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, Bangladesh, in partial fulfillment of the requirements for the Degree of Bachelor of Pharmacy.

Submitted by

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Declaration by the Candidate

I, Md. Kabir Hossain, 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, in the partial fulfillment of the requirement for the award of the degree Bachelor of Pharmacy, work carried out by me during the period 2015-2016 of my research in the Department of Pharmacy, East West University, under the supervision and guidance of Tirtha Nandi, Lecturer, Department of Pharmacy, East West University. The thesis paper has not formed the basis for the award of any other degree/diploma/fellowship or other similar title to any candidate of any university.

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Certificate by the Supervisor

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Endorsement by the Chairperson

This is to certify that the thesis entitled **"*In-vitro* comparative dissolution study of different brands 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, was carried out by Md.Kabir Hossain, ID: 2012-3-70-008, during the period 2015-2016 of his research in the Department of Pharmacy, East West University.

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Dedication

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

Abstract

The aim of the present study was to evaluate and compare dissolution pattern of locally branded drug products of Ranitidine HCl available in Bangladesh with the innovator brand of Ranitidine HCl (Zantac®) marketed by GSK pharmaceutical company. Zantac® is the patent drug of ranitidine hydrochloride. Branded drugs are expensive than locally marketed drug. Substitution of drugs is very essential for the people of under developing country. Two different brands of ranitidine tablets which are available in Bangladesh like Neotack, Ranidin as well as Zantac® were collected from a reputed pharmacy store. Six tablets from each of the brands were used for the *in-vitro* dissolution study. Cumulative drug release was measured up to 50 minutes for all the brands. All the brands were compared with the innovator brand. Differential factor, f1 and similarity factor, f2 were determined. No significant difference was observed during *in-vitro* drug release pattern of brand Neotack and Ranidin with the innovator brand. Here it was found the values of *f*1 are 13.19 and 13.41 so it is acceptable. And the similarity factor it was seen that the values of *f*2 are 51.8 and 50.2, so it is acceptable. In conclusion, further investigations are needed to evaluate better dissolution study.

Keyword: Ranitidine HCl, Generic brand, Innovator drug product, Comparative dissolution, *In-vitro* drug dissolution study

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List of abbreviation

H2 BLOCKER	Histamine Two Receptor Blocker
GERD	Gastro Esophageal Reflux Disease
IP	Indian Pharmacopeia
PPI	Proton Pump Inhibitor
NSAID	Non-Steroidal Anti Inflammatory Disease
ECL	Enterochromaffine-like
ADRs	Adverse Drug Reactions
IR	Immediate Release
BCS	Biopharmaceutical Classification System
IVIVC	In Vivo-In Vitro Correlation
API	Active pharmaceutical Ingredient
FDA	Food and Drug Administration

Chapter One
INTRODUCTION

1.1 Overview

Ranitidine is one the most prescribed drug in Bangladesh. Ranitidine belongs to a class of drugs known as H_2 blockers. Ranitidine is used to treat ulcers of the stomach and intestines. This medication is also used to treat certain stomach and throat (esophagus) problems (such as erosive esophagitis, Gastro esophageal reflux disease-GERD, and Zollinger-Ellison syndrome). It works by decreasing the amount of acid your stomach makes. It relieves symptoms such as cough that doesn't go away, stomach pain, heartburn, and difficulty swallowing. Ranitidine was discovered in 1976 at Glaxo Pharmaceuticals. Around eighty pharmaceutical companies in Bangladesh produce ranitidine at present. Various preparations of ranitidine are available as over the counter drugs in various countries. It is available as various generic versions in Bangladesh and all over the world. Ranitidine comes as a tablet, an effervescent tablet, effervescent granules, and syrup to take by mouth. It is usually taken once a day at bedtime or two to four times a day. Dissolution pattern of ranitidine is very high compare to others. As we know, bioavailability of a drug is directly related to the dissolution pattern of the drug. Studies evolved that, ranitidine has the high dissolution rate in compare to other drugs of this class, thus bioavailability of ranitidine is higher than other drugs of this class (Kerr, 2016). Since in Bangladesh various preparations of ranitidine is available but there is no adequate number of study occurred in Bangladesh to observe the dissolution pattern of ranitidine. The objective of the research project is to observe the dissolution pattern of ranitidine manufactured by various pharmaceutical company of Bangladesh. In our research we conducted experiment to observe the dissolution pattern of ranitidine by using in vitro method. And we compare the dissolution pattern of ranitidine with the inventor drug like Zantac® even we compare the dissolution pattern of ranitidine among the available brand present in Bangladesh. It decrease the acid made in the stomach. Ranitidine comes as a tablet, an effervescent tablet, effervescent granules, and syrup to take by mouth. It is usually taken once a day at bedtime or two to four times a day. Dissolution pattern of ranitidine is very high compare to others. Bioavailability of ranitidine is depends on the dissolution profile. Ten different brands of Ranitidine HCl film coated tablets (150 mg) produced and marketed by Nepalese and Indian

pharmaceutical 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 (Indian Pharmacopoeia,2007). Hardness value requirement was compiled by all brands except IR3. Disintegration time for all brands was within 15 minutes complying with the IP recommendation. All brands showed more than 80 % drug release within 45 minutes. The drug content assay 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 (Aboutgerd.org, 2016).

1.2 H_2 blocker

H_2 receptor blockers are a class of medications that can be used to treat conditions that cause excess stomach acid. These medications are available over the counter and by prescription. The H_2 blockers are also known as H_2 antagonists. H_2 receptor antagonist was the first effective drugs for peptic ulcer. In the 1980s, H_2 blockers were used to treat ulcers and gastro esophageal reflux disease (GERD). Now, antibiotics cure non-NSAID ulcers, and proton pump inhibitors (PPIs) are better for GERD. Therefore, H_2 antagonists face an uncertain future as prescription drugs. They are comparatively cheap, effective, and safe for heartburn relief. Lower dose preparations are available over-the-counter to be used for mild heartburn. Histamine stimulates cells in the stomach lining to produce hydrochloric acid. Histamine also affects the H_1 receptors on the nasal mucosa, bronchi, and skin that participate in allergic reactions such as hay fever and hives. These can be treated by antihistamines that block the H_1 receptor. H_2 blockers are available in nonprescription and prescription forms. Prescription forms are stronger than the nonprescription forms. H_2 blockers are usually taken by mouth, although some can also be given as an injection. Two doses (morning and evening) are typically recommended (morning and evening) to control both daytime and nighttime symptoms. Doctors sometimes recommend a single dose, taken at bedtime, for people who have difficulty remembering to take their medicines. There are available in also generic forms. They are equally effective in their available doses and compete for the same receptor. Side effects

may vary from one drug to another. H_2 receptor blockers are most commonly used to treat gastritis, or inflamed stomach, and to treat peptic ulcers. Peptic ulcers are painful sores that form in the lining of the stomach, lower esophagus, or duodenum, which is the first part of the small intestine. They often develop as a result of inflammation and excess stomach acid. Doctors may also recommend H_2 receptor blockers to keep peptic ulcers from returning. H_2 blockers may also be used to treat less common conditions such as Zollinger-Ellison syndrome, a condition that causes an increased production of stomach acid Doctors may also recommend H_2receptor blockers for off-label use. This means using the medicine to treat a condition that the medication hasn't been approved to treat. For example, H_2 receptor blockers might be used to treat pancreatic problems or used in cases of allergic reaction, even though they aren't traditionally used for these purposes (Patient, 2016).

1.3 H_2 blockers available by prescription

Table 1.1- H_2 blockers available by prescription (Drugs.com, 2016)

Generic Name	**Brand Name**
Cimetidine	Tagamet
Ranitidine	Zantac
Nizatidine	Axid
Famotidine	Pepsid

1.4 Side effect related H_2 receptor blocker

Table 1.2- Side effect related H2 receptor blocker (Drugs.com, 2016)

Constipation	Ringing in the ears
Diarrhea	Trouble urinating
Difficulty sleeping	Headaches
Dry mouth	Hinging in the ears
Dry skin	

Table 1.3- In some cases some serious side effect that may occur (Drugs.com, 2016)

Blistered, Burning, or Scaling skin	Changes in vision
Confusion	Agitation
Difficulty breathing	Wheezing
Chest tightness	Irregular heartbeat
Hallucinations	Suicidal thoughts

1.5 Pharmacology

The H_2 antagonists are competitive antagonists of histamine at the parietal cell's H_2 receptor. They suppress the normal secretion of acid by parietal cells and the meal-stimulated secretion of acid. They accomplish this by two mechanisms. Histamine released by ECL(enterochromaffin-like) cells in the stomach is blocked from binding on parietal cell H_2 receptors, which stimulate acid secretion; therefore, other substances that promote acid secretion (such as gastrin and acetylcholine) have a reduced effect on parietal cells when the H_2 receptors are blocked (Kerr, 2016).

1.6 Mechanism of H2 blockers

The H_2 receptors are competitive antagonists of histamine at the parietal cell H_2 receptor. They suppress the basal and meal-stimulated acid secretion in a dose-dependent manner. The block the action of histamine released from ECL (enterochromaffin-like) cell in the stomach is blocked from binding on parietal cell H_2 receptors, which stimulate acid secretion. Other substances may promote acid secretion such as gastrin and acetylcholine. They inhibit the stimulation of partial cell. They reduced cAMP levels.H_2 blockers reduce the production of stomach acid. This makes the stomach juices less acidic so that any stomach juice that gets into the esophagus is less irritating. This relieves symptoms and allows the esophagus to heal. When you take an H_2receptor blocker, the active

ingredients travel to specific receptors on the surface of the stomach cells that release acids. The medication inhibits certain chemical reactions in these cells so that they aren't able to produce as much acid. According to the National Institutes of Health, H_2receptor 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 (Takafumi and Kazuhiko, 2011).

