Impact of Different types of Multivitamins, Multiminerals, Calcium and Vitamin supplement drugs on dissolution profile of Zantac® & Neoceptine®

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

Submitted by

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Declaration by the Research Candidate

I, MD. Jahidul Haque, ID: 2012-1-70-022, hereby declare that the dissertation entitled "**Impact of Different types of Multivitamins, Multiminerals, Calcium and Vitamin supplement drugs on dissolution profile of Zantac® & Neoceptine®** " submitted by me to the Department of Pharmacy, East West University and in the partial fulfillment of the requirement for the award of the degree Bachelor of Pharmacy, under the supervision and guidance Md. Anisur Rahman, Senior Lecturer, Department of Pharmacy, East West University, Dhaka.

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Certificate by the Supervisor

This is to certify that the thesis entitled " **Impact of Different types of Multivitamins, Multiminerals, Calcium and Vitamin supplement drugs on dissolution profile of Zantac® & Neoceptine®** " submitted to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the award of the degree Bachelor of Pharmacy is a record of original and genuine research work carried out by MD. Jahidul Haque, ID: 2012-1-70-022 during the period 2016 of his research in the Department of Pharmacy, East West University, under the supervision and guidance of me.

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Senior Lecturer

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Certificate by the Chairperson

This is to certify that the thesis entitled **"Impact of Different types of Multivitamins, Multiminerals, Calcium and Vitamin supplement drugs on dissolution profile of Zantac® & Neoceptine®"** submitted to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the award of the degree Bachelor of Pharmacy is a record of original and genuine research work carried out by MD. Jahidul Haque, ID: 2012-1-70-022 during the period 2016 of his research in the Department of Pharmacy, East West University.

Dr. Shamsun Nahar Khan

Associate Professor & Chairperson

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Dedication

This research work is dedicated to my beloved parents, honorable faculties and loving friends.

ABSTRACT

The research work was proposed to find out the impact of Acical-M (Calcium, Vitamin & Minerals tablet), Calbo (Calcium supplement tablet), Aristocal D (Calcium & vitamin-D Tablet), Filwel Silver (Multivitamin Silver Tablet) and Nutrum Gold (Multivitamin & Multiminerals Tablet) on the dissolution of Ranitidine (Zantac & Neoceptine). Zantac is parent product of Ranitidine produced by GlaxoSmithKline Bangladesh and Neoceptine is the brand name of Ranitidine produced by Square Pharmaceutical Ltd. To determine the physical parameters of Ranitidine tablet, some important tests such as weight variation test, hardness test and thickness test were performed. The dissolution test was performed by using distilled water (used as dissolution medium) with USP dissolution apparatus II followed by UV Spectroscopy. The dissolution of individual Ranitidine tablets and also with the combination of following supplements, were determined after 20, 40 and 60 minutes. After 60 minute, the percent dissolved amount of individual Zantac and Zantac with Calbo, Acical-M, Filwel Silver , Aristocal D and Nutrum Gold were 94.09%, 47.84%, 48.47%, 97.22% 72.6% and 94.27% respectively and in case of Neoceptine those values were 106.7% ,58.74%, 57.25%, and 52.71%, 83.43%, and 98.91% respectively. From the result it was assumed that Calbo 500 and Acical-M have extreme effect, Filwel Silver has moderate effect and Nutrum Gold & Aristocal D have less effect on the dissolution of Zantac & Neoceptine. Therefore, the absorbance and bioavailability can be effected in the presence of Calbo 500, Acical-M and Filwel Silver. So, this supplements shouldn't administer with Zantac or Neoceptine. On the other hand Nutrum Gold & Aristocal-D can be administered with as they have less or no effect on the dissolution.

Keywords: Ranitidine, Dissolution, UV-spectroscopy, Distilled water, Absorbance, Dissolution apparatus II.

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Chapter One

Introduction

Introduction

1.1 Histamine 2 blocker:

Histamine 2 blockers or antagonists are widely used in the treatment of acid-peptic disease, duodenal and gastric ulcers, gastro esophageal reflux disease and common heartburn, reflux esophagitis and miscellaneous minor upper gastrointestinal symptoms. H2 antagonists reduce the production of stomach acid. This makes the stomach juices less acidic so that any stomach juice that gets into the esophagus is less irritating. This relieves symptoms and allows the esophagus to heal. Currently, there are four H2 blocker available in the market. They include cimetidine, famotidine, nizatidine and ranitidine. They are also called 'histamine H2-receptor antagonists' but are commonly called H2 blockers**,** H2 blocker antagonist is OTC drug & these drugs are most used in medicine. These blockers are well tolerated. This blockers work by decreasing the amount of acid reduced by the stomach (Manocha, 2016).

1.2 Development of Histamine:

In early 1990s at first Sir James Black developed selective H2 blockers. Sir James Black got novel Nobel Prize for his work developing selective receptor antagonists for clinical use. In 1983 ranitidine are first approved in the United State. Ranitidine was introduced in 1981 and was the world's biggest-selling prescription drug by 1988. The H_2-receptor antagonists have since largely been superseded by the even more effective proton pump inhibitors, with omeprazole becoming the biggest-selling drug for many years. The initial H2 blocker approved for use in the United States was cimetidine (1977), which was followed by ranitidine (1983), famotidine (1986), and nizatidine (1988). All four of these agents are available by prescription and as over-the-counter oral formulations. Intravenous and intramuscular forms are available for cimetidine, ranitidine and famotidine. The four

H2 receptor blockers available in the United States have similar spectra of activity, side effects and clinical indications (Cima and Franchi, 2016).

These medications are extremely well tolerated and are used by a high proportion of the general population to treat peptic ulcer disease, heartburn, esophagitis, and miscellaneous minor upper gastrointestinal symptoms. Their listed indications are for treatment of gastric and duodenal ulcer and esophageal reflux disease, and to prevent stress ulcers. Side effects are uncommon, usually minor and include diarrhea, constipation, fatigue, drowsiness, headache and muscle aches. The H2 receptor blockers are metabolized in the liver by the cytochrome P450 system. Among the four agents, cimetidine is distinctive in its potent inhibition of the P450 system (CYP 1A2, 2C9 and 2D6), which can result in significant drug interactions. All four H2 receptor blockers have been implicated in rare cases of clinically apparent, acute liver injury. The most cases have been linked to ranitidine and cimetidine, but these two agents are also the most commonly used (Azizollahi and Rafeey, 2016).

1.3 Mechanism of H2 receptor antagonist:

Histamine 2 receptors are mainly present in the stomach parietal cell. H2 blocker antagonist binds to the H2 receptor of the on the basolateral (ant luminal) surface of gastric parietal cells. And so, the gastric acid production and secretion pathway blocked and stop the acid secretion into the stomach. H2 selective blockers have little or no effect on the histamine type 1 receptors which are blocked by antihistamine used to treat allergic reaction. But H2 antagonist blockers is less potent in inhibiting acid secretion than the proton pump inhibitors (Panula *et al.,* 2015).

1.4 General information of ranitidine:

1.4.1 Ranitidine

Ranitidine is in a group of drugs called histamine-2 blockers. A non-imidazole blocker of those histamine receptors that mediate gastric secretion (H2 receptors). It is popular drug to treat gastrointestinal ulcers. The chemical or IUPAC name of ranitidine is dimethyl [(5-{[(2-{[(E)-1-(methylamino)-2-nitroethenyl]amino}ethyl)sulfanyl]methyl}furan-2-yl)methyl]amine.The average weight of ranitidine is .314 gm. The chemical formula of the drug is $C_{13}H_{22}N_4O_3S$. The structure of ranitidine is given bellow (Drugbank, 2013).

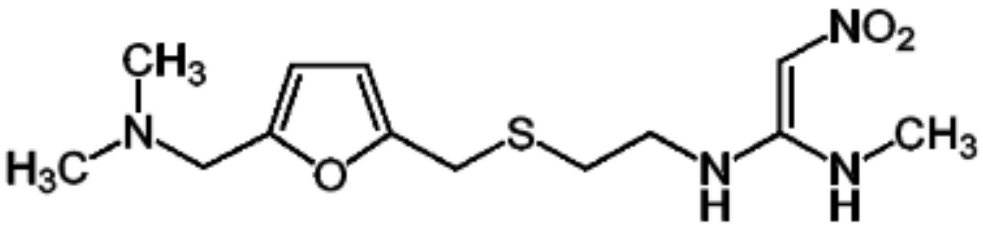

Figure 1.1: Ranitidine (2014) (Roosevelt et al., 2014)

1.4.2 Pharmacology of ranitidine:

1.4.3 Indication of ranitidine: Ranitidine is used to treat

- ✓ duodenal ulcer
- ✓ peptic ulcer disease (PUD)
- ✓ Dyspepsia
- ✓ stress ulcer prophylaxis
- ✓ gastro esophageal reflux disease (GERD)

- ✓ Zollinger-Ellison syndrome
- ✓ erosive esophagitis
- ✓ stomach pain, heartburn
- ✓ difficulty swallowing

(Drugbank, 2013)

1.4.4 Pharmacodynamics:

Ranitidine is a H2 blocker which is similar to cimetidine and famotidine. H2 blocker is a drug 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 (drugbank, 2013).

1.4.5 Mechanism of action:

H2 blocker is a competitive, reversible inhibitor of the action of histamine at the histamine H_2 receptors found in gastric parietal cells. The normal secretion of acid by parietal cells and the meal-stimulated secretion of acid are suppressed by H2 blockers. Histamine released by ECL cells in the stomach is blocked from binding on parietal cell H2 receptors which stimulate acid secretion, and other substances that promote acid secretion (such as gastrin and acetylcholine) have a reduced effect on parietal cells when the H2 receptors are blocked (drugbank, 2013).

These drugs work on the H2 receptor, or histamine-2-receptor, located on the GPC or gastric parietal cell membrane. Gastrin is a hormone produced by G-cells in the stomach antrum (the lower part of your stomach) and normally in response to smell and taste stimulation. Gastrin has an effect on the enterochromaffin like cells or ECL's to produce histamine. Histamine normally stimulates the H2 receptor which activates adenylatecyclase to convert ATP (or adenine triphosphate) to cAMP (cyclic adenine

monophosphate). With this energy production, the enzyme protein kinase is activated which stimulates the proton pump to pump hydrochloric acid in to the stomach and potassium in to the cell. The drugs block the H2 receptor so that this process is blocked and acid isn't 'pumped' in to the stomach (Thatcher et al., 2016).

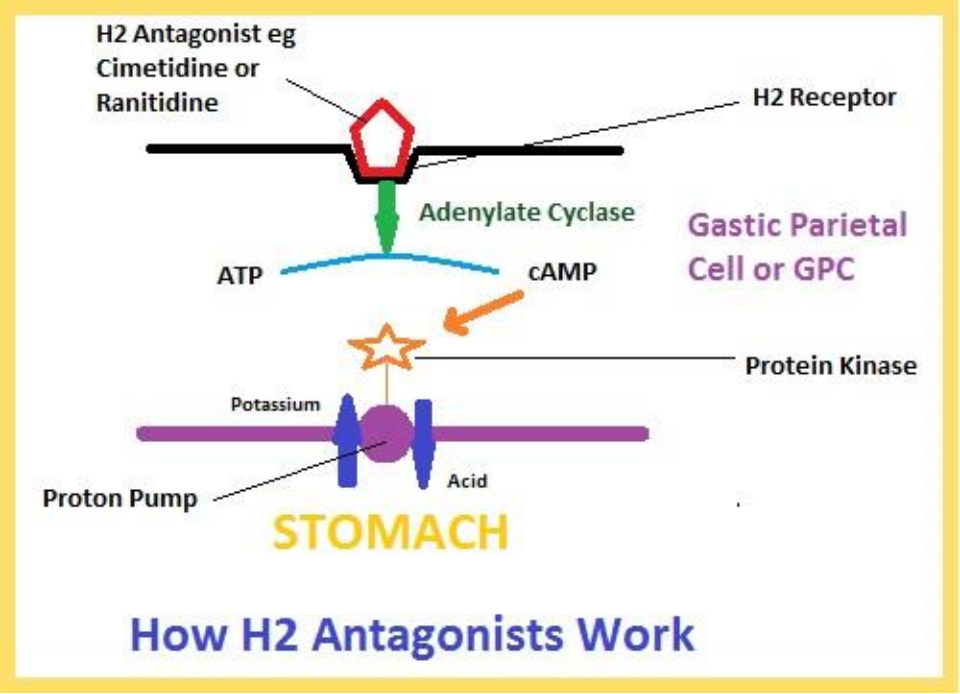

Figure 1.2: Mechanism of ranitidine (Thatcher, 2016)

1.4.6 Pharmacokinetics of Ranitidine:

1.4.6.1 Absorption: Ranitidine is 50% absorbed after oral administration. Approximately 50% bioavailability orally (Drugbank, 2013).

1.4.6.2 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).

1.4.6.3 Protein Binding: Ranitidine protein binding is 15 %.(Drugbank, 2013).

1.4.6.4 Metabolism: Ranitidine is metabolized in liver. It is metabolized to the N-oxide, S-oxide, and N-dimethyl metabolites, accounting for approximately 4%, 1%, and 1% of

the dose, respectively (Drugbank, 2013).

1.4.6.5 Route of elimination:

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

1.4.6.6 Half-life: The half-life of ranitidine is 2.8-3.1 hours (Drugbank, 2013).

1.4.6.7 Clearance: 29 mL/min [clinically significant renal function impairment] ,3 mL/min/Kg [neonatal patients](Drugbank,2013).

1.4.6.8 Toxicity: There has been limited experience with overdose. Symptoms of overdose include muscular tremors, vomiting, and rapid respiration. The LD_{50} on mice orally is 77mg/kg (Drugbank, 2013).

1.4.7 Adverse effect: (Christophoridis *et al.,* 2016)

✓ headache (may be severe);	✓ nausea, vomiting,
✓ anaphylaxis	✓ stomach pain;
✓ drowsiness, dizziness;	✓ diarrhea
✓ sleep problems (insomnia);	✓ constipation
✓ decreased sex drive,	✓ Hypersensitivity
✓ impotence	✓ Rash
✓ difficulty having an orgasm;	✓ Urticarial
✓ swollen	✓ Bronchospasm
✓ tender breasts (in men);	✓ acute eosinophilia pneumonia
✓ nausea, vomiting,	✓ anaphylaxis
✓ stomach pain;	

1.4.8 Drug interaction: (Kim, 2015)

✓ Warfarin	The serum concentration of Warfarin can be increased when it is combined with Ranitidine
✓ Aripriprazole	The serum concentration of Aripiprazole can be increased when it is combined with Ranitidine.
✓ Bupropion	The serum concentration of Ranitidine can be increased when it is combined with Bupropion.
✓ Cefditoren	The serum concentration of Cefditoren can be decreased when it is combined with Ranitidine.
✓ Cefuroxime	Ranitidine can cause a decrease in the absorption of Cefuroxime resulting in a reduced serum concentration and potentially a decrease in efficacy.
✓ Cysteamine	The therapeutic efficacy of Cysteamine can be decreased when used in combination with Ranitidine.
✓ Verapramil	The serum concentration of Ranitidine can be increased when it is combined with Verapamil.
✓ Erlotinib	The serum concentration of Erlotinib can be decreased when it is combined with Ranitidine.
✓ Doxofylline	The serum concentration of Doxofylline can be increased when it is combined with Ranitidine.
✓ Dasatinib	Ranitidine can cause a decrease in the absorption of Dasatinib resulting in a reduced serum concentration and potentially a decrease in efficacy.
✓ Glicazide	The serum concentration of Gliclazide can be increased when it is combined with Ranitidine.

1.4.8.1 Food interactions: (Kakuda and Falcon, 2006)

- ✓ Avoid alcohol
- ✓ Avoid excessive quantities of coffee or tea (caffeine)
- ✓ Take without regards to meal

1.4.9 Dosage from: (Drugbank, 2013)

✓ Oral tablet
✓ Oral syrup
✓ Injectable solution
✓ Oral capsule
✓ Effervescent
✓ Intravenous solution
✓ Oral granule
✓ Compounding powder

1.4.9.1Dose: (Healthline, 2015)

Oral tablet strengths:	75mg, 150mg, 300mg
Oral capsule strengths:	150mg, 300mg
Oral syrup strengths:	75mg/5 ml

1.4.10 Dose schedule: (Healthline, 2015)

1.4.10.1 Usual Adult Dose for Duodenal Ulcer

Oral: 150 mg 2 times a day, or 300 mg once a day after the evening meal or at bedtime. Parenteral: 50 mg, IV or IM, every 6 to 8 hours. Alternatively, a continuous IV infusion may be administered at a rate of 6.25 mg/hour over 24 hours.

1.4.10.2 Usual Adult Dose for Dyspepsia

75 mg orally once daily (Over-the-counter) 30 to 60 minutes before meal. Dose may be increased to 75 mg twice daily. Maximum duration of therapy if self-medicating is 14 days.

1.4.10.3 Usual Adult Dose for Erosive Esophagitis

Oral: Initial: 150 mg 4 times a day.
Maintenance: 150 mg twice daily.

Parenteral: 50 mg, IV or IM, every 6 to 8 hours. Alternatively, a continuous IV infusion may be administered at a rate of 6.25 mg/hour over 24 hours.

1.4.10.4 Usual Adult Dose for Gastro esophageal Reflux Disease

Oral: 150 mg twice daily.
Parenteral: 50 mg, IV or IM, every 6 to 8 hours.

1.4.10.5 Usual Adult Dose for Gastric Ulcer

Benign Gastric Ulcer -
Oral: 150 mg twice a day.
Parenteral: 50 mg, IV or IM, every 6 to 8 hours.

1.5 Introduction of Calbo® 500 (Calcium supplement):

Calbo® 500 is product of square pharmaceutical ltd. It containing calcium carbonate that is used as dietary supplement. Calcium is very important for our body development. Calcium is very important for the bone also.

1.5.1 Composition:

Calbo® 500 each tablet contain calcium carbonate 1.25gm is equivalent to 500mg of calcium.

(Square, 2016)

1.5.2 Pharmacology:

Calcium carbonate reacts with gastric acid to produce a salt and water. For calcium carbonate the postulated chemical reaction is:

$CaCO3 + 2HCl = CaCl2 + H2O + CO2$

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, 2016).

1.5.3 Indication:

Calcium Carbonate is used for the treatment or prevention of calcium depletion in patients in whom dietary measures are inadequate.

- ✓ hypoparathyroidism,
- ✓ achlorhydria,
- ✓ chronic diarrhea,
- ✓ vitamin D deficiency,
- ✓ steatorrhea,
- ✓ sprue,
- ✓ pregnancy and lactation,
- ✓ hyperphosphataemia.

- ✓ hyperphosphataemia

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, 2016).

1.5.4 Dosage & Administration:

Calcium Carbonate is always used orally and when used as an antacid the ecommended doses for adults are equivalent to 540-2000 mg Calcium crbonate per day, doses for children being half of those for adults. As a ietary supplement, such as for the prevention of osteoporosis, 1250-3750

mg Calcium Carbonate (500-1500 mg calcium) daily is recommended in general, but again this will need to be tailored to the individual patient depending on any specific disease such as Calcium deficiency, metabolism roid function. In pregnancy and lactation the recommended daily dose of calcium is 1200-1500 mg. In chronic renal ailure the doses used vary from 2.5 - 9.0 gm Calcium Carbonate per day and need to be adjusted according to the individual patient. To maximize effectiveosphate binding in this context the Calcium Carbonate should be given with meals (Square, 2016).

1.5.5 Side effect: (Square, 2016)

- ✓ Orally administered Calcium Carbonate may be irritating to the GI tract.
- ✓ It may also cause constipation.
- ✓ Hypercalcaemia is rarely produced by administration of calcium alone, but may occur when large doses are given to patients with chronic renal failure.

1.5.6 Contraindication & precaution: (Square, 2016)

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

1.5.7 Drug interaction:

Calcium Carbonate may enhance the cardiac effects of digoxin and other cardiac glycosides, if systemic hypercalcaemia occurs. Calcium Carbonate may interfere with the absorption of concomitantly administered tetracycline preparations and 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, 2016).

1.5.8Use in pregnancy & lactation: (Square, 2016)

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.

1.5.9 Use in children & elderly:

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

1.5.10 Storage condition:

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

Supplied: Calbo® 500: Box containing 3 x 10 tablets in blister pack. (Square, 2016)

Figure1.3: Calbo® 500 (Calcium supplement)

1.6 Introduction of Filwel® Silver (Multivitamins & Multiminerals):

1.6.1 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 250 mcg, Lycopene 300 mcg (Square, 2016).

Figure1.4: Filwel® Silver (Multivitamins & Multiminerals) (Square, 2016)

1.6.2 Indication:

Filwel® Silver is specially formulated for the prevention and treatment of vitamin and mineral deficiencies for adults over 45 years of age. Filwel® Silver is also indicated to meet the increase demands of vitamin and minerals for adults over 45 years of age (Square, 2016).

1.6.3 Dosage & Administration: (Square, 2016)

One tablet daily with food. Not formulated for use in children.

