In-vitro Comparative Dissolution Study of Different Brands of Ranitidine Hydrochloride Tablets Available in Bangladesh

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

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During the course of this research work, a lot of experiences I have received which is of inestimable value for my life.

Declaration by the Research Candidate

I, **Razia Sultana, ID: 2012-3-70-035**, hereby declare that the dissertation entitled "*In- vitro Comparative* Dissolution Study of Different Brands of Ranitidine Hydrochloride Table Available in Bangladesh" submitted by me to the Department of Pharmacy, East West University and in the partial fulfillment of the requirement for the award of the degree Bachelor of Pharmacy, under the supervision and guidance of **Tirtha Nandi**, Lecturer, Department of Pharmacy, East West University, Dhaka.

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Certificate by the Supervisor

This is to certify that the thesis entitled "*In- vitro Comparative* Dissolution Study of Different Brands of Ranitidine Hydrochloride Table Available in Bangladesh" 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, is a original record and genuine research work carried out by **Razia Sultana**, **ID: 2012-3-70-035** in 2016 of his research in the Department of Pharmacy, East West University, under my supervision and guidance.

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Certificate by the Chairperson

This is to certify that the thesis entitled "*In- vitro Comparative* Dissolution Study of Different Brands of Ranitidine Hydrochloride Table Available in Bangladesh" 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 is a record of original and genuine research work carried out by **Razia Sultana**, **ID: 2012-3-70-035** in 2016.

DR. SHAMSUN NAHAR KHAN
Associate Professor and Chairperson
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Dedication

This Research Paper is dedicated to

My beloved parents,

Who are my biggest inspiration …

Abstract

Branded drug products are normally expensive than locally marketed drug product of region of pharmaceutical companies. Generic substitution is very common in under-developed and developing counties including Bangladesh. The aim of the present was to evaluate and compare dissolution pattern of locally branded drug product of Ranitidine HCl (Zantac®) marketed by Glaxo Smith Kline Bangladesh Ltd. I took two brands of Ranitidine tablets available in Bangladesh as well as Zantac® were collected from a reputed pharmacy store in Dhaka. Six tablets from each of the brands were used for *in vitro* dissolution study. Cumulative drug release was measured up to 50 minutes for all two brands named Ethidine and Inseac and then all two brands were compared with innovator brand. The drug release pattern is not an indicator of drug efficacy in the body. Comparison of the dissolution profiles was carried out by calculation of the similarity factor and difference factor. The study was carried out at pH 7.4 normal range and water is used as media and then it was calculated for the values of factors. It was ran for 50 minutes with the intervals of 10 minutes and found the results provided previous discussion. The influence of pH was ignored in this study. The result may vary with them due to API quality, formulation factors and other things. In this study, comparisons of dissolution profiles of Ranitidine HCl oral formulations were made between three generic products.

Key Word: Percentage of Release, Ranitidine (Zantac®), Inseac, Ethidin, Comparison of dissolution study.

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CHAPTER: 1

INTRODUCTION

1.1 Objective

Ranitidine is in a group of drugs called histamine-2 blockers. Ranitidine works by reducing the amount of acid your stomach produces. Ranitidine is used to treat and prevent ulcers in the stomach and intestines. It also treats conditions in which the stomach produces too much acid, such as Zollinger-Ellison syndrome. Ranitidine also treats gastro esophageal reflux disease (GERD) and other conditions in which acid backs up from the stomach into the esophagus, causing heartburn. In Bangladesh all of the leading pharmaceuticals have production of ranitidine tablet, and the number of pharmaceutical company have production of Ranitidine in Bangladesh in more than 70.As it is known bio pharmaceutics classification for drugs scheme for correlating in vitro drug product dissolution and in vivo bioavailability is proposed based on recognizing that drug dissolution and gastrointestinal permeability are the fundamental parameters controlling rate and extent of drug absorption. So to know the potency the bioavailability identification is one of the most marked points (Lennernäs and Crison, 2016).

The existence of poor quality drugs in circulation in many third world countries has been reported. Bangladesh is one of the medium earning countries of the world so it is very important to have a observation of the regular drugs used by the mass population (Birhanu *et al*., 2013).

1.2 H2 blockers

1.2.1 H2 Blockers General Information

H2 blockers which are also sometimes denoted to as acid reducers or H2 receptor antagonists are available in nonprescription and prescription forms. Prescription forms are stronger than the nonprescription forms. H2 blockers are usually taken by mouth, but some can also be given as an injection. Two doses (morning and evening) are typically suggested to control both daytime and nighttime symptoms. Doctors sometimes applaud a single dose, taken at bedtime, for people who have difficulty remembering to take their medicines. Histamine H2-receptor antagonists, are also used to treat duodenal ulcers and prevent their return. They are also used to treat gastric ulcers and for some conditions, such as Zollinger-Ellison disease, in which the stomach produces too much acid. In over-the-counter (OTC) strengths, these medicines are used to relieve or prevent heartburn, acid indigestion, and sour stomach. H2-blockers which may also be used for other conditions as determined by your doctor.H2-blockers work by decreasing the amount of acid produced by the stomach. H2-blockers are available both over-the-counter (OTC) and with your doctor's prescription. Once a medicine has been approved for marketing for

a certain use, experience may show that it is also useful for other medical problems. Although these uses are not included in product labeling, H2-blockers are used in certain patients with the following medical conditions:

- Damage to the stomach and/or intestines due to stress or trauma
- Hives
- Pancreatic problems
- Stomach or intestinal ulcers (sores) resulting from damage caused by medication used to treat rheumatoid arthritis
- This product is available in the following dosage forms:
- Solution
- Tablet
- Capsule
- Suspension
- Injectable
- Granule
- Capsule, Liquid Filled
- Tablet, Effervescent
- Syrup
- Packet
- Powder for Suspension
- Tablet, Chewable (Michael *et al.,* 1974).

1.2.2 Mechanism of Action H2 Blockers

H2 blockers reduce the production of stomach acid. This makes the stomach juices less acidic so that any stomach juice that gets into the esophagus is less irritating. This relieves symptoms and allows the esophagus to heal. Your stomach normally produces acid to help with the digestion of food and to kill germs (bacteria).As this acid is corrosive for our body, our body produces a natural mucous barrier which protects the lining of the stomach from being worn away (eroded).

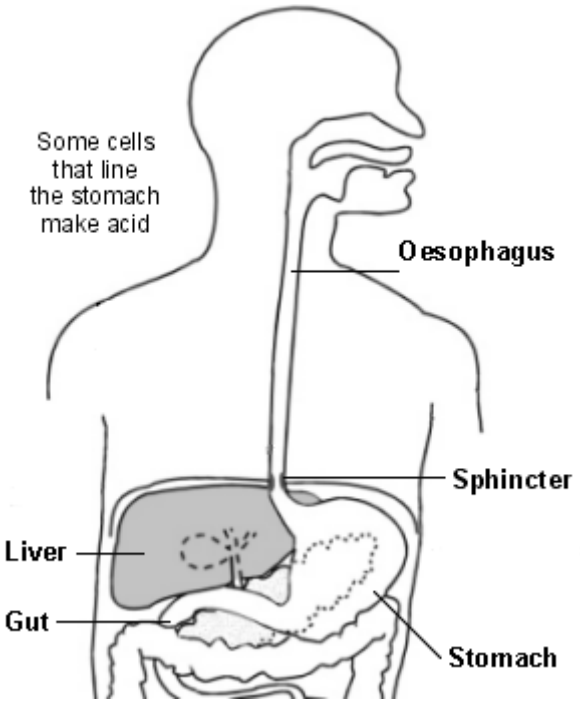


Figure 1.1: Gastrointestinal track

In some people this barrier may have broken down allowing the acid to damage the stomach, causing an ulcer. In others there may be a problem with the muscular band at the top of the stomach (the sphincter) that keeps the stomach tightly closed. This may allow the acid to escape and irritate the gullet (esophagus). This is called 'acid reflux', which can cause heartburn and/or inflammation of the gullet (esophagitis).The letter H in their name stands for histamine. Histamine is a chemical naturally produced by certain cells in the body, including cells in the lining of the stomach, called the enterochromaffin-like cells (ECL cells). Histamine released from ECL cells then stimulates the acid-making cells (parietal cells) in the lining of the stomach to release acid. What H2 blockers do is stop the acid-making cells in the stomach lining from responding to histamine. This reduces the amount of acid produced by your stomach. By decreasing the amount of acid, H2 blockers can help to reduce acid reflux-related symptoms such as heartburn. This can also help to heal ulcers found in the stomach or in part of the gut (the duodenum). H2-blockers are a dissimilar class of drugs to 'antihistamine drugs' which block H1 receptors in cells that are involved in allergy reactions (Gan *etal.,* 1993).

1.2.3 Clinical Use

H2 antagonists are mostly effective in cases of severe heartburn that do not respond to life-style measures Severe heartburn, especially if complicated by inflammation of the

esophagus often know as esophagitis, with bleeding or stricture, requires immediately a proton pump inhibitor.

Notable is H2 antagonists are truly misused if taken for irritable bowel syndrome (IBS), dyspepsia, or other abdominal pains that are unaffected by the presence of gastric acid.

Failure of an H2 blocker to relieve heartburn in a few days, bleeding, or swallowing difficulties should be promptly reported to a physician.

In addition to the four patented drugs named mentioned in 1.2.1, there are many generic versions. These come in a different patterns of formulations; capsules, pills, chewable, liquid, effervescent, or joined with antacids. Physicians and pharmacists always advice users to go through the label before taking these medicines (International foundation for functional gastrointestinal disorders, 2014).

1.2.4 Unwanted actions

Severe adverse of contraindicated effects of H2 Blockers have been reported in different clinical trials. These adverse effects stopped in only 1.5% of patients receiving the drugs in clinical trials, compared to 1.2% for the placebo. Thus, the H2 blocking drugs are relatively safe and thus become one of the most prescriber drugs.

But unwanted side effects and possible interactions with other drugs may sometimes occur. Notable safety has not been proven in pregnant and the drugs also appear in breast milk (Patient, 2014).

Some of the side effects that may occur with H2 receptor blockers include:

- ✓ Constipation
- ✓ Diarrhea
- ✓ Difficulty sleeping
- ✓ Dry mouth
- ✓ Dry skin
- ✓ Headaches
- ✓ Ringing in the ears
- ✓ A runny nose
- ✓ Trouble urinating

In rare cases, H2 receptor blockers might cause more serious side effects, such as:

- ✓ Blistered, Burning, or Scaling skin
- ✓ Changes in vision
- ✓ Confusion

- ✓ Agitation
- ✓ Difficulty breathing
- ✓ Wheezing
- ✓ Chest tightness
- ✓ Irregular heartbeat
- ✓ Hallucinations
- ✓ Suicidal thoughts (Healthline, 2016).

1.2.5 H2 Receptor Blockers vs. Proton Pump Inhibitors (PPIs)

There are other medications reducing the stomach acid like, Proton pump inhibitors (PPIs) are another type of medication used to reduce stomach acid secretion and GERD. Examples of PPIs include esomeprazole (Nexium) and pantoprazole (Pepcid). These are other popular drugs in market to treat the GERD and become the first choose in the case of GERD not in peptic ulcer.

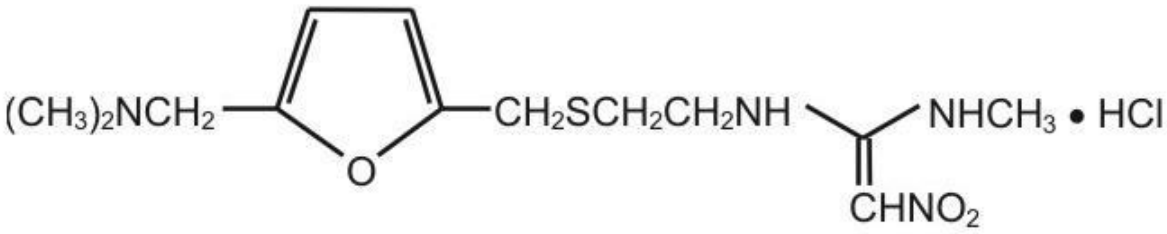
Both medications work by blocking and decreasing the production of stomach acid which is secreted after ingestion of food to digest those and my neutralizing the toxic products of food, but PPIs are considered stronger and faster in reducing stomach acids. However, H2 receptor blockers specifically decrease the acid released in the evening time, which is a common reason of peptic ulcers. This is why H2 receptor blockers are specifically prescribed to people who have ulcers or who are at risk for getting them. PPIs are more often prescribed for people who have GERD or acid reflux.

