Impact of Different Supplement Drugs on the Dissolution Profile of Zantac® & Ranitid®

A Dissertation submitted to the East West University, Bangladesh,

For the partial fulfillment of the Degree of

Bachelor of Pharmacy

Submitted by

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Submitted to

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DECLARATION

The research work entitled “Impact of different supplement drugs on the Dissolution Profile of Zantac® & Ranitid®” is submitted as a dissertation for the partial fulfillment of the Bachelor Degree of Pharmacy, under the supervision and guidance of Md. Anisur Rahman, Senior Lecturer, Department of Pharmacy, East West University, Dhaka.

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Certification by the Supervisor

The under signed certify that the research work which is presented here was completely done by the author as well as to the style and contents. This thesis is therefore suitable for submission. No part or whole of this work was submitted before other degree. We further certify that the source of information has been availed of this connection is duly acknowledged.

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Certificate by the Chairperson

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Dr. Shamsun Nahar Khan
Associate Professor & Chairperson
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Dedicated to

My Parents
&
Honorable Teachers

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All praises to the almighty “ALLAH” for the strengths and blessings given to me in completing this research.

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ABSTRACT

The objective of the research work was to investigate the impact of Calbo®500mg(Calcium supplement tablet), Acical-M (Calcium, Vitamin & Minerals tablet), Aristocal D (Calcium & vitamin-D Tablet), Filwel Silver (Multivitamin Silver Tablet) and Nutrum Gold (Multivitamin & Multimineral Tablet) on the dissolution of Ranitidine (Zantac® & Ranitid®). Zantac® is a patent product of Ranitidine produced by Glaxosmithkline Bangladesh and Ranitid® is the brand name of Ranitidine produced by Opsonin Pharmaceutical Ltd. The physical parameters of Ranitidine tablets were determined by performing weight variation test, hardness test and thickness test. The dissolution test was performed by using distilled water (used as dissolution medium) with USP dissolution apparatus II followed by UV Spectroscopy. A standard curve equation of Ranitidine was established for the calculation of percent dissolved amount of drug. The dissolution of individual Ranitidine (Zantac® & Ranitid®) tablets and also in combination with the following supplement drugs, were determined after 20, 40 and 60 minutes. After an hour, the percent dissolved amount of individual Zantac®, Zantac® with Calbo®500, Zantac® with Acical-M, Zantac® with Aristocal D, Zantac® with Filwel Silver and Zantac® with Nutrum Gold were 94.09%, 47.84% , 48.47%, 72.6%, 97.22% and 94.27% respectively and in case of Ranitid®, those values were 91.89%, 49.79%, 51.18%,70.95%, 98.91% and 95.67% respectively. From the result it was assumed that Calbo® 500 and Acical-M has extreme effect on the dissolution of Zantac® and Ranitid®, Aristocal D has moderate effect for both Zantac® and Ranitid®. So these three supplements cannot be co-administered with Zantac® and Ranitid®. The dissolution of Zantac® and Ranitid® were not decreased by Nutrum Gold or Filwel Silver (Multivitamin and multimineral). As Nutrum Gold and Filwel Silver were not decreased the dissolution of Zantac® and Ranitid®, this supplement drugs can be co-administered with Zantac® or Ranitid®.

Keyword: UV Spectroscopy, USP dissolution apparatus II, Hardness, Thickness, Weight Variation, Dissolution Impact.

Chapter One

Introduction

Co-administration of more than one drug is very common practice among the patients. This type of drug administration may lead to several problems such as drug interaction, effect on drug absorption (higher or lower) to the target site, higher side effects and so on. The main purpose of this research project was to determine the impact of different supplement drugs on dissolution of Ranitidine. During this investigation we measured the percent release of a drug product individually and also in combination with different supplement drugs and then determine the impact on dissolution. In this project work 'Ranitidine'(generic) had been selected as a main drug product and different supplement drugs such as multivitamin (silver and gold) tablet, Calcium tablet, Calcium with minerals tablet and calcium with minerals & vitamin tablet selected as the co-administered product.

My project was on 'Zantac®'(patent product of Ranitidine) and 'Ranitid®', that products are prepared by Glaxosmithkline Bangladesh and Opsonin pharmaceuticals respectively .So in a word, my project was to determine the impact of calcium supplement, multivitamin (silver and gold), calcium with minerals tablet and calcium supplement with minerals & vitamin tablets on the dissolution of 'Ranitidine'.

To finding out the target ,we performed some very essential in vitro tests such as dissolution test of individual Ranitidine (both Zantac® & Ranitid®), dissolution test of Ranitidine with calcium supplement(Calbo® 500mg tablet), dissolution test of Ranitidine with multivitamin silver (Filwel Silver) ,dissolution test of Ranitidine with multivitamin gold (Nutrum Gold), dissolution test of Ranitidine with calcium supplement with minerals (Acical-M) and dissolution test of Ranitidine with calcium supplement with minerals & vitamin D (Aristocal-D).

To perform the dissolution test, we used dissolution test apparatus and distilled water (according to USP) and after the dissolution we collected the sample from the dissolution vessel and prepared it for the UV spectroscopy that provided the absorbance results.

We also prepared a standard curve of Ranitidine by plotting different concentrations of Ranitidine drug against different absorbance. By using this standard curve, we calculated the concentration of drug in the distilled water within 20,40 and 60 minutes .We also determined the concentration of Ranitidine in combination with calcium supplement, multivitamin silver, multivitamin gold ,calcium supplement with

minerals and calcium supplement with minerals & vitamin D within 20,40 and 60 minutes. After that the impact of supplement drugs on the dissolution of Ranitidine had been determined.

During the research work some other physical tests of Ranitidine (Zantac® & Ranitid®) such as hardness, thickness and weight variation were also performed.

If the dissolution of Ranitidine is affected due to the impact of different types of supplement drugs then we should avoid administration of different supplement drugs with Ranitidine.

1.1 Histamine mediator and H2 Receptor

Histamine is the type of chemical substance that is produced from the decarboxylation of amino acid histidine. This chemical reaction is catalyzed by the enzyme L-histidine decarboxylase. It is a part of local immune response that causes inflammation. It has several important functions such as blood vessels dilation, increase the amount of acid secretion by the stomach, constriction of smooth muscle (e.g., in the bronchi), production of mucus, tissue swelling and itching (during allergic reactions). Histamine is released from certain types of cells in the body, including cells that are present in the lining of the stomach (also known enterochromaffin-like cells or ECL cells). Histamine that released from ECL cells stimulates the acid-making cells (parietal cells) in the lining of the stomach to release acid that ultimately resulting the amout of acid. Histamine that is released from mast cells is an important component of type-1 hypersensitive reactions, including asthma (Robertson, 2010).

H2 receptors are mainly responsible for adjusting the level of gastric acid. These are mainly present on parietal cells located in the stomach lining but also present in heart, uterus and vascular smooth muscle cells. Histamine reacts with H2 receptor that present on stomach cell lining and stimulates the release of gastric acid, excess of which can result in gastroenteritis. Histamine encourage smooth muscle relaxation when interact with H2 receptor present in muscle cells. Neutrophils (a common type of white blood cell) are also contains H2 receptor. By interacting with this receptor histamine can inhibit the production of antibody and cytokine (May, 2016).

1.2 H2 Receptor Antagonist

H2 receptor antagonists are a class of medications used to treat the excessive acidic condition of stomach. Those medications are now available as over the counter drug H2 antagonists are widely used to treat gastritis, inflamed stomach and peptic ulcers. Peptic ulcers are formed in the lining of the stomach, lower esophagus, or duodenum. H2 receptor antagonists can also be used to treat the symptoms of gastroesophageal reflux disease (GERD). GERD is a chronic form of acid reflux, which causes acidic stomach contents to flow back up into the esophagus. The continuous exposure to stomach acid can irritate the esophagus and ultimately lead to uncomfortable symptoms, such as heartburn, nausea, or trouble swallowing (Mayoclinic, 2016).

1.3 General Mechanism of H2 Receptor Antagonist

H2-antagonists are mainly performed by competing with the agonist for the histamine receptor site but have in addition a distinct affinity for a secondary site on the receptor. After administration of H2 receptor blocker it binds with specific receptors (H2) on the surface of the stomach cells that release acids. By doing so this agents are inhibit the certain chemical reactions and destroy the ability of those cells to produce as much acid. By reducing the amount of acid in the stomach, any damaged tissues are allowed time to heal (Krielaart, Veenstra and Buuren, 1990).

1.4 Side Effects of H2 Receptor Antagonists

The side effects that associated with H2 receptor blockers are mild. Some of the side effects that may occur with H2 receptor blockers include:

- constipation
- diarrhea
- difficulty sleeping
- dry mouth
- dry skin
- headaches
- ringing in the ears
- a runny nose
- trouble urinating

(Healthline, 2016)

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

- blistered, burning, or scaling skin
- changes in vision
- confusion
- agitation
- difficulty breathing
- wheezing
- chest tightness
- irregular heartbeat
- hallucinations
- suicidal thoughts

(Healthline, 2016)

1.5 Information of 'Ranitidine'(Zantac®/Ranitid®)

Ranitidine is an effective H2 blocker that reduce the acid formation of stomach ,it belongs to an organic class known as aralkylamines. The alkyl group of alkylamine is substituted at one carbon atom by an aromatic hydrocarbyl group. Chemical formula of Ranitidine is $C_{13}H_{22}N_4O_3S$.The IUPAC name of Ranitidine is dimethyl[(5-{[(2-{[(E)-1-(methylamino)-2-nitroethenyl]amino}ethyl)sulfanyl]methyl}furan-2-yl)methyl]amine.The structure of Ranitidine is given below (Drugbank,2013).

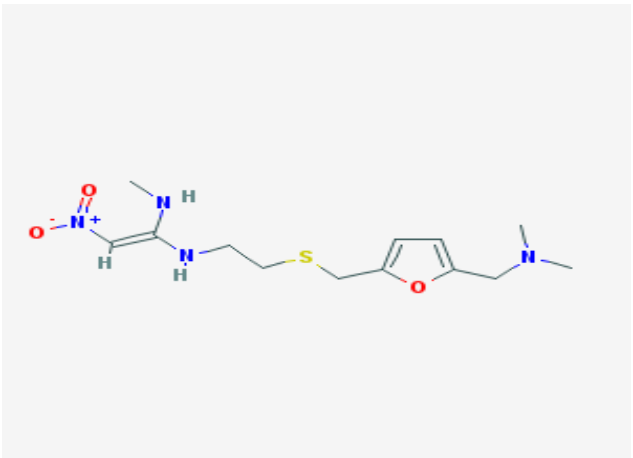

Figure1.1: Molecular Structure of Ranitidine

1.5.1 Description

Ranitidine is a rapid acting and highly effective histamine H2 receptor antagonist, used for the treatment of peptic ulceration and other conditions where the reduction of gastric acid secretion is beneficial (Opsonin,2016).

1.5.2 Composition

- Tablet:Each 150mg film-coated tablet contains Ranitidine 150 mg as Ranitidine Hydrochloride USP.
- Injection: Each 2 ml ampoule contains Ranitidine 50 mg as Ranitidine Hydrochloride USP.

(Opsonin, 2016)

1.5.3 Pharmacodynamics

Ranitidine is compete with histamine to inhibite histamine H2-receptor (similar to cimetidine and famotidine). The drug is used to block the action of histamine on parietal cells in the stomach, decreasing acid production by these cells. These drugs are used in the treatment of dyspepsia, however their use has waned since the advent of the more effective proton pump inhibitors. Like the H1-antihistamines, the H2 antagonists are inverse agonists rather than true receptor antagonists (Opsonin, 2016).

1.5.4 Therapeutic Indication

It is used to treat-

- Peptic ulcers (Gastric and duodenal ulcer)
- reflux oesophagitis
- eradication of Helicobacter pylori from duodenal ulcer
- stress ulcer prophylaxis
- Zollinger-Ellison syndrome
- prevention of NSAID-associated duodenal ulcer

(Opsonin, 2016)

1.5.5 Mode of Action

Ranitidine is a Histamine2 Receptor Antagonist (H2RA). Ranitidine competitively inhibits the interaction of histamine with H2 receptors, thus Ranitidine inhibits gastric acid secretion elicited by histamine, other H2 agonists and gastrin (Opsonin, 2016).

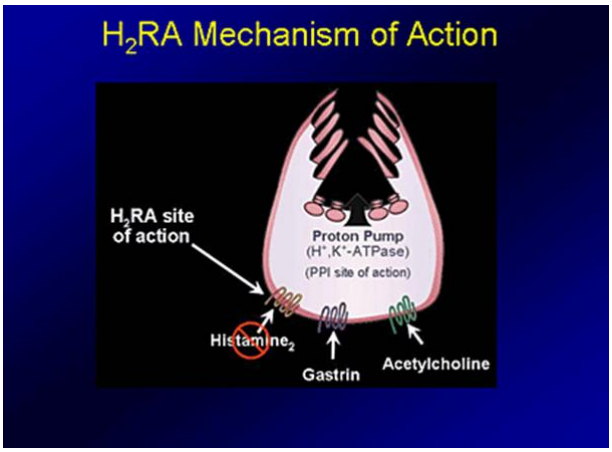

Figure 1.2: Mechanism of Ranitidine.

1.5.6 Pharmacokinetics

About 50% of Ranitidine is bioavailable after oral dosing and there is a significant presystemic metabolism. Food has a minimal effect on absorption. Ranitidine has the plasma half-life between 2 to 3 hours. Excretion of Ranitidine and its metabolites occur largely through kidney (Opsonin, 2016).

1.5.7 Absorption: Approximately 50% bioavailability orally (Drugbank, 2013).

1.5.8 Volume of Distribution:

- 1.4 L/kg
- 1.76 L/kg [clinically significant renal function impairment (creatinine clearance 25 to 35 mL/min)]

(Drugbank, 2013)

1.5.9 Protein Binding: 15% (Drugbank, 2013).

1.5.10 Metabolism: Hepatic. Ranitidine is metabolized to the N-oxide, S-oxide, and N-desmethyl metabolites, accounting for approximately 4%, 1%, and 1% of the dose, respectively (Drugbank, 2013).

1.5.11 Route of Elimination: Urine (active tubular excretion, renal clearance 410mL/min) is the principal route of excretion with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours (Drugbank,2013).

1.5.12 Half Life: 2.8-3.1 hours (Drugbank, 2013).

1.5.13 Clearance

- 29 mL/min [clinically significant renal function impairment]
- 3 mL/min/Kg [neonatal patients]

(Drugbank, 2013)

1.5.14 Toxicity: LD_{50}=77mg/kg (orally in mice). Symptoms of overdose include muscular tremors, vomiting, and rapid respiration (Drugbank, 2013).

1.5.15 Dosage & administration

- **Benign gastric and duodenal ulcer**: 150 mg twice daily or 300 mg at night upto 6 weeks.
- **Reflux esophagitis:** 150 mg twice daily or 300 mg at night for upto 8 weeks.
- **Prevention of NSAID-associated duodenal ulcer**: 150 mg twice daily.
- **Eradication of Helicobacter pylori from duodenal ulcer:** Ranitid® 300 mg at night for 6 weeks given in combination with amoxycillin and metronidazole for 12 days.
- **Zollinger-Ellison syndrome:** 150 mg 3 times daily; doses upto 6 gm daily in divided doses have been used.
- **By slow intravenous Injection**: 50 mg diluted to 20 ml and given over at least two minutes; may be repeated every 6-8 hrs.
- **GERD:** Usual oral doses for treating ulcers and GERD are 150 mg twice daily or 300 mg at bedtime. The maintenance dose is 150 mg daily.

(Opsonin, 2016)

1.5.16 Contraindications

- Hypersensitivity to H2 blocker,
- acute intermittent porphyria,
- rapid intravenous administration owing to rare occurrences of cardiac disease.

(Opsonin, 2016)

1.5.17 Side effects

Ranitidine is well tolerated. Side effects have been reported in <2% of patients taking Ranitidine.

- Headache
- mild gastrointestinal disturbance (e.g. diarrhoea, constipation and nausea)
- rash
- constipation
- nausea
- tiredness and
- dizziness

(Opsonin, 2016)

1.5.18 Use in pregnancy & lactation

Ranitidine should be used in pregnancy only when it is clearly needed. Ranitidine should only be used in nursing mothers if it is considered essential (Opsonin,2016).

1.5.19 Precautions

In renal impairment, Ranitidine should be given in reduced dosage (Opsonin, 2016).

1.5.20 Drug interactions

Table 1.1 : Drugs that interact with Ranitidine.

Name of the drug that interact with Ranitidine	Result of interaction
Warfarin	Ranitidine increased the serum concentration of warfarin when it is co-administered with it.

Verapamil	The combination between Ranitidine and Verapamil can be increased the serum concentration of Ranitidine.
Cefuroxime	Ranitidine can cause a decrease in the absorption of Cefuroxime resulting in a reduced serum concentration and potentially a decrease in efficacy.
Glipizide	The serum concentration of Glipizide can be increased when it is combined with Ranitidine.
Ketoconazole	The serum concentration of Ketoconazole can be decreased when it is combined with Ranitidine.
Nelfinavir	The serum concentration of Nelfinavir can be decreased when it is combined with Ranitidine.
Saquinavir	The serum concentration of Sequinavir is increased due to the combination with Ranitidine.
Tolbutamide	The serum concentration of Tolbutamide can be increased when it is combined with Ranitidine.
Bupropion	The serum concentration of Ranitidine can be increased when it is combined with Bupropion.
Aripiprazole	The serum concentration of Aripiprazole can be increased when it is combined with Ranitidine.

(Drugbank, 2013)

1.5.21 Over dosage

No specific features of overdose have been reported and oral overdose of 18 gm has been reported to be safe (Opsonin, 2016).

1.5.22 Storage

Store in a cool and dry place, protected from light (Opsonin, 2016).

Figure 1.3 : Ranitid® 150 mg tablet

Figure 1.4: Zantac® 150 mg Tablet

1.6 Information of Calbo-500mg

Calbo(500mg) is a product prepared by Square pharmaceuticals and each Calbo(500 mg) tablet contains Calcium Carbonate BP 1.25 gm equivalent to 500mg of calcium (Square Pharmaceuticals Ltd., 2016).

1.6.1 Pharmacology

Calcium carbonate reacts with gastric acid to produce a salt and water.Two grams of calcium carbonate will readily bring 100 ml of hydrochloric acid to a pH above 6. The increase in gastric pH diminishes the activity of pepsin in the gastric secretion. Up to 30% of the oral calcium load may be absorbed (Square Pharmaceuticals Ltd., 2016).

1.6.2 Indication

Calbo®500 (Calcium Carbonate) is used for the treatment or prevention of-

- Calcium depletion in patients in whom dietary measures are inadequate.
- Conditions that may be associated with calcium deficiency include hypoparathyroidism, achlorhydria, chronic diarrhea, vitamin D deficiency, steatorrhea, sprue, pregnancy and lactation, menopause, pancreatitis, renal failure, alkalosis, and hyperphosphataemia.
- Calcium Carbonate is being used increasingly often to treat hyperphosphataemia in chronic renal failure and continuous ambulatory peritoneal dialysis (CAPD) and haemodialysis.
- Calcium carbonate containing preparations can provide short term relief of dyspeptic systems but are no longer recommended for long term treatment of peptic ulceration.

(Square Pharmaceuticals Ltd., 2016)

1.6.3 Dosage and Administration

It is always used orally but in case of antacid the recommended dosage are-

- **For adults**- 540-2000 mg Calcium Carbonate per day.
- **For children**- being half of those for adults.
- **For the prevention of osteoporosis**- 1250-3750 mg Calcium Carbonate (500-1500 mg calcium) daily is recommended in general.

- **In chronic renal failure-** the doses used vary from 2.5 - 9.0 gm Calcium Carbonate per day and need to be adjusted according to the individual patient.
- **In pregnancy and lactation-** the recommended daily dose of calcium is 1200-1500 mg.

For effective maximization of phosphate binding the Calcium Carbonate should be given with meals (Square Pharmaceuticals Ltd., 2016).

1.6.4 Side Effects

Orally administered Calcium Carbonate may causes-

- Irritating to the GI tract.
- Constipation.
- Hypercalcaemia is rarely produced by administration of calcium alone.It may occur when large doses are given to patients with chronic renal failure.

(Square Pharmaceuticals Ltd., 2016)

1.6.5 Contraindication and Precaution

It is contraindicated for the patients with-

- Hypercalcaemia and hyperparathyroidism
- Hypercalciuria and nephrolithiasis
- Zollinger-Ellison syndrome
- Concomitant digoxin therapy (requires careful monitoring of serum calcium level)

Calcium salts should be used cautiously in patients with sarcoidosis, renal or cardiac disease ,and in patients receiving cardiac glycosides (Square Pharmaceuticals Ltd., 2016).

1.6.6 Drug Interaction

If systemic hypercalcaemia occurs then Calcium Carbonate of calbo (500mg) tablet may increase the cardiac effects of –

- digoxin and
- other cardiac glycosides

- interfere with the absorption of concomitantly administered tetracycline preparations

In chronic renal failure modification of vitamin D therapy may be required to avoid hypercalcaemia when Calcium Carbonate is used as the primary phosphate binder (Square Pharmaceuticals Ltd., 2016).

1.6.7 Use in Pregnancy and Lactation

Calcium containing drugs have been widely used in pregnancy by way of oral calcium supplementation or antacid therapy. Calcium Carbonate can be used in lactating women too (Square Pharmaceuticals Ltd., 2016).

1.6.8 Use in Children

Calcium carbonate has been extensively studied in children and infants with chronic renal failure and is both safe and effective (Square Pharmaceuticals Ltd., 2016).

1.6.9 Use in Elderly

In case of elderly patients with renal failure when calcium carbonate is taken constipation may be troublesome one for this group. For this reason, monitoring of serum calcium and phosphate is of course indicated for elderly patients (Square Pharmaceuticals Ltd., 2016).

1.6.10 Storage Condition

Store in a cool , dry place in controlled room temperature (Square Pharmaceuticals Ltd., 2016).

Figure 1.5 : Calbo (500mg) Tablet

1.7 Information of Filwel Silver

1.7.1 Composition

Filwel® Silver : Each tablet contains Vitamin A 3500 IU, Vitamin C 60 mg,Vitamin D 400 IU, Vitamin E 45 IU, Vitamin K 10 mcg, Thiamin 1.5 mg, Riboflavin 1.7 mg, Niacin 20 mg, Vitamin B6 3 mg, Folic acid 400 mcg, Vitamin B12 25 mcg, Biotin 30 mcg, Pantothenic acid 10 mg, Calcium 200 mg, Phosphorous 48 mg, Iodine 150 mcg, Magnesium 100 mg, Zinc 15 mg, Selenium 20 mcg, Copper 2 mg, Manganese 2 mg, Chromium 150 mcg, Molybdenum 75 mcg, Chloride 72 mg,Potassium 80 mg, Boron 150 mcg, Nickel 5 mcg, Silicon 2 mg,Vanadium 10 mcg, Lutein 250mcg, Lycopene 300mcg (Square Pharmaceuticals Ltd., 2016).

1.7.2 Indication

Filwel® Silver is indicated for

- the prevention and treatment of vitamin and mineral deficiencies (adults over 45 years of age.
- Increasing the demands of vitamin and minerals (adults over 45 years of age.)

(Square Pharmaceuticals Ltd., 2016)

1.7.3 Dosage and Administration

One tablet daily with food.It is not formulated for children (Square Pharmaceuticals Ltd., 2016).

1.7.4 Side Effects

This preparation is well tolerated. But occasionally may lead to-

- Diarrhea(when treat with beta carotene)
- Skin discoloration
- Vitamin A lead to reversible side effets
- Diarrhea may cause due to Vitamin C and vitamin E
- Also responsible for other gastrointestinal disturbances.

(Square Pharmaceuticals Ltd., 2016)

1.7.5 Contraindication and Precaution

The product is contraindicated while –

- Patients having hypersensitivity to any of the product ingredients.
- Receiving other vitamin A supplements.

When high levels of vitamin A is administered for longer period of time then it increase the chance of osteoporosis in postmenopausal women (Square Pharmaceuticals Ltd., 2016).

1.7.6 Use in Pregnancy and Lactation

Recommended by the consultation with physician (Square Pharmaceuticals Ltd., 2016).

1.7.7 Drug Indication

No drug interactions have been reported (Square Pharmaceuticals Ltd., 2016).

1.7.8 Storage Condition

Store in a cool and dry place protected from light and moisture. Keep the container tightly closed. Keep out of reach of children (Square Pharmaceuticals Ltd., 2016).

Figure 1.6: Filwel®Silver Tablet

1.8 Information of NUTRUM® GOLD (Multivitamin and Multimineral)

1.8.1. Description

Nutrum Gold tablet is a complete well-balanced multivitamin and multimineral supplement designed for the adult (ACME Laboratories Ltd., 2014).

1.8.2. Composition

Each film-coated tablet contains -

Vitamin A (20% as Beta-Carotene) 5000 IU ,Thiamine 1.5 mg ,Riboflavin 1.7 mg,Pantothenic Acid 10 mg ,Vitamin B6 2 mg ,Vitamin B12 6 mcg ,Vitamin C 60 mg ,Vitamin D 400 IU ,Vitamin E 30 IU ,Vitamin K 25 mcg ,Niacin 20 mg ,Folic Acid 400 mcg ,Lutein 250 mcg, Biotin 30 mcg ,Iodine 150 mcg ,Potassium 80 mg ,Magnesium 100 mg ,Boron 150 mcg Selenium 20 mcg ,Nickel 5 mcg ,Copper 2 mg ,Silicon 2 mg,Manganese 2 mg,Tin 10 mcg ,Calcium 162 mg ,Chromium 120 mcg ,Vanadium 10 mcg ,Iron 18 mg ,Molybdenum 75 mcg Phosphorus 109 mg ,Chloride 72 mg ,Zinc 15 mg (ACME Laboratories Ltd., 2014).

1.8.3. Indications

Nutrum Gold is indicated for adults for treatment & prevention of vitamins and minerals deficiencies (ACME Laboratories Ltd., 2014).

1.8.4. Dosage and Administration

One tablet daily with food or as directed by the physician(ACME Laboratories Ltd., 2014).

1.8.5. Contraindications

This product is contraindicated in patients with known hypersensitivity to any of its ingredients(ACME Laboratories Ltd., 2014).