1.6.4 Side effects:

This preparation is well tolerated. Diarrhea may occasionally occur during treatment with beta carotene and the skin may assume a slightly yellow discoloration. The side effects of vitamin A are reversible. Vitamin C and vitamin E may cause diarrhea and other gastrointestinal disturbances (Square, 2016).

1.6.5 Contraindication & precaution:

This product is contraindicated in patients with known hypersensitivity to any of the ingredients. Do not take this product if taking other vitamin A supplements. Long term intake of high levels of vitamin A (excluding that sourced from beta carotene) may increase the risk of osteoporosis in postmenopausal women (Square, 2016).

1.6.6 Use in pregnancy & lactation:

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

1.6.7 Drug interaction:

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

1.6.8 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, 2016)

Preparation**:** Filwel® Silver: 30 tablets in HDPE bottle. (Square, 2016)

1.7 Introduction of Acical-M® (Calcium +Vitamin D + Minerals tablet):

1.7.1 Description:

In osteoporosis and bone related disorder the most important thing is nutrition. The macro nutrient for bone is Calcium, magnesium and Vitamin D. the calcium absorption is very little. The bone strength and rigidity is increased by the calcium & magnesium. Current 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, 2013).

1.7.2 Indications & Uses: (ACI, 2013)

- ✓ 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

1.7.3 Dose & Administration: 2 tablets per day, preferably 1 tablet in the morning and 1 tablet in the evening (ACI, 2013).

1.7.4 Side effects: (ACI, 2013)

The use of calcium supplements has, rarely, given rise to mild gastro-intestinal disturbances, such as

- ✓ constipation,
- ✓ flatulence,
- ✓ nausea,
- ✓ gastric pain,
- ✓ diarrhoea.
- ✓ occasional skin rash
- ✓ . Hypercalciuria
- ✓ Hypocalcaemia

1.7.5 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 hypercalciuria (ACI, 2013).

1.7.6 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 these agents from other sources (ACI, 2013)

1.7.7 Contraindications:

Hypersensitivity to any of the tablet ingredients. Absolute contraindications are hypercalcaemia resulting for example from myeloma, bone metastases or other malignant bone disease, sarcoidosis; primary hyperparathyroidism and vitamin D overdosage. Severe renal failure (ACI, 2013).

1.7.8 Drug interactions: (ACI, 2013)

- ✓ digoxin,
- ✓ antacids containing calcium,
- ✓ aluminium or magnesium,
- ✓ calcium supplements,
- ✓ calcitriol
- ✓ vitamin D supplements;
- ✓ tetracycline,
- ✓ doxycycline,
- ✓ minocycline
- ✓ oxytetracycline etc.

1.7.9 Overdose:

The most serious consequences of acute or chronic overdose is hypocalcaemia. (ACI, 2013)

1.7.10 Pharmaceutical precautions: Should be stored in cool place (below 30ºc) and dry place. Keep out of reach of children. (ACI, 2013)

Presentation:

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, 2013).

Package quantities:

Acical-M® Tablet: Each container contains 30 tablets. (ACI, 2013)

1.8 Introduction of NUTRUM® GOLD (Multivitamins & Multiminerals):

1.8.1 Introduction:

Nutrum Gold tablet is for adult. It is a complete well-balanced multivitamin and multimineral supplement. It is one of the most comprehensive multivitamins available, this product is suitable for most adults (Acme, 2014).

Figure1.5: Nutrum Gold (Acme, 2014)

1.8.2 Ingredient of Nutrum Gold:

The main ingredient of the Nutrum gold is 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, 2014).

1.8.3 Indications:

This multivitamin and Multiminerals is mainly for the adult treatment. This product is used for the Deficiency of the vitamin & mineral. Some time it may administer for osteoporosis. Over 45 age Patient should take regularly one (Acme, 2014).

1.8.4 Dosage and administration:

This Nutrum gold should take one tablet daily at night. And also this drug should administer with meal (Acme, 2014).

1.8.5 Contraindications:

This product is contraindicated in patients with known hypersensitivity to any of its ingredients.

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 (Acme, 2014).

1.8.7 Side effects: Generally well tolerated. Allergic sensitization has been reported following oral administration of folic acid (Acme, 2014).

1.8.9 Use in pregnancy and lactation: As with any supplement, pregnant women or nursing mother should consult with a doctor.

1.8.10 Drug interactions: No prominent drug interactions have been reported (Acme, 2014).

Information: 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 taking other vitamin A supplements (Acme, 2014).

Supply: (Acme, 2014)

30-Tablet Pack: Each airtight plastic container contains 30 tablets.

15-Tablet Pack: Each airtight plastic container contains 15 tablets.

1.9 Introduction of ARISTOCAL® D *(*Calcium + Vitamin D Tablet):

1.9.1 Description:

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

1.9.2 Indications:

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 hypophosphatemia. Treatment of chronic renal failure (Beximco, 2015).

1.9.3 Dosage and Administration:

One tablet twice daily with food or as directed by the physician (Beximco, 2015).

1.9.4 Contraindications:

Aristocal® D is contraindicated in patients who have known hypersensitivity to any of the components of this preparation. Precautions Caution should be taken in patients with renal impairment, Sarcoidosis, Hypercalcemia and Hypercalciuria (Beximco, 2015).

1.9.5 Adverse Reactions:

Aristocal® D is well tolerated. Mild gastrointestinal disturbances may occur (Beximco, 2015).

1.9.6 Drug Interactions:

Concurrent administration of Thiazide diuretics may increase the risk of hypercalcemia. Bran decreases the gastro-intestinal absorption of calcium, and may therefore decrease the efficacy of calcium supplements. Calcium salts reduce the absorption of a number of other

drugs such as Biphosphonates, Fluoride, some Fluoroquinolones and Tetracyclines (Beximco, 2015).

1.9.7 Pharmaceutical Precaution: Store in a cool and dry place. Keep out of the reach of children (Beximco, 2015).

Figure 1.6: Aristocal® D (Beximco, 2015)

Chapter two

Literature review

Literature review

In the year of 1980, there was conducted a comparative study of cimetidine and new H2-receptor antagonist, ranitidine (Kett *et al*, 1980). The objective of the study was to inhibit gastric secretion in man of new ranitidine. The study was held in nine healthy subjects, the inhibition of pentagastrin-evoked gastric secretion of acid and pepsin was compared with the new ranitidine & cimetidine. Cimetidine & new ranitidine H2 receptor antagonist was administered to the healthy subjects in different days by continuous intravenous infusion. Finally, in the result showed that ranitidine inhibitory effect was 6 & 7.3 times potent as cimetidine respectively on weight & a molar basis.

In the year of 1982 there had been a study of ranitidine that was Ranitidine kinetics in normal subjects. A 1-mg/kg IV bolus injection and a 150-mg (one tablet) oral dose of ranitidine were given to seven normal subjects. At least 1 wk. separated the two doses. Ranitidine disappeared from plasma with a half-life of about 2.5 hr. Half of the oral dose was effectively absorbed and half of the absorbed amount was found unchanged in urine. Total body clearance was 10.1 ml/min/kg. Urinary clearance was the same after oral and intravenous doses (6.4 and 6.9 ml/min/kg, P greater than 0.10). Intravenous ranitidine kinetics included three phases, with a central distribution volume of 0.2 l/kg and a total distribution volume of 1.2 l/kg. Absorption kinetics were apparently order zero: of the 150-mg dose, 75 mg was absorbed during 5 hr at a constant rate of 15 mg/hr (Chau *et al.*, 1982).

The methods available for assaying ranitidine in plasma and both the drug and its metabolites in urine are high-performance liquid chromatography and radioimmunoassay. Following oral administration, the absorption of ranitidine in normal individuals has been found to be rapid, with peak plasma concentrations occurring at 1 to 3 hours. Ranitidine

penetrates very poorly into the cerebrospinal fluid but is concentrated into breast milk. Elimination of ranitidine is not dose-dependent. Hepatic metabolism is the other major route of elimination and there may be some enter hepatic recycling of the drug. Chronic liver disease causes an increase in the bioavailability of ranitidine and some reduction in clearance. In the elderly, there is a reduction in clearance and prolongation of the elimination half-life but little effect on bioavailability. There is a relationship between plasma concentrations of ranitidine and suppression of gastric acid production but wide inter individual variability (Roberts, 1984).

The bioavailability of two brands of ranitidine tablets was studied in 10 healthy volunteers. Formulation factors were compared by performing disintegration, dissolution and content uniformity tests. Plasma concentrations of ranitidine were measured using a sensitive and precise high pressure liquid chromatographic (HPLC) procedure. Pharmacokinetic parameters were determined for both formulations and included: Cmax, AUCt, AUC infinity, tmax, t1/2 and the terminal rate of elimination (k). Statistical analysis revealed that differences between the brands were not significant. The two formulations can be considered to be bioequivalent (Alkaysi *et al*, 1989).

The authors conducted a retrospective review of 21 United States trials of ranitidine in acid peptic diseases and compared the adverse events in elderly (> or = 65 years) and nonelderly (< 65 years) patients. Ranitidine dosages ranged from 150 mg/day to 300 mg twice daily for treatment periods of 4 to 52 weeks. Of the 4041 patients included in this review, 402 elderly and 2188 nonelderly patients received ranitidine and 245 elderly and 1206 nonelderly patients received placebo; 29%, 29%, 32%, and 26% of these patients, respectively, reported some type of adverse event. The authors conclude that ranitidine is as safe in elderly patients as it is in nonelderly patients. No difference in the incidence of adverse events was found between older and younger patients who received ranitidine or placebo (Sirgo *et al.,* 1993).

Impact of different supplement drugs on dissolution profile of Zantac & Neoceptine

The safety of ranitidine in over a decade of use Ranitidine hydrochloride (Zantac) is one of the most extensively studied and widely used drugs of all time. This has provided an excellent opportunity to define its safety profile. Data from 189 controlled clinical trials in which more than 26,000 patients received daily doses of ranitidine for 4 weeks or more were reviewed. More than 80% of patients were treated with up to 300 mg ranitidine daily; the remaining patients received doses of up to 1200 mg daily. Eighty-seven trials were placebo controlled. Analyses of post-marketing surveillance and a database of all spontaneously reported adverse events were also evaluated. Review of data from a large population of controlled clinical trials with analyses of post marketing surveillance studies and spontaneously reported adverse events confirmed the excellent safety profile of ranitidine (Mills *et al.*, 1997).

Approximately 30% of adults in the USA suffer from heartburn or related symptoms monthly; more than 20% of these sufferers experience heartburn at least once per day. To compare the safety and efficacy of low-dose regimens of ranitidine for the relief of heartburn. Adults with at least a 3-month history of heartburn were eligible for this randomized, double-blind, parallel group, multicentre dose-ranging study. Following a 1-week open-label run-in phase to document baseline heartburn frequency, subjects were randomized to receive treatment with one tablet of either ranitidine 75 mg (n = 491), ranitidine 25 mg (n = 504), or placebo (n = 494), to be taken as needed up to four times daily for 2 weeks for the relief of heartburn. Ranitidine 75 mg provides prompt relief of heartburn that lasts for up to 12 h and has a safety profile comparable to that of placebo (Pappa *et al.*, 1999).

In 1996 there had been a study of Ranitidine bismuth citrate (Pylorid, Tritec) is a novel drug which heals peptic ulcers and when co-prescribed with either clarithromycin or amoxycillin eradicates Helicobacter pylori. In controlled clinical studies it was well-tolerated when given alone or when co-prescribed with either antibiotic. Data from 20 clinical studies are reported in this analysis of safety with almost 5000 patients having received ranitidine bismuth citrate (200, 400, or 800 mg twice daily). The incidence of

adverse events reported with this new drug, either alone or with an antibiotic, was not different from or lower than in patients given placebo and was independent of the dose of ranitidine bismuth citrate tested. The safety profile of ranitidine bismuth citrate was thus comparable to that of ranitidine hydrochloride (Zantac), a drug with a well-established record of safety in clinical use (Pipkin *et al.*, 1996)

The 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).

In 2001, there was a study conducted on better dissolution method for ranitidine tablets USP (Cappola, 2001). Intra & inter -variable results had been showed by ranitidine tablets USP. In order to find out the reason for this behavior, ranitidine tablets USP & Zantac tablets (brand of ranitidine USP) of two different pharmaceutical companies BIPI & Glaxo Inc, were selected to the compendia (USP) dissolution testing using paddle and basket apparatus. Different potencies of tablets 150 mg and 300 mg were tested. Ranitidine 300 mg tablet 30 rpm/basket apparatus had an initial slower rate but then rapidly equaled the paddle apparatus dissolution results and had less individual tablet variability. The paddle apparatus tablet sinkers were used to prevent tablets from sticking to the bottom of the dissolution vessel. Finally, the dissolution of all tablets with sinkers was more rapid then the tablets without sinkers. Results showed if the baskets or tablets sinker used it could be reduced dissolution artifacts.

In 2005, This study was undertaken to examine whether the pharmacokinetic profiles of ranitidine and nizatidine, the H2 antagonists, differed with repeated doses in very elderly patients (>80 years old). Ranitidine (150 mg) or nizatidine (150 mg) was given twice daily

in 10 very elderly female patients for 14 days. This study was a randomized, crossover design with a wash-out period of 14 days. Pharmacokinetic profiles were determined after first (on day 1) and 27th (on day 14) doses of each agent. The maximum plasma drug concentration (Cmax) and area under the plasma drug concentration-time curve (AUC) were significantly greater after the 27th than after the first dose in the ranitidine but not in the nizatidine trials. These results suggest that nizatidine is safer for the repeated treatment in very elderly patients (Sasaki *et al.,* 2005).

The effect of small levels of impurities on the water vapor sorption behavior of ranitidine HCl was found the experiment (Guerrieri *et al.*, 2007). The research goal was to investigate the effect of small amounts of impurities or degrades on RH0 for a model deliquescent pharmaceutical salt. Deliquescence was the process by which a solid undergoes dissolution by sorbing moisture from its surroundings when a characteristic relative humidity, RH0 was reached. For mixtures of two or more deliquescent solids, will generally be lowered. It was concluded that small levels of impurities can drastically affect the moisture sorption profile of a deliquescent material, both through affecting the deliquescence relative humidity and by altering the overall interaction of the substance with moisture. The study showed that changes in behavior might have significant effects on both active pharmaceutical ingredient and drug product stability during both processing and storage.

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).

Impact of different supplement drugs on dissolution profile of Zantac & Neoceptine

In this study effect of magnesium stearate concentration on dissolution properties of ranitidine hydrochloride coated tablets were showed (Uzunović and Vranić, 2007). In the most pharmaceutical formulations also include a certain amount of lubricant to improve the flowability and prevent the adhesion to equipment. Objective of this study was to evaluate the effects of two different concentrations of magnesium stearate on dissolution properties of ranitidine hydrochloride coated tablet formulations labeled to contain 150 mg. The obtained values indicate differences in drug release from analyzed ranitidine hydrochloride formulations and could cause differences in therapeutic response.

In the year of 2007 there had been a clinical trial of the effects of adding ranitidine at night to twice daily omeprazole therapy on nocturnal acid breakthrough and acid reflux in patients with systemic sclerosis--a randomized controlled, cross-over trial. To determine the efficacy of adding ranitidine at bedtime to control nocturnal acid breakthrough (NAB) and GERD in patients with systemic sclerosis already prescribed high-dose omeprazole. Patients with systemic sclerosis and GERD symptoms (n = 14) were treated with omeprazole 20 mg b.d. and either placebo or ranitidine 300 mg at bedtime for 6 weeks in a randomized, cross-over, placebo controlled study. At the end of each period a 24 h pH-study with intragastric and oesophageal pH measurement was performed. Many patients with systemic sclerosis experienced NAB and pathological esophageal acid exposure despite high-dose acid suppression with omeprazole b.d. Adding ranitidine at bedtime did not improve NAB, GERD or quality of life in this population (Janiak *at el.*, 2007).

The Leaky enteric coating on ranitidine hydrochloride beads: dissolution and prediction of plasma data research project was conducted in 2008. The research was based on the hypothesis that leaky enteric-coated pellets formulations were able to provide sustained input for drugs that have an absorption window, such as ranitidine hydrochloride. Leaky enteric-coated pellets formulations were defined as enteric-coated pellets that allow some of the drug to be released from the formulation in gastric fluid. The current research demonstrated a new application of knowledge about gastrointestinal transit effects on drug

formulations. It also showed that enteric-coating polymers have new applications in areas other than the usual enteric-coated formulations. The hypothesis that a leaky enteric-coated pellets formulation might maintain or increase the bioavailability of drugs that had a window of absorption was still to be confirmed by further in vivo studies (Bendas and Ayres, 2008).

This investigation examined the effect of a ranitidine hydrochloride (RHCl)-ion exchange resin complication on the drug's moisture uptake behavior. Drug resin complexes (DRCs) were prepared using the batch method with (i) two weak cation exchange resins, Polacrilex with exchangeable H+ and Polacrillin potassium; and (ii) a strong cation exchange resin; Sodium polystyrene sulfonate. RHCl, simple resins, and DRCs were subjected to storage stability under 40 +/- 2 degrees C and 75 +/- 5% relative humidity (RH) for 16 h, and the resulting percent increase in weight was calculated. The results of hygroscopicity testing revealed that both rate and extent of moisture gain in the presence or absence of light by F3 and F4 were significantly less than F1, F2, and marketed coated tablet ($P < 0.05$). Stability studies showed insignificant changes in weight, breaking force, friability, and disintegration time for tablets containing resin, while significant changes in these properties were found in tablets without resin. Thus, Polacrilex resin with exchangeable H+ was found to be the best for protecting RHCl against moisture uptake (Khan *et al.,* 2009).

The Equivalence of ranitidine generic tablets studied using the *in vitro* dissolution test had been conducted in 2009(Smekhova *et al.*, 2009). Using the pharmacopoeic dissolution test, the equivalence of Zantac, 10 domestic & foreign generics of ranitidine as (150mg) had been studied. There hadn’t any significant differences analysis showed in the entering into the ranitidine generic tablet registered. According to the WHO classification, it had been established thatZantac and generics of two manufacturers were rapidly soluble. The dissolution profiles was measured in media with different pH values showed the biological nonequivalence of some generics and the reference drug. It was demonstrated

that the *in vitro* dissolution test recommended by WHO can be used for determining the bioequivalence of ranitidine generics.

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).

In the year of 2012 there was study of comparative evaluation of the anionic superdisintegrants incorporation mode on the quality of ranitidine tablets. The present study was based on the impact of the superdisintegrants incorporation mechanism on the immediate realese of the tablets final performances. The aim was the selection of the working method to obtain Ranitidine 150 mg tablets with the desiderate quality and in reproducible conditions. The addition mode of the disintegrant was realized in three ways: intragranular, extragranular, and distributed equally between the two phases. The distribution range for the tablets weight was established. The disintegration time was identical for all the three disintegrant addition modes, and the hardness and the friability were not significantly influenced by working method, the obtained values were similar. For the developed formulations, the percent of the ranitidine dissolution was high, but higher in the extra granular incorporation. Standard distribution was calculed for the weight and hardness of the uncoated tablets (Postolache and Gafiţanu, 2012).

The present study was carried out with an objective of preparation and in vitro evaluation of floating tablets of hydroxypropyl methyl cellulose and polyethylene oxide using ranitidine hydrochloride as a model drug. The floating tablets were based on effervescent approach using sodium bicarbonate a gas generating agent. 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 containing sodium bicarbonate 20 mg per tablet showed desired buoyancy (floating lag time of about 2 minutes and total floating time of >24 hours). The present study showed that polymers like HPMC K15MCR and Polyox WSR303 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).

The aim of present study is 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 as widely prescribed by doctors and to have better patient compliance. The Immediate release layer of Ranitidine HCl was prepared by direct compression Method. The powders were evaluated for their flow properties and the finished tablets were evaluated for their physical parameters. The drug release study of Ranitidine HCl and Diclofenac Sodium were evaluated using USP-XXII paddle type dissolution apparatus. In case of HPMC E15, HPMC K4M, K100Mbased tablets with the increasing of polymer content the release mechanism moved to super case. Total four trial batches of each drug have been manufactured to optimize and develop a robust and stable formulation, the stability studies of the products also comply with ICH guidelines (Shirse, 2012).

In 2013, 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).

In the study there was on Formulation, characterization and physicochemical evaluation of ranitidine effervescent tablets (Aslani and Jahangiri , 2013). The aim of this study was to design, formulate and physiochemical evaluate effervescent ranitidine hydrochloride (HCl)

tablets since they were easily administered while the elderly and children sometimes have difficulties in swallowing oral dosage forms. Effervescent ranitidine HCl tablets were prepared in a dosage of 300 mg by fusion and direct compression methods. Aspartame, mint and orange flavors were more effective for masking the bitter taste of ranitidine. The fusion method was the best alternative in terms of physicochemical and physical properties. The results showed that the flow ability of fusion method was more than that of direct compression and the F5 and F7 formulations of 300 mg tablets were selected as the best formulations because of their physicochemical characteristics.

