacies or hospitals, it is important to ensure that products containing same active ingredients marketed by different pharmaceutical industries are safe, effective, high quality and clinically equivalent. Different brands of same drug would have been produced by different manufacturing methods and possibly with different excipients that may result in different bio availabilities. Different drug regulatory bodies, like Food and Drug Administration (FDA), have specified some bioequivalence requirements aimed at ensuring that similar dosage forms containing same active pharmaceutical ingredient (API) will have similar efficacy and safety. The increase in number of generic drug products from multiple sources has placed people, involved in the delivery of

health care, in a position of having to select one from among several seemingly equivalent products. However, many developing countries do not have an effective means of monitoring the quality of generic drug products in the market. This results in widespread distribution of substandard and/or counterfeit drug products. Pharmaceutical equivalents are the drug products which contain the same active ingredient, are of same dosage form, route of administration and are identical in strength and concentration. Bioequivalence studies are useful in comparing the bioavailability of drug from various drug products. Once the drug products are demonstrated to be bioequivalent, then the efficacy of these products is assumed to be similar. Generic drug products must satisfy the same standards of quality, efficacy and safety as those applicable to the innovator products. Preliminary physicochemical assessment of the products is very important and in vitro dissolution testing can be a valuable predictor of the in vivo bioavailability and bioequivalence of oral solid dosage forms. The establishment of bioequivalence is essential to interchangeability so that a patient can substitute a generic for a particular product without jeopardizing efficacy or safety. This study aims to provide the proof of safety and effectiveness before the drugs can be used. (Kerr,2016)

Chapter Two

LITERETURE REVIEW

2.1. Literature Review

A literature review was done to evaluate the previous scientific research works that were done on the Levocetirizine Dihydrocloride, their release kinetics as well as dissolution profile. It was observed that the studies done on the Levocetirizine Dihydrocloride were not similar to this current research project. But those studies helped to find the informations that helped in the research work to a great extent and also helped to compare this research work with other research projects. Gist of some studies are listed below:

This research study investigated and compared the absorption and disposition of levocetirizine, the eutomer of cetirizine, when administered alone (10 mg) or in presence of the distomer. An additional objective was also to investigate the configurational stability of levocetirizine in vivo in humans. The study was performed in a randomized, two-way cross-over, single-dose design with a wash-out phase of 7 days between the two periods. A total of 12 healthy male and 12 healthy female volunteers were included in the study. Bioequivalence can be concluded from the analysis of the pharmacokinetic parameters of levocetirizine when administered alone or as the race mate cetirizine. No chiral inversion occurs in humans when levocetirizine is administered, i.e. there is no formation of the distomer. When comparing the pharmacokinetic characteristics of levocetirizine and the distomer, the apparent volume of distribution of the eutomer is significantly smaller than that of the distomer (0.41 and
0.60 L/kg, respectively). For an H_1-antagonist a small distribution volume can be considered as a positive aspect, both in terms of efficacy and safety. Moreover the non-renal clearance of levocetirizine is also significantly lower than that of the distomer (9.70 and 28.70 mL/min, respectively), which constitutes an additional positive aspect particularly as far as metabolism-based drug interactions are concerned. The information collected in the present study on the pharmacokinetics of levocetirizine and the distomer provide additional reasons for eliminating the distomer and developing levocetirizine as an improvement on cetirizine. (Baltes*et al.*, 2001).

In the year 2001,Benedetti, M.S. and his associates conducted a research study and the main goal of the present study was to investigate the absorption and disposition of levocetirizine dihydrochloride, the *R* enantiomer of cetirizine dihydrochloride, following a single oral administration (5 mg) of the ^{14}C-labelled compound in healthy

volunteers. Configurational stability was also investigated. Levocetirizine was rapidly and extensively absorbed: 85.4% and 12.9% of the radioactive dose were recovered 168 h post-dose in urine and faeces, respectively. Levocetirizine and/or its metabolites were not, or only very poorly, associated with blood cells, as the blood-to-plasma ratio was 0.51 to 0.68. The mean apparent volume of distribution (V_D) was 26.9 l (0.3 l/kg) indicating that the distribution of levocetirizine is restrictive. The protein binding of radiolabelled levocetirizine was 96.1% 1 h after administration. At least 13 minor metabolites were detected in urine and represented 2.4% of the dose at 48 h. The metabolic pathways involved in levocetirizine metabolism are oxidation (hydroxylation, O-dealkylation, N-oxidation and N-dealkylation), glucuroconjugation, taurine conjugation and glutathione conjugation with formation of the mercapturic acids. There was no evidence of chiral inversion of levocetirizine in humans. This result is consistent with that obtained in preclinical studies.(Benedetti*et al.*,2001).

The aim of the present study was to determine (1) the extent of levocetirizine binding to human blood cells, plasma and individual plasma proteins; (2) the parameters for levocetirizine binding to individual plasma proteins both at their physiological concentrations and, for human serum albumin (HSA), at a lower saturating concentration; and (3) to simulate levocetirizine distribution in human blood using the information obtained at physiological haematocrit (*H*) for blood cells and at physiological concentrations for individual plasma proteins. The nature of the main binding sites of HSA, i.e. site I (warfarin) and site II (diazepam), preferentially involved in levocetirizine binding was also investigated. . In any case, at therapeutic concentrations of levocetirizine and at physiological protein concentrations, the observation that none of the levocetirizine binding proteins is saturated suggests that very little or no variation of the free fraction will occur although a different distribution of its bound forms is possible. (Breeet*et al.*, 2002).

This study was done to compare the potency, consistency, onset, and duration of action of levocetirizine with other popular antihistamines in 2002. Levocetirizine is the active enantiomer of cetirizine, a potent drug with little metabolism widely used for allergic rhinitis and urticarial.Levocetirizine 5 mg, ebastine 10 mg, fexofenadine 180 mg, loratadine 10 mg, mizolastine 10 mg, or placebo in single doses were given to 18 healthy male volunteers in a double-blind, crossover, randomized fashion. Wheal-and-

flare responses to epicutaneous histamine dihydrochloride (100 mg/mL) challenge were measured at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours after each dosse. The overall effect of each drug was evaluated by the area under the curve (0 to 24 hours). Levocetirizine was the most potent and consistently effective drug for inhibiting the histamine-induced wheal-and-flare surface areas. Levocetirizine, the active enantiomer of cetirizine, is more potent and consistent than other popular H_1 antihistamines for blocking the cutaneous response to histamine. These findings may predict the efficacy of this drug in treating allergic disorders.(Grant *et al.*, 2002).

In this research study we examined that modern H_1-antihistamines differ in their in vitro binding affinity, but their comparative in vivo bioactivity in asthmatic airways is unknown. Objectives: We compared clinically recommended doses of 3 H_1-antihistamines on airway hyperresponsiveness to AMP challenge (the primary outcome variable). Sixteen atopic patients with mild-to-moderate asthma of whom 10 were receiving inhaled corticosteroid therapy (all had positive results to house dust mite on skin prick testing) were randomized in a double-blind, placebo-controlled, cross-over fashion to receive single doses of 5 mg of desloratadine, 180 mg of fexofenadine hydrochloride (FEX), 5 mg of levocetirizine dihydrochloride (LEV), or placebo, with AMP challenge performed 12 hours after dosing. All H_1-antihistamines demonstrated significantly greater ($P < .05$) geometric mean ± SEM AMP PC_{20} values compared with that of placebo (86 ± 29 mg/mL): desloratadine, 189 ± 54 mg/mL; FEX, 176 ± 57 mg/mL; and LEV, 163 ± 48 mg/mL. There were no significant differences in either AMP PC_{20} or lung function values among the H_1-antihistamines. Conclusion: Single doses of H_1-antihistamines improved airway hyperresponsiveness and small-airways caliber to a similar degree. Data for in vitro binding affinity do not therefore translate into commensurate differences in in vivo bioactivity at clinically recommended doses. (Lee*et al.*, 2003).

In this study , some biological properties of cetirizine and levocetirizine, namely enantioselectivity in pharmacological activity and pharmacokinetic properties, with emphasis on the possibility of racemization, the compared behavior of the two enantiomers, and the potential for interactions with other drugs. The potent histamine

H_1-receptor antagonist cetirizine (Zyrtec®) is a racemic mixture of levocetirizine (now available under the trademark Xyzal®) and dextrocetirizine. In this Commentary.Recent data demonstrate that the antihistaminergic activity of the racemate is primarily due to levocetirizine. Levocetirizine is rapidly and extensively absorbed, poorly metabolized, and not subject to racemization. Its pharmacokinetic characteristics are comparable after administration alone or in the racemate. Its apparent volume of distribution is smaller than that of dextrocetirizine (0.41 L kg^{-1} vs. 0.60 L kg^{-1}). Moreover, the non- renal (mostly hepatic) clearance of levocetirizine is also significantly lower than that of dextrocetirizine (11.8 mL min^{-1} vs. 29.2 mL min^{-1}). Our conclusion is that levocetirizine is indeed the eutomer of cetirizine. The evidence reviewed here confirms preclinical findings and offers a rationale for the chiral switch from the racemate to levocetirizine. (Tillement*et al.*,2003).

In the year 2005 a significant research study was accomplished on Levocetirizine. It is the latest of the H1-antihistamines indicated for adults and children (as young as 2 years old) suffering from allergic rhinitis and chronic idiopathic urticaria. Currently, it is the only therapy registered for treatment of persistent allergic rhinitis, as defined by the Allergic Rhinitis & its Impact on Asthma guidelines. Pharmacologic studies have shown levocetirizine to have a more favorable pharmacokinetic/pharmacodynamic profile than other commonly employed H1-antihistamines. This reflects its superiority in controlling the symptoms of seasonal, perennial and persistent allergic rhinitis in well-controlled trials. Clinical trials and postmarketing surveillance have indicated that levocetirizine is safe and well tolerated, and leads to clinically significant improvements in the quality of life of patients. It is also reported to reduce comorbidities as well as overall treatment costs when administered continuously over the longterm.(Bachert, 2005).