1.8.6. Precautions

- Vitamin A, in high doses, may be associated with birth defects. Pregnant women and women who may become pregnant should not exceed the recommended doses without medical advice.

- Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose immediately called a doctor.
- Long-term intake of high levels of vitamin A (excluding that sourced from beta-carotene) may increase the risk of osteoporosis in postmenopausal women. Do not take this product if tacking other vitamin A supplements.

(ACME Laboratories Ltd., 2014)

1.8.7. Side Effects

Generally well tolerated. Allergic sensitization has been reported following oral administration of folic acid(ACME Laboratories Ltd., 2014).

1.8.8. Use in Pregnancy and Lactation

As with any supplement, pregnant women or nursing mother should consult with a doctor(ACME Laboratories Ltd., 2014).

1.8.9. Drug Interactions

No drug interactions have been reported (ACME Laboratories Ltd., 2014).

1.8.10. Storage Condition

Store in a cool and dry place protected from light and moisture. Keep the container tightly closed. Keep out of reach of children (ACME Laboratories Ltd., 2014).

Figure1.7: Nutrum Gold

1.9 Information of Acical-M®(Calcium + Vitamin-D + Minerals)

1.9.1. Description

Nutrition is used to treat osteoporosis and other bone related diseases and the use of nutrition is most important strategy. Calcium, magnesium and Vitamin D are the macro nutrients for bone. Vitamin D is important for the absorption of calcium. Like calcium, magnesium increases bone strength and rigidity. Recent epidemiological studies show that some micro nutrients like copper, manganese, zinc and boron play an important role in bone health. Deficiency of the micro nutrients is noticed in patients with osteoporosis (ACI Pharmaceutical Ltd., 2016).

1.9.2. Composition

Acical-M® Tablet: A light orange color, vanilla flavor, oblong film coated tablet, break line on one side & another side engraved with ACI. Each tablet contains Colecalciferol (as vitamin D3) 200 IU, Calcium (as Calcium Carbonate) 600 mg, Copper (as Cupric oxide) 1 mg, Magnesium (as Magnesium Oxide) 40 mg, Manganese (as manganese Sulphate) 1.8 mg, Zinc (as Zinc Oxide) 7.5 mg, Boron (as Boron citrate) 0.25 mg (ACI Pharmaceutical Ltd., 2016).

1.9.3. Indications & Uses

- Prevention and treatment of osteoporosis
- To maintain strong bone growth and teeth
- For proper functioning heart, muscle and nerves
- As nutritional supplement
- For bone development and constant regeneration of bone
- Pregnancy & lactation
- Deficiency state of calcium, vitamin D, magnesium, zinc, copper, manganese & boron

(ACI Pharmaceutical Ltd., 2016)

1.9.4. Dose & Administration

2 tablets per day, preferably 1 tablet in the morning and 1 tablet in the evening (ACI Pharmaceutical Ltd., 2016).

1.9.5. Side effects

The use of calcium supplements has, rarely, given rise to mild gastro-intestinal disturbances, such as constipation, flatulence, nausea, gastric pain, diarrhoea. Following administration of vitamin D supplements occasional skin rash has been reported. Hypercalciuria, and in rare cases hypocalcaemia have been seen with long term treatment at high dosages .Side effects from micronutrient are rare (ACI Pharmaceutical Ltd., 2016).

1.9.6. Precautions

Patients with mild to moderate renal failure or mild hypercalciuria should be supervised carefully. Periodic checks of plasma calcium levels and urinary calcium excretion should be made in patients with mild to moderate renal failure or mild hypercalciura (ACI Pharmaceutical Ltd., 2016).

1.9.7. Pregnancy and Lactation

During pregnancy and lactation treatment should always be under the direction of a physician. During pregnancy and lactation, requirements for calcium and vitamin D are increased but in deciding on the required supplementation allowances should be made for availability of this agents from other sources (ACI Pharmaceutical Ltd., 2016).

1.9.8. Contraindications

It is contraindicated when-

- Hypersensitivity to any of the tablet ingredients.
- Absolutely contraindicated when hypercalcaemia is resulting for example from myeloma, bone metastases or other malignant bone disease, sarcoidosis; primary hyperparathyroidism and vitamin D overdosage.
- Several renal failure .

(ACI Pharmaceutical Ltd., 2016)

1.9.9. Drug interactions

It has possible interaction with-

- Digoxin
- Antacids containing calcium, aluminium or magnesium, other calcium supplements, calcitriol or other vitamin D supplements
- Tetracycline
- Doxycycline, minocycline or oxytetracycline etc.

So before taking any of this drugs with Acical-M® suggestions of the physicians are needed (ACI Pharmaceutical Ltd., 2016).

1.9.10. Overdose

The most serious consequences of acute or chronic overdose is hypercalcaemia (ACI Pharmaceutical Ltd., 2016).

1.9.11. Storage

It should keep in cool place (below 30ºc) and dry place. Keep out of reach of children (ACI Pharmaceutical Ltd., 2016).

Figure 1.8: Acical-M tablet

1.10 Information of Aristocal D (Calcium & Vitamin D Tablet)

Aristocal®D is a combined preparation ofCalcium and Vitamin D (Cholecalciferol) specially designed to promote bone health (Beximco Pharmaceuticals Ltd., 2015).

1.10.1. Indications

It is indicated for-

- Prevention and treatment of osteoporosis.
- For the treatment of hypocalcemic states dietary supplementation.
- Healthy bone formation and maintenance.
- To reduce phosphate absorption from the gut in patients with hyperphosphatemia.
- Treatment of chronic renal failure.

(Beximco Pharmaceuticals Ltd., 2015)

1.10.2. Dosage and Administration

One tablet twice daily with food or as directed by the physician (Beximco Pharmaceuticals Ltd., 2016).

1.10.3. Contraindications

Aristocal®D is contraindicated in patients who have known hypersensitivity to any of the component of the preparation (Beximco Pharmaceuticals Ltd., 2015).

1.10.4. Adverse Reactions

Aristocal®D is well tolerated. But it may lead to gastrointestinal disturbance (Beximco Pharmaceuticals Ltd., 2015).

1.10.5. Drug Interactions

It is contraindicated for-

- The concurrent administration of Thiazide diuretics because it may lead to hypercalcemia.
- The gastrointestinal absorption of calcium due to Bran which ultimately decrease the efficacy of calcium suppliments.
- Calcium salts reduce the absorption of a number of other drugs such as Biphosphonates, Fluoride, some Fluoroquinolones and Tetracyclines.

- Caution should be taken in patients with renal impairment, sarcoidosis,hypercalcemia and hypercalciuria.

(Beximco Pharmaceuticals Ltd., 2015)

1.10.6. Use in Pregnancy & Lactation

Aristocal®D should be used considering the risk benefit retio (Beximco Pharmaceuticals Ltd., 2015).

1.10.7. Storage

Store in a cool and dry place. Keep out of the reace of children (Beximco Pharmaceuticals Ltd., 2015).

Figure 1.9 : Aristocal® D Tablet

Chapter Two

Literature Review

Literature Review

Different types of research work with Ranitidine had completed by researchers before I did. Among those research study some of are mentioned here-

In the year of 1989 an important study was performed with Ranitidine where the aim of the study was to determine the identity, strength and purity of Ranitidine. During the study high performance liquid chromatographic and thin-layer chromatographic analyses of Ranitidine hydrochloride were described. The result of that analysis was ensured the identity, strength and purity of that drug (Evans et al., 1989).

At 1993 another study was conducted where the tablet and injection dosage forms of Ranitidine hydrochloride was determined. During this study the ultraviolet spectrophotometry (UVS) at 313 nm and the visible spectrophotometry (VISS) at 615 nm were used. This determination was done after the reaction with 3-methyl-2-benzothiazolinone hydrazone hydrochloride (MBTH) and ferric chloride.In the range of$_{5.0}$ – 18.0 μg/mL the Beer's law was obeyed. Butthe Beer's law was observed atthe of range 1.44 – 5.76 μg/mL for UVS. Finally, the precision and accuracy of the following two methods were compared (Orsine and Martins, 1993).

The study was performed to develop the rapid assay of Ranitidine hydrochloride in dosage forms and samples from tablet dissolution testing using a HPLC method with photometric detection. This method was helpful to separate Ranitidine from its related compound Ranitidine S-oxide. During analyses a Microsorb-MV C18 column was used and detection was done at 320 nm. The result of that study was the samples from tablet dissolution tests required no preliminary preparation. Assay values by the proposed method were found to agree closely with those obtained using methods in the USP XXII (Lau-Cam, Rahman and Roos, 1994).

An investigation was done on the control of the production cycle of Ranitidine hydrochloride tablets. During this investigation a near-infrared reflectance spectrometric method was applied. The result of this investigation was good for the detection of Ranitidine hydrochloride drug substance,mixtures for tablets, cores and coated tablets (Dreassi et al., 1996).

Ranitidine hydrochloride was determined in pure form and pharmaceutical formulations. During this determination purpose four simple spectrophotometric methods were used. The aim was to observe the application of azine dyes to the determination of Ranitidine hydrochloride.The methods were tested with spectrophotometric reference method and all tests were provided the appreciable results(Sastry et al., 1997) .

The impurities of Ranitidine was determined from the drug substance and various pharmaceutical formulations.The objective of their work was to theOptimisation, validation and application of a capillary electrophoresis method for the determination of Ranitidine hydrochloride and related substances. During this determination researchers used thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC) and capillary electrophoresis (CE) methods.The result of their study wasexplained that an optimised CE method offered better selectivity against TLC and HPLC andin terms of sensitivity and precision its performance was equivalentto that of a HPLC method that was used for a similar purpose (Kelly et al., 1998).

The purity of polymorphic crystalline Ranitidine-HCL as a bulk drug and from a tablet formulation was determined by using a sensitive,rapid,new and simple method. During the study diffuse reflectance infrared Fourier transform (DRIFT) spectroscopy and Artificial Neural Networks (ANNs) were used. The result of that study showed that all components in tablet formulation with reasonable accuracy was successfully quantified and identified by ANN and this method was fast, simple and more selective over the conventional analytical methods (Agatonovic-Kustrin,Tucker and Schmierer, 1999).

A method was developed which was able to assay the two crystalline modifications of Ranitidine-HCl qualitatively and quantitatively. The name of that method was X-ray powder diffract metric method. A conventional mixture design method was used to compare with the ANN approach.The result from ANN was provided a smaller standard deviation and a better precision at lower concentrations and relative error (Agatonovic-Kustrin et al., 1999).

Another research was explained that the variable intra and inter-lab dissolution results of Ranitidine tablets USP. Thepaddle apparatus andthe basket apparatus both were used during the study. To prevent tablets from sticking to the bottom of the dissolution vessel, Paddle apparatus tablet sinkers were used. All tablets showed more rapid and complete dissolution with sinker then tablets without sinkers.Finally, the result was confirmed that the dissolution artifacts for Ranitidine tablets could be reduced by the use of baskets or tablet sinkers (Cappola, 2001).

The polymorphic form of Ranitidine-HCL was determined. This determination was done by the combined application of DRIFTS(diffuse reflectance infrared Fourier transform spectroscopy) and XRPD (X-ray powder diffractometry) method.The experiment was finally showed that the combined method could be used successfully to differentiate between the Ranitidine-HCl polymorphs (Agatonovic-Kustrin et al., 2001).

The Ranitidine hydrochloride residues on various surfaces in the manufacture of pharmaceuticals was described by using a liquid chromatographic method.The study was conducted by high-performance liquid chromatography and 320nm was used for the detection.The study was showed that ,the detection method was validated for the detection or the residues of Ranitidine hydrochloride (Nozal et al., 2001).

A study was designed with Ranitidine hydrochloride where the aim was to compare the dissolution rate ,solubility and phase transition of tautomeric forms of Ranitidine hydrochloride.During the study the composition of two solid forms of Ranitidine hydrochloride was determined by using two peaks of Fourier transform infrared (FTIR) spectra.According to the solubility data Form 2 was more soluble than Form 1. Solution-mediated transformation was very slow and occurs from Form 2 to Form 1 and not the reverse. Grinding technique was found increasing the bulk solid density of the Ranitidine hydrochloride without any risk of solid–solid transformation. Dissolution rate was found to be equally fast for both forms (Mirmehrabia et al.,2004).

In a study Ranitidine, methylparaben (MP) and propylparaben (PP) in oral liquids was simultaneously determined by using an accurate and selective high-performance liquid chromatographic method. UV detection was done at 254 nm.All the parameters

that examined during the study were fulfilled the current recommendations for bioanalytical method validation. So it was found that, the novel gradient HPLC method was applicable for the routine analysis (assays and stability tests) of active compound (Ranitidine) and preservatives (MP and PP) (Kokoletsi, Kafkala and Tsiaganis, 2005).

By using four new methods Ranitidine hydrochloride (RNH) was determined in bulk drug and in formulations. During the study a titrimetric method (method A) and three spectrophotometric methods (method B, C and D) were applied. The proposed methods were applied by the researchers to the analysis of RNH in the tablet and the injection forms, and the results were in agreement with those obtained by the reference method (Basavaiah and Somashekar, 2007).

A study was conducted with Ranitidine syrup where the aim of the study was to determine the stability of that syrup in repackaged unit-dose containers. Stability was measured by observing the pH changes and sample weight. Stability was also assessed by using high-performance liquid chromatography. The result of the study showed that the repackaged Ranitidine syrup was stable (Shah et al., 2008).

A study was performed according to the pharmacopoeia (USP 29) dissolution test with Ranitidine hydrochloride, where the objective of the study was to determine the pharmaceutical equivalence of Zantac® (reference drug) and 10 domestic and foreign generics of Ranitidine hydrochloride as 150-mg coated tablets. An insignificant difference was observed the excipients entering into the compositions of Ranitidine generic tablets registered in Russia. According to the WHO classification, Zantac® and generics of two manufacturers are rapidly soluble.The biological nonequivalence of some generics and the reference drug was observed. So the in vitro dissolution test that recommended by WHO can be used for the determination of bioequivalence of Ranitidine generics (Smekhova, Moldaver and Perova, 2009).

The handling properties of Ranitidine HCL was explored. The aim of that study was to reduce the deliquescent character of Ranitidine which ultimately help to formulate the drug. During their study they used Karl Fischer titration method to determine the moisture content.They were also used Thermo gravimetric analysis and differential thermal analysis (TG - DTA) plots. After their study the result showed that the resonates of Ranitidine have less moisture uptake rate and moisture content than resin

and Ranitidine alone. So this form of Ranitidine can be used to minimize the hygroscopicity of that drug product (Mangesh et al., 2009).

A study was conducted to characterize the solid state and crystal structure of Ranitidine base (RAN-B). Different analytical techniques were used during the study including microscopy, thermal analysis, Fourier transform infrared spectrometry, (13)C-CPMAS-NMR spectroscopy and X-ray powder diffraction. A comparison between the raninitidine HCL and crystal structure of Ranitidine base was also determined .The result of that study was ensured that the polymorphs of RAN-B were monotropic polymorphic pairs (Armas et al., 2009).

A study was conducted with Ranitidine hydrochloride where the purpose was to evaluate the effect of formulation variables on floating lag time, the release properties, and hardness, when developing floating tablets of Ranitidine hydrochloride. The study was done by the statistical optimization technique. The result of that study was encouraged the probability of the model in the development of floating tablets of Ranitidine hydrochloride (Jain et al., 2010).

The pharmaceutical equivalent of different brands of Ranitidine Hydrochloride tablets was evaluated by a study by using some important quality control test such as weight variation test, friability test, hardness test and disintegration test according to the USP. The result was indicated that all the tablets in the three brands were pharmaceutically equivalent (Mullaicharam, Jehangir Ahmed and Halligudi, 2012).

The impact of superdisintegrants incorporation on the immediate release of the tablets final performance was studied.The aim of this study was to select the working method to obtain Ranitidine 150 mg tablets with the desiderate quality and in reproducible conditions.During the study flowing properties of the lubricated product, granules size distribution, hardness, friability ,disintegration, weight uniformity and dissolution of the Ranitidine 150 mg tablets that were prepared by dry granulation technique was studied. The Result of the study showed that in the developed formulations the percent of the Ranitidine dissolution was high,but higher in extragranular incorporation (Postolache and Gafitanu,2012).

The aim of present study was to formulate and evaluate the bilayered tablets containing Diclofenac Sodium in the sustained release (SR) portion and Ranitidine HCl in the immediate release (IR) portion in order to produce a single tablet containing two different classes of drugs. Direct compression method was used to prepare immediate release layer of Ranitidine HCl . This evaluation was done by using USP-XXII paddle type dissolution apparatus. Total four trial batches were manufactured to optimize and develop a robust and stable formulation. The stability study result of the products also complied with ICH guidelines (Shirse, 2012).

This study was carried out with an objective of preparation and in vitro evaluation of floating tablets of hydroxypropyl methyl cellulose and polyethylene oxide that were used in Ranitidine hydrochloride as a model drug. The tablets were prepared by dry granulation method. The effect of sodium bicarbonate and stearic acid on drug release profile and floating properties were also investigated. Sodium bicarbonate and stearic acid in combination showed no significant effect on drug release profile. The formulations having sodium bicarbonate 20 mg per tablet showed desired buoyancy (total floating time of >24 hours and floating lag time of about 2 minutes). The present study showed that polymers like Polyox WSR303 and HPMC K15MCR in combination with sodium bicarbonate as a gas generating agent can be used to develop sustained release floating tablets of Ranitidine hydrochloride (Gharti et al., 2012).

An important study was conducted to determine the solubility of Ranitidine hydrochloride in different mixture at 25ºC.During this experiment the measured data were fitted to the Jouyban–Acree equation and the mean percentage deviations (MPD) for different solvent mixture were calculated (Soleymani et al., 2013).

The pharmaceutical properties of some selected generic products of Ranitidine hydrochloride tablets that were available in retail pharmacies of Bangladesh were evaluated.During the study various parameters including weight,size,shape,diameter,hardness,thickness,weight variation,potency,disintegration and dissolution were determined based on requirements of the American Pharmacopoeia USP 27.The result of that study showed that all the selected products met the required USP specifications and considered as quality products in terms of the mentioned parameters (Azad, Islam and Azizi,2013).

A study was conducted with effervescent Ranitidine hydrochloride tablets where the aim was to formulate, design and evaluate those tablets physicochemically. Fusion and direct compression methods were used to make effervescent Ranitidine hydrochloride tablets. During the study angle of repose, compressibility index, mean particle size and Hausner's ratio were used for the evaluation of pre-compression characteristics. The post-compression features were evaluated by determining the weight variation, hardness, friability, drug content, dissolution time, carbon dioxide content, effervescence time, pH, content uniformity and water content.The result of that study was cleared the fact that the flow ability of fusion method was better than the direct compression. Tablets that were prepared by fusion method were selected as the best formulations due to their physicochemical characteristics (Aslani and Jahangiri,2013).

An important study was conducted where the purpose of the study was to determine the similarity among the different brands of Ranitidine HCl tablets available in local market of Karachi, Pakistan. During this study weight variation test, hardness test, thickness, friability, disintegration test and dissolution test were carried out specified by USP were used. It was found that, all the brands were comply within limits for hardness, weight variation, thickness, friability, disintegration and dissolution.15 minutes was the Disintegration time for all brands that was complying with the USP recommendation (Naveed,Dilshad and Jaweed, 2014).

In a study the dissolution profile of enteric coated Ranitidine (150mg) tablets were determined and compared with reference drug and a generic and a similar drug marketed in Bahia, Brazil for establishing the similarities of pharmaceutical forms .This study was conducted by using a simple, fast and inexpensive ultraviolet method.Experiment was done with USP type 2 apparatus at 50 rpm with 900 ml of distilled water at 37±0.5ºC for 1hr.Based on American Pharmacopoeia (USP-32) the dissolution test was performed. The result of that study showed that,Ranitidine was released satisfactorily from all products and at least 80% of the drug dissolved within 30 minutes (Santos Júnior et al., 2014).

A study was conducted with Ranitidine Hydrochloride where the aim of the study was to improve the moisture stability of that sustained release tablet for getting better therapeutic efficacy. During the study researchers used Pan coating technique for coating of the tablet. Differential scanning calorimetry and Fourier transform infrared spectroscopy study was used for determining the drug and excipient compatibility.The result of their final sustained release drug formulation was contained less moisture thus resulting the desired cumulative drug release (CDR).Better drug release also given by the tablet that was coated by using the combination of 10% Eudragit RLPO and 10% Eudragit EPO. Stability study was shown that the parameter such asfriability, hardness, and dissolution were in the range. Their formulated moisture sensitive drug Ranitidine hydrochloride provided the promising result for the drug release up to 12 hour (Patel et al., 2015).

Four accurate,simple,precise and specifc spectrophotometric methods were developed and validated for the simultaneous determination of Ranitidine Hydrochloride (RT) and Domperidone (DP) in bulk powder as well as in different pharmaceutical formulation.Those methods were- simultaneous ratio subtraction (SRS), ratio subtraction (RS) coupled with zero order spectrophotometry (D^0), the first derivative of the ratio spectra (^1DD) and mean centering of ratio spectra (MCR).The result was showed no significant difference (Abdel-Ghany, Abdel-Aziz and Mohammed, 2015).

The effect of experimental parameters due to removal of Ranitidine (RAN) during ozonation was studied and also identified the formed transformation products (TPs).During this study Hydrophilic Interaction Liquid Chromatography (HILIC) quadrupole time of flight tandem mass spectrometry (Q-ToF-MS/MS) and Reversed Phase (RP) Chromatography were used. The study results indicated the higher reactivity of RAN with molecular aqueous ozone which resulting the most of TPs. The separation and identification of TPs was done by HILIC complementary to RP (Christophoridis et al., 2016).

Chapter Three

Materials

&

Methods

3.1 Materials

3.1.1. Sample collection

To observe the change in dissolution of Ranitidine-HCL with the presence of different supplements- 50 tablets of Ranitid® (150mg),50 tablets of Zantac® (150mg),10 tablets of Calbo (500mg),10 tablets of filwel silver (500mg),10 tablets of Nutrum gold (500mg),10tablets of Acical-M(500mg),10 tablets of Aristocal-D (500mg) were collected from local drug store in Dhaka as a sample.

Table 3.1: Samples used in the experiment and their sources

Sample Name	Source (supplier name)
Ranitid® tablets	Opsonin pharmaceuticals Limited
Zantac® tablets	GlaxoSmithKline Bangladesh Limited
Nutrum Gold tablet	Acme pharmaceuticals Limited
Acical-M®	ACI Pharmaceuticals limited
Filwel® Silver	Square Pharmaceuticals Ltd
Calbo® 500	Square Pharmaceuticals Ltd
Filwel® Gold	Square Pharmaceuticals Ltd

3.1.2.Reagent(s)

Distill water that was prepared in the laboratory of East West University.

3.1.3. Equipment & Instruments

Table 3.2: List of Equipments used in the experiment

Serial No.	Equipment	Source (supplier name)	Origin
1.	UV-spectrophotometer	Shimadazu UV-1800	Japan
2.	Electronic balance	Precise XB120A	Switzerland
3.	Distill water plant	SMIC	China
4.	Dissolution tester	SMIC	China
5.	Vernier caliper	China supplier	Shanghai, china
6.	Hardness tester	Manually operated hardness tester	India

3.1.4 Apparatus:

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

Table 3.3: List of Apparatus

Serial No.	Apparatus
1.	Beaker
2.	Test tubes
3.	Volumetric flasks (25ml , 50ml, 100ml, 1L)
4.	Filter papers
5.	Mortar & pestles
6.	Spatula
7.	Glass Rod
8.	Syringe (5ml ,10ml)
9.	Pipette pumper
10.	Pipette (1ml, 2ml, 10ml)
11.	Glass and plastic funnel

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

Figure 3.1: Dissolution Apparatus

Figure 3.2: UV-1800 Double Beam Spectrophotometer

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

Figure 3.3: Distill Water Propagating apparatus

Figure 3.4: Electronic Balance

Figure 3.5: Vernier caliper

Figure 3.6: Hardness tester

3.2 Methods

3.2.1. Standard curve preparation

3.2.1.1. Preparation of dissolution medium for Standard Curve

Ranitidine is soluble in water. So distilled water was used as dissolution medium to make the standard curve. 500 ml of distilled water was prepared by using the distilled water propagating apparatus of East West University and that water was used to prepare the standard curve.

3.2.1.2. 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-

1. First Zantac® (Ranitidine) tablet was crushed in mortar and pestle.
2. From the crushed tablet 25 mg was taken and then dissolved in 50 ml of distilled water. By this procedure the concentration of the stock solution became 0.5mg/ml or 500 µg/ml.
3. Then the solution was filtered in the volumetric flask.
4. After that the solution was 50 times diluted and the concentration of the solution become 50 µg/ml.

For the preparation of 5 µg/ml,

S_1= 50 µg/ml

S_2= 5 µg/ml

V_2= 10 ml

V_1=?

$V_1 = S_2 * V_2 / S_1$

= 1 ml

This 1 ml stock solution was added with 9 ml of distilled water to obtain 10 ml.

Same calculation was followed for the preparation of 10, 15, 20, 25 µg/ml

For,

10 µg/ml, 2ml stock solution was added with 8 ml of distilled water.

15 µg/ml, 3ml stock solution was added with 7 ml of distilled water.

20 µg/ml, 4 ml stock solution was added with 6ml of distilled water.

25 µg/ml, 5ml stock solution was added with 5 ml of distilled water.

- Then spectrophotometer was 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 3.4 : Concentrations of Ranitidine

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

3.2.2. Preparation for dissolution test

3.2.2.1. Preparation of dissolution medium

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

3.2.2.2. Method for dissolution test of Zantac® (Ranitidine) or Ranitid® (Ranitidine)

1. 6L (6000ml) of distilled water (dissolution medium) was prepared.
2. Each vessel of dissolution tester was filled with 900 ml of distilled water.
3. Time 1 hour, rpm 50 was set up in the dissolution machine.
4. Then the machine was allowed to warm up until it reached at 37.5 degree C.
5. Then 1 Zantac® or Ranitid® tablet was placed in every vessel.
6. 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.
7. At last UV absorbance off the solutions were taken where the wave length was 314nm.