Test of dissolution and comparison of in vitro dissolution profiles of coated ranitidine tablets marketed in Bahia, Brazil in 2014 (Santos *et al.*, 2014). Ranitidine is an antisecretory drug with H2 antagonist action useful in treating gastric and duodenal disorders. The ranitidine dissolution test was used to obtain and compare dissolution profiles and establish similarities of pharmaceutical forms. The goal of this study was to compare the dissolution profiles of 150-mg coated ranitidine tablets of a reference drug product A and a generic product B and a similar product C drug marketed in Brazil using a simple and inexpensive ultraviolet method. According to American Pharmacopoeia (USP-32) dissolution test had been performed. The result showed that all the products were released ranitidine satisfactorily, with at least 80% of the drug dissolved within 30 min.

In 2014, there was a study Ranitidine is used in peptic ulcer therapy and available as several brands in the market which makes it difficult to select the safe, effective and economic one. The aim of this study is to establish similarity among the different brands of ranitidine HCl tablets available in local market of Karachi, Pakistan. Four different brands of (150 mg) were selected for the study. Six quality control parameters: weight variation test, hardness test, thickness, friability, disintegration test and dissolution test were carried out specified by USP. Result revealed that all brands comply within limits for hardness, weight variation, thickness, friability, disintegration and dissolution. Disintegration time for all brands was within 15 minutes complying with the USP commendation. All brands showed Q-value

more than 80% within 45 minutes. The present findings suggested that almost all the brands of ranitidine HCl that were available in Karachi meet the USP specification for quality control analysis and were interchangeable (Huma and Dilshad, 2014).

In 2014, there was study of Pharmacokinetics and pharmacodynamics of famotidine and ranitidine in critically ill children to characterize and compare acid suppression (pharmacodynamics) and pharmacokinetics of IV famotidine and ranitidine in critically ill children at risk for stress gastritis. Single-blind, randomized study in PICU patients 6 months to 18 years requiring mechanical ventilation with continuous gastric pH monitoring, randomized to IV famotidine 12 mg/m(2) or ranitidine 60 mg/m(2) when gastric pH < 4.0 >1 hour with serial blood sampling following first dose. Twenty-four children randomized to either famotidine (n = 12) or ranitidine (n = 12). Greater potency of famotidine may offer clinical advantage due to lower drug exposure and less frequent dosing to achieve same pH lowering effect (Deeken *et al.*, 2014).

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The aim of this study was to evaluate the effect of administration of acid-reducing agents on the pharmacokinetic exposure of orally administered epidermal growth factor receptor

inhibitor erlotinib, a drug that displays pH-dependent solubility. After the washout a subsequent study period evaluated 150 mg erlotinib administered with the acid-reducing agent. Omeprazole (40 mg once daily) was given on days 11-14, concomitantly with erlotinib on day 15, and for two additional days (days 16-17). Therefore, it is recommended that the concomitant use of erlotinib with proton pump inhibitors be avoided. If treatment with an H2-receptor antagonist such as ranitidine is required, erlotinib must be administered 10 h after the H2-receptor antagonist dosing and at least 2 h before the next dose of the H2-receptor antagonist (Kletzl *et al.,* 2015).

Gastric acid suppressants frequently are used in cats with acid-related gastric disorders. However, it is not known if these drugs effectively increase intragastric pH in cats. To examine the effects of PO administered ranitidine and omeprazole on intragastric pH in cats and to compare the efficacy of once-daily versus twice-daily dosage regimens for omeprazole. Intragastric pH was monitored continuously for 96 hours using the Bravo (™) system, starting on day 4 of treatment, followed by a median washout period of 12 days. Mean percentage of time pH was ≥3 and ≥4 was compared among groups using repeated measures ANOVA. Only twice-daily PO administered omeprazole significantly suppressed gastric acidity in healthy cats, whereas once-daily omeprazole and standard dosages of ranitidine were not effective acid suppressants in cats (Šutalo *et al.,* 2015).

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).

In 2015, there was a study of Safety and efficacy of cetirizine versus cetirizine plus ranitidine in chronic urticarial: Double-blind randomized placebo-controlled study. First-line treatment for chronic urticaria is H1 non-sedating antihistamines. When these fail, guidelines recommend combination with H2 antihistamines. Thirty-two patients with chronic urticaria were included. Group A (16 subjects) treated with cetirizine plus ranitidine and Group B (16 subjects) with cetirizine plus placebo, both for 30 days. Efficacy measures were Urticaria Activity Score (UAS), Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) and time of symptom remission, safety measures were clinical and laboratory effects. Combination of cetirizine with ranitidine was not more effective than cetirizine alone in chronic urticaria. Both treatments resulted equally safe; however, our main limitation is the small sample size (Guevara *et al.,* 2015).

The H2-receptor antagonist, ranitidine, is among the most widely used pharmaceuticals to treat gastroesophageal reflux disease and peptic ulcers. While previous studies have demonstrated that amines can form N-nitrosamines when exposed to nitrite at stomach-relevant pH, N-nitrosamine formation from ranitidine, an amine-based pharmaceutical, has not been demonstrated under these conditions. In this work, we confirmed the production of N-nitrosodimethylamine (NDMA), a potent carcinogen, by nitrosation of ranitidine under stomach-relevant pH conditions in vitro we also evaluated the urinary NDMA excretion attributable to ingestion of clinically used ranitidine doses. Our results suggest a need to evaluate the risks attributable to NDMA associated with chronic consumption of ranitidine, and to identify alternative treatments that minimize exposure to N-nitrosamines (Zeng and Mitch, 2016).

The purpose of this study was to determine the incidence, clinical features, and diagnostic methods for ranitidine-induced anaphylaxis. Ranitidine-related pharmacovigilance data from 2007 to 2014 were reviewed. Adverse drug reactions with causal relationships were selected, and clinical manifestations, outcomes, and drug-related information were assessed. For further investigation, 8 years of pharmacovigilance data were collected at a single centre. Twenty-three patients participated in in vivo and in vitro studies. Skin tests, oral provocation tests, and laboratory tests were performed, including tests using other kinds of histamine H2 receptor antagonists. Although ranitidine is known as a safe drug, it can also cause diverse adverse reactions, including anaphylaxis. This study demonstrates the need to pay attention to adverse reactions to ranitidine and consider ranitidine as a cause of anaphylaxis (Park *et al.,* 2016).

Chapter three

Materials & Methods

Materials & Methods

3.1 Materials

3.1.1 Sample collection:

The examination purpose and to observe the change in dissolution in ranitidine with other different types multivitamin and calcium , mineral supplement 30 tablets of Ranitidine (150mg) , 6 tablets Filwel gold , 6 tablets of Filwel silver , 6 tablets Acical-M , 6 tablets of Calbo which were collected from the local drug store in Dhaka as a sample.

3.1.2 Samples:

Table *3.1*: sample used in the experiment including source

Sample Name	Source (supplier name)
Neoceptine tablets	Beximco pharmaceutical Limited
Zantac tablets	GlaxoSmithKline Bangladesh Limited
Nutrum Gold tablet	Acme pharmaceutical Limited
Acical-M®	ACI limited
Filwel® Silver	Square Pharmaceuticals Ltd
Calbo® 500	Square Pharmaceuticals Ltd
Aristocal-D	Beximco Pharmaceuticals Ltd

3.1.3 Reagents:

Distill water

3.1.4 Equipment & Instruments:

Table *3.2*: lists of equipment's used for 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

3.1.5 Apparatus:

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

Table 3.3: table representing the 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

3.1.6 Instrument Images:

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

Figure 3.1: Dissolution Apparatus

Figure 3.2: UV-1800 Double Beam Spectrophotometer

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

Figure 3.3: Distill Water Test 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 stock solution for Standard Curve:

Ranitidine is soluble in water. So distilled water was used as stock solution to make the standard curve. By using distilled water apparatus in the East West University 500 ml distilled water was made and that was used to prepare the standard curve.

3.2.1.1 Preparation of Standard Curve:

1. To prepare the standard curve, at first different concentrations (5, 10, 15, 20 and 25) µg/ml of Ranitidine was prepared.
2. For the preparation of different concentrations of ranitidine,
3. First Zantac (Ranitidine) tablet was crushed in mortar and pestle.
4. From the crushed tablet 25 mg was taken and was dissolved in 50 ml of distilled water.
5. By this procedure the concentration of the stock solution became 0.5mg/ml or 500 µg/ml.
6. This solution was filtered in the volumetric flask.
7. 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 stock solution:

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

3.2.2.2 Method for dissolution test of Zantac (Ranitidine) or Neoceptine (Ranitidine)

1. 6L (6000ml) of stock solution (distilled water) was prepared.
2. Each vessel of dissolution tester was filled with 900 ml of stock solution (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 Xantid 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 Neoceptine (Ranitidine) with Calbo (calcium supplement):

1. 6L (6000ml) of stock solution (distilled water) was prepared.
2. Each vessel of dissolution tester was filled with 900 ml of stock solution (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 Xantid 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 in the dissolution tests of Zantac or Neoceptine 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:

- ✓ 10 tablets were taken and weighed.
- ✓ The average was taken and it was considered as the standard weight of an individual tablet.
- ✓ All the tablet were weighed individually and observed whether the individual tablets were 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 the weight variation test of tablets.

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

Equation:

Following equation was used to determined % Weight Variation of tablets

$$\% \text{ weight variation} = (A \sim I/A) \times 100$$

Where,

Initial weight of tablet, I (gm)

Average weight of tablet, A (gm)

3.2.3.2 Thickness test:

Procedure:

- ✓ Frist the tablet was placed between the two jaws of the Vernier caliper.
- ✓ The main scale reading was taken.
- ✓ Next the Vernier scale reading was taken also.
- ✓ The two reading were added together by multiplying the Vernier constant 0.1cm.

Calculation:

Following formula was used to determine thickness of the tablets.

Thickness of the tablet= reading of cm scale + reading of Vernier scale X
Vernier constant(0.01)+ Vernier error

3.2.3.3 Hardness test:

Procedure:

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

Chapter Four:

Results

Results

4.1 Standard curve preparation:

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

Serial No.	Concentration	Absorbance
1	0	0
2	5	.247
3	10	.471
4	15	.698
5	20	.937
6	25	1.132

By plotting the concentration against the absorbance of ranitidine we found straight line. From the standard curve ranitidine, we derived the equation y=37.89x+0.0125 & R^2=.9992. We use this equation to get the concentration from different samples absorbance of ranitidine.

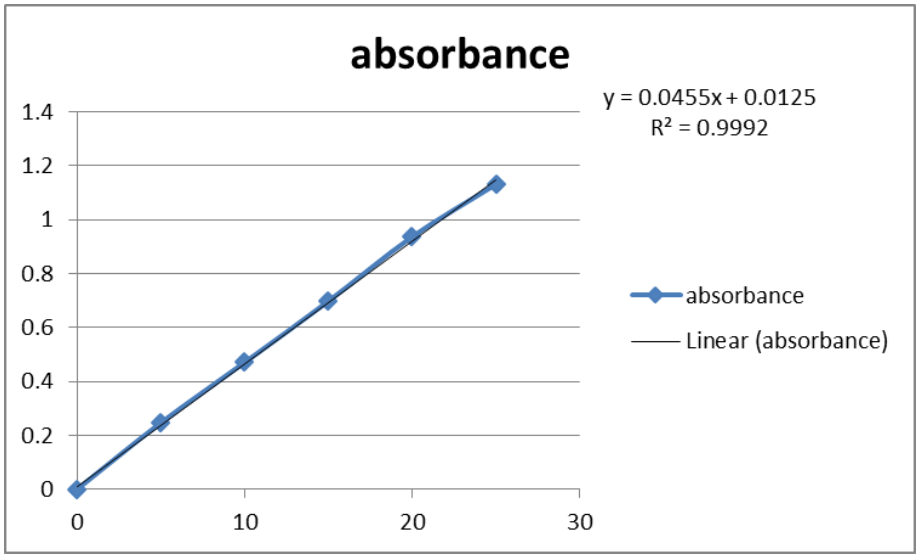

Figure *4.1:* Plot showing straight line for absorbance with respect to concentration for ranitidine.

4.2 Dissolution test of Ranitidine (Neoceptine):

Table *4.2*: UV absorbance of ranitidine (Neoceptine):

Sample number	Absorbance (after 20 min)	Absorbance (after 40 min)	Absorbance (after 60 min)
1	.380	.620	.741
2	.378	.603	.727
3	.402	.523	.947
4	.481	.683	.876
5	.429	.871	.733
6	.582	.750	.847

Calculation of dissolved amount for ranitidine (Neoceptine):

From the standard curve we get an equation which is Y=0.0455x+0.0125

For the drug with an absorbance of .38, the dissolved amount is 72.69mg.

Y=0.0455x+0.0125

.38=.0455x+.0115

X=8.07

Dissolved amount =8.07× (9000/1000) [Dilution factor= 9000/1000]

Dissolved amount = 72.69

Table 4.3: determination of dissolved amount Ranitidine (Neoceptine)

Sample number	Absorbance (after 20 min)	Dissolved amount(after 20 min)	Absorbance (after 40 min)	Dissolved amount(after 40 min)	Absorbance(after 60 min)	Dissolved amount(after 60 min)
1	.380	72.69	.620	120.16	.741	144.09
2	.378	72.29	.603	116.80	.727	141.32
3	.402	77.04	.523	100.97	.947	184.84
4	.481	92.47	.683	132.62	.876	170.80
5	.429	60.82	.871	169.81	.733	142.51
6	.582	51.52	.750	145.87	.625	121.15
		Average =71.18		Average =131.03		Average =150.7

4.3 Dissolution test of ranitidine with Acical-M® (Calcium + Vitamin D + Minerals tablet):

Table 4.4: determination of dissolved amount Ranitidine (Neoceptine) with Acical-M® (Calcium + Vitamin D + Minerals tablet):

Sample number	Absorbance (after 20 min)	Dissolved amount(after 20 min)	Absorbance (after 40 min)	Dissolved amount(after 40 min)	Absorbance(after 60 min)	Dissolved amount(after 60 min)
1	.134	24.03	.190	41.63	.678	131.63
2	.194	35.90	.277	52.31	.387	74.07
3	.101	17.50	.387	74.07	.445	85.54
4	.125	22.25	.126	22.64	.425	81.59
5	.490	94.45	.348	66.36	.451	86.73
6	.223	41.63	.371	70.91	.489	94.25
		Average =39.29		Average =54.64		Average =92.31

Impact of different supplement drugs on dissolution profile of Zantac & Neoceptine

Calculation of dissolved amount of ranitidine with Acical-M® (Calcium + Vitamin D + Minerals tablet):

For the ranitidine with Acical-M® (Calcium + Vitamin D + Minerals tablet) of is .134, the dissolved amount is 24.03mg.

From the standard curve we get an equation which is Y=.0455x+.0125

.134=.0455x+.0125

.0455x=.134-.0115

x= 2.67

Dissolved amount =2.67× (9000/1000) [Dilution factor= 9000/1000]

Dissolved amount =24.03mg

Table *4.5:* percentage calculation for dissolved amount (20min) of ranitidine & ranitidine with Acical-M® (Calcium + Vitamin D + Minerals tablet):

Dissolved amount of ranitidine (mg)	Percent Dissolved amount of ranitidine without supplement (%)	Average percentage Dissolved amount of ranitidine without supplement (%)	Dissolved amount of ranitidine with Acical-M(mg)	Percent Dissolved amount of ranitidine in presence of supplement (%)	Average Percent Dissolved amount of ranitidine in presence of supplement (%)	Impact on dissolution (%)
72.69	109.03		24.03	36.04		
72.29	108.43		35.90	53.85		
77.04	115.56		17.50	26.25		
92.47	138.70	106.70	22.25	33.37	58.74	45.95
60.82	91.23		94.45	141.45		
51.52	77.28		41.63	61.5		

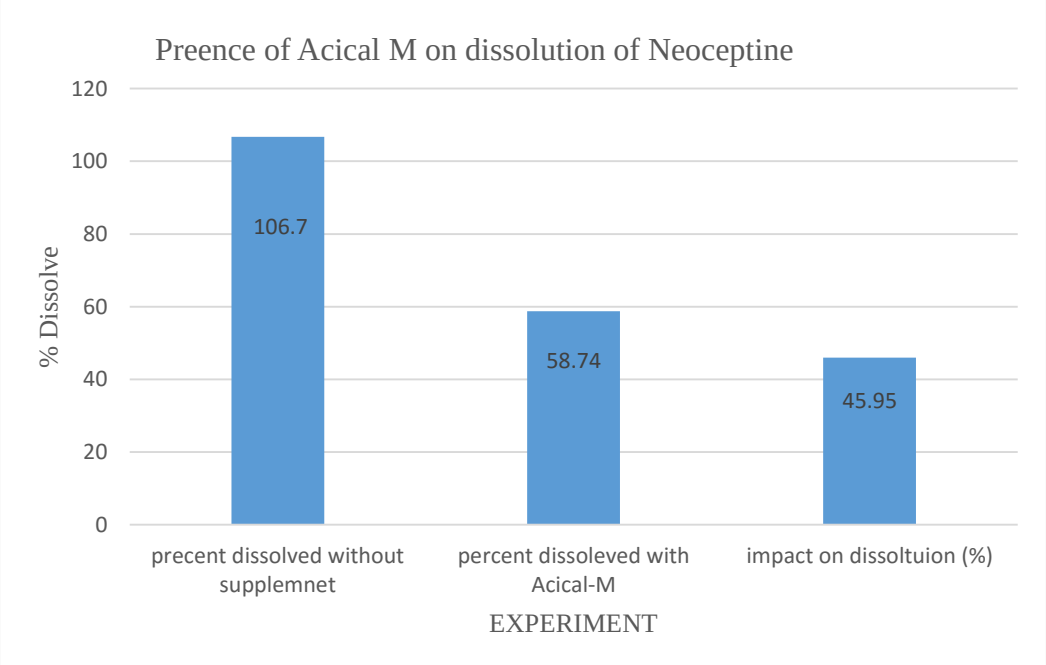

Figure *4.2:* Graph represents the presence of Acical-M on the dissolution of Ranitidine

Table *4.6:* percentage calculation for dissolved amount (40min) of ranitidine & ranitidine with Acical-M® (Calcium + Vitamin D + Minerals tablet):

Dissolved amount of ranitidine (mg)	Percent Dissolved amount of ranitidine without supplement (%)	Average percentage Dissolved amount of ranitidine without supplement (%)	Dissolved amount of ranitidine with Acical-M(mg)	Percent Dissolved amount of ranitidine in presence of supplement (%)	Average Percent Dissolved amount of ranitidine in presence of supplement (%)	Impact on dissolution (%)
120.16	180.24		41.63	62.44		
116.80	175.20		52.31	78.46		
100.97	151.45		74.07	111.10		
132.62	198.93	195.05	22.64	33.96	81.97	57.98
169.81	254.71		66.36	99.54		
145.87	218.80		70.91	106.36		

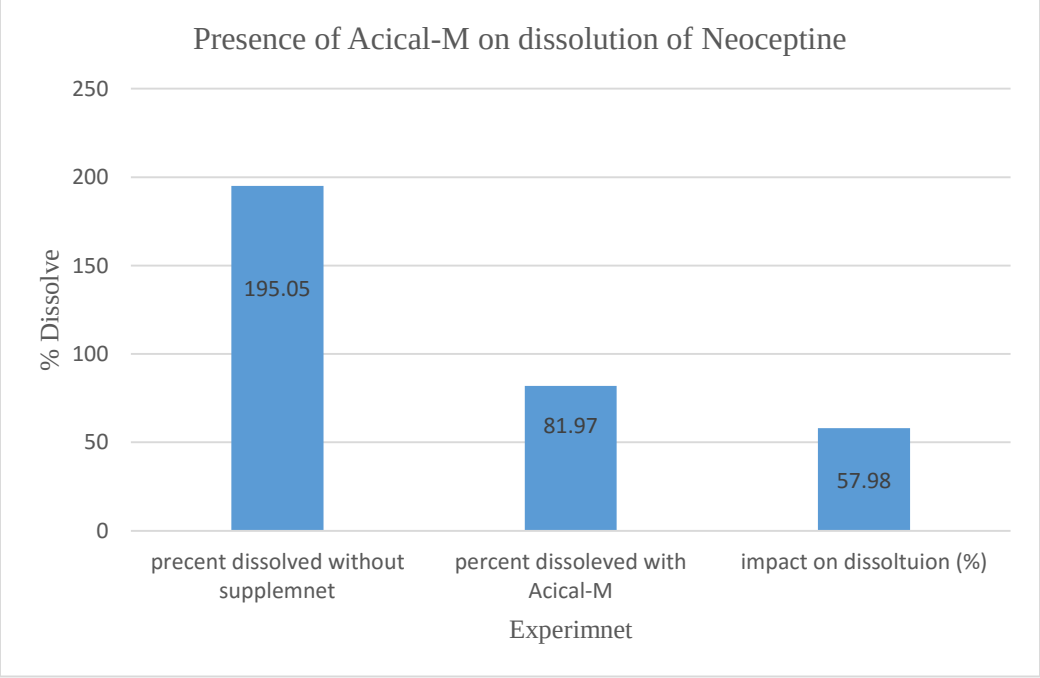

Figure *4.3:* Graph represents the presence of Acical-M on the dissolution of Ranitidine