It is not recommend taking both a PPI and an H2 receptor blocker at a time. H2 receptor blockers can interfere with the effectiveness of PPIs. Thus the unwanted or adverse effect cane be observed. It may possible that the PPI or H2 antagonist can diminish one another's action. If GERD symptoms don't improve with the use of a PPI, your doctor may recommend an H2 receptor blocker instead. So the first choose is the PPI then H2 blocker can be prescribed (DeVault and Castell, 2005).

1.3 Ranitidine

1.3.1 Ranitidine general information

The active ingredient in Ranitidine Tablets is N [2-[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, HCl. Which is found in the USP 150 mg and Ranitidine Tablets and USP 300 mg is Ranitidine hydrochloride (HCl), USP. Basically it is a histamine H2-receptor antagonist. It has the following structure:



Structure1.1: Ranitidine Chemical Structure

Structure 1.3.1: N [2-[5-[(dimethylamino) methyl]-2-furanyl] methyl] thio] ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, HCl.

The empirical formula of ranitidine is C13H22N4O3S·HCl, having the molecular weight of 350.87. Ranitidine HCl seems white to pale yellow, granular substance. This is highly soluble in water, having slightly bitter taste and sulfur like odor.

Each Ranitidine Tablets, USP 150 mg for oral administration contains 167.4 mg of Ranitidine HCl equivalent to 150 mg of Ranitidine. Except ranitidine each tablet also contains the inactive ingredients which are known as excipients like microcrystalline cellulose, croscarmellose sodium, titanium dioxide, colloidal silicon dioxide, hypromellose, magnesium stearate, polydextrose, triethyl citrate and FD & C Yellow.

Each Ranitidine Tablets, USP 300 mg for oral administration contains 334.8 mg of Ranitidine HCl equivalent to 300 mg of Ranitidine. Each tablet also contains the inactive ingredients colloidal silicon dioxide, croscarmellose sodium, polydextrose, microcrystalline cellulose, titanium dioxide, hypromellose, magnesium stearate, triethyl citrate and D&C Yellow (Drugs.com, 2016).

1.3.2 Synthesis:

Ranitidine Synthetic procedure/method of synthesis

The reaction of 5-dimethylaminomethyl-2-furanylmethanol (I) with 2-mercaptoethylamine (II) by means of aqueous HCl gives 2-[[(5-dimethylamino-methyl-2-

furanyl)methylthio]ethaneamine (III), which is then condensed with N-methyl-1-methylthio-2-nitrotheneamine (IV) by heating at 120 C. Compound (IV) is obtained by reaction of 1,1-bis(methylthio)-2-nitroethene (V) with methylamine in refluxing ethanol.

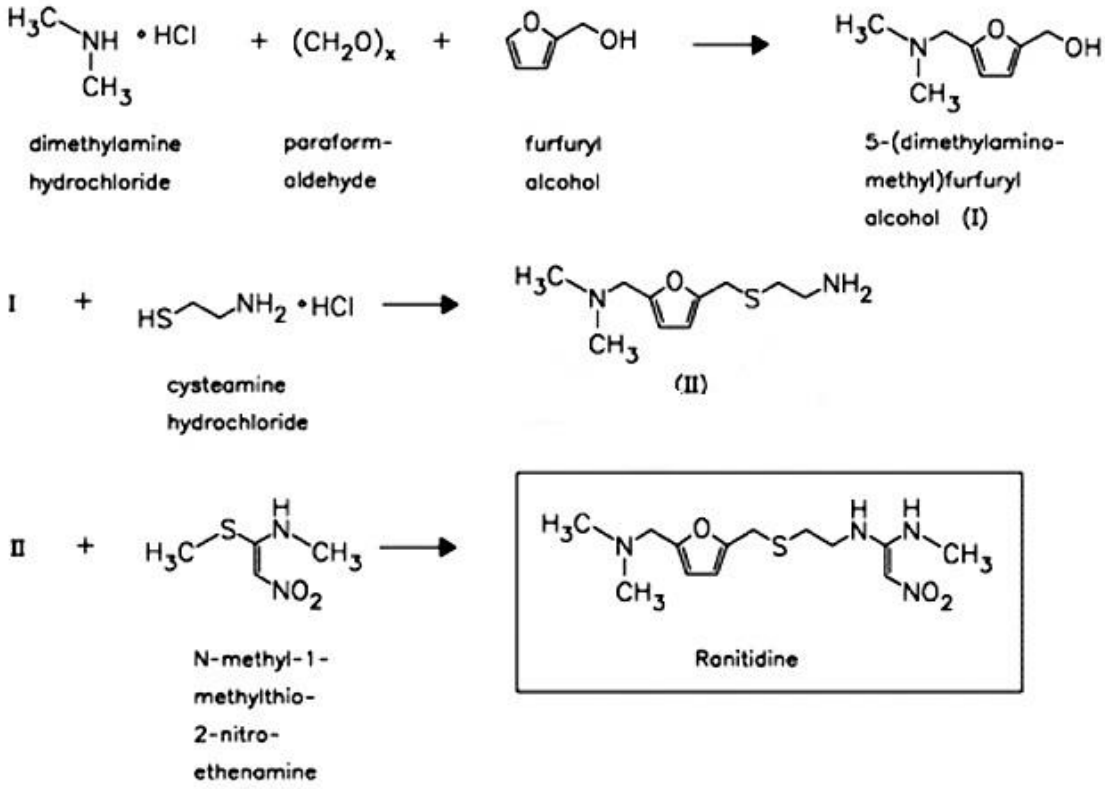


Figure1.2: Synthesis of Ranitidine (Synthesis of Drugs, 2012).

1.3.3 Ranitidine: Pharmacology

Ranitidine, a substituted aminoalkylfuran compound which has the ability to do selectively and competitively antagonise the histamine effects at H2-receptors in the stomach. There is an inhibition of gastric secretion triggered by histamine, pentagastrin, a test meal, or another stimulus. The drug reduces the amount as well as the concentration of produced gastric acid. Secretion of pepsin is also indirectly reduced. The effect is dose dependent; a nightly dose of 300 mg reduces the nocturnal acid production by approximately 95% (Infomed, 2016).

1.3.4 Ranitidine (Ranitidine Hydrochloride) - Indications and Dosage

- ✓ It can be used in the short-term treatment of active, benign gastric ulcer, where most patients heal within 6 weeks and the usefulness of further treatment has not been

demonstrated. Different studies available to date have not assessed the safety of ranitidine in uncomplicated, benign gastric ulcer for periods of more than 6 weeks.

- ✓ For the maintenance therapy of gastric ulcer patients at reduced dosage after healing of acute ulcers. Placebo-controlled studies have been carried out for 1 year.
- ✓ Basic treatment of GERD (Gastro Esophegal Rreflux Disorder) . Symptomatic relief commonly occurs within 24 hours after starting therapy with Ranitidine Tablets, USP 150 mg double time at a day.
- ✓ Treatment of erosive esophagitis. This can be diagnosed by endoscopically. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with Ranitidine Tablets, USP 150 mg four times at a day.
- ✓ Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; GERD; and erosive esophagitis (Druglib, 2015).

1.3.5 Contraindications:

Ranitidine Tablets, USP is contraindicated for patients known to have hypersensitivity to the drug or any of its ingredients.

Precautions

General:

1. Symptomatic response to therapy with Ranitidine Tablets, USP does not preclude the presence of gastric malignancy.
2. Since the excretion of ranitidine occurs primarily by the kidney, dosage should be adjusted in patients with impaired renal function. In the case of the patients with hepatic dysfunction this drug should be prescribed carefully since Ranitidine is metabolized in the liver.
3. Very few reports claimed that Ranitidine may precipitate acute porphyric attacks in patients with acute porphyria. Ranitidine Tablets, USP should therefore be avoided in patients with a history of acute porphyria (Drugs.com, 2016).

Laboratory Tests:

False-positive tests for urine protein with MULTISTIX® may occur during therapy with Ranitidine Tablets, USP therapy, and therefore testing with sulfosalicylic acid is recommended (Dailymed, 2016).

1.3.6 Drug Interactions

Different studies has claimed that Ranitidine Tablets, USP can affect the bioavailability of other drugs through several different mechanisms such as competition for renal tubular secretion, alteration of gastric pH, and inhibition of cytochrome P450 enzymes.

Here are some drugs that can be affected by the use of Ranitidine:

Warfarin:

It is reported that altered prothrombin time among patients on concomitant warfarin and Ranitidine therapy occurs. Due to the very narrow therapeutic index, close monitoring of increased or decreased prothrombin time is maintained during concurrent treatment with Ranitidine. Ranitidine may alter the absorption of drugs in which gastric pH is an important determinant of bioavailability. This can result in either an increase in absorption (e.g., triazolam, midazolam, glipizide) or a decrease in absorption (e.g., ketoconazole, atazanavir, delavirdine, gefitinib). Appropriate clinical monitoring is recommended (Drugs.com, 2016).

Procainamide:

Ranitidine, a substrate of the renal organic cation transport system, may affect the clearance of other drugs eliminated by this route. High doses of Ranitidine which is used in the treatment of Zollinger-Ellison syndrome have been shown to reduce the renal excretion of procainamide and N-acetylprocainamide resulting in increased plasma levels of these drugs. Although this interaction is unlikely to be clinically relevant at usual Ranitidine doses, it may be prudent to monitor for procainamide toxicity when administered with oral Ranitidine at a dose exceeding 300 mg per day (Drugs.com, 2016).

Gefitinib:

Gefitinib activity reduced by 44% with the co-administration of Ranitidine and sodium bicarbonate (dosed to maintain gastric pH above 5.0) (Dailymed, 2016).

Delavirdine:

Delavirdine absorption may be hampered by known interactions with other agents that increase gastric pH. Chronic use of H2-receptor antagonists with delavirdine is not recommended (Usdrugbase, 2016).

Atazanavir:

Atazanavir absorption got impaired for the interactions with other agents that increase gastric pH.. So this drug is used carefully in when ranitidine is under use (Dailymed, 2016).

Ketoconazole:

When ketoconazole when taken orally got reduced by up to 95%, when oral Ranitidine was co-administered in a regimen to maintain a gastric pH of 6 or above. The degree of interaction occurs with the usual dose of Ranitidine which is 150 mg twice daily (Drugs.com, 2016).

Midazolam:

A study has shown that midazolam orally exposure in 5 healthy volunteers was increased by up to 65% when administered with oral Ranitidine at a dose of 150 mg twice daily. However, in another interaction study in 8 volunteers when receiving IV midazolam, a 300 mg oral dose of Ranitidine increased midazolam exposure by about 9% (Usdrugbase, 2016).

Glipizide:

Especially in diabetic patients, glipizide exposure was increased by 34% following a single 150-mg dose of oral Ranitidine. So appropriate clinical monitoring is recommended when initiating or discontinuing Ranitidine (Druglib, 2014).

Triazolam:

Exposure of triazolam in healthy volunteers was increased by approximately 30% when administered with oral Ranitidine at a dose of 150 mg twice daily. Monitor patients for excessive or prolonged sedation. Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in life-span studies in mice and rats at dosages up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (Salmonella, Escherichia coli) for mutagenicity at concentrations up to the maximum recommended for these assays. In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of 2 matings per week for the next 9 weeks (Drugs.com, 2016).

