EVALUATION OF PHARMACEUTICAL EQUIVALENCE OF DIFFERENT BRANDS OF DIAZEPAM TABLET IN BANGLADESH

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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This Thesis Paper is Dedicated to My Mother

Declaration by the Research candidate

I, Ismot Ara, hereby declare that the dissertation entitled "**Evalution of pharmaceutical equivalence of different brand of diazepam tablet in Bangladesh",** submitted by me to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the award of the degree of Bachelor of Pharmacy (B.PHARM) is a complete record of original research work carried out by me during the period 2011-2012 under the supervision and guidance of **Md. Razibul Habib ,** Lecturer, Department of Pharmacy, East West University and it has not formed the basis for the award of any other Degree/Diploma/Fellowship or other similar title to any candidate of any University.

Place: Dhaka

Date: 12.07.12

Signature of the candidate

(Ismot Ara)

2008-1-70-006

Thesis Certificate

This is to certify that the thesis entitled "**Evalution of pharmaceutical equivalence of different brand of diazepam tablet in Bangladesh**", submitted to the Department of Pharmacy, East West University, in partial fulfillment of the requirement for the award of the degree of Bachelor of Pharmacy (B.PHARM) is a complete record of original research work carried out by Ismot Ara (ID. 2008-1-70-006) during the period 2011-2012 of her research in the Department of Pharmacy at East West University, under my supervision and guidance and the thesis has not formed the basis for the award of any other Degree/Diploma/Fellowship or other similar title to any candidate of any University.

Date: 12.07.12

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Abstract

The quality of pharmaceutical finished dosage forms is of major concern to the pharmaceutical industries. An important aspect of the development of any pharmaceutical product is to maintain the quality standards of the product. Pharmaceutical preparations take many shapes and forms and are administered through variety of routes. Oral solid dosage forms particularly the tablet dosage form is the most well known of all. Tablet dosage form of any pharmaceutical company goes through many research studies and experiments to maintain the proper quality standards. Different quality control tests are done to ensure quality product. The aim of this study was to investigate the quality of different brands of diazepam tablets which are manufactured in Bangladesh. Diazepam is a drug affects on the central nervous system. So the quality of diazepam tablet such that it gives better pharmacological action, should not produce toxicity and the general appearance of a tablet, its visual identity and overall elegance is essential for consumer acceptance. Different physical parameters like hardness, thickness, friability as well as disintegration time were conducted to evaluate the quality of the tablets of different brands of diazepam. The range of hardness test result was 3.3-6.9 kg.. The friability test result were 0.198% and 0.177%. The thickness and weight variation results are in range of standerd value. The disintegration test has a range value of 1.32-3.33 min. The hardness test of Easium 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 and weight variation test of two brands was complied with the standard values. Quality of a product is the major issue for any pharmaceutical company. To ensure quality product a pharmaceutical industry follows the international standards. So it can be said that quality is the main theme of any product. So to maintain the proper quality, quality control parameters must be followed.

CHAPTER - 01

Introduction

1.1 Anxiolytic and Hypnotic Drugs

Anxiety is an unpleasant state of tension, apprehension, a fear that seems to arise from a sometimes unknown source. Disorders involving anxiety are the most common mental disturbances. The physical symptoms of severe anxiety are similar to those of fear (such as tachycardia, sweating, trembling, and palpitations) and involve sympathetic activation. Episodes of mild anxiety are common life experiences and do not warrant treatment. However, the symptoms of severe, chronic, debilitating anxiety may be treated with antianxiolytic drugs (sometimes called anxiolytic or minor tranquilizers) and/or some form of behavioral or psychotherapy. Because many of the antianxiety drugs also cause some sedation, the same drugs often function clinically as both anxiolytic and hypnotic (sleep-inducing) agents. In addition, some have anticonvulsant activity. (Finkel et al., 2009)