In 2006, a clinical study was done to evaluate the additional benefits of 5 mg levocetirizine dihydrochloride in seasonal AR patients using 200 mcg fluticasone propionate nasal spray once daily. The additional effects of H1 antagonists to intranasal corticosteroid treatment of allergic rhinitis (AR) is common in clinical practice and recommended by guidelines, despite some evidence that the additive benefits are negligible. In a double-blind placebo-controlled crossover study of 27 patients, following 2 weeks without treatment, subjects used fluticasone with levocetirizine or

identical placebo for 2 weeks each. Assessments were the Juniper mini RhinoconjunctivitisQuality-of-Life Questionnaire (mini-RQLQ), domiciliary peak nasal inspiratory flow (PNIF), total nasal symptoms (TNS) scores and nasal nitric oxide concentrations. Effects were interpreted and tested against minimal clinically important differences. The results demonstrated that for the majority of patients, antihistamine add-on to effective nasal steroid treatment is inappropriate. Further work is required to confirm that this is also true in the most severe cases, and the available evidence needs to be put into guidelines and implemented. (Barnes, M.L. *et al.*, 2006).

This study was performed byChaudhari, P.D, *et. al*. in 2007, in order to mask the taste, by complexation technique using ion-exchange resin, Tulsion 335 (polyacrylic hydrogen with carboxylic functionality) and to formulate into an orodispersible dosage form. Formulation and in vitro evaluation of taste masked orodispersible dosage form of Levocetirizine dihydrochloride was the main concern here.LevocetrizineDihydrochloride is an active nonsedative antihistamine. Allergic rhinitis is a significant public health concern in many developed and developing countries. Thus formulating Levocetrizine into an orodispersible dosage form would provide fast relief. The drug loading onto ion-exchange resin was optimized for concentration of resin, swelling time of resin, stirring time, pH of resin solution and stirring temperature. The tablets were evaluated for drug content, content uniformity, weight variation, hardness, friability, water absorption ratio, invitro and invivo disintegration time and invitro drug release. The tablets disintegrated invitro and invivo within 18 and 22 s respectively. Complete drug was released from tablet within 2 minutes. The results showed that Levocetrizine dihydrochloride was successfully taste masked and formulated into an orodispersible dosage form as an alternative to conventional tablets.(Chaudhari*et al.* 2007).

This study was done to compare the efficacy and safety profiles of the newest second-generation antihistamines — desloratadine, fexofenadine and levocetirizine. Second-generation histamine H_1 receptor antagonists were developed to provide efficacious treatment of allergic rhinitis (AR) and chronic idiopathic urticaria (CIU) while decreasing adverse effects associated with first-generation agents. As a class, second- generation antihistamines are highly selective for the H_1 receptor. Some bind to it with

high affinity, although there is marked heterogeneity among the various compounds. They have a limited effect on the CNS, and clinical studies have noted almost no significant drug drug interactions in the agents studied. No major cytochrome P450 inhibition has been reported with desloratadine, fexofenadine and levocetirizine, and the bioavailability of desloratadine is minimally affected by drugs interfering with transporter molecules. Of the second-generation antihistamines, desloratadine has the greatest binding affinity for the H_1 receptorHowever, differences among the antihistamines in relation to a lack of significant interaction with drug transporter molecules and somnolence in excess of placebo may provide some advantages for the overall profile of desloratadine compared with fexofenadine and levocetirizine. (Devillier*et al.*, 2008).

In the year 2008,Prabhu, S.L.et. al., conducted a study for simultaneous estimation of ambroxol hydrochloride and levocetirizine dihydrochloride through a novel, simple, sensitive and rapid spectrophotometric method. The method involved solving simultaneous equations based on measurement of absorbance at two wavelengths 242 nm and 231 nm, the γ max of ambroxol hydrochloride and levocetirizine dihydrochloride, respectively. Beer's law was obeyed in the concentration range 10–50 µg/ml and 8–24 µg/ml for ambroxol hydrochloride and levocetirizine dihydrochloride respectively. Results of the method were validated statistically and by recovery studies.(Prabhu*et al.*, 2008).

In the present paper, a simultaneous method has been developed and validated for estimation of gliquidone in the presence of H_1- receptor antagonists (fexofenadine hydrochloride, buclizine hydrochloride, and levocetirizine dihydrochloride) using reversedphase high-performance liquid chromatographic technique. A good chromatographic separation between these drugs was achieved using a mobile phase containing methanol-water (80:20 v/v) at pH 3.5 with a flow rate of 1.0 mL/min; and detection was performed at 230 nm with a UV detector. Validation of the method was performed in terms of linearity, accuracy, precision, and limit of detection and quantification. . Thus, the proposed method is suitable for the simultaneous analysis of active ingredients in tablet dosage forms and human serum.(Arayne*et al.*, 2010).

A research was accomplished for the simultaneous determination of simple, accurate, precise, and sensitive spectrophotometric method for estimation of Montelukast (MON) and Levocetirizine (LEV) in combined tablet dosage form have been developed and validated. Theratio derivative spectroscopic method involves measurement of first derivative amplitude of ratio spectra at 250.4 nm for MON and 238.4 nm for LEV as two wavelengths for estimation. Beer's law is obeyed in the concentration range of 4-12 and 2-6 µg/mL for MON and LEV, respectively. LOD values for MON and LEV are found to be 0.09 µg/mL and 0.178 µg/mL, respectively. LOQ values for MON and LEV are found to be 0.277µg/mL and 0.591 µg/mL, respectively. The results of analysis have been validated statistically and recovery studies carried out in the range 80-120% to confirm the accuracy of the proposed method**.**(Choudhari*etal.*,2010).

A research was accomplished to see the effects of levocetirizine 2HCl .Allergic rhinitis (AR) and chronic idiopathic urticaria (CIU) are common causes of substantial illness and disability in preschool children. Antihistamines are commonly used to treat preschool children with these conditions, but their use is based mostly on extrapolated efficacy from adult populations; it is thus important to characterize the safety of antihistamines in the pediatric population. This study was designed to assess the safety of levocetirizine dihydrochloride oral liquid drops in infants and children with AR or CIU. Two multicenter, double-blind, randomized, parallel-group studies randomized infants aged 6-11 months (study 1, n = 69) and children aged 1-5 years (study 2, n = 173) to levocetirizine, 1.25 mg (q.d. or b.i.d., respectively), or placebo for 2 weeks, using a 2:1 ratio. Safety evaluations included treatment-emergent adverse events (TEAEs), vital signs, electrocardiographic (ECG) assessments, and laboratory tests. The overall incidence of TEAEs was similar between levocetirizine and placebo in both studies. Most TEAEs were mild or moderate in intensity. No clinically relevant changes from baseline in vital signs or laboratory parameters were apparent in either study; changes from baseline in these evaluations were similar between groups. No significant changes were observed in ECG parameters, including corrected QT interval. Levocetirizine, 1.25 and 2.5 mg/day, was well tolerated in infants aged 6-11 months and in children aged 1-5 years, respectively, with AR or CIU.(Hampel*et al.*, 2010).

On January 1, 2010 a research article published by Mahesh, A. et. al.,for the development of taste masked fast disintegrating films of Levocetirizine

Dihydrochloride for Oral Use levocetirizine dihydrochloride useful for the treatment of acute allergic rhinitis and chronic urticaria have been developed by using the taste masking ability of cyclodextrins. The fast disintegrating films were prepared by solvent casting method. The films contained water-soluble polymers such as Kollicoat IR or pullulan, aspartame and sucralose as sweeteners and pre-gelatinized starch as disintegrant. Levocetirizine dihydrochloride was incorporated into these films by in-situ complex formation with hydroxy propyl β-cyclodextrin. The optimized films were evaluated for weight variation, film thickness, folding endurance, tackiness, tensile strength, assay, content uniformity, in vitro disintegration and dissolution, in vivo disintegration and taste masking ability by human gustatory sensation test. Results revealed that the organoleptic properties of levocetirizine dihydrochloride were improved by complexation with hydroxy propyl β-cyclodextrin and the complex could be successfully formulated into a fast disintegrating film.(Mahesh*et al.*,2010).

The prime objective of this study was to determine the better agent among rupatadinefumarate and levocetirizine dihydrochloride for seasonal allergic rhinitis. Although treating and ensuring a decent quality of life to patients is challenging, an increasing understanding of pathomechanismshas revealed the potentiality of new-generation antihistamines in the treatment of seasonal allergic rhinitis.A 2-week, single-center, randomized, open, parallel group comparative clinical study between rupatadine and levocetirizine in patients with seasonal allergic rhinitis. Setting was a tertiary care center here. Allergic rhinitis (AR) is one of the most common diseases, representing approximately 20% of the general population.*Allergic rhinitis* is the general term that encompasses seasonal AR, perennial AR, and perennial AR with seasonal exacerbations. Allergic rhinitis has a relevant impact on society because of its high prevalence, association with an impaired quality of life, and the presence of comorbidities such as atopy and asthma. Rupatadine is a novel chemical entity that shows both antihistamine and anti–platelet-activating factor effects through its interaction with specific receptors and not through physiological antagonism. Levocetirizine—the R-enantiomer of cetirizine dihydrochloride with pharmacodynamically and pharmacokinetically favorable characteristics—has been proved to be safe and effective for the treatment of AR with a minimal number of adverse effects in many clinical trials. In this study, we found that differential and

absolute eosinophil counts were significantly lowered by both drugs, but rupatadine was superior. (Maiti*et al*., 2010).

This study protocol utilized two chromatographic methods for the simultaneous determination of levocetirizine dihydrochloride and Montelukast sodium in tablets. The first method was a high performance thin layer chromatographic (HPTLC) separation followed by densitometric measurements on normal phase silica gel 60 F254. The second method was a high performance liquid chromatographic (HPLC) separation on a BDS Hypersil C18 column using disodium hydrogen phosphate buffer (0.02 M): Methanol (25: 75, v/v) pH adjusted to 7 with ortho-phosphoric acid as the mobile phase. The proposed methods were validated as per ICH guidelines and successfully applied for the determination of investigated drugs in tablets. (Rathore*et al*., 2010).