Pregnancy:

Teratogenic Effects:

Ranitidine took place in the Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ranitidine Tablets, USP. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug

should be used during pregnancy only if clearly needed. So it is not that harmful to the human. That's the reason doctor can prescribe the ranitidine in the time of pregnancy when patient got peptic ulcer (Medlibrary, 2014).

Nursing Mothers:

It is reported that ranitidine is secreted in human milk. So caution should be maintained when Ranitidine Tablets, USP are administered to a nursing mother (Medlibrary, 2014).

Pediatric Use:

According to the previous studies the safety and effectiveness of Ranitidine Tablets, USP have been established in the age-group of 1 month to 16 years for the treatment of duodenal and gastric ulcers, gastroesophageal reflux disease and erosive esophagitis, and the maintenance of healed duodenal and gastric ulcer. Use of Ranitidine Tablets, USP in this age-group is supported by adequate and well-controlled studies in adults, as well as additional pharmacokinetic data in pediatric patients and an analysis of the published literature. So ranitidine can be made in syrup for the pediatric population. But in this case the syrup must be kept in light protector bottle.

Safety and effectiveness in pediatric patients for the treatment of pathological hypersecretory conditions or the maintenance of healing of erosive esophagitis have not been established. Very notable point is this safety and effectiveness in neonates means less than 1 month of age have not been established (RxList, 2015).

Geriatric Use:

It was found that the total number of patients enrolled in US and foreign controlled clinical trials of oral formulations of Ranitidine Tablets, USP, for which there were subgroup analyses, 4,197 were 65 and over, while 899 were 75 and more than that. No overall differences in safety or effectiveness were observed between these subjects and younger subjects in the study, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. This drug is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, caution should be exercised in dose selection, and it may be useful to monitor renal function (Drugs.com, 2016).

1.3.7 ADVERSE REACTIONS

The following have been reported as events in clinical trials or in the routine management of patients treated with Ranitidine Tablets, USP. The relationship to therapy with Ranitidine Tablets, USP has been unclear in many cases. Headache, sometimes severe, seems to be related to administration of Ranitidine Tablets, USP.

Central Nervous System:

Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported. Rare reports of reversible involuntary motor disturbances have been received (Medlibrary, 2014).

Cardiovascular:

As with other H2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats (RxList, 2015).

Gastrointestinal:

Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis (Druglib, 2015).

Hepatic:

It was found that occasional reports of hepatocellular, cholestatic, or mixed hepatitis, with or without jaundice. In such cases, ranitidine should be immediately discontinued. These events are usually reversible, but in rare cases death has been reported. Rare cases of hepatic failure have also been reported. In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg four times in a day. Intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg four times in a day. Intravenously for 5 days (Medlibrary, 2014).

Musculoskeletal:

Rare reports have been found of arthralgias and myalgias (Druglib, 2015).

Hematologic:

Blood count changes in the situations like leucopenia, granulocytopenia, or thrombocytopenia have occurred in a few patients. These were usually reversible

occurrence. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia are found and exceedingly rare cases of acquired immune hemolytic anemia have been reported (RxList, 2015).

Endocrine:

This drug has no very potential effect on the endocrine system. Studies in animals and man have shown no stimulation of any pituitary hormone by Ranitidine Tablets, USP and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Ranitidine Tablets, USP has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been found in male patients having Ranitidine Tablets, USP, but the incidence did not differ from that in the general population (Medlibrary, 2014).

Integumentary:

It was found that rash, including rare cases of erythema multiform can occur in the person having ranitidine. Rare cases of alopecia and vasculitis (RxList, 2015).

Respiratory:

Different studies have shown that the increased risk of developing pneumonia in current users of histamine-2-receptor antagonists (H2RAs) compared to patients who had stopped H2RA treatment, with an observed adjusted relative risk of 1.63. However, a causal relationship between use of H2RAs and pneumonia has not been established till now (Druglib, 2015).

1.4 Pharmacokinetics of Ranitidine

Absorption

Ranitidine is well water soluble drug and Ranitidine Tablets, USP are 50% absorbed after oral administration, compared to intravenous (IV) injection with mean peak levels from 440 to 545 ng/mL within 2 to 3 hours after a 150-mg dose. Absorption is not impaired by the interference of food or other antacids. Propantheline may slightly delay and increase the peak blood levels of Ranitidine, probably by delaying gastric emptying time. In another study, simultaneous administration of high-potency antacid like 150 mmol in fasting patient has been reported to decrease the absorption of Ranitidine Tablets, USP (Medlibrary, 2014).

1.4.2 Distribution

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%. As ranitidine is a well water soluble drug thus it is well distributed in the plasma that makes the drug having this VD in normal condition (Drugs.com, 2016).

1.4.3Metabolism

N-oxide is the principal metabolite in the urine; however, this amounts to <4% of the dose. Other metabolites are the S-oxide is 1% and the desmethyl Ranitidine is 1%. The remainder of the administered dose can be founded in the stool. Studies in subjects with hepatic dysfunction like compensated cirrhosis indicate that there are minor, but clinically insignificant, alterations in Ranitidine half-life, distribution, clearance, and bioavailability (Drugs.com, 2016).

1.4.3 Excretion

Route of excretion of ranitidine is the urine, with approximately 30% of the orally administered dose founded in the urine as unchanged drug in 24 hours. Renal clearance is about 410 mL/min, which indicates active tubular excretion in the kidney. The elimination half-life is 2.5 to 3 hours (Medlibrary, 2014).

1.4.5 Geriatrics

In different studies it was found that the plasma half-life is prolonged and total clearance is reduced in the elderly population due to a decrease in renal function. The elimination half-life is 3 to 4 hours. Peak levels average 526 ng/mL following by 150-mg twice dose daily and occur in about 3 hours (MedTechUSA, 2016).

1.4.6 Pediatrics:

There are no significant differences in the pharmacokinetic parameter values for Ranitidine in pediatric patients who are enrolled from 1 month up to 16 years of age and healthy adults when correction is made for body weight. The found average bioavailability of Ranitidine given orally to pediatric patients is about 48% which is very comparable to the bioavailability of Ranitidine in the adult population. All other pharmacokinetic parameter values like t1/2, Vd, and CL are similar to those founded with intravenous Ranitidine use in pediatric patients (MedTech USA, 2016).

Table 1.2 Estimates of Cmax and Tmax are displayed in

Ranitidine Pharmacokinetics in Pediatric Patients Following Oral Dosing				
Population (age)	n	Dosage Form (dose)	Cmax (ng/mL	Tmax (hours)
Gastric or duodenal ulcer (3.5 to 16 years)	12	Tablets| (1 to 2 mg/kg)	54 to 492	2.0
Otherwise healthy requiring Ranitidine (0.7 to 14 years, Single dose)	10	Syrup (2 mg/kg)	244	1.61
Otherwise healthy requiring Ranitidine (0.7 to 14 years, Multiple dose)	10	Syrup (2 mg/kg)	320	1.66

Plasma clearance measured in 2 neonatal patients (less than 1 month of age) was considerably lower (3 mL/min/kg) than children or adults and is likely due to reduced renal function observed in this population (Drugs.com, 2016).

1.5 Photo degradation

Present study the mechanisms of solar photodegradation of H(2)-receptor antagonist ranitidine were studied in a well-defined system of a pilot plant scale Compound Parabolic Collector (CPC) reactor. In this study two types of heterogeneous photocatalytic study were performed: catalyzed by titanium-dioxide or (TiO(2)) semiconductor and by Fenton reagent which is (Fe(2+)/H(2)O(2)), both of each one with synthetic wastewater effluent matrix and distilled water. Complete disappearance of the parent compounds and discreet mineralization were found in all experiments. Furthermore, kinetic parameters, release of heteroatoms, main intermediate products and formation of carboxylic acids are discussed. The main intermediate products of photocatalytic degradation of Ranitidine have been structurally elucidated by using the tandem mass spectrometry (MS(2)) experiments performed at quadrupole-time of flight (QqToF) mass analyzer coupled to ultra-performance liquid chromatograph (UPLC). Ranitidine had displayed high reactivity towards OH free radicals, although a product of conduction band electrons reduction was also present in the experiment with given TiO(2). In the absence of standards, quantification of intermediates was not possible. But only qualitative profiles of their evolution could be determined (Radjenovic *et al.*, 2010).

Whitout this study another study has found that the effects of degradation of ranitidine hydrochloride exposed to UVB radiation (l = 310 nm) and oxygen in a weathering chamber were studied by Fourier Transform Infrared spectroscopy (FTIR) and Attenuated Total Reflectance Fourier Transform Infrared spectroscopy (ATR-FTIR). However the ATR-FTIR profile indicated that the degradation was spatially heterogeneous in nature. Major damages or changes were reflected in the appearance of broad, extended group of signals near the wave number of 3600-3200 cm-1 or and 3500-3400 cm-1 (Ftir and Atr-Ftir, 2009).

1.6 BCS Classification

1.6.1 The BCS

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. The industry is using the BCS as a technique in drug product development. As a simple example, BCS can be used to indicate drugs that should not be tested clinically unless appropriate formulation strategies are employed. As an example, a BCS Class II compound, permeable but relatively insoluble, would likely not be a good clinical candidate without the use of enhanced formulation techniques aimed at increasing solubility or rate of dissolution. It is true that various schemes exist that attempt to funnel a given API towards particular drug delivery techniques depending on the API's BCS category. But till now most approaches remain fragmented in their methodology, ignoring commercially and biologically important factors. Briefly, the BCS places a given API in one of four categories depending on its solubility and permeability as they pertain to oral doses. A drug substance is considered "highly soluble" when the highest clinical dose strength is soluble in 250 mL or less of aqueous media over a pH range of 1–7.5 at 37 °C. A drug substance is considered to be "highly permeable" when the capacity of the absorption in humans is determined to be ≥90% of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose. Permeability can be determined a number of ways but is most often done using

Caco-2 cell lines an assay that lends itself to high throughput automation. A monolayer of cells is grown and drug permeation from the drug donor to the acceptor compartments is assessed, usually by using a direct UV or LC-MS assay. Potential issues with Caco-2 based systems range from variation in transport mechanisms to drug interactions with the apparatus itself. Commercial companies focused on this assay have developed multiple approaches to alleviate these issues but a review is beyond the scope of this paper and the reader is encouraged to contact the various suppliers. As a drug candidate moves up the development ladder, developers will often confirm and refine their BCS assessments with increasingly complex *in vivo* models (Mitchnick, 2016).

1.6.2 BCS and Dosage Form Trends

It is commonly recognized that most new drugs present formulation challenges. In fact, older drugs as compared to newer ones have higher solubility in general. One reference noted that BCS Class II compounds as a percentage of compounds under development had increased from 30% to 60%. BCS Class I compounds have fallen correspondingly from 40% to 20% over that same period[3]. In practice, low solubility is the most common theme encountered. In our own experience the majority of compounds formulated at Particle Sciences on the behalf of our clients have low to no aqueous solubility (Figure 2). It should be noted that not every drug is classified the same by each investigator. The variability can be due to a number of things including the way permeability is measured. As above, *in vivo* permeability is impacted by, among other things, drug transporters. Both uptake and efflux transporters exist and can contribute to the differences seen by the various techniques. For the majority of APIs a solid oral dosage form (SOD) is the preferred option. Sometimes the physicochemical and physiologic mechanisms do not allow this and alternatives are pursued such as suspensions or oral solutions. Other times, the target and other factors dictate that a non-oral dosage form is most sensible. Examples include the local delivery of female hormones, nasal allergy preparations, and ocular therapeutics and combination products aimed at prolonged drug release. In all these cases, even though not orally dosed, the concepts inherent in the BCS can be important tools in dosage form design. Literature and experimental data relevant to the decision to allow a waiver of in vivo bioequivalence testing for the approval of immediate release (IR) solid oral dosage forms containing ranitidine hydrochloride are reviewed. According to the current Bio pharmaceutics Classification System (BCS), ranitidine hydrochloride should be assigned to Class III. However, based on its therapeutic and therapeutic index,

pharmacokinetic properties and data related to the possibility of excipient interactions, a biowaiver can be recommended for IR solid oral dosage forms that are rapidly dissolving and contain only those excipients as reported in this study (Kortejärvi *et al.*, 2005).