1.2 Classes of anxiolytic and hypnotic drugs

1. Benzodiazepines: the most important class, used for treating both anxiety states and insomnia.
2. Buspirone: a 5-HT_{1A} receptor agonist with anxiolytic activity but little sedation, although other side effects.
3. B-Adrenoceptor antagonists: used mainly to reduce physical symptoms of anxiety (tremor, palpitations, etc.); no effect on affective component.
4. Miscellaneous other agents (e.g. methaqualone, chloral hydrate) are still used occasionally to treat insomnia (benzodiazepines are preferable in most cases).
5. Barbiturates: now largely obsolete as anxiolytic/sedative agents. (Rang et al.,2007)

1.3 Benzodiazepines

Benzodiazepines are the most widely used anxiolytic drugs. They have largely replaced barbiturates and meprobamate in the treatment of anxiety, because the benzodiazepines are safer and more effective Diazepam is in a group of drugs called benzodiazepines (ben-zoe-dye-AZE-eh-peens). Diazepam affects chemicals in the brain that may become unbalanced and cause anxiety.Diazepam is used to treat anxiety disorders, alcohol withdrawal symptoms, or muscle spasms. It is sometimes used with other medications to treat seizures.

1.4 Mechanism of Action of Benzodiazepines

All benzodiazepines in clinical use have the capacity to promote the binding of the major inhibitory neurotransmitter □-aminobutyric acid (GABA) to the $GABA_A$ subtype of GABA receptors, which exist as multisubunit, ligand-gated chloride channels, thereby enhancing the GABA-induced ionic currents through these channels. Pharmacological investigations have provided evidence for heterogeneity among sites of binding and action of benzodiazepines, whereas biochemical and molecular biological investigations have revealed the numerous varieties of subunits that make up the GABA-gated chloride channels expressed in different neurons. Since receptor subunit composition appears to govern the interaction of various allosteric modulators with these channels, there has been a surge in efforts to find agents displaying different combinations of benzodiazepine like properties that may reflect selective actions on one or more subtypes of GABA receptors. (Denim et al., 2006)

1.5 Therapeutic effects of Benzodiazepines

Virtually all effects of the benzodiazepines result from their actions on the CNS. The most prominent of these effects are sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia, and anticonvulsant activity. Only two effects of these

drugs result from peripheral actions: coronary vasodilation, seen after intravenous administration of therapeutic doses of certain benzodiazepines, and neuromuscular blockade, seen only with very high doses. (Denim et al., 2006)

1.6 Other clinical considerations in the rational selection of therapy

While benzodiazepines affect activity at all levels of the neuraxis, some structures are affected preferentially. The benzodiazepines do not produce the same degrees of neuronal depression as do barbiturates and volatile anesthetics. All the benzodiazepines have similar pharmacological profiles. Nevertheless, the drugs differ in selectivity, and the clinical usefulness of individual benzodiazepines thus varies considerably. As the dose of a benzodiazepine is increased, sedation progresses to hypnosis and then to stupor. The clinical literature often refers to the "anesthetic" effects and uses of certain benzodiazepines, but the drugs do not cause a true general anesthesia because awareness usually persists, and relaxation sufficient to allow surgery cannot be achieved. However, at "preanesthetic" doses, there is amnesia for events subsequent to administration of the drug; this may create the illusion of previous anesthesia. Although considerable attempts have been made to separate the anxiolytic actions of benzodiazepines from their sedative-hypnotic effects, distinguishing between these behaviors still is problematic. Measurements of anxiety and sedation are difficult in human beings, and the validity of animal models for anxiety and sedation is uncertain. (Denim et al., 2006)

A significant advantage of the benzodiazepines over other central nervous system depressants (e.g., the barbiturates) is that they possess a much greater separation between the dose that produces sleep and the dose that produces death. This increased margin of safety has been one of the major reasons benzodiazepines have largely replaced the barbiturates and other types of sedative hypnotics in the treatment of anxiety and insomnia. In addition, benzodiazepine administration is associated with few side effects. (Jhon, 2004)