Table *4.7:* Percentage calculation for dissolved amount (60min) of ranitidine & ranitidine with Acical-M® (Calcium + Vitamin D + Minerals tablet):

Dissolved amount of ranitidine (mg)	Percent Dissolved amount of ranitidine without supplement (%)	Average percentage Dissolved amount of ranitidine without supplement (%)	Dissolved amount of ranitidine with Acical-M(mg)	Percent Dissolved amount of ranitidine in presence of supplement (%)	Average Percent Dissolved amount of ranitidine in presence of supplement (%)	Impact on dissolution (%)
144.09	216.13		131.63	197.61		
141.32	211.98		74.07	111.105		
184.84	277.26		85.54	128.31		
170.80	256.2	226.17	81.59	122.38	130.47	42.32
142.51	213.76		86.73	130.09		
121.15	181.72		94.25	141.37		

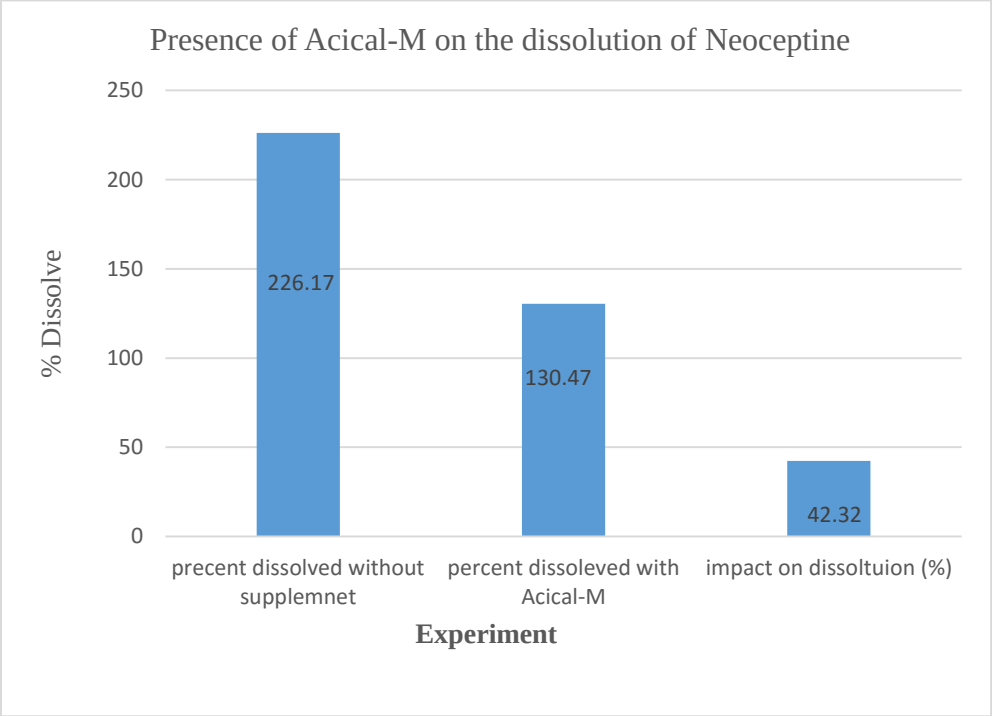

Figure *4.4:* Graph represents the presence of Acical-M on the dissolution of Ranitidine

4.4 Dissolution test of ranitidine with Calbo 500 (Calcium supplement):

Table *4.8:* determination of dissolved amount Ranitidine (Neoceptine) with Calbo 500 (Calcium supplement):

Sample number	Absorbance (after 20 min)	Dissolved amount(after 20 min)	Absorbance (after 40 min)	Dissolved amount(after 40 min)	Absorbance(after 60 min)	Dissolved amount(after 60 min)
1	.180	33.13	.293	55.48	.372	73.30
2	.184	33.92	.287	54.26	.338	64.38
3	.308	58.45	.425	81.59	.567	109.68
4	.192	35.50	.275	51.92	.362	69.13
5	.257	48.16	.283	53.50	.388	74.27
6	.113	19.87	.447	91.87	.656	127.28
		Average= 38.17		Average= 64.77		Average= 86.34

Calculation of dissolved amount of ranitidine with Calbo 500 (Calcium supplement):

For the ranitidine with Calbo 500(Calcium supplement) of is .180, the dissolved amount is 33.13mg

From the standard curve we get an equation which is Y=.0455x+.0125

.180=.0455x +.0115

.0455x =.180-.0115

x= 3.68

Dissolved amount =3.68× (9000/1000) [Dilution factor= 9000/1000]

Dissolved amount =33.13mg

Impact of different supplement drugs on dissolution profile of Zantac & Neoceptine

Table *4.9*: Percentage calculation for dissolved amount (20min) of ranitidine & ranitidine with Calbo 500 (Calcium supplement):

Dissolved amount of ranitidine (mg)	Percent Dissolved amount of ranitidine without supplement (%)	Average percentage Dissolved amount of ranitidine without supplement (%)	Dissolved amount of ranitidine with Calbo 500(mg)	Percent Dissolved amount of ranitidine in presence of supplement (%)	Average Percent Dissolved amount of ranitidine in presence of Calbo supplement (%)	Impact on dissolution (%)
72.69	109.03		33.13	49.69		
72.29	108.43		33.92	50.88		
77.04	115.56		58.45	87.67		
92.47	138.70	106.70	35.50	53.25	57.255	46.38
60.82	91.23		48.16	72.24		
51.52	77.28		19.87	29.80		

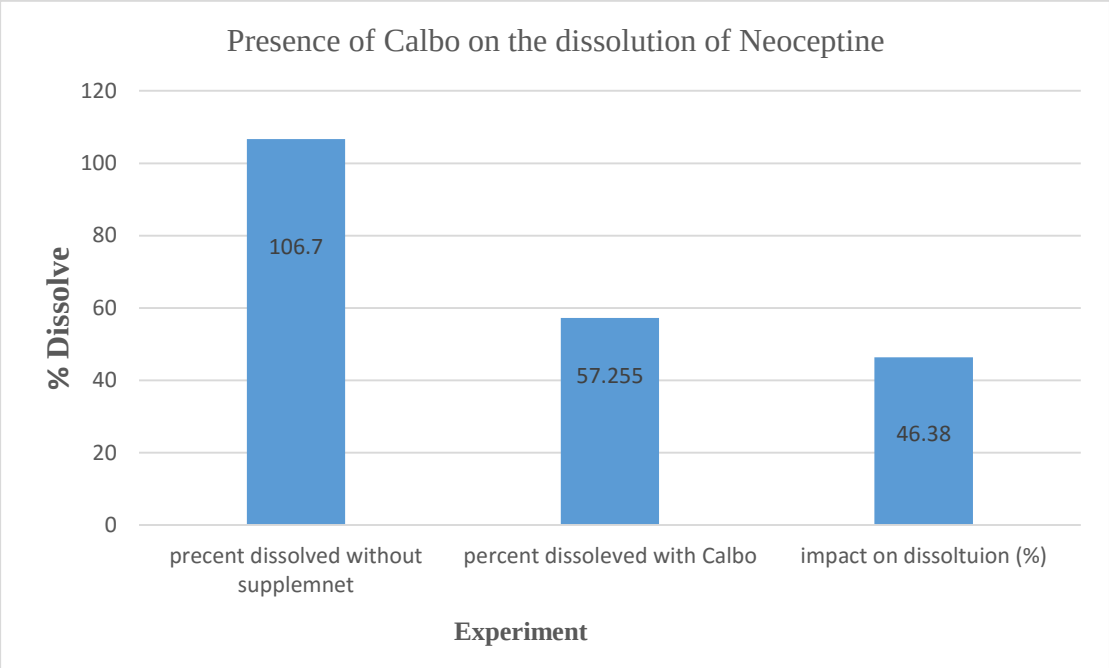

Figure 4.5: Graph represents the presence of Calbo 500 on the dissolution of Ranitidine

Table *4.10:* Percentage calculation for dissolved amount (40min) of ranitidine & ranitidine with Calbo 500 (Calcium supplement):

Dissolved amount of ranitidine (mg)	Percent Dissolved amount of ranitidine without supplement (%)	Average percentage Dissolved amount of ranitidine without supplement (%)	Dissolved amount of ranitidine with Calbo 500(mg)	Percent Dissolved amount of ranitidine in presence of supplement (%)	Average Percent Dissolved amount of ranitidine in presence of supplement (%)	Impact on dissolution (%)
120.16	180.24		55.48	83.22		
116.80	175.20		54.26	81.39		
100.97	151.45		81.59	122.38		
132.62	198.93	195.05	51.92	77.88	97.15	50.2
169.81	254.71		53.50	80.25		
145.87	218.80		91.87	137.80		

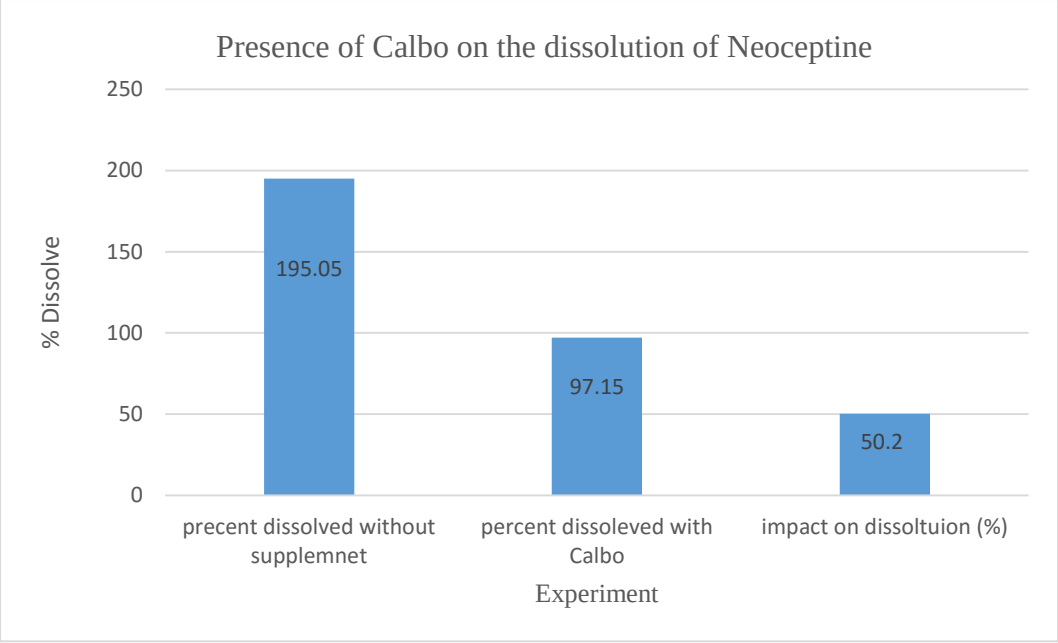

Figure *4.6:* Graph represents the presence of Calbo 500 on the dissolution of Ranitidine

Impact of different supplement drugs on dissolution profile of Zantac & Neoceptine

Table *4.11*: Percentage calculation for dissolved amount (60min) of ranitidine & ranitidine with Calbo 500 (Calcium supplement):

Dissolved amount of ranitidine (mg)	Percent Dissolved amount of ranitidine without supplement (%)	Average percentage Dissolved amount of ranitidine without supplement (%)	Dissolved amount of ranitidine with Calbo 500(mg)	Percent Dissolved amount of ranitidine in presence of supplement (%)	Average Percent Dissolved amount of ranitidine in presence of supplement (%)	Impact on dissolution (%)
144.09	216.13		73.30	109.95		
141.32	211.98		64.38	96.57		
184.84	277.26		109.68	164.52		
170.80	256.2	226.17	69.13	103.69	129.52	42.74
142.51	213.76		74.27	111.50		
121.15	181.72		127.28	190.92		

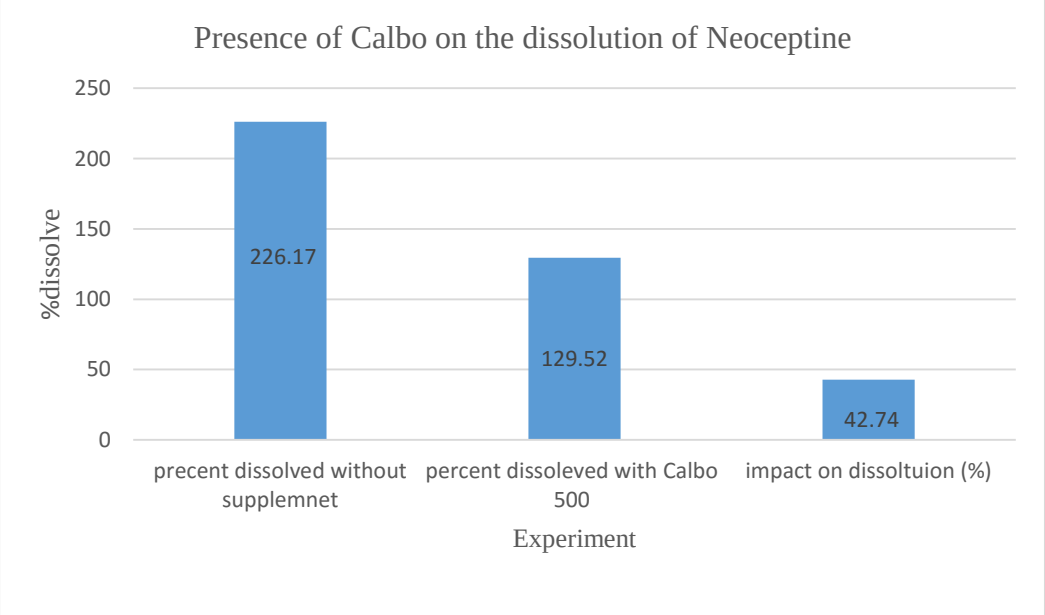

Figure *4.7:* Graph represents the presence of Calbo 500 on the dissolution of Ranitidine

4.5 Dissolution test of ranitidine with Filwel® Silver:

Table *4.12*: Determination of dissolved amount Ranitidine (Neoceptine) with Filwel® Silver:

Sample number	Absorbance (after 20 min)	Dissolved amount(after 20 min)	Absorbance (after 40 min)	Dissolved amount(after 40 min)	Absorbance (after 60 min)	Dissolved amount(after 60 min)
1	.105	18.29	.127	22.64	.590	114.23
2	.115	20.27	.338	64.38	.589	114.03
3	.238	44.60	.372	71.10	.627	121.54
4	.217	40.45	.602	116.60	.322	61.21
5	.136	24.42	.334	63.59	.520	100.38
6	.331	63	.348	66.36	.538	103.94
		Average= 35.17		Average= 67.44		Average= 102.55

Calculation of dissolved amount of ranitidine with Filwel® Silver:

For the ranitidine with Filwel® Silver of is .105, the dissolved amount is 29.09mg.

From the standard curve we get an equation which is Y=.0455x+.0125

.105=.0455x+.0125

.0455x =.105-.0125

x= 2.03

Dissolved amount =2.03× (9000/1000) [Dilution factor= 9000]

Dissolved amount =18.29mg

Table *4.13:* Percentage calculation for dissolved amount (20min) of ranitidine & ranitidine with Filwel® Silver:

Dissolved amount of ranitidine (mg)	Percent Dissolved amount of ranitidine without supplement (%)	Average percentage Dissolved amount of ranitidine without supplement (%)	Dissolved amount of ranitidine with Filwel® Silver(mg)	Percent Dissolved amount of ranitidine in presence of supplement (%)	Average Percent Dissolved amount of ranitidine in presence of supplement (%)	Impact on dissolution (%)
72.69	109.03		18.29	27.43		
72.29	108.43		20.27	30.40		
77.04	115.56		44.60	66.90		
92.47	138.70	106.70	40.45	60.67	52.71	50.6
60.82	91.23		24.42	36.36		
51.52	77.28		63	94.50		

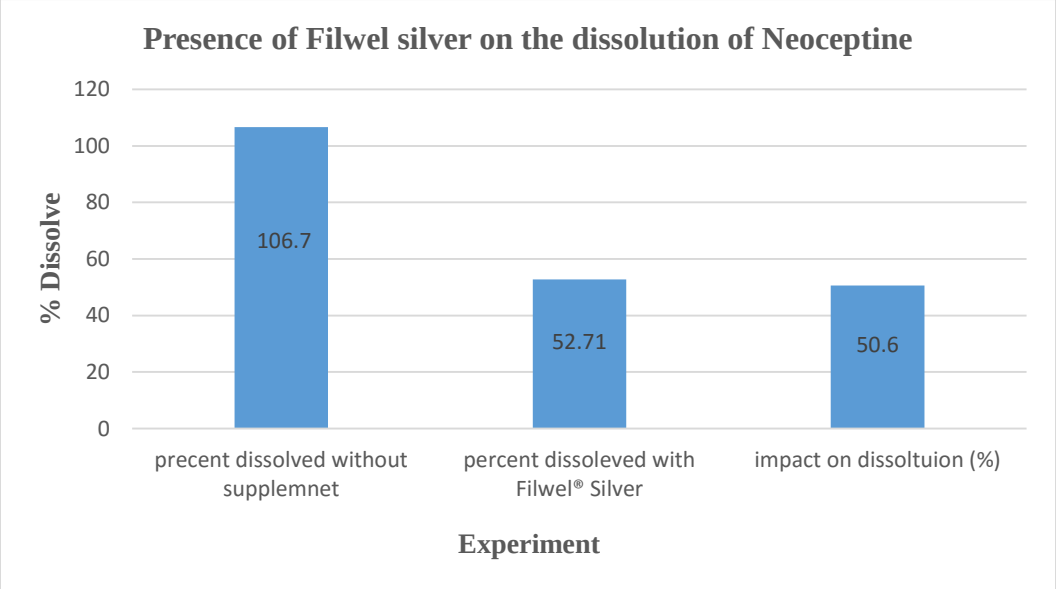

Figure *4.8:* Graph represents the presence of Filwel Silver on the dissolution of Ranitidine

Table *4.14*: Percentage calculation for dissolved amount (40min) of ranitidine & ranitidine with Filwel® Silver:

Dissolved amount of ranitidine (mg)	Percent Dissolved amount of ranitidine without supplement (%)	Average percentage Dissolved amount of ranitidine without supplement (%)	Dissolved amount of ranitidine with Filwel® Silver mg)	Percent Dissolved amount of ranitidine in presence of supplement (%)	Average Percent Dissolved amount of ranitidine in presence of supplement (%)	Impact on dissolution (%)
120.16	180.24		22.64	33.96		
116.80	175.20		64.38	96.57		
100.97	151.45		71.10	106.65		
132.62	198.93	195.05	116.60	175.9	101.16	48.14
169.81	254.71		63.59	94.38		
145.87	218.80		66.36	99.54		

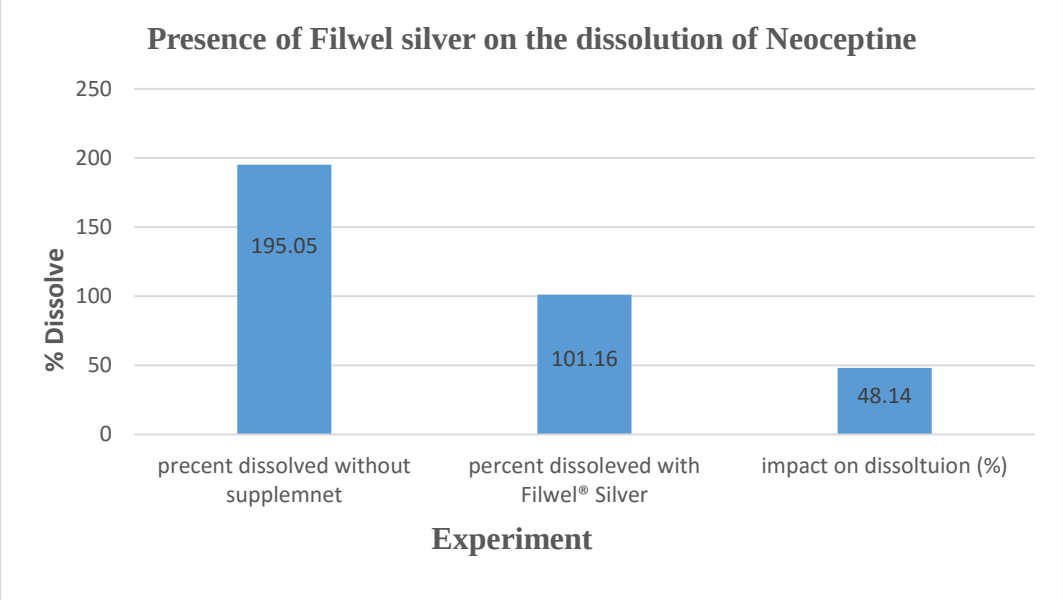

Figure *4.9:* Graph represents the presence of Filwel® Silver on the dissolution of Ranitidine