1.7 Dissolution

1.7.1 Dissolution General information

The transfer of molecules of loins form solute state in a solution is known as dissolution. It is the process of dissolving solid part (solute) in the solvent (liquid) In more simple way, Dissolution is the process by which a substance turns in to solution in a solvent. For solids, dissolution is explained as the breakdown of the crystal lattice into individual ions, atoms or molecules. Dissolution is a total kinetic process. The result of dissolution is controlled by the thermodynamic energies involved in the process, such as the heat of solution and entropy of solution, but the dissolution itself is not. Overall the free energy must be negative for net dissolution to occur. In turn, those energies are controlled by the way in which different chemical bond types interact with those in the solvent (Sirius-analytical, 2016).

1.7.2 Rate of Dissolution

The rate of dissolution determines the speed of the total process. It depends on the chemical natures of the solvent and solute these are the temperature, the degree of unsaturation, the interfacial surface area, and the presence of "inhibitors" Like, substances adsorbed on the surface.

The rate can be often expressed by the *Noyes-Whitney* Equation or the Nernst and Brunner equation of the form:

$dm/dt = Ax\{D/d\}x(C_s-C_b)$

Where:

m, mass of solute material

t is time

A is surface area of the interface between the dissolving substance and the solvent

D is diffusion coefficient

d is thickness of the boundary layer of the solvent at the surface of the dissolving substance

C_s is mass concentration of the substance on the surface

C_b is mass concentration of the substance in the bulk of the solvent

For dissolution limited by diffusion, Cs is equal to the solubility of the solute. When the dissolution rate of a pure substance is normalized to the surface area of the solid, then it is expressed in kg/m^2S and termed as "intrinsic dissolution rate", which is defined by the United States Pharmacopeia (Lentle & Janssen, 2011).

1.7.3 Process of dissolution:

According to the rule *like dissolves like*, means that substances must have the same intermolecular forces to form solutions. After introducing a soluble solute is to solvent, the particles of solute interact with the particles of solvent. In the case of a solid or liquid solute, the interactions between the solute particles and the solvent particles are so strong that the individual solute particles separate from each other and, surrounded by solvent molecules, enter the solution. This process is known as solvation and is illustrated in Figure 1.1. When the solvent is water, then the salvation word is replaced by the word hydration.

In the case of molecular solutes like carbohydrates e.g. glucose, the particles are individual molecules. However, if the solute is ionic, the individual ions got separated from each other and become surrounded by solvent particles. That is, the ions of solute separate when the solute dissolves. This process is called dissociation.

Soluble ionic compounds are often referred to as electrolytes. Many ionic compounds dissociate completely thus called strong electrolytes. Sodium salts are example of strong electrolytes. Some compounds dissolve but get dissociated only in partial amount, and solutions of such solutes may conduct electricity only weakly. These solutes are called weak electrolytes. Acetic acid (CH_3COOH) is counted as a very weak electrolyte (Chemwiki, 2014).

1.7.4. Factors influence the dissolution of a substance:

1. Temperature.
2. Particular size of solute
3. Agitation
4. Solvent selection

Temperature:

In most cases of dissolution of solute in a liquid depends on the absorption of heat. If the

temperature is raised then the dissolution will be more rapid but in lower temperature the dissolution will be less. So, temperature has the significant influence on dissolution.

Particle Size:

The dissolution rate depends on its particle size. In the case of small particle size, dissolution will be more but in the time of large particle size, dissolution will be less. The absorption depends upon the dissolution rate. So determination of dissolution rate of any solute is very important.

Agitation:

Dissolution also depends on the concentration of the solvent. If the solvent is more concentrated dissolution will be less. If the solvent is less concentrated dissolution will be raised.

Solvent selection:

Dissolution also depends on the type of the solvent. In water dissolution rate will be more than oily solvent (Pharmacyebook, 2016).

1.8 Comparative dissolution

1.8.1 Introduction

Comparative dissolution testing is very important tool in drug development. Including serving as routine quality control tests, comparative dissolution tests is one of the best tools to support waivers for bioequivalence requirements, for approval of generic drug products. Accepting product sameness under Scale-up and Post Approval (SUPAC)-related changes depends on the comparative dissolution test (Anand *et al.*, 2011).

1.8.2 Specifications and Experimental Conditions

For immediate release products In United States the Centre for Drug Evaluation and Research (CDER) of the Food and Drug Administration (US FDA) pointed three categories of dissolution test specifications. These are single point specifications, two point specifications and dissolution profile comparison. Single and two-point specifications are sufficient to identify drug products containing high solubility-high permeability substances. But the thing is, this is not suitable for characterization of low solubility products because such products have produced different dissolution profiles. Consequently, they may comply with the point estimates, thereby giving an erroneous impression of pharmaceutical equivalence in dissolution characteristics. It is

recommended that dissolution profile comparison is for such products, as it is more precise and discriminative than point estimates others (Yuksel *et al.*, 2000).

At least three dissolution media is needed for comparative dissolution profile testing of drugs in order to study their stability and release describe in the different physiological conditions that they may be subjected to in vivo. The recommended dissolution media are 0.1 M HCl or buffer solution of pH 1.2 as well as buffer solutions of pH 4.5 and 6.8. Water can be used as an additional medium in the studies (EMEA, 2010).

1.8.3 Methods for Comparison of Dissolution Profile Data

For in vitro dissolution profile there are three groups to taste the comparative dissolution profile:

i. Methods based on analysis of variance (ANOVA)

ii. Model-dependent methods

iii. Model-independent methods.

ANOVA-based methods use in variety and multivariate approaches to measure the quantity in dissolution percentages. The cubic root law, which is a model depended method (Hixson and Crowell) mathematical model, the Weibull distribution model and the logistics (Rowlings) model for sigmoidal dissolution curves (Yuksel et al. 2000).

Moore and Flanner (1996) proposed a very simple model independent method to produce the fit factors to compare dissolution profile data of a pair of products under similar conditions. These fit factors directly compare the difference between percent drug dissolved per unit time for a test and a reference product. These factors are denoted f1 (difference factor) and f2 (similarity factor) (Krishnamoorthy, 2005).

CHAPTER: 02

LITERATURE REVIEW

Literature Review

Comparative analysis is carried out to check, compare and evaluate the quality standards of commercially available local pharmaceutical brands of tablets with that of multinational pharmaceutical brands in Pakistan as prescribed by B.P. & U.S.P. Local and Multinational brands of drugs were evaluated comparatively for their physical and chemical parameters. It is said that marketed oral drugs will generally possess favorable physiochemical properties with respect to absorption, metabolism, distribution, and clearance. On a weight basis, ranitidine is 4 to 10 times more potent than cimetidine in inhibiting stimulated gastric acid secretion in humans. Ranitidine has a greater selectivity of action than cimetidine so avoiding certain unwanted effects such as interference with enzymatic degradation of a wide range of drugs metabolized by the liver (Dilshad, 2000).

DiPadova, Carlo, etal conducted this study in 1992 and the aim of this study to Effects of ranitidine on blood alcohol levels after ethanol ingestion.H_1-type antihistamines have recently been reported to inhibit cytokine secretion from human and murine mast cells and basophils. Antihistamines had no effect on calcium flux in resting or stimulated cells. At the mRNA level, inhibition was only seen with KU812 cells and IL-8 in the presence of azelastine at 10^{-10} M. These data show thus distinct inhibitory patterns for different antihistamines during cytokine production from human mast cells and basophils which may contribute to the anti-inflammatory effects of these drugs during treatment of allergic diseases. Patients treated with ranitidine or cimetidine should be warned of possible functional impairments after consumption of amounts of ethanol considered safe in the absence of such therapy (DiPadova *et al*., 2000).

This study was conducted by Cappola, M. L. in 2001. The aim of this study was find out a better dissolution method for Ranitidine tablets USP. Ranitidine tablets USP showed variable intra- and inter-lab dissolution results. In order to ascertain the reason for this behavior, showed increase in rate and extent of drug dissolved, with less individual tablet variability compared to the paddle apparatus at 50 rpm. The 300 mg tablet (30 rpm/basket apparatus) had an initial slower rate, but then rapidly equaled the paddle apparatus dissolution results, and had less individual tablet variability. Paddle apparatus tablet sinkers were used to prevent tablets from sticking to the bottom of the dissolution vessel. Overall dissolution for all tablets with sinkers showed a trend which was more rapid and

complete than tablets without sinkers. Results showed that dissolution artifacts for ranitidine tablets could be reduced by the use of baskets or tablet sinkers (Cappola,.2001).

The bioavailability of two brands of ranitidine tablets was studied in 10 healthy volunteers. Formulation factors were compared by performing disintegration, dissolution and content uniformity tests. Plasma concentrations of ranitidine were measured using a sensitive and precise high pressure liquid chromatographic (HPLC) procedure. Pharmacokinetic parameters were determined for both formulations and included: C_{max}, AUC_t, AUC_x, t_{max}, $t_{1/2}$ and the terminal rate of elimination (k). Statistical analysis revealed that differences between the brands were not significant. The two formulations can be considered to be bioequivalent. (Alkaysi *et al*., 2000)

The effect of moisture on the physical properties of ranitidine hydrochloride tablets prepared by direct-compression and by wet-granulation method using PVP or EC as binders was studied. Tablets adsorbed moisture at 50 and 75 % RH (relative humidity) but lost moisture at 30% RH. Except storage at 75% RH, however, tablet volumes did not change significantly during the test period. Moisture sorption caused a decrease in strength of tablets except low humidity (30% RH). Also, the disintegration time of tablets showed a decrease at all conditions except 30% RH. Furthermore, generally dissolution profiles of tablets prepared by direct-compression and by ethyl cellulose remained unchanged. Changes in the binder type in the tablet formulations changed the water uptake properties and also the physical properties of tablets. Directly-compressed tablets were much susceptible to change caused by humidity than tablets prepared by wet-granulation (Uzunarslan, 2000)

Ten double-blind randomized studies with omeprazole versus ranitidine in duodenal ulcer healing have been published. The total number of patients in the trials amounted to 2225. To detect treatment differences, a meta-analysis was performed. After 2 and 4 weeks of treatment results have been evaluated. After 2 weeks of treatment omeprazole produced higher healing rates than ranitidine in nine studies. However, at 4 weeks numerical differences in favor of omeprazole were found in nine studies. Relief of ulcer symptoms occurred more rapidly with omeprazole than ranitidine. No major clinical or biochemical side effects were recorded. However, no data are available about maintenance therapy in

double-blind randomized studies comparing both drugs or about rebleeding rates in bleeding duodenal ulcer treatment (Mulder *et al*.,2001).

Ranitidine is an ant secretory drug with H_2 antagonist action useful in treating gastric and duodenal disorders. The dissolution test was used to obtain and compare dissolution profiles and establish similarities of pharmaceutical forms. The aim of this study was to compare the dissolution profiles of 150-mg coated ranitidine tablets of a reference drug (product A) and a generic (product B) and a similar (product C) drug marketed in Bahia, Brazil using a simple, fast and inexpensive ultraviolet method. Dissolution was determined using a USP type 2 apparatus at 50 rpm with 900 ml of distilled water at 37.0 ± 0.5 ^{o}C for 1h.Factors were calculated and showed that the profiles of products A, B and C were dissimilar. However, all the products released ranitidine satisfactorily, with at least 80% of the drug dissolved within 30 min. (Junior *et al*., 2014)

It is shown that under sink conditions a percent dissolved value at time *t* may simply be equivalent to the percent surface area generated to time *t*. If this is so, then percent dissolved-time data may best be described by a distribution function and the parameters of the distribution employed to describe the data. Simulated percent dissolved-time data, generated by means of the logarithmic normal distribution function, are shown to yield apparent first-order plots. Hence, if the new concept is correct, apparent first-order kinetics, derived from *in vitro* dissolution tests on conventional tablets and capsules, may be an artifact in some cases. In the special case when surface area of drug available for dissolution decreases exponentially with time after some lag time, *to*, then first-order kinetics appear applicable to the dissolution data. Relationships between many of the constants in formerly derived dissolution rate equations and some equations derived in this report are shown. Dimensions of the constants are clarified. The new method of dissolution rate data examination is capable of providing characterizing parameters of greater potential utility than conventional treatments heretofore used (Shah *et al*.,2000).

