PHARMACEUTICAL EQUIVALENCE INVESTIGATIONS OF DIFFERENT BRANDS OF NAPROXEN TABLET

Submitted by:

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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

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Kamrun Nahar

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This Thesis Paper is Dedicated to My Niece Raya

The thesis paper on “Pharmaceutical equivalence investigations of different brands of naproxen tablet” submitted to Department of Pharmacy, East West University, Dhaka in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy by Kamrun Nahar (ID: 2008-1-70-034) on July,2012

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CERTIFICATE

This is to certify that the thesis “Pharmaceutical equivalence investigations of different brands of naproxen tablet” submitted to the Department of Pharmacy, East West University, Rampura, Dhaka in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (B.Pharm) was carried out by Kamrun Nahar (ID: 2008-1-70-034) under my guidance and supervision and that no part of the thesis has been submitted for any other degree. I further certify that all the sources of information and laboratory facilities availed of this connection is duly acknowledged.

……

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Abstract

The quality of pharmaceutical finished dosage forms is of major concern to the pharmaceutical industries. Tablet dosage form of any pharmaceutical company goes through many research studies and experiments to maintain the proper quality standards. The aim of this study was to investigate the quality of different brands of naproxen tablets which are manufactured in Bangladesh. Different physical parameters like hardness, thickness, friability as well as disintegration time, and dissolution rates were conducted to evaluate the quality of the tablets of different brands of naproxen. To assess its effectiveness potency test was conducted. The range of hardness test result of Naprosyn, Sonap, Naspro and Naid are respectively 7.75, 7.25, 4.0 and 5.83 kg. Among four brands two selected brands were shown more than the standard hardness value. The friability test results were all in range of the standard value. The thickness of Naprosyn, Sonap, Naspro and Naid are 4.1, 7.1, 6.0 and 5.32 mm. The disintegration test has mean time of Naprosyn, Naspro and Naid are 4.16,6.61 and 15.28 minute. The potency results were 95.62% , 56.1% , 102.62% and 74.46% whereas the standard contain 99.29 % potency. The average dissolution test results have values are 95.16% , 95.47% , 96.06% and 94.63%. The hardness test of half of the selected brands was more than the usual standards. The excess hardness can delay the tablet breakdown process in the biological system. The friability test results are all in range. A good quality product must be able to withstand the undesired pressure. To determine this, friability test is necessary. The thickness test of all the brands was complied with the standard values except sonap. The potency value of some brands of naproxen tablet showed some higher and lower than the standard value. These values can be a result of experimental error. The dissolution test results showed values in the range of standards except Sonap and Naspro which showed a lower then standard value. Quality of a product is the major issue for any pharmaceutical company. To ensure quality product a pharmaceutical industry follows the international standards.

CHAPTER– 1

Introduction

1.1 NSAIDs Non steroidal anti inflammatory drugs

Nonsteroidal antiiflammatory drugs (NSAIDs) may also be used for their analgesic effect. All NSAIDs, including the traditional nonselective drugs and the subclass of selective cyclooxygenase-2 (COX-2) inhibitors, are anti-inflammatory, analgesic, and antipyretic. The NSAIDs consist of drugs like aspirin, ketoprofen, acetaminophen, flunixin and ketorolac. NSAIDs are a chemically heterogeneous group of organic acids that share certain therapeutic actions and adverse effects. There are a large number of these drugs available. NSAIDs are, in general, less potent analgesics than are the narcotics. However, in specific instances they can have similar activity. The advantages of the NSAIDs are that they do not cause sedation nor are they addictive as are the narcotic analgesics. There are no special recordkeeping requirements. In addition, they are more effective against pain caused by inflammation, such as is seen with tissue repair, orthopedic surgery, infection and injury (Raffa, 2008).

1.2 Mechanism of Action of NSAIDs

Although it had been used for almost a century, the mechanism of action of NSAIDs was elucidated only in 1971. Salicylic acid was the first chemical synthesized in 1860 and was used as an antiseptic, an antipyretic, and an antirheumatic. Almost 40 years later, aspirin was developed as a more palatable form of salicylate. Soon after, other drugs having similar actions to aspirin were discovered, and the group was termed the aspirin-like drugs (also now termed the nonsteroidal anti-inflammatory drugs (NSAIDs). Twenty-five years ago, it was proposed that the mechanism of action of NSAIDs was through their inhibition of prostaglandin biosynthesis.

Since then, there has been general acceptance of the concept that these drugs work by inhibition of the enzyme cyclo-oxygenase (COX), which we now know to have at least two distinct isoforms: the constitutive isoform, COX-1, and the inducible isoform, COX-2. COX-1 has clear physiologic functions. Its activation leads, for instance, to the production of prostacyclin, which when released by the endothelium is antithrombogenic

and when released by the gastric mucosa is cytoprotective. COX-2, discovered 6 years ago, is induced by inflammatory stimuli and cytokines in migratory and other cells. It is therefore attractive to suggest that the anti-inflammatory actions of NSAIDs are due to inhibition of COX-2, whereas the unwanted side-effects, such as irritation of the stomach lining, are due to inhibition of COX-1. Drugs that have the highest COX-2 activity and a more favorable COX-2: COX-1 activity ratio will have a potent antiinflammatory activity with fewer side-effects than drugs with a less favorable COX-2: COX-1 activity ratio. The identification of selective inhibitors of COX-2 will therefore lead to advances in therapy (Vane & Botting, 1998).

1.3 Naproxen

Naproxen is a proprionic acid derivative related to the arylacetic acid group of nonsteroidal anti-inflammatory drugs. Naproxen is commonly used for the reduction of mild to moderate pain, fever, inflammation and stiffness caused by conditions such as osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout, ankylosing spondylitis, injury, menstrual cramps, tendinitis, bursitis, and the treatment of primary dysmenorrhea.

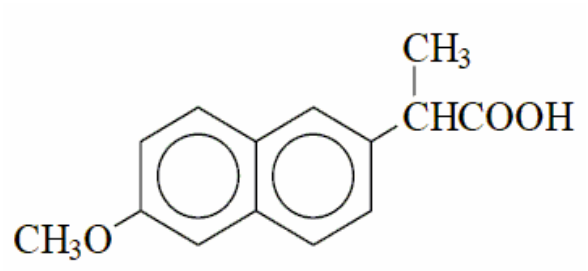
Naproxen works by blocking the cyclo-oxygenase which is involved in the production of certain irritant chemicals in response to injury or disease. By blocking the action of COX, naproxen reduce the symptoms of pain and inflammation. Some forms of naproxen have a special enteric coating to help protect stomach against irritation. There is also a modified-release form of tablets which allows naproxen to be released slowly to give a more even pain-relieving effect. Naproxen can be used alone, or alongside medicines such as misoprostol or esomeprazole which help protect against stomach irritation.

1.4 Chemistry of naproxen

Chemical name :(S)-6-methoxy-α-methyl-2-naphthaleneacetic acid;

Empirical formula: $C_{14}H_{14}O_3$.

Structural formula of naproxen:



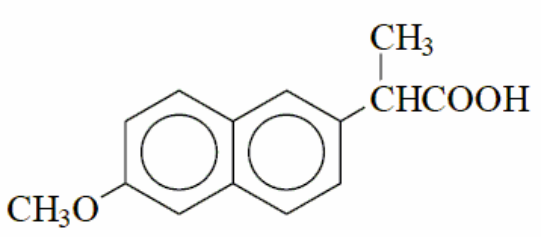
- Molecular weight: 230.2628.
- Solubility & pH: It is lipid-soluble, practically insoluble in water with a low pH (below pH 4), while freely soluble in water at 6 pH and above.
- Melting point: 153 °C.
- Odor: It is odorless
- Colour: white to off white, crystalline substance.(Mosby,2000)

1.5 History of naproxen

Since aspirin was introduced in 1897, a number of other over-the-counter analgesics have become available. Aspirin can be wonderful stuff, but it isn't perfect. Sometimes it may be better to use a different pain reliever. In the early 1960s scientists figured out that certain organic acids, like aspirin, were good at reducing inflammation. The Boots Company, a British drug maker, synthesized over 600 new organic acids looking for anti-inflammatory drugs. Naproxen is a powerful pain reliever that became available over-the-counter in the mid-1990s. Naproxen was sold by Bayer under the name Aleve. It appears

to work by inhibiting prostaglandins, like aspirin does. But also like aspirin, they can cause stomach upset and other gastrointestinal problems (Brunton, et al., 2006).