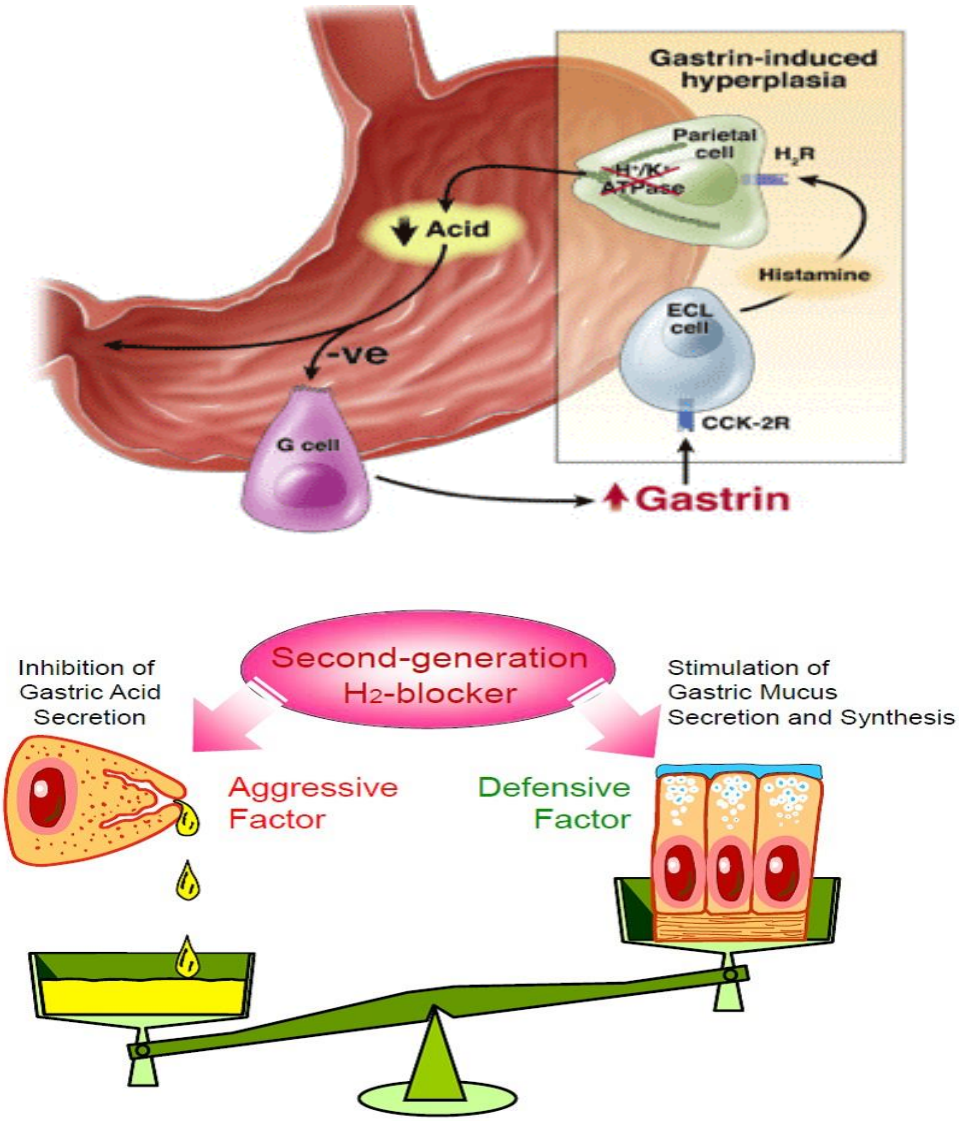

Fig1.1- Mechanism of H2 receptor blockers (Takafumi and Kazuhiko, 2011)

Stomach normally produces acid to help with the digestion of food and to kill germs (bacteria). This acid is corrosive so body produces a natural mucous barrier which protects the lining of the stomach from being worn away (Kerr, 2016).

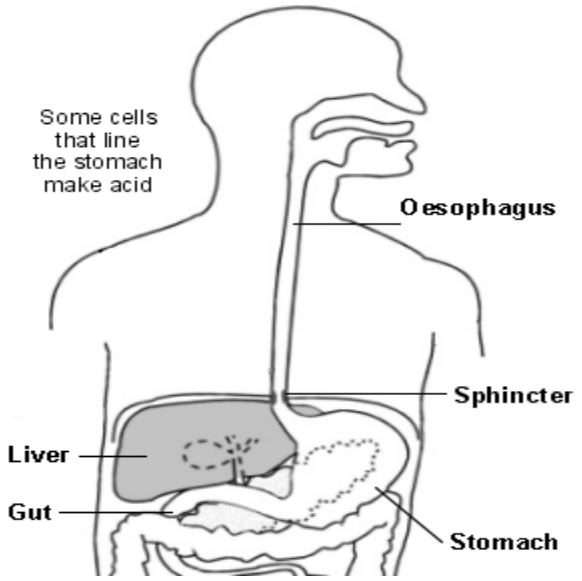

Fig 1.2: Gastrointestinal track (Patient, 2016)

In some people this barrier may have broken down allowing the acid to damage the stomach, causing an ulcer. In others there may be a problem with the muscular band at the top of the stomach (the sphincter) that keeps the stomach tightly closed. This may allow the acid to escape and irritate the gullet (oesophagus). This is called 'acid reflux', which can cause heartburn and/or inflammation of the gullet (oesophagitis).The letter H in their name stands for histamine. Histamine is a chemical naturally produced by certain cells in the body, including cells in the lining of the stomach, called the enterochromaffin-like cells (ECL cells). Histamine released from ECL cells then stimulates the acid-making cells (parietal cells) in the lining of the stomach to release acid. What H_2 blockers do is stop the acid-making cells in the stomach lining from responding to histamine. This reduces the amount of acid produced by your stomach.By decreasing the amount of acid, H_2 blockers can help to reduce acid reflux-related symptoms suchas heartburn. This can also help to heal ulcers found in the stomach or in part of the gut (the duodenum).

The H2 blockers are reversible, competitive antagonists of the actions of histamine on H2 receptors. They are highly selective in their action and are virtually without effect on H1 receptors. The effects of histamine that are mediated by H2 receptors are stimulation of gastric acid secretion, and it is the ability of the H2 blockers to inhibit this effect that explains much of their importance. Despite the widespread distribution of H2 receptors in the body, H2 blockers interfere remarkably little with physiological function other than gastric secretion, implying that extra gastric H2 receptors are of minor physiological importance H2 blockers are used in treatment of peptic ulcer disease. Peptic ulcer is a disease in which ulceration occurs in the lower esophagus, stomach, duodenum, or jejunum. The synthesis of H2 antagonists was achieved by stepwise modifications of the histamine molecule. These compounds retained the imidazole ring of histamine which possessed a much bulkier side chain. Cimetidine, the first H2 blocker to be introduced for general clinical use, won rapid acceptance for the treatment of ulcers and other gastric hyper secretory conditions and soon became one of the most widely prescribed of all drugs. This success led to the synthesis of numerous congeners. Some of the more popular drugs

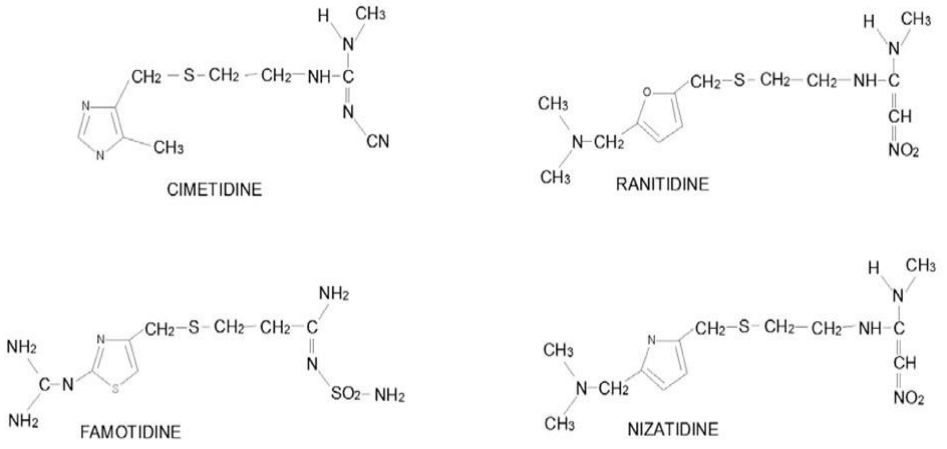

Fig 1.3: Structure of different H2 blocker (Woo-Jung *et al.,* 2010)

1.7 Adverse effects

H_2 antagonists are well-tolerated, except for cimetidine, where in all of the following adverse drug reactions (ADRs) are common. Infrequent ADRs include hypotension. Other rare adverse drug reactions are including headache, tiredness, dizziness, confusion, diarrhea, constipation, and rash. In addition, gynecomastia occurred in 0.1% to .5% of men treated for non-hyper secretory conditions with cimetidine for 1 month or longer and in about 2% of men treated for pathologic hyper secretory conditions; in even fewer men. Cimetidine may also cause loss of libido, and impotence, all of which are reversible upon discontinuation. A study review found that overall risk of pneumonia is about 1 in 4 higher among H_2 antagonist users (Drugs.com, 2016).

1.7.1 Considerations about H_2 blocker

If someone experiences any of the following problems which can indicate a serious gut disorder:

Bringing up (vomiting) blood: This may be obviously fresh blood but altered blood in vomit can look like ground coffee. Doctors call this 'coffee-ground vomit'. Blood in your stools (feces): This may be obvious blood, or it may just make your stools black. Some other problems like unintentional weight loss, difficulty swallowing, including food getting stuck in the gullet (esophagus) and persistent tummy (abdominal) pain or persistent vomiting may occur (Drugs.com, 2016).

1.8 Synthesis of ranitidine

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]ethane amine (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 (Sanal, 2013).

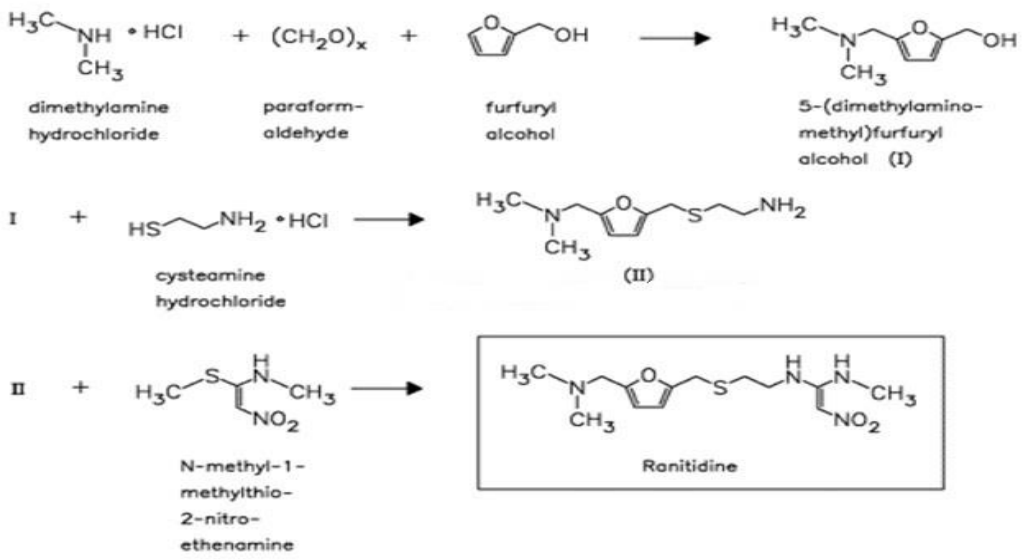

Fig1.4- Synthesis of ranitidine (Profile, 2012)

1.9 Drug information

Ranitidine is in a group of drugs called histamine-2 blockers. Ranitidine works by reducing the amount of acid your stomach produces. Ranitidine is used to treat and prevent ulcers in the stomach and intestines. It also treats conditions in which the stomach produces too much acid, such as Zollinger-Ellison syndrome. Ranitidine also treats gastro esophageal reflux disease (GERD) and other conditions in which acid backs up from the stomach into the esophagus, causing heartburn.