An HPLC method has been developed for the quantification of ranitidine in plasma for pharmacokinetic studies. Metoclopramide was used as internal standard. The method uses a simple and rapid sample clean-up procedure involving single-step extraction with organic solvent to extract ranitidine from plasma. After evaporation and reconstitution the samples are chromatographed on a 250 mm×4 mm base-stable reversed-phase column

with 0.05 M ammonium acetate-acetonitrile, 75:25 (*v/v*) as mobile phase and UV detection at 313 nm. The calibration graph was linear for quantities of ranitidine between 10 and 2000 ng mL^{-1}. Intra- and inter-day*CV* did not exceed 11.64%. The quantitation limit was 10 ng mL^{-1} for human plasma. The applicability of this method for pharmacokinetic studies of ranitidine after oral administration are described. Approximately 90 samples can be processed in 24h (Campanero *et al*., 2001).

Oral ranitidine was given to 68 healthy subjects between 18 and 75 years old at a dosage of 150 mg twice a day for seven doses. Fifteen subjects were 18 to 35 years old (group I), 19 subjects were 36 to 50 years old (group II), 19 subjects were 51 to 65 years old (group III), and 15 subjects were 66 to 75 years old (group IV). Venous blood samples were drawn and the AUC from 0 to 12 hours, the maximum plasma concentration, the time of the maximum plasma concentration, the minimum plasma concentration, and the elimination t1/2 were determined. When groups III and IV were compared with groups I or II, significant (P less than 0.05) increases were seen in the AUC (0-12) (42% and 50%), the maximum plasma concentration (36% and 41%), the minimum plasma concentration (91% and 85%), and the elimination t1/2 (29% and 33%) (Greene *et al*, 2001).

Understanding the polymorphic behavior of pharmaceutical solids during the crystallization process and further in post-processing units is crucial to meet medical and legal requirements. In this study, an analytical technique was developed for determining the composition of two solid forms of ranitidine hydrochloride using two peaks of Fourier transform infrared (FTIR) spectra without the need to grind the samples. Solubility studies of ranitidine hydrochloride showed that Form 2 has a higher solubility than Form 1. Solution-mediated transformation is very slow and occurs from Form 2 to Form 1 and not the reverse. No solid–solid transformation was observed due to grinding or compressing the pure samples of either forms and of a 50/50 wt.% mixture. Grinding was found to be a proper technique for increasing the bulk solid density of the ranitidine hydrochloride without the risk of solid–solid transformation. Dissolution rate found to be equally fast for both forms (Mirmehrabi *et al.*,2004).

This study was conducted by Kortejarvi, H. *et al.*, in 2005 with the aim to assess the biowaiver monographs for immediate release solid oral dosage forms: Ranitidine

hydrochloride. Literature and experimental data relevant to the decision to allow a waiver of *in vivo* bioequivalence testing for the approval of immediate release (IR) solid oral dosage forms containing ranitidine hydrochloride are reviewed. According to the current Bio pharmaceutics Classification System (BCS), ranitidine hydrochloride should be assigned to Class III. However, based on its therapeutic and therapeutic index, pharmacokinetic properties and data related to the possibility of excipient interactions, a biowaiver can be recommended for IR solid oral dosage forms that are rapidly dissolving and contain only those excipients as reported in this study (Kortejarvi *et al.*, 2005).

Omeprazole 60 mg once daily was compared with ranitidine 150 mg twice daily in an endoscopically-controlled, double-blind randomized trial in 51 outpatients with erosive or ulcerative reflux esophagitis (grade 2 or 3). Endoscopy was repeated after 4 weeks and, in the absence of healing, again after 8 weeks. Symptoms were assessed before entry and after 2, 4, and 8 weeks. Patients who were unhealed after 8 weeks were blindly switched to the other drug and treatment was continued for another 4 to 8 weeks. The healing rate (change to grade 0 or 1 esophagitis) after 4 weeks was 19 of 25 patients treated with omeprazole and 7 of 26 patients treated with ranitidine ($p = 0{\cdot}002$). The corresponding figures after 8 weeks were 22 of 25 and 10 of 26 ($p = 0{\cdot}001$). The higher healing rate with omeprazole was reflected in a significantly faster and stronger improvement of reflux symptoms. 13 patients, who were unhealed after 8 weeks on ranitidine, were healed after switching treatment. Healing was achieved in 1 of 3 patients who were switched to ranitidine. There were no adverse events or changes in laboratory variables of clinical importance. Omeprazole is superior to ranitidine in the short-term treatment of reflux esophagitis (Klinkenberg *et al.*, 2000).

Comparative analysis is carried out to check, compare and evaluate the quality standards of commercially available local pharmaceutical brands of tablets with that of multinational pharmaceutical brands in Pakistan as prescribed by B.P. & U.S.P. Local and Multinational brands of drugs were evaluated comparatively for their physical and chemical parameters. It is said that marketed oral drugs will generally possess favorable physiochemical properties with respect to absorption, metabolism, distribution, and clearance. Histamine is a natural chemical that stimulates the stomach cells to produce acid. Ranitidine is a new histamine H2- receptor antagonist which does not contain imidazole group unlike cimetidine. On a weight basis, ranitidine is 4 to 10 times more

potent than cimetidine in inhibiting stimulated gastric acid secretion in humans. Ranitidine has a greater selectivity of action than cimetidine so avoiding certain unwanted effects such as interference with enzymatic degradation of a wide range of drugs metabolized by the liver. Ranitidine acts by inhibiting parietal cell H2-receptor competitively and suppress the normal secretion of acid which is stimulated by meal (Dilshad, 2014).

Study was targeted to evaluate the pharmaceutical properties of few selected generic products of ranitidine hydrochloride tablets available in retail pharmacies of Bangladesh. We collected 10 nationally manufactured generic ranitidine HCl tablets from local Market who followed USP specifications and examined their physical parameters and potency to check their compliance with the USP. The intention was to evaluate the quality of this pharmaceuticals after 20 years of implementing the National Drug Policy in1982. The various parameters of the selected samples such as diameter, shape, size, weight variation, thickness, hardness, disintegration, dissolution and potency have been determined according to the American Pharmacopoeia USP 27 requirements. It was found that all ten selected products met the USP 27 specifications. The differences in hardness among the tablets were significant. Interestingly, dissolution profiles of some tablet products were not weighty different from one another, whereas those of tablets were significantly different. However, all brands complied with USP 27(Azad, Islam and Azizi, 2013).

The current requirement of the Mexican Authorities to demonstrate the interchangeability of ranitidine formulations is to establish that the dissolution profile of the drug shows similarity. In order to establish if this requirement is adequate, the bioavailability of two formulations that did not meet this similarity were compared. Twenty-five female volunteers received 150 mg ranitidine under fasting conditions in two separate sessions using a cross-over design. Plasma samples were obtained at selected times for a period of 12 h and stored frozen at -80 degrees C until analyzed. Ranitidine plasma levels were determined and pharmacokinetic parameters were obtained. No statistically significant difference was obtained in the parameters evaluated. Moreover, 90% confidence limits were 96.6%-116.2% and 90.7%-105.1% for Cmax and AUC12 h ratios, respectively, indicating that the formulations tested are bioequivalent, despite the dissimilarity in the dissolution profile of the formulations. These results suggest that the

comparative dissolution profile is not an adequate test to demonstrate the interchangeability of ranitidine formulations (Murrieta *et al*., 2000).

Ranitidine is an ant secretory drug with H2 antagonist action useful in treating gastric and duodenal disorders. The dissolution test is used to obtain and compare dissolution profiles and establish similarities of pharmaceutical forms. The aim of this study was to compare the dissolution profiles of 150-mg coated ranitidine tablets of a reference drug (product A) and a generic (product B) and a similar (product C) drug marketed in Bahia, Brazil using a simple, fast and inexpensive ultraviolet method. Dissolution efficiency and difference (f1) and similarity (f2) factors were calculated and evaluated. The proposed quantification methodology for drug dissolution test was validated, presenting accuracy, linearity and precision within the acceptance criteria. Products A, B and C showed dissolution efficiency values of 59.29, 73.59 and 66.67%, respectively. Factors f1 and f2 were calculated and showed that the profiles of products A, B and C were dissimilar. However, all the products released ranitidine satisfactorily, with at least 80% of the drug dissolved within 30 min (Junior etal, 2000).

Ranitidine is used in peptic ulcer 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 ranitidine HCl tablets available in local market of Karachi, Pakistan. Four different brands of (150 mg) were selected for the study. Six quality control parameters: weight variation test, hardness test, thickness, friability, disintegration test and dissolution test were carried out specified by USP. Result revealed that all brands comply within limits for hardness, weight variation, thickness, friability, disintegration and dissolution. Disintegration time for all brands was within 15 minutes complying with the USP commendation. All brands showed Q-value more than 80% within 45 minutes. The present findings suggest that almost all the brands of ranitidine HCl that are available in Karachi meet the USP specification for quality control analysis and are interchangeable (Dilshad, 2004).

Ranitidine tablets USP showed variable intra- and inter-lab dissolution results. In order to ascertain the reason for this behavior, ranitidine tablets USP produced by (BIPI) Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, and Zantac® Tablets (brand of ranitidine USP), Glaxo Inc., Research Triangle, NC, were subjected to the compendia

(USP) dissolution testing using paddle and basket apparatus. Overall dissolution for all tablets with sinkers showed a trend which was more rapid and complete than tablets without sinkers. Results showed that dissolution artifacts for ranitidine tablets could be reduced by the use of baskets or tablet sinkers (Cappola, 2000).

The new H_2-receptor blocker ranitidine, together with the effect on histamine H_2-receptors, possesses a series of cholinergic-like actions: it provokes atropine-sensitive contractions of several isolated smooth muscle preparations from different animal species and it potentiates the stimulant effect of acetylcholine. Moreover it contracts human lower esophageal sphincter *in vivo,* an effect which is completely prevented by small doses of atropine. Finally, ranitidine potentiates the stimulant effect of bethanechol and of carbachol on salivary glands of the rat while leaving unaffected the secretagogue effect of physalaemin which is known to be completely independent of the cholinergic system. In the *in vivo* experiments the doses of ranitidine capable of eliciting cholinergic-like effects were of the same order of magnitude as those necessary to cause the H_2-receptor blockade. (Bertaccini and Coruzzi, 2000).

Neutrophil functions, which play an important role in the antibacterial host defense system, are inhibited by various anesthetics and surgical procedures. Histamine H2-receptor antagonists are preoperatively used as a prophylaxis against acid aspiration syndrome or stress ulceration. We examined the effect of cimetidine, ranitidine, and famotidine, at clinically relevant concentrations and at 10 and 100 times this concentration, on several aspects of human neutrophil function using an in vitro system. The three H2-receptor antagonists did not impair neutrophils' chemotaxis or phagocytosis. Cimetidine and famotidine inhibited superoxide (O2-) and hydrogen peroxide (H2O2) production of the neutrophils in a dose-dependent manner, although the inhibitory effects were minimal. In contrast, ranitidine failed to change O2- or H2O2 production of neutrophils. The three H2-receptor antagonists did not scavenge these reactive oxygen species generated by the xanthine-xanthine oxidase system. The increase in intracellular calcium concentrations in neutrophils by a stimulant were dose-dependently attenuated with cimetidine or famotidine. This decreasing effect of the drugs on [Ca2+]i in neutrophils may represent one of mechanisms responsible for inhibition of reactive oxygen species generation (Mikawa *et al.*,2001).