1.6 Structure activity relationship



Structure of naproxen

In a series of substitution 2-naphthylacetic acids, substitution in the 6-position led to maximum anti-inflammatory activity. Small lipophilic groups such as Cl,CH_3S,&CHF_2O were active analogue with CH_3O being the most potent. Larger groups were found to be less active. Derivatives of 2-nahthylpropionic acids are more potent than the corresponding acetic acid analogues. Replacing the carboxyl group with functional groups capable of being metabolized to the carboxyl function (e.g, -CO_2CH_3,-CHO or –CH_2OH) led to a retention of activity.

The (S)(+)isomer is more potent enantiomer .Naproxen is the only arylalkanoic acid NSAID marketed as optically active isomers.(Willium D.A., 2007)

1.7 Mechanism of action Naproxen

Naproxen inhibite the cyclooxygenase activity. There are two form of cyclooxygenase ,termed COX-1 & COX-2. COX-1 is expressed in all tissue & responsible for the production of protective prostaglangins in the kidney & stomach as well as the functional

thromboxane of platelets. The constitutive cyclooxygenase, COX-1, synthesizes prostaglandins necessary for normal gastrointestinal and renal function. COX-2 not found in most tissues, expressed under condition of tissue damage & plays an active role in the inflammatory response. The inducible cyclooxygenase, COX-2, generates prostaglandins involved in inflammation. Inhibition of COX-1 is thought to be associated with gastrointestinal and renal toxicity while inhibition of COX-2 provides anti-inflammatory activity (Harvey, R.A. & Champe, P.C. 2006)

1.8 Therapeutic activity

Naproxen is usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present. Research continues into their potential for prevention of colorectal cancer, and treatment of other conditions, such as cancer and cardiovascular disease.

Naproxen is generally indicated for the symptomatic relief of the following conditions:

- Rheumatoid arthritis
- Osteoarthritis
- Inflammatory arthropathies (e.g. ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome)
- Acute gout
- Dysmenorrhoea (menstrual pain)
- Metastatic bone pain
- Headache and migraine
- Postoperative pain
- Mild-to-moderate pain due to inflammation and tissue injury

- Pyrexia (fever)
- Renal colic (Brunton, et al., 2006).

1.9 Pharmacokinetics

The compound naproxen is a weak acid, with a pKa of 3-5. Naproxen is absorbed fully when administered orally. Food delays the rate but not the extent of absorption. Peak concentration in plasma occurs in 2 to 4 hours and is somewhat more rapid after the administration of naproxen sodium. Absorption is accelerated by the concurrent administration of sodium bicarbonate but it is delayed by magnesium oxide or aluminum hydroxide. Naproxen is also absorbed rectally, but more slowly than after oral administration. The half life of naproxen in plasma is variable. About 14 hours in the young, it may increase about tenfold in the elderly because of age-related decline in renal function.

Naproxen is metabolized in the liver by oxidation and conjugation to inactive metabolites which are excreted almost entirely in the urine, although some other NSAIDs drugs are partially excreted in bile. About 30% of the drug undergoes 6-demethylation, and most of this metabolite, as well as naproxen itself, is excreted as the glucuronide or other conjugates. Metabolism may be abnormal in certain disease states, and accumulation may occur even with normal dosage.

Naproxen is highly protein-bound in plasma (typically >95%), usually to albumin, so that its volume of distribution typically approximates to plasma volume. After normal therapeutic dose, naproxen crosses the placenta and appears in the milk of lactating women at approximately 1% of the maternal plasma concentration (Brunton, et al., 2006).

1.10 Adverse effects

Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis is listed below. In general, reactions in patients treated chronically were reported 2 to 10 times more frequently than they were in short-term studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea. The most frequent complaints reported related to the gastrointestinal tract. A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking daily doses of 1500 mg naproxen compared to those taking 750 mg naproxen.

In controlled clinical trials with about 80 pediatric patients and in well-monitored, open-label studies with about 400 pediatric patients with juvenile arthritis treated with naproxen, the incidence of rash and prolonged bleeding times were increased, the incidence of gastrointestinal and central nervous system reactions were about the same, and the incidence of other reactions were lower in pediatric patients than in adults.

In patients taking naproxen in clinical trials, the most frequently reported adverse experiences in approximately 1% to 10% of patients are:

Gastrointestinal (GI) Experiences, including: heartburn, abdominal pain, nausea, constipation, diarrhea, dyspepsia, stomatitis

Central Nervous System: headache, dizziness, drowsiness, lightheadedness, vertigo

Dermatologic: pruritus (itching), skin eruptions, ecchymoses, sweating, purpura

Special Senses: tinnitus, visual disturbances, hearing disturbances

Cardiovascular: edema, palpitations

General: dyspnea, thirst

Also including:

Gastrointestinal (GI) Experiences, including: flatulence, gross bleeding/perforation, GI ulcers (gastric/duodenal), vomiting

General: abnormal renal function, anemia, elevated liver enzymes, increased bleeding time, rashes.

The following are additional adverse experiences reported in less than 1% of patients taking naproxen during clinical trials and through postmarketing reports. Those adverse reactions observed through post marketing reports are italicized.

Body as a Whole: *anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills and fever)*

Cardiovascular: *congestive heart failure, vasculitis, hypertension, pulmonary edema*

Gastrointestinal: gastrointestinal bleeding and/or *perforation, hematemesis, pancreatitis, vomiting, colitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn' disease), nonpeptic gastrointestinal ulceration, ulcerative stomatitis, esophagitis, peptic ulceration*

Hepatobiliary: jaundice, *abnormal liver function tests, hepatitis (some cases have been fatal)*

Hemic and Lymphatic: *eosinophilia, leucopenia,* melena, thrombocytopenia, agranulocytosis, *granulocytopenia, hemolytic anemia, aplastic anemia*

Metabolic and Nutritional: *hyperglycemia, hypoglycemia*

Nervous System: inability to concentrate, *depression, dream abnormalities, insomnia, malaise, myalgia, muscle weakness, aseptic meningitis, cognitive dysfunction, convulsions*

Respiratory: *eosinophilic pneumonitis, asthma*

Dermatologic: *alopecia, urticaria, skin rashes, toxic epidermal necrolysis, erythema multiforme, erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, systemic lupus erythematoses, bullous reactions, including Stevens-Johnson syndrome, photosensitive dermatitis, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa. If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.*

Special Senses: *hearing impairment, corneal opacity, papillitis, retrobulbar optic neuritis, papilledema*

Urogenital: *glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis, raised serum creatinine*

Reproduction (female): *infertility*

In patients taking NSAIDs, the following adverse experiences have also been reported in less than 1% of patients.

Body as a Whole: fever, infection, sepsis, anaphylactic reactions, appetite changes, death

Cardiovascular: hypertension, tachycardia, syncope, arrhythmia, hypotension, myocardial infarction

Gastrointestinal: dry mouth, esophagitis, gastric/peptic ulcers, gastritis, glossitis, eructation

Hepatobiliary: hepatitis, liver failure.