In the present study a simple, accurate and precise reverse phase liquid chromatographic method has been developed for simultaneous estimation of Levocetirizine Hydrochloride and Montelukast Sodium from tablet dosage form. The detection was carried out at 225 nm. The retention time of Levocetirizine and Montelukast were found to be around 3.2 min and 4.2 min respectively. The method was validated with respect to linearity, robustness, precision and accuracy and was successfully applied for the simultaneous quantitative determination of Levocetirizine Hydrochloride and Montelukast Sodium from the tablet dosage form (Basu*et al.*, 2011).

Kanungo, S.,et. al. performed a research work and the Purpose of undertaken project was to formulate crosslink polyacrilic resin based, technologically optimised, melt-in- mouth tablet (MIMT) containing 5 mg of Levocetirizine Dihydrochloride that was intended to disintegrate rapidly in the oral cavity so as to form a stabilised dispersion and possessing adequate physicochemical stability. Different grades of crosslink polyacrilic resin were utilised to prepare MIMTs; employing complexation technique; and using additives like Mannitol DC, Ac-di-sol, Avicel-pH 112, Tusilpinapple, Saccharine sodium, Aerosil and Magnesium stearate. MIMTs were evaluated for compliance to pharmacopoeial specifications. From in-vitro dissolution profile plot, values for the kinetic constant and the regression coefficient of model-dependent approaches were determined to find the best fit release kinetic model while from in- vitro dissolution profile data the difference factor, the similarity factor and the indices

of rescigno of model-independent approaches were determined for comparing pair of in-vitro dissolution profiles. MIMTs of levocetirizine was successfully developed complying pharmacopoeial specifications, with adequate stability at room temperature.(Kanungo*et al.*, 2011).

Evidence is presented to show that a simple, accurate, and precise AUC curve spectrophotometric method was developed for simultaneous determination of Montelukast sodium (MTKT) and Levocetirizine dihydrochloride (LCTZ) in combined pharmaceutical dosage forms. The principle for AUC curve method is –the area under two points on the mixture spectra is directly proportional to the concentration of the component of interest‖. The area selected were 263.6 to 293.6 and 222 to 242 nm for determination of MTKT and LCTZ respectively. The two drugs follow Beer-Lambert‘s law over the concentration range of 5-30 µg/ml for MTKT and LCTZ. The % estimation of the drugs was found near to 100 % representing the accuracy of the method. The recovery of the MTKT and LCTZ were found near to 100 %. Validation of the proposed methods was carried out by Patel Nilam, K. and Pancholi, S.S., for its accuracy, precision, specificity and ruggedness according to ICH guidelines. The proposed methods can be successfully applied in routine work for the determination of MTKT and LCTZ in combined dosage form. (Patel NilamandPancholi,2011).

In this study,the fast dissolving oral films were designed using optimal design and numerical optimization technique was applied to find out the best formulation. Film forming agent HPMC, sodium CMC was considered as independent variables. Drug release rate from 45sec to990sec, T50%and release exponent (n) were taken as responses. Decrease the viscosity of film former a specific limit, changes the release from zero order to Hixson-Crowell based release. The IR and DSC studies revealed that no physicochemical interaction between excipients and drug. The influence of pH and agitation intensity on the release of drug was studied and the release mechanism was through disintegration. Stability studies revealed that optimized formulation was stable. The observed independent variables were found to be very close to predicted values of most satisfactory formulation which demonstrates the feasibility of the optimization procedure in successful development of fast dissolving oral film containing levocetirizine Dihydrochloride by using HPMC, sodium CMC and PEG- 400 as key excipients. (Jadhav*et al.*, 2012).

The aim of this study was to develop taste masked oral soluble films (OSFs) for levocetirizine dihydrochloride (LCT) and ambroxol hydrochloride (AMB) using different combination of polymers such as polyvinyl pyrrolidone (PVP) K30, propylene glycol (PG), gelatin, sodium alginate (SA), pectin, gaur gum (GG), and hydroxypropyl methylcellulose (HPMC) K15M and super disintegrants like carboxymethyl cellulose (CMC) and sodium starch glycolate (SSG). The different basic formulations were developed using solvent casting method for with and without drugs loading and prepared films were evaluated different morphological and mechanical parameters facilitated the screening of a formulation with best characteristics. The films made from HPMC K15M (42.2% w/w) and pectin (35.2% w/w) and considered as an optimized batch among the other formulations. Developed OSFs can be considered as one of the promising formulation to administer bitter drugs such as LCT and AMB especially for pediatric, geriatric, and non-cooperative patients.(Senthil*et al.*, 2013).

This research work deals with the formulation and evaluationof Levocetirizine hydrochloride and Montelukast sodium bilayered tablet for treating nasal allergic rhinitis effectively. By combining Levocetirizine with Montelukast gives additional benefits in comparison with either drug alone and could be considered for patients whose quality of life is impaired by persistent allergic rhinitis. Bilayered tablet may be designed for one layer for the immediate release of the drug and second layer for extended release thus maintaining a prolonged blood level. To achieve patient compliance by reduced frequency of drug administration, and reduced side effects. It was concluded that optimized bilayered Levocetirizine dihydrochloride F8 and Montelukast F5, is successful formulation and can be manufactured with reproducible characteristics from batch to batch. The optimized formulation f8, f5 was compared to the marketed product and hence found to be superior over the marketed product. (Ashrafaand, 2014).

This research study contributed to the development of novel topical formulation of levocetirizine based on flexible vesicles (FVs) with an aim to have targeted peripheral antihistaminic effect in 2014.The FVs were prepared by thin film hydration method and characterized for drug content, entrapment efficiency, pH, vesicular size, spreadability,

morphological characteristics and drug leakage studies. Franz diffusion cell assembly was used to carry out the *ex vivo* permeation studies through mice skin and the permeation profile of the developed FV formulation was compared with conventional formulations of levocetirizine.The *ex vivo* permeation studies revealed 1.78-fold increase in percent permeation of levocetirizine from FV formulation as compared to conventional formulations of levocetirizine in 8 h. Further, oxazolone induced atopic dermatitis murine model was selected to study the *in vivo* pharmacodynamic activity. The developed formulation was evaluated for scratching score, erythema score and histological evaluation. There was marked reduction in scratching score from 15.25 scratches/20 min with conventional levocetirizine cream to 6.75 scratches/20 min with application of levocetirizine FV formulation. Also, there was significant reduction in erythema score as well as dermal eosinophil count. Results of skin sensitivity and toxicity studies suggest that the developed formulation was dermally safe and nontoxic.A novel FVs based topical formulation of levocetirizine was successfully developed for treatment of atopic dermatitis. (Goindi*et al*., 2014)

The purpose of this study was to prepare and characterize levocetirizine hydrochloride loaded liposome of by film hydration technique followed by sonication. Sorbitol was added to facilitate the hydration of dried liposome into vesicles or to prepare rehydration system. The liposomes were characterized for size, shape, entrapment efficiency, invitro drug release and stability. The morphology of liposomes was characterized through a phase-contrast microscope and transmission electron microscope. On the other hand, it was observed that the drug release was decreased at higher concentration of cholesterol. The preliminary results of this study suggest that the developed multi-lamellar vesicles containing levocetirizine hydrochloride could enhance drug entrapment efficiency, reduce the initial burst release and modulate the drug release.(Visht*et al.*,2014).

In his research work, a simple, fast and reliable spectrophotometric methods were developed for determination of Levocetirizine in bulk and pharmaceutical dosage forms. The solutions of standard and the sample were prepared in methanol. The quantitative determination of the drug was carried out using the zero order derivative

values measured at 230 nm and the area under the curve method values measured at 227-234 nm (n=2). Calibration graphs constructed at their wavelengths of determination were linear in the concentration range of Levocetirizine using 5-25µg/ml (r^2=0.998 and r^2=0.999) for zero order and area under the curve spectrophotometric method. All the proposed methods have been extensively validated as per ICH guidelines. There was no significant difference between the performance of the proposed methods regarding the mean values and standard deviations. Developed spectrophotometric methods in this study are simple, accurate, precise and sensitive to assay of Levocetirizine in tablets (Mali *et al.*, 2015).

In 2016, three simple, precise, accurate and validated derivative spectrophotometric methods have been developed for the simultaneous determination of levocetirizine dihydrochloride (LCD) and ambroxol hydrochloride (ABH) in bulk powder and in pharmaceutical formulations. The first method is a first derivative spectrophotometric method using a zero-crossing technique of measurement at 210.4 nm for LCD and at 220.0 nm for ABH. The second method employs a second derivative spectrophotometry where the measurements were carried out at 242.0 and 224.4 nm for LCD and ABH, respectively. In the third method, the first derivative of the ratio spectra was calculated and the first derivative of the ratio amplitudes at 222.8 and 247.2 nm was selected for the determination of LCD and ABH, respectively. The developed methods have been successfully applied to the simultaneous determination of both drugs in commercial tablet dosage form. (Ali *et al.*, 2016).

This study includes that levocetirizine is a second-generation nonsedative antihistaminic agent that has been demonstrated to be safe and effective for treating allergic disease. There was only one case report of levocetirizine-induced liver toxicity, but a liver biopsy was not performed. In this article, we present the first case of levocetirizine-induced liver injury with histologic findings. A 48-year-old man was hospitalized with jaundice and generalized pruritus that had developed after 2 months of therapy with levocetirizine for prurigonodularis. Laboratory findings revealed acute hepatitis with cholestasis. A liver biopsy demonstrated portal inflammation and

hepatitis with apoptotic hepatocytes. The patient fully recovered 3 weeks after withdrawing levocetirizine. Although levocetirizine is safe and effective, physicians should be aware of its potential hepatotoxicity. (Jung *et al.*, 2016).