3.2.2.3. Method for dissolution test of Zantac® (Ranitidine) or Ranitid® (Ranitidine) With Calbo (Calcium supplement)

1. 6L (6000ml) of distilled water was prepared.
2. Each vessel of dissolution tester was filled with 900 ml of distilled water.
3. Time 1 hour, rpm 50 was set up in the dissolution machine.
4. Then the machine was allowed to warm up until it reached at 37.5 degree C.
5. Then 1 Zantac® or Rantid tablet and 1 Calbo was placed in every vessel.
6. 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.
7. At last UV absorbance off the solutions were taken where the wave length was 314nm.

Same procedure was followed for the dissolution study of Zantac® or Rantid with Aristocal D, Acical M, Nutrum Gold and Filwel Silver.

3.2.3. Determination of physical parameters

3.2.3.1. Weight Variation Test

Procedure

1. 10 tablets were taken and weighed.
2. The average was taken and it was considered as the standard weight of an individual tablet.
3. 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 3.5 : 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%

Equation:

Following equation was used to determine % weight variation of tablets

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

Where,

Initial Weight of Tablet, I (gm)

Average weight of Tablets, A (gm)

3.2.3.2. Thickness test

Procedure-

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

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

3.2.3.3. Hardness test

Procedure-

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

Chapter Four

Results & Discussion

4.1 RESULTS

4.1.1. Standard curve preparation

Table 4.1 : Concentration and Absorbance for Standard curve of Ranitidine (Zantac®).

Serial No.	Concentration(µg/ml)	Absorbance
1	0	0
2	5	0.247
3	10	0.471
4	15	0.698
5	20	0.937
6	25	1.132

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). We use this equation to get the concentration from different samples absorbance of Ranitidine.

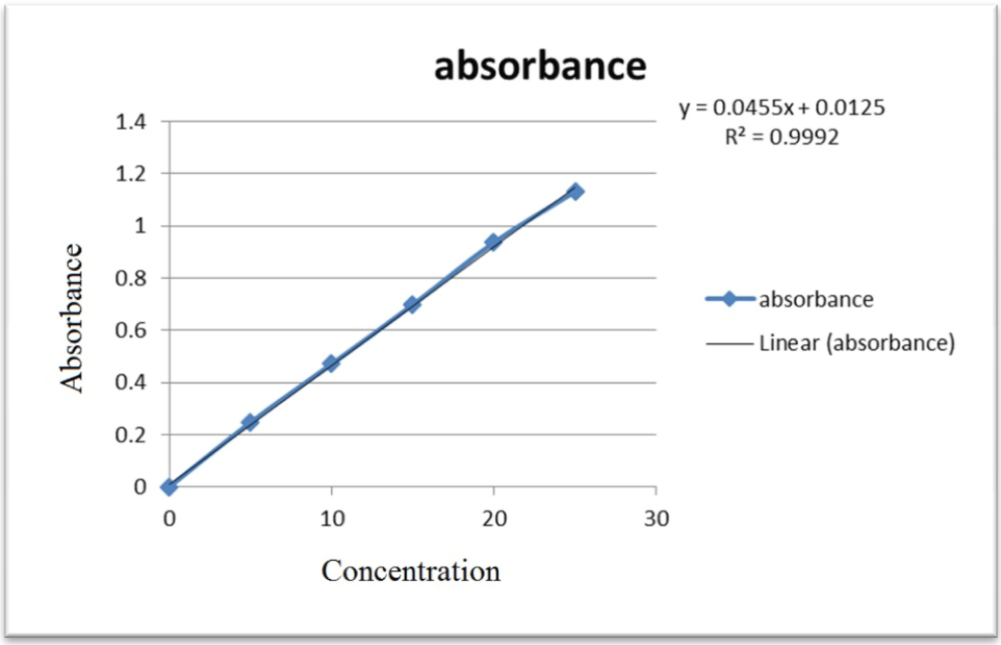

Figure 4.1: Graph showing straight line for absorbance with respect to concentration for Ranitidine.

4.1.2 Results of the dissolution test of individual Zantac®, Zantac® with different supplement drugs and the impact of supplements on the dissolution of Zantac® after 20minute, 40minute and 60 minute.

4.1.2.1. Dissolution test of Zantac® (Ranitidine) without any supplement

Table 4.2 : UV absorbance of only Zantac® (Ranitidine) 150mg tablets.

	Absorbance		
Serial number	After 20 minutes	After 40 minutes	After 60 minutes
1	0.564	0.653	0.603
2	0.415	0.605	0.694
3	0.486	0.707	0.761
4	0.424	0.659	0.744
5	0.439	0.643	0.753
6	0.438	0.651	0.751

Calculation of dissolved amount for Zantac® (Ranitidine)

From the standard curve an equation was found which was, Y= 0.045x+0.012

Here, Y= Absorbance

X=concentration=?

Dilution factor=9000

When the absorbance was 0.564, the following equation can be written as-

0.564=0.045x + 0.012

0.045X=0.564-0.012

0.045x=0.552

X=0.552/0.045

X=12.27

So, Dissolve amount of Zantac® (Ranitidine) was =12.27*9000/1000=110.40mg

By putting the other absorbance values in the same equation different dissolved amounts of Zantac® (Ranitidine) was calculated.

Table 4.3 : Determination of Dissolved amount of Zantac® (Ranitidine) without any supplement.

	After 20 minutes		After 40 minutes		After 60 minutes	
Serial number	**Absorbance**	**Dissolved amount (mg)**	**Absorbance**	**Dissolved amount (mg)**	**Absorbance**	**Dissolved amount (mg)**
1	0.564	110.40	0.653	128.20	0.603	118.20
2	0.415	80.60	0.605	118.60	0.694	136.40
3	0.486	94.80	0.707	139.00	0.761	149.80
4	0.424	82.40	0.659	129.40	0.744	146.40
5	0.439	85.40	0.643	126.20	0.753	148.20
6	0.438	85.20	0.651	127.80	0.751	147.80

4.1.2.2. Dissolution test of Zantac® (Ranitidine) with Calbo (Calcium supplement)

Table 4.4 : UV absorbance of Zantac® (Ranitidine) with Calbo 500 (Calcium suppliment.

	Absorbance		
Serial number	**After 20 minutes**	**After 40 minutes**	**After 60 minutes**
1	0.314	0.331	0.367
2	0.211	0.346	0.372
3	0.206	0.35	0.414
4	0.236	0.361	0.421
5	0.313	0.329	0.33
6	0.268	0.319	0.321

Calculation for dissolved amount (mg) of Zantac® (Ranitidine) with Calbo (Calcium supplement) .

By using, Y= 0.045x+0.012 equation dissolved amount of Zantac® (Ranitidine) with Calbo (Calcium supplement) was calculated.

Table 4.5 : Determination of Dissolved amount of Zantac® (Ranitidine) with Calbo 500 (Calcium supplement).

	After 20 minutes		After 40 minutes		After 60 minutes	
Serial number	**Absorbance**	**Dissolved amount (mg)**	**Absorbance**	**Dissolved amount (mg)**	**Absorbance**	**Dissolved amount (mg)**
1	0.314	60.40	0.331	63.80	0.367	71.00
2	0.211	39.80	0.346	66.80	0.372	72.00
3	0.206	38.80	0.35	67.60	0.414	80.40
4	0.236	44.80	0.361	69.80	0.421	81.80
5	0.313	60.20	0.329	63.40	0.33	63.60
6	0.268	51.20	0.319	61.40	0.321	61.80

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4.1.2.2.1 Impact of Calbo 500 on the dissolution of Zantac® after 20 minutes.

Table 4.6 : Percentage calculation for dissolved amount of Zantac® (Ranitidine), Zantac® (Ranitidine) with Calbo 500 (Calcium supplement) and the impact of Calbo on the dissolution of Zantac® after 20 minutes.

Zantac® without any supplement				Zantac® with Calbo				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
110.40		73.60		60.40		40.27		
80.60		53.73		39.80		26.53		
94.80	89.80	63.20	59.87	38.80	49.20	25.87	32.80	-45.21
82.40		54.93		44.80		29.87		
85.40		56.93		60.20		40.13		
85.20		56.80		51.20		34.13		

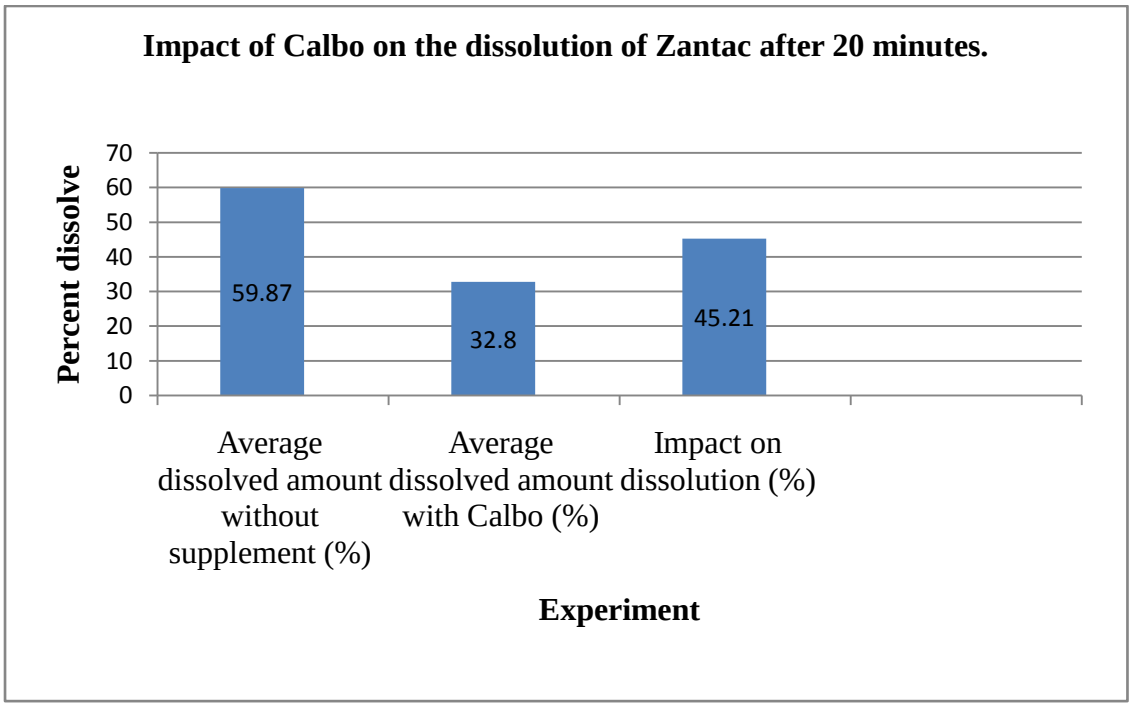

Figure 4.2 : Graphical representation of Calbo 500 on the dissolution of Zantac® after 20 minutes.

4.1.2.2.2 Impact of Calbo 500 on the dissolution of Zantac® after 40 minutes.

Table 4.7 : Percentage calculation for dissolved amount of Zantac® (Ranitidine), Zantac® (Ranitidine) with Calbo (Calcium supplement) and the impact of Calbo on the dissolution of Zantac® after 40 minutes.

Zantac® without any supplement				Zantac® with Calbo				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
128.20		85.47		63.80		42.53		
118.60		79.07		66.80		44.53		
139.00	128.20	92.67	85.47	67.60	65.47	45.07	43.64	-48.94
129.40		86.27		69.80		46.53		
126.20		84.13		63.40		42.27		
127.80		85.20		61.40		40.93		

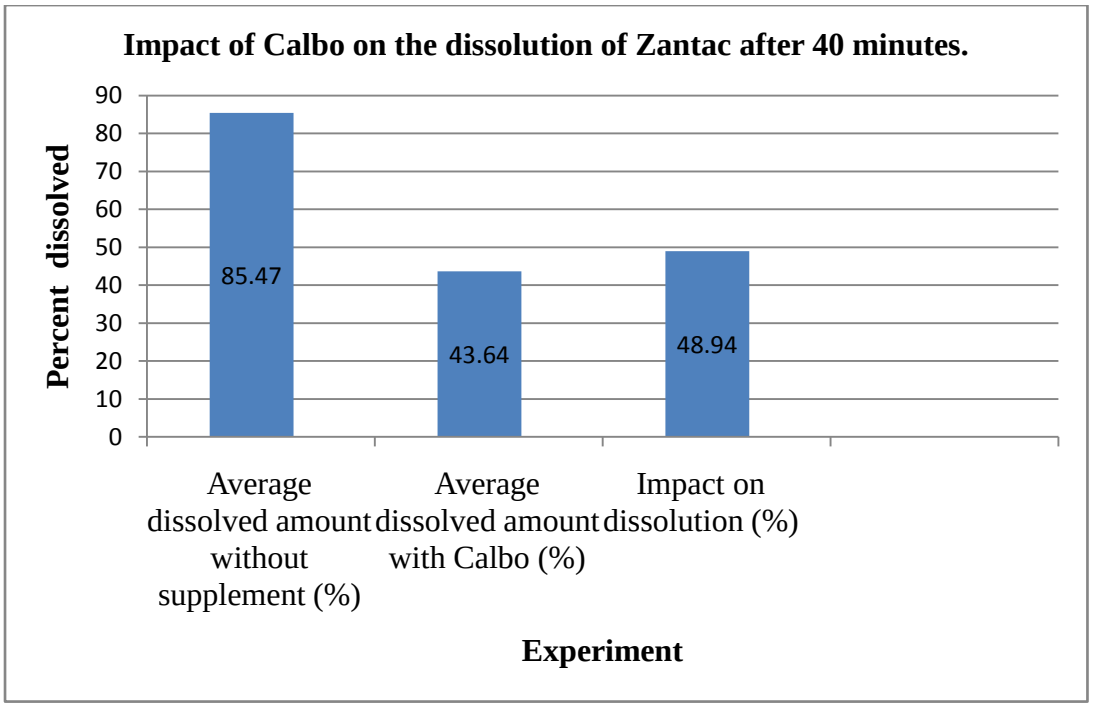

Figure 4.3 **:** Graphical representation of Calbo 500 on the dissolution of Zantac® after 40 minutes.

4.1.2.2.3 Impact of Calbo 500 on the dissolution of Zantac® after 60 minutes.

Table 4.8 : Percentage calculation for dissolved amount of Zantac® (Ranitidine), Zantac® (Ranitidine) with Calbo 500 (Calcium supplement) and the impact of Calbo on the dissolution of Zantac® after 60 minutes.

Zantac® without any supplement				Zantac® with Calbo				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
118.20		78.80		71.00		47.33		
136.40		90.93		72.00		48.00		
149.80	141.13	99.87	94.09	80.40	71.77	53.60	47.84	-49.87
146.40		97.60		81.80		54.53		
148.20		98.80		63.60		42.40		
147.80		98.53		61.80		41.20		

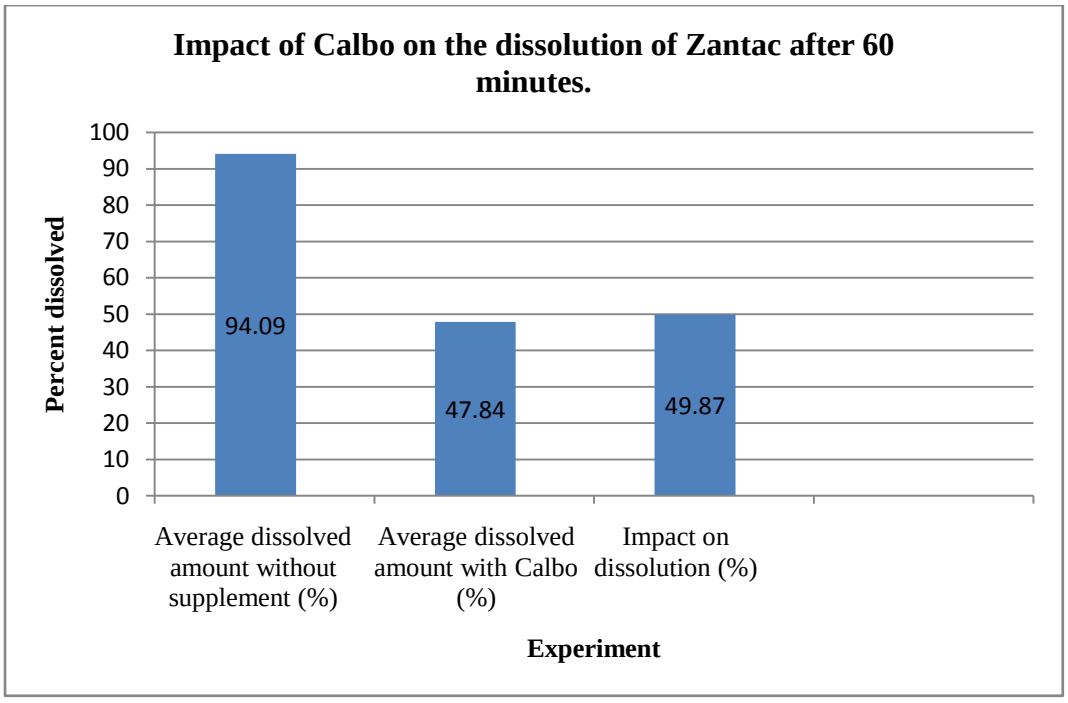

***Figure 4.4* :** Graphical representation of the impact of Calbo 500 on the dissolution of Zantac® after 60 minutes.

4.1.2.3. Dissolution test of Zantac® (Ranitidine) with Aristocal D (Calcium and vitamin D supplement):

Table 4.9 : UV absorbance of Zantac® (Ranitidine) with Aristocal D (Calcium and vitamin D supplement.

	Absorbance		
Serial number	After 20 minutes	After 40 minutes	After 60 minutes
1	0.315	0.506	0.509
2	0.370	0.498	0.566
3	0.476	0.581	0.606
4	0.359	0.485	0.528
5	0.390	0.487	0.599
6	0.321	0.468	0.531

Calculation for dissolved amount (mg) of Zantac®(Ranitidine) with Aristocal D (Calcium and vitamin D supplement.

By using, Y= 0.045x+0.012 equation dissolved amount of Zantac® (Ranitidine) with Aristocal D (Calcium and vitamin D supplement) was calculated.

Table 4.10 : Determination of Dissolved amount of Zantac® (Ranitidine) with Aristocal D (Calcium and vitamin D supplement).

	After 20 minutes		After 40 minutes		After 60 minutes	
Serial number	Absorbance	Dissolved amount (mg)	Absorbance	Dissolved amount (mg)	Absorbance	Dissolved amount (mg)
1	0.315	60.60	0.506	98.80	0.509	99.40
2	0.370	71.60	0.498	97.20	0.566	110.80
3	0.476	92.80	0.581	113.80	0.606	118.80
4	0.359	69.40	0.485	94.60	0.528	103.20
5	0.390	75.60	0.487	95.00	0.599	117.40
6	0.321	61.80	0.468	91.20	0.531	103.80

4.1.2.3.1 Impact of Aristocal D on the dissolution of Zantac® after 20 minutes.

Table 4.11 : Percentage calculation for dissolved amount of Zantac® (Ranitidine), Zantac®(Ranitidine) with Aristocal D (Calcium and vitamin D supplement) and the impact of Aristocal D on the dissolution of Zantac® after 20 minutes.

Zantac® without any supplement				Zantac® with Aristocal D				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
110.40		73.60		60.60		40.40		
80.60		53.73		71.60		47.73		
94.80	89.80	63.20	59.87	92.80	71.97	61.87	47.98	- 19.86
82.40		54.93		69.40		46.27		
85.40		56.93		75.60		50.40		
85.20		56.80		61.80		41.20		

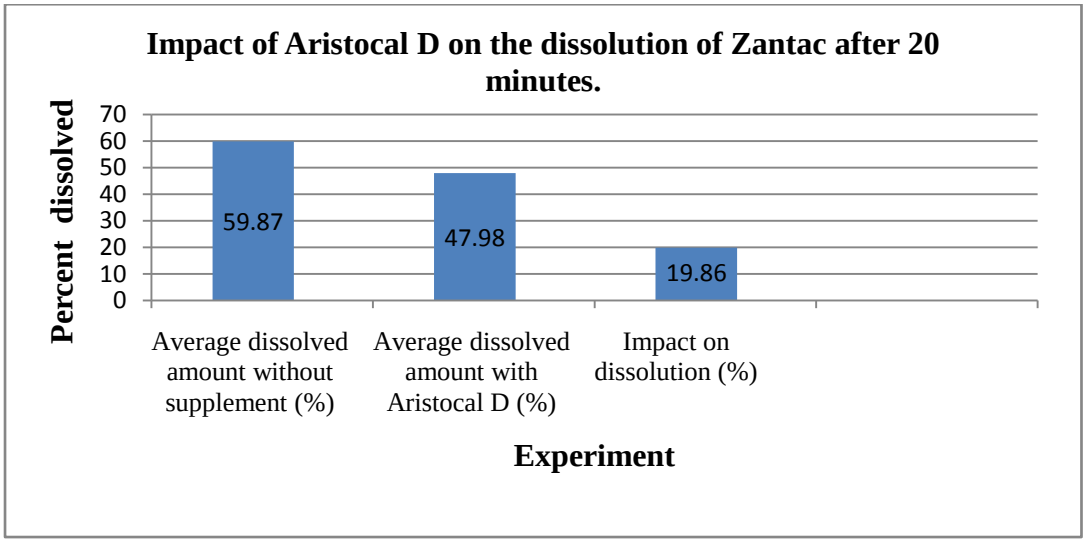

***Figure 4.5* :** Graphical representation of the impact of Aristocal D on the dissolution of Zantac® after 20 minutes.

4.1.2.3.2 Impact of Aristocal D on the dissolution of Zantac® after 40 minutes.

Table 4.12 : Percentage calculation for dissolved amount of Zantac® (Ranitidine), Zantac®(Ranitidine) with Aristocal D (Calcium and vitamin D supplement) and the impact of Aristocal D on the dissolution of Zantac® after 40 minutes.

Zantac® without any supplement				Zantac® with Aristocal D				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
128.20		85.47		98.80		65.87		
118.60		79.07		97.20		64.80		
139.00	128.20	92.67	85.47	113.80	98.43	75.87	65.62	-23.22
129.40		86.27		94.60		63.07		
126.20		84.13		95.00		63.33		
127.80		85.20		91.20		60.80		

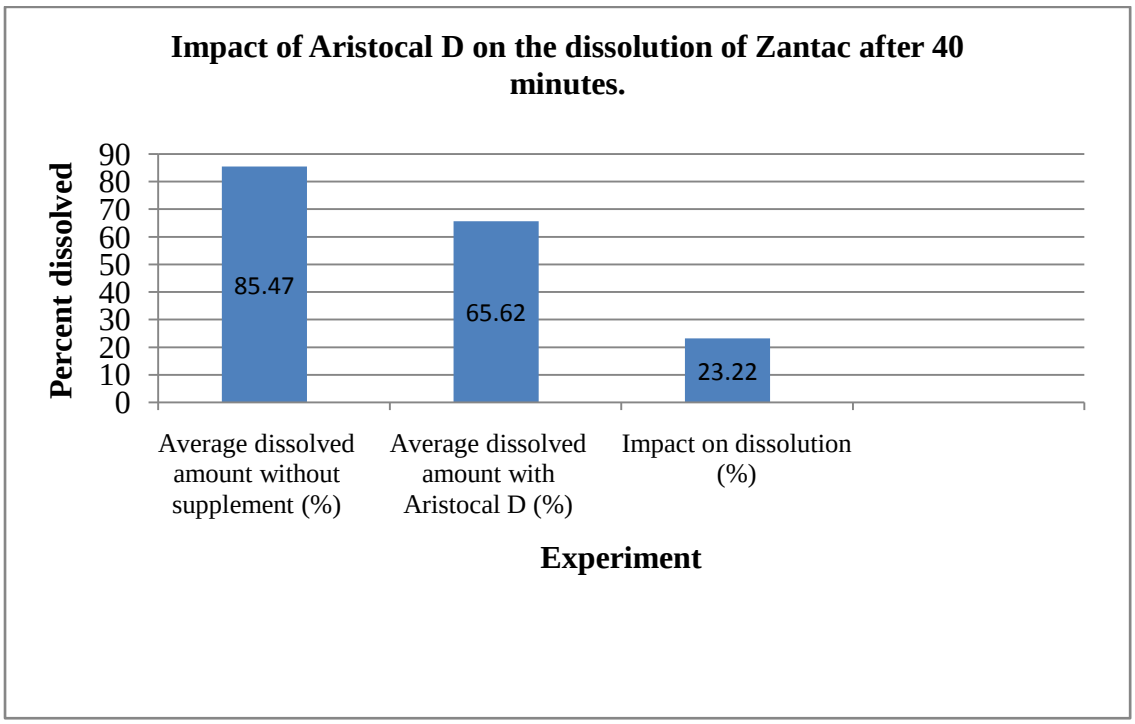

Figure 4.6 : Graphical representation of the impact of Aristocal D on the dissolution of Zantac® after 40 minutes.

4.1.2.3.3 Impact of Aristocal D on the dissolution of Zantac® after 60 minutes.

Table 4.13 : Percentage calculation for dissolved amount of Zantac® (Ranitidine), Zantac®(Ranitidine) with Aristocal D (Calcium and vitamin D supplement) and the impact of Aristocal D on the dissolution of Zantac® after 60 minutes.