Table *4.15:* Percentage calculation for dissolved amount (60min) of ranitidine & ranitidine with Filwel® Silver:

Dissolved amount of ranitidine (mg)	Percent Dissolved amount of ranitidine without supplement (%)	Average percentage Dissolved amount of ranitidine without supplement (%)	Dissolved amount of ranitidine with Calbo 500(mg)	Percent Dissolved amount of ranitidine in presence of supplement (%)	Average Percent Dissolved amount of ranitidine in presence of supplement (%)	Impact on dissolution (%)
144.09	216.13		114.23	171.34		
141.32	211.98		114.03	171.45		
184.84	277.26		121.54	181.5		
170.80	256.2	226.17	61.21	91.81	153.76	32.02
142.51	213.76		100.38	150.57		
121.15	181.72		103.94	155.91		

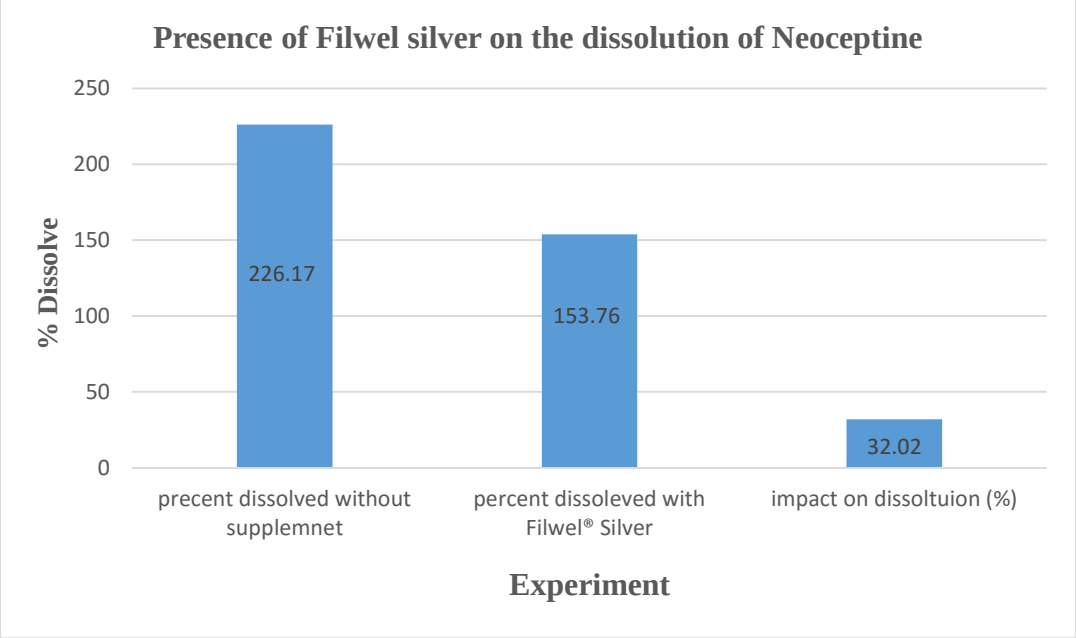

Figure *4.10:* Graph represents the presence of Filwel® Silver on the dissolution of Ranitidine

4.6 Dissolution test of ranitidine with Nutrum gold:

Table *4.17:* Determination of dissolved amount Ranitidine (Neoceptine) with Nutrum gold:

Sample number	Absorbance (after 20 min)	Dissolved amount(after 20 min)mg	Absorbance (after 40 min)	Dissolved amount(after 40 min)mg	Absorbance (after 60 min)	Dissolved amount(after 60 min)mg
1	.217	40.45	.357	68.14	.418	92.67
2	.326	60.23	.625	121.15	.714	138.75
3	.418	80.20	.605	117.19	.755	146.86
4	.397	60.55	.693	136.60	.821	159.92
5	.314	59.63	.722	140.34	.850	165.65
6	.179	32.93	.680	132.03	.788	153.39
		Average= 55.66		Average= 119.26		Average= 142.87

Calculation of dissolved amount of ranitidine with Nutrum gold:

For the ranitidine with Nutrum gold of is .134, the dissolved amount is 29.09mg.

From the standard curve we get an equation which is Y=.0455x+.0125

.217=.0455x +.0125

.0455x =.217-.0115

x= 4.49

Dissolved amount =4.49× (9000/1000) [Dilution factor= 9000/1000]

=40.45

Dissolved amount =40.45mg

Impact of different supplement drugs on dissolution profile of Zantac & Neoceptine

Table *4.18:* Percentage calculation for dissolved amount (20min) of ranitidine & ranitidine with Nutrum gold:

Dissolved amount of ranitidine (mg)	Percent Dissolved amount of ranitidine without supplement (%)	Average percentage Dissolved amount of ranitidine without supplement (%)	Dissolved amount of ranitidine with Nutrum gold(mg)	Percent Dissolved amount of ranitidine in presence of supplement (%)	Average Percent Dissolved amount of ranitidine in presence of supplement (%)	Impact on dissolution (%)
72.69	109.03		40.45	60.67		
72.29	108.43		60.23	90.34		
77.04	115.56		80.20	120.3		
92.47	138.70	106.70	60.55	90.82	83.43	21.81
60.82	91.23		59.63	89.44		
51.52	77.28		32.93	49.39		

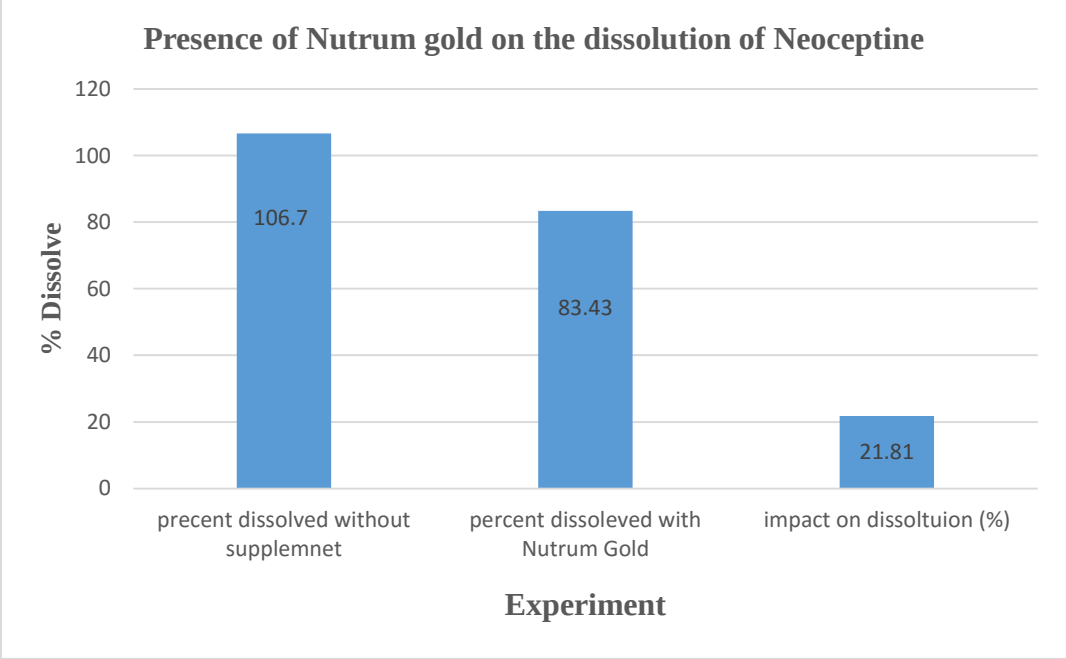

Figure *4.11:* Graph represents the presence of Nutrum Gold on the dissolution of Ranitidine

Impact of different supplement drugs on dissolution profile of Zantac & Neoceptine

Table *4.19*: Percentage calculation for dissolved amount (40min) of ranitidine & ranitidine with Nutrum gold:

Dissolved amount of ranitidine (mg)	Percent Dissolved amount of ranitidine without supplement (%)	Average percentage Dissolved amount of ranitidine without supplement (%)	Dissolved amount of ranitidine with Nutrum gold(mg)	Percent Dissolved amount of ranitidine in presence of supplement (%)	Average Percent Dissolved amount of ranitidine in presence of supplement (%)	Impact on dissolution (%)
120.16	180.24		68.14	102.21		
116.80	175.20		121.15	181.712		
100.97	151.45		117.19	175.78		
132.62	198.93	195.05	136.60	204.5	179.01	8.23
169.81	254.71		140.34	210.51		
145.87	218.80		132.03	198.04		

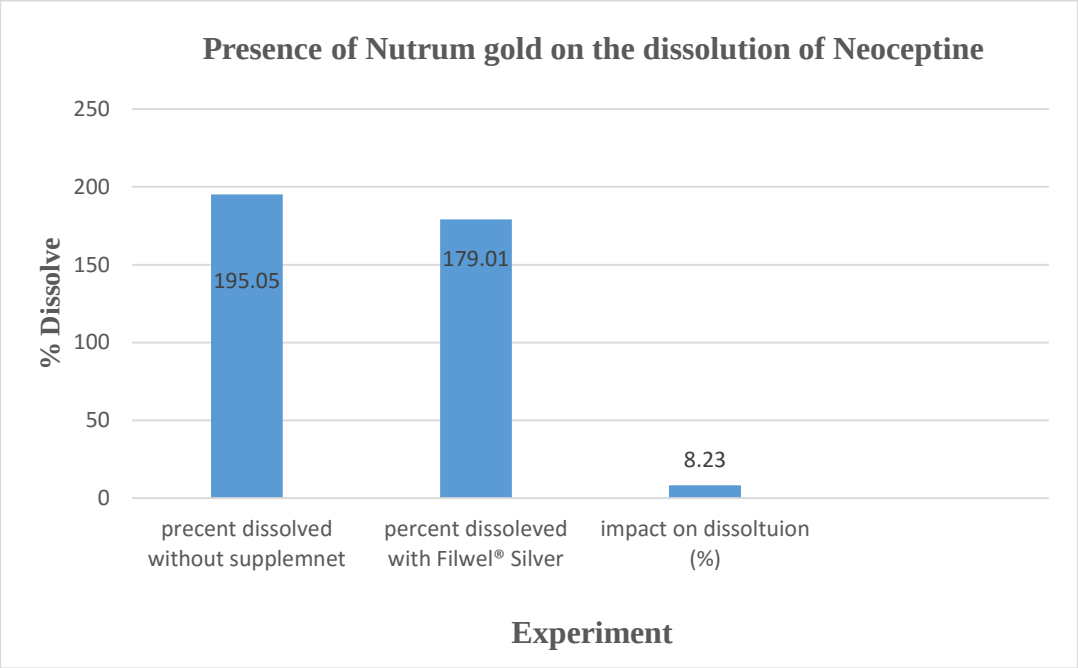

Figure *4.12*: Graph represents the presence of Nutrum Gold on the dissolution of Ranitidine

Impact of different supplement drugs on dissolution profile of Zantac & Neoceptine

Table *4.20:* Percentage calculation for dissolved amount (60min) of ranitidine & ranitidine with Nutrum gold:

Dissolved amount of ranitidine (mg)	Percent Dissolved amount of ranitidine without supplement (%)	Average percentage Dissolved amount of ranitidine without supplement (%)	Dissolved amount of ranitidine with Nutrum gold(mg)	Percent Dissolved amount of ranitidine in presence of supplement (%)	Average Percent Dissolved amount of ranitidine in presence of supplement (%)	Impact on dissolution (%)
144.09	216.13		92.67	139.05		
141.32	211.98		138.75	208.125		
184.84	277.26		146.86	220.89		
170.80	256.2	226.17	159.92	239.88	214.49	5.17
142.51	213.76		165.65	248.47		
121.15	181.72		153.39	230.08		

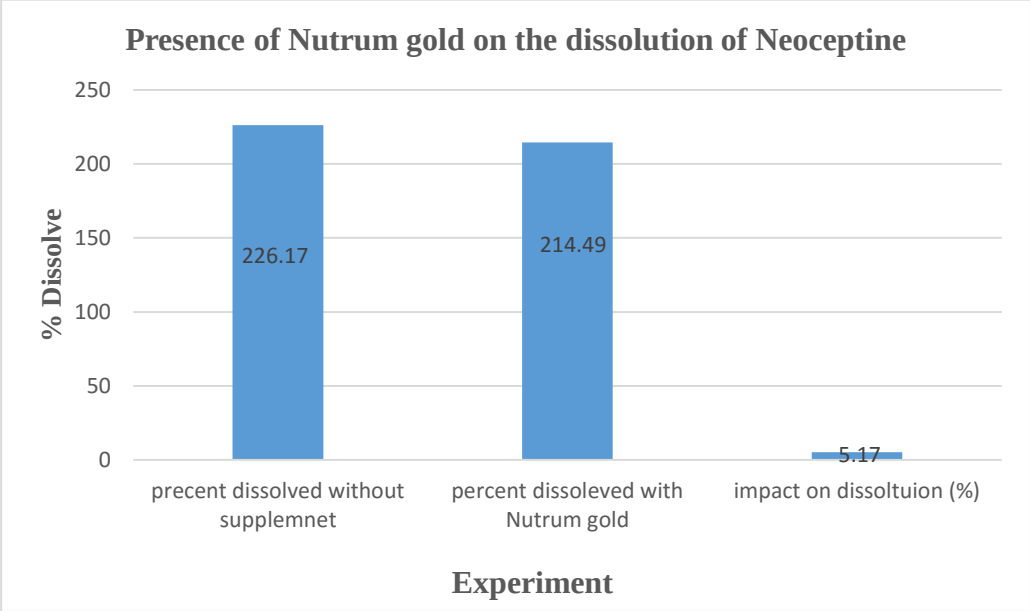

Figure *4.13:* Graph represents the presence of Nutrum Gold on the dissolution of Ranitidine

4.7 Dissolution test of ranitidine with AristoCal-D:

Table *4.21:* Determination of dissolved amount Ranitidine (Neoceptine) with AristoCal-D:

Sample number	Absorbance (after 20 min)	Dissolved amount(after 20 min)mg	Absorbance (after 40 min)	Dissolved amount(after 40 min)mg	Absorbance(after 60 min)	Dissolved amount(after 60 min)mg
1	.248	46.58	.406	77.83	.501	96.62
2	.376	71.90	.581	112.45	.520	100.38
3	.215	40.05	.490	94.45	.588	113.83
4	.276	52.22	.180	33.13	.485	93.41
5	.516	99.56	.476	91.68	.519	99.59
6	.390	75.85	.485	93.41	.606	117.23
		Average= 64.36		Average= 83.82		Average= 103.51

Calculation of dissolved amount of ranitidine with AristoCal-D:

For the ranitidine with Nutrum gold of is .134, the dissolved amount is 29.09mg.

From the standard curve we get an equation which is Y=.0455x+.0125

.248=.0455x+.0125

.0455x =.248-.0115

x= 5.17

Dissolved amount =5.17×9000 [Dilution factor= 9000]

=46.58

Dissolved amount =46.58mg

Table *4.22:* Percentage calculation for dissolved amount (20min) of ranitidine & ranitidine with AristoCal-D:

Dissolved amount of ranitidine (mg)	Percent Dissolved amount of ranitidine without supplement (%)	Average percentage Dissolved amount of ranitidine without supplement (%)	Dissolved amount of ranitidine with AristoCal-D(mg)	Percent Dissolved amount of ranitidine in presence of supplement (%)	Average Percent Dissolved amount of ranitidine in presence of supplement (%)	Impact on dissolution (%)
72.69	109.03		.248	69.87		
72.29	108.43		.376	107.85		
77.04	115.56		.215	60.07		
92.47	138.70	106.70	.276	78.18	96.51	9.56
60.82	91.23		.516	49.34		
51.52	77.28		.390	113.75		

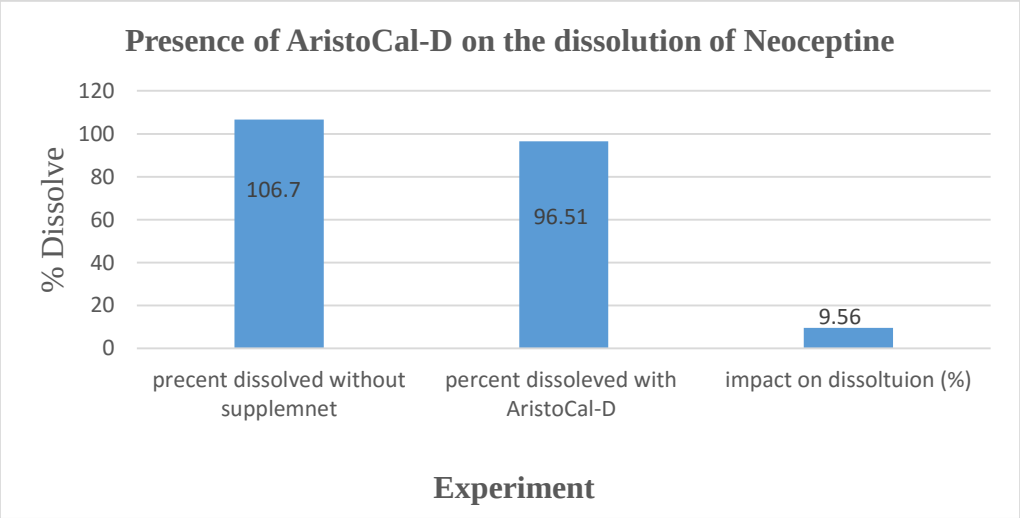

Figure *4.14:* Graph represents the presence of AristoCal-D on the dissolution of Ranitidine

Table *4.23:* Percentage calculation for dissolved amount (40min) of ranitidine & ranitidine with AristoCal-D:

Dissolved amount of ranitidine (mg)	Percent Dissolved amount of ranitidine without supplement (%)	Average percentage Dissolved amount of ranitidine without supplement (%)	Dissolved amount of ranitidine with AristoCal-D(mg)	Percent Dissolved amount of ranitidine in presence of supplement (%)	Average Percent Dissolved amount of ranitidine in presence of supplement (%)	Impact on dissolution (%)
120.16	180.24		46.58	116.75		
116.80	175.20		71.90	168.67		
100.97	151.45		40.05	141.67		
132.62	198.93	195.05	52.22	127.69	125.73	35.46
169.81	254.71		99.56	137.52		
145.87	218.80		75.85	140.11		

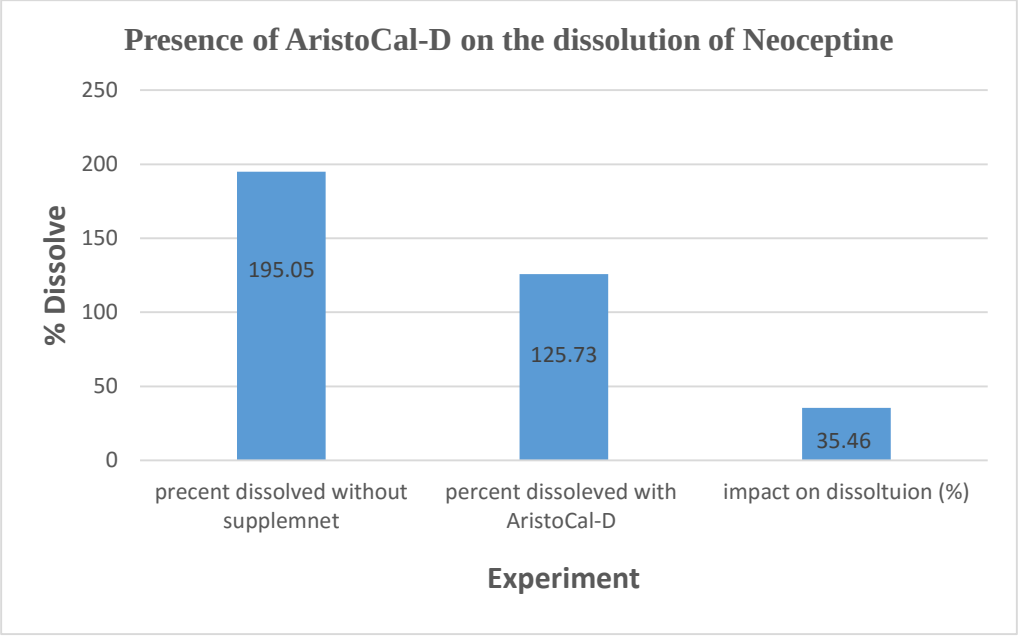

Figure *4.15*: Graph represents the presence of AristoCal-D on the dissolution of Ranitidine

Table *4.24:* Percentage calculation for dissolved amount (60min) of ranitidine & ranitidine with AristoCal-D:

Dissolved amount of ranitidine (mg)	Percent Dissolved amount of ranitidine without supplement (%)	Average percentage Dissolved amount of ranitidine without supplement (%)	Dissolved amount of ranitidine with AristoCal-D(mg)	Percent Dissolved amount of ranitidine in presence of supplement (%)	Average Percent Dissolved amount of ranitidine in presence of supplement (%)	Impact on dissolution (%)
144.09	216.13		96.62	144.93		
141.32	211.98		100.38	150.57		
184.84	277.26		113.83	170.74		
170.80	256.2	226.17	93.41	140.11	155.26	31.36
142.51	213.76		99.59	149.38		
121.15	181.72		117.23	175.85		

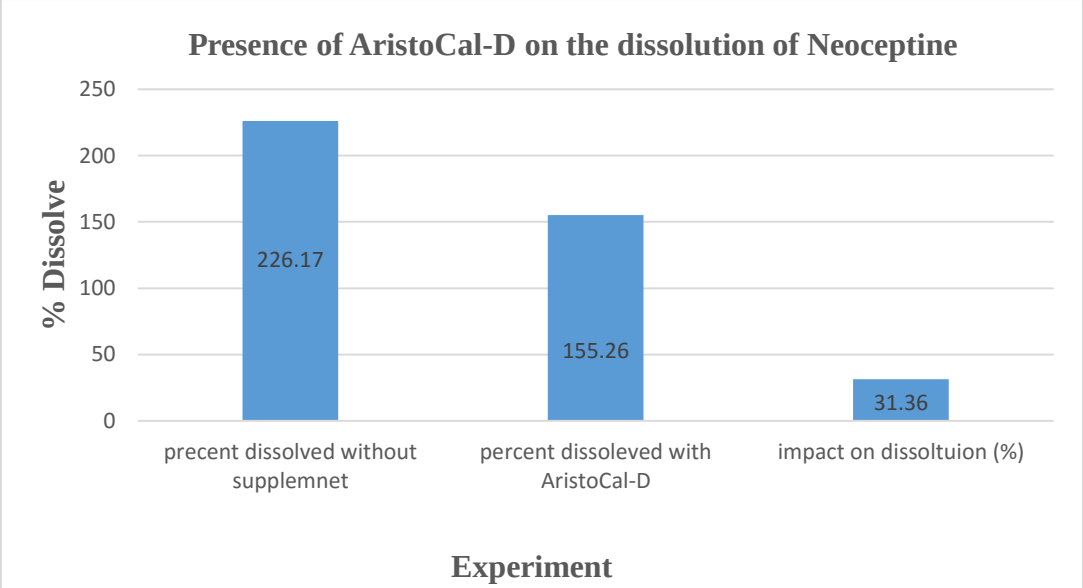

Figure *4.16*: Graph represents the presence of AristoCal-D on the dissolution of Ranitidine

4.8 Comparison among the dissolved amount (after 20min) Of Ranitidine, Ranitidine with Acical-M, Calbo 500, Filwel® Silver, Nutrum gold and AristoCal-D.