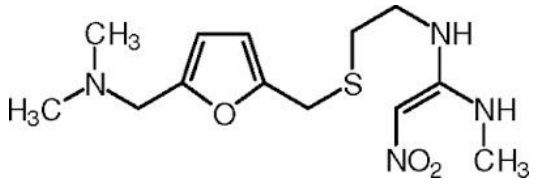

Fig 1.5- chemical structure of ranitidine (Profile, 2012)

The empirical formula is C13H22N4O3S·HCl, representing a molecular weight of 350.87. Ranitidine HCl is a white to pale yellow, granular substance that is soluble in water. It has a 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. Each tablet also contains the inactive ingredients colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, titanium dioxide, triethyl citrate and FD&C Yellow #6.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, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, titanium dioxide, triethyl citrate (Haywood, 1987)

1.9.1 Clinical Pharmacology

Ranitidine Tablets, USP are a competitive, reversible inhibitor of the action of histamine at the histamine H_2-receptors, including receptors on the gastric cells. Ranitidine Tablets, USP ds not lower serum Ca^{++} in hypercalcemic states. Ranitidine Tablets, USP are not an anticholinergic agent (RxList, 2016).

1.9.2 Pharmacokinetics

1.9.2.1 Absorption

Ranitidine Tablets, USP are 50% absorbed after oral administration, compared to an intravenous (IV) injection with mean peak levels of 440 to 545 ng/mL occurring 2 to 3 hours after a 150-mg dose. Absorption is not significantly impaired by the administration of food or antacids. Propantheline slightly delays and increases peak blood levels of Ranitidine, probably by delaying gastric emptying and transit time. In one study, simultaneous administration of high-potency antacid (150 mmmol) in fasting subjects has been reported to decrease the absorption of Ranitidine Tablets, USP (RxList, 2016).

1.9.2.2 Distribution

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

1.9.2.3 Metabolism

In humans, the N-oxide is the principal metabolite in the urine; however, this amounts to <4% of the dose. Other metabolites are the S-oxide (1%) and the dimethyl Ranitidine (1%). The remainder of the administered dose is found in the stool. Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there are minor, but clinically insignificant, alterations in Ranitidine half-life, distribution, clearance, and bioavailability (RxList, 2016).

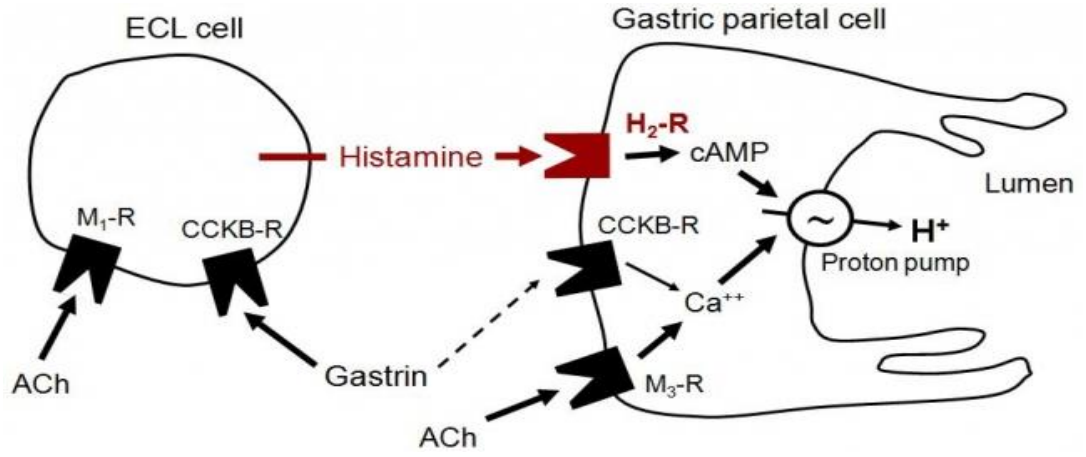

Fig 1.6- metabolism of H2 receptor blocker (PercevalSwan's blog, 2012)

1.9.2.4 Excretion

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 mL/min, indicating active tubular excretion. The elimination half-life is 2.5 to 3 hours. Four patients with clinically significant renal function impairment (creatinine clearance 25 to 35 mL/min) administered 50 mg of Ranitidine intravenously had an average plasma half-life of 4.8 hours, a Ranitidine clearance of 29 mL/min, and a volume of distribution of 1.76 L/kg. In general, these parameters appear to be altered in proportion to creatinine clearance (Haywood, 1987).

1.9.3 Pharmacodynamics

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36 to 94 mg/mL. Following a single oral dose of 150 mg, serum concentrations of ranitidine are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition. In a pharmacodynamics comparison of the Efferdose with the ZANTAC (ranitidine hcl) Tablets, during the first hour after administration, the Efferdose tablet formulation gave a significantly higher intra gastric pH, by approximately 1 pH unit, compared to the ZANTAC (ranitidine hcl) Tablets (Haywood, 1987).

1.10 Photo degradation of ranitidine

Hydrolytic degradative studies on ranitidine hydrochloride (**1**) have shown that two different pathways are operative under strongly acid and strongly alkaline conditions. At intermediate pH values both pathways are operative whilst at very low pH values ranitidine hydrochloride is resistant to hydrolytic cleavage. This resistance to hydrolysis may be ascribed to *C*-protonation of the enediamine. The chance of degradation increases as the time proceeds and also due to the photosensitivity. So the release profile of a drug will be reduced (Haywood, 1987).

1.11 BCS Classification

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. It allows for the prediction of in vivo pharmacokinetics of oral immediate-release (IR) drug products by classifying drug compounds into four classes based on their solubility related to dose and intestinal permeability in combination with the dissolution properties of the dosage form. The interest in this classification system stems largely from its application in early drug development and then in .The Biopharmaceutical Classification System (BCS) is one of the experimental models that measures permeability and solubility under specific conditions. The main purpose of the system was to aid in the regulation of post-approval

changes, providing acceptance based on in vitro data when appropriate is available. Importantly, the system was designed around on oral drug delivery since the majority of drugs is and remains orally dosed. Waivers, permission to skip *in vivo* bioequivalence studies, are kept for drug products that meet certain requirements like solubility and permeability and that are also rapidly dissolving characters (Knott, 2016).

Table 1.4- The Bio pharmaceutics classification system

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

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

1.11.1 Class I

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

1.11.2 Class II

The drugs of this class have a high absorption number but a low dissolution number. In vivo drug dissolution is then a rate-limiting step for absorption except at a very high dose number. The absorption for Class II drugs is usually slower than for Class I and occurs over a longer period of time. In vitro–in vivo correlation (IVIVC) is usually accepted for

Class I and Class II drugs. The bioavailability of these products is limited by their solvation rates. Hence, a correlation between the in vivo bioavailability and the in vitro solvation can be found (7, 9, and 10). Examples include glibenclamide, phenytoin, danazol, mefenamic acid, nifedinpine, ketoprofen, naproxen, carbamezapine, and ketoconazole (Knott, 2016).

1.11.3 Class III

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

1.11.4 Class IV

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

1.12 Dissolution

Dissolution is the primary quality control test to determine whether a drug product can release its active pharmaceutical ingredients in a timely manner.A dissolution test is a means of identifying and proving the availability of active drug materials in their delivered form. A dissolution test simulates the availability of active substance and allows the prediction of the time for complete release of the material from the dosage form. In the pharmaceutical industry, drug dissolution testing is routinely used to provide critical in vitro drug release information for both quality control purposes, i.e., to assess

batch-to-batch consistency of solid oral dosage forms such as tablets, and drug development, i.e., to predict in vivo drug release profiles (Knott, 2016).

1.13 Factors influence dissolution from drug products

The properties of the API,

The quality and design of the drug product,

The conditions under which the test is run and the coating material.

1.14 Properties of the API important to dissolution include

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

1.15 Applications of Dissolution in the Pharmaceutical Industry

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

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

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

4. To predict performance under various dosing conditions (“biorelevant“ methods)

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

6. To obtain approval for a multisource drug product (‘‘generic“ version of an existing drug product) – in certain cases a pharmacokinetic study is not required

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

Optimization of therapeutic effectiveness during product development and stability assessment; routine assessment of production quality to ensure uniformity between production lots; assessment of 'bioequivalence', that is to say, production of the same biological availability from discrete batches of products from one or different manufacturers and prediction of *in-vivo* availability, i.e. bioavailability (where applicable).

Although initially developed for oral dosage forms, the role of the dissolution test has now been extended to drug release studies on various other forms such as topical and transdermal systems and suppositories (Knott, 2016).

1.16 Comparative dissolution

In a dissolution test a drug product is added to media, simulating gastrointestinal fluids in a patient. At several time points the concentration of the dissolved API is determined. Drug dissolution testing is routinely used to provide critical in vitro drug release information for both drug development purposes and quality control. Dissolution testing

during drug development is important to predict in vivo drug release profiles. In vitro drug dissolution data generated from dissolution testing experiments can be related to in vivo pharmacokinetic data by means of in vitro-in vivo correlations (IVIVC). A well-established predictive IVIVC model can be very helpful for drug formulation design and post-approval manufacturing changes

Ranitidine is used in peptic ulcer therapy and available as several brands in the market which makes it difficult to select the safe, effective and economic one. The aim of this study is to establish similarity among the different brands of ranitidine tablets available in local market. 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.

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

developing countries do not have an effective means of monitoring the quality of generic drug products in the market. This results in widespread distribution of substandard and/or counterfeit drug products. Pharmaceutical equivalents are the drug products which contain the same active ingredient, are of same dosage form, route of administration and are identical in strength and concentration. Bioequivalence studies are useful in comparing the bioavailability of drug from various drug products. Once the drug products are demonstrated to be bioequivalent, then the efficacy of these products is assumed to be similar. Generic drug products must satisfy the same standards of quality, efficacy and safety as those applicable to the innovator products. Preliminary physicochemical assessment of the products is very important and in vitro dissolution testing can be a valuable predictor of the in vivo bioavailability and bioequivalence of oral solid dosage forms. The establishment of bioequivalence is essential to interchangeability so that a patient can substitute a generic for a particular product without jeopardizing efficacy or safety. Ranitidine belongs to a class of drugs known as H_2-blockers, which blocks the action of histamine on stomach cells and hence reduces stomach acid production. The H_2 receptor antagonists inhibit acid production by reversibly competing with histamine binding to H_2 receptors on the basolateral membrane of parietal cells in stomach the major therapeutic indications for H_2 receptor antagonists are to promote healing of gastric and duodenal ulcers, to treat uncomplicated gastrointestinal esophageal reflux disease (GERD) and to prevent the occurrence of stress ulcers. This study was conducted to evaluate the pharmaceutical equivalence of different brands of Ranitidine HCl tablets that are available within the Pokhara valley from different companies of Nepal and India. Comparison of the technical quality aspects of this product will help for the selection of best brand of drug by the pharmacies or hospitals. This study aims to provide the proof of safety and effectiveness before the drugs can be used (Kerr, 2016).