Zantac® without any supplement				Zantac® with Aristocal D				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
118.20		78.80		99.40		66.27		
136.40		90.93		110.80		73.87		
149.80	141.13	99.87	94.09	118.80	108.90	79.20	72.60	-22.83
146.40		97.60		103.20		68.80		
148.20		98.80		117.40		78.27		
147.80		98.53		103.80		69.20		

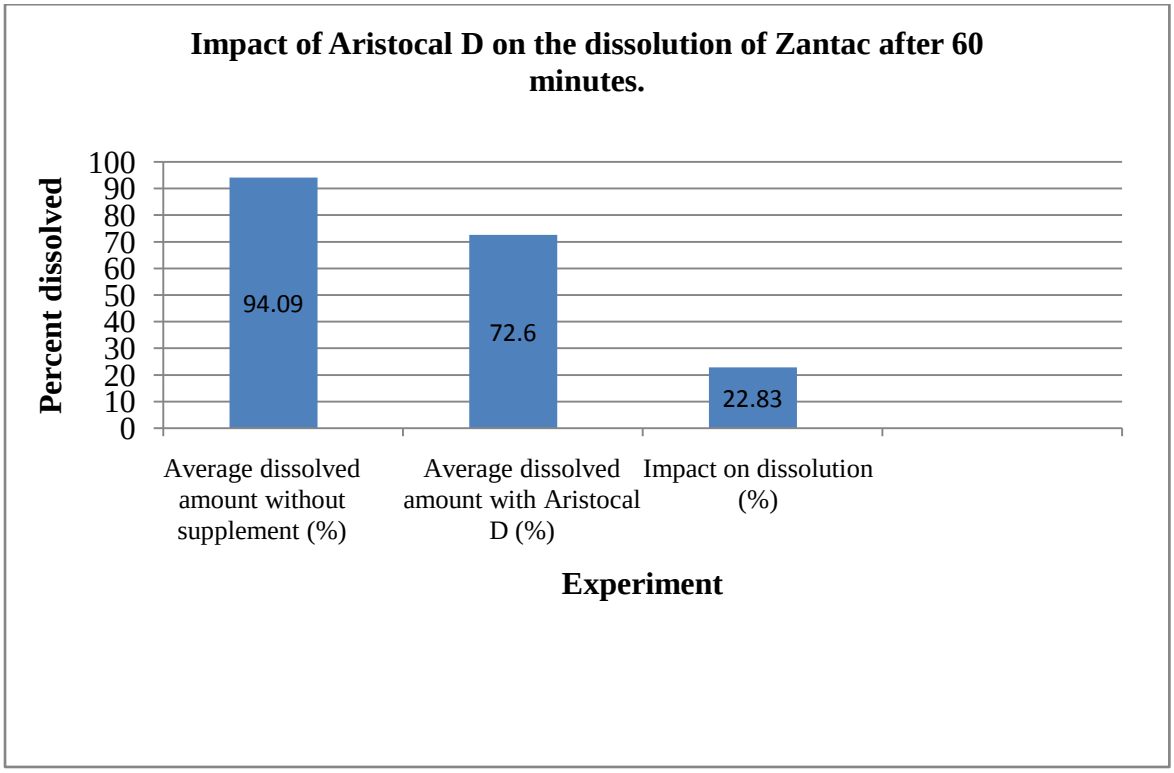

Figure 4.7 **:** Graphical representation of the impact of Aristocal D on the dissolution of Zantac® after 60 minutes.

4.1.2.4.Dissolution test of Zantac® (Ranitidine) with Acical M (Calcium, vitamin D and multimineral supplement).

Table 4.14 : UV absorbance of Zantac® (Ranitidine) with Acical M (Calcium, vitamin D and multimineral supplement).

	Absorbance		
Serial number	**After 20 minutes**	**After 40 minutes**	**After 60 minutes**
1	0.145	0.237	0.327
2	0.217	0.316	0.413
3	0.316	0.325	0.347
4	0.266	0.398	0.401
5	0.253	0.321	0.353
6	0.322	0.406	0.412

Calculation for dissolved amount (mg) Zantac® (Ranitidine) with Acical M (Calcium, vitamin D and multimineral supplement).

By using, Y= 0.045x+0.012 equation dissolved amount of Zantac® (Ranitidine) with Acical M (Calcium, vitamin D and multimineral supplement) was calculated.

Table 4.15 : Determination of Dissolved amount of Zantac® (Ranitidine) with Acical M (Calcium, vitamin D and multimineral supplement).

	After 20 minutes		After 40 minutes		After 60 minutes	
Serial number	**Absorbance**	**Dissolved amount (mg)**	**Absorbance**	**Dissolved amount (mg)**	**Absorbance**	**Dissolved amount (mg)**
1	0.145	26.60	0.237	45.00	0.327	63.00
2	0.217	41.00	0.316	60.80	0.413	80.20
3	0.316	60.80	0.325	62.60	0.347	67.00
4	0.366	50.80	0.398	77.20	0.401	77.80
5	0.253	48.20	0.321	61.80	0.353	68.20
6	0.322	62.00	0.406	78.80	0.412	80.00

4.1.2.4.1 Impact of Acical M on the dissolution of Zantac® after 20 minutes.

Table 4.16 : Percentage calculation for dissolved amount of Zantac® (Ranitidine), Zantac® (Ranitidine) with Acical M (Calcium, vitamin D and multimineral supplement) and the impact of Acical M on the dissolution of Zantac® after 20 minutes.

Zantac® without any supplement				Zantac® with Acical M				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
110.40		73.60		26.60		17.73		
80.60		53.73		41.00		27.33		
94.80	89.80	63.20	59.87	60.80	48.23	40.53	32.16	-46.28
82.40		54.93		50.80		33.87		
85.40		56.93		48.20		32.13		
85.20		56.80		62.00		41.33		

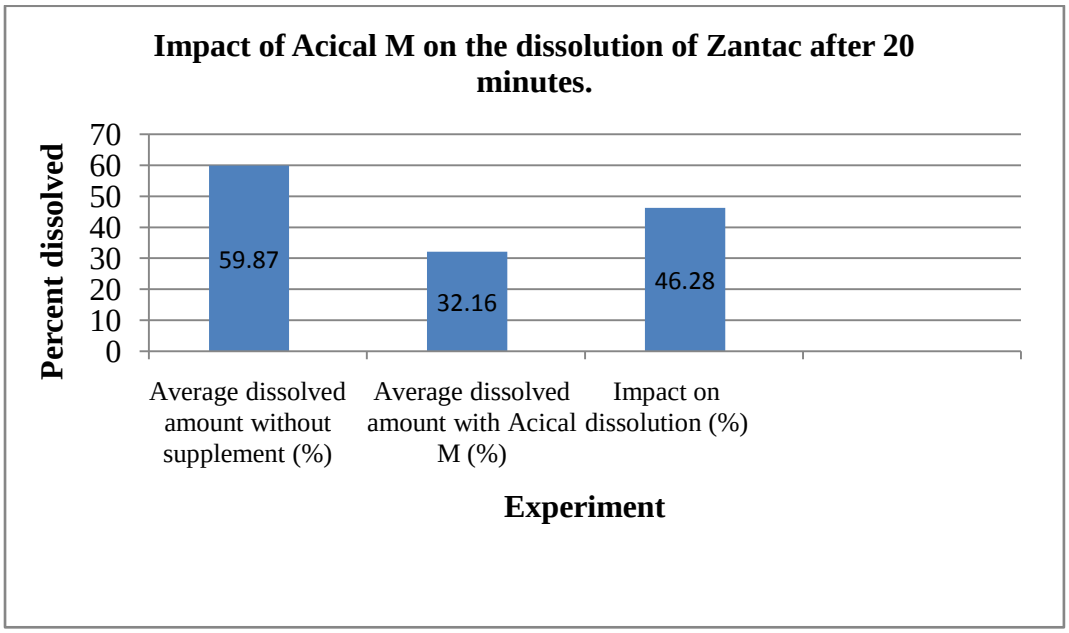

Figure 4.8 **:** Graphical representation of the impact of Acical M on the dissolution of Zantac® after 20 minutes.

4.1.2.4.2 Impact of Acical M on the dissolution of Zantac® after 40 minutes.

Table 4.17 : Percentage calculation for dissolved amount of Zantac® (Ranitidine), Zantac® (Ranitidine) with Acical M (Calcium, vitamin D and multimineral supplement) and the impact of Acical M on the dissolution of Zantac® after 40 minutes.

Zantac® without any supplement				Zantac® with Acical M				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
128.20		85.47		45.00		30.00		
118.60		79.07		60.80		40.53		
139.00	128.20	92.67	85.47	62.60	64.37	41.73	42.91	-49.80
129.40		86.27		77.20		51.47		
126.20		84.13		61.80		41.20		
127.80		85.20		78.80		52.53		

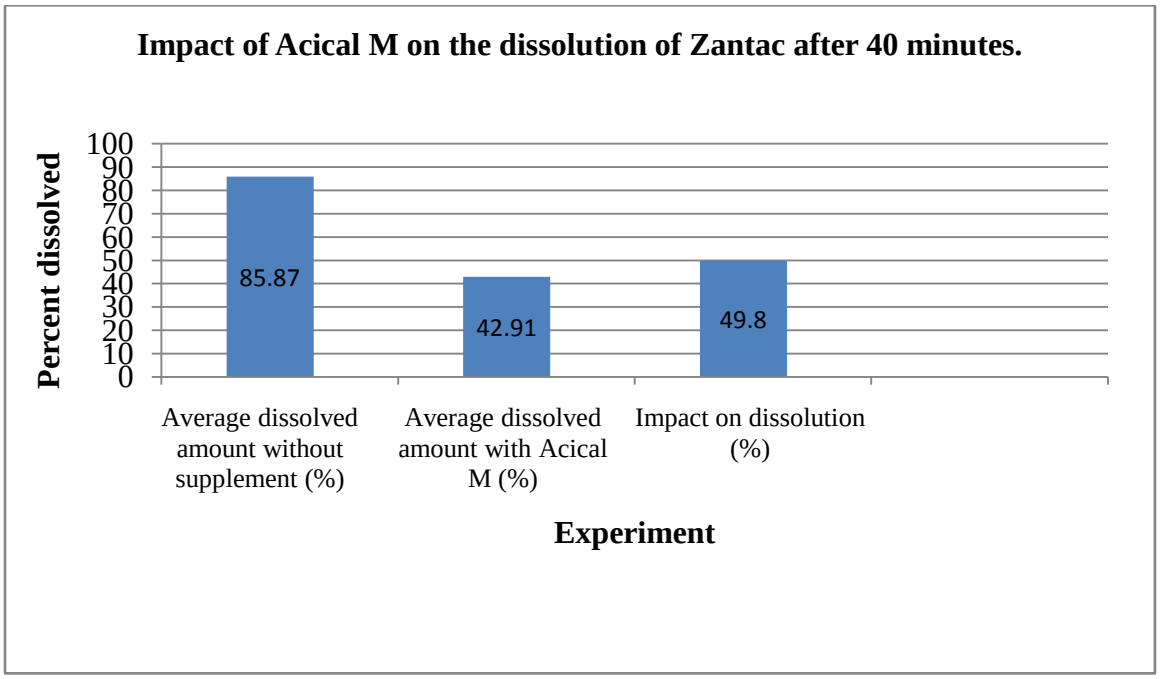

Figure 4.9 **:** Graphical representation of the impact of Acical M on the dissolution of Zantac® after 40 minutes.

4.1.2.4.3 Impact of Acical M on the dissolution of Zantac® after 60 minutes.

Table 4.18 : Percentage calculation for dissolved amount of Zantac® (Ranitidine), Zantac® (Ranitidine) with Acical M (Calcium, vitamin D and multimineral supplement) and the impact of Acical M on the dissolution of Zantac® after 60 minutes.

Zantac® without any supplement				Zantac® with Acical M				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
118.20		78.80		63.00		42.00		
136.40		90.93		80.20		53.47		
149.80	141.13	99.87	94.09	67.00	72.70	44.67	48.47	-48.49
146.40		97.60		77.80		51.87		
148.20		98.80		68.20		45.47		
147.80		98.53		80.00		53.33		

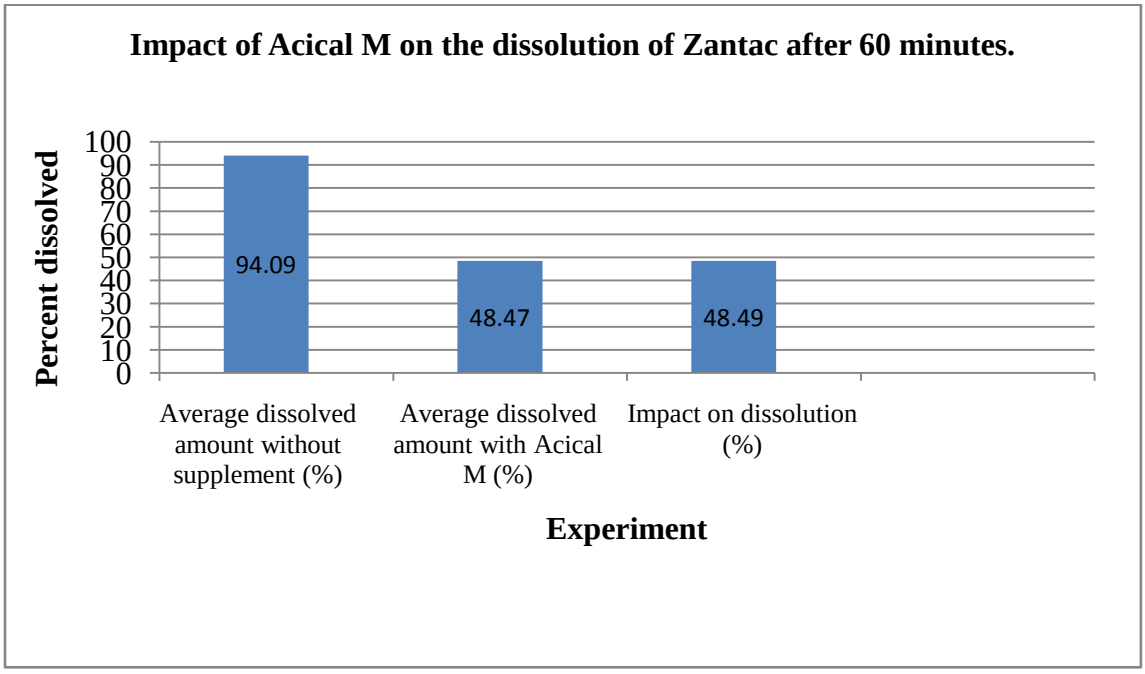

Figure 4.10 **:** Graphical representation of the impact of Acical M on the dissolution of Zantac® after 60 minutes.

4.1.2.5.Dissolution test of Zantac® (Ranitidine) with Nutrum Gold (Multivitamin and multimineral supplement).

Table 4.19 : UV absorbance of Zantac® (Ranitidine) with Nutrum Gold (Multivitamin and multimineral supplement).

	Absorbance		
Serial number	**After 20 minutes**	**After 40 minutes**	**After 60 minutes**
1	0.352	0.589	0.654
2	0.387	0.577	0.712
3	0.366	0.509	0.679
4	0.321	0.615	0.764
5	0.639	0.822	0.738
6	0.654	0.815	0.767

Calculation for dissolved amount (mg) Zantac®(Ranitidine) with Nutrum Gold (Multivitamin and multimineral supplement).

By using, Y= 0.045x+0.012 equation dissolved amount of Zantac® (Ranitidine) with Nutrum Gold (Multivitamin and multimineral supplement) was calculated.

Table 4.20 : Determination of Dissolved amount of Zantac®(Ranitidine) with Nutrum Gold (Multivitamin and multimineral supplement).

	After 20 minutes		After 40 minutes		After 60 minutes	
Serial number	**Absorbance**	**Dissolved amount (mg)**	**Absorbance**	**Dissolved amount (mg)**	**Absorbance**	**Dissolved amount (mg)**
1	0.352	68.00	0.589	115.40	0.654	128.40
2	0.387	75.00	0.577	113.00	0.712	140.00
3	0.366	70.80	0.509	99.40	0.679	133.40
4	0.321	61.80	0.615	120.60	0.764	150.40
5	0.639	125.40	0.822	162.00	0.738	145.20
6	0.654	128.40	0.815	160.60	0.767	151.00

4.1.2.5.1 Impact of Nutrum Gold on the dissolution of Zantac® after 20 minutes.

Table 4.21 : Percentage calculation for dissolved amount of Zantac® (Ranitidine), Zantac® (Ranitidine) with Nutrum Gold (Multivitamin and multimineral supplement) and the impact of Nutrum Gold on the dissolution of Zantac® after 20 minutes.

Zantac® without any supplement				Zantac® with Nutrum Gold				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
110.40		73.60		68.00		45.33		
80.60		53.73		75.00		50.00		
94.80	89.80	63.20	59.87	70.80	88.23	47.20	58.82	1.75
82.40		54.93		61.80		41.20		
85.40		56.93		125.40		83.60		
85.20		56.80		128.40		85.60		

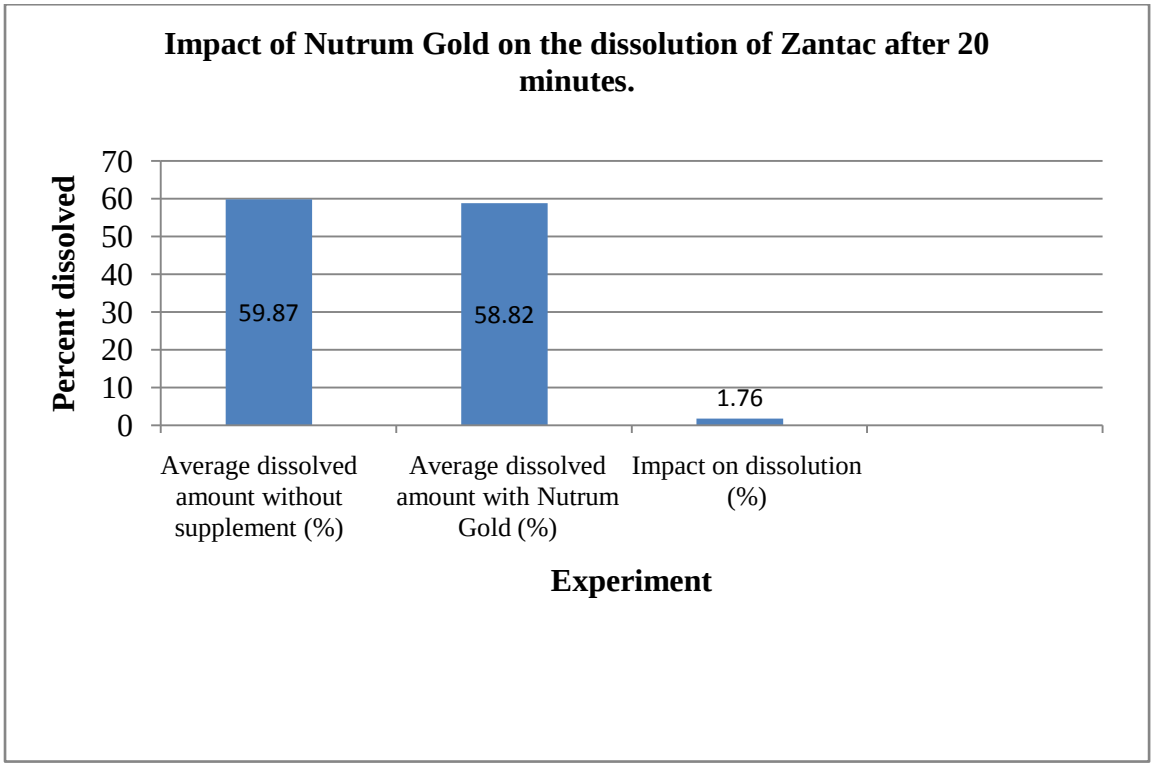

Figure 4.11 **:** Graphical representation of the impact of Nutrum Gold on the dissolution of Zantac® after 20 minutes.

4.1.2.5.2 Impact of Nutrum Gold on the dissolution of Zantac® after 40 minutes.

Table 4.22 : Percentage calculation for dissolved amount of Zantac® (Ranitidine), Zantac® (Ranitidine) with Nutrum Gold (Multivitamin and multimineral supplement) and the impact of Nutrum Gold on the dissolution of Zantac® after 40 minutes.

Zantac® without any supplement				Zantac® with Nutrum Gold				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
128.20		85.47		115.40		76.93		
118.60		79.07		113.00		75.33		
139.00	128.20	92.67	85.47	99.40	128.50	66.27	85.67	0.23
129.40		86.27		120.60		80.40		
126.20		84.13		162.00		108.00		
127.80		85.20		160.60		107.07		

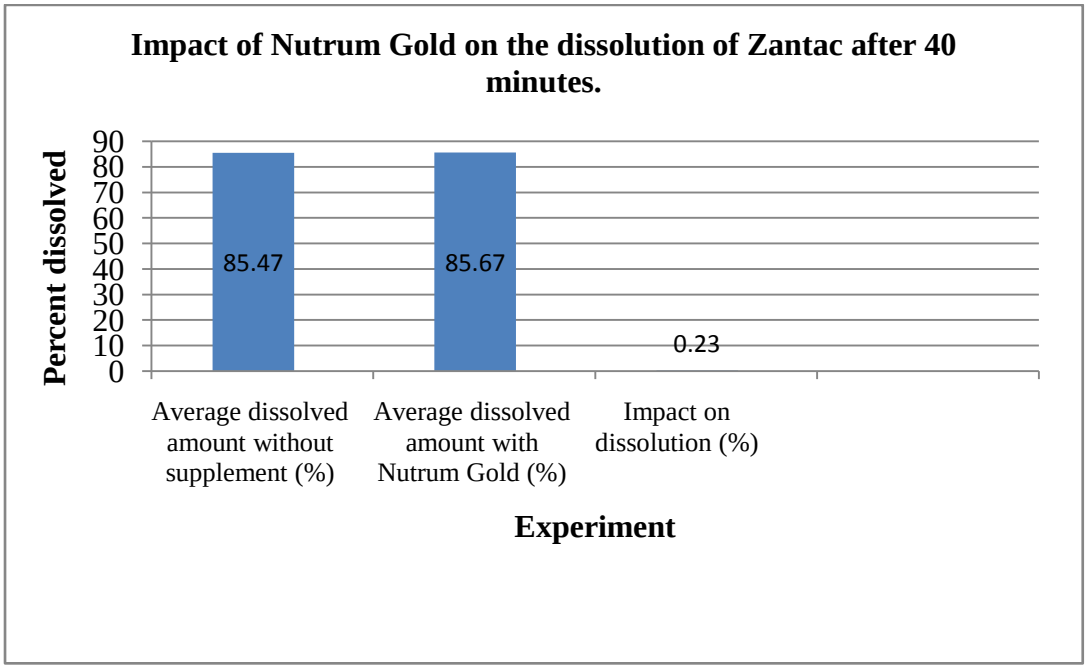

Figure 4.12 **:** Graphical representation of the impact of Nutrum Gold on the dissolution of Zantac® after 40 minutes.

4.1.2.5.3 Impact of Nutrum Gold on the dissolution of Zantac® after 60 minutes.

Table 4.23 : Percentage calculation for dissolved amount of Zantac® (Ranitidine), Zantac® (Ranitidine) with Nutrum Gold (Multivitamin and multimineral supplement) and the impact of Nutrum Gold on the dissolution of Zantac® after 60 minutes.

Zantac® without any supplement				Zantac® with Nutrum Gold				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
118.20		78.80		128.40		85.60		
136.40		90.93		140.00		93.33		
149.80	141.13	99.87	94.09	133.40	141.40	88.93	94.27	0.19
146.40		97.60		150.40		100.27		
148.20		98.80		145.20		96.80		
147.80		98.53		151.00		100.67		

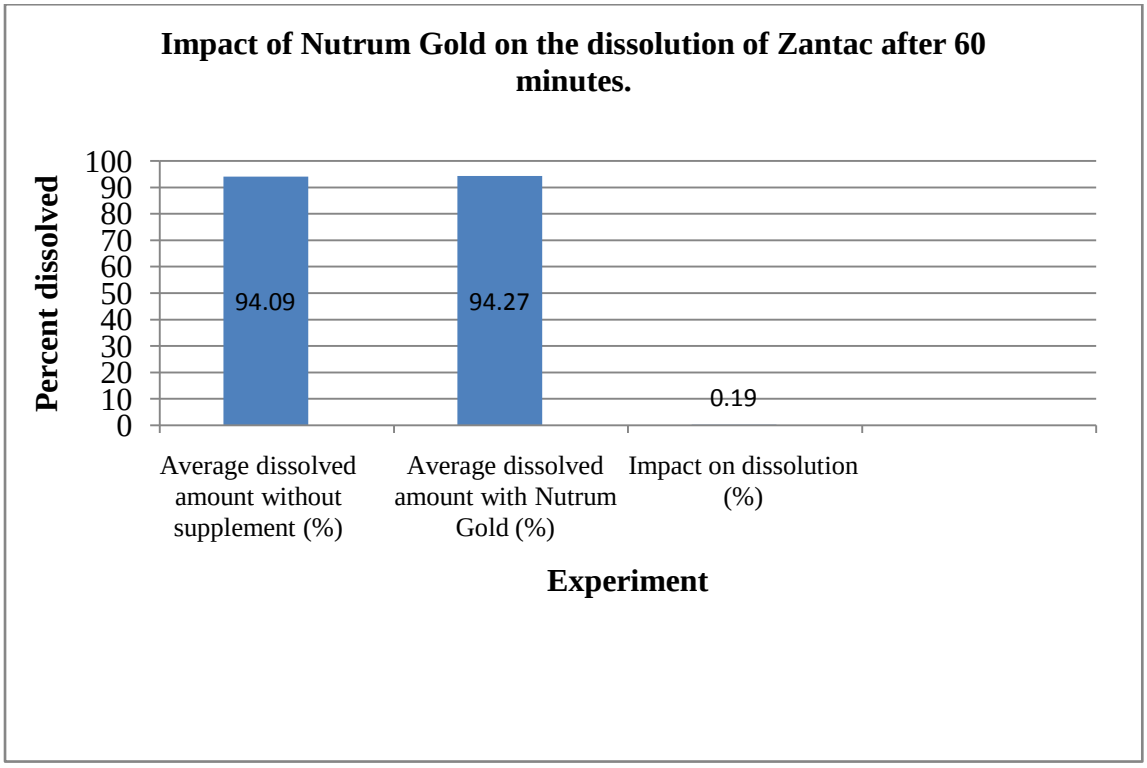

Figure 4.13 **:** Graphical representation of the impact of Nutrum Gold on the dissolution of Zantac® after 60 minutes.

4.1.2.6. Dissolution test of Zantac® (Ranitidine) with Filwel Silver (Multivitamin and multimineral supplement).

Table 4.24 : UV absorbance of Zantac® (Ranitidine) with Filwel Silver (Multivitamin and multimineral supplement)

	Absorbance		
Serial number	After 20 minutes	After 40 minutes	After 60 minutes
1	0.472	0.712	0.835
2	0.469	0.627	0.737
3	0.563	0.825	0.857
4	0.494	0.598	0.657
5	0.432	0.602	0.658
6	0.474	0.653	0.703

Calculation for dissolved amount (mg) Zantac® (Ranitidine) with Filwel Silver (Multivitamin and multimineral supplement).
By using, Y= 0.045x+0.012 equation dissolved amount of Zantac® (Ranitidine) with Filwel Silver (Multivitamin and multimineral supplement) was calculated

Table 4.25: Determination of Dissolved amount of Zantac®(Ranitidine) with Filwel Silver (Multivitamin and multimineral supplement).

