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.

Submitted By

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Declaration by the Research Candidate

Omer Fayshal Pavel, ID: 2012-3-70-037, hereby declare that the dissertation entitled "*In-vitro* comparative dissolution study of different brands of Ranitidine hydrochloride tablets 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 tablets 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 **Omer Fayshal Pavel**, **ID: 2012-3-70-037** 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 tablets 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 **Omer Fayshal Pavel**, **ID: 2012-3-70-037** in 2016.

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Dedication

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

Table of contents

List of Table

List of Figure

Abstract

The aim of the study is to find the similarity and difference among the local brands of ranitidine with the innovator brand in Bangladesh. Ranitidine is an antiulcerant 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. In this study the dissolution profiles of 150-mg coated ranitidine tablets of a reference drug Zantac and a generic Gepin and a similar Xantid drug marketed in Dhaka, Bangladesh 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 ºC for 1h. The dissolution test was performed in compliance with the United States Pharmacopoeia (USP-32). Dissolution efficiency and difference (*f*1) and similarity (*f*2) factors were calculated and evaluated. Here the both values of *f*1 are within the range, below the 15. In this case of *f2* though Gepin has the value of 50.78 that means it is in the range of 50-100 and made the brand accepted but in the other hand the Xantid has the value of 47.63 which is below the range so and not accepted. This problem can be due to manufacturing problems or for instrumental limitations.

Key Words: *Comparative dissolution, Ranitidine HCL, Difference factor, Similarity factor.*

CHAPTER ONE

Introduction

1.1 Objective

To assure the quality of pharmaceutical products are very important because avoiding the standard of quality can bring useless effect or adverse effect. Ranitidine is one most prescribed antiulcer drug used in worldwide. As ulcer or GID is one of the most common problems among people, so the use of ranitidine has raised more than before day by day. Ranitidine become the prior choose of drugs in GID. WHO had declared Ranitidine as essential drug in 2015 with in 19th updated list (Aiache, 2008).

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. Among the pharmaceuticals all has production of tablets including syrup, suspension, I.V. infusion and other dosage forms (BDdrugs, 2016).

As it is known biopharmaceutics 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 an observation of the regular drugs used by the mass population (Birhanu et al., 2013).

Under the research protocol local brands of Ranitidine of Bangladesh is compared with the standard patent drug Zantac. Drugs are Neotack (Square Pharmaceuticals Ltd), RANID (Ziska Pharmaceuticals Ltd.), Ranidin (ACME Laboratories Ltd.), Xantid (ACI pharmaceuticals Ltd.), Gepin (General Pharmaceuticals Ltd.), Inseac (Ibn Sina Pharmaceutical Ind. Ltd.) EDITIN R (Edruc Ltd).

1.2H2 blockers

1.2.1 H2 Blockers General Information

The H2 blockers or H2 antagonists were the first effective drugs against peptic ulcer. Recently drugs from this group are mostly used to treat the peptic ulcer and GERD as well. From the very beginning of 1980s, these were the leading drugs of treatment for ulcers and gastroesophageal reflux disease or (GERD).

Though now a day's antibiotics cure non-NSAID ulcers, and proton pump inhibitors (PPIs) are better for GERD. As these drugs are comparatively cheap, effective, and safe for heartburn relief, so lower dose preparations are available over-the-counter to be used for mild heartburn.

There are four H2 blockers available by prescription

1. Cimetidine (Tagamet,Tagamet HB)
2. Ranitidine (Zantac)
3. Nizatidine (Axid)
4. Famotidine (Pepsid, Pepcid, Pepcid AC)

There are generic available forms. They are equally effective in their available doses. Side effects may vary from one drug to another (International foundation for functional gastrointestinal disorders, 2014).

1.2.2 Mechanism of Action H2 Blockers

When patient takes an H2 receptor blocker, the active ingredients travel to specific receptors on the surface of the stomach cells that release acids. The medication inhibits those specific chemical reactions, producing the acid in gut so that they aren't able to produce as much acid. According to the National Institutes of Health, H2 receptor blockers decrease stomach acid secretions over a 24-hour period by 70 percent. By reducing the amount of acid in the stomach, any damaged tissues are allowed time to heal (Healthline, 2016).

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

1. Constipation
2. Diarrhea
3. Difficulty sleeping
4. Dry mouth
5. Dry skin
6. Headaches
7. Ringing in the ears

8. A runny nose
9. Trouble urinating (Healthline, 2016).

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

1. Blistered, Burning, or Scaling skin
2. Changes in vision
3. Confusion
4. Agitation
5. Difficulty breathing
6. Wheezing
7. Chest tightness
8. Irregular heartbeat
9. Hallucinations
10. 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).

1.3Ranitidine

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:

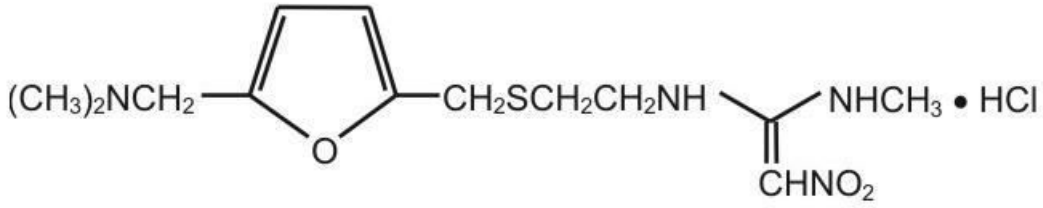

Figure 1.1: Ranitidine Chemical Structure (Synthesis of Drugs, 2012).

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.