Chapter Two
LITERETURE REVIEW

2.0 Literature review:

Dave, *et. al.* conducted a study on gastroretentive drug delivery system of ranitidine hydrochloride: Formulation and in vitro evaluation in 2004. The purpose of this research was to prepare a gastroretentive drug delivery system of ranitidine hydrochloride. The amounts of citric acid anhydrous (X_1) and stearic acid (X_2) were selected as independent variables. The times required for 50% (t_{50}) and 80% drug dissolution (t_{80}), and the similarity factor f_2 were selected as dependent variables. A theoretical dissolution profile was generated using pharmacokinetic parameters of ranitidine hydrochloride. From this study the result shows that the proper balance between a release rate enhancer and a release rate retardant can produce a drug dissolution profile similar to a theoretical dissolution profile. (Dave, *et. al.* 2004)

Mirmehrabi, *et al.* performs a study in 2004 on Solubility, dissolution rate and phase transition studies of ranitidine hydrochloride tautomeric forms. The aim of this study to determine the understanding the polymorphic behavior of pharmaceutical solids during the crystallization process and further in post-processing units is crucial to meet medical and legal requirements. In this study they used an analytical technique for determining the composition of two solid forms of ranitidine hydrochloride using two peaks of Fourier transform infrared (FTIR) spectra without the need to grind the samples.As a result the dissolution rate found to be equally fast for both forms. And also from this study there was a good agreement between the experimental solubility data of ranitidine hydrochloride and the results of UNIQUAC equation. (Mirmehrabi, *et. al.* 2004)

SoleymanI, *et. al*. studied in 2013 on Solubility of ranitidine hydrochloride in solvent mixtures of PEG 200, PEG 400, ethanol and propylene glycol at 25 °C. The aim of this study to determine the understanding the Experimental solubilities of ranitidine hydrochloride in binary mixtures of ethanol (EtOH)-polyethylene glycol 200 (PEG 200), EtOH-polyethylene glycol 400 (PEG 400), EtOH-1, 2-propanediol (PG), PEG 200-PG and PG-PEG 400 and ternary mixtures of EtOH-PG-PEG 400 at 25 °C are reported. They used the method for measured data were fitted to the Jouyban–Acree model. R From this study they found that, the experimental densities of the saturated solutions were measured

and then fitted to the Jouyban–Acree equation with the overall MPD of 1.5% (SoleymanI, *et. al.* 2013).

This study was performed by Yu, *et. al*. in 2002 in order to evaluate whether U.S. Pharmacopeia (USP) apparatus 3 can be used as an alternative to USP apparatus 2 for dissolution testing of immediate-release (IR) dosage forms. For this study highly soluble drugs, metoprolol and ranitidine, and poorly soluble drugs, acyclovir and furosemide, were chosen as model drugs. From the result they found that, 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. Also found incomplete dissolution was observed for the furosemide tablets using USP apparatus 3. (Yu, *et. al.* 2002).

This study was done by Cappola, in 2001. The aim of this study was find out a better dissolution method for Ranitidine tablets USP. Ranitidine tablets USP showed variable intra- and inter-lab dissolution results. In order to ascertain the reason for this behavior, ranitidine tablets USP produced by (BIPI) Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, and Zantac® Tablets (brand of ranitidine USP), Glaxo Inc., Research Triangle, NC, were subjected to the compendia (USP) dissolution testing using paddle and basket apparatus. Result showed increase in rate and extent of drug dissolved, with less individual tablet variability compared to the paddle apparatus at 50 rpm and for the 300 mg tablet had an initial slower rate. This results showed that dissolution artifacts for ranitidine tablets could be reduced by the use of baskets or tablet sinkers (Cappola, 2001).

Uzunovic and Vranic, conducted this study in 2007. The objective of this study was to evaluate the effects of two different concentrations of magnesium stearate on dissolution properties of ranitidine hydrochloride coated tablet formulations labeled to contain 150 mg. For this study, they used two formulations containing 0.77% and 1.1% of magnesium stearate. From the result we can see that the obtained values indicate differences in drug release from analyzed ranitidine hydrochlorideformulations and could cause differences in therapeutic response (Uzunovic and Vranic, 2007).

This study was performed by Kortejarvi, *et. al.* in 2005 with the aim to assess the biowaiver monographs for immediate release solid oral dosage forms: Ranitidine hydrochloride. Result showed based on its therapeutic and therapeutic index, pharmacokinetic properties and data related to the possibility of excipient interactions, tat IR solid oral dosage forms that are rapidly dissolving and contain only those excipients as reported in this study (Kortejarvi, *et. al.*, 2005).

Bendas & Ayres, conducted this study in 2008. The present research is based on the hypothesis that leaky enteric-coated pellets formulations are able to provide sustained input for drugs that have an absorption window, such as ranitidine hydrochloride, without jeopardizing their bioavailability their bioavailability.For the investigation they used extrusion–spheronization followed by spray coating. And result showed that**,** the hypothesis that a leaky enteric-coated pellets formulation may maintain or increase the bioavailability of drugs that have a window of absorption is still to be confirmed by further in vivo studies (Bendas, 2008).

The study was done by Ameen, *et. al.* in 2006. The purpose of this study is to compare taste preferences for ranitidine (Zantac®) syrup and ranitidine effervescent tablets dissolved in water (Zantac® EFFERdose®) in healthy children aged 4–8 years and their adult caregivers. A randomized, single-blind, crossover, taste test trial was conducted in 102 children and 102 parents/legal guardians. This study found that, the taste of the ranitidine effervescent formulation dissolved in water is preferred over the ranitidine syrup. And also better taste acceptance may facilitate ease of administration and compliance in pediatric patients (Ameen, *et. al.,* 2006).

This study was performed by Wei & Zhao in 2008. The purpose of this study was to develop the hollow microspheres as a new dosage form of floating drug delivery systems with prolonged stomach retention time. Hollow microspheres containing ranitidine hydrochloride (RH) was prepared by a novel solvent diffusion-evaporation method using ethyl cellulose (EC) dissolved in a mixture of ethanol and ether (6:1.0, v/v).

The results demonstrated that RH hollow microspheres were capable of sustained delivery of the drug for longer period with increased bioavailability (Wei & Zhao, 2008).

Kelly, *et. al.* and his co-scientists conducted a study in 2003 about Comparison of the Rates of Disintegration, Gastric Emptying, and Drug Absorption Following Administration of a New and a Conventional Paracetamol Formulation, For the study they used γ Scintigraphy to investigate that the hypothesis that faster drug absorption from a new paracetamol formulation containing sodium bicarbonate compared to that from a conventional formulation results from a combination of enhanced gastric emptying and disintegration/dissolution. Form the result they found that, the rate of paracetamol absorption reflected the gastric emptying profiles as shown by significant correlation of emptying times with partial AUC. From the study they suggested that, it would seem that a combination of faster disintegration and gastric emptying of the new tablets is responsible for the faster rate of absorption of paracetamol from PA compared to P observed in both this study and in previous studies. (Kelly, *et. al*. 2003).

Lau-Cam, *et. al*. 2001 and his research group applied general approaches to see Rapid Reversed Phase High Performance Liquid Chromatographic Assay Method for Ranitidine Hydrochloride in Dosage Forms. Result of this study was, the sssay values by the proposed method were found to agree closely with those obtained using methods in the USP XXII (Lau-Cam, *et. al*. 2001).

Chey, *et. al.* 2003 with his colleagues examined the Lansoprazole and Ranitidine Affect the Accuracy of the 14C-Urea Breath Test by a pH-Dependent Mechanism To determine the effect of lansoprazole and high dose ranitidine on the accuracy of the ¹⁴C-urea breath test (UBT). Result showed that Lansoprazole significantly affected the accuracy of the UBT, causing equivocal or false negative results in 61%. High dose ranitidine affected the breath test in only 18%. The ability of these drugs to suppress gastric acid secretion predicted those patients who developed equivocal or false-negative UBTs. The effect on the accuracy of the UBT resolved within 5 days of drug cessation. (Chey, *et. al.* 2003).

Otsuka *et. al.*, 2005 a studied about uniformity and dissolution of ranitidine. Purpose of this study was to compare the technical quality of commercial American and Japanese ranitidine tablets. They used 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. And they found that, the difference in hardness between American and Japanese tablets was significant. Also the 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. (Otsuka, *et. al.* 2005)

Dilshad carried out a test in 2014 where Ranitidine is an H2-receptor antagonist that inhibits the acid production from stomach, it is used in the treatment of duodenal and gastric ulcer caused by helicobacter pylori infection, and for the treatment of gastrointestinal reflux disease. This study showed that the Ranitidine has a greater selectivity of action than cimetidine so avoiding certain unwanted effects such as interference with enzymatic degradation of a wide range of drugs metabolized by the liver. Ranitidine acts by inhibiting parietal cell H2-receptor competitively and suppress the normal secretion of acid which is stimulated by meal (Dilshad, 2014).

Azad and Azizi, 2013 tested ranitidine tablet samples (Rt1-Rt10) were selectively collected from local retail pharmacies in Savar, Dhaka-1344, Bangladesh. The various parameters of the selected samples suchas 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 and Azizi, 2013)

Flores-Murrieta, *et al.* 2006 studied the bioavailability of two formulations that did not meet similarity that was compared. Twenty-five female volunteers received 150 mg

ranitidine (Azantac or Midaven) 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 analysed. Ranitidine plasma levels were determined and pharmacokinetic parameters were obtained. Values (mean+/-SEM) were: Cmax 528.85+/-25.34 and 563.03+/-33.25 ng/ml, tmax 2.76+/-0.19 and 2.79+/-0.18 h, and AUC12 h 2694.94+/-99.50 and 2648.51+/-133.38 ng.h/ml, for Azantac or Midaven, respectively. No statistically significant difference was obtained in the parameters evaluated. Moreover, 90% confidence limits were 96.6%-116.2% and 90.7%-105.1% for Cmax and AUC12 h ratios, respectively, indicating that the formulations tested are bioequivalent, despite the dissimilarity in the dissolution profile of the formulations. These results suggest that the comparative dissolution profile is not an adequate test to demonstrate the interchangeability of ranitidine formulations (Flores-Murrieta, *et. al.* 2006).

Santos Júnior, *et. al.* 2014 conducted dissolution test which is used to obtain and compare dissolution profiles and establish similarities of pharmaceutical forms. The aim of this study was to compare the dissolution profiles of 150-mg coated ranitidine tablets of a reference drug (product A) and a generic (product B) and a similar (product C) drug marketed in Bahia, Brazil using a simple, fast and inexpensive ultraviolet method. Dissolution 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 (f1) and similarity (f2) factors were calculated and evaluated. The proposed quantification methodology for drug dissolution test was validated, presenting accuracy, linearity and precision within the acceptance criteria. Products A, B and C showed dissolution efficiency values of 59.29, 73.59 and 66.67%, respectively. Factors f1 and f2 were calculated and showed that the profiles of products A, B and C were dissimilar. However, all the products released ranitidine satisfactorily, with at least 80% of the drug dissolved within 30 min (Santos Júnior, *et. al.* 2014).

Naveed, *et. al*. 2014 studied about comparison of four different ranitidine. Ranitidine is used in peptic ulcer therapy and available as several brands in the market which makes it

difficult to select the safe, effective and economic one. The aim of this study is to establish similarity among the different brands of ranitidine HCl tablets available in local market of Karachi, Pakistan. Four different brands of (150 mg) were selected for the study. Six quality control parameters: weight variation test, hardness test, thickness, friability, disintegration test and dissolution test were carried out specified by USP. Result revealed that all brands comply within limits for hardness, weight variation, thickness, friability, disintegration and dissolution. Disintegration time for all brands was within 15 minutes complying with the USP commendation. All brands showed Q-value more than 80% within 45 minutes. The present findings suggest that almost all the brands of ranitidine HCl that are available in Karachi meet the USP specification for quality control analysis and are interchangeablem (Naveed, *et. al*. 2014).