	After 20 minutes		After 40 minutes		After 60 minutes	
Serial number	Absorbance	Dissolved amount (mg)	Absorbance	Dissolved amount (mg)	Absorbance	Dissolved amount (mg)
1	0.472	92.00	0.712	140.00	0.835	164.60
2	0.469	91.40	0.627	123.00	0.737	145.00
3	0.563	110.20	0.825	162.60	0.857	169.00
4	0.494	96.40	0.598	117.20	0.657	129.00
5	0.432	84.00	0.602	118.00	0.658	129.20
6	0.474	92.40	0.653	128.20	0.703	138.20

4.1.2.6.1 Impact of Filwel Silver on the dissolution of Zantac® after 20 minutes.

Table 4.26 : Percentage calculation for dissolved amount of Zantac® (Ranitidine), Zantac®(Ranitidine) with Filwel Silver (Multivitamin and multimineral supplement) and the impact of Filwel Silver on the dissolution of Zantac® after 20 minutes.

Zantac® without any supplement				Zantac® with Filwel Silver				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
110.40		73.60		92.00		61.33		
80.60		53.73		91.40		60.93		
94.80	89.80	63.20	59.87	110.20	94.40	73.47	62.93	5.01
82.40		54.93		96.40		64.27		
85.40		56.93		84.00		56.00		
85.20		56.80		92.40		61.60		

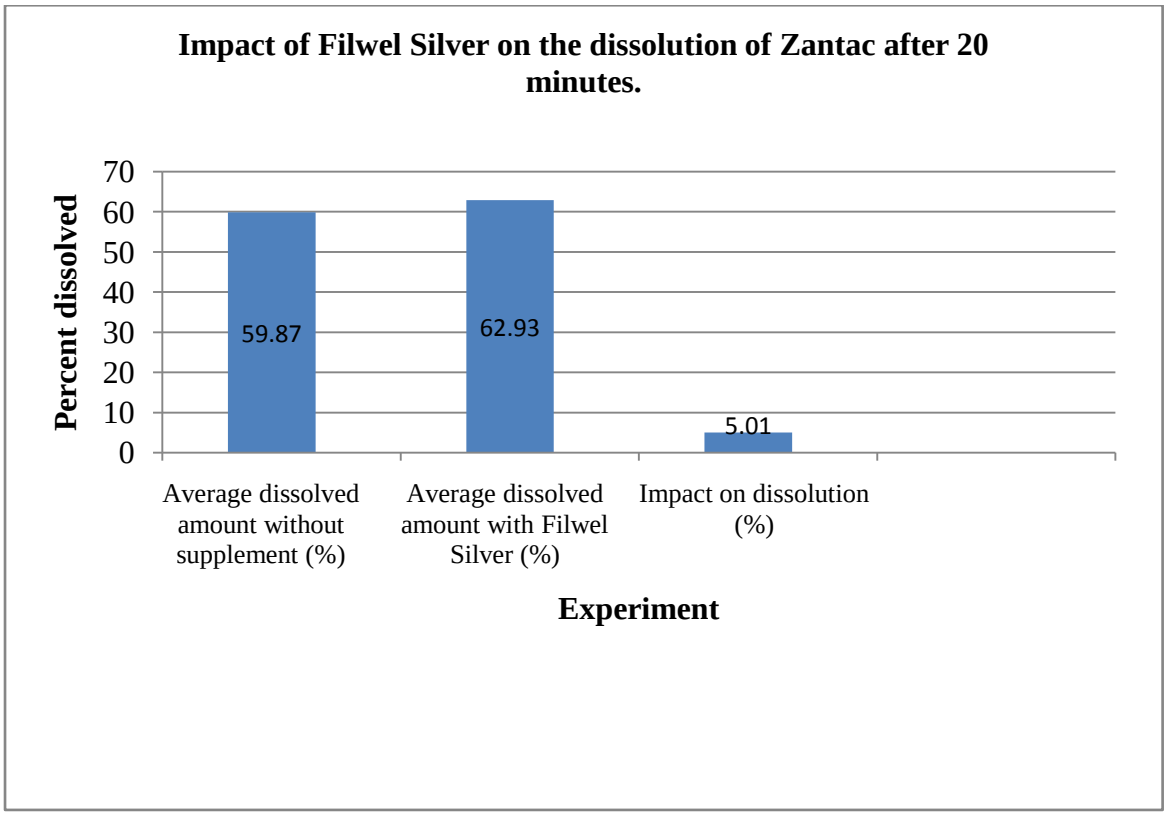

Figure 4.14 **:** Graphical representation of the impact of Filwel Silver on the dissolution of Zantac® after 20 minutes.

4.1.2.6.2 Impact of Filwel Silver on the dissolution of Zantac® after 40 minutes.

Table 4.27 : Percentage calculation for dissolved amount of Zantac® (Ranitidine), Zantac®(Ranitidine) with Filwel Silver (Multivitamin and multimineral supplement) and the impact of Filwel Silver on the dissolution of Zantac® after 40 minutes.

Zantac® without any supplement				Zantac® with Filwel Silver				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
128.20		85.47		140.00		93.33		
118.60		79.07		123.00		82.00		
139.00	128.20	92.67	85.47	162.60	131.50	108.40	87.67	2.57
129.40		86.27		117.20		78.13		
126.20		84.13		118.00		78.67		
127.80		85.20		128.20		85.47		

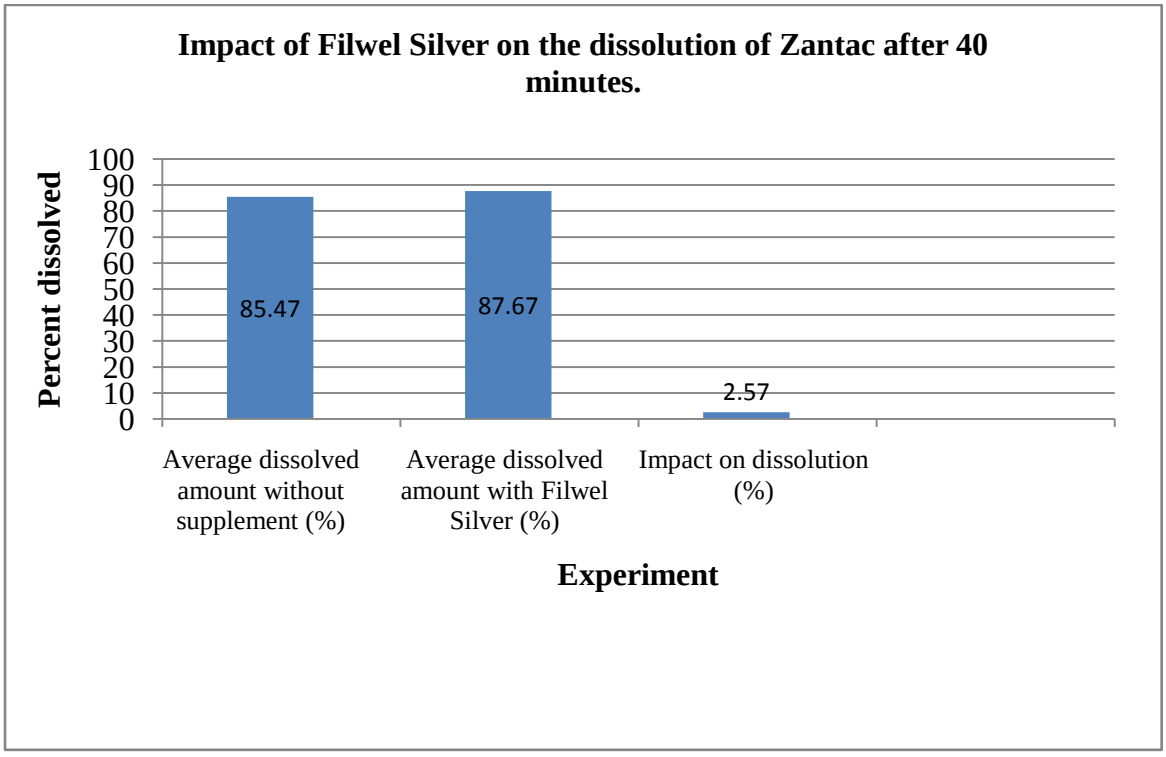

***Figure 4.15*:** Graphical representation of the impact of Filwel Silver on the dissolution of Zantac® after 40 minutes.

4.1.2.6.3 Impact of Filwel Silver on the dissolution of Zantac® after 60 minutes.

Table 4.28 : Percentage calculation for dissolved amount of Zantac® (Ranitidine), Zantac®(Ranitidine) with Filwel Silver (Multivitamin and multimineral supplement) and the impact of Filwel Silver on the dissolution of Zantac® after 60 minutes.

Zantac® without any supplement				Zantac® with Filwel Silver				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
118.20		78.80		164.60		109.73		
136.40		90.93		145.00		96.67		
149.80	141.13	99.87	94.09	169.00	145.83	112.67	97.22	3.33
146.40		97.60		129.00		86.00		
148.20		98.80		129.20		86.13		
147.80		98.53		138.20		92.13		

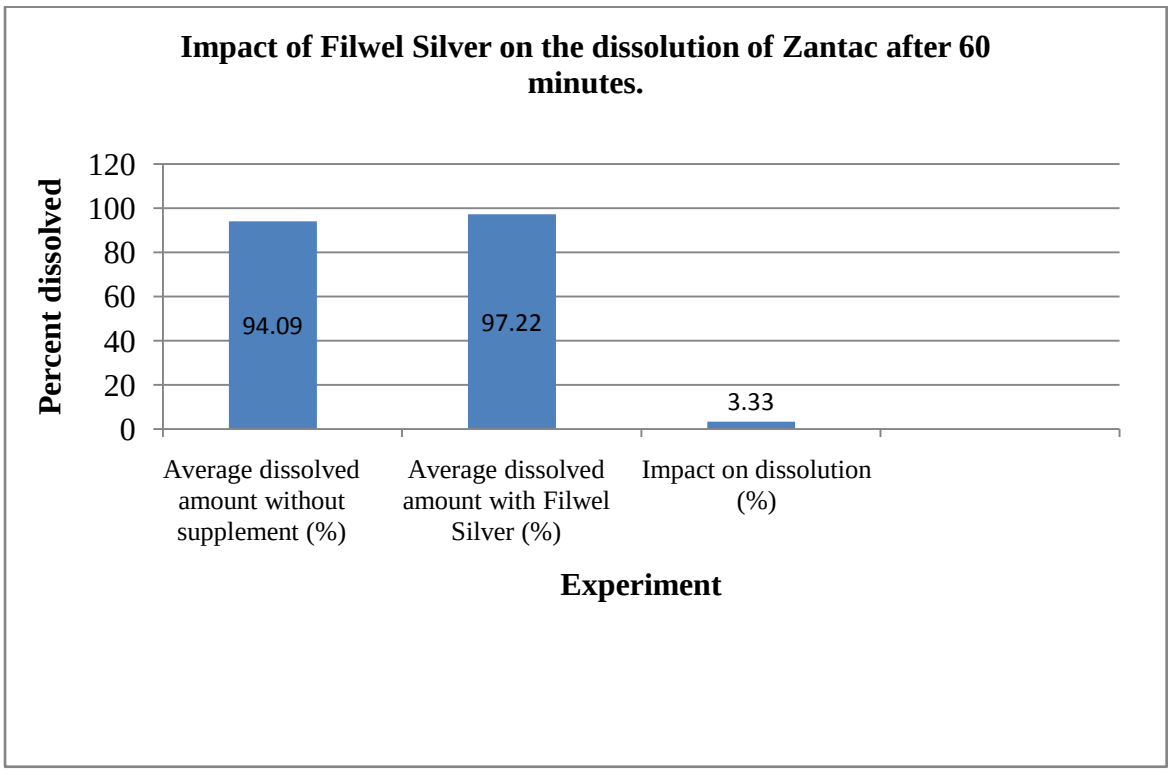

Figure 4.16 **:** Graphical representation of the impact of Filwel Silver on the dissolution of Zantac® after 60 minutes.

4.1.3 Comparison among the average percent dissolved amount of individual Zantac® and Zantac® with different supplement drugs 20, 40 and 60 minutes.

4.1.3.1Comparison among the average percent dissolved amount of individual Zantac® and Zantac® with different supplement drugs 20 minutes.

Table 4.29 : The differences among the average percent dissolve (%) amount of individual Zantac®, Zantac® with Calbo, Zantac® with Aristocal D, Zantac® with Acical M, Zantac® with Nutrum Gold and Zantac® with Filwel silver after 20 minute.

Average percent dissolved amount of Zantac® without supplement (%)	Average percent dissolved amount of Zantac® with calbo (%)	Average percent dissolved amount of Zantac® with Aristocal D (%)	Average percent dissolved amount of Zantac® with Acical M (%)	Average percent dissolved amount of Zantac® with Nutrum Gold (%)	Average percent dissolved amount of Zantac® with Filwel Silver (%)
59.87	32.80	47.98	32.16	58.82	62.93

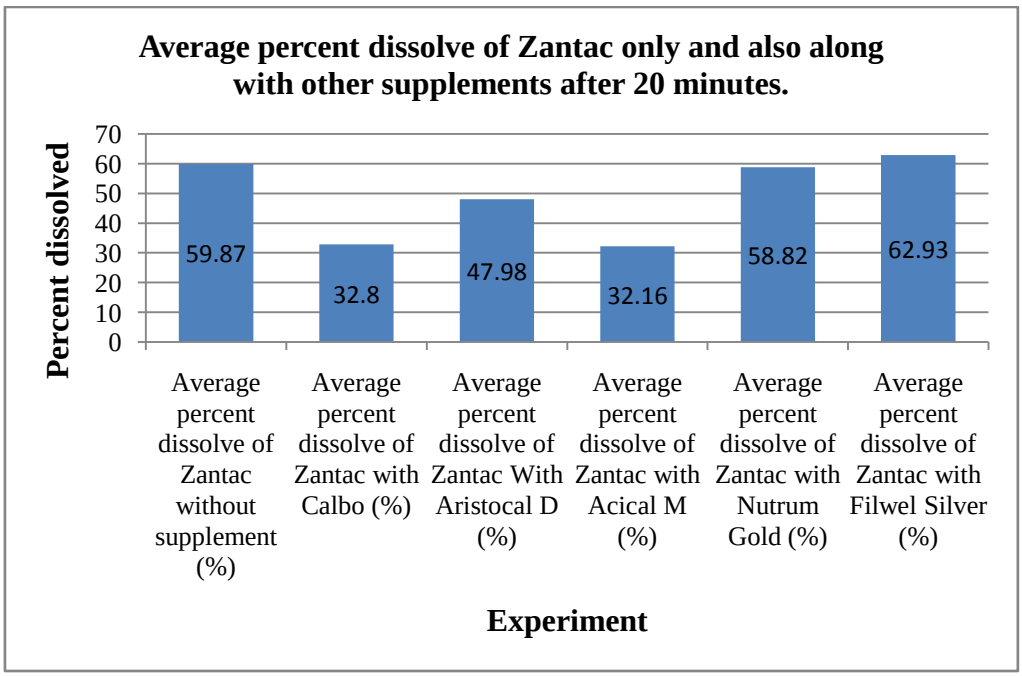

Figure 4.17 : Graphical representation of the average percent dissolve of individual Zantac® and also in combination with Calbo, Aristocal D, Acical M, Nutrum Gold, and Filwel after 20 minute.

4.1.3.2Comparison among the average percent dissolved amount of individual Zantac® and Zantac® with different supplement drugs 40 minutes.

Table 4.30 : The differences among the average percent dissolve (%) amount of individual Zantac®, Zantac® with Calbo, Zantac® with Aristocal D, Zantac® with Acical M, Zantac® with Nutrum Gold and Zantac® with Filwel silver after 40 minute.

Average percent dissolved amount of Zantac® without supplement (%)	Average percent dissolved amount of Zantac® with calbo (%)	Average percent dissolved amount of Zantac® with Aristocal D (%)	Average percent dissolved amount of Zantac® with Acical M (%)	Average percent dissolved amount of Zantac® with Nutrum Gold (%)	Average percent dissolved amount of Zantac® with Filwel Silver (%)
85.47	43.64	65.62	42.91	85.67	87.67

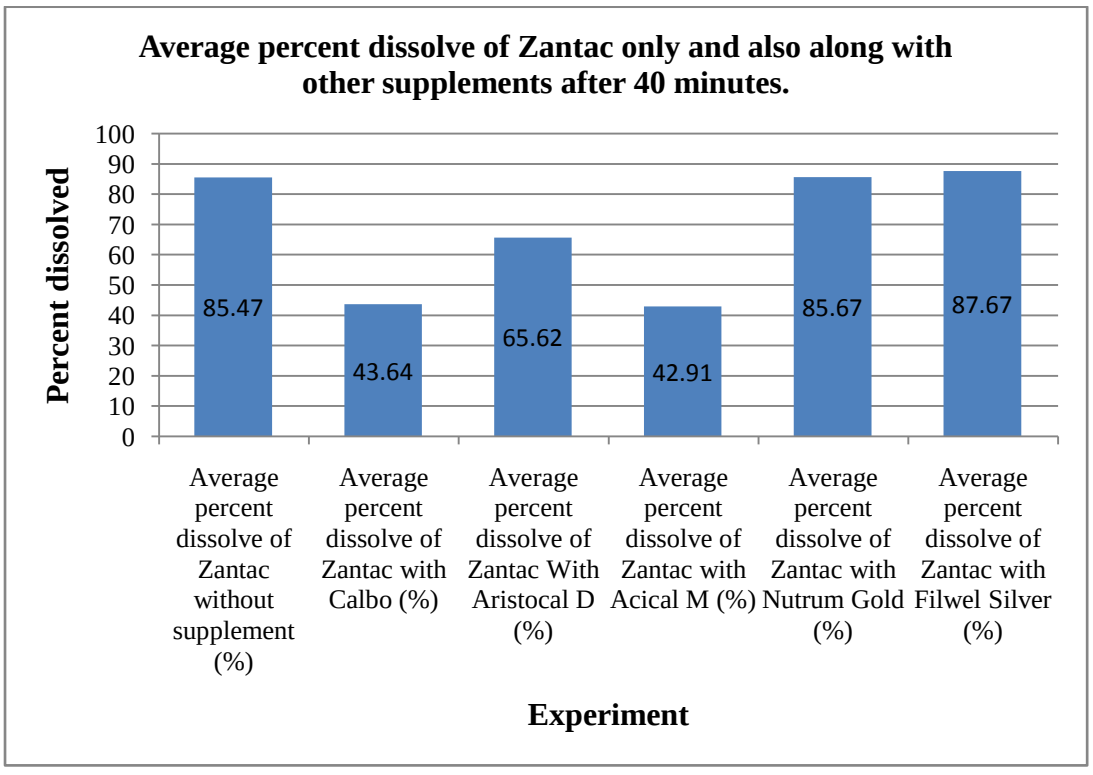

Figure 4.18: Graphical representation of the average percent dissolve of individual Zantac® and also in combination with Calbo, Aristocal D, Acical M, Nutrum Gold, and Filwel after 40 minute.

4.1.3.3 Comparison among the average percent dissolved amount of individual Zantac® and Zantac® with different supplement drugs 60 minutes.

Table 4.31 : The differences among the average percent dissolve (%) amount of individual Zantac®, Zantac® with Calbo, Zantac® with Aristocal D, Zantac® with Acical M, Zantac® with Nutrum Gold and Zantac® with Filwel silver after 60 minute.

Average percent dissolved amount of Zantac® without supplement (%)	Average percent dissolved amount of Zantac® with calbo (%)	Average percent dissolved amount of Zantac® with Aristocal D (%)	Average percent dissolved amount of Zantac® with Acical M (%)	Average percent dissolved amount of Zantac® with Nutrum Gold (%)	Average percent dissolved amount of Zantac® with Filwel Silver (%)
94.09	47.84	72.6	48.47	94.27	97.22

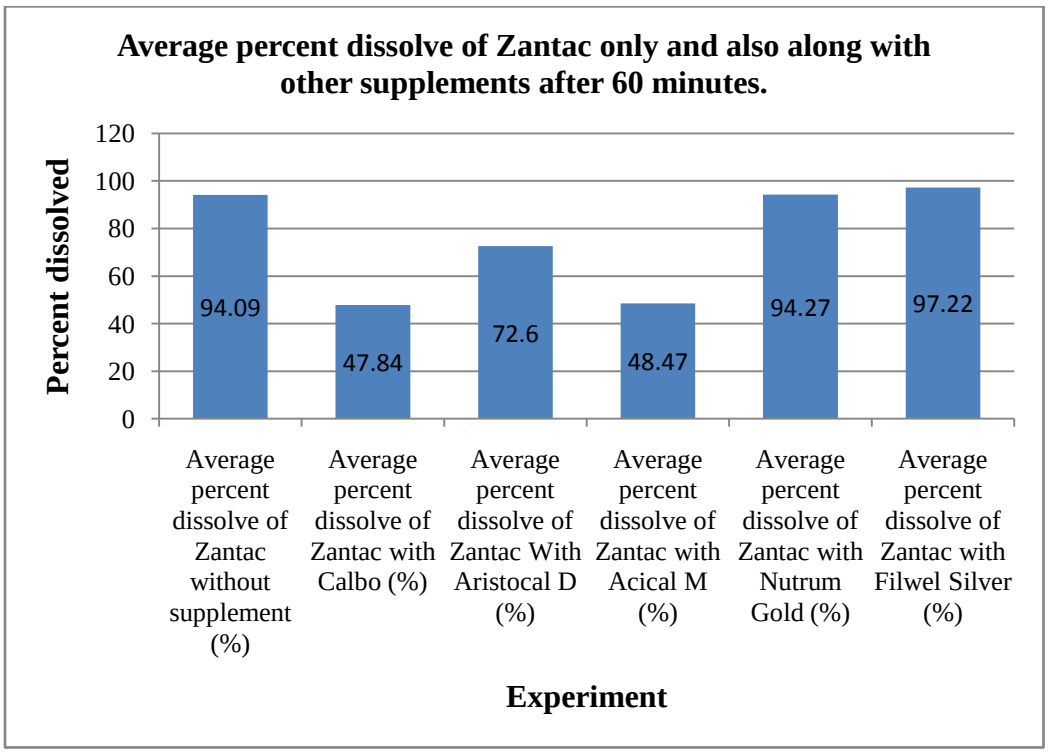

Figure 4.19 : Graphical representation of the average percent dissolve of individual Zantac® and also in combination with Calbo, Aristocal D, Acical M, Nutrum Gold, and Filwel Silver after 60 minute.

4.1.4 Results of the dissolution test of individual Ranitid®, Ranitid® with different supplement drugs and the impact of supplements on the dissolution of Ranitid® after 20minute, 40minute and 60 minute.

4.1.4.1 Dissolution test of Ranitid® (Ranitidine) without any supplement.

Table 4.32 : UV absorbance of only Ranitid® (Ranitidine) 150mg tablets.

	Absorbance		
Serial number	After 20 minutes	After 40 minutes	After 60 minutes
1	0.409	0.603	0.610
2	0.425	0.580	0.670
3	0.458	0.590	0.692
4	0.398	0.551	0.839
5	0.476	0.819	0.701
6	0.531	0.757	0.695

Calculation of dissolved amount for Ranitid® (Ranitidine)

By using, Y= 0.045x+0.012 equation dissolved amount of Zantac® (Ranitidine) with Calbo (Calcium supplement) was calculated.

Table 4.33: Determination of Dissolved amount of Ranitid® (Ranitidine) without any supplement.

	After 20 minutes		After 40 minutes		After 60 minutes	
Serial number	**Absorbance**	**Dissolved amount (mg)**	**Absorbance**	**Dissolved amount (mg)**	**Absorbance**	**Dissolved amount (mg)**
1	0.409	79.4	0.603	118.20	0.610	119.60
2	0.425	82.6	0.580	113.60	0.670	131.60
3	0.458	89.2	0.590	115.60	0.692	136.00
4	0.398	77.2	0.551	107.80	0.839	165.40
5	0.476	92.8	0.819	161.40	0.701	137.80
6	0.531	69.2	0.757	149.00	0.695	136.60

4.1.4.2 Dissolution test of Ranitid® (Ranitidine) with Calbo (Calcium supplement)

Table 4.34 : UV absorbance of Ranitid® (Ranitidine) with Calbo 500 (Calcium suppliment.

	Absorbance		
Serial number	After 20 minutes	After 40 minutes	After 60 minutes
1	0.186	0.318	0.378
2	0.181	0.386	0.394
3	0.219	0.356	0.408
4	0.212	0.402	0.365
5	0.679	0.398	0.389
6	0.268	0.421	0.328

Calculation for dissolved amount (mg) of Ranitid® (Ranitidine) with Calbo (Calcium supplement).

By using, Y= 0.045x+0.012 equation dissolved amount of Zantac® (Ranitidine) with Calbo (Calcium supplement) was calculated.

Table 4.35 : Determination of Dissolved amount of Ranitid® (Ranitidine) with Calbo 500 (Calcium supplement).

	After 20 minutes		After 40 minutes		After 60 minutes	
Serial number	Absorbance	Dissolved amount (mg)	Absorbance	Dissolved amount (mg)	Absorbance	Dissolved amount (mg)
1	0.186	34.8	0.318	61.20	0.378	73.20
2	0.181	33.8	0.386	74.80	0.394	76.50
3	0.219	41.4	0.356	68.80	0.408	89.20
4	0.212	40	0.402	78.00	0.365	70.60
5	0.679	133.4	0.398	77.20	0.389	75.40
6	0.268	51.2	0.421	81.80	0.328	63.20

4.1.4.2.1 Impact of Calbo on the dissolution of Ranitid® after 20 minutes.

Table 4.36 : Percentage calculation for dissolved amount of Ranitid® (Ranitidine), Ranitid® (Ranitidine) with Calbo 500 (Calcium supplement) and the impact of Calbo 500 on the dissolution of Ranitid® after 20 minutes.