While the analysis of in vitro dissolution–in vivo absorption relationships from oral solid dosage forms provides biopharmaceutical insight and regulatory benefit, no well-developed method exists to predict dissolution–absorption relationships a priori to human studies. The objective was to develop an integrated dissolution/Caco-2 system to predict dissolution–absorption relationships, and hence the contributions of dissolution and intestinal permeation to overall drug absorption for fast and slow formulations of piroxicam, metoprolol, and ranitidine. Dissolution studies were conducted on fast and slow dissolving immediate-release formulations of piroxicam, metoprolol tartrate, and ranitidine HCl. Dissolution samples were treated with concentrated buffers to render them suitable (i.e. isotonic and neutral pH) for Caco-2 monolayer permeation studies. The dissolution/Caco-2 system yielded a predicted dissolution–absorption relationship for each formulation which matched the observed relationship from clinical studies. The dissolution/Caco-2 system's prediction of dissolution or permeation rate-limited absorption also agreed with the clinical results (Ginski,2001)

Prophylactic maintenance therapy for one year using ranitidine 150 mg at night or a placebo was assessed in 68 patients whose gastric or duodenal ulcers had previously healed after therapy with ranitidine 150 mg twice daily or placebo. Gastroscopy was carried out on symptomatic relapse and at the end of the year. Of the duodenal ulcer group, seven out of 20 relapsed on ranitidine compared with 15 out of 17 on placebo (p less than 0.001). Of the gastric ulcer group one of 15 patients relapsed on ranitidine compared with 11 of 16 patients on placebo (p less than 0.005). There were no adverse effects from ranitidine during the trial period. Ranitidine in low dose maintenance therapy is therefore reasonably effective in the prevention of relapse of duodenal ulcers and appears to be particularly effective in preventing relapse of gastric ulcers at least for one year. As gastric ulcers occur more frequently in the older patients in whom there are often medical contraindications to surgery, maintenance treatment may be appropriate (Alstead *et al.*,2001).

Ranitidine interacts with liver microsomes from rats pretreated with different inducers of cytochrome P-450 to produce substrate difference optical spectra with a peak at 426–429 nm and a trough at 390–400 nm. Cytochrome P-450 reduced with dithionite in the presence of ranitidine produced substrate difference spectra with a peak at 447 nm. K_s values for the interaction of ranitidine with cytochrome P-450 (not reduced),

calculated from double reciprocal plots, were in the range 1.4—2.8 mM. The O-dealkylation of 7-ethoxycoumarin and of *p*-nitroanisole was inhibited by the presence of ranitidine and the inhibition was of a mixed type. K_{ii} and K_{is} values were: for inhibition of 7-ethoxycoumarin dealkylation, 0.8 to 9 mM, and 0.16 to 0.67 mM, respectively; for inhibition of *p*-nitroanisole dealkylation, 0.8 to 13.7 mM, and 1 to 4.5 mM, respectively (Rendic *et al*.,2001).

The authors firstly review the literature dealing with drug absorption sites in the gastrointestinal tract. Descriptions are given of the methods used in determining the location of these sites, and the advantages and disadvantages of each method are critically discussed. The results obtained concerning the absorption sites of the drugs used in the in vivo methods studied are given in a tabular form and several factors influencing drug absorption are briefly reported. Mechanisms of drug absorption in the human body and their influence on absorption sites are examined. Finally, there is a discussion of various dosage forms which are used for targeting drug absorption to specific sites. (Rouge *etal.*2002).

Significant recent work has focused on predicting drug absorption from structure. Several misperceptions regarding the nature of absorption seem to be common. Among these is that intestinal absorption, permeability, fraction absorbed, and, in some cases, even bioavailability, are equivalent properties and can be used interchangeably. A second common misperception is that absorption, permeability, etc. are discrete, fundamental properties of the molecule and can be predicted solely from some structural representation of the drug. In reality, drug absorption is a complex process dependent upon drug properties such as solubility and permeability, formulation factors, and physiological variables, including regional permeability differences, pH, luminal and mucosal enzymology, and intestinal motility, among others. This article will explore the influence of these different variables on drug absorption and the implications with regards to attempting to develop predictive drug absorption algorithms (Burton *et al*.,2002).

Two randomized double-blind crossover studies and one randomized crossover study were performed to document possible drug-drug interactions between antacids (aluminum magnesium hydroxide, 10 ml per dose for 10 doses), ant muscarinic drugs (pirenzepine, 50 mg per dose for 4 doses), and H2-blockers (ranitidine, 150 mg per dose for 3 doses)

and amoxicillin (1,000 mg), cephalexin (1,000 mg), doxycycline (200 mg), and amoxicillin-clavulanic acid (625 mg). Ten healthy volunteers participated in each study. Concentrations in serum and urine were measured by bioassay, and pharmacokinetic parameters were calculated by the usual open one- or two-compartment models (statistics were determined by the Wilcoxon test). The antacid, pirenzepine, and ranitidine had no influence on the bioavailability of amoxicillin, cephalexin, and amoxicillin-clavulanic acid. Only small differences could be observed in the pharmacokinetic parameters, but they are not of therapeutic importance. However, the antacid caused a significant (P less than 0.01) reduction in the gastrointestinal absorption of doxycycline (area under the concentration-time curve, 38.6 +/- 22.7 mg.h/liter, fasting; 6.0 +/- 3.2 mg.h/liter, with antacid), resulting in sub therapeutic levels of doxycycline (Deppermann *et al*., 2000).

The pharmaceutical equivalence of Zantac (reference drug) and 10 domestic and foreign generics of ranitidine hydrochloride as 150-mg coated tablets were studied using the pharmacopoeic (USP 29) dissolution test. Analyses showed insignificant differences in the excipients entering into the compositions of ranitidine generic tablets registered in Russia. It was established that Zantac and generics of two manufacturers were rapidly soluble (according to the WHO classification). It was demonstrated that the in vitro dissolution test recommended by WHO could be used for determining the bioequivalence of ranitidine generics. (Smekhova and Perova, 2009)

CHAPTER: 03

METERIALS AND METHOD

3.1 Specifications and Experimental Conditions

The Centre for Drug Evaluation and Research (CDER) at the United States Food and Drug Administration (US FDA) describes three categories of dissolution test specifications for immediate release products. These are single point specifications, two point specifications and dissolution profile comparison. Single and two-point specifications are sufficient to characterize drug products containing high solubility-high permeability substances. However, this is not suitable for characterization of low solubility products because such products have inherent different dissolution profiles. Consequently, they may comply with the point estimates, thereby giving an erroneous impression of pharmaceutical equivalence in dissolution characteristics. Dissolution profile comparison is recommended for such products, as it is more precise and discriminative than point estimates. Comparative dissolution profile testing of drugs is carried out in at least three dissolution media in order to study their stability and release characteristics in the different physiological conditions that they may be subjected to *in vivo*. The recommended dissolution media 900ml distill water. (Ahmed *et al*.,1993)

3.2 Methods for Comparison of Dissolution Profile Data

The methods for the comparison of *in vitro* dissolution profiles can be classified into three groups:

i. Methods based on analysis of variance (ANOVA)

ii. Model-dependent methods

iii. Model-independent methods.

ANOVA-based methods use univariate and multivariate approaches to quantify differences in dissolution percentages at each time point and among different products.

Model-dependent methods include the cubic root law (Hixson and Crowell) mathematical model, the Weibull distribution model and the logistics (Rowlings) model for sigmoidal dissolution curves. (Yuksel *et al.* 2000).

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 a reference product. These factors are denoted f1 (difference factor) and f2 (similarity factor) (Yuksel*et al.* 2000).

Comparison of the dissolution profiles of ranitidine can be satisfactorily carried out using the model independent approaches. 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:

$$f_1 = \{[\Sigma_{t=1}^{n} |R_t - T_t|] / [\Sigma_{t=1}^{n} R_t]\} \times 100$$

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% (Yuksel*et al.* 2000).

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:

$$f_2 = 50 \times \log \{[1 + (1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\}$$

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 (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 (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 points 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%. (Polli *et al*.,1997)

3.3 Comparative Dissolution Studies and Generic Prescribing

The *in vitro* dissolution test is important in characterization of drug product performance. It is useful for quality control and in the prediction of *in vivo* performance of pharmaceutical products. Comparative *in vitro* dissolution testing of generic drugs versus innovator products serves as a tool to determine pharmaceutical equivalence of the two products. Two products are considered pharmaceutically equivalent if they contain the same amounts of API in the same dosage forms that meet the same or comparable standards. Determination of pharmaceutical equivalence serves as a surrogate for *in vivo* bioequivalence tests that are expensive and not readily undertaken by generic drug manufacturers. The *in vitro* dissolution test is therefore a useful surrogate for assessment of bioequivalence. It plays an important role in comparison of therapeutic performances of pharmaceutical products containing the same API and has for this reason gained importance since the inception of generic equivalents of innovator drugs as a cost-cutting measure in healthcare. (Yuksel*et al.* 2000).Establishment of bioequivalence is essential to interchangeability of drug products. Whereas pharmaceutical equivalence does not necessarily imply bioequivalence, it is an important determinant in establishing interchangeability. Theoretically, any generic drug 15 that is bioequivalent to its innovator counterpart may be interchanged with it. It is expected that the generic formulations have an equivalent clinical effect and safety profile to the innovator formulation. In settings where bioequivalence studies are not viable, comparative dissolution testing can be used to determine which products can be used interchangeably. (Ruiz *et al.,* 2012).

3.4 Dissolution Testing Sample, Reagents and Instruments:

3.4.1 Sample of Ranitidine

Sample name	**Manufacturer**	**Source**
Zantac	GlaxoSmithKline Bangladesh Ltd.	Lazz Pharma
Ethidin	Ethical Pharmaceuticals	Raw Pharmacy
Inseac	Ibn Sina Pharmaceutical Ind. Ltd.	Foraizy Pharmacy

3.2. Reagents:

Reagent name	**Source(Supplier name)**
Distilled water	Laboratory(East West University)
Ranitidine API	Incepta Pharmaceutical Ltd.

3.3. Instruments:

Serial no.	Equipments	Source(supplier name)	Origin
1	UV-Spectrophotometer	Shimadzu UV-1800	Japan
2	Dissolution tester	SMIC	China
3	Distill water plant	SMIC	China
4	Electronic balance	PrecisaXB120A	Switzerland
5	Friability tester	Veegoindia	India
6	Vernier caliper	China supplier	Shanghai,China
7	Hardness tester	Manually operated hardness tester	India

3.4. Chart: Apparatus used throughout the experiments

Serial no.	Apparatus
1	Beaker
2	Test tube
3	Filter paper
4	Glass rod
5	Morter and pastle
6	Spatula
7	Volumetric flask(25ml,50ml,100ml,1000ml)
8	Pipette pumper
9	Funnel
10	Pipette(1ml,5ml,10ml)

3.5. In vitro dissolution study:

Dissolution medium	Distilled water
RPM	50
Time	50 minutes

Procedure:

The release rate of ranitidine tablet was determined by using tablet dissolution tester USPXXII. The dissolution test was performed using 900ml water pH (7.4) at 37 degree C and 50 r.p.m. At first 5 min and the with interval 10 minutes sample of 10 ml were collected from the dissolution medium and the amount was replace by 10 ml distill water. The sample was filtered through a filter paper named whatmaan filter paper and diluted to a suitable concentration of distilled water. The absorbance of the solution was measured 332nm for drug ranitidine by using a Shimadzu UV-1201 UV/visible double beam

spectrophotometer. Percentage of drug release was calculated using an equation obtained from standard curve. The dissolution was continued for 60 minutes to get simulated picture of drug release in vivo condition and drug dissolve at specified time periods was plotted as percent release versus time curve. (Shah, Vinod P, et al.1998)

3.5.4 Preparation of Standard Curve:

To prepare standard curve, at first different concentrations (5, 10, 15, 20 and 25) ug/ml of ranitidine was prepared.