Thapa, *et. al*. 2005, 2005 conducted a study about the quality of Nepaliese ana Indian ranitidine hydrochloride. Ranitidine is available in several brands in the market which makes it difficult to select the safe and effective one for peptic ulcer therapy. Study aimed to establish pharmaceutical equivalence among the different brands of Ranitidine HCl tablets available in Pokhara. 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. 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. Nepalese brands showed higher price to patient value than Indian brands. The present findings suggest that almost all the brands of Ranitidine HCl that are available in Pokhara valley meet the IP specification for quality control analysis. However, significant differences in quality control parameters are observed between the different brands (Thapa, *et. al*. 2005).

Shah, *et. al.* 2007 studies about in-vitro dissolution profile of ranitidine. To describe the properties of the similarity of factor (f2) as a measure for assessing the similarity of two dissolution profiles. Discuss the statistical properties of the estimate based on sample means. The f2 metrics and the decision rule is evaluated using examples of dissolution

profiles. The confidence interval is calculated using bootstrapping method. The bias of the estimate using sample mean dissolution is evaluated.f2 values were found to be sensitive to number of sample points, after the dissolution plateau has been reached. 2. The statistical evaluation of f2 could be made using 90% confidence interval approach. 3. The statistical distribution of f2 metrics could be simulated using 'Bootstrap' method. A relatively robust distribution could be obtained after more than 500 'Bootstraps'. 4. A statistical 'bias correction' was found to reduce the bias. The similarity factor f2 is a simple measure for the comparison of two dissolution profiles. But the commonly used similarity factor estimate f2 is a biased and conservative estimate of f2. The bootstrap approach is a useful tool to simulate the confidence interval (Shah, *et. al.* 2007).

Galia, *et. al.* 2003 studied about evaluation of various dissolution media. In this paper they seek to verify the differences in dissolution behavior between class I and class II drugs and to evaluate the suitability of two new physiologically based media, of Simulated Gastric Fluid (SGF) and of milk for their ability to forecast trends in the *in vivo* performance of class II compounds and their formulations. Acetaminophen dissolution in milk was slow from one tablet formulation; in all other cases dissolution was more than 85% complete in 15 minutes. Dissolution of the weak acid mefenamic acid from a capsule formulation is dependent on both pH and bile salt concentration, which leads to an offset between increased bile salt concentration and lower pH in the fed state compared to the fasted state medium. The weak base ketoconazole showed complete dissolution from a tablet formulation in Simulated Gastric Fluid without pepsin (SGF_{sp}) within 30 minutes, 70% dissolution in 2 hours under fed state simulated upper jejunal conditions but only 6% dissolution in 2 hours under fasted state conditions. As predicted, dissolution of class II drugs proved to be in general much more dependent on the medium than class I drugs. With the array of compendial and physiological media available, it should be possible to design a suitable set of tests to predict the *in vivo* dissolution of both class I and II drugs from immediate release formulations (Galia, *et. al.* 2003).

Dressman, *et. al.* 2002 studied about dissolution testing for oral drug abosorption. Dissolution tests are used for many purposes in the pharmaceutical industry in the

development of new products, for quality control and, to assist with the determination of bioequivalence. Therefore, there is a need to develop dissolution tests that better predict the *in vivo* performance of drug products. This could be achieved if the conditions in the gastrointestinal tract were successfully reconstructed *in vitro*. The aims of this article are, first, to clarify under which circumstances dissolution testing can be prognostic for *in vivo* performance, and second, to present physiological data relevant to the design of dissolution tests, particularly with respect to the composition, volume, flow rates and mixing patterns of the fluids in the gastrointestinal tract. Finally, brief comments are made in regard to the composition of *in vitro* dissolution media as well as the hydrodynamics and duration of the test (Dressman, ***et. al.*** 2002)

Ginski and Polli, 2005 shows that a study about absorption relationships from dissolution. While the analysis of in vitro dissolution–in vivo absorption relationships from oral solid dosage forms provides biopharmaceutical insight and regulatory benefit, no well-developed method exists to predict dissolution–absorption relationships a priori to human studies. The objective was to develop an integrated dissolution/Caco-2 system to predict dissolution–absorption relationships, and hence the contributions of dissolution and intestinal permeation to overall drug absorption for fast and slow formulations of piroxicam, metoprolol, and ranitidine. The dissolution/Caco-2 system's prediction of dissolution or permeation rate-limited absorption also agreed with the clinical results. For example, the dissolution/Caco-2 system successfully predicted the slow piroxicam formulation to be dissolution rate-limited, and the fast piroxicam formulation to be permeation rate-limited. Moreover, the system predicted this change from dissolution rate-limited absorption for slow piroxicam to permeation rate-limited absorption for fast piroxicam, in spite of piroxicam's high permeability and low solubility. (Ginski and Polli, 2005)

Joshi, ***et. al.*** 2010 conducted a study about control release of ranitidine.The objective of this work was to illustrate the suitability of montmorillonite (MMT) as a drug delivery carrier, by developing a new clay–drug composite of ranitidine hydrochloride (RT) intercalated in MMT. The MMT–RT composite was prepared by ion-exchange process..

The prepared MMT–RT hybrid was coated with cationic polymer Eudragit® E-100 by oil-in-water solvent evaporation method. The release processes of RT from MMT–RT and MMT–RT/Eudragit® E-100 were monitored under in vitro condition in the gastric fluid.The in vitro release studies showed that MMT–RT released RT in a controlled manner. In the case of MMT–RT/Eudragit® E-100, both the release rate and the release percentages noticeably increased in the presence of Eudragit® E-100, because of its effective exchange with intercalated RT molecules. The release kinetics followed parabolic diffusion mechanism. MMT has great potential as a drug delivery carrier with various scenarios. The dosage of the MMT–RT/Eudragit® E-100 can be in the tablet form. The hybrid material and polymer-coated hybrids are microparticles (Joshi, *et. al* 2010).

Alkaysi, *et. al.* 2001 investgate a study about bioequivalence of ranitidine. The bioavailability of two brands of ranitidine tablets was studied in 10 healthy volunteers. Formulation factors were compared by performing disintegration, dissolution and content uniformity tests. Plasma concentrations of ranitidine were measured using a sensitive and precise high pressure liquid chromatographic (HPLC) procedure. Pharmacokinetic parameters were determined for both formulations and included: Cmax, AUCt, AUCx, tmax, t1/2 and the terminal rate of elimination (k). Statistical analysis revealed that differences between the brands were not significant. The two formulations can be considered to be bioequivalent (Alkaysi, *et. al.* 2001).

Uzunarsla and Akbuğa 2003 conducted a study about the effect of moisture on the physical properties of ranitidine hydrochloride tablets prepared by direct-compression and by wet-granulation method using PVP or EC as binders was studied. They found that the tablets adsorbed moisture at 50 and 75 % RH (relative humidity) but lost moisture at 30% RH. Except storage at 75% RH, however, tablet volumes did not change significantly during the test period. Furthermore, generally dissolution profiles of tablets prepared by direct-compression and by ethyl cellulose remained unchanged. Changes in the binder type in the tablet formulations changed the water uptake properties and also the physical properties of tablets. Directly-compressed tablets were much susceptible to

change caused by humidity than tablets prepared by wet-granulation (Uzunarslan and Akbuğa, 2003).

Mody, Doshi, and Joshi JB Chemicals & Pharmaceuticals Limited, 2002 studied about control release of ranitidine. The present invention provides oral formulations of Ranitidine Hydrochloride in the form of coated tablets and capsules which produce controlled or regulated dissolution and release at a fairly uniform rate over long periods--as long as 12 to 24 hours--to maintain Ranitidine at desired levels above the MEC. (Mody, *et. al.* 2002)

Chapter Three

MATERIALS AND METHODS

3.1 Introduction:

The study on comparative dissolution profiles of ranitidine was carried out by using dissolution method to see the release pattern of ranitidine with different time interval. The method was verified and the rotating condition of the dissolution machine is optimized before application for sample analysis.

Comparative dissolution testing is a valuable tool in drug development and Characterization. In addition to serving as routine quality control tests, comparative dissolution tests have been used to support waivers for bioequivalence requirements, for approval of generic drug products and accepting product sameness under Scale-up and Post Approval (SUPAC) related changes (Ulrich, *et. al.* 2009).

3.2 Reagents, Chemicals and Solvents

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

For preparing a standard curve I used zantac tablet from GlaxoSmithKline. Other tablets I used to see the release pattern with different time interval like Neotac, Ranidin, Gepin, Inseac, Editin etc.

3.3 Methods for Comparison of Dissolution Profile Data

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

3.4 Difference factor

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

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

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

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

3.5 Similarity factor

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

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

Where, n is the number of testing time points; Rt is the average dissolution value of the reference product units at time t and it is the average dissolution value of the test product units at time t (US FDA, 1997; Hasan, *et. al.* 2007; Shah 2001; Yuksel, *et. al.* 2000). The proviso for evaluation for similarity is availability of data for six (6) or twelve (12) units of each product, availability of three or more dissolution time points, same conditions of testing for reference and test products and same dissolution time points for both profiles. As a further recommendation, it is suggested that only one measurement be considered after 85% dissolution of both products.

(US FDA, 1997; Hasan, *et. al.* 2007; Ochekpe, *et. al.* 2006).The similarity factor has been adopted by the US FDA and the European Medicines Agency (EMEA) for dissolution profile comparison. When two dissolution profiles are identical, f2 = 100%. An average dissolution

difference of 10% at all measured time point's results in an f2 value of 50%. For this reason, the public standard for similarity of two dissolution profiles has been set at 50 - 100% (EMEA 2010; USFDA 1997; Shah, 2001).

3.6 Dissolution Testing Methods for Ranitidine

Table 3.1- Dissolution parameter

Dissolution media	Distilled water
RPM	50
Temperature	37ºC
Time	60 minutes
Wavelength	314nm

The release rate of ranitidine tablet was determined by using tablet dissolution tester USP XXII. The dissolution test was performed using 900ml water pH (7.4) at 37+-0.5 degree C and 50 r.p.m. At every 20 min interval sample of 10 ml were withdrawn 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 (Hach, Japan).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 thw in vivo condition and drug dissolve at specified time periods was plotted as percent release versus time(hours) curve (Shah,*et al.*1998).

3.7 Preparation of Standard Curve:

To prepare the 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, First Zantac® (Ranitidine) tablet was crushed in mortar and pestle. From the crushed tablet 25 mg was taken and was dissolved in 50 ml of distilled water. By this procedure the concentration of the stock solution became 0.5mg/ml or 500µg/ml.This solution was filtered in the volumetric flask. After that the solution was 50 times diluted and the concentrations of the solution become 50µg/ml. 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, and 5 ml. Then spectrophotometer is turned on and 314nm wave length was set up. Then the spectrophotometer was adjusted for 0 and 100%.The solutions were placed on spectrophotometer to measure the absorbance. Then the absorbance was plotted against concentration. A straight line was found.