Recently on 27 February, 2017, a research work investigated the formulation and dissolution of orally disintegrating films of levocetirizine dihydrochloride.To enhance the convenience and compliance by the elderly or paediatric or bedridden and non-cooperative patients, due to its ease of administration,the present investigation was undertaken with the objective of formulating taste-masked orally-disintegrating films of the bitter levocetirizine dihydrochloride.Scope of this study was to explore the film forming properties of various film formers like modified starch, pullulan, hydroxypropyl methylcellulose and polyvinyl alcohol-polyethylene glycol based polymers. Plasticizers like glycerin, propylene glycol, sorbitol and polyethylene glycol 400 were evaluated by studying their effect on folding endurance, peelablity and in vitro disintegration time. Films were prepared by solvent casting method. The formulation developed is simple, easy to prepare and economical with great applicability during the emergency cases such as allergic reactions, whenever immediate onset of action is desired.

(Kathpalia and Patil, 2017).

Chapter Three

MATERIALS AND METHODS

Materials and methods

3.1 Introduction

The study on comparative dissolution profiles of levocetirizine dihydrochloride was carried out by using dissolution method to see the release pattern of levocetirizine dihydrochloride with different time interval. The method was verified and the rotating condition of the dissolution machine is optimized before application for sample analysis. Comparative dissolution testing is a valuable tool in drug development and Characterization. In addition to serving as routine quality control tests, comparative dissolution tests have been used to support waivers for bioequivalence requirements, for approval of generic drug products and accepting product sameness under Scale-up and Post Approval (SUPAC) related changes.

3.2 Reagents, Chemicals and Solvents

All reagents used were of analytical reagent grade and distilled water was used for the preparation of all solutions. To observe the change in dissolution levocetirizine dihydrochloride in dissolution media I used different brands of levocetirizine dihydrochloride tablet. I used active pharmaceutical ingredient (API) of levocetirizine dihydrochloride which was collect from Square Pharmaceuticals Ltd. As the dissolution media is water for dissolution of ranitidine we used water as a solvent.

For preparing a standard curve I used Purotrol tablet from Square Pharmaceuticals Ltd. Other tablets I used to see the release pattern with different time interval like Alcet , Seasonix, Lozin, Clarigen, and lecet etc.

3.3 Methods for Comparison of Dissolution Profile Data

A simple model independent method proposed by Moore and Flanner (1996) uses fit factors to compare dissolution profile data of a pair of products under similar testing conditions. These fit factors directly compare the difference between percent drug dissolved per unit time for a test and reference product. These factors are denoted f1 (difference factor) and f2 (similarity factor). (US FDA approvals, 1997; Saranadasa and Krishnamurthy, 2005; Sath, et. al. 1996; Yuksel et. al. 2000). Comparison of the dissolution profiles of clarithromycin can be satisfactorily carried out using the model independent approaches.

3.4 Difference factor

The difference factor (f1) is a measurement of the percent difference between two dissolution curves under comparison at each time point.

It is a measure of the relative error between the two curves and is given by the formula:

$$f1 = \frac{\sum_{t=1}^{n} |Rt - Tt|}{\sum_{t=1}^{n} Rt} \; x \; 100$$

where, n is the number of testing time points; Rt is the average dissolution value of the reference product units at time t and Tt is the average dissolution value of the test product units at time t. Similarity of two dissolution curves is indicated by f1 values of 0 - 15% (US FDA, 1997; Hasan, et. al. 2007; Yuksel, et. al. 2000).

3.5 Similarity factor

The similarity factor (f2) is a measurement of the similarity in the percent dissolution between two dissolution curves. It is inversely proportional to the average squared difference between the two profiles. It is a logarithmic reciprocal square root transformation of the sum of squared error and is given by the formula:

$$f2 = 50.log\left[1 \Big/ \sqrt{\left\{1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2\right\}} \; x \; 100\right]$$

Where, n is the number of testing time points; Rt is the average dissolution value of the reference product units at time t and it is the average dissolution value of the test product units at time t (US FDA, 1997; Hasan, et. al. 2007; Shah 2007; Yuksel, et. al. 2000). The proviso for evaluation for similarity is availability of data for six (6) or twelve (12) units of each product, availability of three or more dissolution time points, same conditions of testing for reference and test products and same dissolution time points for both profiles. As a further recommendation, it is suggested that only one measurement be considered after 85% dissolution of both products.

(US FDA, 1997; Hasan, et. al. 2007; Ochekpe, et. al. 2006).

The similarity factor has been adopted by the US FDA and the European Medicines Agency (EMEA) for dissolution profile comparison. When two dissolution profiles are identical, f2 = 100%. An average dissolution difference of 10% at all measured time point‘s results in an f2 value of 50%. For this reason, the public standard for similarity of two dissolution profiles has been set at 50 - 100% (EMEA 2010; USFDA 1997; Shah, 2007).

3.6 Dissolution testing methods for levocetirizine dihydrochloride

Dissolution media	Distilled water
Temperature	37ºC
RPM	50
Time	30 minutes
Wavelength	231 nm

Table 3.1: Parameters of dissolution of levocetirizine dihydrochloride

The release rate of levocetirizine dihydrochloride tablet was determined by using tablet dissolution tester USP XXII. The dissolution test was performed using 900ml water pH (7.4) at 37ºC and 50 rpm at every 10- min interval sample of 10 ml were withdrawn from the dissolution medium and the amount was replacing by 10 ml distill water. The sample was filtered through a filter paper named Whitman Filter paper and diluted to a suitable concentration of distilled water. The absorbance of the solution was measured 231 nm for drug clonazepam by using a Shimadzu UV- 1201 UV/visible double beam spectrophotometer (Hatch, Japan). Percentage of drug release was calculated using an equation obtained from standard curve. The dissolution was continued for 30 minutes to get simulated picture of drug release in the in vivo condition and drug dissolve at specified time periods was plotted as percent release versus time(hours) curve (Shah,*et al.*2007).

3.7 Preparation of Standard Curve

To prepare the standard curve, at first different concentrations (2, 4, 6, 8, 10) µg/ml of levocetirizine dihydrochloride was prepared. For the preparation of different concentrations of ranitidine, first tablets were crushed in mortar and pestle. From the crushed tablet 5 mg was taken and was dissolved in 100 ml of distilled water. By this procedure, the concentration of the stock solution became 10 µg/ml. This solution was filtered in the volumetric flask Then taken solution was 2 ml, 4 ml, 6 ml, 8 ml, 10 ml and added water was 8 ml, 6 ml, 4 ml, 2 ml, 0 ml. Then spectrophotometer is turned on and 231 nm wave length was set up. Then the spectrophotometer was adjusted for 0 and 100%. The solutions were placed on spectrophotometer to measure the absorbance. Then the absorbance was plotted against concentration. A straight line was found.

Serial No	Concentrations (µg/ml)
1	2
2	4
3	6
4	8
5	10

Table 3.2. Concentrations of levocetirizine dihydrochloride

3.8Preparation for dissolution test

3.8.1 Preparation of stock solution

Distilled water was prepared in the laboratory and was used as stock solution for dissolution test. For each batch 6L of distilled water was prepared.

3.8.2 Method for dissolution test of levocetirizine dihydrochloride tablets

6L (6000ml) of stock solution (distilled water) was prepared. Each vessel of dissolution tester was filled with 900 ml of stock solution (distilled water) Time 30 minute; rpm 50 was set up in the dissolution machine. Then the machine was allowed to warm up until it reached at 37.5

degree Celsius. Then tablets were placed in every vessel. After 10, 20 and 30 minutes 5 ml of solution was collected from each vessel and filtered, then from that 1 ml of solution was taken in another test tube and 9 ml distilled water was added to make it 10 ml. At last UV absorbance off the solutions were taken where the wave length was 231 nm.

3.9 Materials

3.9.1 Sample Collection

To observe the change in dissolution pattern of Different brands levocetirizine dihydrochloride of tablets were collected from the local drug store in Dhaka.

Brand Name	Source
Purotrol	Square Pharma Ltd.
Seasonix	Incepta Pharma Ltd
Lozin	Chemico Pharma Ltd.
Clarigen	Drug International Pharma Ltd.
Alcet	Healthcare Pharma Ltd.
Lecet	Pacific Pharma Ltd.

Table 3.3: Brand names of levocetirizine dihydrochloride under dissolution study

3.9.2. Stock solution

As levocetirizine dihydrochloride is soluble in water so distilled water was prepared in the laboratory of East West University and was used as stock solution for dissolution.

3.9.3. Equipment

In the characterization of matrix tablets of levocetirizine dihydrochloride (Kuss, 1992)

No.	Equipments	Source	Origin
1	Dissolution tester USPXXII	RC-6B	CHINA
2	UV-Spectrometer	HANNA1201PC	JAPAN
3	pH meter	HANNA pH 210	PORTUGAL
4	Distill Water Plant	SMIC	CHINA
5	Safety Pipette Filler	Saffron	ENGLAND
6	Filter	Copley Instruments	ENGLAND
7	Electronic Balance	Precisa XB120A	SWITZERLAND
8	Friability tester	VEEGO(EF-2)	INDIA
9	Vernier Slide Calipers	TRICLYCLE RING	INDIA
10	Hardness tester	Monasnto manually operating hardness tester	CHINA

Table.3.4. Details about equipment

3.10 Instrumentation

3.10.1 Dissolution Test Apparatus

A Dissolution tester USPXXII (source RC-6B, made in China) was used for dissolution experiments. It incorporated a clear acrylic water bath, a stirrer hood with paddle shafts, an automatic sampling unit and a control unit supported by microcontroller software with a nonvolatile memory for 15 methods. The water bath incorporated an immersion circulator with an in-built thermostat for temperature control, an external temperature sensor, a water level sensor and a lid with support for eight dissolution bowls. The stirrer hood was equipped with 8 paddle shafts fitted with USP apparatus 2 and a tablet dispenser with 8 conical shaped dissolution bowl lids. The automatic sampling unit consisted of 10in-line filters, a bi-directional 12- channel peristaltic pump with tygon tubing‘s, a microprocessor controlled sample collector and a sample tray capable of collecting 10 x 6 sets of samples. Polycarbonate dissolution vessels with a hemispherical bottom and a capacity of 1000 ml were used for the study. Bromide (E. Merck, Darmstadt, Germany) and a manually operated hydraulic pellet press (Perking Elmer GmbH, Uberlingen, Germany).