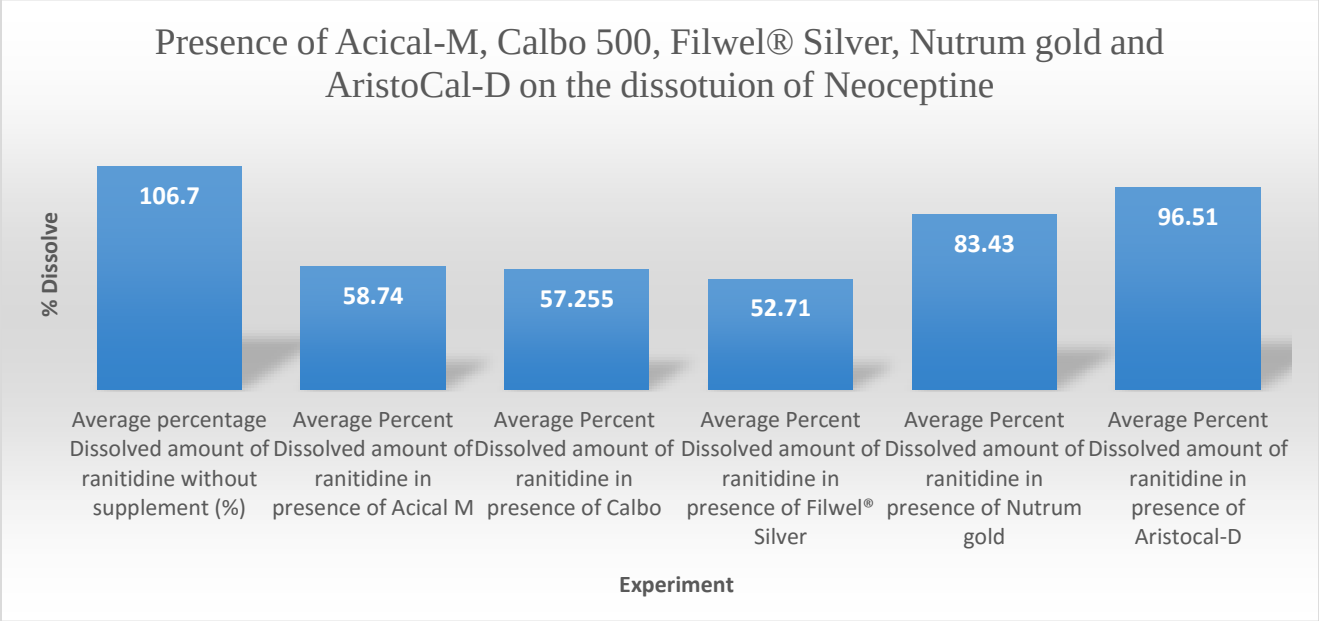

Figure *4.17*: Graph represents the presence of Acical-M, Calbo 500, Filwel® Silver, Nutrum gold and AristoCal-Don the dissolution of Ranitidine (after 20min)

4.9 Comparison among the dissolved amount(after 40 min) of Ranitidine, Ranitidine with Acical-M, Calbo 500, Filwel® Silver, Nutrum gold and AristoCal-D.

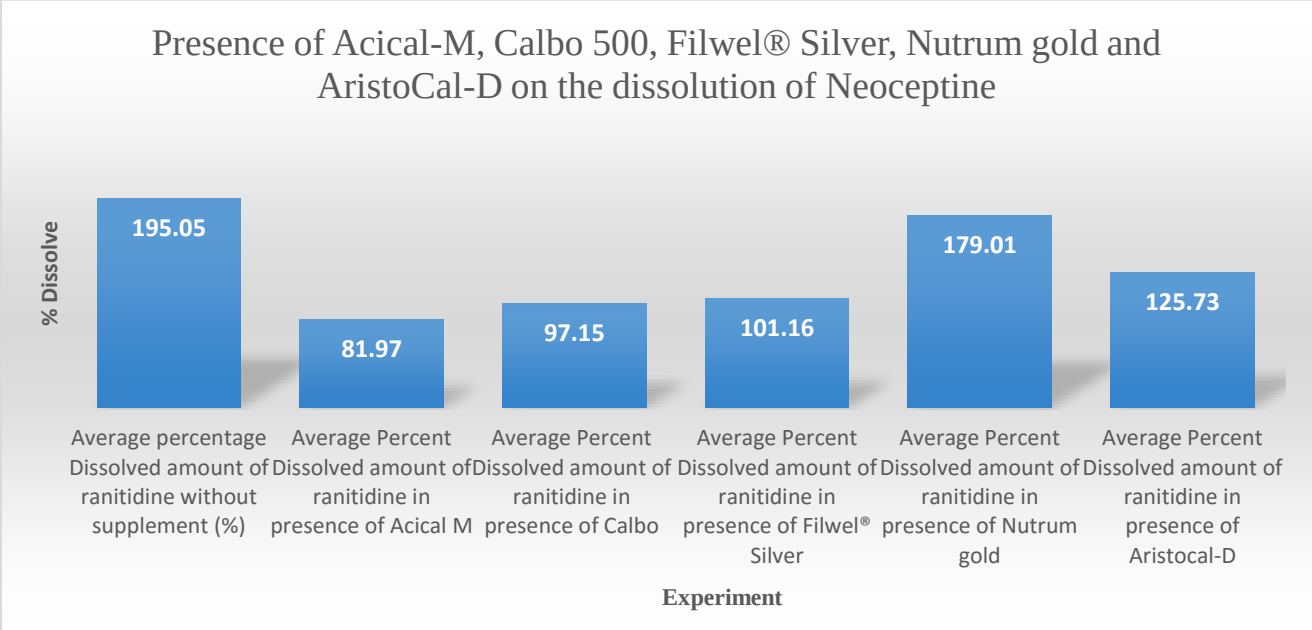

Figure *4.18*: Graph represents the presence of Acical-M, Calbo 500, Filwel® Silver, Nutrum gold and AristoCal-D on the dissolution of Ranitidine (after 40min)

4.10 Comparison among the dissolved amount(after 60 min) of Ranitidine, Ranitidine with Acical-M, Calbo 500, Filwel® Silver, Nutrum gold and AristoCal-D.

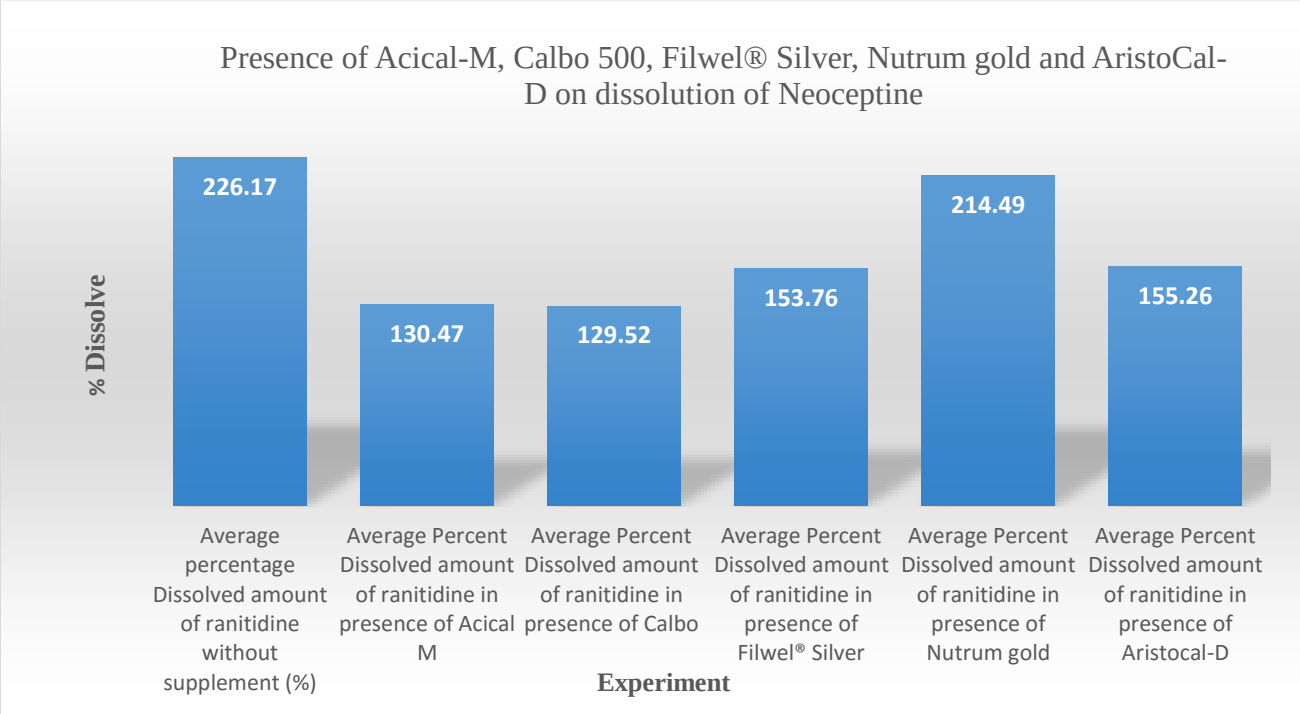

Figure *4.19*: Graph represents the presence of Acical-M, Calbo 500, Filwel® Silver, Nutrum gold and AristoCal-D on the dissolution of Ranitidine (after 60min)

4.11 Result of the dissolution test of individual Zantac and Zantac with Calbo, Aristocal D, Acical M, Nutrum Gold and Filwel Silver.

4.12 Dissolution test of Zantac (Ranitidine) without any supplement:

Table 4.25: UV absorbance of Zantac (Ranitidine)

	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 is, Y= 0.045x+0.012

Here, Y= Absorbance

X=concentration=?

Dilution factor=9000

If the absorbance is 0.564, then by putting the value in this equation,

0.564=0.045x + 0.012

0.045X=0.564-0.012

0.045x=0.552

X=0.552/0.045

X=12.27

Dissolve amount=12.27*9000/1000= 110.40mg

By putting the other absorbance value in this equation different dissolved amount of zantac (ranitidine) was calculated.

Table 4.26: 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

4.13 Dissolution test of Zantac (ranitidine) with Calbo (Calcium supplement):

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 4.27: Determination of Dissolved amount of Zantac (Ranitidine) with Calbo (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

Comparison of dissolved amount and percent dissolved amount between Zantac (Ranitidine) and Zantac (Ranitidine) with Calbo (Calcium supplement) and impact on dissolution calculation after 20, 40 and 60 minutes.

Impact of different supplement drugs on dissolution profile of Zantac & Neoceptine

Impact of Calbo on the dissolution of Zantac after 20 minutes.

Table 4.28: Percentage calculation for dissolved amount of Zantac (Ranitidine) and Zantac (Ranitidine) with Calbo (Calcium supplement) and impact on dissolution calculation 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		

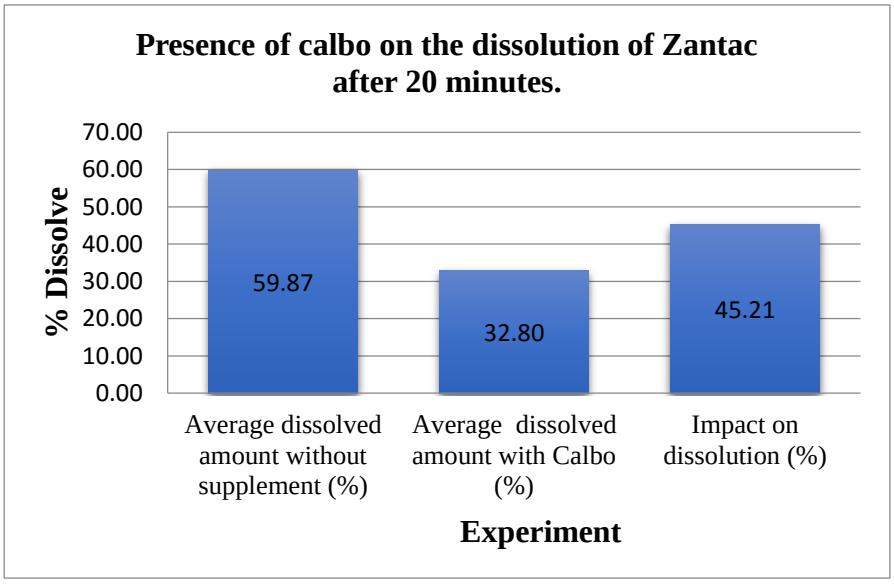

Figure 4.20: Graph represents the presence of Calbo on the dissolution of Zantac after 20 minutes.

Impact of Calbo on the dissolution of Zantac after 40 minutes.

Table 4.29: Percentage calculation for dissolved amount of Zantac (Ranitidine) and Zantac (Ranitidine) with Calbo (Calcium supplement) and impact on dissolution calculation 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		

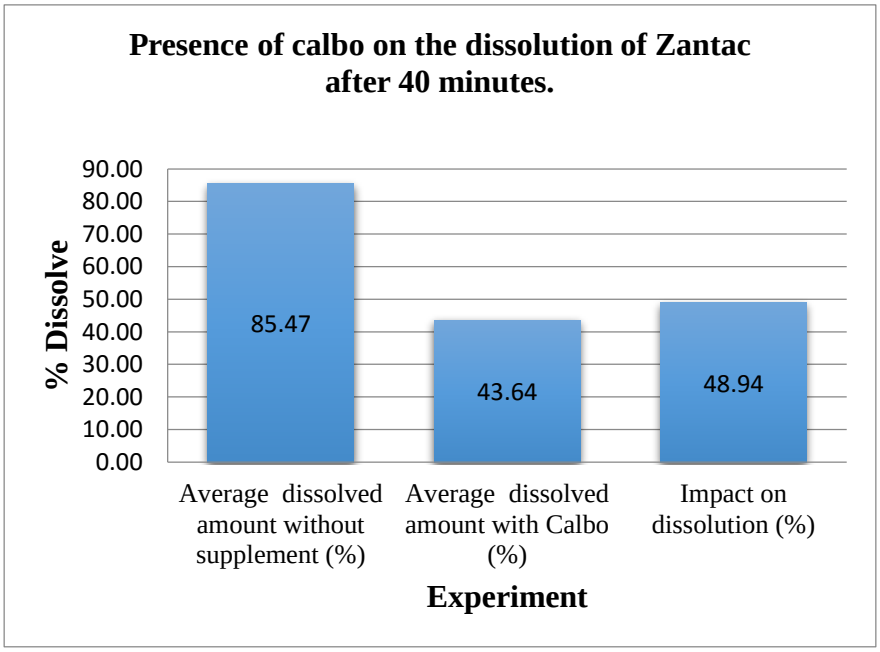

Figure 4.21: Graph represents the presence of Calbo on the dissolution of Zantac after 40 minutes.

Impact of Calbo on the dissolution of Zantac after 60 minutes.

Table 4.30: Percentage calculation for dissolved amount of Zantac (Ranitidine) and Zantac (Ranitidine) with Calbo (Calcium supplement) and impact on dissolution calculation.

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		

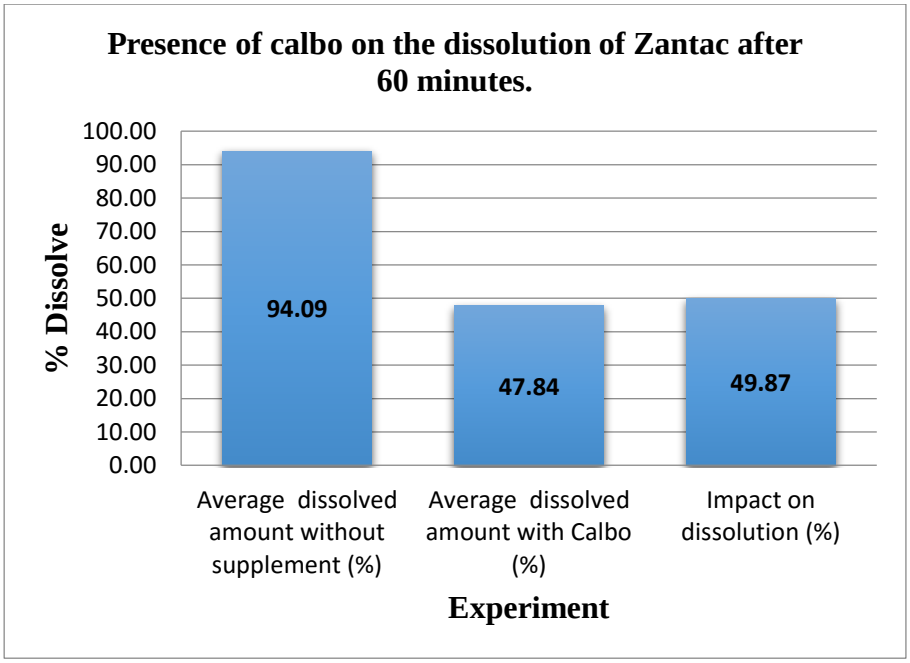

Figure 4.22: Graph represents the presence of Calbo on the dissolution of Zantac after 60 minutes.

4.14 Dissolution test of Zantac (ranitidine) with Aristocal D (Calcium and vitamin D supplement):

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 4.31: 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

Comparison of dissolved amount and percent dissolved amount between Zantac (Ranitidine) and Zantac(Ranitidine) with Aristocal D (Calcium and vitamin D supplement) and impact on dissolution calculation after 20, 40 and 60 minutes.

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

Table 4.32: Percentage calculation for dissolved amount of Zantac (Ranitidine) and Zantac (Ranitidine) with Aristocal D (Calcium and vitamin D supplement) and impact on dissolution calculation 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		

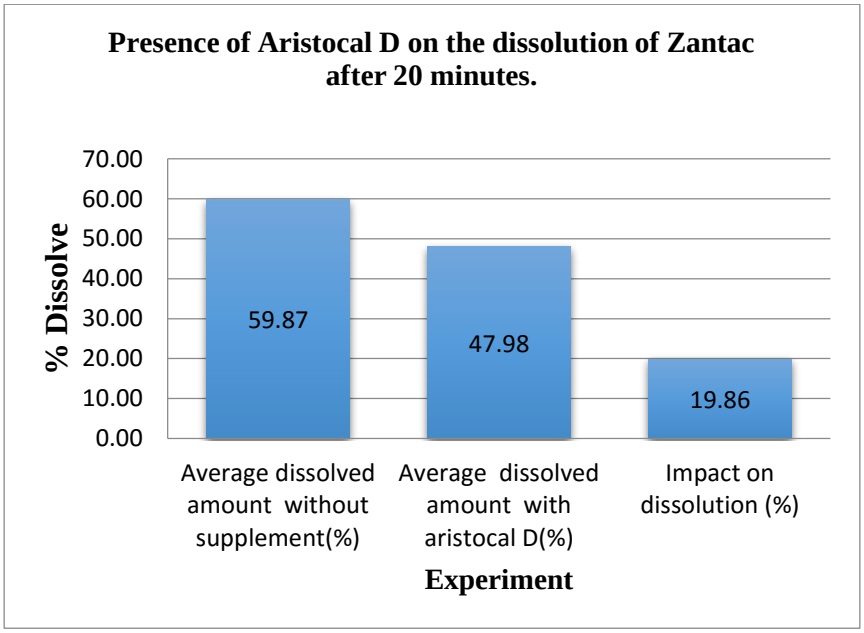

Figure 4.23: Graph represents the presence of Aristocal D on the dissolution of Zantac after 20 minutes.