Table 3.2- Concentrations of Ranitidine (Campanero, *et. al.*1998)

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

3.8 Preparation for dissolution test:

3.8.1 Preparation of stock solution:

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

3.8.2 Method for dissolution test of Zantac® (Ranitidine)

6L (6000ml) of stock solution (distilled water) was prepared. Each vessel of dissolution tester was filled with 900 ml of stock solution (distilled water) Time 1 hour; rpm 50 was set up in the dissolution machine. Then the machine was allowed to warm up until it reached at 37.5 degree C. Then 1 Zantac® tablet was placed in every vessel. After 20, 40 and 60 minutes 10 ml of solution was collected from each vessels and filtered, then from that 1 ml of solution was taken in another test tube and 9 ml distilled water was added to make it 10 ml. At last UV absorbance off the solutions were taken where the wave length was 314nm. (Lawrence, *et. al.,* 2002).

3.8.3 Method for Neotack and Ranidine

The dissolution test method for Neotack and Ranidine were done in a procedure which was as similar as Zantac®.

3.9 Determination of physical parameters

3.9.1 Weight Variation Test

3.9.1.1 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.

N.B: The variation from the average weight in the weights not more than two tablets must not differ more than the percentage listed below:

Table 3.3: 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%

3.9.1.2 Equation:

Following equation was used to determine % weight variation of tablets

$$\textbf{\% Weight Variation} = (A\text{-}I/A) \times 100$$

Where,

Initial Weight of Tablet, I (gm)

Average weight of Tablets, A (gm) **(**Dunnett, C. W., and R. Crisafio.1995)

3.9.2 Thickness test

3.9.2.1 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.

3.9.2.2 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

3.9.3 Hardness test

3.9.3.1 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 (Dunnett and Crisafio, 1995).

3.9.3.2 Materials

3.9.3.2.1 Sample Collection

To observe the change in dissolution pattern of Different brands of Ranitidine tablets with innovator drug (Zantac®), Samples were collected from the local drug store in Dhaka.

Table 3.4: Samples used in the experiment including source

Brand Name	**Source**
Zantac® tablets	GlaxoSmithKline Bangladesh Limited
Neotack tablets	Square Pharmaceuticals Ltd
Ranidine tablets	Biopharma

3.9.3.2.2 Stock solution:

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

3.9.3.2.3 Equipment's:

Table 3.5: In the characterization of matrix tablets of Ranitidine (Kuss, 1992)

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

3.10 Instrumentation

3.10.1 Dissolution Test Apparatus

A Dissolution tester USPXXII (source RC-6B, made in China) was used for dissolution experiments. It incorporated a clear acrylic water bath, a stirrer hood with paddle shafts, an automatic sampling unit and a control unit supported by microcontroller software with a 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 tygon tubing's, a microprocessor controlled sample collector and a sample tray capable of collecting 10 x 6 sets of samples. Polycarbonate dissolution vessels with a hemispherical bottom and a capacity of 1000 ml were used for the study. Bromide (E. Merck, Darmstadt, Germany) and a manually operated hydraulic pellet press (Perking Elmer GmbH, Uberlingen, Germany).

3.10.2 Ultra- Violet Spectrophotometer

The ultra-violet absorption spectrum for 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 (HACH UV-1201 PC, JAPAN) over a 10 mm path length using quartz cuvettes.

3.11 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 (Kuss,1992).

3.12 Images of Instruments:

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

Figure 3.1: Dissolution apparatus

Figure 3.2: (left to right) UV-1800 Double Beam Spectrophotometer

Figure 3.3: Distilled Water apparatus

Figure 3.4: Hardness tester

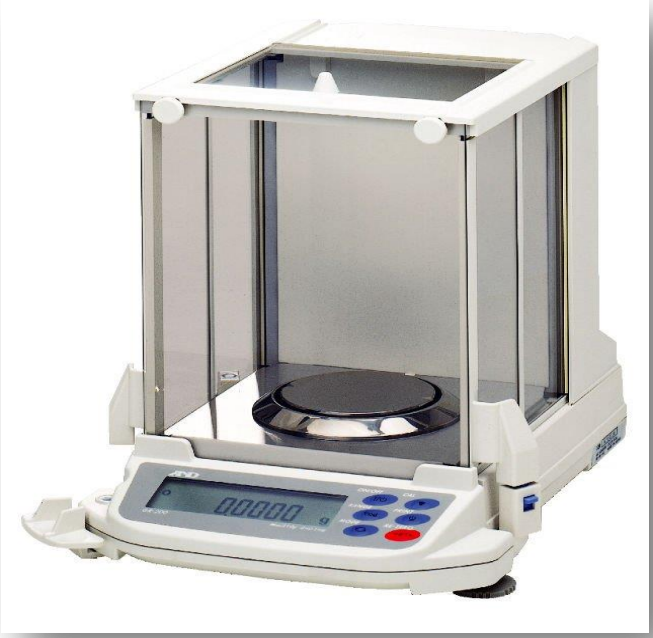

Figure 3.5: Electronic Balance

3.13 Dissolution Efficiency

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

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

In the above equation, y is the percentage of drug release. The numerator of the equation indicates the area under within the time frame. The denominator indicates the rectangle of 100% drug release from 0 times throughout the time frame. The area under the curve is calculated by the help of Microsoft Excel software (Anderson et al. 1998; Parakh and Patil 2014).

3.14 Apparatus:

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

Table 3.6- Representing the apparatus (Kuss, 1992)

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

Chapter Four

RESULTS AND DISSCUSSION

4.1 Physical properties

4.1.1 Weight Variation Test

Table 4.1: Average weight of tablets of different brands

Name of the Drug	**Weight of tablets (mg)**
Zantac	305.00
Neotac	324.00
Ranidin	301.00

The experiments were done with two different brands of ranitidine. After the test it was seen that variations of the weight of the tablets were not very close to each other. The weight of the innovator brand Zantac is 305.00 mg. Ranidin was similar with innovator brand andNeotacwas higher than Zantac.

4.1.2 Hardness test

Table 4.2: Hardness test

Formulation Name	Hardness (Pa)
Zantac®	11.00
Neotac	10.00
Ranidin	14.00

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

4.1.3 Disintegration time:

Table 4.3: Disintegration test

Formulation	Sample I Time (Minutes)	Sample II Time (Minutes)	Sample III Time (Minutes)	Average Time (Minutes)
Zantac®	13.56	13.12	14.10	13.59
Neotac	4.15	4.10	5	4. 41
Ranidin	9	9.15	9.50	9.36

Here the disintegration time of each three tablets of same brand is much more similar but the average value of two different brands is not similar with innovator brand Zantac®.

4.2 Standard curve of Zantac

For the calculation of drug release from the innovator brand as well as test brands, a standard curve was prepared within the concentration range of 0-25 microgram/mL. The curve displayed sufficient linearity with a correlation coefficient (R2) value of 0.9992 and provided an equation y=0.0455x+0.0125. The standard curve is shown in figure 4.1.

Table 4.4: Standard curve of Zantac® Tablets

Concentration (µg/ml)	Absorbance
0	0
5	0.247
10	0.471
15	0.698
20	0.937
25	1.132

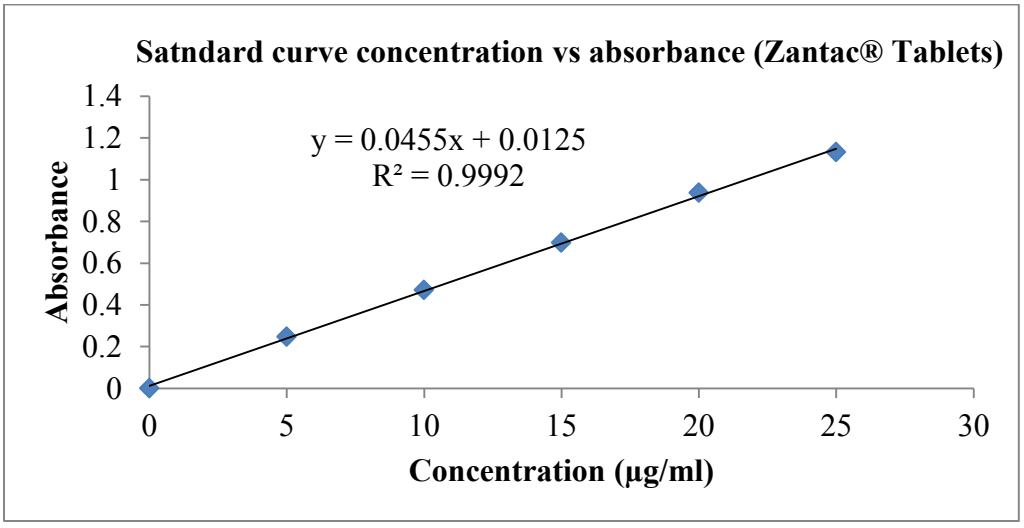

Figure 4.1: Standard curve Concentration Vs Absorbance (Zantac®)

By plotting the concentration against the absorbance of ranitidine we found a straight line. From the standard curve ranitidine, we derived an equation y=37.89x+0.0125 & R^2=0.9992(Here, y= Absorbance and x=Concentration of drug).

4.3 Percent (%) release of Zantac® Tablets samples:

Table 4.6: Percent (%) release of Zantac® samples

Time (Minutes)	Sample 1 Release %	Sample 2 Release %	Sample 3 Release %	Sample 4 Release %	Sample 5 Release %	Sample 6 Release %
0.00	0.00	0.00	0.00	0.00	0.00	0.00
5.00	14.53	18.53	16.05	17.87	38.13	12.00
10.00	41.47	37.47	30.70	29.73	45.60	27.73
20.00	73.60	63.20	65.86	53.73	54.93	56.80
30.00	78.53	79.60	91.67	66.27	81.87	78.53
40.00	79.20	80.53	94.33	79.07	83.60	85.20
50.00	85.47	92.67	103.53	88.00	86.27	97.73

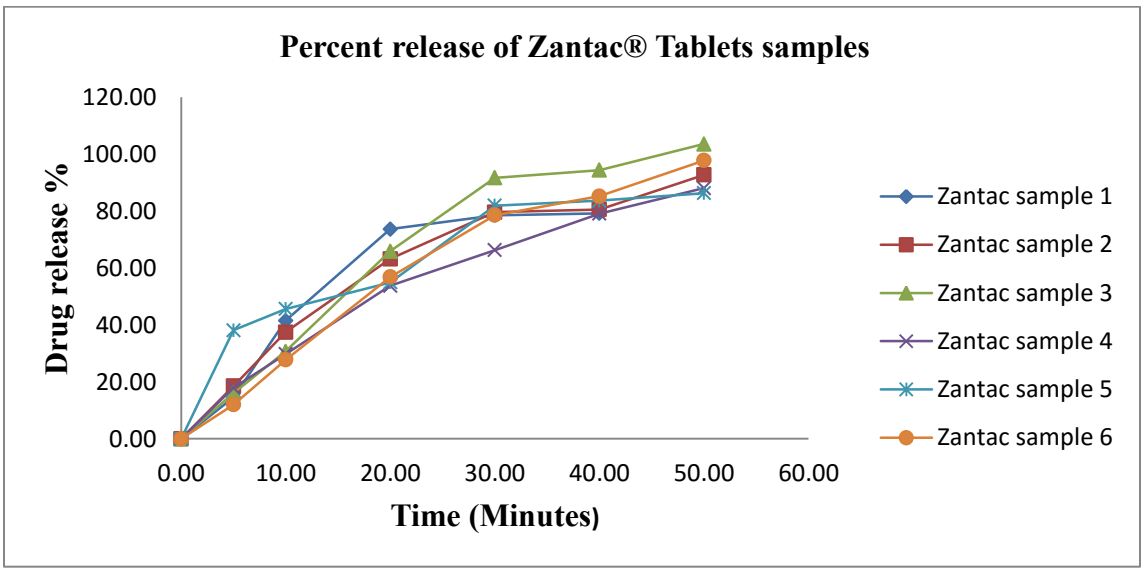

Figure 4.3: Time Vs Drug Release (%) of Zantac® samples.