3.10.2 Ultra- Violet Spectrophotometer

The ultra-violet absorption spectrum for clonazepam working standard was recorded using a double beam T90+ UV/VIS spectrometer controlled via a computer using UVWIN spectrophotometer

Software version 5.2.0 (HACH UV-1201 PC, JAPAN) over a 10-mm path length using quartz cuvettes.

3.11 Samples and Chemical Reference Substances

Clonazepam tablets from different manufacturers were used in the study. The samples were obtained from different private retail outlets within Bangladesh (Kuss, 1992).

3.12 Some Images of Instruments

Images of important instruments those were used in different testes during research work are given below-

Fig 3.1. Dissolution apparatus

Fig 3.2. UV spectrophotometer

Fig. 3.3. Distilled water apparatus

Figure 3.4. Hardness tester

Fig 3.5. Electronic Balance

3.13 Dissolution Efficiency

The dissolution efficiency is not a parameter to compare dissolution pattern between two brands. It is just a parameter to indicate drug release. It is calculated by the following equation:

$$DE = \frac{\int_{t1}^{t2} y.dt}{y100 \times (t2 - t1)} \times 100$$

In the above equation, y is the percentage of drug release. The numerator of the equation

indicates the area under within the time frame. The denominator indicates the rectangle of 100% drug release from 0 times throughout the time frame. The area under the curve is calculated by the help of Microsoft Excel software,

(Anderson et al. 1998; Parakh and Patil 2014).

3.14 Apparatus:

Some apparatus is listed in following table those were used throughout the experiments.

Serial No	Apparatus
1	Beakers
2	Test tubes
3	Volumetric flasks
4	Filter paper
5	Spatula
6	Mortar and pestle
7	Pipette pumper
8	Pipette (1 ml &10 ml)

Table 3.5: Representing the apparatus (Kuss, 1992)

Chapter Four

RESULTS

AND

DISSCUSSION

4.1 Standard curve of levocetirizine drugs

4.1.1 Standard curve of Purotrol

For the calculation of drug release from the innovator brand as well as test brands, a standard curve was prepared within the concentration range of 0-25 microgram/mL. The curve displayed sufficient linearity with a correlation coefficient (R^2) value of 0.9914provided an equation y=0.0331x+0.0093.

Table: Standard curve of Purotrol

conc.(µg/ml)	Absorbance
0	0
2	0.06
4	0.115
6	0.174
8	0.25
10	0.337

Table 4.1: Standard curve of Purotrol

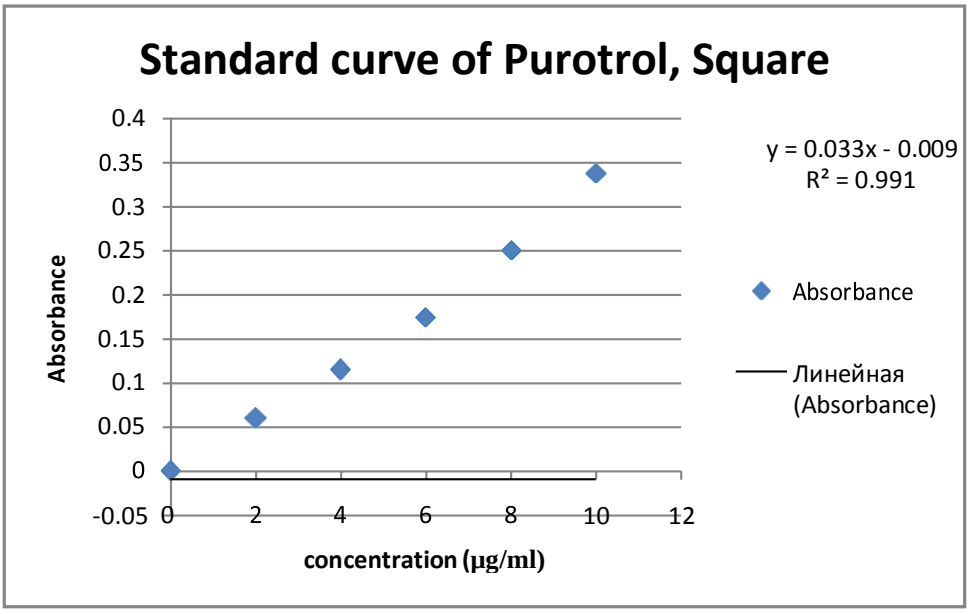

Figure 4.1: Standard curve of Purotrol

4.1.2 Standard curve of Alcet

For the calculation of drug release from the innovator brand as well as test brands, a standard curve was prepared within the concentration range of 0-25 microgram/mL. The curve displayed sufficient linearity with a correlation coefficient (R^2) value of 0.9917provided an equation y=0.038x+0.012.

Table: Standard curve of Alcet.

Concentration (µg/ml)	absorbance
0	0
2	0.113
4	0.18
6	0.243
8	0.315
10	0.398

Table4.2: Standard curve of Alcet.

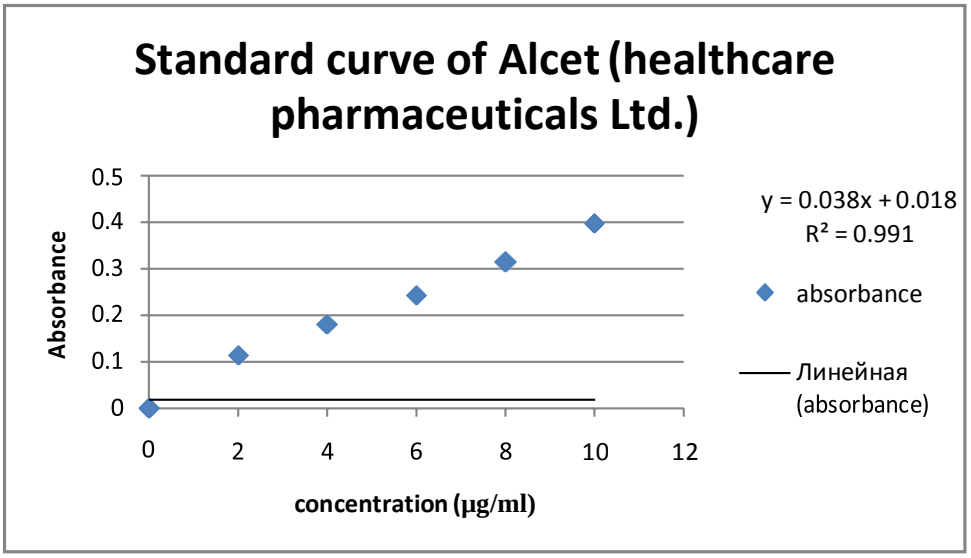

Figure 4.2: Standard curve of Alcet.

4.1.3 Standard curve of Lecet

For the calculation of drug release from the innovator brand as well as test brands, a standard curve was prepared within the concentration range of 0-25 microgram/mL. The curve displayed sufficient linearity with a correlation coefficient (R^2) value of 0.994provided an equation y=0.0357x+0.0091.

Table: Standard curve of Lecet.

conc.(µg/ml)	absorbance
0	0
2	0.066
4	0.121
6	0.194
8	0.276
10	0.359

Table 4.3: Standard curve of lecet.

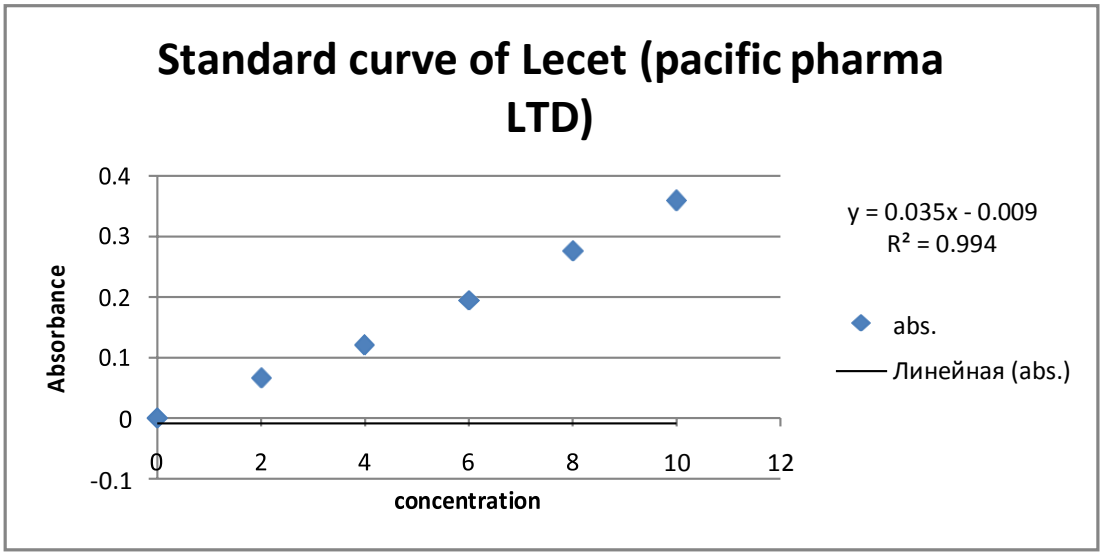

Figure 4.3: Standard curve of Lecet.

4.1.4 Standard curve of seasonix

For the calculation of drug release from the innovator brand as well as test brands, a standard curve was prepared within the concentration range of 0-25 microgram/mL. The curve displayed sufficient linearity with a correlation coefficient (R^2) value of 0.991 provided an equation y=0.0455x+0.081.

.

Table: Standard curve of seasonix.

Concentration (µg/ml)	absorbance
0	0
2	0.079
4	0.15
6	0.233
8	0.305
10	0.343

Table 4.4: Standard curve ofseasonix .