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

Table 4.33: Percentage calculation for dissolved amount of Zantac (Ranitidine) and Zantac (Ranitidine) with Aristocal D (Calcium and vitamin D supplement) and impact on dissolution calculation 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		

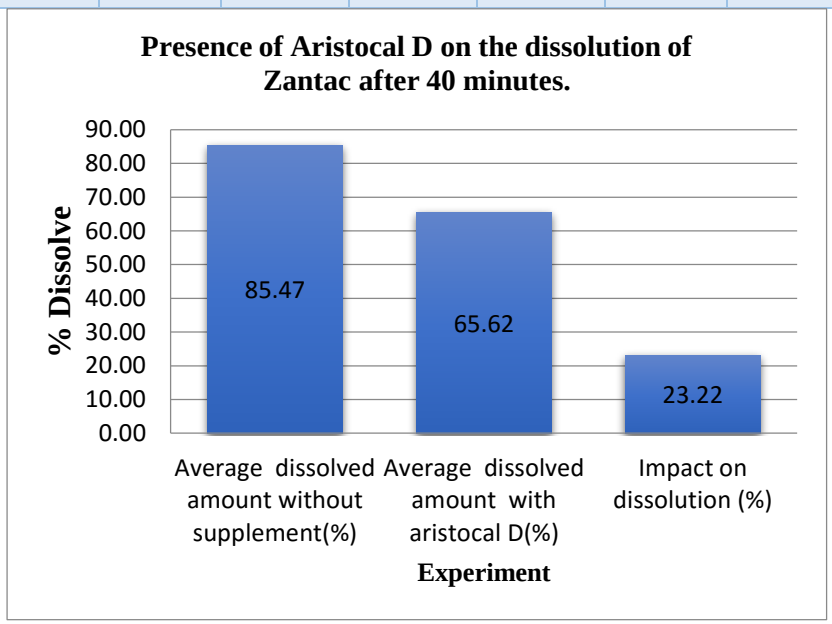

Figure 4.24: Graph represents the presence of Aristocal D on the dissolution of Zantac after 40 minutes.

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

Table 4.34: Percentage calculation for dissolved amount of Zantac (Ranitidine) and Zantac (Ranitidine) with Aristocal D (Calcium and vitamin D supplement) and impact on dissolution calculation 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 dissolve 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		

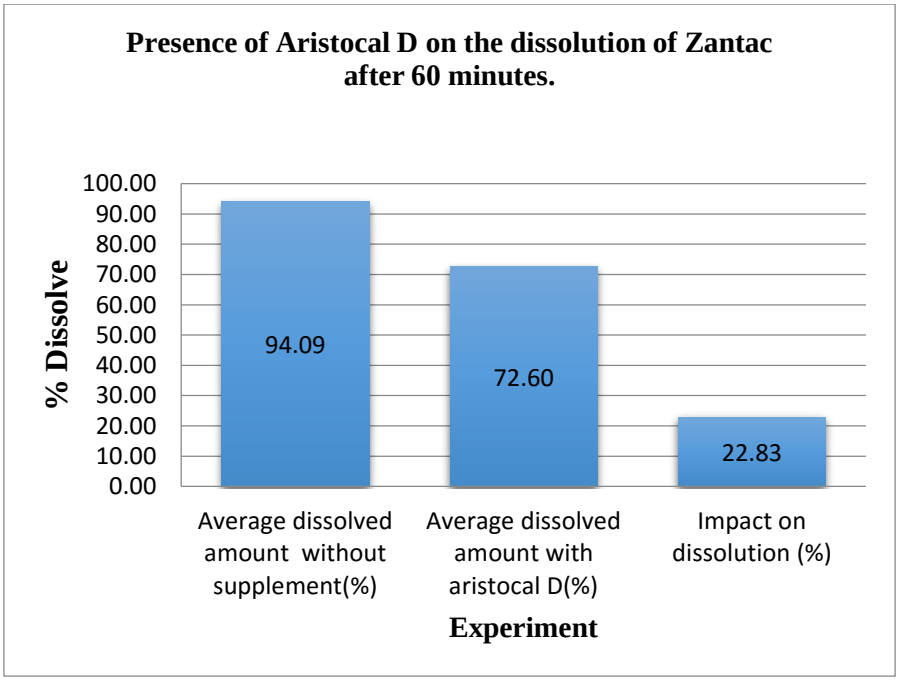

Figure 4.25: Graph represents the presence of Aristocal D on the dissolution of Zantac after 60 minutes.

4.15 Dissolution test of Zantac (ranitidine) with Acical M (Calcium, vitamin D and Multiminerals supplement)

Calculation for dissolved amount (mg) Zantac (ranitidine) with Acical M (Calcium, vitamin D and Multiminerals supplement)
By using, Y= 0.045x+0.012 equation dissolved amount of Zantac (ranitidine) with Acical M (Calcium, vitamin D and Multiminerals supplement) was calculated.

Table 4.36: Determination of Dissolved amount of Zantac (Ranitidine) with Acical M (Calcium, vitamin D and Multiminerals 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

Comparison of dissolved amount and percent dissolved amount between Zantac (Ranitidine) and Zantac (Ranitidine) with Acical M (Calcium, vitamin D and Multiminerals supplement) and impact on dissolution calculation 20, 40 and 60 minutes.

Impact of different supplement drugs on dissolution profile of Zantac & Neoceptine

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

Table 4.37: Percentage calculation for dissolved amount of Zantac (Ranitidine) and Zantac (Ranitidine) with Acical M (Calcium, vitamin D and Multiminerals supplement) and impact on dissolution calculation 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		

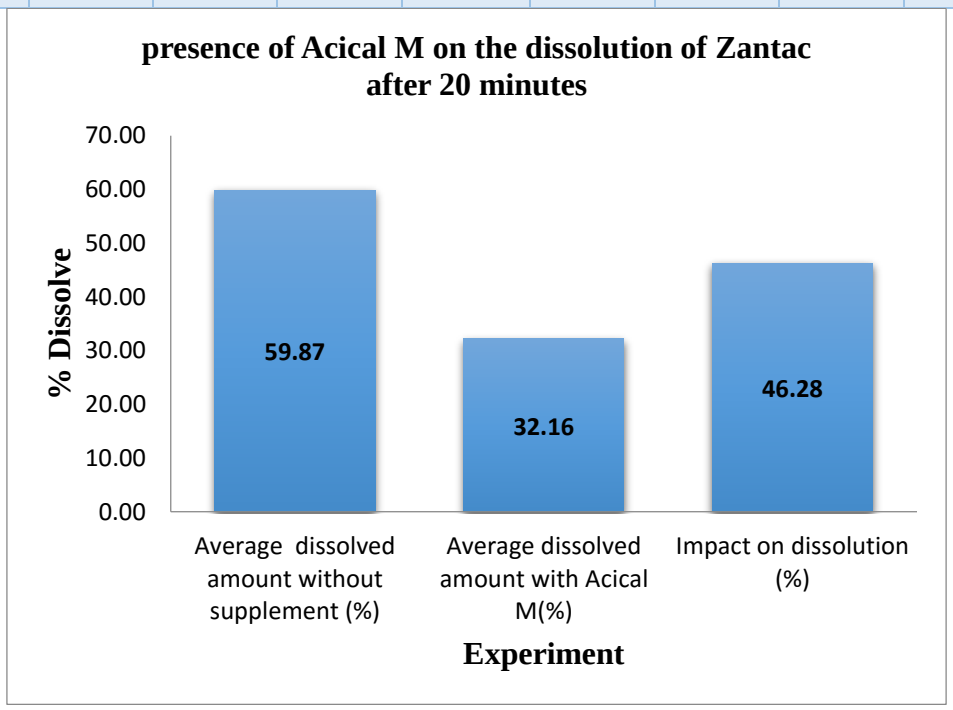

Figure 4.26: Graph represents the presence of Acical M on the dissolution of Zantac after 20 minutes.

Impact of different supplement drugs on dissolution profile of Zantac & Neoceptine

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

Table 4.38: Percentage calculation for dissolved amount of Zantac (Ranitidine) and Zantac (Ranitidine) with Acical M (Calcium, vitamin D and Multiminerals supplement) and impact on dissolution calculation 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		

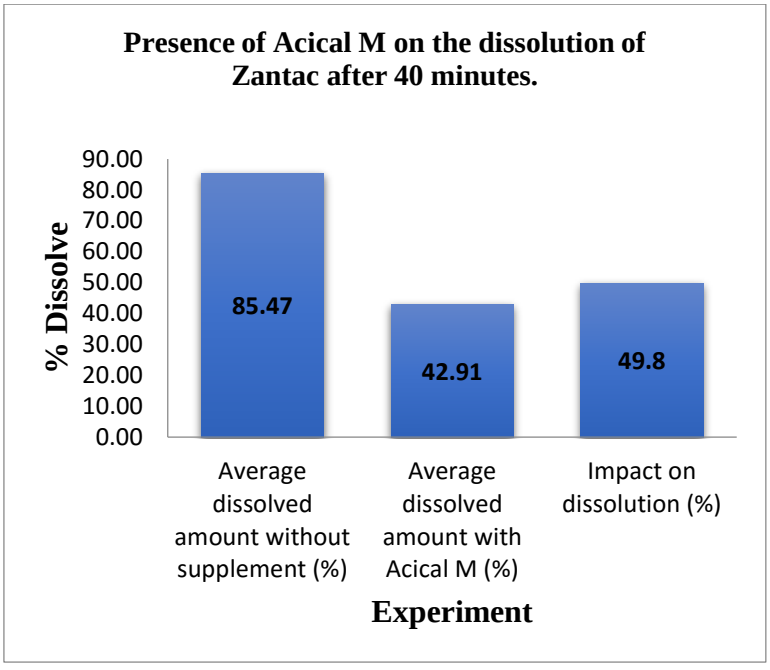

Figure 4.27: Graph represents the presence of Acical M on the dissolution of Zantac after 40 minutes.

Impact of different supplement drugs on dissolution profile of Zantac & Neoceptine

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

Table 4.39: Percentage calculation for dissolved amount of Zantac (Ranitidine) and Zantac (Ranitidine) with Acical M (Calcium, vitamin D and Multiminerals supplement) and impact on dissolution calculation 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		

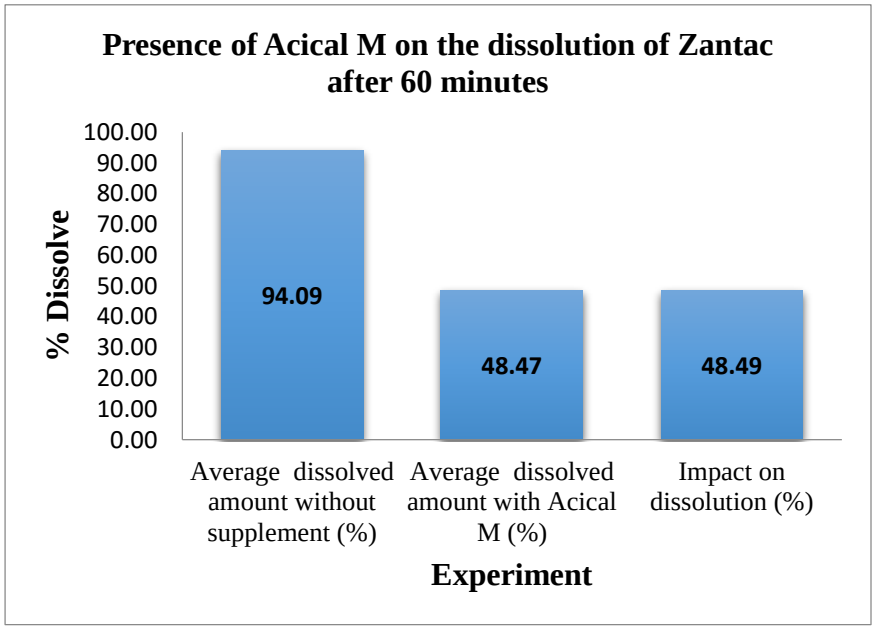

Figure 4.28: Graph represents the presence of Acical M on the dissolution of Zantac after 60 minutes.

4.16 Dissolution test of Zantac (ranitidine) with Nutrum Gold (Multivitamin and Multiminerals supplement)

Calculation for dissolved amount (mg) Zantac (Ranitidine) with Nutrum Gold (Multivitamin and Multiminerals supplement).
By using, Y= 0.045x+0.012 equation dissolved amount of Zantac (ranitidine) with Nutrum Gold (Multivitamin and Multiminerals supplement) was calculated.

Table 4.40: Determination of Dissolved amount of Zantac (Ranitidine) with Nutrum Gold (Multivitamin and Multiminerals 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

Comparison of dissolved amount and percent dissolved amount between Zantac (Ranitidine) and Zantac (Ranitidine) with Nutrum Gold (Multivitamin and Multiminerals supplement) and impact on dissolution calculation 20, 40 60 minutes.

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

Table 4.41: Percentage calculation for dissolved amount of Zantac (Ranitidine) and Zantac (Ranitidine) with Nutrum Gold (Multivitamin and Multiminerals supplement) and impact on dissolution calculation 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 dissolve 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		

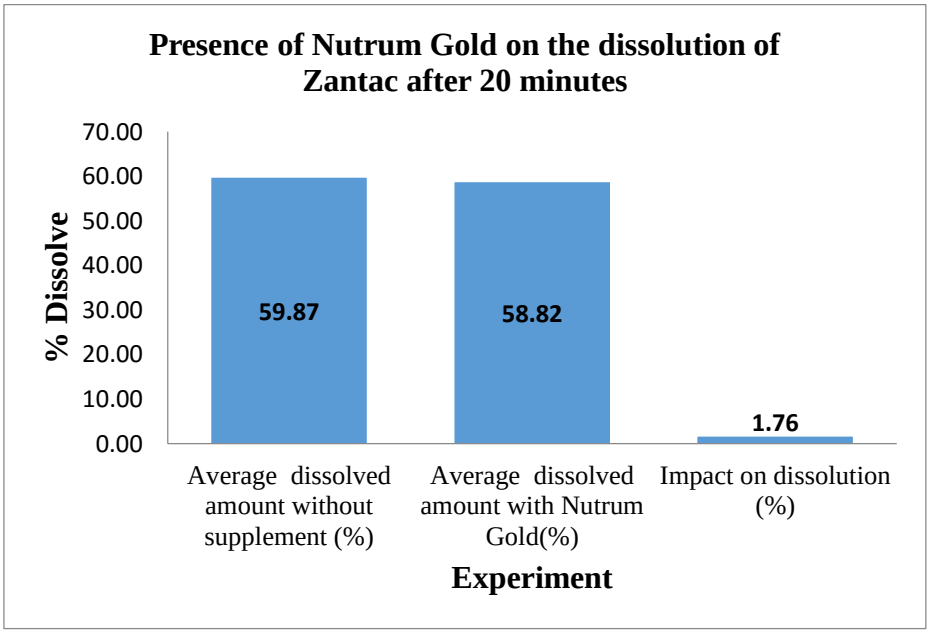

Figure 4.29: Graph represents the presence of Nutrum Gold on the dissolution of Zantac after 20 minutes.

Impact of different supplement drugs on dissolution profile of Zantac & Neoceptine

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

Table 4.42: Percentage calculation for dissolved amount of Zantac (Ranitidine) and Zantac (Ranitidine) with Nutrum Gold (Multivitamin and Multiminerals supplement) and impact on dissolution calculation 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 (%)
128.20		85.47		115.40		76.93		
118.60		79.07		113.00		75.33		
139.00	128.2	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		

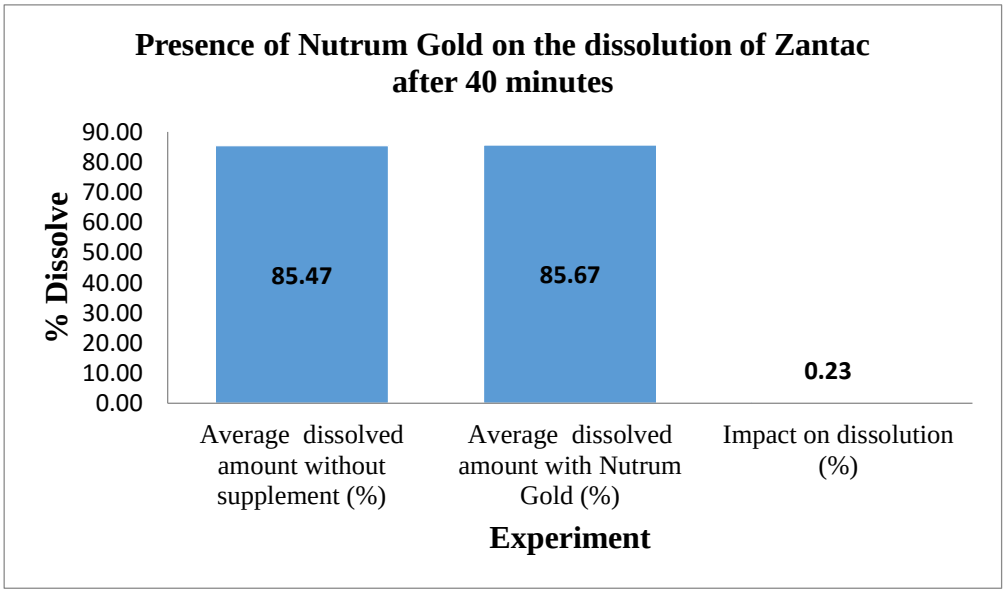

Figure 4.30: Graph represents the presence of Nutrum Gold on the dissolution of Zantac after 40 minutes.

Impact of different supplement drugs on dissolution profile of Zantac & Neoceptine

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

Table 4.43: Percentage calculation for dissolved amount of Zantac (Ranitidine) and Zantac (Ranitidine) with Nutrum Gold (Multivitamin and Multiminerals supplement) and impact on dissolution calculation 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		

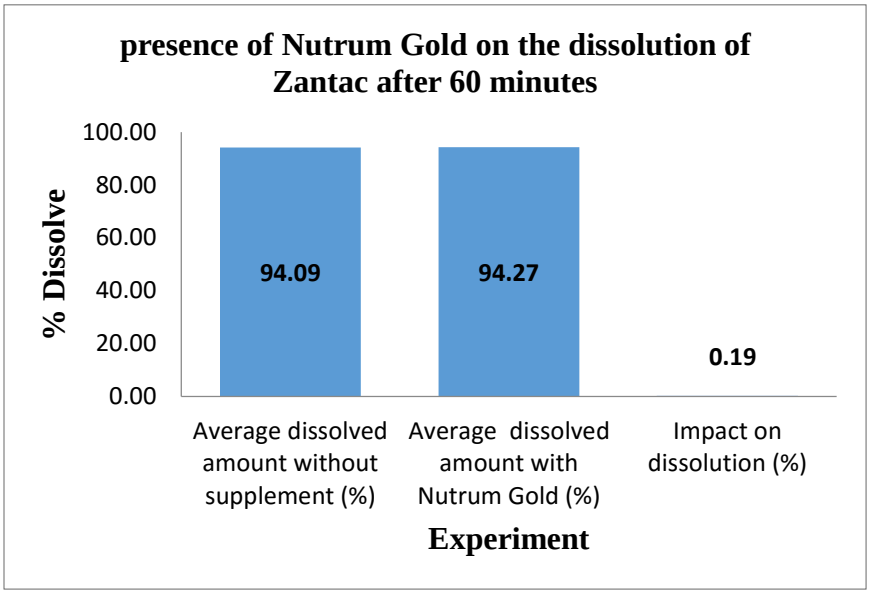

Figure 4.31: Graph represents the presence of Nutrum Gold on the dissolution of Zantac after 60 minutes.

4.17 Dissolution test of Zantac (ranitidine) with Filwel Silver (Multivitamin and Multiminerals supplement)

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

Table 4.44: Determination of Dissolved amount of Zantac (Ranitidine) with Filwel Silver (Multivitamin and Multiminerals 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

Comparison of dissolved amount and percent dissolved amount between Zantac (Ranitidine) and Zantac (Ranitidine) with Filwel Silver (Multivitamin and Multiminerals supplement) and impact on dissolution calculation 20, 40 and 60 minutes.