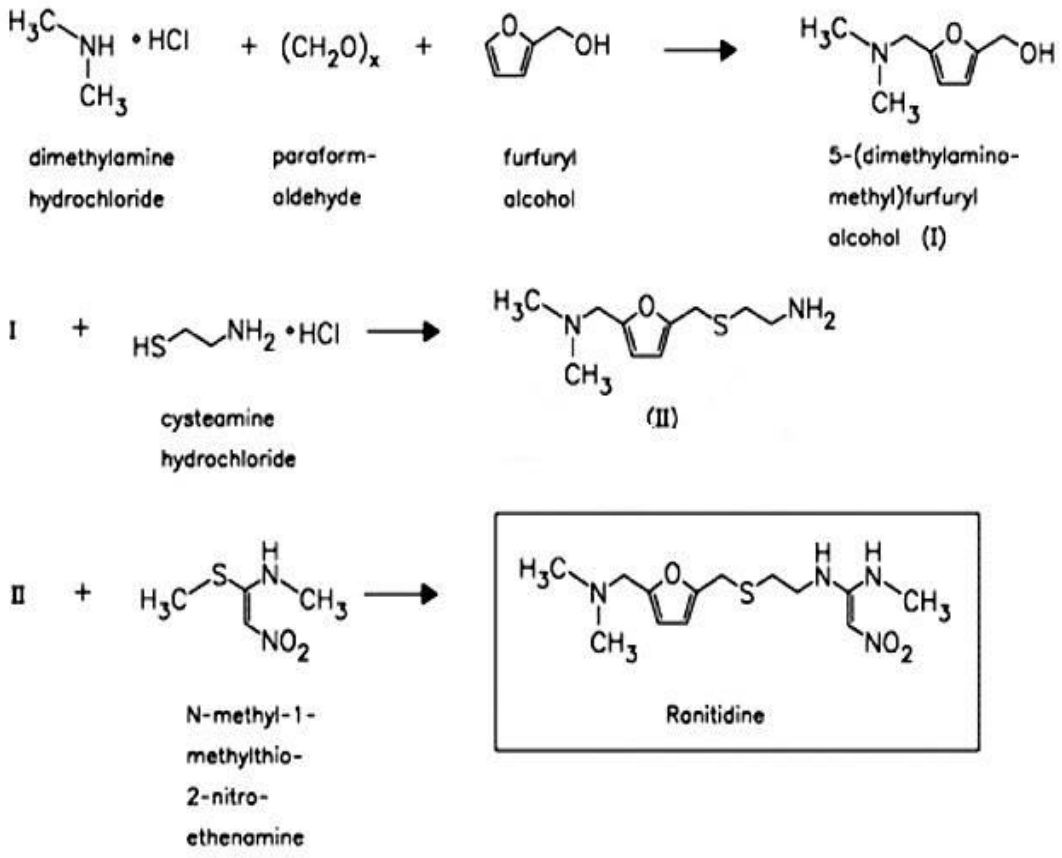

Figure1.2: Synthesis of Ranitidine (Synthesis of Drugs, 2012).

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% (Informed, 2016).

1.3.4 Ranitidine (Ranitidine Hydrochloride) - Indications and Dosage

1. Treatment of active duodenal ulcer. Most patients heal within 4 weeks. Studies available indicate that date has not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than 8 weeks.
2. Maintenance therapy after healing of acute ulcers for duodenal ulcer patients at reduced dosage. No placebo-controlled comparative studies have been carried out for periods of longer than 1 year.
3. The treatment of pathological hypersecretory conditions like Zollinger-Ellison syndrome and systemic mastocytosis etc.
4. 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.
5. 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.
6. 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.
7. 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 neonate's 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).

1.4Pharmacokinetics of Ranitidine

1.4.1 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).

1.4.3 Metabolism

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).

1.4.4 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 (McGuire, 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 $t_{1/2}$, V_d, and CL are similar to those founded with intravenous Ranitidine use in pediatric patients (McGuire, 2016).

Table 1.1: Estimates of C*max* and T*max*

Table 1. 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 photo-degradation of H2-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 photo-catalytic 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 chromatography (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).

Whit out 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 (Tradeindia,2016).

1.6BCS 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 (Sundler, 2004).

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 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 Biopharmaceutics 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 bio-waiver 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).

1.6.3 Formulation Approach

Having a pre-defined system in which one can make decisions based on data is necessary for efficient drug development. Inputs into such a system include, in addition to BCS class, a detailed solubility profile, polymorph status, desired dosage form, target dose and dosing regimen, drug stability, excipient compatibility and knowledge of transporter and metabolic pathways. Non-technical factors that, as a practical matter, need to be considered are such things as cost, intellectual property and distribution chain limitations. Integration of these into a methodical systematic approach will maximize the chances of a successful outcome. As R&D dollars become ever more scarce, it becomes increasingly evident that early consideration of as many factors as possible is the most efficient way to proceed. This is true independent of the route of administration. In practice, this leads to the strategy of getting to FIH as quickly as possible with a formulation strategy that accounts for both physicochemical properties and physiologic influences. A complete set of algorithms covering the four classes and all possible dosage forms is well beyond the scope of this article. However, a few fundamental principles can be covered. First, it is critical to characterize your compound. Understanding the basic behavior of a given compound in various solvents and across a range of pHs is fundamental to designing a dosage form. For instance, a compound soluble only at lower pHs will require a different formulation than one freely soluble at, for example, pH 7. Likewise, a soluble yet impermeable compound will require yet another strategy. Very importantly, this is true whether one is administering the drug, for example, IV or orally. The implications to formulation are different for the different routes of administration but the fact that these properties need to be accounted for is universal. It is important that the drug developer or the CRO be equipped with a range of technologies to address the various patterns that emerge. Nothing wastes more time and money than trying to fit a drug to a specific preordained delivery technology. Armed with the proper set of tools one can rapidly narrow down the potential approaches. For the most part, all drug delivery strategies are trying to control drug exposure. Most often, one is trying to maximize it over time and/or concentration but frequently goals also include extended release and/or site specific delivery. In addition to the delivery goals, other functions are often required such as API

stabilization or taste masking as two examples. In short, no one formulation approach will ever satisfy all or even a substantial portion of drug delivery demands. For oral drug delivery, a simplified summary of approaches based on properties might look like Table 1. Each approach must then be tailored to meet the other demands of that particular API and desired product profile.

Table 1

BCS Class	Solubility	Permeability	Oral Dosage Form Approach	Chances of Non-oral Dosage Form being Required
1	High	High	Simple solid oral dosage form	
2	Low	High	• Techniques to increase surface area like particle size reduction, solid solution, solid dispersion • Solutions using solvents and/ or surfactants	
3	High	Low	Incorporate permeability enhancers, maximize local lumenal concentration	
4	Low	Low	Combine 2 and 3	

Figure1.3: BCS Classification (Particlesciences, 2011)

If formulation conditions dictate that a non-oral dosage form be used, similar charts exist for virtually all routes of administration. Each route of administration will of course have different options but they are all ruled by the interplay of the drug's physicochemical properties and the local and systemic physiology they encounter. Independent of the final dosage form, ideal drug development involves an iterative process of setting goals, performing formulation work and developmental stage appropriate testing. Early on, for example, after physicochemical evaluations are complete, screening BCS testing and early polymorph screens might be performed. After thorough preformulation including solubility and stability testing, early formulations might again be screened for their impact on dissolution or bioavailability. This approach is repeated such that at each inflection point data is gathered to support the development plan. In this way, FIH is achieved most efficiently and in such a way as to insure clinically relevant data is obtained (Particlesciences, 2011).

1.7Dissolution

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 and 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.