Hemic and Lymphatic: rectal bleeding, lymphadenopathy, pancytopenia

Metabolic and Nutritional: weight changes

Nervous System: anxiety, asthenia, confusion, nervousness, paresthesia, somnolence, tremors, convulsions, coma, hallucinations

Respiratory: asthma, respiratory depression, pneumonia

Dermatologic: exfoliative dermatitis

Special Senses: blurred vision, conjunctivitis Urogenital: cystitis, dysuria, oliguria/polyuria, proteinuria (Brunton, et al., 2006).

Photosensitivity

Photosensitivity is a commonly overlooked adverse effect of many of the NSAIDs. It is somewhat ironic that these anti-inflammatory agents may themselves produce inflammation in combination with exposure to sunlight. The 2-arylpropionic acids also

known as naproxen have proven to be the most likely to produce photosensitivity reactions.

1.11 During pregnancy

Naproxen is not recommended during pregnancy, particularly during the third trimester. While NSAIDs as a class are not direct teratogens, they may cause premature closure of the fetal ductus arteriosus and renal ADRs in the fetus. Additionally, they are linked with prematur birth. In France, the country's health agency contraindicates the use of NSAIDs after the sixth month of pregnancy.

Nursing mother

A small amount of naproxen is excreted in breast milk. Because the concentration in breast milk is low, breastfeeding while taking naproxen probably is not harmful to the infant (Ogbru, 2008).

1.12 Important information about naproxen

Naproxen can increase the risk of life-threatening heart or circulation problems, including heart attack or stroke. This risk will increase the longer use of naproxen. This medicine should not be used just before or after having heart bypass surgery (also called coronary artery bypass graft, or CABG).

Naproxen can also increase the risk of serious effects on the stomach or intestines, including bleeding or perforation (forming of a hole). These conditions can be fatal and gastrointestinal effects can occur without warning at any time while taking naproxen. Older adults may have an even greater risk of these serious gastrointestinal side effects.

One should not drink alcohol while taking naproxen. Alcohol can increase the risk of stomach bleeding caused by naproxen. Avoid prolonged exposure to sunlight. Naproxen can make the skin more sensitive to sunlight, and sunburn may result (Multum, 1996).

1.13 Drug interactions

ACE-inhibitors

Reports suggest that naproxen may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking naproxen concomitantly with ACE-inhibitors.

Antacids and Sucralfate

Concomitant administration of some antacids (magnesium oxide or aluminum hydroxide) and sucralfate can delay the absorption of naproxen.

Aspirin

When naproxen as Suspension is administered with aspirin, its protein binding is reduced. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of naproxen and aspirin is not generally recommended because of the potential of increased adverse effects.

Cholestyramine

As with other NSAIDs, concomitant administration of cholestyramine can delay the absorption of naproxen.

Diuretics

Clinical studies, as well as postmarketing observations, have shown that naproxen suspension can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure, as well as to assure diuretic efficacy.

Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. Naproxen and other nonsteroidal anti-inflammatory drugs have been reported to reduce the tubular secretion of methotrexate in an animal model. This may

indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Warfarin

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone. No significant interactions have been observed in clinical studies with naproxen. However, caution is advised since interactions have been seen with other nonsteroidal agents of this class. The free fraction of warfarin may increase substantially in some subjects and naproxen interferes with platelet function.

Selective Serotonin Reuptake Inhibitors (SSRIs)

There is an increased risk of gastrointestinal bleeding when selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs. Caution should be used when NSAIDs are administed concomintantly with SSRIs.

1.14 Overdose

Significant naproxen overdosage may be characterized by lethargy, dizziness, drowsiness, epigastric pain, abdominal discomfort, heartburn, indigestion, nausea, transient alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis, apnea, disorientation or vomiting. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose. A few patients have experienced convulsions, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening. The oral LD_{50} of the drug is 543 mg/kg in rats, 1234 mg/kg in mice, 4110 mg/kg in hamsters, and greater than 1000 mg/kg in dogs.

Patients should be managed by symptomatic and supportive care following a NSAID overdose. There are no specific antidotes. Hemodialysis does not decrease the plasma

concentration of naproxen because of the high degree of its protein binding. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine or hemoperfusion may not be useful due to high protein binding.(Mosby,2000)

1.15 Quality

Quality is essential for the survival and growth of any organization. Quality signifies excellence of a product or service, which is measured, based on customer's experience with the product or service against his or her requirements. The quality of a product may be defined as "its ability to fulfill the customer's needs and expectations". Quality needs to be defined firstly in terms of parameters or characteristics, which vary from product to product. For example, for a mechanical or electronic product these are performance,

reliability, safety and appearance. For pharmaceutical products, parameters such as physical and chemical characteristics, medicinal effect, toxicity, taste and shelf life may be important. For a food product they will include taste, nutritional properties, texture and shelf life etc (Waleed, et al., 2001).

1.16 Quality of pharmaceutical products

Quality of product is the main precursor for any pharmaceutical industry to maintain its existence. In pharmaceutical industry, the quality is a measure of high degree of managerial, scientific and technical sophistication. Quality is always an obligatory prerequisite when we consider any product. It becomes primary when it relates to life saving products like pharmaceuticals. Although it is mandatory from the government and regulatory bodies but it is also a fact that quality of a pharmaceutical product cannot be adequately controlled solely by pharmacopoeia analysis of the final product. Today quality has to be built in to the product right from its inception and rigorous international

environmental, safety and regulatory standards need to be followed. Validation had proven to be an important tool for quality management of pharmaceuticals (Aulton, 2002).

Most traditional pharmaceutical drugs are relatively simple molecules that have been found primarily through trial and error to treat the symptoms of a disease or illness. Over period of time these molecules were perfected to ensure quality. The quality is very much related to every pharmaceutical product. Without quality pharmaceutical drug cannot be marketed or sold, because it can cause many problems such as sub therapeutic or over dose.

If a drug of any brand or company does not maintain it then may cause serious problems when prescribed to the patients. The patients may suffer from the adverse effects because of its faulty quality which may sometimes prove to be fatal.

1.17 Quality control

The term “quality control” comprises of two words quality and control. Control is a universal regulatory process. In the industry, it takes the form of meeting standards. The process through which we establish and meet standards is called “control”. Quality control deals with a system which accepts or rejects any activities which affect the Quality and prevents Quality deficiency and imparts consistency in the quality of the product or service (Marayya, 2005).

Quality is important in every product or service but it is vital in medicine as it involves life. Quality control is a concept which strives to produce a perfect product by a series of measures designed to prevent and eliminate errors at different stages of production. Although the responsibility for assuring product quality belongs principally to quality assurance personnel, it involves many departments and disciplines within a company.

The quality of products is dependent upon that of the participating constituents, some of which are sustainable and effectively controlled while others are not.

To be effective, it must be supported by a team effort. Quality must be built into a drug product during product and process design, and it is influenced by the physical plant design, space, ventilation, cleanliness, and sanitation during routine production. The product and process design begins in research and development. It also includes preformulation and physical, chemical, therapeutic and toxicologic considerations (Lachman, 2008).

1.18 Quality assurance:

Design, development and implementation of quality assurance is the most vital function in the pharmaceutical industry. In pharmaceutical industry, the quality is a measure of a high degree of managerial, scientific and technical sophistication. Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use (Marayya and Anjaneyulu, 2005).

Quality control emphasizes testing of products to uncover defects, and reporting to management who make the decision to allow or deny the release, whereas quality assurance attempts to improve and stabilize production, and associated processes, to avoid, or at least minimize, issues that led to the defects in the first place. The assurance of product quality depends on more than just proper sampling and adequate testing of various components and the finished dosage form. Prime responsibility of maintaining product quality during production rests with the manufacturing department. Removal of responsibility from manufacturing for producing a quality product can result in imperfect composition, such as ingredients missing, subpotent or superpotent addition of ingredients, or mixing of ingredients; mistakes in packaging or filling, such as product contamination, mislabeling, or deficient package; and lack of conformance to product

registration. Quality assurance personnel must establish control or checkpoints to monitor the quality of the product as it is processed and upon completion of manufacture.