Impact of different supplement drugs on dissolution profile of Zantac & Neoceptine

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

Table 4.45: Percentage calculation for dissolved amount of Zantac (Ranitidine) and Zantac (Ranitidine) with Filwel Silver (Multivitamin and Multiminerals supplement) and impact on dissolution calculation 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		

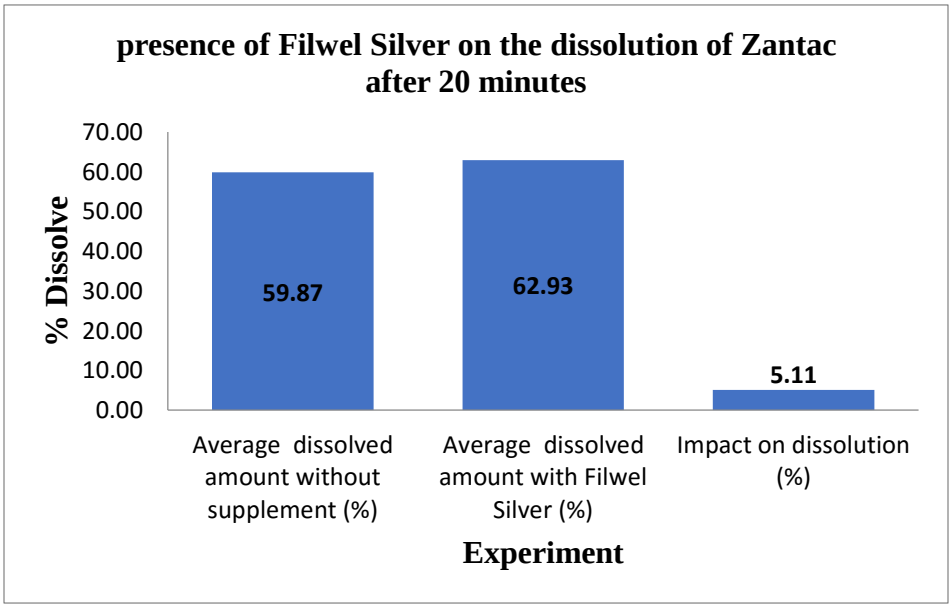

Figure 4.32: Graph represents the presence of Filwel Silver on the dissolution of Zantac after 20 minutes.

Impact of different supplement drugs on dissolution profile of Zantac & Neoceptine

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

Table 4.45: Percentage calculation for dissolved amount of Zantac (Ranitidine) and Zantac (Ranitidine) with Filwel Silver (Multivitamin and Multiminerals supplement) and impact on dissolution calculation 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		

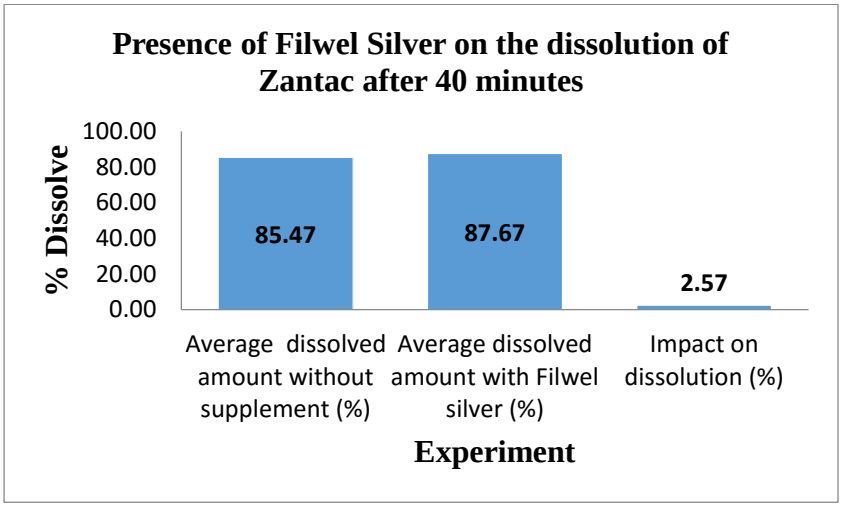

Figure 4.33: Graph represents the presence of Filwel Silver on the dissolution of Zantac after 40 minutes.

Impact of different supplement drugs on dissolution profile of Zantac & Neoceptine

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

Table 4.46: Percentage calculation for dissolved amount of Zantac (Ranitidine) and Zantac (Ranitidine) with Filwel Silver (Multivitamin and Multiminerals supplement) and impact on dissolution calculation.

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		

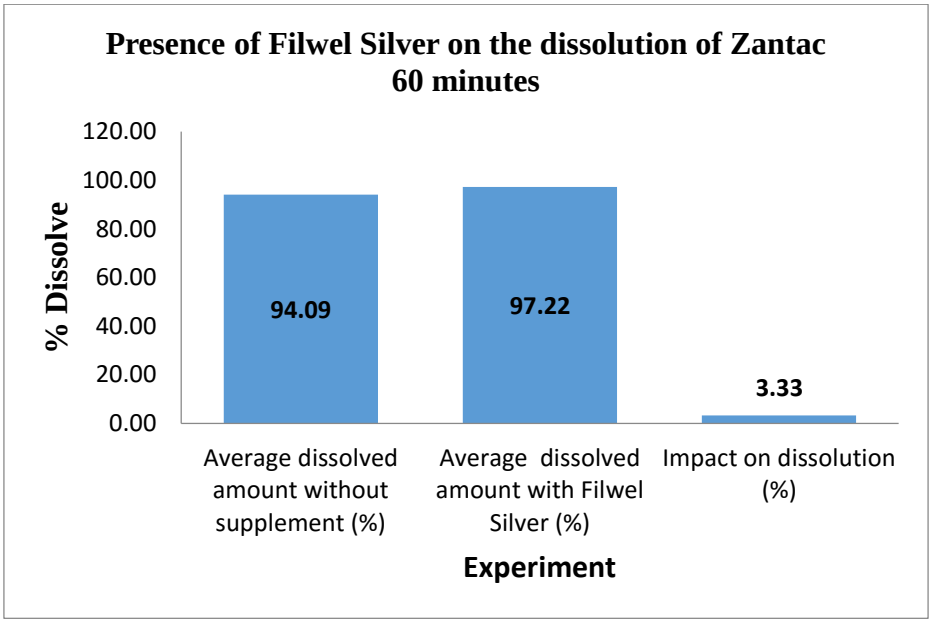

Figure 4.34: Graph represents the presence of Filwel Silver on the dissolution of Zantac 60 minutes.

4.18 Comparison among the average percent dissolved (%) amount of individual Zantac, Zantac with Calbo, Zantac with Aristocal D, Zantac with Acical M, and Zantac with Nutrum Gold and Zantac with Filwel silver after 20, 40 and 60 minutes.

Table 4.47 : Table showing 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

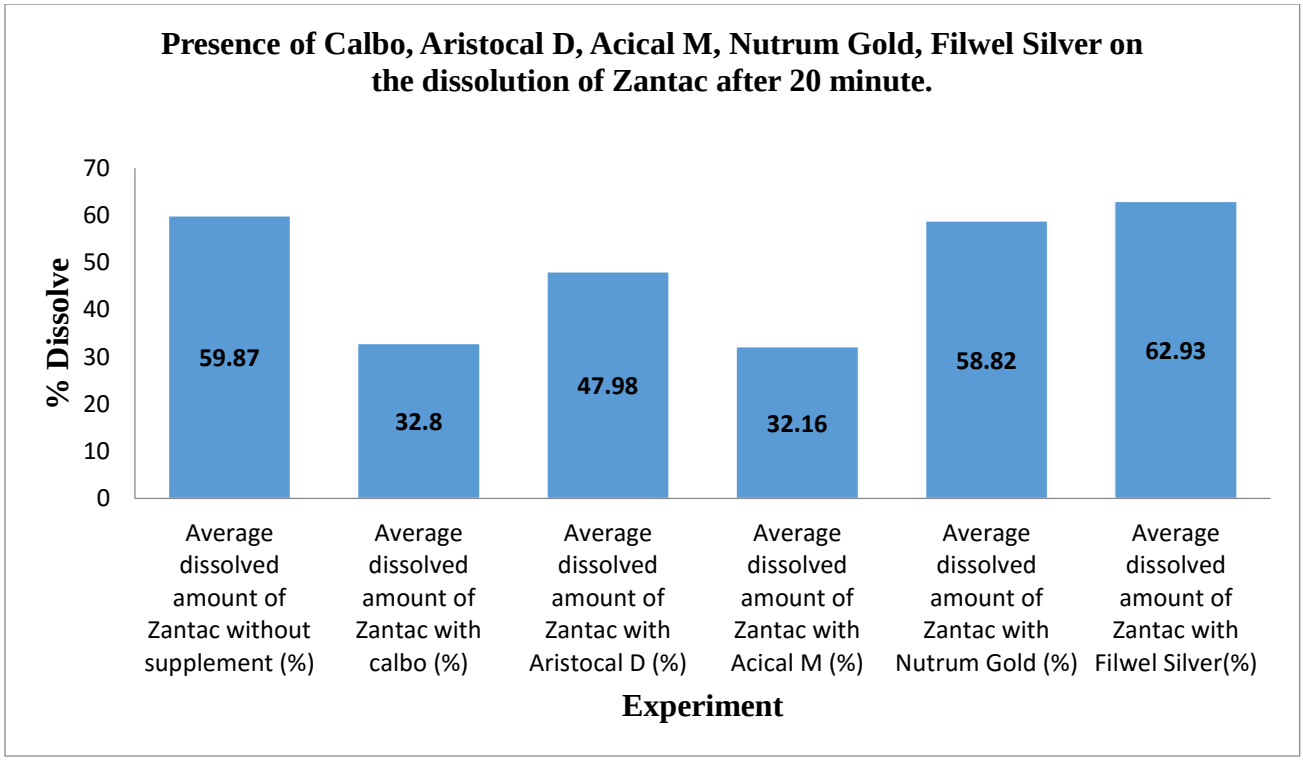

Figure 4.35: Graph represents the presence of Calbo, Aristocal D, Acical M, Nutrum Gold, and Filwel Silver on the dissolution of Zantac after 20 minute.

Table 4.48: Table showing 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

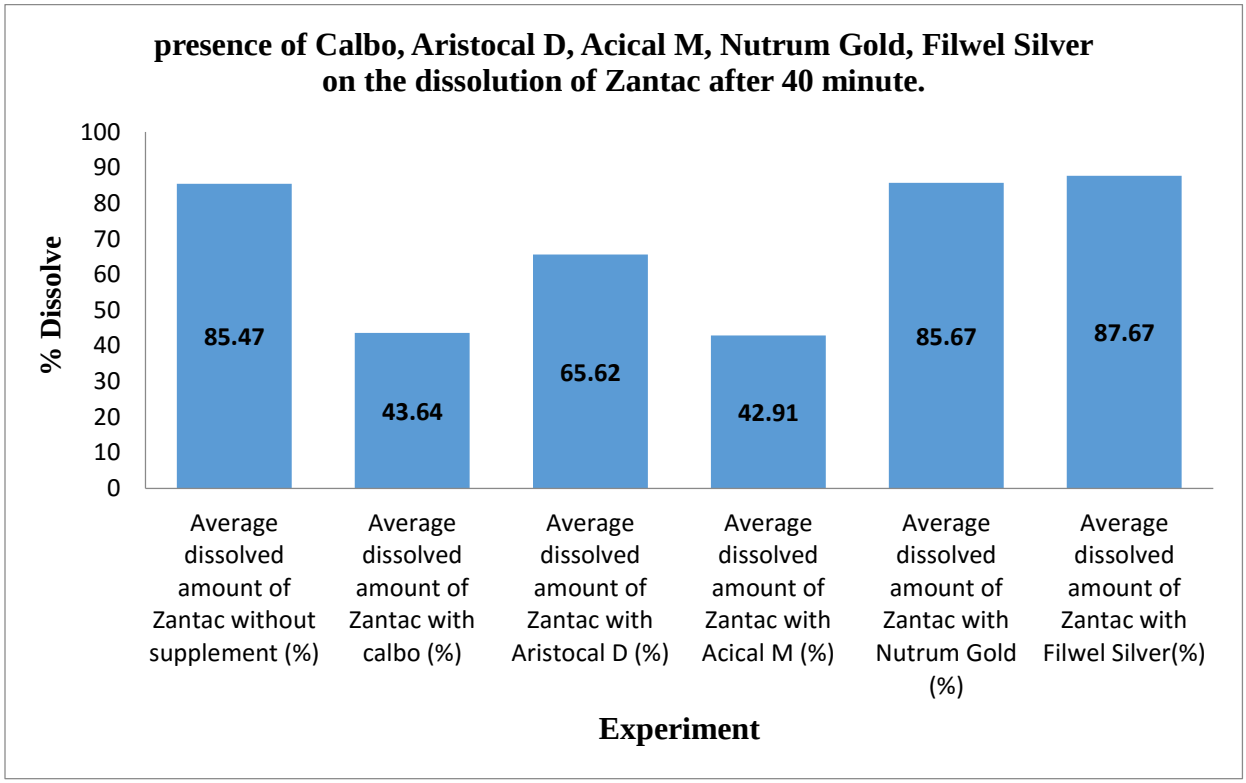

Figure 4.36: Graph represents the presence of Calbo, Aristocal D, Acical M, Nutrum Gold, and Filwel Silver on the dissolution of Zantac after 40 minute.

Table 4.49: Table showing 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

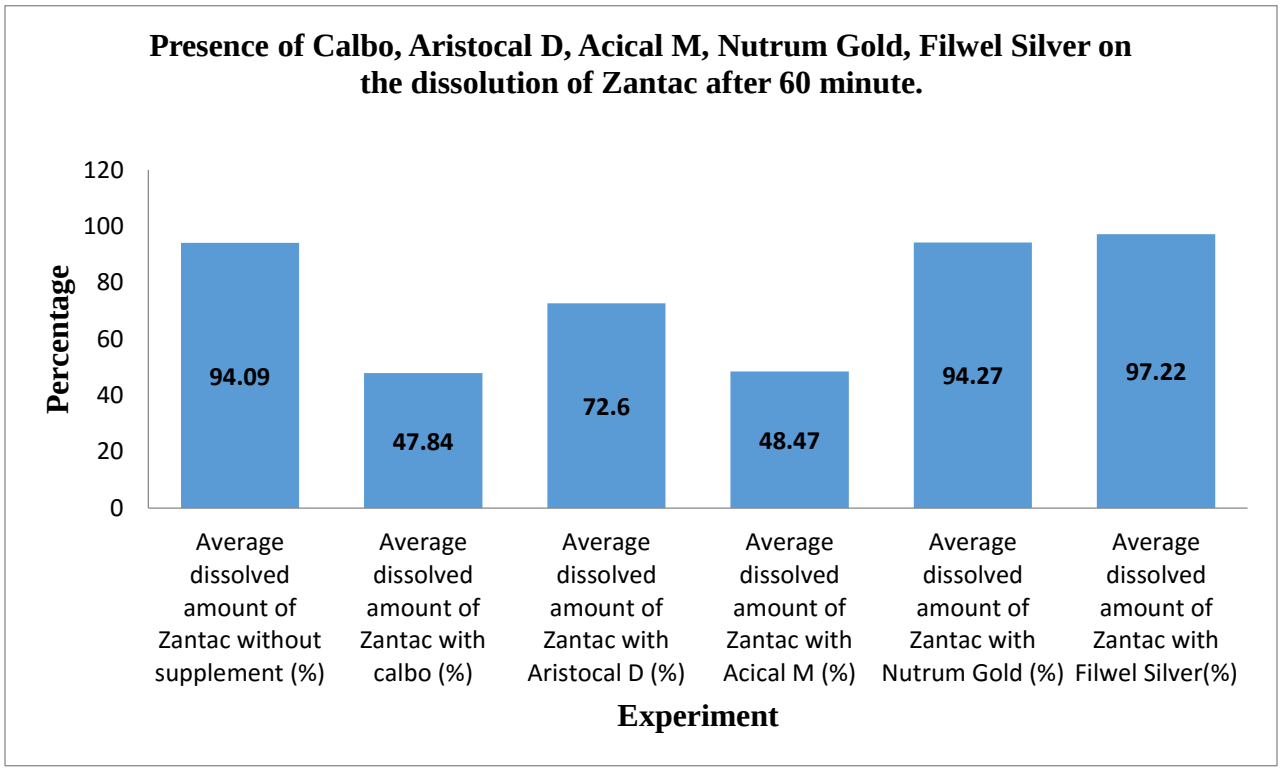

Figure 4.37: Graph represents the presence of Calbo, Aristocal D, Acical M, Nutrum Gold, and Filwel Silver on the dissolution of Zantac after 60 minute.

4.19 Results from weight variation test:

Table 4.50: Table showing weight variation test of Neoceptine:

Table no.	Initial Weight I (gm)	Average weight A (gm)	% Weight variation (A-I/I)×100
1	.252		14.57
2	.301		-2.03
3	.294		.33
4	.298		.30
5	.312	.295	-5.76
6	.301		-2.03
7	.296		-.33
8	.299		-.135
9	.292		1.01
10	.301		-2.03

4.20 Results from thickness test:

Table 4.51: table showing test of Neoceptine:

Table no.	Main scale(cm), M	Vernier scale reading(cm), V	Thickness of the table tablet (cm), (M+V)
1	.4	0.09	0.49
2	.4	0.09	0.49
3	.4	0.095	0.495
4	.4	0.09	0.49
5	.4	0.095	0.495
6	.4	0.09	0.49
7	.4	0.095	0.495
8	.4	0.095	0.495
9	.4	0.09	0.49
10	.4	0.095	0.495

4.21 Results showing Hardness test:

Table 4.52: table showing hardness test of Neoceptine:

Table no.	Hardness (Kg)	Average
1	7	
2	8	
3	7	
4	9	
5	9	8.4
6	8.5	
7	8.5	
8	9	
9	9	
10	9	

4.22 Results from thickness test:

Table 4.53: Table showing thickness test 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

4.23 Result from weight variation test:

Table 4.54: Table showing weight variation test of Zantac tablets.

Tablet No.	Initial weight I (mg)	Average weight 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

4.24 Results from Hardness tests:

Table 4.66: Table showing harness test of Zantac Tablets.

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

Chapter Five

Discussion

Discussion

The experiment showed the dissolution of ranitidine in presence of Acical-M is significantly decreased. As the dissolution is affected indicates the absorption may be affected. So there is a chance of Ranitidine not to reach the Minimum Effective Concentration (EMC) (Rang and dale, 2014) and cannot able to give the therapeutic effect. So, the Ranitidine should not be administer with Acical-M. The supplement can be administer 1 or 2 hour before after ranitidine intake.

The experiment showed the dissolution of ranitidine in presence of Calbo 500 is significantly decreased. As the dissolution is affected indicates the absorption may be affected. So there is a chance of Ranitidine not to reach the Minimum Effective Concentration (EMC) (Rang and dale, 2014) and cannot able to give the therapeutic effect. So, the Ranitidine should not be administer with Calbo 500.The supplement can be administer 1 or 2 hour before after ranitidine intake.

The experiment showed the dissolution of ranitidine in presence of Filwel Silver is significantly decreased. As the dissolution is affected indicates the absorption may be affected. So there is a chance of Ranitidine not to reach the Minimum Effective Concentration (EMC) (Rang and dale, 2014) and cannot able to give the therapeutic effect. So, the Ranitidine should not be administer with Filwel Silver. The supplement can be administer 1 or 2 hour before after ranitidine intake.

The experiment showed the dissolution of ranitidine is not significantly changed in the presence of Nutrum Gold. So the ranitidine can be administer with Nutrum Gold.

The experiment showed the dissolution of ranitidine is not significantly changed in the presence of Aristocal D. So the ranitidine can be administer with Aristocal-D.

In our experiment it was found that the percentage of weight variation of the sample tablets was within the accepted range according to U.S.P if no more than 2 tablets are outside the percentage limit and if no tablets differ by more 2 times the percentage limit the tablet pass thee tests, all the sample tablets were the limit .

The thickness of all the tablets determination and all the values are closed. Thickness is important parameter of a tablet because if thickness of the tablets of same batch varies then dissolution time will vary (kett *et al.,* 2001).

The hardness of the sample was determined to evaluate its physical parameter. Hardness tests were done to observe the strength of the tablets. If tablet is too hard, it may not disintegrate in the required period of time and will fail dissolution test. If tablet is too soft it may not be able to withstand handling during subsequent processing such as coating or packaging and shipping operations (Aulton *et al.,* 1999)

Chapter Six

Conclusion

Conclusion

In this study it observed that there is a significant impact of Acical-M, Calbo 500 and Filwel Silver on the dissolution of Ranitidine. But Nutrum Gold and Aristocal-D don't show significant impact on dissolution of Ranitidine. So, Nutrum Gold and Aristocal-D can be administered with Ranitidine, but Acical-M, Calbo 500 and Filwel Silver shouldn't be administered.

Chapter seven

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Reference

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