For the preparation of different concentrations of ranitidine:

3 tablets were crushed finely in mortar pestle. The average weight of tablets was taken and the 50 mg was dissolved in 50 ml of distilled water. Then the concentration of the solution was (150/300 = 0.5mg/ml or 500 ug/ml). Then the solution was filtered in a volumetric flask. Then 5ml solution with a concentration of 500ug/ml was 10 times diluted in a taken in a volumetric flask. Now it is 50 ug/ml solutions. Then taken solution was 1 ml, 2 ml, 3 ml, 4 ml, 5 ml and added water was 9 ml, 8 ml, 7 ml, 6 ml, 5 ml.

For the preparation of 5 ug/ml the calculation is given below:

S_1= 50 ug/ml

S_2= 5 ug/ml

V_2=10 ml

So, $V_1= S_2XV_2/S_1$=1 ml

So, 1ml of solution was taken and 9ml of distilled water was added to obtain 10 ml solution with a concentration of 5 ug/ml or 0.005 mg/ml.

For the preparation of 10 ug/ml the calculation is given below:

S_1= 50 ug/ml

S_2= 10 ug/ml

V_2=10 ml

V_1=?

V_1= S_2XV_2/S_1= 2ml

So, 8ml of solution was taken and 2ml of distilled water was added to obtain 10 ml solution with a concentration of 10 ug/ml.

For the preparation of 0.003 mg/ml the calculation is given below:

S_1= 50 ug/ml

S_2= 15 ug/ml

V_2=10 ml

V_1=?

V_1= S_2XV_2/S_1= 3ml

So, 3ml of solution was taken and 7ml of distilled water was added to obtain 10 ml solution with a concentration of 15 ug/ml.

Further followed the same rule.

Then spectrophotometer is turned on and 314nm wave length was set up. Then the spectrophotometer was adjusted for 0 and 100% T. The solutions were placed on spectrophotometer to measure the absorbance. Then the absorbance was plotted against concentration. A straight line was found.

Table 3.6 Concentrations of Ranitidine

Serial no	Concentration(ug/ml)
1	5
2	10
3	15
4	20
5	25

3.6 Preparation for dissolution test:

3.6.1 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.

3.6.2 Method for dissolution test of Zantac (Ranitidine)

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 1 hour, rpm 50 was set up in the dissolution machine. Then the machine was allowed to warm up until it reached at 37.5 degree C. Then 1 Zantac tablet was placed in every vessel. After 20, 40 and 60 minutes 10 ml of solution was collected from each vessels 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 314nm..

3.6.3 Method for dissolution test of Ethidine (Ranitidine)

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 1 hour, rpm 50 was set up in the dissolution machine. Then the machine was allowed to warm up until it reached at 37.5 degree C. Then 1 Ethidine tablet was placed in every vessel. After 20, 40 and 60 minutes 10 ml of solution was collected from each vessels 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 314nm.

3.6.8 Method for Iseac:

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 1 hour, rpm 50 was set up in the dissolution machine. Then the machine was allowed to warm up until it reached at 37.5 degree C. Then 1Inseac tablet was placed in every vessel.

After 20, 40 and 60 minutes 10 ml of solution was collected from each vessels 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 314nm.

3.7 Determination of physical parameters

3.7.1 Weight Variation Test

Procedure:

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

Noted, the variation from the average weight in the weights not more than two tablets must not differ more than the percentage listed below:

Table 3.7.: Accepted percentage list for weight variation test of tablets

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

3.7.2 Equation:

Following equation was used to determine % weight variation of tablets

% Weight Variation = (A-I/A) × 100

Where,

Initial Weight of Tablet, I (gm)

Average weight of Tablets, A (gm) **(**Dunnett and Crisafio,1995)

3.7.3 Thickness test

Procedure

First the tablet was placed between the two jaws of the vernier caliper. Then the main scale reading was taken. Next vernier scale reading was taken also. The two readings were added together for multiplying with the vernier constant 0.1Cm.

3.7.4 Calculation

Following formula was used to determine thickness of tablets.

Thickness of the tablet = Reading of Cm scale + Reading of vernier scale ×Vernier constant (0.01) + Vernier error

3.7.4. Hardness test

Procedure:

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

3.8 Instrumentation

3.8.1 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 non-volatile 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 tygontubings, 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.

3.8.3 Infra-Red Spectrophotometer

The Infra-red spectrum of ranitidine working standard was determined using a Shimadzu IRPrestige 21 Fourier Transform Infra-Red (FTIR) spectrophotometer (Shimadzu Corp., Kyoto, Japan) supported by IRSolution Software Ver. 1.3. Sample discs for recording the spectrum were prepared using spectroscopic grade potassium bromide (E. Merck, Darmstadt, Germany) and a manually operated hydraulic pellet press (Perking Elmer GmbH, Uberlingen, Germany).

3.8.4 Ultra- Violet Spectrophotometer

The ultra-violet absorption spectrum for ranitidine working standard was recorded using a double beam T90+ UV/VIS spectrometer controlled via a computer using UVWIN spectrophotometer software version 5.2.0. Over a 10 mm path length using quartz cuvettes.

3.8.5 Samples and Chemical Reference Substances

Ranitidine tablets from different manufacturers were used in the study. The samples were obtained from different private retail outlets within Bangladesh.

3.9 Images of Instruments:

Some images of important instruments those were used in different testes during research work.

Figure3.1: Dissolution apparatus (Tradeindia.com, 2016).

Figure3.2: Distilled Water apparatus (Tresnainstrument.com, 2016)

Figure3.3: (left to right) UV-1800 Double Beam Spectrophotometer (Tradeindia.com, 2016)

Figure3.4: Hardness tester(Tradein.com,2016)

CHAPTER: 04

RESULT AND DISCUSSION

4.1 Physical Properties of Ranitidine Tablet:

Disintegration time:

Name of Drug	I	II	III	Average(minutes)
Zantac	13.36	13.12	14.10	14 minutes
Ethidin	11.36	11.15	11.43	11.31 minutes
Inseac	13.50	14	13	13.50 minutes

[N.B: Here all time was calculated in Minutes and Second.]

Weight:

Name of drug	Weight(mg)
Zantac	305
Ethidine	324
Inseac	312

4.2 Standard Curve:

150 mg Ranitidine (Zantac) was taken for this assay and the concentration was raised gradually 0.00 to 5.00, 10.00, 15.00, 20.00, 25.00 and found results are listed below.

Table 4.2. Standard Curve value

Concentration(µg/ml)	**Absorbance**
0.00	0.00
5.00	0.25
10.00	0.47
15.00	0.70
20.00	0.94
25.00	1.13

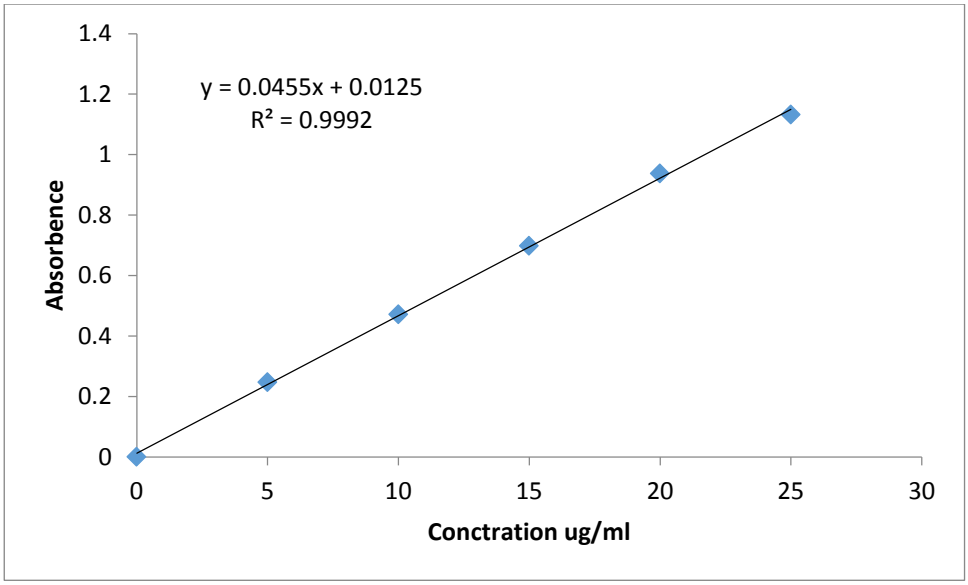


Figure 4.1: Standard Curve of Zantac

Here the Drag release is increasing with the increasing of time. This makes the graph accurate. This graph is taken as the standard curve for the following drugs. Zantac was chosen as it is the patent drug worldwide. Here X axis represents the time and Y axis is for Drug release.

4.3. Drug Release and time of Zantac 150 tablets:

Time(Minutes)	Drug Release%
0.00	0.00
5.00	19.52
10.00	35.45
20.00	61.35
30.00	79.68
40.00	87.17
50.00	88.50

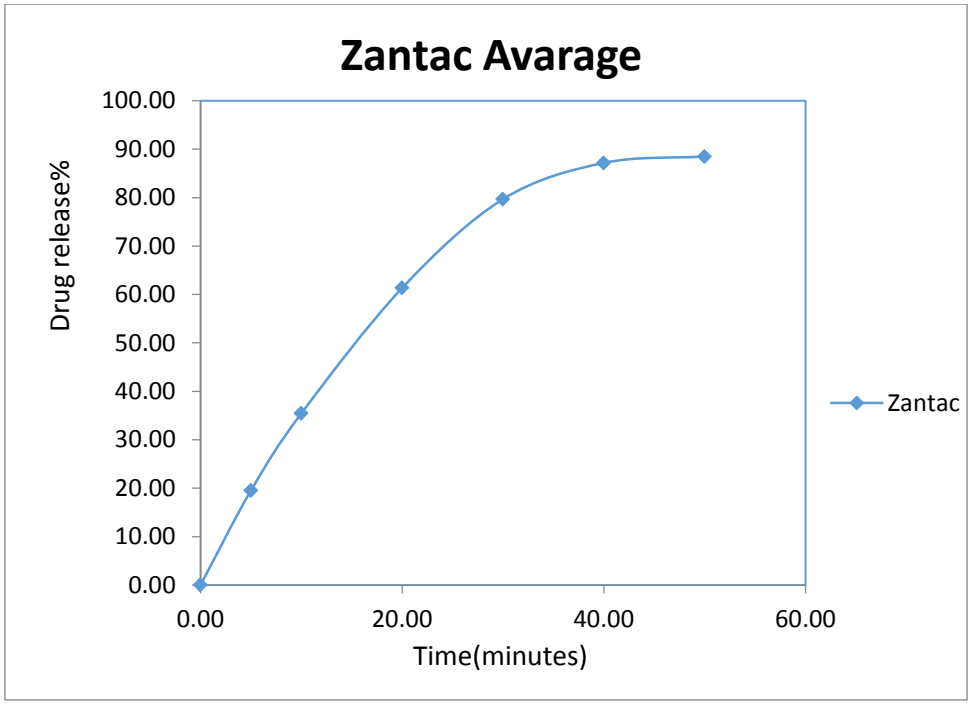


Figure 4.2.: Relation between time and Drug release of Zantac.

This graph does mean the increasing of drug release in according to the counting of time. in 0.00 the drug release was 0.00 and then 5.00 minutes has 19.52 then 10.00 minutes was 35.45, 20.00 minutes has 61.35, 30.00 minutes has 79.68, 40.00 has 87.17 and 50.00 has 88.50. Here X axis represents the time and Y axis is for Drug release.