Because of the increasing complexity of modern pharmaceutical manufacturing arising from a variety of unique drugs and dosage forms, complex ethical, logical and economic responsibilities have been placed on those concerned with the manufacture of modern pharmaceuticals. An awareness of these factors is the responsibility of all those involved in the development, manufacture, control, and marketing of quality products (Lachman, 2009).

1.19 Quality control parameters:

Solid dosage forms are most important when drug administration is concerned. Among the solid dosage forms tablet is main attraction for the patients. Tablet is the most advantageous over all the other solid dosage forms. So tablets have to be a proper quality product. To maintain the quality of tablet dosage form, quality control parameters are truly needed. For tablets, there are several quality control parameters which are used in the pharmaceutical industry to make effective and quality tablets. The quality control parameters are known as hardness test, thickness test, friability test, weight variation test, disintegration test etc. Some other tests are also done to check the release profile of the manufactured tablets such as dissolution test and potency determination test

1.20 Aim and objectives of the study

The aim and objectives of the study were-

- To analyze different brands of naproxen in terms of physical parameters like hardness test, thickness test, friability test, disintegration test etc.
- To determine the potency of selected brands of naproxen.
- To assess and compare the rates of dissolution among different brands of naproxen

CHAPTER - 2

Materials and Methods

2.1 Sample

From the entire Bangladeshi companies produce naproxen tablet, 4 brands were selected from 4 individual companies randomly. The name and brand of the selected companies are given below:

Table 2.1: Name and company of the selected brand of naproxen

Company	**Brand**
Roche	Naprosyn
Square	Sonap
Popular	Naspro
Pacific	Naid
Delta Pharma	Standard sample

2.2Hardness test

Tablet hardness is usually expressed as the load required crushing a tablet placed on its edge. Hardness is thus sometimes termed the tablet crushing strength. The suitability of a tablet in regard to mechanical stability during packaging and shipment can usually be predicted on the basis of hardness. Tablet hardness, in turn, influences tablet density and porosity. It may affect tablet friability and disintegration time. It usually affects drug dissolution and release and it may affect bioavailability.

Table 2.2: Name and specification of materials required in hardness test

Materials	**Specification**
Hardness tester	Monsanto Type hardness tester

Method:

1. The sliding scale of hardness tester has been set off to zero

2. The tablets have been placed vertically between the two jaws.

3. Force has been applied with the screw thread and spring until the tablets has been fractured.

4. A force of about 4-5 kg is considered to be the minimum for hardness according to The British Pharmacopoeia (Lachman, et al., 2008)

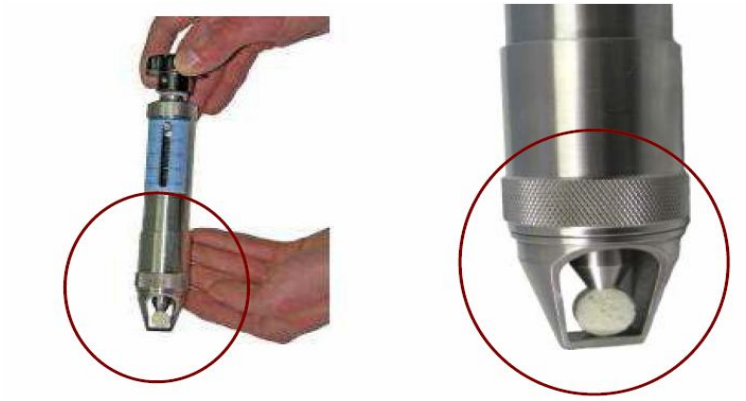


Figure 2.1: Monsanto Hardness tester

2.3 Thickness test:

At constant compressive load, tablet thickness varies with change in die fill and tablet weight; with constant die fill, thickness varies with variations in compressive load. Some variation in tablet thickness in a particular lot of tablets or between different lots of the product is inevitable. Variation in tablet thickness should not be immediately apparent to the unaided eye under normal conditions, for obvious reasons of product acceptance by the consumer.

In general, tablet thickness is controlled within 5 percent of standard value. Tablet thickness control may be impossible unless (1) the physical properties of raw materials are closely controlled, (2) the upper and lower punch lengths are accurately and continuously standardized, (3) the granulation properties, including density, particle size, and particle size distribution are also carefully controlled .

Table 2.3: Name and specification of materials required to thickness test:

Materials	**Specification**
Vernier calliper	Shimadzu, Japan.

Method:

1. Tablets have been placed between two jaws horizontally.
2. The screw of the slide calipers has been ran to hold the tablets.
3. The reading of the thickness of the tablet has been taken in cm.

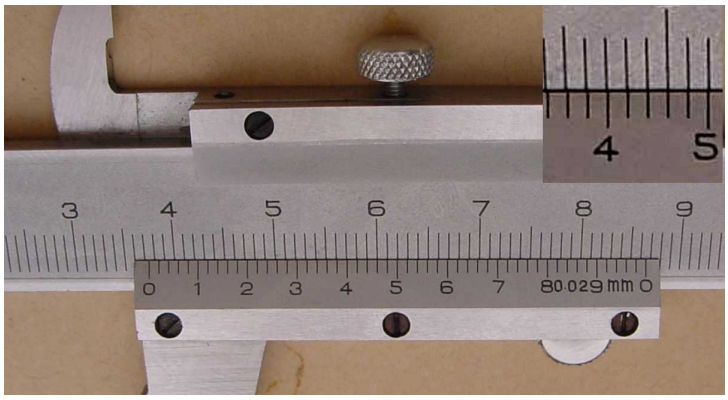


Figure 2.2: Vernier Callipers

2.4 Friability test

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up. Normally, when capping occurs, friability values are not calculated. A thick tablet may have less tendency to cap whereas thin tablets of large diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress.

Table 2.4: Name and specification of materials required to friability test.

Materials	**Specification**
Friability Tester	Friability Tester
Electronic Balance	Shimadzu, Japan

Method:

1. The experiment has been started by weighing 10 tablets which is considered as the initial reading

2. All the tablets have been placed in the drum of friability tester and rotate 100 times

3. The percentage loss has been calculated.

4. According to BP the tablets should not lose more than 1% of their total weight. (B.P. appendix: XVII, 2003)

Figure 2.3 : Friability tester.

2.5 Disintegration test:

Disintegration is one the most important step of a drug beside dissolution. The breakdown of a drug within its optimum time is the prerequisite for better absorption and consequently better therapeutic action. Disintegration time may vary considering to its disintegrator used. Higher the disintegration time required lower the dissolution rate and

followed to poor absorption. So disintegration is the crucial part of a drug for therapeutic action**.**

Table 2.5: Name and specification materials required to disintegration test:

Materials	**Specification**
Disintegration tester	(BJ-2Vanguard pharmaceutical machinery, INC. USA) 1000 ml beaker, 6 tubes and disc, Demineralized water

Method:

1. The disintegration tester was assembled.

2 . An arbitrary figure appeared in the digital display

3 . Then the time and temperature was set at prescribed in specification.

4 .600ml of the medium was placed in each 1000ml beaker.

5 . The temperature of the liquid was maintained at 35-39^{0}C.

6 . In each of the 3 tubes one tablet was placed.

7 . After placement of the tablet 3 disc was placed above the tablet

8 . The machine was then operated for the prescribed period.

9 . The entire tablet must disintegrate within the prescribed time (Lachman, et al., 2008).