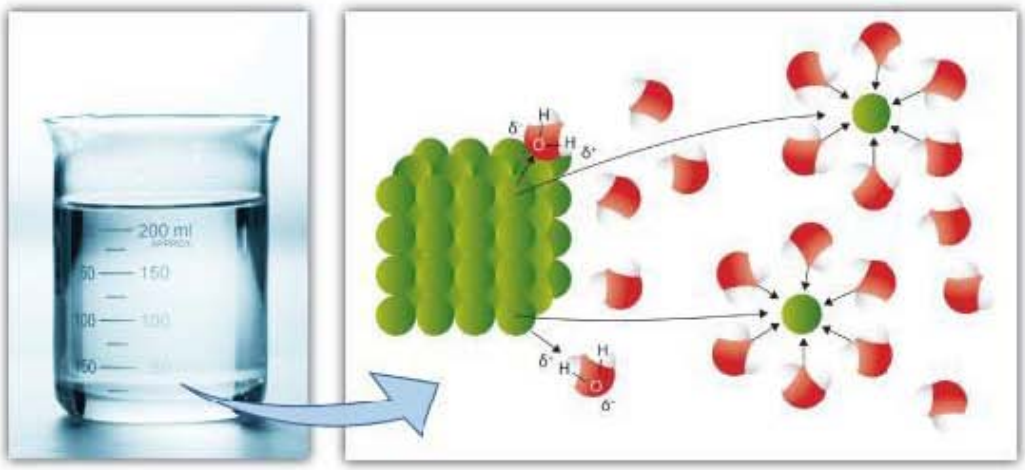

Figure 1.4: *Solvation* (Lapsurgery, 2014)

When a solute dissolves, the individual particles of solute become surrounded by solvent particles. Eventually the particle detaches from the remaining solute, surrounded by solvent molecules in solution (Lapsurgery, 2014).

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 (Lapsurgery, 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 (Yeomans, 2000).

1.8Comparative dissolution

1.8.1 Basic concept of Comparative dissolution

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 indentify 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. 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 (Yuksel *et al*. 2000).

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 *f*1 (difference factor) and *f*2 (similarity factor) (Patel, 2009).

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:

$$f_1 = \frac{\sum_{t=1}^{n}(\mathrm{IRt} - \mathrm{TtI})}{\sum_{t=1}^{n}\mathrm{Rt}}\ X100$$

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% (Hasan *et al.,* 2007)

The similarity factor (*f*2) 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:

$$f_2 = 50\log\{1 + (1/n)\sum_{t=1}^{n}(Rt - Tt)^{-0.5}\}X100$$

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). It is recommended 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% (Shah, 2001).

CHPTER 2

Literature Review

Purpose of this study was to compare the technical quality of commercial American and Japanese ranitidine tablets. Five brands of 150-mg USP tablets and six brands of 150-mg JP tablets were compared on hardness, friability, average weight, average content, content uniformity, and dissolution. The difference in hardness between American and Japanese tablets was significant. Dissolution profiles of Japanese tablets were not significantly different from one other, whereas those of American tablets were significantly different. However, all brands complied with USP 27. Since all brands can be expected to be in therapeutic use, this result supports the use of the USP criterion as an indicator for therapeutic efficacy (Otsuka *et al.,* 2001).

In 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 (Naveed, 2004).

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 spectra without the need to grind the samples. 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. 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. There was a good agreement between the experimental solubility data of ranitidine hydrochloride and the results of UNIQUAC equation (Mirmehrabia and Rohania, 2004).

The aim of this study was to compare the dissolution profiles of 150-mg coated ranitidine tablets of a reference drug and a generic and a similar 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. The dissolution test was performed in compliance with the American Pharmacopoeia (USP-32). Dissolution efficiency and difference (*f*1) and similarity (*f*2) factors were calculated and evaluated. Factors f1 and *f*2 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 (Santos *et al.,* 2005).

This work represents a comprehensive evaluation of the performance of a developed CE method in the determination of drug-related impurities in both drug substance and various pharmaceutical formulations. The data obtained clearly shows that the performance of an optimized CE method can be equivalent in terms of sensitivity and precision to that of a HPLC method employed for a similar purpose and offers better selectivity against TLC and HPLC (Kellya, Altriab and Clarka, 2005).

Ten different brands of Ranitidine HCl film coated tablets (150 mg) produced and marketed by Nepalese and Indian pharmacy companies available in Pokhara were included in study. Five quality control parameters: weight and weight variation test, hardness test, disintegration test, dissolution test and assay along with price variation study were carried out. All the brands met the compendia requirement for weight and weight variation test specified by IP. Hardness value requirement was complied by all brands except IR3. Disintegration time for all brands was within 15 minutes complying the IP recommendation. All brands showed more than 80 % drug release within 45 minutes. The drug content assays for all brands fell within the IP specification except for IR4 which was found to exceed the limit. There was a large range of price variation between all the brands. However, significant differences in quality control parameters are observed between the different brands (Mihaly, 2007).

In these study two potencies of tablets 150 mg and 300 mg were tested. Comparison of BIPI tablets and matching Zantac tablets indicated that both brands of ranitidine tablets USP had similar dissolution behavior. BIPI 150 mg tablets using the basket apparatus, but at reduced rotational speed of 30 rpm, 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 had an initial slower rate, but then rapidly equaled the paddle apparatus dissolution results, and had

less individual tablet variability. Results showed that dissolution artifacts for ranitidine tablets could be reduced by the use of baskets or tablet sinkers (Cappola, 2008).

In this study co-milling of γ-indomethacin and ranitidine hydrochloride form 2 at various weight ratios was investigated with a particular interest in the physicochemical properties. Results showed that both indomethacin and ranitidine hydrochloride were fully converted into the amorphous state after 60 min of co-milling. DRIFTS spectra of the co-milled amorphous samples showed peaks at 1610, 1679 and 1723 cm−1, that were not present in the individually milled samples and that are indicative of an interaction at the carboxylic acid carbonyl of the indomethacin molecule with the aci-nitro of ranitidine hydrochloride (Chieng, 2008).

The mean (+/- s.d.) distribution half-life was 6.6 +/- 1.6 min; plasma half-life was 1.7 +/- 0.2 h; the volume of distribution (V) was 96 +/- 9 1; total body clearance (CL) was 647 +/- 94 ml/min and renal clearance (CLR) 520 +/- 123 ml/min. 3 Following oral administration plasma levels showed a bimodal pattern with a first peak at 1.1 +/- 0.4 h and a second peak at 3 +/- 0 h. The absolute availability was 60 +/- 17%. The plasma half- life (t 1/2) of 2.3 +/- 0.4 h was significantly longer (P less than 0.05) after oral than after i.v. administration. Renal excretion of unchanged ranitidine accounted for 79 +/- 9% of the dose after i.v. administration and for 27 +/- 7% after oral administration. Results suggest a more extensive biotransformation of ranitidine and biliary excretion of metabolites after oral administration while i.v. administration ranitidine is preferentially excreted unchanged in the urine (Hecken *et al.,* 2009).