Ranitid® without any supplement				Ranitid® with Calbo				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
79.4		52.93		34.80		23.20		
82.6		55.07		33.80		22.53		
89.2	81.73	59.47	54.49	41.40	55.77	27.60	37.18	-31.77
77.2		51.47		40.00		26.67		
92.8		61.87		133.40		88.93		
69.2		46.13		51.20		34.13		

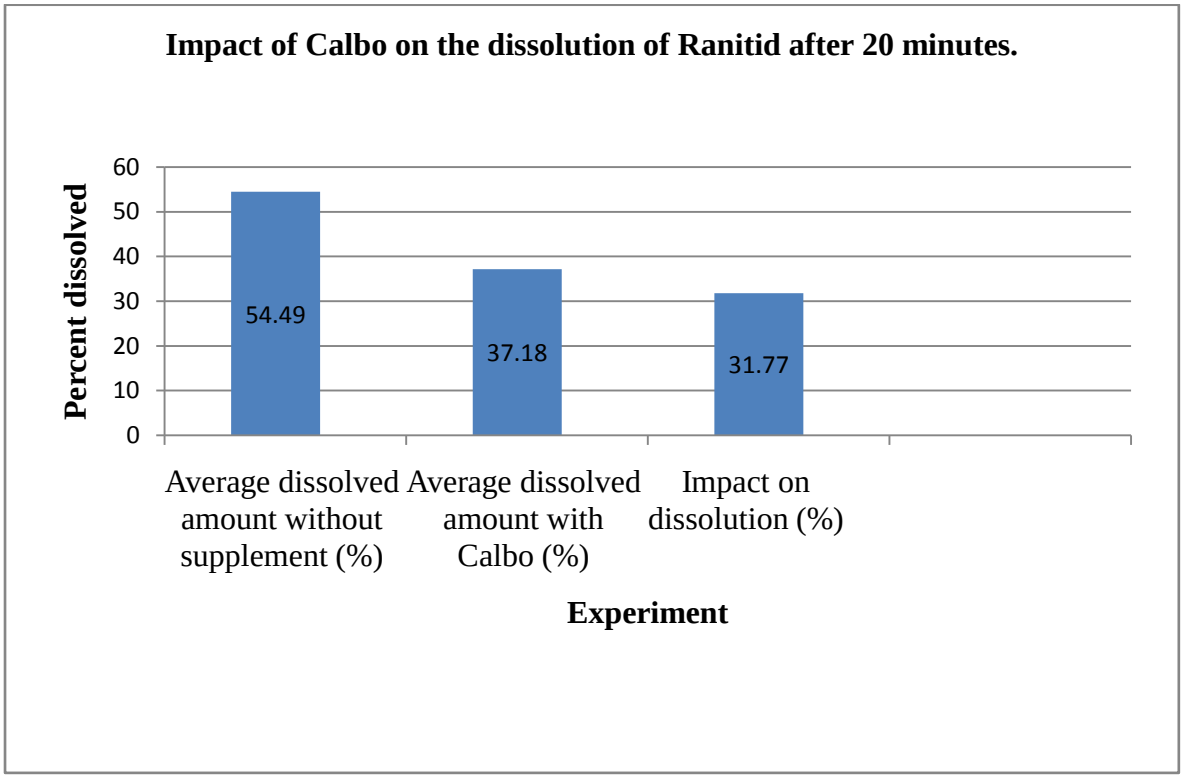

Figure 4.20 : Graphical representation of the impact of calbo 500 on the dissolution of Ranitid® after 20 minutes.

4.1.4.2.2 Impact of Calbo on the dissolution of Ranitid® after 40 minutes.

Table 4.37 : Percentage calculation for dissolved amount of Ranitid® (Ranitidine), Ranitid® (Ranitidine) with Calbo 500 (Calcium supplement) and the impact of Calbo 500 on the dissolution of Ranitid® after 40 minutes.

Ranitid® without any supplement				Ranitid® with Calbo				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
118.20		78.80		61.20		40.80		
113.60		75.73		74.80		49.86		
115.60	127.6	77.07	85.07	68.80	73.63	45.87	49.09	-42.29
107.80		71.87		78.00		52.00		
161.40		107.60		77.20		51.47		
149.00		99.33		81.80		54.53		

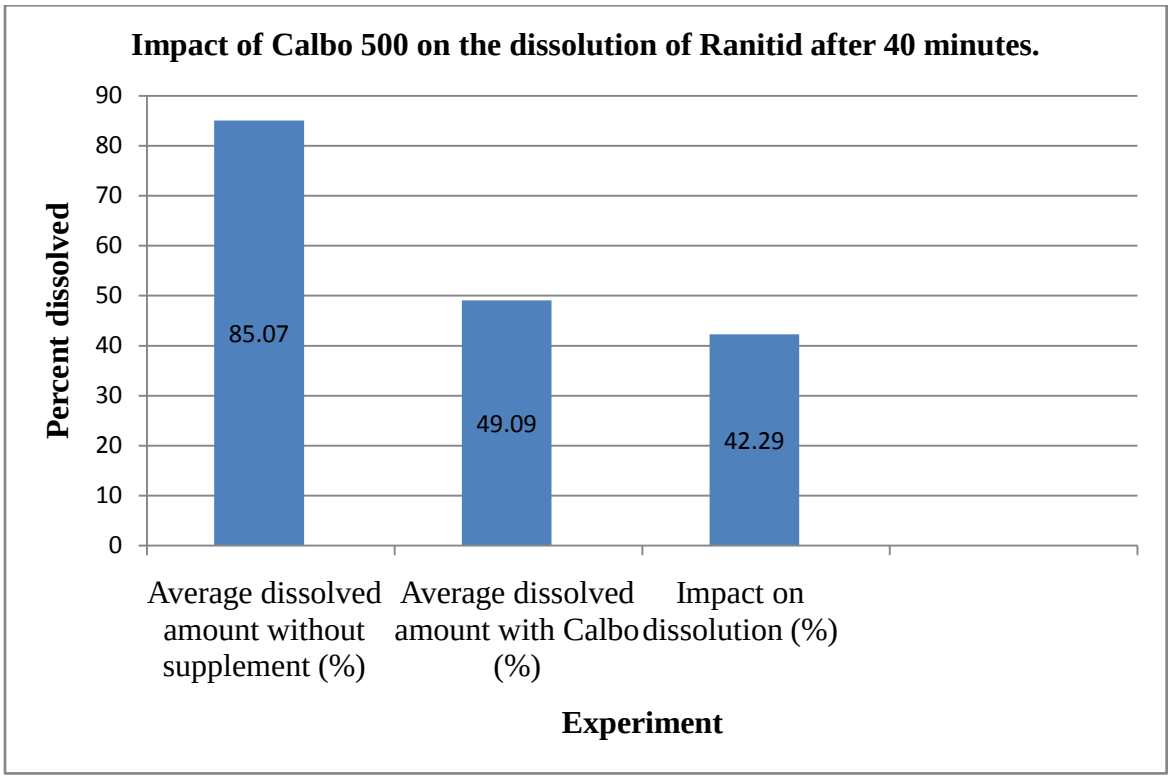

Figure 4.21 **:** Graphical representation of the impact of calbo on the dissolution of Ranitid® after 40 minutes.

4.1.4.2.3 Impact of Calbo 500 on the dissolution of Ranitid® after 60 minutes.

Table 4.38 : Percentage calculation for dissolved amount of Ranitid® (Ranitidine), Ranitid® (Ranitidine) with Calbo 500 (Calcium supplement) and the impact of Calbo 500 on the dissolution of Ranitid® after 60 minutes.

Ranitid® without any supplement				Ranitid® with Calbo				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
119.60		79.73		73.20		48.80		
131.60		87.73		76.50		51.00		
136.00	137.83	90.67	91.89	89.20	74.69	59.47	49.79	-45.82
165.40		110.27		70.60		47.07		
137.80		91.87		75.40		50.27		
136.60		91.07		63.20		42.13		

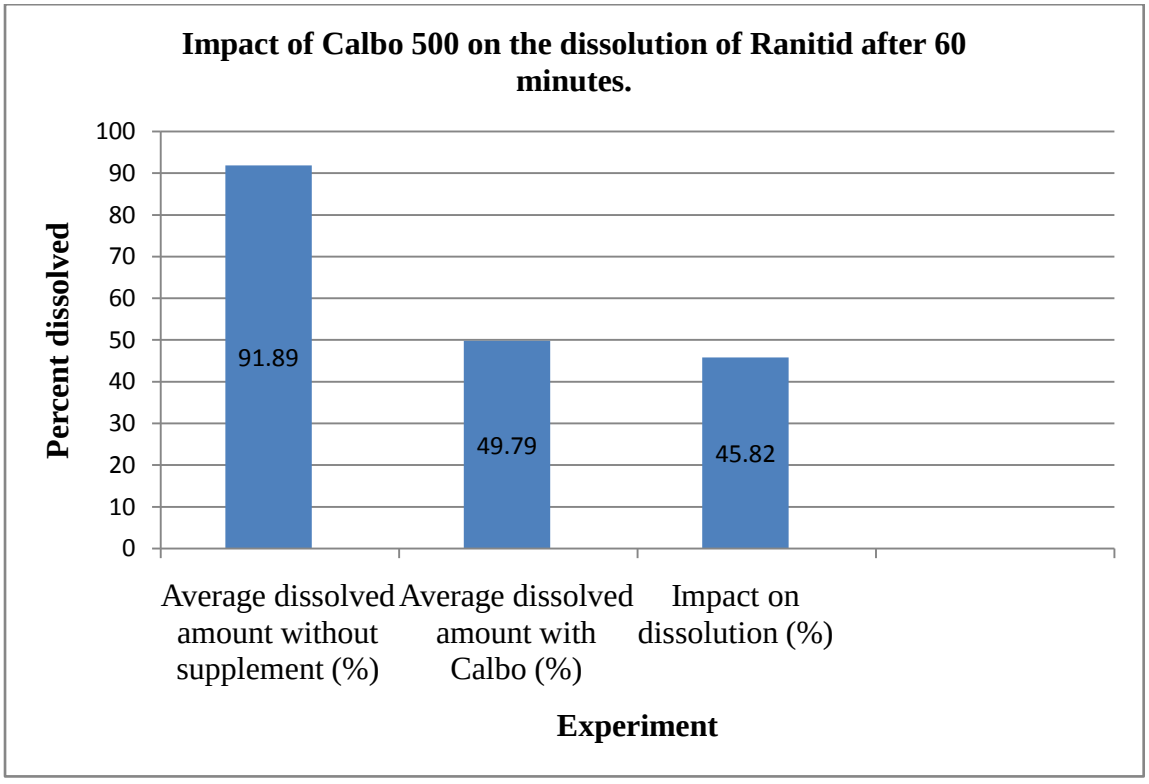

***Figure 4.22*:** Graphical representation of the impact of Calbo on the dissolution of Ranitid® after 60 minutes.

4.1.4.3 Dissolution test of Ranitid® (Ranitidine) with Aristocal D (Calcium and vitamin D supplement):

Table 4.39 : UV absorbance of Ranitid® (Ranitidine) with Aristocal D (Calcium and vitamin D supplement.

	Absorbance		
Serial number	After 20 minutes	After 40 minutes	After 60 minutes
1	0.355	0.499	0.586
2	0.340	0.508	0.544
3	0.389	0.521	0.562
4	0.398	0.533	0.489
5	0.401	0.50	0.498
6	0.378	0.538	0.586

Calculation for dissolved amount (mg) of Ranitid® (Ranitidine) with Aristocal D (Calcium and vitamin D supplement.

By using, Y= 0.045x+0.012 equation dissolved amount of Ranitid® (Ranitidine) with Aristocal D (Calcium and vitamin D supplement) was calculated.

Table 4.40 : Determination of Dissolved amount of Ranitid® (Ranitidine) with Aristocal D (Calcium and vitamin D supplement).

	After 20 minutes		After 40 minutes		After 60 minutes	
Serial number	Absorbance	Dissolved amount (mg)	Absorbance	Dissolved amount (mg)	Absorbance	Dissolved amount (mg)
1	0.355	68.60	0.499	97.40	0.586	114.80
2	0.340	65.60	0.508	99.20	0.544	106.40
3	0.389	75.40	0.521	101.80	0.562	110.00
4	0.398	77.20	0.533	104.20	0.489	95.40
5	0.401	77.80	0.50	97.60	0.498	97.20
6	0.378	73.20	0.538	105.20	0.586	114.80

4.1.4.3.1 Impact of Aristocal D on the dissolution of Ranitid® after 20 minutes.

Table 4.41 : Percentage calculation for dissolved amount of Ranitid® (Ranitidine), Ranitid® (Ranitidine) with Aristocal D (Calcium and vitamin D supplement) and the impact of Aristocal D on the dissolution of Ranitid® after 20 minutes.

Ranitid® without any supplement				Ranitid® with Aristocal D				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
79.40		52.93		68.60		45.73		
82.60		55.07		65.60		43.73		
89.20	81.73	59.47	54.49	75.40	72.97	50.27	48.64	-10.74
77.20		51.47		77.20		51.47		
92.80		61.87		77.80		51.87		
69.20		46.13		73.20		48.80		

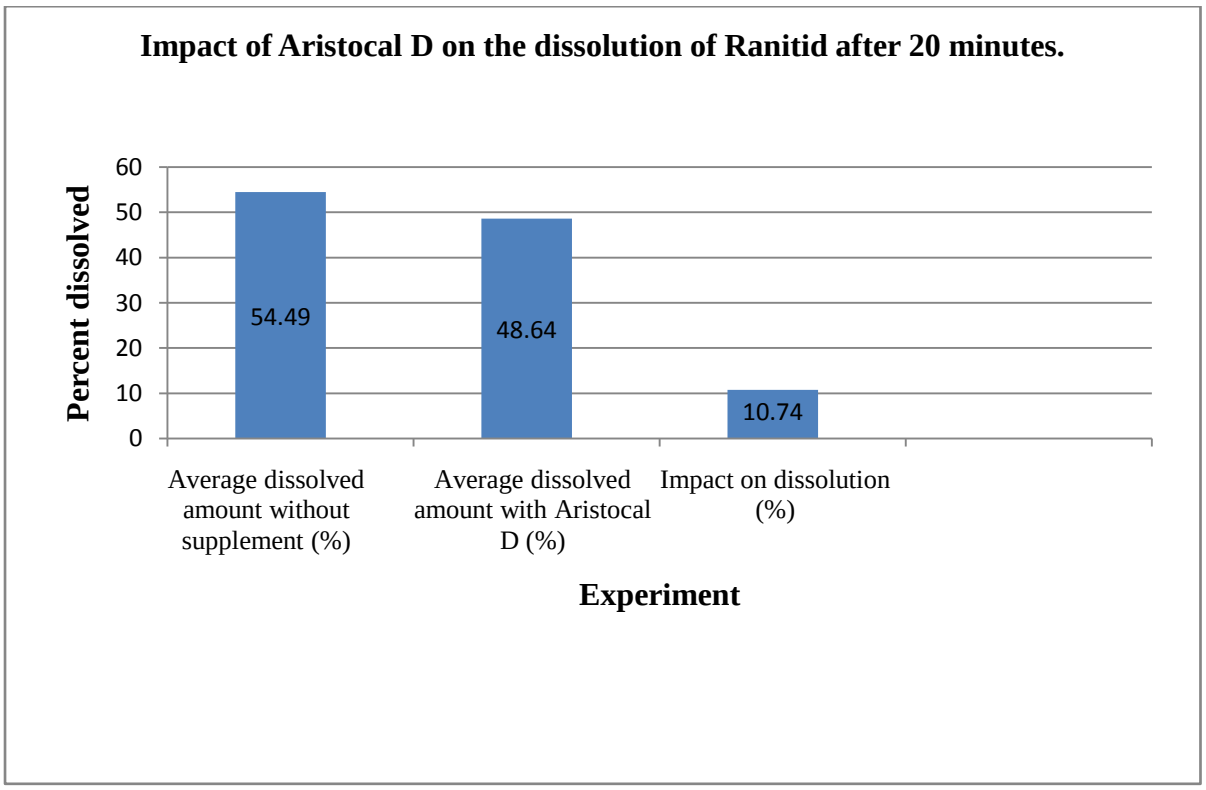

***Figure 4.23*:** Graphical representation of the impact of Aristocal D on the dissolution of Ranitid® after 20 minutes.

4.1.4.3.2 Impact of Aristocal D on the dissolution of Ranitid® after 40 minutes.

Table 4.42 : Percentage calculation for dissolved amount of Ranitid® (Ranitidine), Ranitid® (Ranitidine) with Aristocal D (Calcium and vitamin D supplement) and the impact of Aristocal D on the dissolution of Ranitid® after 40 minutes.

Ranitid® without any supplement				Ranitid® with Aristocal D				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
118.20		78.80		97.40		64.93		
113.60		75.73		99.20		66.13		
115.60	127.6	77.07	85.07	101.80	100.90	67.87	67.27	-20.93
107.80		71.87		104.20		69.47		
161.40		107.60		97.60		65.07		
149.00		99.33		105.20		70.13		

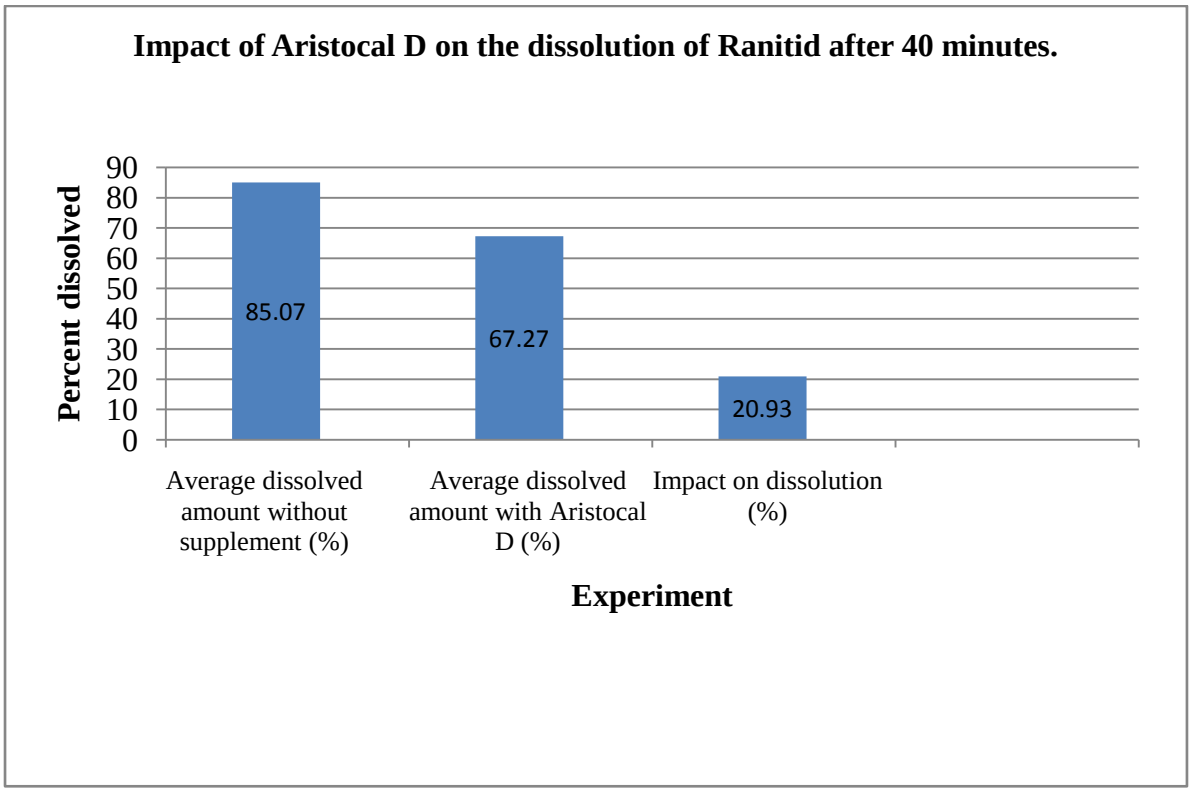

Figure 4.24: Graphical representation of the impact of Aristocal D on the dissolution of Ranitid® after 40 minutes.

4.1.4.3.3 Impact of Aristocal D on the dissolution of Rnitid after 60 minutes.

Table 4.43 : Percentage calculation for dissolved amount of Ranitid® (Ranitidine), Ranitid® (Ranitidine) with Aristocal D (Calcium and vitamin D supplement) and the impact of Aristocal D on the dissolution of Ranitid® after 60 minutes.

Ranitid® without any supplement				Ranitid® with Aristocal D				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
119.60		79.73		114.80		76.53		
131.60		87.73		106.40		70.93		
136.00	137.83	90.67	91.89	110.00	106.43	73.33	70.96	-22.79
165.40		110.27		95.40		63.60		
137.80		91.87		97.20		64.80		
136.60		91.07		114.80		76.53		

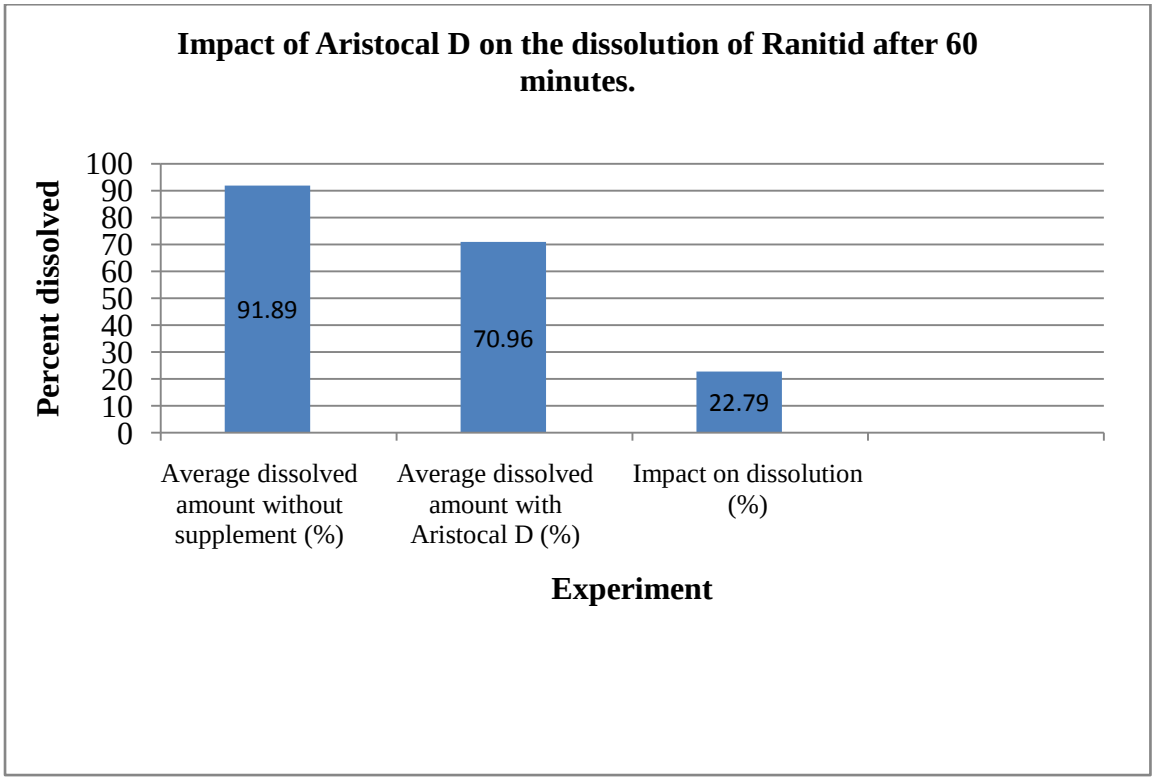

***Figure 4.25*:** Graphical representation of the impact of Aristocal D on the dissolution of Ranitid® after 60 minutes.

4.1.4.4 Dissolution test of Ranitid® (Ranitidine) with Acical M (Calcium, vitamin D and multimineral supplement).

Table 4.44 : UV absorbance of Ranitid® (Ranitidine) with Acical M (Calcium, vitamin D and multimineral supplement).

	Absorbance		
Serial number	After 20 minutes	After 40 minutes	After 60 minutes
1	0.247	0.378	0.437
2	0.293	0.360	0.361
3	0.239	0.405	0.383
4	0.289	0.356	0.397
5	0.211	0.390	0.399
6	0.289	0.362	0.398

Calculation for dissolved amount (mg) Ranitid® (Ranitidine) with Acical M (Calcium, vitamin D and multimineral supplement).

By using, Y= 0.045x+0.012 equation dissolved amount of Ranitid® (Ranitidine) with Acical M (Calcium, vitamin D and multimineral supplement) was calculated.

Table 4.45 : Determination of Dissolved amount of Ranitid® (Ranitidine) with Acical M (Calcium, vitamin D and multimineral supplement).

	After 20 minutes		After 40 minutes		After 60 minutes	
Serial number	Absorbance	Dissolved amount (mg)	Absorbance	Dissolved amount (mg)	Absorbance	Dissolved amount (mg)
1	0.247	47.00	0.378	73.20	0.437	85.00
2	0.293	56.20	0.360	69.60	0.361	69.80
3	0.239	45.40	0.405	78.60	0.383	74.20
4	0.289	55.40	0.356	68.80	0.397	77.00
5	0.211	45.00	0.390	75.60	0.399	77.40
6	0.289	55.40	0.362	70.00	0.398	77.20

4.1.4.4.1 Impact of Acical M on the dissolution of Ranitid® after 20 minutes.

Table 4.46 : Percentage calculation for dissolved amount of Ranitid® (Ranitidine), Ranitid® (Ranitidine) with Acical M (Calcium, vitamin D and multimineral supplement) and the impact of Acical-M on the dissolution of Ranitid® after 20 minutes.