1.7 Pharmacological properties

Although it is widely claimed that the benzodiazepine drugs have a specific calming or anxiolytic effect, their most prominent and easily quantifiable action is central nervous system depression. In very low therapeutic doses, this depression manifests as relief of anxiety that is often accompanied by a feeling of sluggishness or drowsiness. As the dose is increased, the degree of depression is intensified such that muscle relaxation, hypnosis, and a more intense central nervous system depression occur. This depression is related to the ability of these drugs to facilitate the inhibitory actions of GABA**.** (Jhon, 2004)

1.8 Drug interactions

When used with other sedative–hypnotics or alcohol,the benzodiazepines will produce additive central nervous system depression. Many benzodiazepines are metabolized by the cytochrome P450 (CYP) enzyme designated CYP3A4.CYP3A4 is inhibited by grapefruit juice and by drugs such as ketoconazole, itraconazole, nefazodone, erythromycin, and ritonavir. Coadministration of these substances along with a benzodiazepine may result in intensification and prolongation of the benzodiazepine effect. Conversely, rifampin, carbamazepine, and phenytoin can induce the CYP3A4 enzyme, and therefore their coadministration can reduce the therapeutic effect of the benzodiazepines. (Jhon, 2004)

1.9Diazepam

Diazepam is in a group of drugs called benzodiazepines (ben-zoe-dye-AZE-eh-peens). Diazepam affects chemicals in the brain that may become unbalanced and cause anxiety.Diazepam is used to treat anxiety disorders, alcohol withdrawal symptoms, or muscle spasms. It is sometimes used with other medications to treat seizures.

1.10 Structure and details

Diazepam is the group of benzodiazepine of the diazepam type. Off white to yallow, practically odorless, crystalline powder, tasteless at first with a bitter after taste, slightly soluble in water, freely soluble in chloroform, and soluble in alcohol. (Korolkovas, 1988)

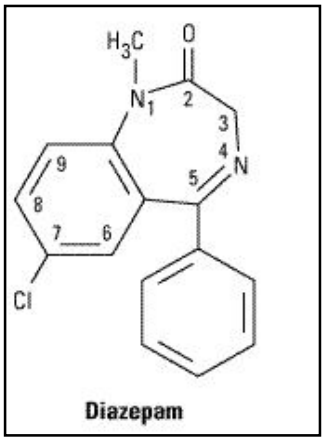

Figure 1.1: Structure of diazepam

Chemical Formula $\mathbf{C_{16}H_{13}ClN_2O}$

Mol. mass 284.7 g/mol

1.11 History

Since its discovery, alcohol has been widely used as anxiolytic sedative. Several other sedative have also been employed: barbiturates, for example, but they produce generalized depression. The first real perspective of management of anxiety was opened in 1955 with the introduction of meprobamate. The drug is an offspring of mephenesine, a muscle relaxant and sedative synthesized by Berger in 1946 that had showen some activity, although of short duration, as anxiolytic. In planned search for better antianxiety sedatives, several derivatives of mephenesine were prepared, especially by molecular modification through esterification of parent compound. This approach resulted, after screening of over 1200 compounds, in several new drugs, including maprobamate, first

synthesized by Ludwig and Piech in 1950 as potential muscle relaxant. Extensive molecular variation of this prototype yielded several other potent drugs against anxiety, such as ethinamate, mebutamate, and tybamate.

Benzodiazepine, first used as muscle relaxants, were introduced as anxiolytic sedatives in 1964 and following years. To chlordiazepoxide, the first member of this class and a result of an apparent error of synthesis, were added soon diazepam, oxazepam, and prazepam, besides some very recent acquisitions. The development of this types of drugs is due primarily to Sternbach and Reeder, who synthesized most of them, and Randall, who performed the pharmacological testing. (Korolkovas, 1988)

1.12 Classes

Benzodiazepines can be broadly classified based on their chemical structure. Diazepam falls into the category of benzodiazepines of the diazepam types.