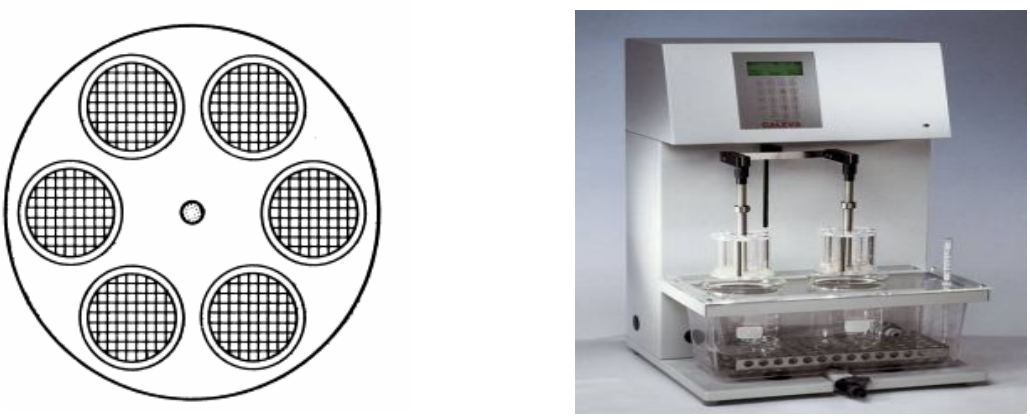


Figure 2.4: Disintegration tester

2.6 Potency determination:

Potency is the strength of a dosage form. Potency determination is the chemical characteristics of a dosage form. The potency of official tablet is usually given in terms of milligrams of drug per tablet and is determined by means of an official analytical method which involves grinding several tablets in a mortar and analyzing a portion of the resulting powder (Lachman, et al., 2008).

Table 2.6: Name and source of materials required to determine sample potency

Materials	**Specification**
UV-Vis spectrophotometry	Shimadzu, Japan
Electronic Balance	ELB 3000, Shimadzu, Japan.

Preparation of the standard solution:

50 mg of standard naproxen was weighed accurately in a 100 ml volumetric flask. 70 ml of methanol was added in it. It was shaked for 30 minutes and sufficient methanol was added to make volume up to 100ml. It was then mixed well and 10 ml of the solution was taken in a 50 ml volumetric flask. The volume was made up to 50 ml with methanol and mixed. 10 ml of the resulting solution was taken in a 100 ml volumetric flask and was added to volume up to the mark with methanol and mixed.

Method:

1. 2 tablets were weighed and crushed to make fine powder.
2. Take a quantity of the powder containing 50 mg naproxen in a 100 ml volumetric flask.
3. Add 70 ml methanol in the flask and shaked for 30 minutes and sufficient methanol was added to make volume up to 100 ml.
4. It was mixed well and then filtered.
5. 10 ml of the filtrate was taken in a 50 ml volumetric flask. The volume was made up to 50 ml with methanol and mixed.
6. 10 ml of the resulting solution was taken in a 100 ml volumetric flask and was added to volume up to the mark with methanol and mixed. (BP, 2003)

Measurement:

The absorbance of both the standard and assay solutions was measured in a suitable spectrophotometer having 1-cm quartz cell at 331 nm using methanol as blank.

The UV region consists of wavelengths from 200 to 400 nanometers (nm). The visible region extends from 400 to 800 nm, and the near IR (NIR) region covers 0.8 to 2.50 micrometers. Nanometer units are commonly used in the UV/VIS region, while micrometers or microns are normally used in the NIR region.

The Main Components of UV Analyzer:

Photometers and spectrophotometers can be used for on-line monitoring of process streams. These essential components are:

1. Source-provides radiation for the spectral region being measured.
2. Monochromator-a device used to select narrow bands of wavelengths.
3. Sample cell-contains the sample at an appropriate path length.
4. Detector-a device that measures transmitted energy and converts it into electrical energy.
5. Readout device-provides a means of recording the measurement results.

Figure 2.5: UV Spectrophotometer

Content Determination of the Samples

Content of Naproxen can be measured by using the following equation:

Content of Naproxen = $As / A_{std} \times W_{std} / W_s \times Wa$

Here,

As = Absorbance of the Sample

A_{std} = Absorbance of the standard

W_{std} = Weight of standard

W_s = Weight of the sample

W a = Amount of per tablet

$$\% \text{ potency} = \frac{\text{Oserved Value}}{\text{Declared Value}} \text{ X } 100$$

2.7 Dissolution test:

Drugs administered orally in solid dosage forms, such as tablet or capsules, must dissolve in the contents of the gastrointestinal tract before drug absorption can occur. Often the rate of drug absorption is determined by the rate of drug dissolution from the dosage form. Therefore, if it is important to achieve high peak blood levels for a drug, it will usually be important to obtain rapid drug dissolution from the dosage form (Lchman, et al., 2008).

Table 2.7: Name and source of materials required to conduct dissolution test

Materials	**Specification**
Dissolution tester	(BJ-2Vanguard pharmaceutical machinery, INC. USA) 1000 ml beaker, 6 tubes and disc, Demineralized water
pH meter	(pHep, HANNA, United States)
NaH_2PO_4	(BDH Chemicals LTD Poole, England)
Na_2HPO_4	(BDH Chemicals LTD Poole, England)

Condition:

Medium: 900ml phosphate buffer

Apparatus: apparatus 2 (paddle)

RPM: 50

Time: 45 minutes

Tolerance: NTL 85%

Lambda max: 332nm

Preparation of Phosphate Buffer (pH 7.4):

NaH_2PO_4 : 2.62gm

Na_2HPO_4 : 11.50 gm

Dissolve NaH_2PO_4 and Na_2HPO_4 in sufficient water to produce 1000 ml and adjust the pH at 7.4 with either 0.1 M sodium hydroxide or 0.1 M hydrochloric acid.

Method:

1. On the dissolution test apparatus the water tank was filled and temperature was set.
2. 900 ml of the phosphate buffer was poured into one of the vessels and instruments were run till the set temperature was attained. The remaining 100ml of the medium for used as a blank.
3. One of the sample tablets was placed into the vessel and starts the run.
4. Rotate the paddle at 50 revolutions per minute.
5. Run the test for 45 minutes.
6. At the end of the time specified, 10ml of the sample was collected and filtered.
7. 10ml of the filtered sample was diluted with the buffer medium.
8. Using the same procedure, as for the blank sample, use the phosphate buffer.
9. Finally the absorbance was measured at 332nm (BP, 2003).

Standard solution preparation:

50 mg of naproxen working standard (WS) was weighed accurately and dissolved in 100 ml volumetric flask with phosphate buffer of pH 7.4 and volume up to 100 ml by the same and mixed. 10 ml of the above solution was pipette in 50 ml volumetric flask and volume up to 50 ml with the phosphate buffer medium and mixed.