According to the study the possibility of applying near-infrared reflectance spectrometry to the control of the production cycle of ranitidine hydrochloride tablets was investigated. The results were good for the identification of ranitidine hydrochloride drug substance, mixtures for tablets, cores and coated tablets. The determination of the compound and of its water content also gave satisfactory results (Dreassi *et al.,* 2009).

The dissolution profiles from USP apparatus 3 were compared to those from USP apparatus 2 using the f 2 similarity test. It was found that USP apparatus 3 at the extreme low end of the possible agitation range, such as 5 dpm, gave hydrodynamic conditions equivalent to USP apparatus 2 at 50 rpm. With appropriate agitation rate, USP apparatus 3 can produce similar dissolution profiles to USP apparatus 2 or distinguish dissolution characteristics for the IR

products of metoprolol, ranitidine, and acyclovir. It is primarily designed for the release testing of extended-release products. USP apparatus 3 offers the advantages of avoiding cone formation and mimicking the changes in physiochemical conditions and mechanical forces experienced by products in the gastrointestinal tract (Yu, Wang and Husan, 2010).

Omeprazole 60 mg once daily was compared with ranitidine 150 mg twice daily in an endoscopically-controlled, double-blind randomised trial in 51 outpatients with erosive or ulcerative reflux oesophagitis. The healing rate 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 ($p = 0{\cdot}001$). 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 oesophagitis (Klinkem *et al.*, 2010).

It was done to evaluate the prophylactic effect of ranitidine 150 mg twice daily in patients requiring one of the following non-steroidal anti-inflammatory drugs. Ranitidine 150 mg twice daily or placebo (plus the selected non-steroidal anti-inflammatory drug) was prescribed within five days after the baseline endoscopy for two consecutive periods of four weeks. The cumulative incidence of peptic ulceration by eight weeks was 10.3%; 2 out of 135 (1.5%) developed duodenal ulceration in the ranitidine group, compared with 10 out of 126 (8%) taking placebo. The frequency of non-ulcerative lesions in the duodenum did not differ greatly for the two groups at either time point. Twelve out of 75 (16%) patients taking piroxicam developed peptic ulceration, of who two thirds had duodenal ulceration (Ehsanullah *et al.,* 2011).

This study compared the effect of a third dose of omeprazole at bedtime with that of a dose of ranitidine at bedtime on residual nocturnal acid secretion in patients receiving omeprazole twice daily. Twelve volunteers underwent overnight intragastric pH monitoring after 7 days of treatment with omeprazole, 20 mg twice daily, additional omeprazole, 20 mg; ranitidine, 150 mg; and ranitidine, 300 mg. Additional omeprazole at bedtime reduced the percentage of time with intragastric pH compared with omeprazole twice daily with placebo at bedtime. Ranitidine at bedtime reduced this parameter more, 5% with 150 mg and 6% with 300 mg. Eleven subjects had acid breakthrough with placebo at bedtime; 7 with omeprazole at bedtime ; 4 with ranitidine, 150 mg at bedtime; and 3 with ranitidine, 300 mg at bedtime (Peghini, Katz and Castell, 2011).

In this paper it was found that floating tablets of Ranitidine HCl were developed to prolong gastric residence time and increase its bioavailability. The tablets were prepared using different polymers like HPMC 4 K, HPMC 100K, Xanthan gum, Guar gum, Moringa gum and sodium CMC in different ratios. Sodium bicarbonate was incorporated as a gas generating agent. The functionality of Moringa gum powder as a carrier in floating tablets was also studied. A lesser floating lag time and prolonged floating duration could be achieved and also very promising *in vitro* results were observed with floating tablets of Ranitidine HCl. This designed system could possibly be advantageous in terms of increased bioavailability of Ranitidine HCl (Cappola, 2012).

The study deals with the influence of superdisintegrants on the croscarmellose sodium and sodium starch glycolate on dissolution time, wetting time etc were studied. The prepared tablets were evaluated for weight variation, content, hardness, friability, thickness and diameter and *In vitro* disintegrants such as croscarmellose sodium and sodium starch glycolate are used in combinations with the drug and the combination containing 25mg of croscarmellose sodium and 125 mg of sodium starch glycolate showed faster dispersion time and maximum drug release in 14 min. Key words: Ranitidine HCL, Croscarmellose sodium, Sodium starch glycolate, FDT (Prasanthi and Katyayani, 2012).

In this study the tablet was subjected to evaluation for physical characteristics like weight variation, hardness, friability, drug content uniformity, floating lag time and floating time and invitro drug release. Three different formulations of ranitidine hydrochloride were formulated by variation in the ratio of hydroxy propyl methyl cellulose. From the investigation it's found that Ranitidine hydrochloride incorporated with 120mg of HPMC was found to be better formulation by considering all the evaluated parameters like lag time, hardness, friability and weight variation and percentage drug release (Nishanthi and Gobalakrishnan, 2012).

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. Before purchasing the samples, their physical appearance, name of manufacturer, batch number, date of manufacturing, expiry date, manufacturing license number and Maximum Retail Price (MRP) were properly checked. 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).

In order to establish if this requirement is adequate, the bioavailability of two formulations that did not meet this similarity was 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. 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, 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. (Flores *et al.,* 2013).

Experimental data of this study 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 Biopharmaceutics 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.,* 2013).

In this study two other identified metabolites of ranitidine, the S-oxide and N-oxide, were separated chromatographically from both ranitidine and the desmethyl metabolite.The sensitivity limits were 5 ng/ml for ranitidine and 15 ng/ml for desmethylranitidine. Plasma samples from two volunteers who were given oral ranitidine at 1-week intervals were assayed. Peak levels of 30–130 ng/ml were achieved between 40 and 120 min after dosage, followed by an elimination

half-life of 2.9–3.9 hr. Plasma levels of ranitidine were still detectable at 8 hr but were below the sensitivity of the assay by 24 hr. Plasma levels of the desmethyl metabolite were seldom above the threshold sensitivity of the assay. Urinary excretion of unmetabolized ranitidine accounted for 77% of the administered dose, whereas only 4% appeared as desmethylranitidine (Aboofazeli and Shafaati, 2013).

The study focuses on the present study was to develop a simple method to measure ranitidine, using 100 μl of plasma, by high-performance liquid chromatography with a Symmetry C18 column and UV detection at 313 nm. Linearity was assessed in the range from 50 to 1500 ng ml−1 and had a correlation coefficient of 0.999. The inter- and intra-day coefficients of variation were less than 7%. The limits of detection and quantitation were 5 and 15 ng ml−1, respectively. Drug levels were determined satisfactorily in three patients. A simple and reliable method was developed which uses a microvolume of plasma, particularly useful in low-weight children (Flores, Juárez and Flores, 2013).