Some example benzodiazepines of the diazepam types of derivatives are:

1. Diazepam
2. Bromazepam
3. Clorazepam
4. Alprazolam
5. Triazolam
6. Oxazepam
7. Nitrazepam
8. Lorazepam

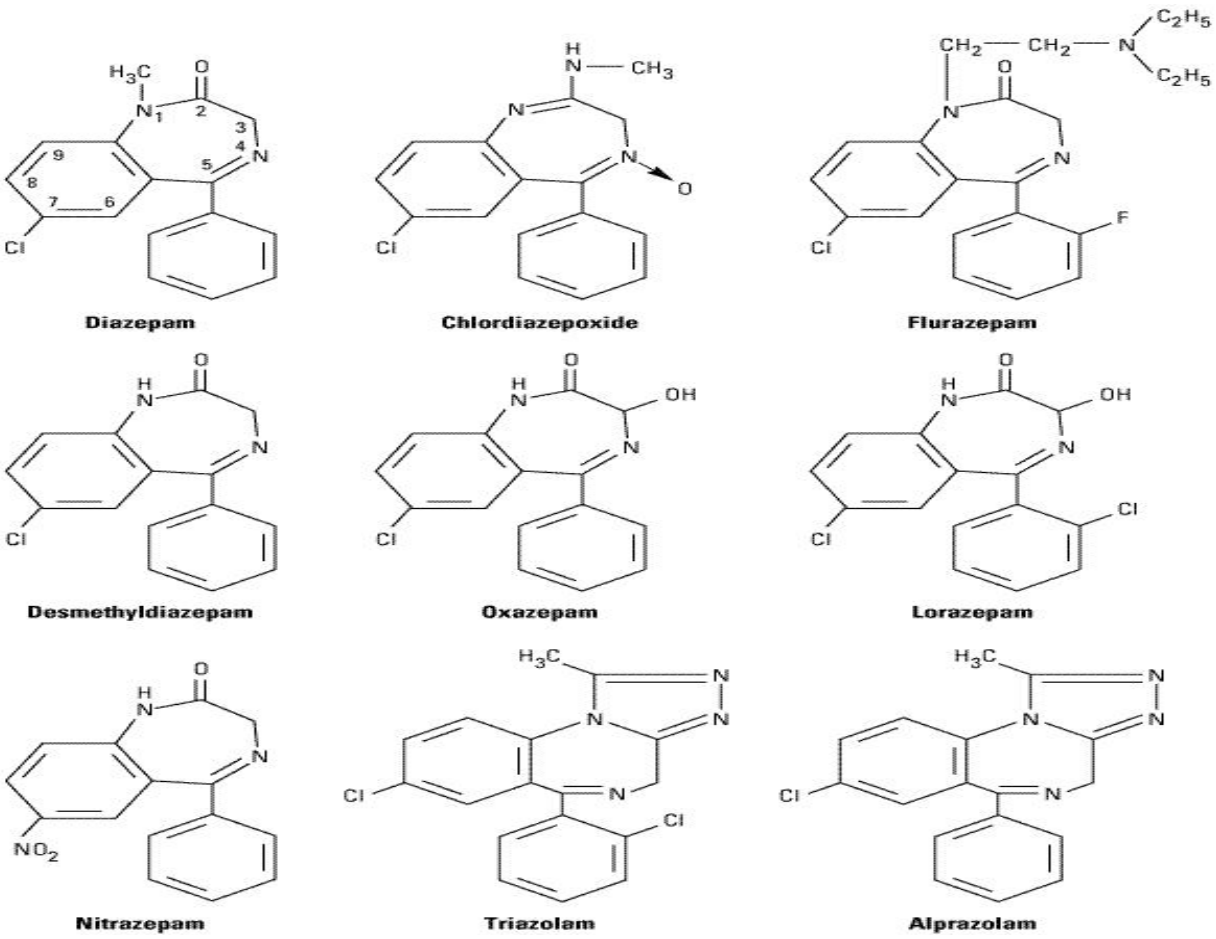

Fig 1.2: Structures of Benzodiazepins

1.13 Mechanism of Action of diazepam

In the case of benzodiazepines, biochemical and electrophysiological studied revealed that these anxiolyticsbind to highly specific receptor in the brain and thereby produce most, if not all of their numerous effect on central nervous system by enhancing the GABAergic synaptic transmission by an increasing in chloride conductance of the post synaptic membrane. According to Mohler and Richard (1983), the benzodiazepine receptor is considered to be part of a supramolecular complex, which consist of functionally linked membrane proteins,such as GABA receptor, its associated chloride ionophore, the benzodiazepine receptor, and possibly, other protein components. In the