Figure 2.6: Dissolution tester

Determination of the samples:

Dissolution of naproxen can be measured by using the following equation,

% dissolution =

Wt. of STD × dilution of sample × abs. of sample × potency of STD. × avg. wt. of sample

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Wt. of sample × dilution of STD × abs. of STD × label claim

Chapter -3

Result

3.1 Hardness Test:

Three tablets from each brand of naproxen were selected to conduct the hardness test. Test results were given below:

Table 3.1: Result of hardness test

Brand name	Number of tablet	Hardness test(kg/cm)	Average
Naprosyn	1. 2. 3. 4. 5. 6.	8.0 8.0 7.5 8.0 7.5 7.5	7.75
`Sonap	1. 2. 3. 4. 5. 6.	7.0 7.0 7.5 7.5 7.5 7.0	7.25
Naspro	1. 2. 3. 4. 5. 6.	4.0 40 4.0 4.0 4.0 4.0	4.0
Naid	1. 2. 3. 4. 5. 6.	5.5 6.0 5.5 6.0 6.0 6.0	5.83

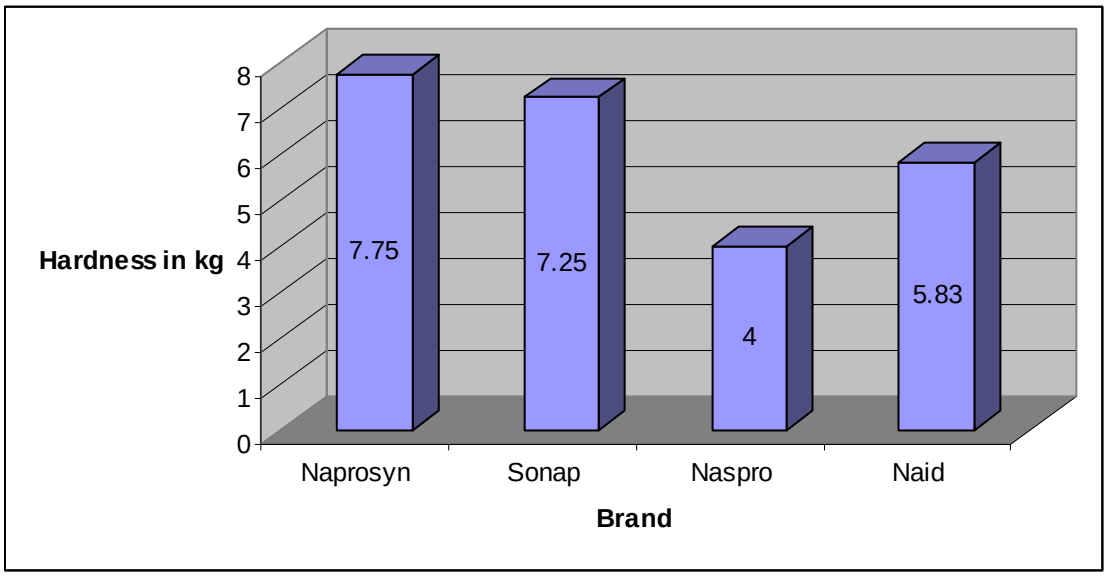

Figure 3.1: Hardness test of Naproxen

The highest value of hardness was Naprosyn (7.75). The lowest value of hardness was Naspro (4.0)

3.2 Thickness Test:

Tablets from each brand of naproxen were selected to conduct the thickness test. Test results were given below:

Table 3.2: Result of thickness test

Brand name	Reading of scale (mm)	Reading of vernier scale(mm)	Vernier constant	Error	Thickness of the tablet	Average
Naprosyn	4.0 4.0 4.0 4.0 4.0	1 1 1 1 1	0.1 0.1 0.1 0.1 0.1	0 0 0 0 0	4.1 4.1 4.1 4.1 4.1	4.1

	4.0	1	0.1	0	4.1	
Sonap	7.0	1	0.1	0	7.1	
	7.0	1	0.1	0	7.1	
	7.0	1	0.1	0	7.1	7.1
	7.0	1	0.1	0	7.1	
	7.0	1	0.1	0	7.1	
	7.0	1	0.1	0	7.1	
Naspro A	5.5	5.0	0.1	0	6.0	
	5.5	5.0	0.1	0	6.0	
	5.5	5.0	0.1	0	6.0	6.0
	5.5	5.0	0.1	0	6.0	
	5.5	5.0	0.1	0	6.0	
	5.5	5.0	0.1	0	6.0	
Naid	5.5	4.0	0.1	0	5.9	
	5.0	2.0	0.1	0	5.2	5.32
	5.0	2.0	0.1	0	5.2	
	5.0	2.0	0.1	0	5.2	
	5.0	2.0	0.1	0	5.2	
	5.0	2.0	0.1	0	5.2	

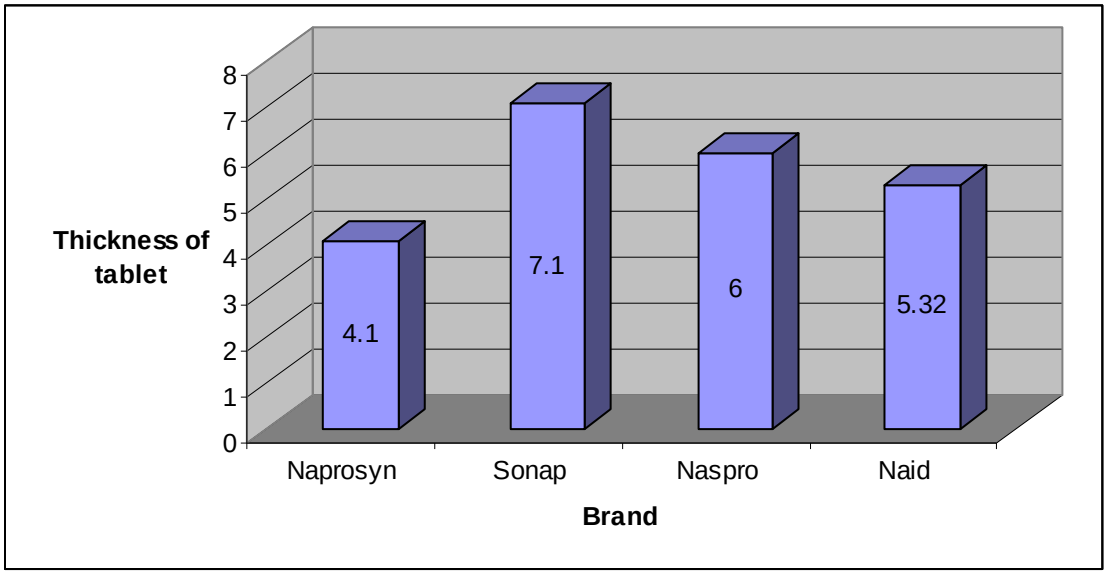

Figure 3.2: Thickness test of Naproxen

The thickness of all the brands of naproxen was complied with the BP tandards. The highest value was Sonap (7.1) and the lowest value was Naprosyn (4.1)

3.3 Friability Test:

Ten tablets from each brand of naproxen were selected to conduct the friability test. Test results were given below:

Table 3.3: Result of friability test

Brand	**Initial weight of 10 tablets**	**Final weight of 10 tablets**	**Friability test (%)**
Naprosyn	5.4877	5.4728	0.2715
Sonap	10.0292	10.0278	0.01695

Naspro	5.5149	5.4978	0.3101
Naid	6.7979	6.7875	0.1529

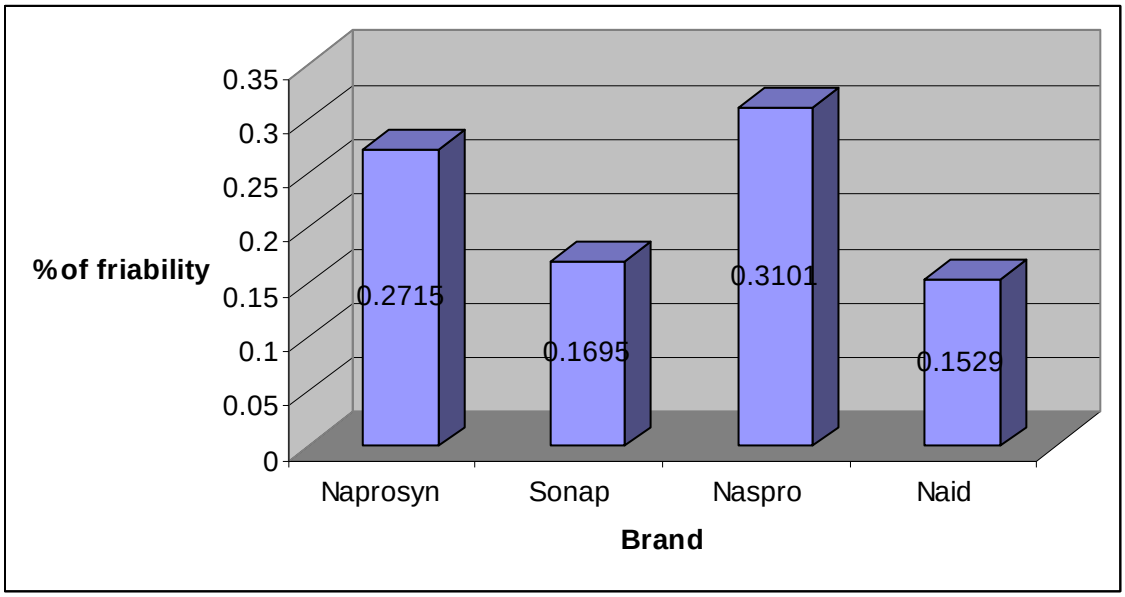

Figure 3.3: Friability test of Naproxen

All the brands of naproxen has a in standard range friability values.