Here the graph shows that, the release pattern of six different tablets of Zantac® is increasing with time. So, the dissolution pattern is increased with time.

4.4 Percent (%) Release of Zantac® average

Table 4.5: Percent (%) Release of Zantac® Tablets average

Time (Minutes)	**Drug Release (%)**
0.00	0.00
5.00	19.52
10.00	35.45
20.00	61.45
30.00	79.68
40.00	87.17
50.00	88.50

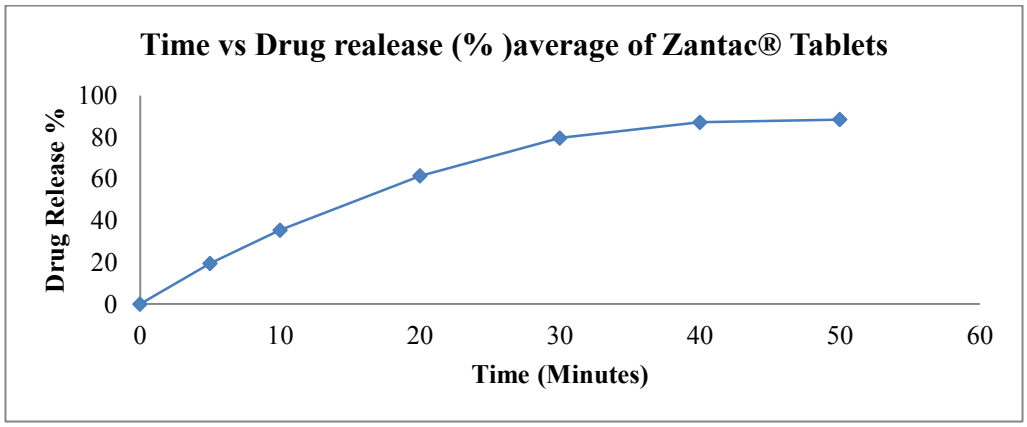

Figure 4.2: Time Vs Drug Release (%) average of Zantac® Tablets

Here the graph shows that average release of Zantac® (Ranitidine) tablets is increased with time. We can see that the release pattern of drug is increased after time with increasing the concentration. 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 have 88.50. Here X axis represents the time and Y axis is for Drug release.

4.5 Percent (%) release of Neotack tablets samples

Table 4.7 Percent (%) release of Neotack tablets samples

Time (Minutes)	Neotack Release %	Neotack Release %	Neotack Release %	Neotack Release %	Neotack Release %	Neotack Release %
0.00	0.00	0.00	0.00	0.00	0.00	0.00
5.00	35.73	37.50	38.64	36.89	40.56	48.55
10.00	46.27	55.65	51.64	55.69	47.07	56.27
20.00	73.60	76.96	71.20	75.66	59.33	73.20
30.00	79.20	78.56	76.96	79.59	77.60	78.46
40.00	85.20	89.56	79.54	85.20	87.33	85.20
50.00	98.80	100.45	97.73	98.80	101.56	99.46

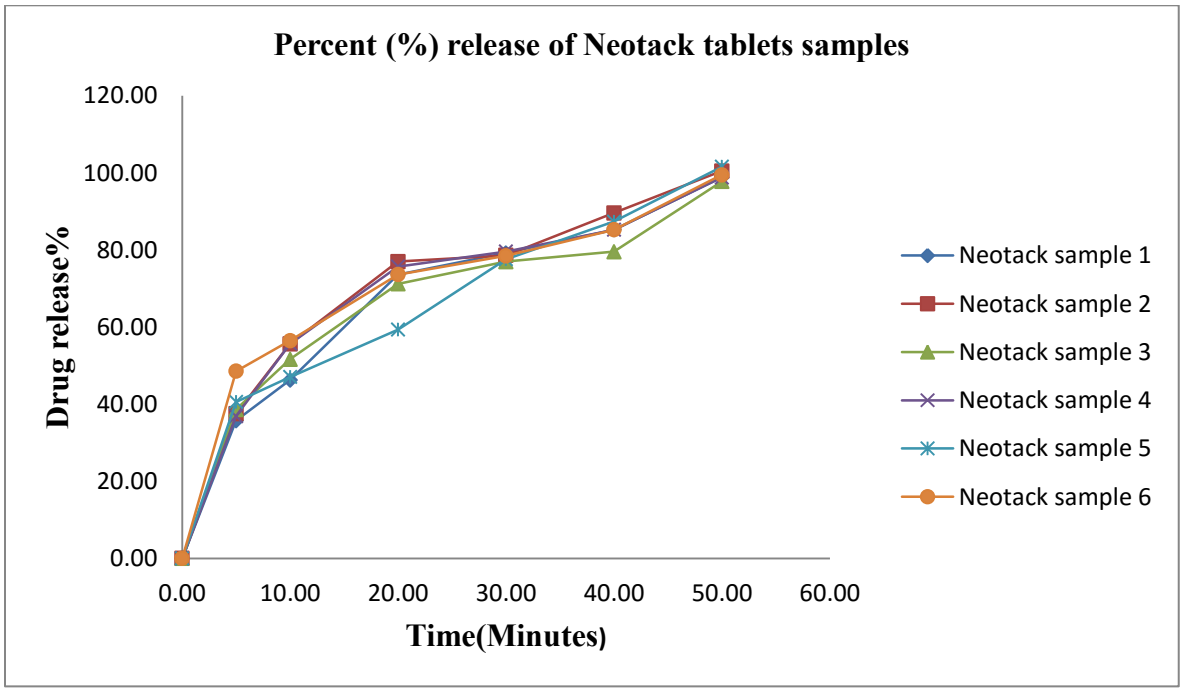

Figure 4.4: Time vs Drug Release (%) of Neotack samples.

This graph represents that, the increasing of drug release in according to the counting of time release pattern of Neotack is much more similar with the innovator drug Zantac.

4.6 Percent (%) Release of Neotack tablets average

Table 4.8: Percent (%) Release of Neotack average

Time (Minutes)	**Release (%)**
0.00	0.00
5.00	34.67
10.00	45.67
20.00	57.07
30.00	73.87
40.00	83.71
50.00	98.62

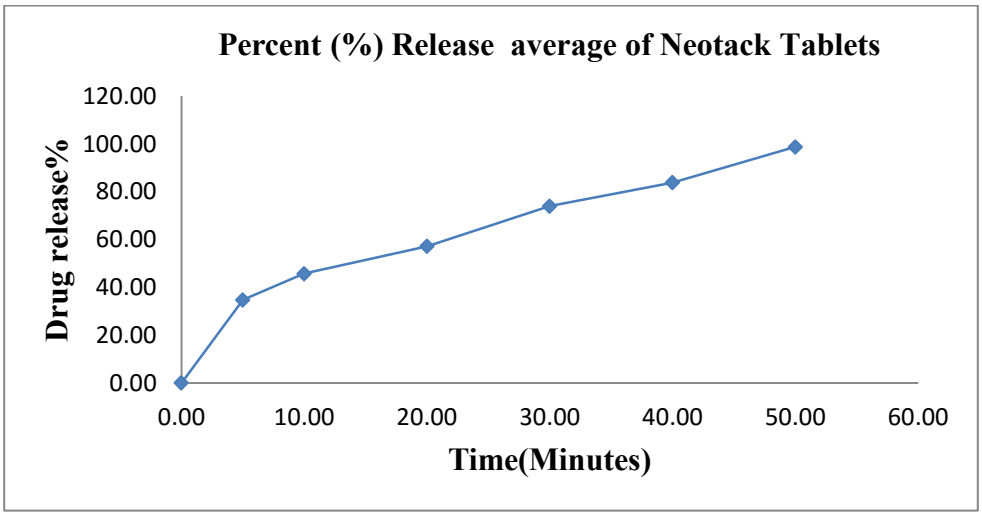

Figure 4.5: Time Vs Drug Release (%) average of Neotack Tablets

This graph represents that, the increasing of drug release in according to the counting of time in 0.00the drug release was 0.00 and then 5.00 minutes has 34.67 then 10.00 minutes was 45.07, 20.00 minutes has 57.07, 30.00 minutes has73.87 , 40.00 has 83.71 and 50.00 has 98.62. Here X axis represents the time and Y axis is for Drug release.

4.7 Percent (%) release of Ranidin tablets samples

Table 4.9: percent (%) release of Ranidin tablets samples

Time (Minutes)	Sample Release %	Sample Release %	Sample Release %	Sample Release %	Sample Release %	Sample Release %
0.00	0.00	0.00	0.00	0.00	0.00	0.00
5.00	14.53	16.27	15.80	15.33	20.20	15.60
10.00	41.47	40.00	46.56	38.56	41.87	42.00
20.00	51.07	57.20	55.20	46.00	50.53	53.65
30.00	53.33	72.53	65.73	61.60	60.80	55.60
40.00	75.87	75.65	72.40	89.60	77.60	64.53
50.00	78.27	87.65	82.27	93.07	90.40	77.20

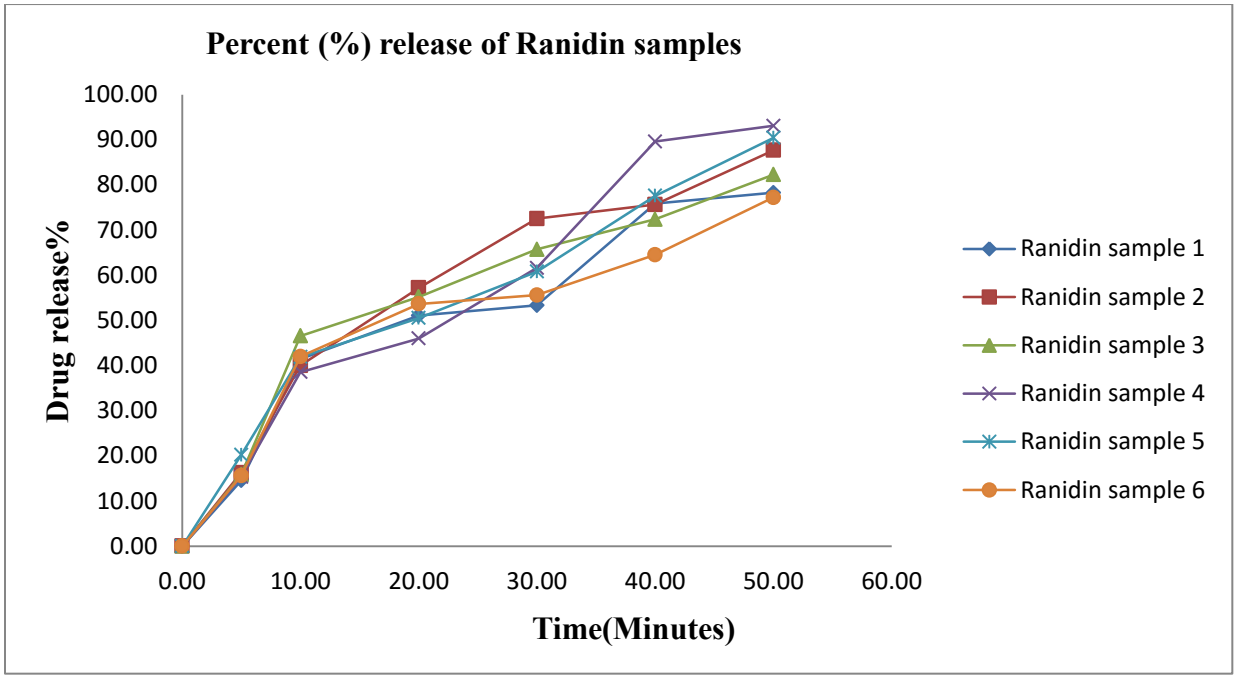

Figure 4.6: Time Vs Drug Release (%) of Ranidin samples.