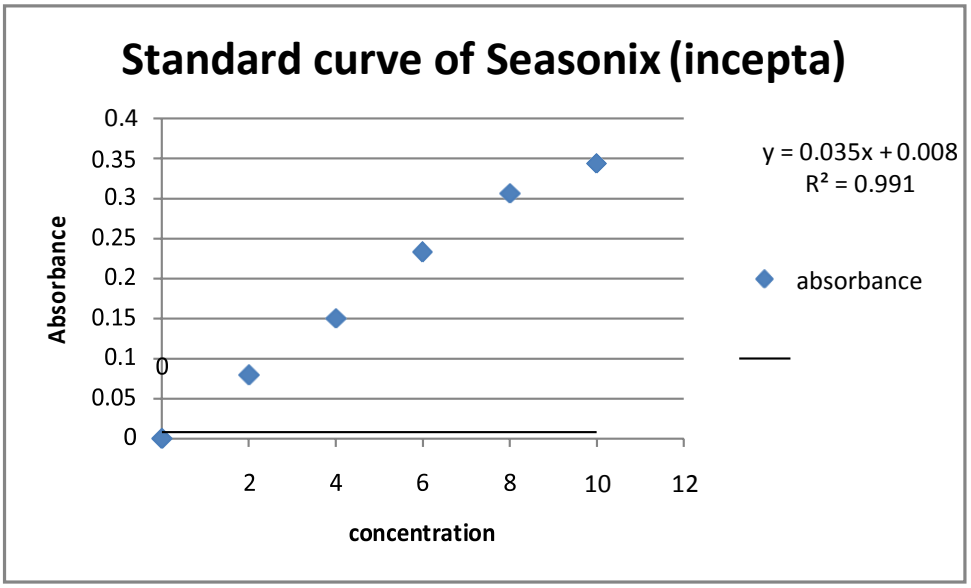

Figure 4.4: Standard curve of seasonix

4.1.5 Standard curve of lozin:

For the calculation of drug release from the innovator brand as well as test brands, a standard curve was prepared within the concentration range of 0-25 microgram/mL. The curve displayed sufficient linearity with a correlation coefficient (R^2) value of 0.996provided an equation y=0.0455x+0.0125.

Table: Standard curve of lozin.

concentration	absorbance
0	0
2	0.088
4	0.151
6	0.218
8	0.315
10	0.394

Table 4.5: Standard curve of lozin.

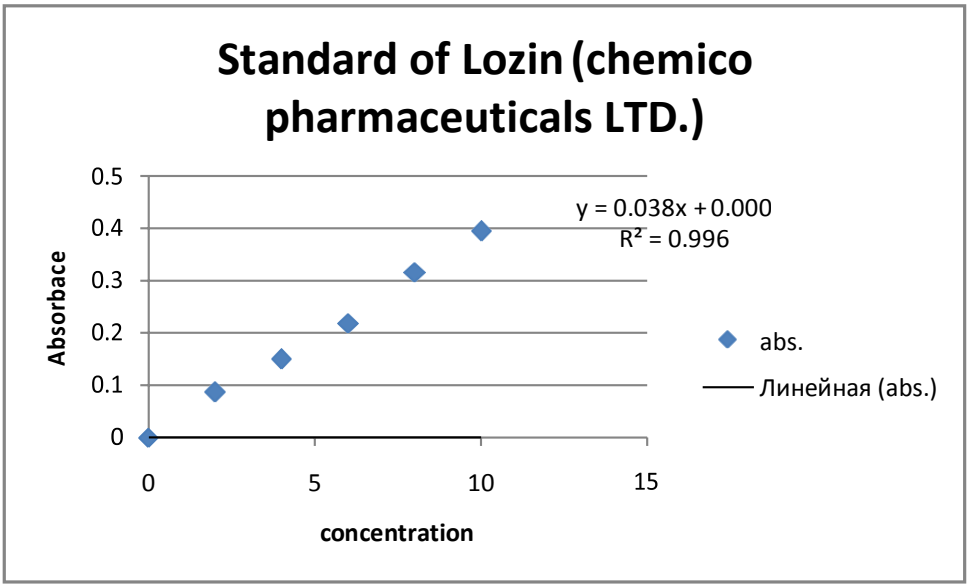

Figure 4.5: Standard curve of Lozin

4.1.6 Standard curve of clarigen :

For the calculation of drug release from the innovator brand as well as test brands, a standard curve was prepared within the concentration range of 0-25 microgram/mL. The curve displayed sufficient linearity with a correlation coefficient (R^2) value of 0.9916and provided an equation y=0.0455x+0.0125.

Table: Standard curve of clarigen

concentration	Absorbance
0	0
2	0.088
4	0.236
6	0.38
8	0.484
10	0.569

Table 4.6: Standard curve of clarigen.

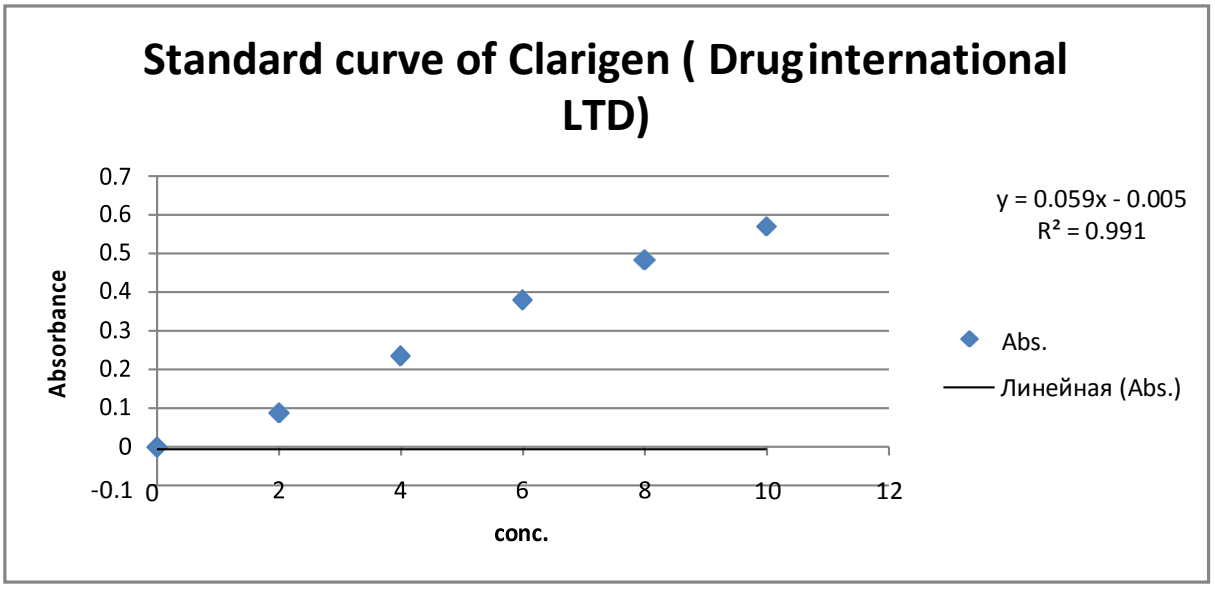

Figure 4.6: Standard curve of clarigen.

4.2 Percent (%) release &Dissolution curves of levocetirizine drugs

4.2.1 Percent (%) Release of purotrol tablets average

time	%release
0	0
10	52.02797
20	93.14685
30	93.98601

Table 4.7: Time and release pattern of purotrol.

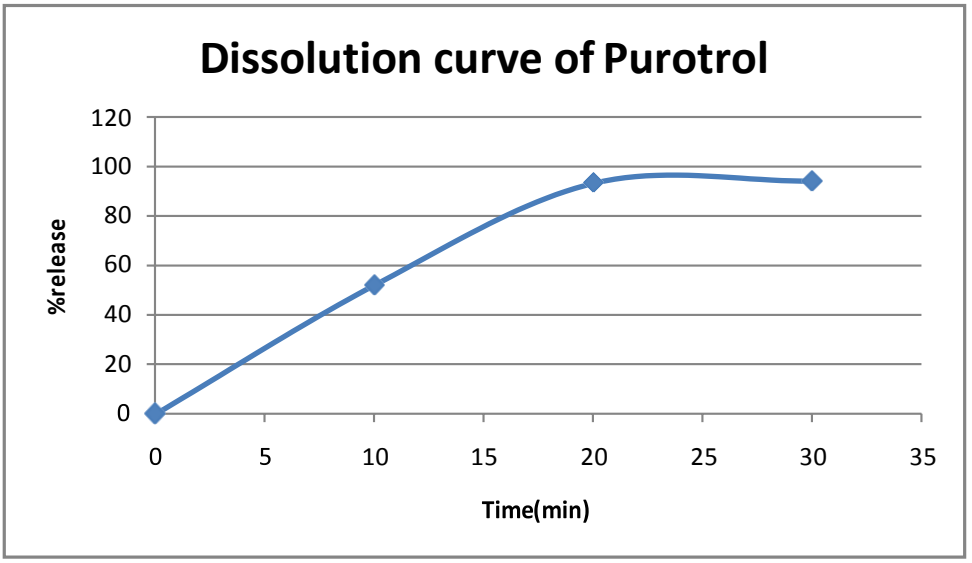

Figure 4.7: Time Vs Drug Release (%) average of purotrol tablets

This graph represents that, the increasing of drug release in according to the counting of time in 0.00 the drug release was 0.00 and then in 10 minutes was 52.028, then 20.00 minutes was 93.14685, then 30.00 minutes has93.98601. Here X axis represents the time and Y axis is for % Drug release.