The taste of a drug plays an important role in patient compliance. Ranitidine HCl is a Histamine blocker drug with bitter taste. The drug Ranitidine HCl was treated with a cation exchange resin, which forms complex with the drug and mask the bitterness of Ranitidine HCl. The loading process was optimized for the resin type, pH of loading solution and drug:resin ratio. The resin-drug complex was evaluated for taste by panel method. The rate of dissolution was studied and the drug had showed good release. These findings can be utilized to formulate a non bitter dosage form for Ranitidine HCl with good bioavailability (Kumar, 2013).

Ranitidine Hydrochloride also indicated for the treatment of "Post-operative ulcer". Ranitidine Hydrochloride is also used for the treatment of where reduced acid output is desirable and reduction of gastric secretion. It is used for the treatment of "chronic episodic dyspepsia" which is related to food and disturbs the sleep. Ranitidine Hydrochloride is a drug which reduces the acid production by the cells and blocks the behavior of histamine on the parietal cells in the stomach. The H_2 antagonists are competitive inhibitors of histamine. It will suppress the acid secreted by the food and the secretion of acid by parietal cells (Bradshaw, 2013).

The characterization studies involve measurement of apparent density, porosity, swelling studies, mechanical strength studies, and scanning electron microscopy. The prepared system floated and

delivered the ranitidine hydrochloride for about 17 hours. To ascertain the drug release kinetics, the dissolution profiles were fitted to different mathematical models that include zero-order, first-order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas, Weibull, and Hopfenberg models. It is concluded that the proposed mechanically stable floating drug-delivery system based on superporous hydrogel composite containing sodium carboxymethylcellulose as a composite material is promising for stomach specific delivery of ranitidine hydrochloride. (Chavda and Patel, 2013).

Prior approaches to preventing the side effects of NSAIDs have included treatment with histamine H2-receptor antagonists to inhibit acid secretion and the administration of prostaglandin analogues to replace the depleted endogenous prostaglandins. In short-term studies, the proton-pump inhibitor omeprazole prevented aspirin-induced gastric mucosal damage and lesions. Omeprazole heals ulcers effectively and is equally efficacious for gastric or duodenal ulcers in the presence or absence of NSAID treatment. We compared the efficacy of omeprazole and ranitidine in patients with gastroduodenal ulcers and erosions associated with continuous NSAID therapy. (Dhivya *et al.,* 2013)

This study Unoperated female rats were subjected to daily oral treatment with omeprazole, ranitidine, or vehicle and antrectomized rats were treated with omeprazole or vehicle. A close correlation (r = 0.89, p less than 0.0001) was found between the plasma gastrin level and the oxyntic mucosal enterochromaffinlike cell density in all groups. During a recovery period of 10 wk after the 10-wk treatment, the enterochromaffinlike cell density and histamine concentration decreased by 30%-40% in the rats treated with the high dose of omeprazole, whereas the corresponding values increased by 50% and 40%, respectively. The results suggest that the observed changes in enterochromaffinlike cell density are related to the plasma gastrin levels and that they are reversible. (Aiache *et al.,* 2014)

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. and 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 (Naveed, 2014).

In this research applied principal components analysis (PCA) of Raman spectra to binary mixtures of the two polymorphs and to binary mixtures prepared by adding one polymorph to powdered tablets of the other. Based on absorption measurements of seven spectral regions, it was found that >97% of the spectral variation was accounted for by three principal components. Quantitative calibration models generated by multiple linear regression predicted a detection limit and quantization limit for either forms I or II in mixtures of the two of 0.6 and 1.8%, respectively (Bardhan, 2014).

This study was conducted to determine the efficacy and short-term safety of lansoprazole at dosage of 30 mg or 60 mg once daily, compared with ranitidine 150 mg twice daily. This was a double-blind, stratified, randomized, comparative, parallel group study conducted in five centres in the UK. A total of 229 patients (155 men) aged 18-79 years. Lansoprazole 30 mg and 60 mg were superior at 4 and 8 weeks to ranitidine in healing reflux oesophagitis: respective healing rates being 84%, 72% and 39% after 4 weeks and 92%, 91% and 53% after 8 weeks. Sixty-four patients experienced a total of 85 adverse events, one-third of which were considered drug-related. The incidence and severity were similar in the three groups. Lansoprazole 30 mg and 60 mg once daily are more effective than ranitidine 150 mg twice daily in the short-term treatment of reflux oesophagitis (Pratiwia *et al.,* 2014).

CHAPTER THREE

Experimental and Methodology

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 *f*1 (difference factor) and *f*2 (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 (*f*1) 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

$$f_1 = \frac{\sum_{t=1}^{n}(\mathrm{IRt}-\mathrm{TtI})}{\sum_{t=1}^{n}\mathrm{Rt}}\ X100$$

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 (*f*2) 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:

$$f_2 = 50\log\{1 + (1/n)\sum_{t=1}^{n}(Rt - Tt)^{-0.5}\}X100$$

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.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, *f*2 = 100%. An average dissolution difference of 10% at all measured time points

results in an *f*2 value of 50%. For this reason, the public standard for similarity of two dissolution profiles has been set at 50 - 100% (Ochekpe *et al.,* 2006).

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

Table 3.1 Sample of Ranitidine used in the experiment

Sample name	**Manufacturer**	**Source**
Zantac	GSK Pharmaceutical	Lazz Pharma
Xantid	ACI Pharmaceuticals	Raw Pharmacy
Gepin	General Pharmaceuticals Ltd.	Foraizy Pharmacy

Table 3.2 Reagents used in the experiment

Reagent name	**Source (Supplier name)**
Distilled water	Laboratory (East West University)
Ranitidine API	Insecpta Pharmaceuticals

Table 3.3 Instruments used in the experiment

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

Table 3.4 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)

Table 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 *et al.*1998).

3.5 Preparation of Standard Curve

To prepare standard curve, at first different concentrations (5, 10, 15, 20 and 25) µg/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 µg/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 µg/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 µg/ml the calculation is given below:

S_1= 50 µg/ml

S_2= 5 µg/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 µg/ml or 0.005 mg/ml.

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

S_1= 50 µg/ml

S_2= 10 µg/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 µg/ml.

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

S_1= 50 µg/ml

S_2= 15 µg/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 µg/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(µg/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

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 Xantid

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 Xantid 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.

3.6.4 Method for dissolution test of Gepin

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 ℃. Then 1 Gepine 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) (Dunnet 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

3.7.5 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.

3.8.2 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).

3.8.3 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.

3.8.4 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 Distilled Water apparatus (Tresnainstrument, 2016)

Figure 3.2 Dissolution apparatus (Tradeindia,2016).