This graph represents that, the increasing of drug release in according to the counting of time. With the increasing time, the release pattern of drug is increases.

4.8 Percent (%) Release of Ranidin tablets average

Table 4.10: Percent (%0 Release of Ranidin average

Time (Minutes)	**Release (%)**
0.00	0.00
5.00	16.96
10.00	39.16
20.00	51.93
30.00	61.60
40.00	76.22
50.00	83.36

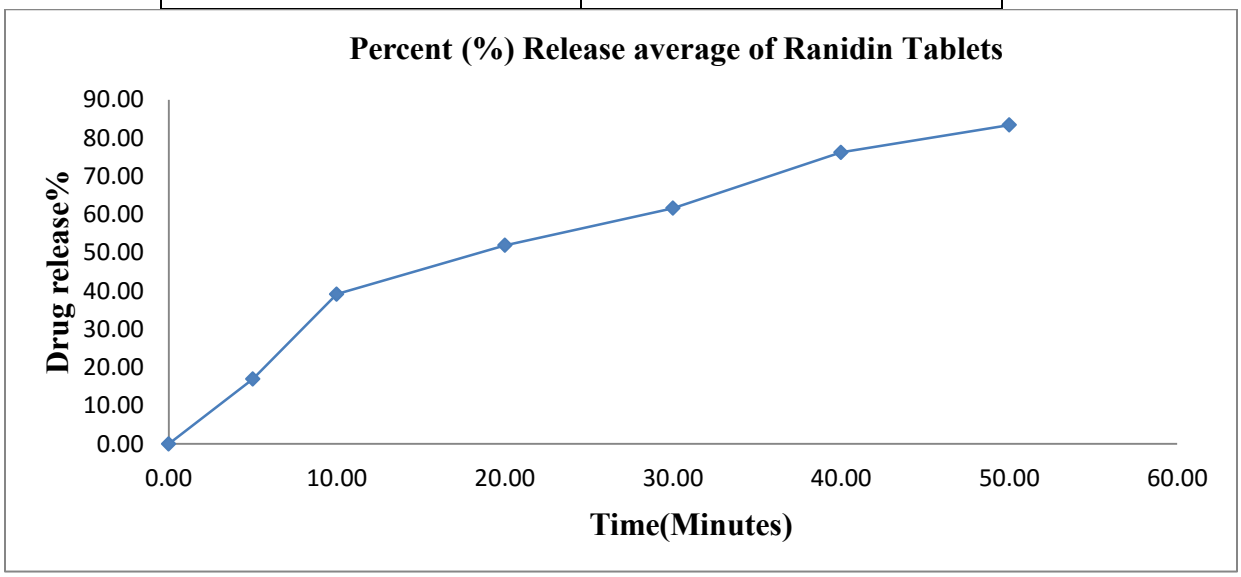

Figure 4.7: Time vs Drug Release (%) avarage of Ranidin tablets sample.

This graph shows that, 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 16.96 then 10.00 minutes was 39.16, 20.00 minutes has 51.93, 30.00 minutes has 61.60 , 40.00 has 76.22 and 50.00 has 83.36. Here X axis represents the time and Y axis is for Drug release

4.9 Drug dissolution of different brands:

Table 4.11- Drug dissolution of different brands:

Time (Minutes)	**Zantac Release (%)**	**Ranidin (A) Release (%)**	**Neotack (B) Release (%)**
0.00	0.00	0.00	0.00
5.00	19.52	16.96	34.67
10.00	35.45	39.16	45.67
20.00	61.35	51.93	57.07
30.00	79.68	61.60	73.87
40.00	87.17	76.22	83.71
50.00	88.50	83.36	98.62

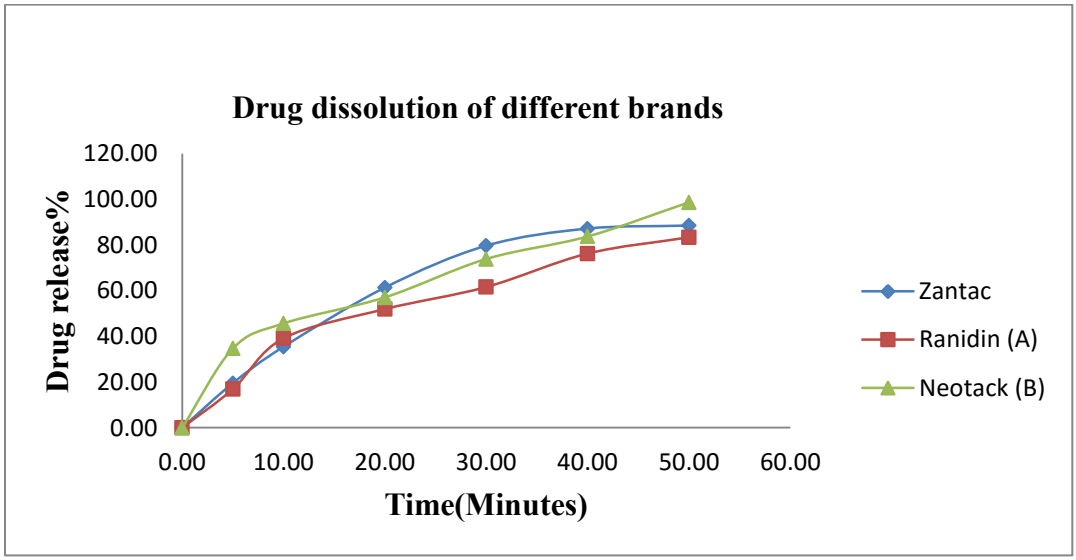

Figure 4.8: Drug dissolution profile of different brands

The graph shows that, the comparison of dissolution pattern of two different brands of drug with innovator drug (Zantac).As the innovator drug Zantac is the patent drug of ranitidine the release profile is better. In comparison of two other brands with Zantac the release profile was increasing with time. Brand B is more similar with the innovator drug. But the brand A is not similar in dissolution pattern with Zantac.

4.10 *f*1 Calculation for Neotac tablets

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

Table 4.12- *f*1 Calculation for Neotac tablets

Time (Minutes)	Zantac (R) **Release %**	Neotac (T) **Release %**	R-T	IR-TI	F1
5	19.52	34.67	-15.15	15.15	
10	35.45	45.67	-10.22	10.22	
20	61.35	57.07	4.28	4.28	
30	79.68	73.87	5.81	5.81	13.19
40	87.17	83.71	3.46	3.46	
50	88.50	98.62	-10.12	10.12	
Total	371.67			49.04	

Table 4.13- *f*1 Calculation for Ranidin tablets

Time (Minutes)	Zantac (R) **Release %**	Ranidin (T) **Release %**	R-T	IR-TI	F1
5	19.52	16.96	2.56	2.56	
10	35.45	39.16	-3.71	3.71	
20	61.35	51.93	9.42	9.42	
30	79.68	61.60	18.08	18.08	13.41
40	87.17	76.22	10.95	10.95	
50	88.50	83.36	5.14	5.14	
Total	371.67			49.86	

Acceptable range of *f*1 is between 0-15. *f*1 value greater than 15 means significant difference between two brands which is not accepted. From the table 4.9 and 4.10 we see that the values of *f*1 are 13.19 and 13.41 so it is acceptable.

4.11 *f*2 Calculation for Neotac tablets:

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

Table 4.14- *f*2 Calculation for Neotac tablets

Time (Minutes)	Zantac (R) Release %	Neotac (T) Release %	R-T	IR-TI	IR-TI^2	F2
5	19.52	34.67	-15.15	15.15	229.5225	
10	35.45	45.67	-10.22	10.22	104.4484	
20	61.35	57.07	4.28	4.28	18.3184	51.8
30	79.68	73.87	5.81	5.81	33.7561	
40	87.17	83.71	3.46	3.46	11.9716	
50	88.50	98.62	-10.12	10.12	102.4144	
Total	371.67			49.04	500.43	

Table 4.15- *f*2 Calculation for Ranidin tablets

Time (Minutes)	Zantac (R) Release %	Ranidin (T) Release %	R-T	IR-TI	IR-TI^2	F2
5	19.52	16.96	2.56	2.56	6.5536	
10	35.45	39.16	-3.71	3.71	13.7641	
20	61.35	51.93	9.42	9.42	88.7364	50.2
30	79.68	61.60	18.08	18.08	326.8864	
40	87.17	76.22	10.95	10.95	119.9025	
50	88.50	83.36	5.14	5.14	26.4196	
Total	371.67			49.86	582.26	

The range of the f2 value is between 0 to 100. If the value remains between 50 to 100, it is acceptable. From the table 4.11 and 4.12 we see that the values of *f*2 are 51.8 and 50.2, so it is acceptable.

4.12 Dissolution Efficiency

The dissolution efficiency is not a parameter to compare dissolution pattern between two brands. It is just a parameter to indicate drug release. The area under the curve is calculated by the help of Microsoft Excel software (Anderson et al. 1998; Parakh and Patil 2014).

Table 4.15: Dissolution efficiency

Brand	Dissolution efficiency	Difference with Zantac
Zantac	61.76%	0.00%
Neotac	68.36%	06.60%
Ranidin	66.82%	05.06%

The innovator brand Zantac® in this study was found with Very low dissolution efficiency (DE) i.e. 61.76%. All the brands satisfied the USP requirements of drug release. They passed the f1 and f2 analysis when comparing with Zantac®.

Chapter Five
CONCLUSION

Conclusion

Ranitidine is classified as a Class III drug (high solubility and low permeability) by the BCS. Dissolution tests are essential for the prognosis of dosage form oral absorption and bioequivalence of drugs. In this study we have compared the dissolution profile of two local brands (Neotac) and Renidin with Zantac® (patent drug of ranitidine).It was found that the difference factor of Neotack with Zantac® is 13.19 and Ranidin with Zantac® is 13.4.And similarity factor of both Neotac and Ranidin with Zantac® is 51.8 and 51.2 respectively. No significant difference was observed during *in-vitro* drug release pattern of brand Neotack and Ranidin with the innovator brand. The similarity factor and Difference factors of these two brands was in the acceptable range. In conclusion, further investigations are needed to find out the better dissolution profile for these two brands.

Chapter Six
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