Table4.4: Ethidine average % release of sample

Time(Minutes)	Percentage of Release
0.00	0.00
5.00	21.51
10.00	36.09
20.00	75.29
30.00	85.91
40.00	92.22
50.00	101.24

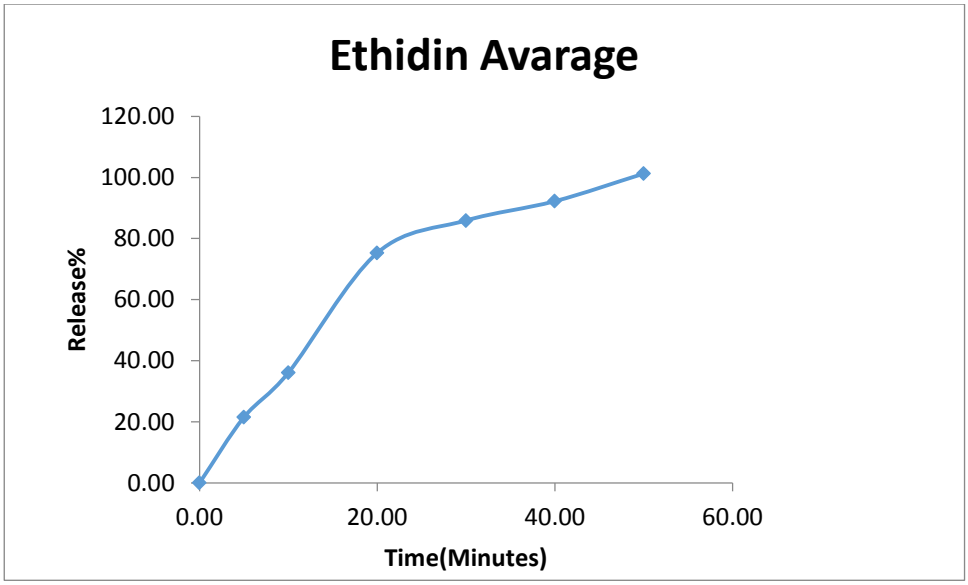


Figure4.3: Ethidine average % release of samples

DISCUSSION

This graph does mean the increasing of drug release in according to the counting of time in 0.00 the drug release was 0.00 and then 5.00 minutes has21.51 then 10.00 minutes was36.09,20.00 minutes has 75.29, 30.00 minutes has 85.91, 40.00 has 92.22, and 50.00 has 101.24.

Table4.4: Inseac average % release of samples

Time(Minutes)	Percentage release of Inseac
0.00	0.00
5.00	31.11
10.00	52.00
20.00	75.96
30.00	84.09
40.00	88.04
50.00	96.93

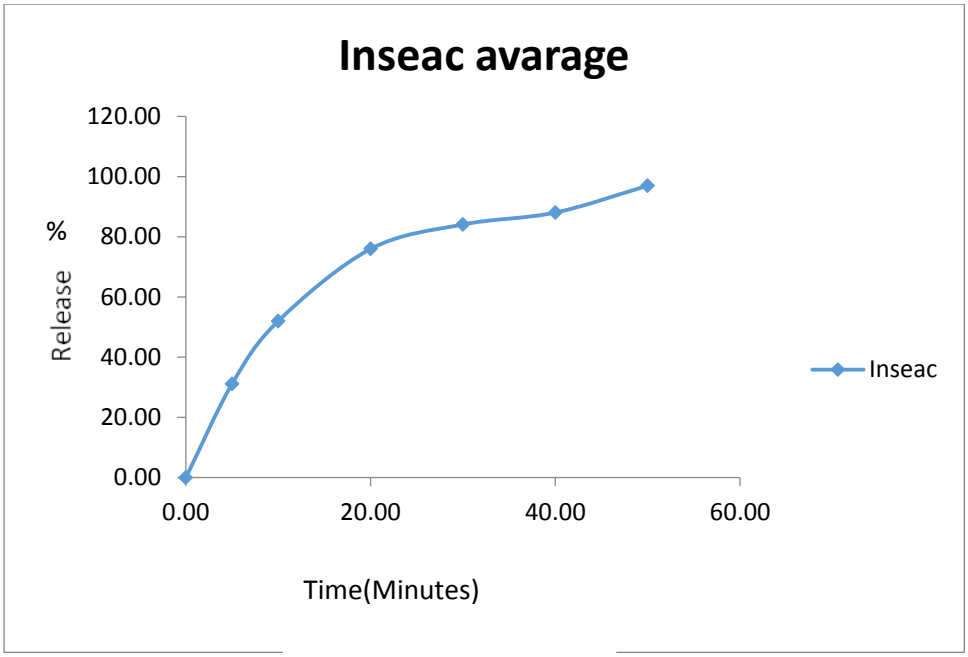


Figure 4.4: A graph on Inseac average % release of samples

DISCUSSION

This graph does mean the increasing of drug release in according to the counting of time. in 0.00the drug release was 0.00 and then 5.00 minutes has31.11 then 10.00 minutes was 52.00, 20.00 minutes has 75.96, 30.00 minutes has 84.09, 40.00 has 88.04, and 50.00 has 96.93.

Table4.5: Comparison among percentage Release of Zantac, Inseac, Ethidin.

Time(Minutes)	Percentage release Zantac	Percentage release Inseac	Percentage release Ethidin
0.00	0.00	0.00	0.00
5.00	19.52	31.11	21.51
10.00	35.45	52.00	36.09
20.00	61.35	75.96	75.29
30.00	79.68	84.09	85.91
40.00	87.17	88.04	92.22
50.00	88.50	96.93	101.24

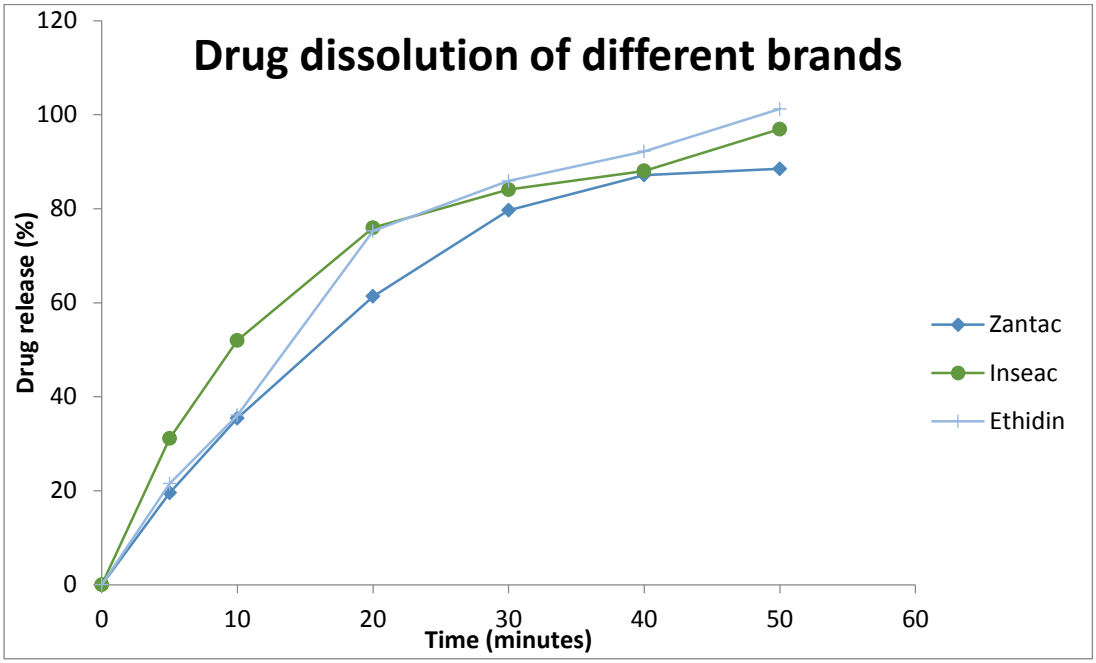


Figure: 4.5: A graph showing comparison of percentage release among Zantac, Ethidin and Inseac.

Here, In X-axis time (minutes) and in Y-axis % of release of Zantac, Ethidin and Inseac are taken. This graph showing comparison of percentage release among Zantac, Ethidin and Inseac. Drug release percentage of Inseac is better than Ethidin but not Zantac.

Calculation of f1 and f2

***f*1 calculation for Ethidine and Inseac**

Difference Factor, *f*1 the 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. The equation of *f*1 is given below:

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

Rt is the percentage of drug release from the reference drug product and Tt is the percentage of drug release from the test drug product at t time. 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 (Qazi *et al*., 2013).

Table 4.6- *f*1 calculation for Ethidin

Time	Zantac (R)	Ethidin (T)	R-T	I R-T I	F1
5	19.52	21.51	-1.99	1.99	
10	35.45	36.09	-0.64	0.64	
20	61.35	75.29	-13.94	13.94	10.92%
30	79.68	85.91	-6.23	6.23	
40	87.17	92.22	-5.05	5.05	
50	88.50	101.24	-12.74	12.74	
Total	371.67			40.59	

Table 4.7- *f*1 calculation for Inseac

Time	Zantac (R)	Inseac (T)	R-T	I R-T I	F1
5	19.52	31.11	-11.59	11.59	
10	35.45	52.00	-16.55	16.55	
20	61.35	75.96	-14.61	14.61	15.19%
30	79.68	84.09	-4.41	4.41	
40	87.17	88.04	-0.87	0.87	
50	88.50	96.93	-8.43	8.43	
Total	371.67			56.46	

*f*2 calculation for Ethidin and Inseac

Similarity Factor, *f*2 Similarity factor is calculated to determine significant similarity between two brands. The equation of f2 is given below:

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

The range of the *f*2 value is between 0 to 100. If the value remains between 50 to 100, it is acceptable (Qazi et al. 2013).

Table 4.8- *f*2 calculation for Ethidin

Time(Minutes)	Zantac (R)	Ethidin (T)	R-T	I R-T I	I R-T I^2	F2
5	19.52	21.51	-1.99	1.99	3.9601	
10	35.45	36.09	-0.64	0.64	0.4096	
20	61.35	75.29	-13.94	13.94	194.3236	32.60%
30	79.68	85.91	-6.23	6.23	38.8129	
40	87.17	92.22	-5.05	5.05	25.5025	
50	88.50	101.24	-12.74	12.74	162.3076	
Total	371.67			40.59	425.31	

Table4.9: *f*2 calculation for Inseac

Time(Minutes)	Zantac (R)	Inseac (T)	R-T	I R-T I	I R-T I^2	F2
5	19.52	31.11	-11.59	11.59	134.3281	
10	35.45	52.00	-16.55	16.55	273.9025	
20	61.35	75.96	-14.61	14.61	213.4521	26.99%
30	79.68	84.09	-4.41	4.41	19.4481	
40	87.17	88.04	-0.87	0.87	0.7569	
50	88.50	96.93	-8.43	8.43	71.0649	
Total	371.67			56.46	712.95	

CHAPTER: 05

CONCLUSION

5.2. Conclusion

In the study, significant differences were observed in the dissolution profiles of the ranitidine products tested. While all products complied with assay specifications, one of generic products tested did not comply with the specifications for similarity factor f2 in relation to the innovator product. A significant percentage of generic products in the market may not be pharmaceutically equivalent to their innovator counterparts. As such, results of clinical studies conducted on the innovator product may not necessarily be applicable to generic products. Consequently, the generic products in the Bangladesh market may not be interchangeable with the innovator product and their efficacy may also not be comparable to that of innovator drugs. The results obtained from this study can be extrapolated to the wider Bangladesh market. Results of assays and single-point dissolution tests should not be taken as proof of pharmaceutical equivalence, product quality, safety and efficacy. In vitro dissolution profile data for generic drug products should be included in routine QC and post-market surveillance tests in order to demonstrate consistent pharmaceutical equivalence to the innovator products. These measures are important steps in curbing sub-optimal therapeutic outcomes, treatment failures and microbial resistance incidences resulting from exposure to substandard therapeutic agents and will ensure patients get benefit from the generic drug products.

CHAPTER: 06

REFERENCE

REFERENCE

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