3.4 Disintegration Test:

Three tablets from each brand of naproxen were selected to conduct the friability test. Test results were given below:

Table 3.4: result of the disintegration test

Brand	**Sample 01**	**Sample 02**	**Sample 03**	**Mean disintegration time (min)**
Naprosyn	3.5	4.5	4.5	4.166
Naspro	6.40	6.45	7.0	6.61
Naid	15.5	15.15	15.20	15.28

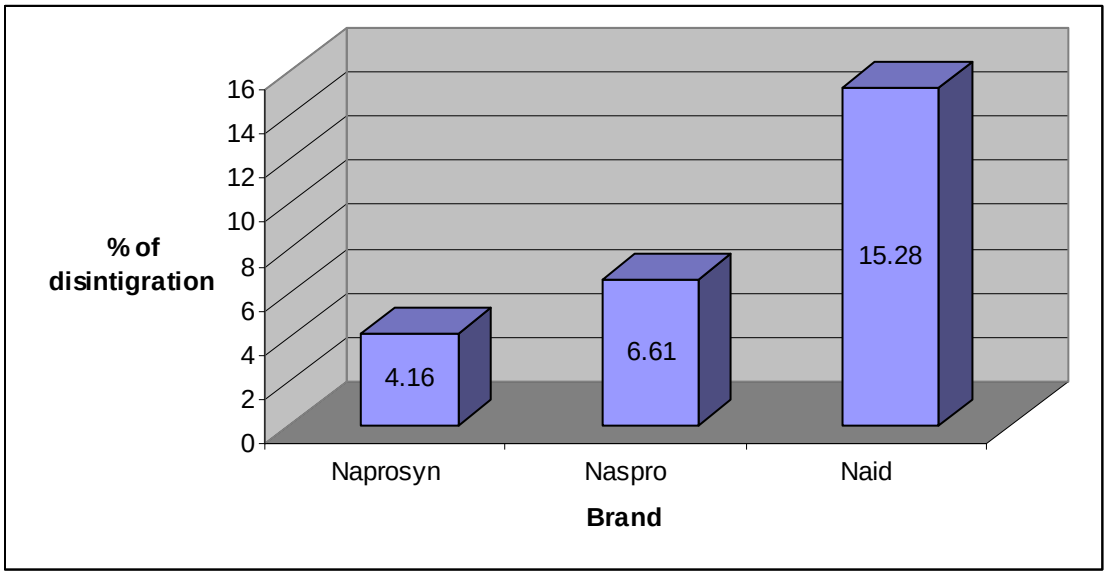

Figure 3.4: Disintegration test of Naproxen

The disintegration time of Naprosyn, Naspro and Naid within the time limit which is described by USP. But we did not experiment the sample Sonap because it is an enteric coted tablet and we know that enteric coated tablet does not disintegrate into water, and our media was distilled water.

3.5 Potency test:

Two tablets from each brand of naproxen were selected to conduct the potency test. Test results were given below:

Table 3.5: Result of the potency test

Tablet brand	Average weight of tablet (gm)	Absorbance of the sample	Weight of the sample (gm)	Potency(%)
Naprosyn	0.5309	0.797	0.05309	95.62
Sonap	0.995	0.875	0.0995	56.1
Naspro	0.5475	0.883	0.0548	102.62
Naid	0.6726	0.787	0.0673	74.46

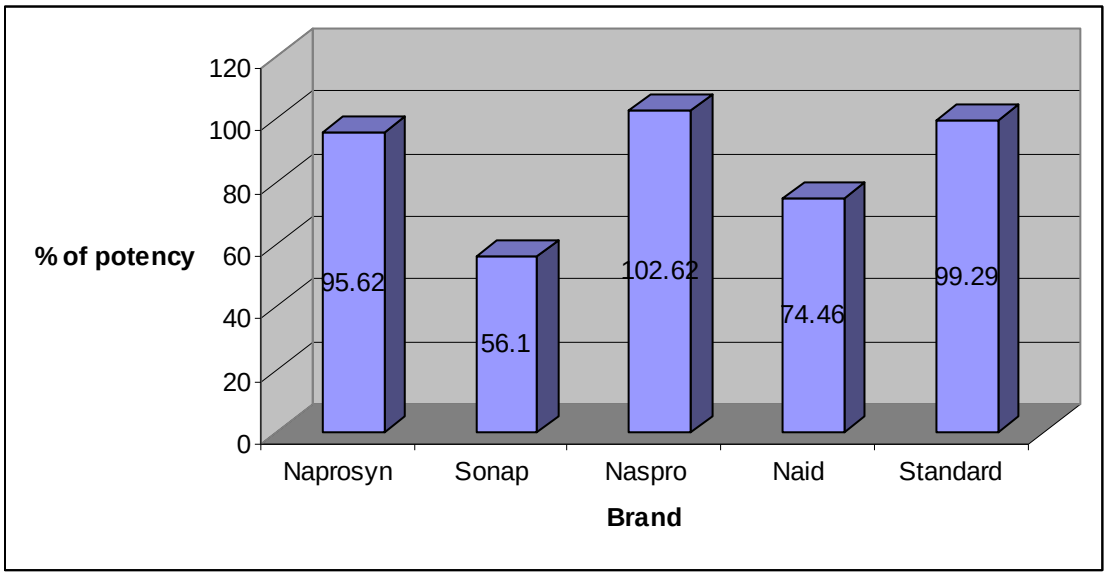

Figure 3.5: Potency test of Naproxen

The potency determination test showed some higher and lower values. Compare with the standard sample (99.29%), the highest value is 102.62% (Naspro) &the lowest value is 56.1% (Sonap).