4.2.2 Percent (%) Release of Alcet tablets average

Time	%release
0	0
10	85
20	86.68
30	99

Table 4.8: Time and release pattern of Alcet

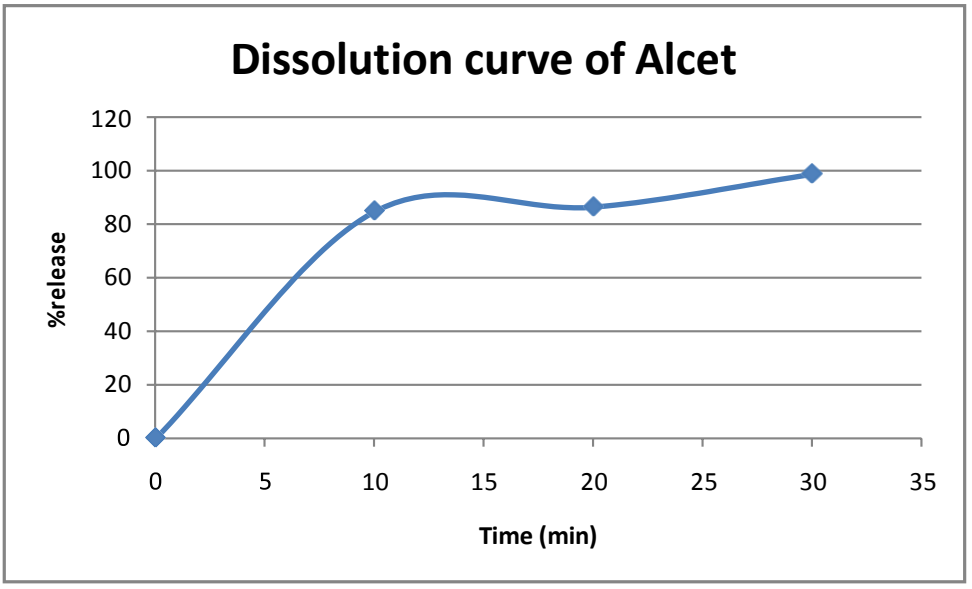

Figure 4.8: Time Vs Drug Release (%) average of Alcet Tablets

This graph represents that, the increasing of drug release in according to the counting of time in 0.00the drug release was 0.00 and then in 10 minutes was 85, then 20.00 minutes was 86.68, then 30.00 minutes has 99. Here X axis represents the time and Y axis is for % Drug release.

4.2.3 Percent (%) Release of seasonix tablets average

time	%release
0	0
10	81.20301
20	92.84211
30	93.65414

Table 4.9: Time and release pattern of seasonix

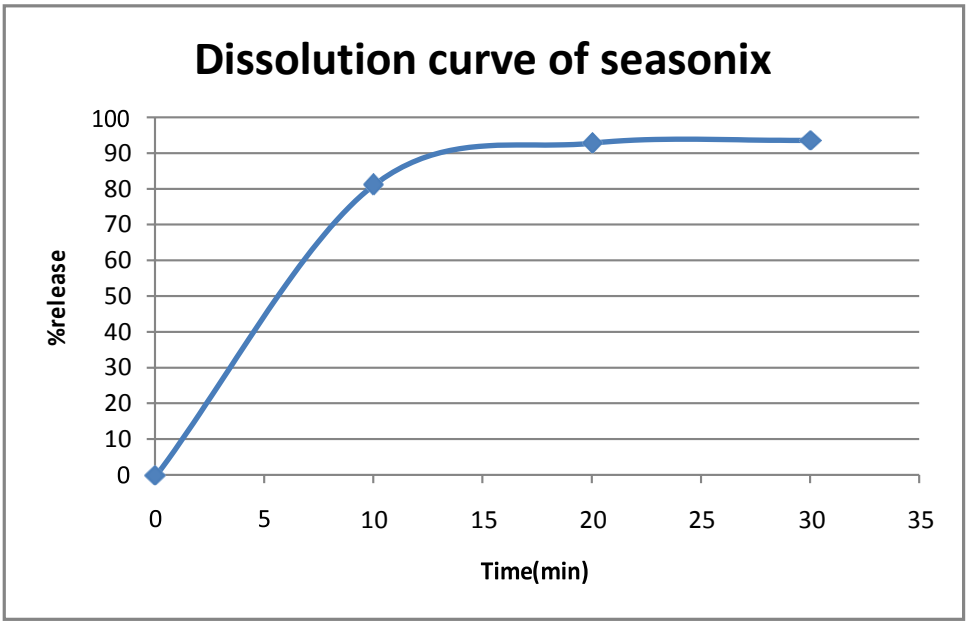

Figure 4.9: Time Vs Drug Release (%) average of seasonix tablets

This graph represents that, the increasing of drug release in according to the counting of time in 0.00 the drug release was 0.00 and then in 10 minutes was 81.20301, then 20.00 minutes was 92.84211, then 30.00 minutes has93.65414. Here X axis represents the time and Y axis is for%Drug release.

4.2.4 Percent (%) Release of Lozin tablets average:

time	%release
0	0
10	76.57895
20	96
30	98

Table 4.10: Time and release pattern of Lozin

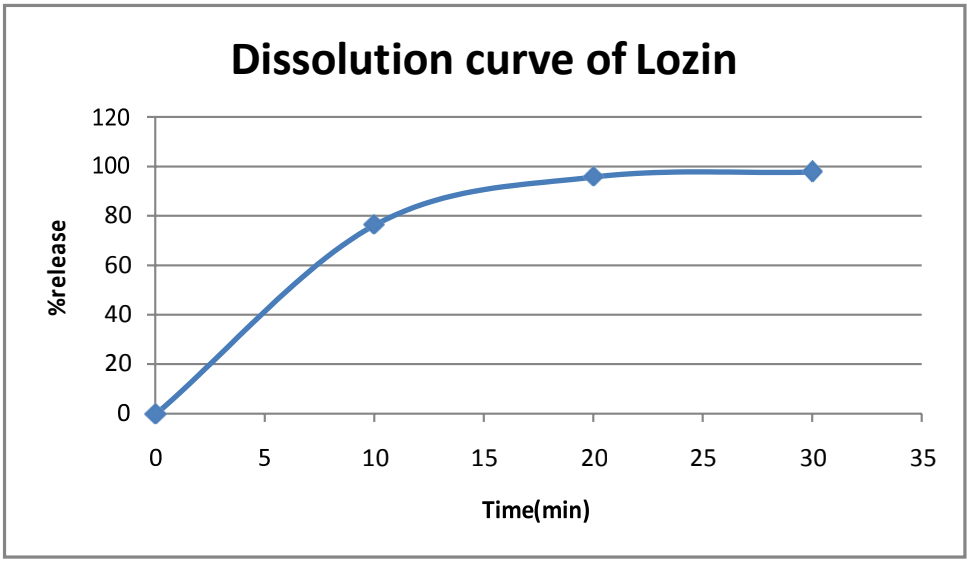

Figure 4.10: Time Vs Drug Release (%) average of Lozin Tablets

This graph represents that, the increasing of drug release in according to the counting of time in 0.00the drug release was 0.00 and then in 10 minutes was76.57895, then 20.00 minutes was96, then 30.00 minutes has 98. Here X axis represents the time and Y axis is for % Drug release.

4.2.5 Percent (%) Release of Clarigen tablets average:

time	%release
0	0
10	36.30508
20	67.42373
30	75.35593

Table 4.11: Time and release pattern of Clarigen

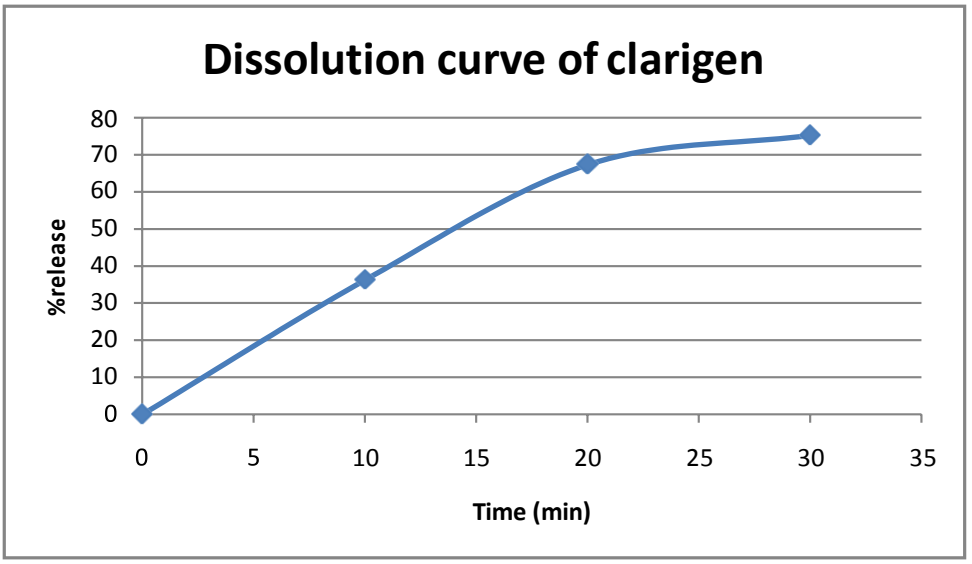

Figure 4.11: Time Vs Drug Release (%) average of Clarigen Tablets

This graph represents that, the increasing of drug release in according to the counting of time in 0.00the drug release was 0.00 and then in 10 minutes was 36.31, then 20.00 minutes was67.42 , then 30.00 minutes has 75.36. Here X axis represents the time and Y axis is for % Drug release.

4.2.6 Percent (%) Release of Lecet tablets average

time	%release
0	0
10	81.85714
20	91.71429
30	99.85714

Table 4.12: Time and release pattern of Lecet.

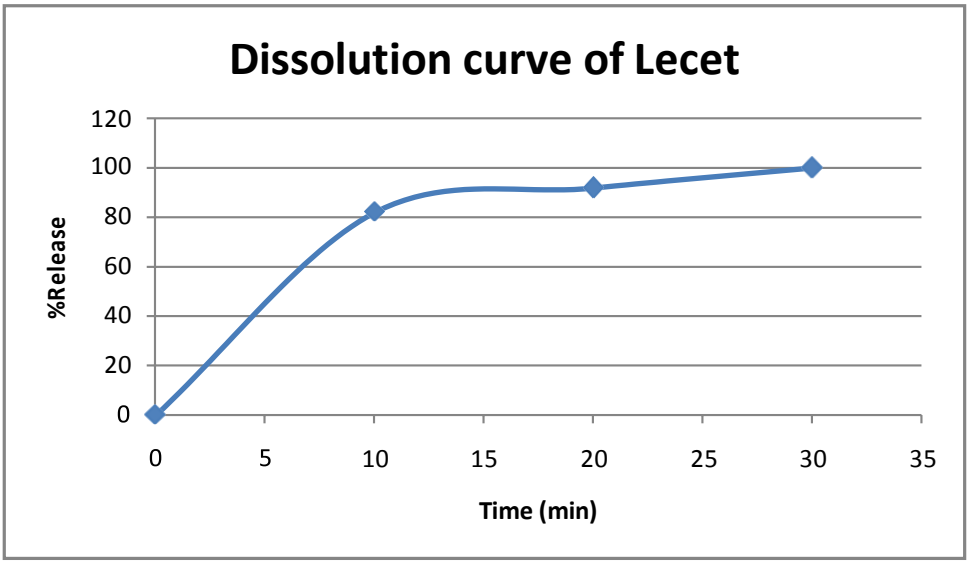

Figure 4.12: Time Vs Drug Release (%) average of Lecet Tablets

This graph represents that, the increasing of drug release in according to the counting of time in 0.00the drug release was 0.00 and then in 10 minutes was81.85, then 20.00 minutes was91.71 , then 30.00 minutes has99.86. Here X axis represents the time and Y axis is for % Drug release.