Ranitid® without any supplement				Ranitid® with Acical M				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
79.40		52.93		47.00		31.33		
82.60		55.07		56.20		37.47		
89.20	81.73	59.47	54.49	45.40	50.73	30.27	33.82	-37.93
77.20		51.47		55.40		36.93		
92.80		61.87		45.00		30.00		
69.20		46.13		55.40		36.93		

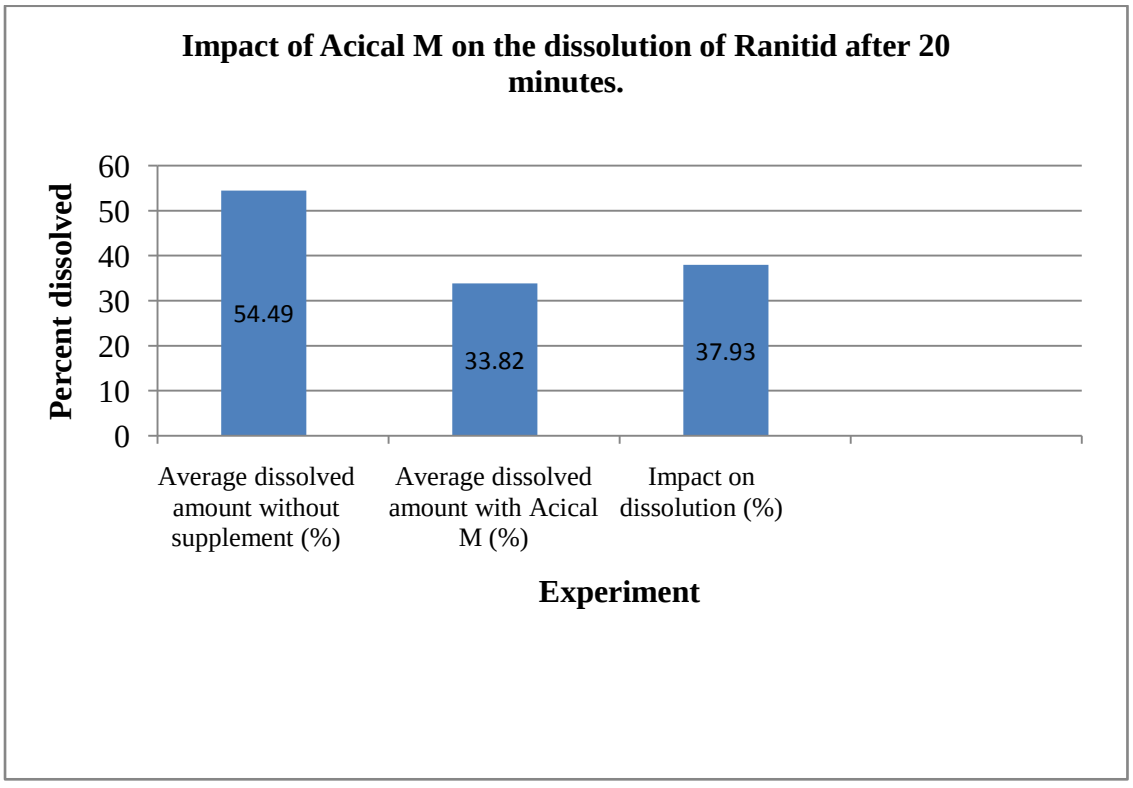

Figure 4.26 **:** Graphical representation of the impact of Acical M on the dissolution of Ranitid® after 20 minutes.

4.1.4.4.2 Impact of Acical M on the dissolution of Ranitid® after 40 minutes.

Table 4.47 : Percentage calculation for dissolved amount of Ranitid® (Ranitidine), Ranitid® (Ranitidine) with Acical M (Calcium, vitamin D and multimineral supplement) and the impact of Acical-M on the dissolution of Ranitid® after 40 minutes.

Ranitid® without any supplement				Ranitid® with Acical M				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
118.20		78.80		73.20		48.80		
113.60		75.73		69.60		46.40		
115.60	127.6	77.07	85.07	78.60	72.63	52.40	48.42	-43.07
107.80		71.87		68.80		45.87		
161.40		107.60		75.60		50.40		
149.00		99.33		70.00		46.67		

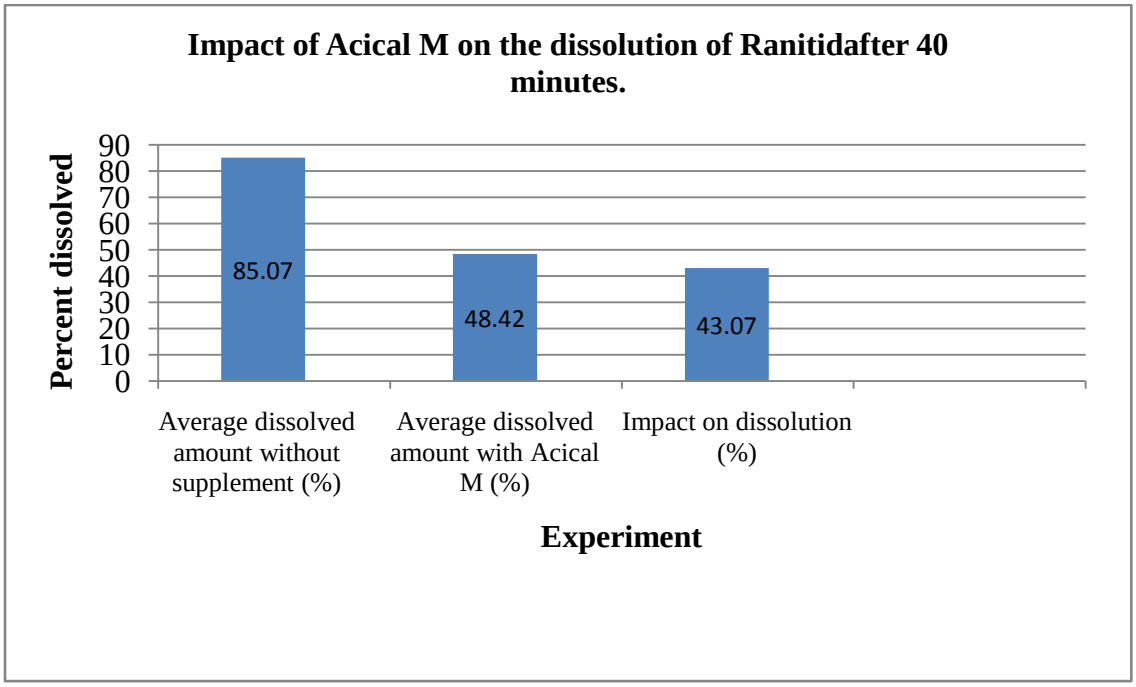

Figure 4.27 **:** Graphical representation of the impact of Acical M on the dissolution of Ranitid® after 40 minutes.

4.1.4.4.3 Impact of Acical M on the dissolution of Ranitid® after 60 minutes.

Table 4.48 : Percentage calculation for dissolved amount of Ranitid® (Ranitidine), Ranitid® (Ranitidine) with Acical M (Calcium, vitamin D and multimineral supplement) and the impact of Acical-M on the dissolution of Ranitid® after 60 minutes.

Ranitid® without any supplement				Ranitid® with Acical M				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
119.60		79.73		85.00		56.67		
131.60		87.73		69.80		46.53		
136.00	137.83	90.67	91.89	74.20	76.77	49.47	51.18	-44.30
165.40		110.27		77.00		51.33		
137.80		91.87		77.40		54.60		
136.60		91.07		77.20		51.47		

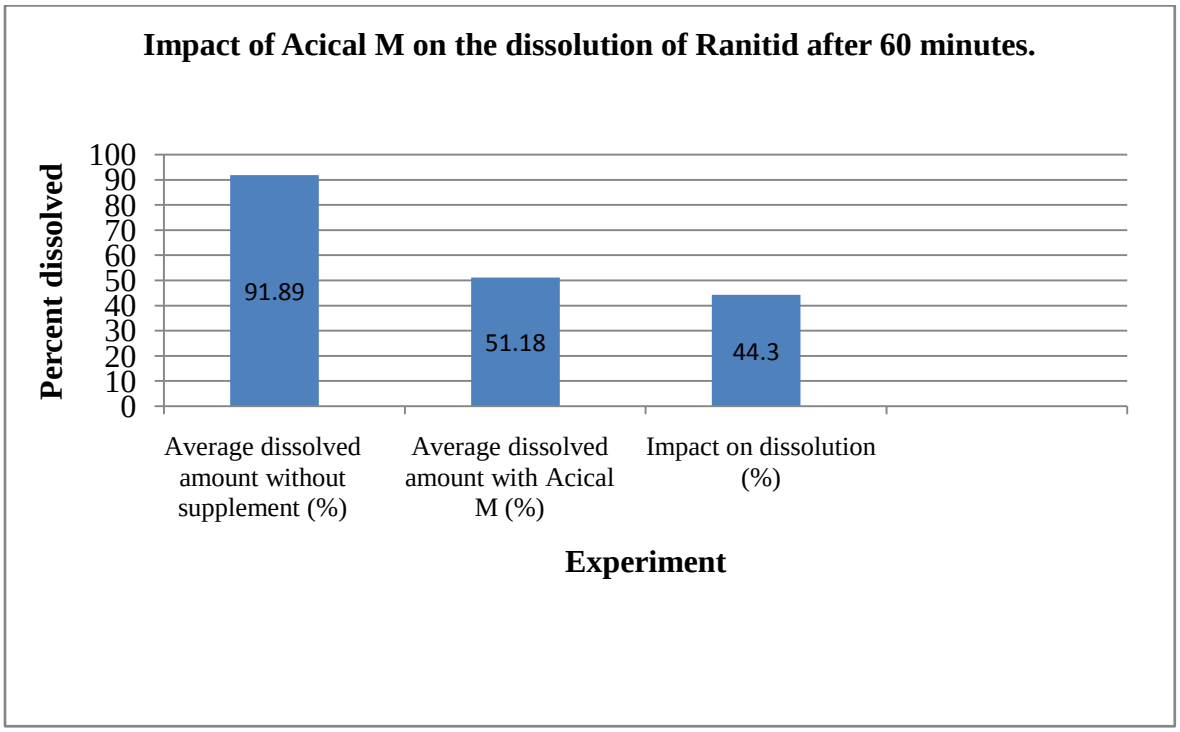

***Figure 4.28* :** Graphical representation of the impact of Acical M on the dissolution of Ranitid® after 60 minutes.

4.1.4.5 Dissolution test of Ranitid® (Ranitidine) with Nutrum Gold (Multivitamin and multimineral supplement).

Table 4.49 : UV absorbance of Ranitid® (Ranitidine) with Nutrum Gold (Multivitamin and multimineral supplement).

	Absorbance		
Serial number	After 20 minutes	After 40 minutes	After 60 minutes
1	0.468	0.538	0.689
2	0.436	0.519	0.721
3	0.502	0.589	0.658
4	0.475	0.753	0.718
5	0.452	0.612	0.786
6	0.453	0.613	0.805

Calculation for dissolved amount (mg) Zantac®(Ranitidine) with Nutrum Gold (Multivitamin and multimineral supplement).

By using, Y= 0.045x+0.012 equation dissolved amount of Zantac® (Ranitidine) with Nutrum Gold (Multivitamin and multimineral supplement) was calculated.

Table 4.50 : Determination of Dissolved amount of Zantac®(Ranitidine) with Nutrum Gold (Multivitamin and multimineral supplement).

	After 20 minutes		After 40 minutes		After 60 minutes	
Serial number	Absorbance	Dissolved amount (mg)	Absorbance	Dissolved amount (mg)	Absorbance	Dissolved amount (mg)
1	0.468	91.20	0.538	105.20	0.689	135.40
2	0.436	84.80	0.519	101.40	0.721	141.80
3	0.502	98.00	0.589	115.40	0.658	129.20
4	0.475	92.60	0.753	148.20	0.718	141.20
5	0.452	88.00	0.612	120.00	0.786	154.80
6	0.453	88.20	0.613	120.20	0.805	158.60

4.1.4.5.1 Impact of Nutrum Gold on the dissolution of Ranitid® after 20 minutes.

Table 4.51 : Percentage calculation for dissolved amount of Ranitid® (Ranitidine), Ranitid® (Ranitidine) with Nutrum Gold (Multivitamin and multimineral supplement) and the impact of Nutrum Gold on the dissolution of Ranitid® after 20 minutes.

Ranitid® without any supplement				Ranitid® with Nutrum Gold				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
79.40		52.93		91.20		60.80		
82.60		55.07		84.80		56.53		
89.20	81.73	59.47	54.49	98.00	90.47	65.33	60.31	10.69
77.20		51.47		92.60		61.73		
92.80		61.87		88.00		58.67		
69.20		46.13		88.20		58.80		

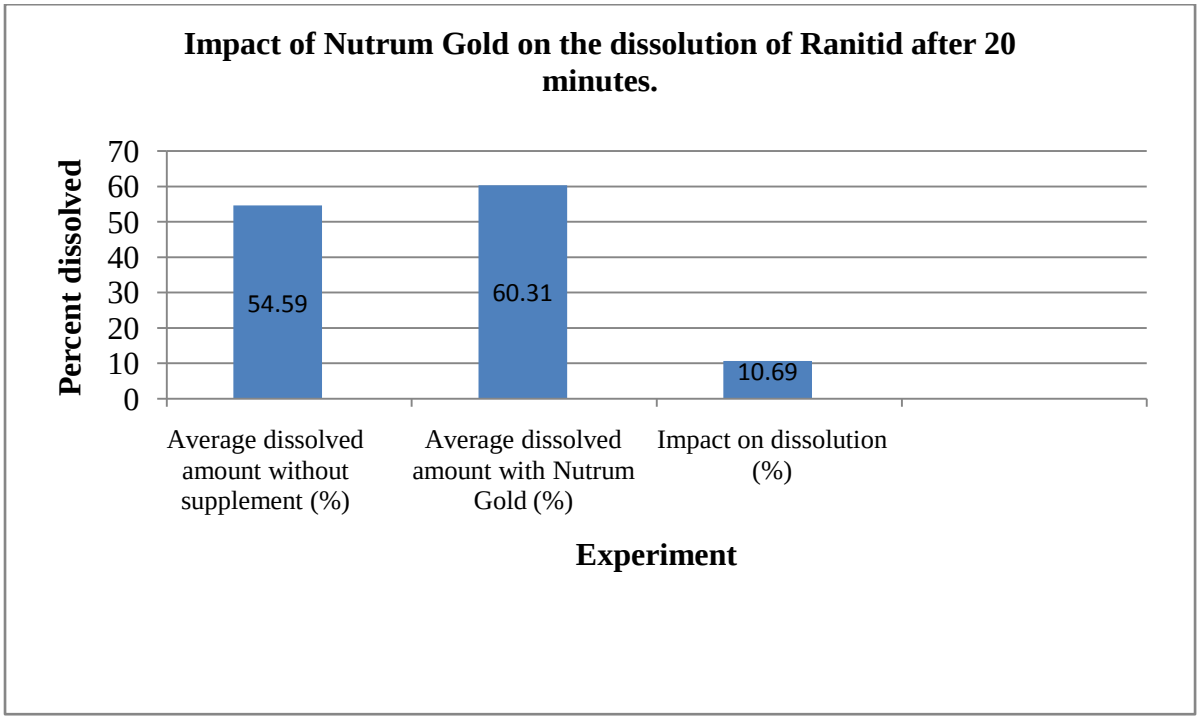

Figure 4.29 **:** Graphical representation of the impact of Nutrum Gold on the dissolution of Ranitid® after 20 minutes.

4.1.4.5.2 Impact of Nutrum Gold on the dissolution of Ranitid® after 40 minutes.

Table 4.52 : Percentage calculation for dissolved amount of Ranitid® (Ranitidine), Ranitid® (Ranitidine) with Nutrum Gold (Multivitamin and multimineral supplement) and the impact of Nutrum Gold on the dissolution of Ranitid® after 40 minutes.

Ranitid® without any supplement				Ranitid® with Nutrum Gold				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
118.20		78.80		105.20		70.13		
113.60		75.73		101.40		67.60		
115.60	127.6	77.07	85.07	115.40	118.40	76.93	78.93	-7.21
107.80		71.87		148.20		98.80		
161.40		107.60		120.00		80.00		
149.00		99.33		120.20		80.13		

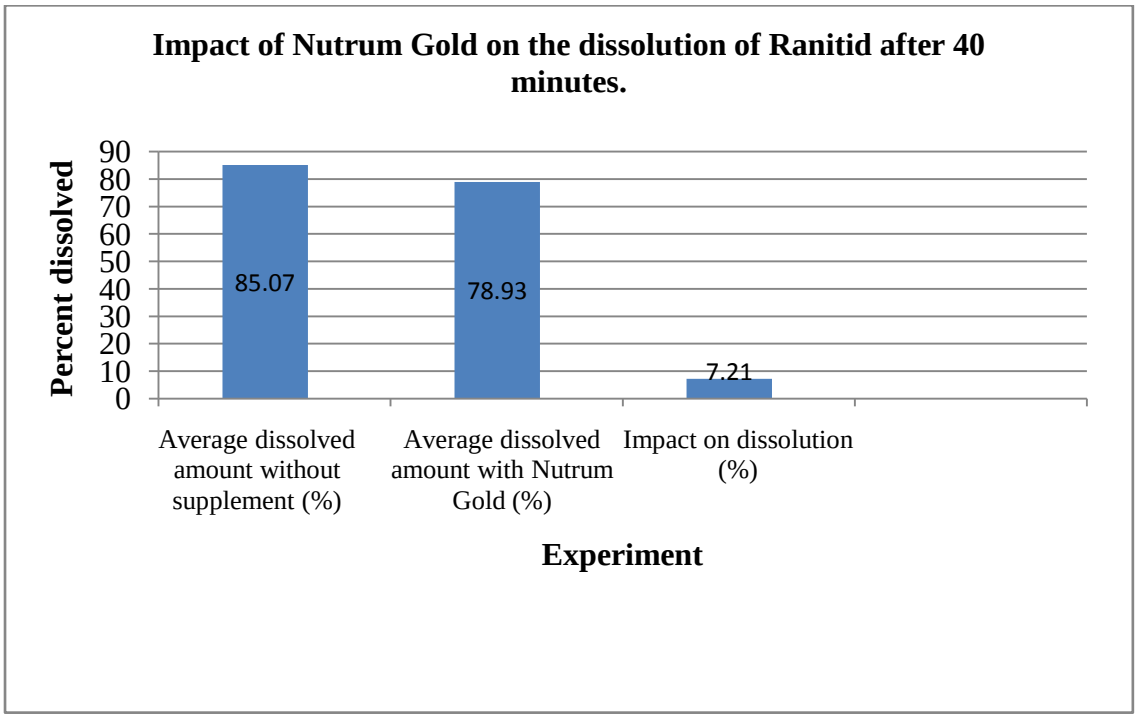

Figure 4.30 **:** Graphical representation of the impact of Nutrum Gold on the dissolution of Ranitid® after 40 minutes.

4.1.4.5.3 Impact of Nutrum Gold on the dissolution of Ranitid® after 60 minutes.

Table 4.53 : Percentage calculation for dissolved amount of Ranitid® (Ranitidine), Ranitid® (Ranitidine) with Nutrum Gold (Multivitamin and multimineral supplement) and the impact of Nutrum Gold on the dissolution of Ranitid® after 60 minutes.

Ranitid® without any supplement				Ranitid® with Nutrum Gold				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
119.60		79.73		135.40		90.27		
131.60		87.73		141.80		94.53		
136.00	137.83	90.67	91.89	129.20	143.50	86.13	95.67	4.11
165.40		110.27		141.20		94.13		
137.80		91.87		154.80		103.20		
136.60		91.07		158.60		105.73		

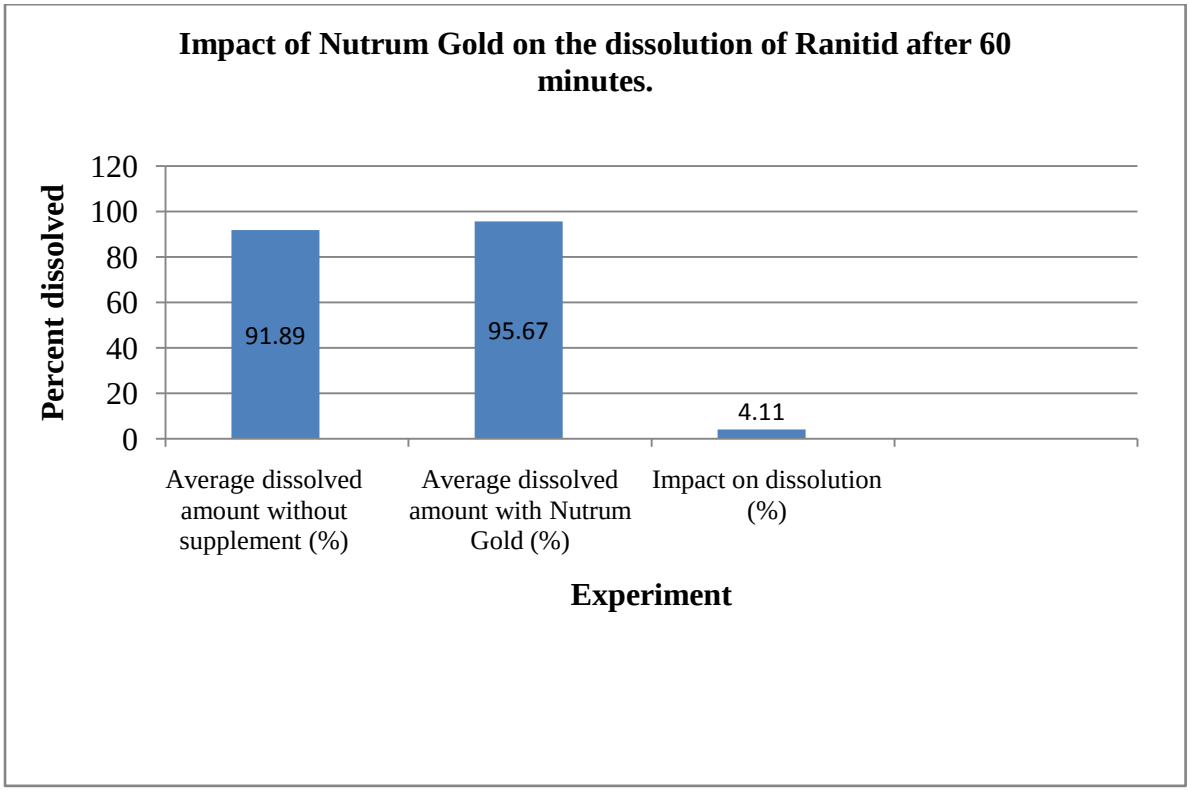

Figure 4.31 **:** Graphical representation of the impact of Nutrum Gold on the dissolution of Ranitid® after 60 minutes.

4.1.4.6 Dissolution test of Ranitid® (Ranitidine) with Filwel Silver (Multivitamin and multimineral supplement).

Table 4.54 : UV absorbance of Ranitid® (Ranitidine) with Filwel Silver (Multivitamin and multimineral supplement)

	Absorbance		
Serial number	After 20 minutes	After 40 minutes	After 60 minutes
1	0.423	0.689	0.738
2	0.488	0.672	0.731
3	0.400	0.659	0.788
4	0.509	0.712	0.743
5	0.428	0.699	0.754
6	0.493	0.700	0.769

Calculation for dissolved amount (mg) Ranitid® (Ranitidine) with Filwel Silver (Multivitamin and multimineral supplement).
By using, Y= 0.045x+0.012 equation dissolved amount of Ranitid® (Ranitidine) with Filwel Silver (Multivitamin and multimineral supplement) was calculated

Table 4.55 : Determination of Dissolved amount of Ranitid® (Ranitidine) with Filwel Silver (Multivitamin and multimineral supplement).

	After 20 minutes		After 40 minutes		After 60 minutes	
Serial number	Absorbance	Dissolved amount (mg)	Absorbance	Dissolved amount (mg)	Absorbance	Dissolved amount (mg)
1	0.423	82.20	0.689	135.4	0.738	145.20
2	0.488	95.20	0.672	132.00	0.731	143.80
3	0.400	77.60	0.659	129.40	0.788	155.20
4	0.509	99.40	0.712	140.00	0.743	146.20
5	0.428	83.20	0.699	137.40	0.754	148.40
6	0.493	96.20	0.700	137.60	0.769	151.40

4.1.4.6.1 Impact of Filwel Silver on the dissolution of Ranitid® after 20 minutes.

Table 4.56 : Percentage calculation for dissolved amount of Ranitid® (Ranitidine), Ranitid®(Ranitidine) with Filwel Silver (Multivitamin and multimineral supplement) and the impact of Filwel Silver on the dissolution of Ranitid® after 20 minutes.

Ranitid® without any supplement				Ranitid® with Filwel Silver				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
79.40		52.93		82.20		54.80		
82.60		55.07		95.20		63.47		
89.20	81.73	59.47	54.49	77.60	88.97	51.73	59.31	8.85
77.20		51.47		99.40		66.27		
92.80		61.87		83.20		55.47		
69.20		46.13		96.20		64.13		

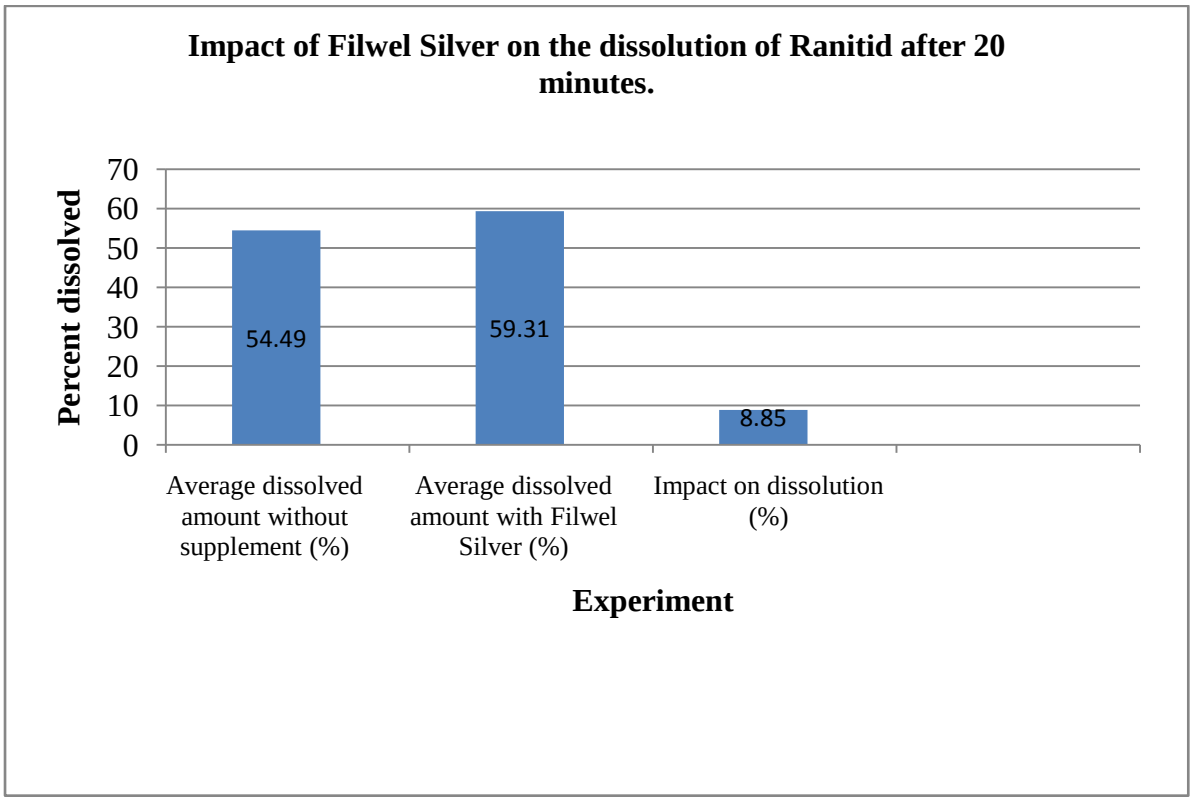

Figure 4.32 **:** Graphical representation of the impact of Filwel Silver on the dissolution of Ranitid® after 20 minutes.