3.6 Dissolution test:

Two tablets form each of brands of naproxen tablets were selected to conduct the tablet dissolution test. Test results were given below:

Table 3.6.1: Result of dissolution test for Naprosyn

Brand Name Naprosyn	Weight of sample(gm)	Absorbance of sample	Dissolution %	Average dissolution %
Sample 1	0.5540	0.345	97.12	95.16
Sample 2	0.5470	0.362	95.94	
Sample 3	0.5420	0.354	95.05	
Sample 4	0.5312	0.338	92.18	
Sample 5	0.5223	0.332	92.13	
Sample 6	0.5354	0.364	98.56	

Table3.6.2: Result of dissolution test for Naspro

Brand Name Naspro	Weight of sample(gm)	Absorbance of sample	Dissolution %	Average dissolution %
Sample 1	0.5548	0.372	99.40	96.06
Sample 2	0.5538	0.348	93.17	
Sample 3	0.5510	0.353	94.99	
Sample 4	0.5466	0.357	96.88	
Sample 5	0.5448	0.361	98.26	
Sample 6	0.5550	0.373	99.69	

Table 3.6.3: Result of dissolution test for Naid

Brand Name Naid	Weight of sample(gm)	Absorbance of sample	Dissolution %	Average dissolution %
Sample 1	0.6670	0.353	95.69	94.63
Sample 2	0.6815	0.356	94.46	
Sample 3	0.6756	0.362	96.87	
Sample 4	0.6709	0.349	94.06	
Sample 5	0.6620	0.340	92.88	
Sample 6	0.6748	0.350	93.79	

Table 3.6.4: Result of dissolution test for Sonap in HCL

Brand Name Sonap	Weight of sample(gm)	Absorbance of sample	Dissolution %	Average dissolution %
Sample 1	1.0127	0.018	20.97	25.79
Sample 2	0.9960	0.021	23.66	
Sample 3	1.0177	0.025	28.96	
Sample 4	0.9930	0.025	29.68	
Sample 5	0.9805	0.023	27.65	
Sample 6	0.9888	0.021	23.86	

Table 3.6.5: Result of dissolution test for Sonap in phosphate buffer

Brand Name Sonap	Weight of sample(gm)	Absorbance of sample	Dissolution %	Average dissolution %
Sample 1	1.0127	0.372	98.66	95.47
Sample 2	0.9960	0.351	94.65	
Sample 3	1.0177	0.356	93.65	
Sample 4	0.9930	0.352	95.20	
Sample 5	0.9805	0.345	94.50	
Sample 6	0.9888	0.354	96.15	

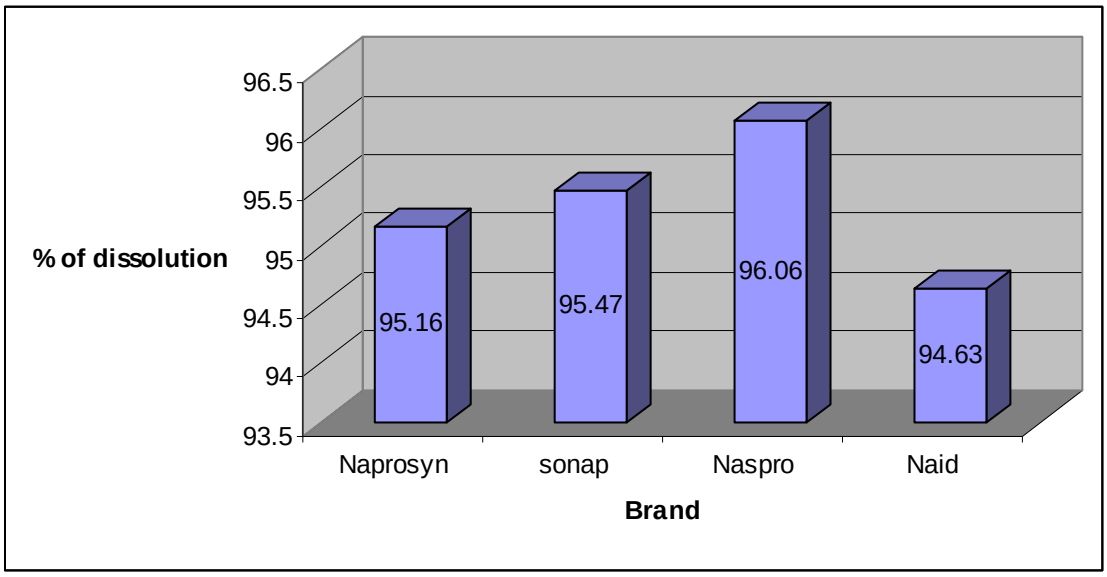

Figure 3.6: Dissolution test of Naproxen

The dissolution tolerance in the USP is not less than 75% dissolved in 45 minute.So the disslotuin time of tablets are within in the range.

4.1 Discussion:

Quality Control is an essential function of the Pharmaceutical industry. Drug manufacturers must thoroughly test materials, processes, equipment, techniques, environments and personnel in order to ensure their final products are consistent, safe, effective and predictable. If a tablet is not a quality product than the dose as well as the manufacturing of the tablet can hamper. Also the tablet will have other problems such as hardness, thickness or disintegration.

Tablet Hardness testing is also called tablet breaking force and measures the tablet mechanical integrity. Hardness tests helps to measure whether a tablet inherits adequate hardness to withstand consumer handling and also provide satisfactory disintegration and dissolution results.

Ideally all the different varieties of testing machines would give the same result if tablets of the same batch were used. In case of tablets from naproxen, the highest value of hardness was showed by Naprosyn (7.75) and Sonap (7.25). The lowest hardness value was showed by the brand Naspro (4.0),which is in range. High hardness causes the tablets to break slowly in the system, which is a major obstacle for the tablets to work efficiently.

Tablet thickness is an important quality control test for tablet packaging.Very thick tablet affects packaging either in blister or plastic container. Tablet thickness test provides an idea about the compressive strength during compression process. The highest value of thickness was 7.1 (Sonap) and Naspro (6.0) respectively. Difference between the thicknesses of the brands was quite small. Thickness was always an issue when tablets are considered. If the tablet is thicker than it cannot be swallowed by an average person. On the other hand, if the tablet is less thick then it can breakdown easily. So that thickness is important QC test.

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. Conventional compressed tablets that lose less than 0.5 to 1 % of their weight are considered acceptable. From the graph, we can view that the % friability values for all the brands were within acceptable range. Difference between the brands friability percentage was quite small ,the highest friability value was Naspro (0.3101) and lowest was Sonap (0.0169).

Disintegration is the pre step of dissolution. Disintegration is a process by which the surface area of a tablet is increased by fragmentation to promote rapid release of the drug. Disintegration tests helps to measure whether a tablet has the ability to break down into particles under specified conditions. Release rate of drug is greater from disintegrated particles than from the intact tablet or tablet fragments. The highest value of disintegration test was Naid (15.28) and Naspro (6.61). Several factors such as selection of disintegrants, binders, lubricants, tablet hardness, manufacturing procedure etc can

significantly affect the disintegration time of compressed tablets. Despite having a high hardness value all the brands of naproxen tablet showed an in standard range of disintegration value.

Potency test is done for determine the quantity of active ingredient in the drug. In case of tablets of the different brands of naproxen, the highest value of potency was the brand Naspro (102.62) and the lowest value of potency was the brand sonap (56.1%), which is very poor. The potency test differs due to the Analytical error, manufacturing error, tablet to tablet variation.

Dissolution test is performed to determine the rate of release of the drug. In order to be absorbed, a drug must first be dissolved in the fluid at the absorption site.All the values was within the range except Naid (94.63). May be due to manufacturing error (should be confirmed by more extensive study) and experimental error. It has been shown that the dissolution of a pure drug can be altered significantly when mixed with various adjuncts during the manufacturing process of solid doses forms. These adjuncts are added to satisfy certain pharmaceutical functions such as diluents, binders, granulating agents, disintegrants and lubricants. These adjuncts can also affect the rate of dissolution.

If a tablet contains more than its effective dose than it can cause overdose related complications. If a tablet contains less than its effective dose than it does not give desire effect. Right quantity of active ingredient in drug is necessary to give the desire effect of drugs.

4.2 Conclusion:

For the growing human population, pharmaceutical products necessities are increased rapidly. The qualities of these products are the prime concern for the regulatory bodies. Quality parameters of the pharmaceutical products are very important for optimum efficacy and safety. To prevent any contamination or errors quality control studies must

be needed. The quality parameters also should be followed by the specification of the standards.

Most of the tested samples met the quality specifications of BP standards with some exceptions. More extensive studies should be conducted to draw any conclusion regarding the quality of these brands considering the batch to batch variation. To understand their actual therapeutic effectiveness, bioavailability or bioequivalence study is essential.

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