Figure 3.3 UV-1800 Double Beam Spectrophotometer (Tradeindia, 2016)

Figure3.4: Vernier Caliper (Tradeindia, 2016)

Figure3.5: Hardness tester (Tradeindia, 2016)

Figure3.6: Electronic Balance (Tradeindia, 2016)

CHAPTER FOUR

Result

4.1. General Information:

The Ranitidine samples were subjected to assay and dissolution profile analysis under the optimum conditions. The purpose of assay was to assess the samples for compliance with pharmacopoeias limits for content.

4.2 Physical Parameters

Table 4.1 Disintegration time of different samples

Name	Sample I (Minutes)	Sample II (Minutes)	Sample III (Minutes)	Average (Minutes)
Gepin	13.50	14	13	13 minutes and 50 seconds
Xantid	11.36	11.15	11.43	11 minutes and 31 seconds
Zantac	13.56	13.12	14.10	14 minutes

Table 4.2 Weight

Name of drug	Weight (mg)
Ranidin	234
Gepin	301
Xantid	277
Ethidin	324
Neotack	255
Zantac	305

4.2.1 Hardness test

Table 4.3: Hardness test

Brand Name	Hardness (Pa)
Zantac	11.00
Xantid	13.00
Gepin	12.00

From table 4.2 we can see that, Hardness of two different brands is much more similar with innovator brands (Zantac).

4.3 Standard Assay:

4.3.1 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 4.4 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

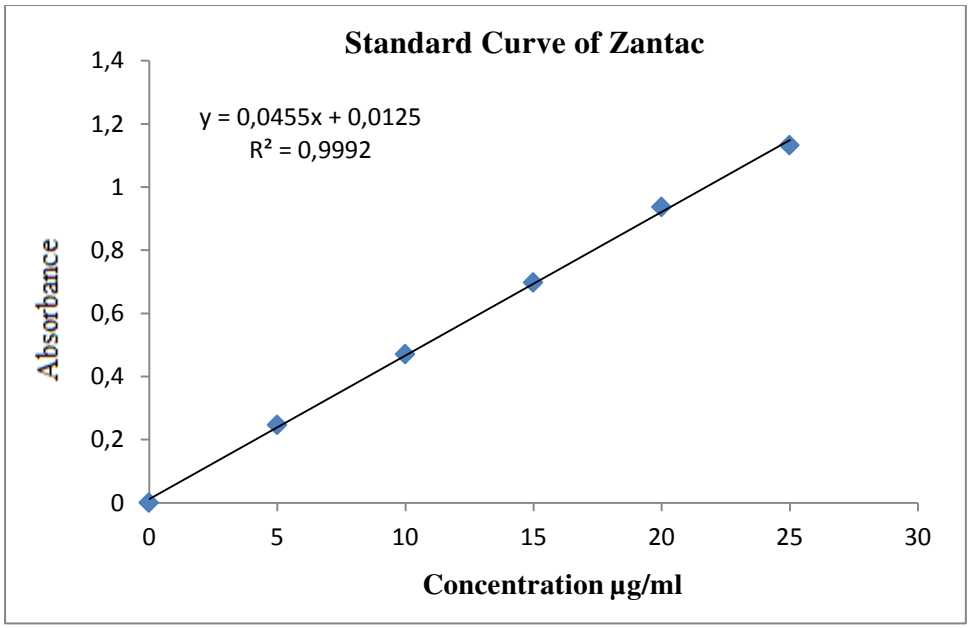

Figure 4.1 Standard Curve of Zantac

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.

4.5 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

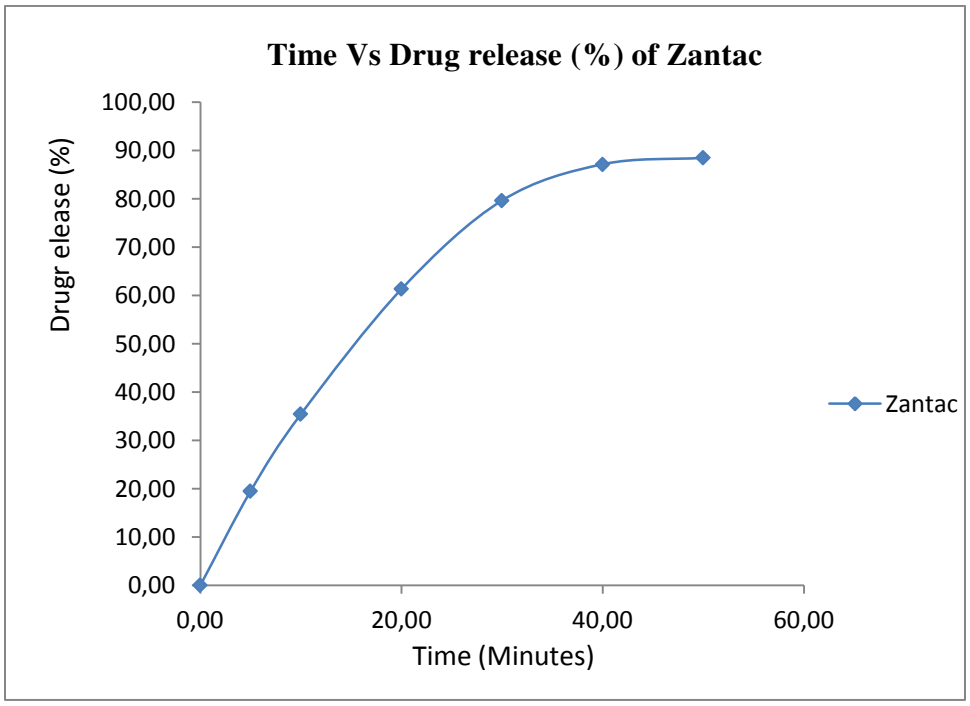

Figure 4.2 Time Vs Drug release (%) of Zantac.

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 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.

4.3.2. Assay of Sample two (Xantid),

Table 4.6 Drug release of Xantid

Time (Minutes)	Drug Release (%)
0.00	0.00
5.00	36.72
10.00	53.59
20.00	69.80
30.00	76.41
40.00	88.13
50.00	94.21