4.1.4.6.2 Impact of Filwel Silver on the dissolution of Ranitid® after 40 minutes.

Table 4.57 : Percentage calculation for dissolved amount of Ranitid® (Ranitidine), Ranitid®(Ranitidine) with Filwel Silver (Multivitamin and multimineral supplement) and the impact of Filwel Silver on the dissolution of Ranitid® after 40 minutes.

Ranitid® without any supplement				Ranitid® with Filwel Silver				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
118.20		78.80		135.40		90.27		
113.60		75.73		132.00		88.00		
115.60	127.6	77.07	85.07	129.40	135.3	86.27	90.20	6.03
107.80		71.87		140.00		93.33		
161.40		107.60		137.40		91.60		
149.00		99.33		137.60		91.73		

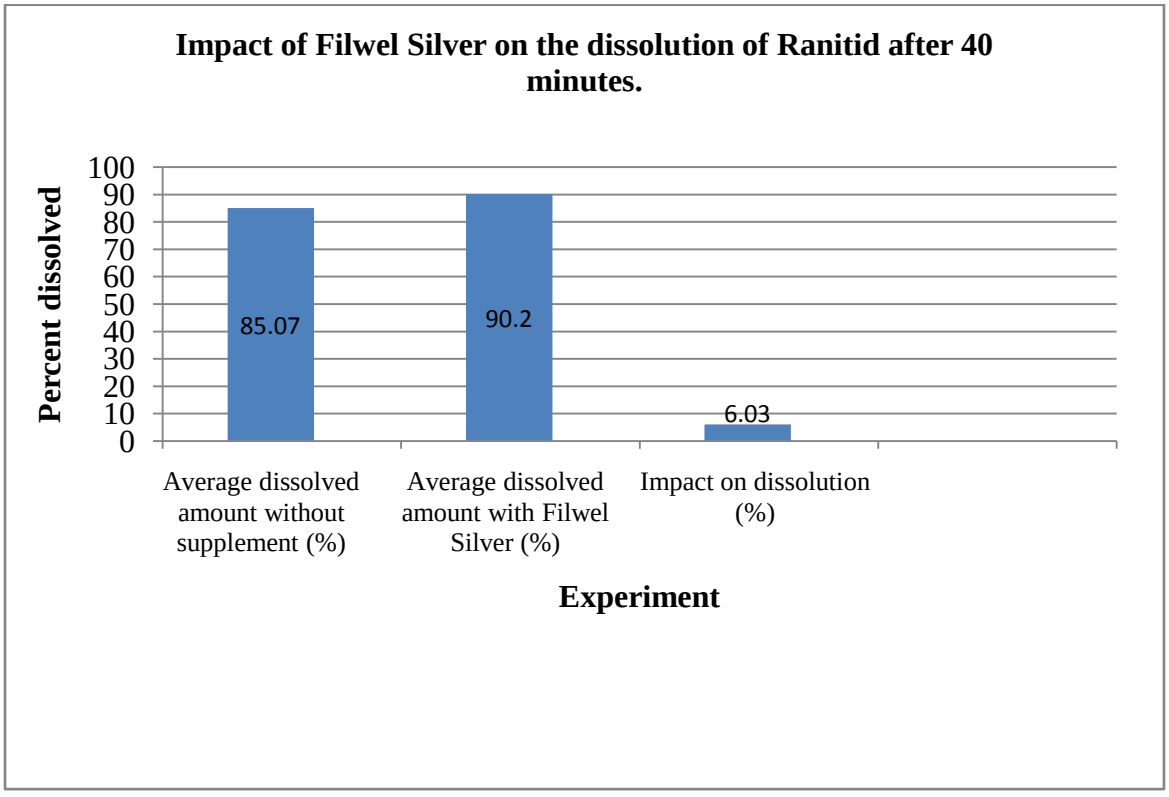

***Figure 4.33*:** Graphical representation of the impact of Filwel Silver on the dissolution of Ranitid® after 40 minutes.

4.1.4.6.3 Impact of Filwel Silver on the dissolution of Ranitid® after 60 minutes.

Table 4.58: Percentage calculation for dissolved amount of Ranitid® (Ranitidine), Ranitid®(Ranitidine) with Filwel Silver (Multivitamin and multimineral supplement) and the impact of Filwel Silver on the dissolution of Ranitid® after 60 minutes.

Ranitid® without any supplement				Ranitid® with Filwel Silver				
Dissolved amount (mg)	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Dissolved amount (mg)**	**Average dissolved amount (mg)**	**Percent dissolved amount (%)**	**Average percent dissolved amount (%)**	**Impact on dissolution (%)**
119.60		79.73		145.20		96.80		
131.60		87.73		143.80		95.87		
136.00	137.83	90.67	91.89	155.20	148.37	103.47	98.91	7.64
165.40		110.27		146.20		97.47		
137.80		91.87		148.40		98.93		
136.60		91.07		151.40		100.93		

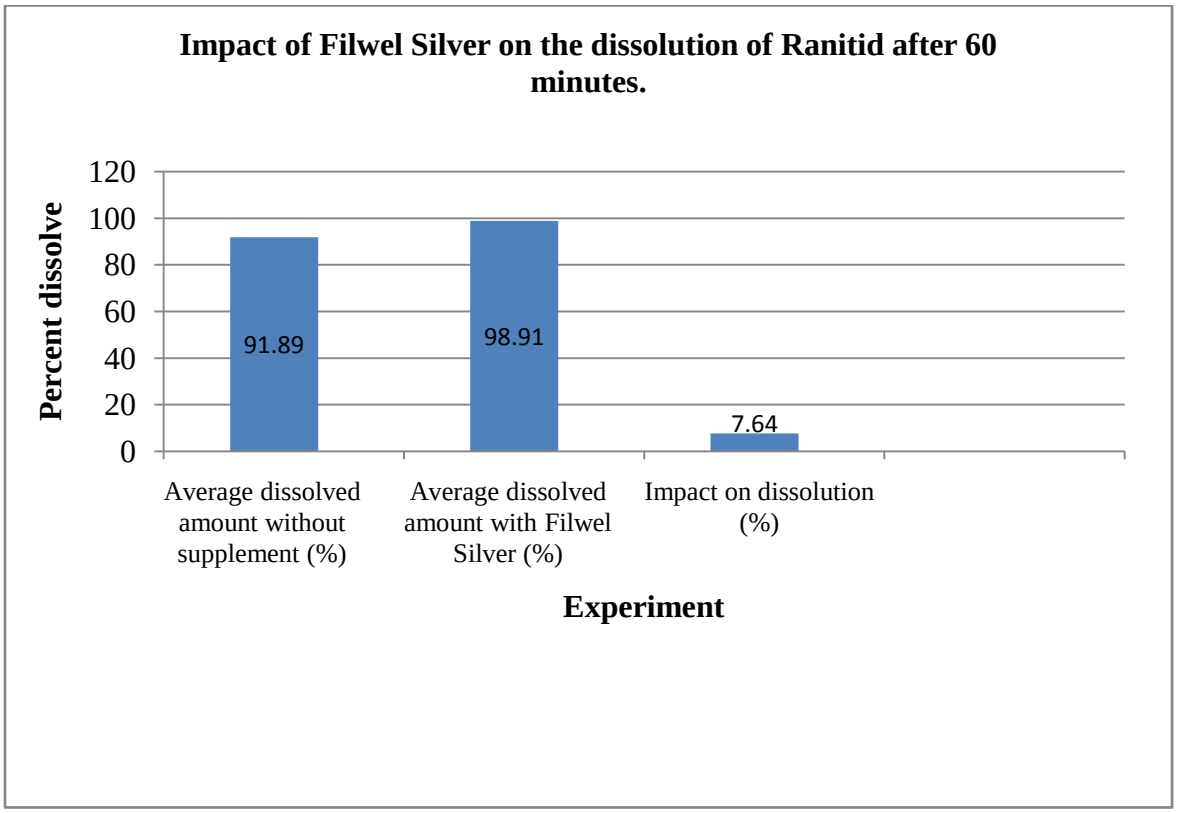

***Figure 4.34*:** Graphical representation of the impact of Filwel Silver on the dissolution of Ranitid® after 60 minutes.

4.1.5 Comparison among the average percent dissolved amount of individual Ranitid® and Ranitid® with different supplement drugs 20, 40 and 60 minutes.

4.1.5.1 Comparison among the average percent dissolved amount of individual Ranitid® and Ranitid® with different supplement drugs after 20 minutes.

Table 4.59 : Table showing the differences among the average percent dissolve (%) amount of individual Ranitid®, Ranitid® with Calbo, Ranitid® with Aristocal D, Ranitid® with Acical M, Ranitid® with Nutrum Gold and Ranitid® with Filwel silver after 20 minute.

Average percent dissolved amount of Ranitid® without supplement (%)	Average percent dissolved amount of Ranitid® with calbo (%)	Average percent dissolved amount of Ranitid® with Aristocal D (%)	Average percent dissolved amount of Ranitid® with Acical M (%)	Average percent dissolved amount of Ranitid® with Nutrum Gold (%)	Average percent dissolved amount of Ranitid® with Filwel Silver (%)
54.49	37.18	48.64	33.82	60.31	59.31

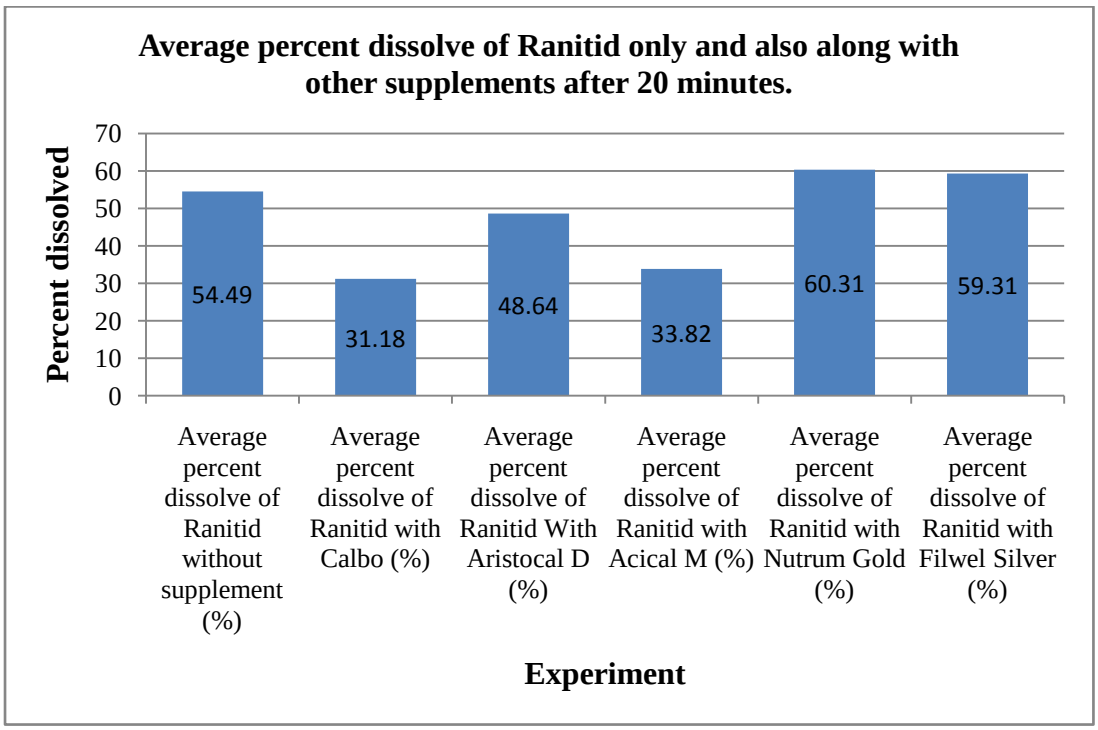

Figure 4.35: Graphical representation of the average percent dissolve of individual Ranitid® and also in combination with Calbo, Aristocal D, Acical M, Nutrum Gold, and Filwel after 20 minute.

4.1.5.2 Comparison among the average percent dissolved amount of individual Ranitid® and Ranitid® with different supplement drugs after 40 minutes.

Table 4.60 : Table showing the differences among the average percent dissolve (%) amount of individual Ranitid®, Ranitid® with Calbo, Ranitid® with Aristocal D, Ranitid® with Acical M, Ranitid® with Nutrum Gold and Ranitid® with Filwel silver after 40 minute.

Average percent dissolved amount of Ranitid® without supplement (%)	Average percent dissolved amount of Ranitid® with calbo (%)	Average percent dissolved amount of Ranitid® with Aristocal D (%)	Average percent dissolved amount of Ranitid® with Acical M (%)	Average percent dissolved amount of Ranitid® with Nutrum Gold (%)	Average percent dissolved amount of Ranitid® with Filwel Silver (%)
85.07	49.09	67.27	48.42	78.93	90.20

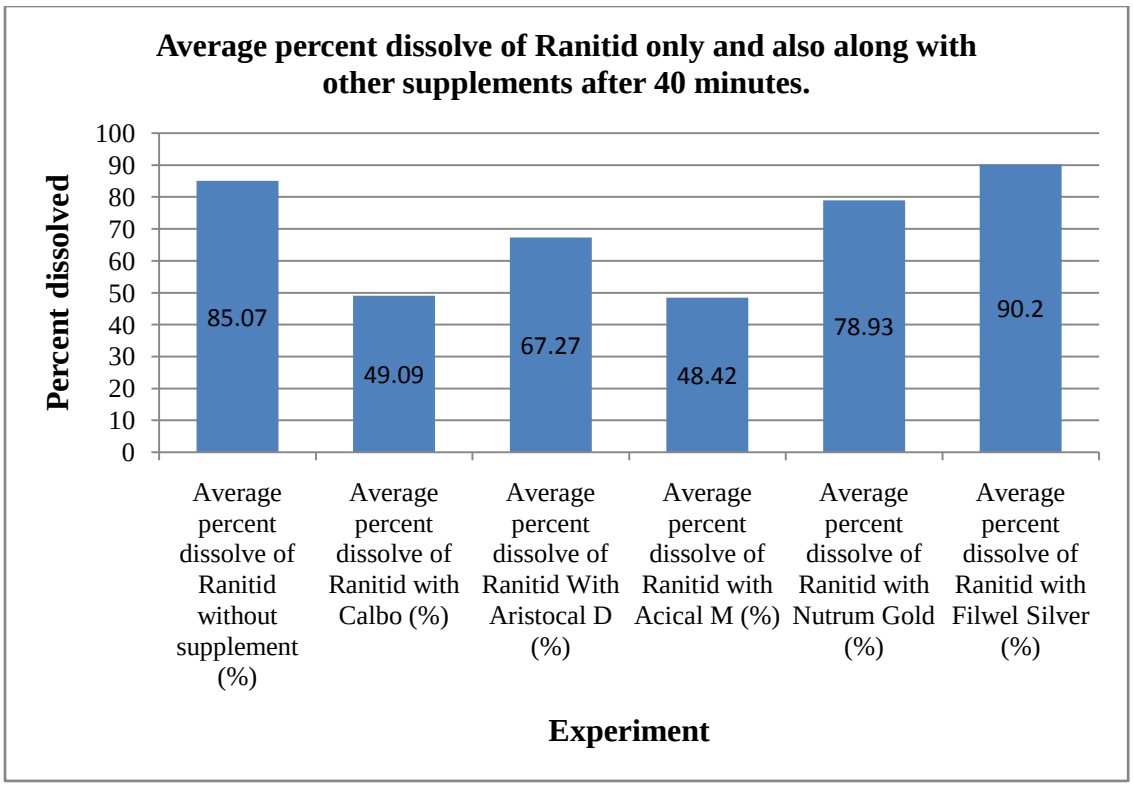

Figure 4.36: Graphical representation of the average percent dissolve of individual Ranitid® and also in combination with Calbo, Aristocal D, Acical M, Nutrum Gold, and Filwel after 40 minute.

4.1.5.3 Comparison among the average percent dissolved amount of individual Ranitid® and Ranitid® with different supplement drugs after 60 minutes.

Table 4.61 : Table showing the differences among the average percent dissolve (%) amount of individual Ranitid®, Ranitid® with Calbo, Ranitid® with Aristocal D, Ranitid® with Acical M, Ranitid® with Nutrum Gold and Ranitid® with Filwel silver after 60 minute.

Average percent dissolved amount of Ranitid® without supplement (%)	Average percent dissolved amount of Ranitid® with calbo (%)	Average percent dissolved amount of Ranitid® with Aristocal D (%)	Average percent dissolved amount of Ranitid® with Acical M (%)	Average percent dissolved amount of Ranitid® with Nutrum Gold (%)	Average percent dissolved amount of Ranitid® with Filwel Silver (%)
91.89	49.79	70.95	51.18	95.67	98.91

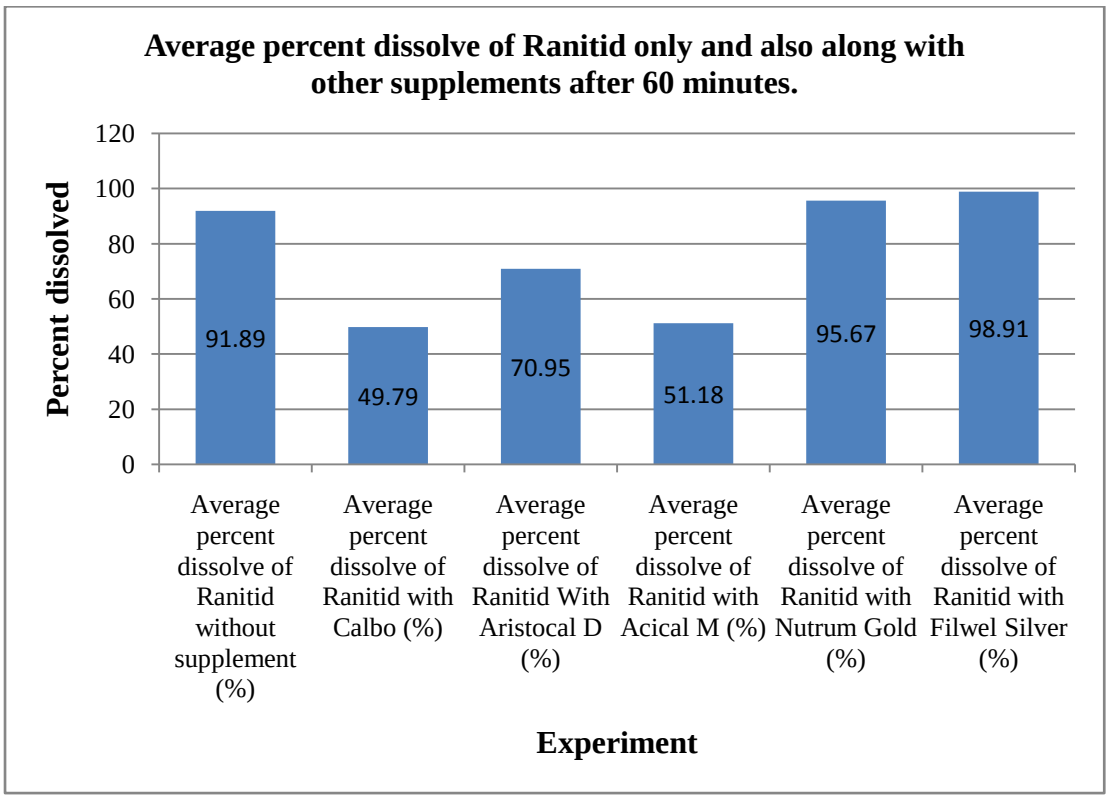

Figure 4.37: Graphical representation of the average percent dissolve of individual Ranitid® and also in combination with Calbo, Aristocal D, Acical M, Nutrum Gold, and Filwel Silver after 60 minute.

4.1.6 Result from weight variation test

Table 4.62: Weight variation of Zantac® tablets

Tablet No.	Initial weight I (mg)	Averageweight A (mg)	% Weight variation (A-I)/I *100
1	0.32		-4.06
2	0.31		-0.97
3	0.31		-0.97
4	0.31		-0.97
5	0.3	0.307	2.33
6	0.31		-0.97
7	0.3		2.33
8	0.31		-0.97
9	0.3		2.33
10	0.3		2.33

Table 4.63: Weight variation of Ranitid® tablets.

Tablet No.	Initial weight I (mg)	Average weight A (mg)	% Weight variation (A-I)/I *100
1	0.255		-4.71
2	0.239		1.65
3	0.241		0.82
4	0.242		0.41
5	0.249	0.243	-2.41
6	0.241		0.82
7	0.241		0.82
8	0.240		1.25
9	0.240		1.25
10	0.238		2.10

4.1.7 Results from thickness test

Table 4.64: Thickness of Zantac® Tablets.

Tablet No.	Main scale reading (cm), M	Vernier scale reading (cm), V	Thickness of the tablet (cm), (M+V)
1	0.3	0.06	0.36
2	0.3	0.07	0.37
3	0.3	0.05	0.35
4	0.3	0.07	0.37
5	0.3	0.06	0.36
6	0.3	0.04	0.34
7	0.3	0.08	0.38
8	0.3	0.02	0.32
9	0.3	0.08	0.38
10	0.3	0.06	0.36

Table 4.65: Thickness of Ranitid® Tablets.

Tablet No.	Main scale reading (cm), M	Vernier scale reading (cm), V	Thickness of the tablet (cm), (M+V)
1	0.3	0.06	0.36
2	0.3	0.06	0.36
3	0.3	0.06	0.36
4	0.3	0.07	0.37
5	0.3	0.06	0.36
6	0.3	0.06	0.36
7	0.3	0.06	0.36
8	0.3	0.06	0.36
9	0.3	0.08	0.38
10	0.3	0.07	0.37

4.1.8 Results from Hardness tests:

Table 4.66: Hardness of Zantac® Tablets.

Tablet No.	Hardness (Kg)	Average
1	10	
2	11	11
3	12	

Table 4.67: Hardness of Ranitid® Tablets.

Tablet No.	Hardness (Kg)	Average
1	15.8	
2	16	16.27
3	17	

4.2 Discussion

Weight variation of sample tablets (Zantac® & Ranitid®) indicated the uniformity of the solid dosage forms. USP provides an accepted percentage for weight variation test and our products were within that range. The hardness of the tablets are slightly increased with the increase in weight content without much variation in content uniformity of weight. Weight variation test indicates the good manufacturing practice (GMP), appropriate size of the tablets and the content uniformity of the formulation (Nasrin et al., 2011).

The thickness of all tablets (Zantac® & Ranitid®) were determined by vernier calipers and all values were closed. Thickness determination was important because it relates with tablet hardness. If the thickness of a tablet is materially changed, then all tablet hardness comparisons will become incorrect (Pitt and Heasley, 2013).

Hardness determination was important because the dissolution of a drug product depends on its hardness. The hardness increase caused by higher compression loads in the absence of a moisture-induced effect, which is responsible for decrease in the in vitro dissolution as the hardness was increased (Chowhan and Palagyi, 1978). If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications (Nasrin et al., 2011).

The result of dissolution tests showed that the dissolution of Zantac® or Ranitid® (Ranitidine) was extremely decreased in the presence of Calbo (Calcium supplement) and Acical M (Calcium,vitamin D & mineral supplement) .Dissolution in the presence of Calbo and Acical-M were 47.84% and 48.47% respectively for Zantac® and 49.79% and 51.18% respectively for Ranitid® after 60 minutes. As the dissolution was affected, there is a chance of Zantac® or Ranitid® not to reach to the Minimum Effective Concentration (MEC) (Le, 2016), and it will fail to give the therapeutic effect. So Zantac® or Ranitid® should not be administered with Calbo and Acical M. The dissolution of Zantac® or Ranitid® was moderately decreased in the presence of Aristocal D (Percent dissolve in presence of Aristocal D was 72.6% for Zantac® and 70.95% for Ranitid® after 60 minutes). As the dissolution was affected, this indicates the absorption can also be affected (Le, 2016). So Zantac® or Ranitid® should not be administered with Aristocal D.

Nutrum Gold and Filwel Silver (Multivitamin and multimineral) were not decreased the dissolution of Zantac® & Ranitid® (Percent dissolved in presence of Nutrum Gold and Filwel Silver were 94.27% and 97.22% respectively for Zantac®; 95.67% and 98.91% respectively for Ranitid® after 60 minutes). So absorption of Zantac® & Ranitid® will not be affected in the presence of Nutrum Gold or Filwel Silver (Multivitamin and multimineral) and efficacy will not be hampered. So Nutrum Gold or Filwel Silver (Multivitamin and multimineral) can be co-administered with Zantac® or Ranitid®.

Chapter Five

Conclusion

The investigation report of the study showed the extreme impact of Calbo(Calcium tablet) and Acical M (Calcium, vitamin D and mineral supplement) on the dissolution of Zantac® and Ranitid® (Ranitidine tablet). Aristocal D(calcium and vitamin D supplement) was moderately decreased the dissolution of Zantzc and Ranitid® (Ranitidine tablet) but the dissolution of Zantac® and Ranitid® were not decreased by the presence of Nutrum Gold or Filwel Silver (Multivitamin and multimineral). So Zantac® or Ranitid® can be co-administered with Nutrum Gold or Filwel Silver.

Chapter Six

References

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