4.3 Drug dissolution of different brands

Time(Minutes)	Purotrol Release (%)	Alcet Release (%)	Lecet Release (%)	Clarigen Release (%)	Lozin Release (%)	Seasonix Release (%)
0	0	0	0	0	0	0
10	52.02	85	81.85	36.30	76.57	81.20
20	93.14	86.68	91.71	67.42	96	92.84
30	93.98	99	99.85	75.35	98	93.65

*4.4 f*1 value of different brands of levocetirizine(Alcet , lecet , lozin , clarigen) with respect to purotrol*:*

Difference Factor, f1 is the average difference between all the points of sampling between two brands e.g. reference brand and one of the two test brands. Acceptable range of f1 is between 0-15. f1 value greater than 15 means significant difference between two brands which is not accepted (Lokhandwala et al. 2013; Parakh and Patil 2014; Patel, et. al. 2015; Qazi et al.2013).Acceptable range of *f*1 is between 0-15. *f*1 value greater than 15 means significant difference between two brands which is not accepted.

4.4.1*f*1 Calculation for Purotrol and Alcet

Time	Purotrol (R)	Alcet (T)	R-T	IR-TI	*f 1*
0	0	0	0	0	
10	52.027	99.236	47.209	47.209	
20	93.146	86.684	6.462	6.462	26.08
30	93.986	85.263	8.723	8.723	
	239.160			62.392	

Acceptable range of *f*1 is between 0-15. *f*1 value greater than 15 means significant difference between two brands which is not accepted. From the table we see that the values of *f*1 is 26.08 so it is not acceptable.

4.4.2*f*1 Calculation for Purotrol and Lecet

Time	Purotrol (R)	Lecet (T)	R-T	IR-TI	*f 1*
0	0	0	0	0	
10	52.027	81.857	-29.83	29.83	
20	93.146	91.714	1.432	1.432	15.52
30	93.986	99.857	-5.871	5.871	
	239.160			37.133	

Acceptable range of *f*1 is between 0-15. *f*1 value greater than 15 means significant difference between two brands which is not accepted. From the table we see that the values of *f*1 is 15.52 so it is not acceptable.

4.4.3*f*1 Calculation for Purotrol and Clarigen

Time	Purotrol (R)	Clarigen (T)	R-T	IR-TI	*f 1*
0	0	0	0	0	
10	52.027	36.305	15.722	15.722	
20	93.146	67.423	25.723	25.723	25.11
30	93.986	75.355	18.631	18.631	
	239.160			60.076	

Acceptable range of *f*1 is between 0-15. *f*1 value greater than 15 means significant difference between two brands which is not accepted. From the table we see that the values of *f*1 is 25.11 so it is not acceptable

4.4.4*f*1 Calculation for Purotrol and Lozin

Time	Purotrol (R)	Lozin (T)	R-T	IR-TI	*f 1*
0	0	0	0	0	
10	52.027	76.578	-24.661	24.661	
20	93.146	98.289	-5.143	5.143	13.7
30	93.986	96.710	-2.724	2.724	
	239.160			35.528	

Acceptable range of *f*1 is between 0-15. *f*1 value greater than 15 means significant difference between two brands which is not accepted. From the table we see that the values of *f*1 is 13.7 so it is acceptable

4.5 *f*2 value of different brands of levocetirizine(Alcet , lecet , lozin , clarigen) with respect to purotrol:

Similarity Factor, *f*2 Similarity factor is calculated to determine significant similarity between two brands. The range of the *f*2 value is between 0 to 100. If the value remains between 50 to 100, it is acceptable (Lokhandwala et al. 2013; Parakh and Patil 2014; Patel et al. 2015; Qazi et al.2013).

4.5.1 *f*2 Calculation for Purotrol and Alcet

Time	Purotrol (R)	Alcet (T)	R-T	IR-TI	IR-TI^2	*f 2*
0	0	0	0	0	0	
10	52.027	99.236	47.209	47.209	2228.686	
20	93.146	86.684	6.462	6.462	41.757	30.77
30	93.986	85.263	8.723	8.723	76.311	
	239.160			62.392	2347.232	

The range of the f2 value is between 0 to 100. If the value remains between 50 to 100, it is acceptable. From the table we see that the values of *f*2 is30.77 so it is not acceptable.

4.5.2 *f*2 Calculation for Purotrol and Lecet

Time	Purotrol (R)	Lecet (T)	R-T	IR-TI	IR-TI^2	*f 2*
0	0	0	0	0	0	
10	52.027	81.857	-29.83	29.83	8889.822	
20	93.146	91.714	1.432	1.432	2.050	16.27
30	93.986	99.857	-5.871	5.871	34.464	
	239.160			37.133	8926.234	

The range of the f2 value is between 0 to 100. If the value remains between 50 to 100, it is acceptable. From the table we see that the values of *f*2 is16.27 , so it isnotacceptable.

4.5.3 *f*2 Calculation for Purotrol and Clarigen

Time	Purotrol (R)	Clarigen (T)	R-T	IR-TI	IR-TI^2	*f 2*
0	0	0	0	0	0	
10	52.027	36.305	15.722	15.722	247.181	
20	93.146	67.423	25.723	25.723	661.674	37.54
30	93.986	75.355	18.631	18.631	347.114	
	239.160			60.076	1255.969	

The range of the f2 value is between 0 to 100. If the value remains between 50 to 100, it is acceptable. From the table we see that the values of *f*2 is37.54, so it is not acceptable.

4.5.4 *f*2 Calculation for Purotrol and Lozin

Time	Purotrol (R)	Lozin (T)	R-T	IR-TI	IR-TI^2	*f 2*
0	0	0	0	0	0	
10	52.02797	76.578	-24.661	24.661	608.164	
20	93.14685	98.289	-5.143	5.143	26.456	44.79
30	93.98601	96.710	-2.724	2.724	7.432	
	239.160			35.528	642.164	

The range of the f2 value is between 0 to 100. If the value remains between 50 to 100, it is

Acceptable. From the table we see that the values of *f*2 is44.79, so it is not acceptable

4.6 Final Discussion:

In this study from the above charts, comparisons of dissolution profiles of levocetirizine tablets were done to see the release pattern of levocetirizine dihydrochloride with different time interval. Comparative dissolution testing is a valuable tool in drug development and Characterization. In addition to serving as routine quality control tests, comparative dissolution tests have been used to support waivers for bioequivalence requirements, for approval of generic drug products and accepting product sameness under Scale-up and Post Approval (SUPAC) related changes. Here I used Purotrol tablet from Square Pharmaceuticals Ltd. Other tablets I used to see the release pattern with different time interval like Alcet, Seasonix, Lozin, Clarigen, and Lecet etc. with respect to purotrol. The criteria for similarity were taken as f1= (0 to 15) and f2 value of (50 to 100) for the tablets . The study was carried out at pH 7 normal range, media was water and values were calculated .the influence of pH was ignored . the extreme variations in the API release profiles for levocetirizine tablets reflect significant differences in the quality of manufacturing .This could be due to different sources and quality of coating process , relative comparison of content of polymers and other excipients .

From the above study we know that difference Factor, f1 is the average difference between all the points of sampling between two brands e.g. reference brand and one of the test brands. Acceptable range of f1 is between 0-15. f1 value greater than 15 means significant difference between two brands which is not accepted . Here we observed Alcet, Lecet , Clarigen has f1 value greater than 15 i.e. (26.08,15.52, and 25.11) , therefore they are not acceptable . Only Lozin has f1 value less than 15 i.e.(13.7) therefore that is accepted .

Again we observed the f2 values for different brands of levocetirizine .The similarity factor (f2) is a measurement of the similarity in the percent dissolution between two dissolution curves. It is inversely proportional to the average squared difference between the two profiles. The range of the *f*2 value is between 0 to 100. If the value remains between 50 to 100, it is acceptable. The f2 values of Alcet, Lozin, Lecet and Clarigen is observed that 30.77, 44.79, 15.52 and 25.11 respectively. Therefore they were not acceptable at all. To sum up, it is clearly observed that these have impacts on efficacy of the products raising further concerns about the effect sub therapeutic outcomes and repercussions of treatment failures especially for levocetirizine.

Chapter Five
CONCLUSION

Conclusion

Levocetirizine dihydrochloride is classified in Class II as it has high solubility and low permeability by the BCS. Dissolution tests are essential for the prognosis of dosage form oral absorption and bioequivalence of drugs. In this study we have compared the dissolution profile of local brands Alcet , Seasonix, Lozin, Clarigen ,and Lecet etc. with respect to purotrol(square) .It was found that the difference factor of observed Alcet , Lecet , Clarigen has f1 value greater than 15 i.e. (26.08,15.52, and 25.11 respectively) , therefore they are not acceptable . Only Lozin has f1 value less than 15 i.e. (13.7) therefore that is accepted .The similarity factor i.e. f2 values of Alcet, Lozin, Lecet and Clarigen is observed that 30.77, 44.79, 15.52 and 25.11 respectively. Therefore they were not acceptable at all. The similarity factor and Difference factors of these local brands Levocetirizine was not in the acceptable range. In conclusion, further investigations are needed to find out the better dissolution profile for these brands.

Reference

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