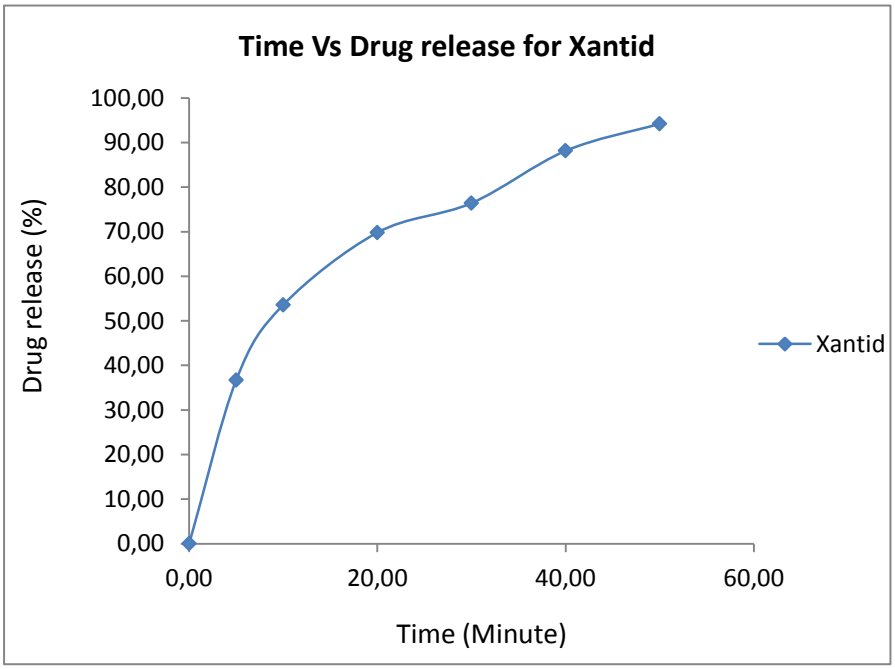

Figure 4.3: Time Vs Drug release of Xantid.

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 has36.72 then 10.00 minutes was 53.59, 20.00 minutes has 69.80, 30.00 minutes has 76.41, 40.00 has 88.13, and 50.00 has 94.21.

4.3.3 Assay of Sample three (Gepin)

Table 4.7 Drug release of Gepin

Time (Minutes)	Drug Release (%)
0.00	0.00
5.00	33.50
10.00	42.91
20.00	55.04
30.00	68.65
40.00	77.39
50.00	95.34

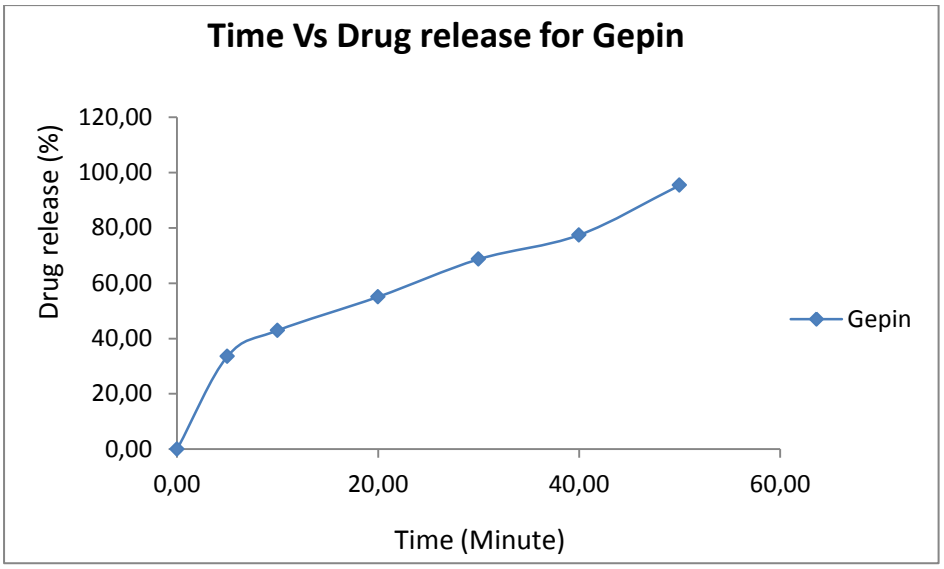

Figure 4.4: Time Vs Drug release (%) of Gepin.

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 33.50 then 10.00 minutes was 42.91 , 20.00 minutes has 55.04, 30.00 minutes has 68.65, 40.00 has 77.39 and 50.00 has 95.34. Here X axis represents the time and Y axis is for Drug release.

4.3.4. Compiled result of Zantac, Ethidin and Gepin

Table 4.8 Compiled data of Zantac, Xantid and Gepin

Time (Minutes)	Zantac (A) Drug Release (%)	Xantid (C) Drug Release (%)	Gepin (D) Drug Release (%)
0.00	0.00	0.00	0.00
5.00	19.52	36.72	33.50
10.00	35.45	53.59	42.91
20.00	61.35	69.80	55.04
30.00	79.68	76.41	68.65
40.00	87.17	88.13	77.39
50.00	88.50	94.21	95.34

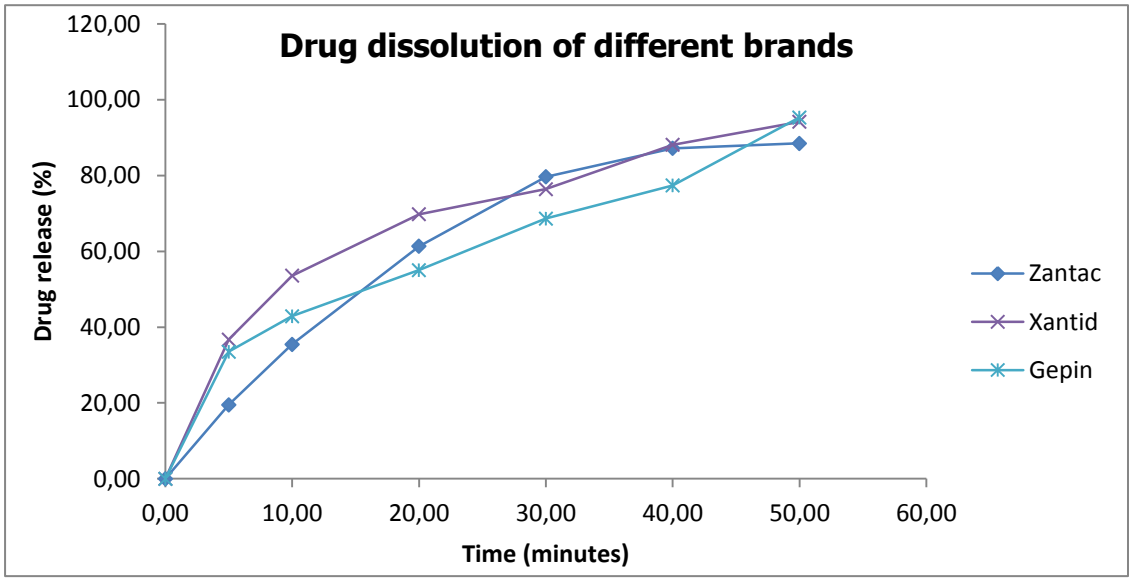

Figure 4.5: Time Vs Drug release (%) (Zantac, Xantid, Gepin)

This graph does mean the increasing of drug release in according to the counting of time. Here drug release is given in the serial of Zantac, Ethidin and Gepin In 0.00 all drug release was 0.00 and then 5.00 minutes has 19.52, 36.72 and 33.50 then 10.00 minutes was 35.45, 53.59 and 42.91, 20.00 minutes has 61.35, 69.80 and 55.04, 30.00 minutes has 79.68, 76.41 and 68.65, 40.00 has 87.17, 88.13 and 77.39, and 50.00 has 88.50, 94.21 and95.34. Here X axis represents the time and Y axis is for Drug release.

4.4. Calculation

4.4.1. *f*1 (Difference factor) calculation

Among several methods investigated for dissolution profile comparison, *f*2 is the simplest. Moore and Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors, *f*1 and *f*2. f1 or difference factor should be between 0 to 15, more than this will not be accepted.

*f*1 measures the difference between two profiles at different time points.

Table 4.9 *f*1 calculation for Xantid

Time (Minutes)	Zantac (R)	Xantid (T)	R-T	| R-T |	*f*1
5	19.52	36.72	-17.20	17.20	
10	35.45	53.59	-18.14	18.14	
20	61.35	69.80	-8.45	8.45	14.45%
30	79.68	76.41	3.27	3.27	
40	87.17	88.13	-0.96	0.96	
50	88.50	94.21	-5.71	5.71	
Total	371.67			53.72	

Table 4.10 *f*1 calculation for Gepin

Time (Minuets)	Zantac Drug release (%) (R)	Gepin Drug release (%) (T)	R-T	|R-T |	*f*1
5	19.52	33.50	-7.46	13.97	
10	35.45	42.91	6.31	7.44	
20	61.35	55.04	11.03	6.3	14.86%
30	79.68	68.65	9.78	11.01	
40	87.17	77.39	-6.84	9.73	
50	88.50	95.34	-13.98	6.8	
Total	371.67			55.25	

Here the both values of f1 are within the range means it is below the 15. Both of the brands can be accepted as well manufactured.

4.4.2. *f*2 (Similarity factor) calculation for

***f*2** measures the degree of closeness between two profiles. Since *f*2 tells how close the two dissolution profiles, it is widely used in pharmaceutical industry to measure the profile similarity between generic and innovator products.

*f*2 value should be between50-100.

Table 4.11 *f*2 calculation for Xantid

Time (Minutes)	Zantac Drug release (%) (R)	Xantid Drug release (%) (T)	R-T	| R-T |	$\|R-T\|^2$	*f*2
5	19.52	36.72	-17.20	17.20	295.84	
10	35.45	53.59	-18.14	18.14	329.06	
20	61.35	69.80	-8.45	8.45	71.40	47.62
30	79.68	76.41	3.27	3.27	10.69	
40	87.17	88.13	-0.96	0.96	0.92	
50	88.50	94.21	-5.71	5.71	32.60	
Total	371.67			53.72	740.51	

Table 4.12 *f*2 calculation for Gepin

Time	Zantac Drug release (%) (R)	Gepin Drug release (%) (T)	R-T	|R-T |	$\|R-T\|^2$	*f*2
5	19.52	33.50	-7.46	13.97	195.16	
10	35.45	42.91	6.31	7.44	55.35	
20	61.35	55.04	11.03	6.3	39.69	50.78
30	79.68	68.65	9.78	11.01	121.22	
40	87.17	77.39	-6.84	9.73	94.67	
50	88.50	95.34	-13.98	6.8	46.24	
Total	371.67			55.25	552.34	

In this case though Gepin has the value of 50.78 that means it is in the range of 50-100 and made the brand accepted but Xantid has the value of 47.63 with is below the range so it can't be accepted. This problem can be due to manufacturing problems or can have instrumental problems too.

CHAPTER FIVE

General Discussion

5.1 General Discussion

In this study, comparisons of dissolution profiles of Ranitidine HCL oral formulations were made between three generic products. Comparison of the dissolution profiles was carried out by calculation of the similarity factor and difference factor. The criteria for similarity were taken as up to 15 an *f*2 value of 50 - 100 for both tablets and suspensions. The study was carried out at pH 7 normal range and with the media water and then it was calculated for the values of factors. It was ran for 50 minutes with the intervals of 5 or 15 minutes and found the results provided previous discussion. The influence of pH was ignored in this study.

The extreme variations in the API release profiles for ranitidine tablet reflect differences in the quality of manufacturing. This could be due to differences in the source and quality of coating, formulation factors like the coating process, relative composition of the content of the polymers and other excipients.

According to the result, Though Gepin has the value approved by the FDA Xantid is less than the desired value. According to the FDA approval rule Gepin and Xantid has the legal value in *f*1 calculation.

Generally, the similarity factor patterns observed in this study indicate that assay and single point dissolution tests are not sufficient to prove efficacy or pharmaceutical equivalence of the products tested. Lack of comparative dissolution data for pharmaceutical equivalence and subsequently, bioequivalence raises questions of product quality. These impacts on efficacy of the products raising further concerns about the effect of sub-therapeutic outcomes and repercussions of treatment failures especially for H_2 blocker drugs.

Drug regulatory authorities are major to controlling the quality of products in circulation in any market. The Conference of Experts on the Rational Use of Drugs, held in Nairobi in 1985, and WHO's Revised Drug Strategy, adopted by the World Health Assembly in May 1986, identified effective functioning of national drug regulation and control systems as a vital means to assure safety and quality of medicines (WHO 2007). The Pharmacy and Poisons Board (PPB) is the regulatory body responsible for approvals and granting of market authorization of drugs in Bangladesh. This includes determining the requirements and content of drug registration dossiers as per the Common Technical Document (CTD) guidelines, dossier review, quality control (QC)

tests and good manufacturing practices (GMP) inspections. After market authorization, the PPB is responsible for conducting post-marketing surveillance through its pharmacovigilance programme with a view to ensuring consistent good quality products in circulation. The pharmacovigilance (PV) programme must therefore be effective, sustained and targeted with clear regulatory actions on non-compliant products. The success of the PV programme also depends on sufficient manpower with the necessary education, training and experience to perform the PV functions. The PPB thus plays a key role in assuring the quality of drug products circulating in the Bangladesh market.

CHAPTER SIX

Conclusion and Recommendation

6.1 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 *f*2 in relation to the innovator product. The results obtained from this study can be extrapolated to the wider Bangladesh market. The city harbours many pharmaceutical manufacturing industries and acts as a centre of distribution for imported drugs. In addition, the sub-counties in Dhaka focus the economic capacities of the Bangladesh population, which in turn affects stocking patterns for the drug products. 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.

6.2 Recommendation

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. In addition, stringent GMP inspections should be consistently conducted by the national drug regulatory authority, the PPB to ensure adherence to quality standards during the manufacture and storage of pharmaceutical products. As a further measure, post-market surveillance activities by the PPB should be regular and sustained as a tool for determining the consistency of good quality products in circulation. 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.

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