presence of benzodiazepines the dynamics of the protein-protein interaction may be modulated in such a way that the affinity of the GABA receptor for GABA might be increased or coupling between the GABA receptor and its associated chloride channel might be improved. Guidotti et al. attribute an essential role in modulatory process to an additional protein, GABA modulin. Whatever the precise nature of the protein interaction in the supramolecular complex may be, the final result of the activation of the benzodiazepine receptor appear to be an increase in the frequency of chloride channel opening….This change in the kinetics of GABA-activated chloride channels can be account for the potentiation of the GABA response observed with benzodiazepines.

A similar stochastic model of benzodiazepine-GABA-chloride ionophore receptor comclex was presented by Skolnick and Paul in 1981. Accorading to this model, a drug may produce its anxiolytic effecy by direct occupation of the benzodiazepine recognition site or by allosteric interaction with another component of this complex.

Based on charge densities for diazepam obtained in molecular orbital studies, in 1984, Loew et al. postulated that for high affinity benzodiazepine interaction with receptor three cationic sites are required:at C7, the C2=O1 group and the imino nitrogen N4, in which the net atomic charges calculated were, respectively, -0.034, +0.419 and -.359, and –0.309. (Korolkovas, 1988)

1.14 Therapeutic activity

Diazepam possesses antianxiety, hypnotic, sedative, anticonvulsant, and antispastic action.It is also used in the management of anxiety and tension states, as adjunct to anesthesia to produce basal sedation, as anticonvulsant especially in status epilepticus and in the management of persistent convultions, in the control of muscle spasm, and in urinary retention.It is equally useful in vertigo, Meniere’s disease, nausea, vomiting of phychogenic origin, fenfluramine overdose and to counteract lindane toxicity.It is also used for premedication, as a component of neuroleptanalgesia. (Korolkovas, 1988)

1.15 Pharmacokinetics

Diazepam is usually given orally and are well absorbed by this route. Since the weak diazepin is bases, they are less ionized in the relatively alkaline environment of the small intestine, and therefore, most of their absorption takes place at this site. For emergency treatment of seizures or when used in anesthesia, also can be given parenterally.Diazepam and lorazepam are available for intravenous administration.

The distribution of the drug from blood to tissues and back again is a dynamic process with considerable influence on the onset and duration of the therapeutic effects produced by these compounds. Those having greater lipid solubility tend to enter the central nervous system more rapidly and thus tend to produce their effects more quickly. Diazepam have therapeutic effects that are much shorter in duration than would be predicted based on their rates of metabolism and excretion; redistribution away from the central nervous system is of primary importance in terminating their therapeutic effects.

Metabolism takes place both by dealkylation (phase 1) and conjugation (phase 2) reactions. In many instances, dealkylation can result in the formation of pharmacologically active compounds. Diazepam converted in the liver to one or more active metabolites. In several cases the active metabolites have a much longer half-life than the parent compound. The water-soluble metabolites of the diazepam are excreted primarily in the urine. (Jhon, 2004)

1.1 Table: Pharmacokinetics data of diazepam

Pharmacokinetics data	
Bioavaibility	93-100%
Metabolism	Hepatic - CYP2C19
Half life	20–100 hours (36-200 hours for main active metabolite desmethyldiazepam)
Excretion	Renal

1.16 Diazepam: formulation development

An ethyl laurate-based microemulsion system with Tween 80 as surfactant, propylene glycol and ethanol as cosolvents was developed for intranasal delivery of diazepam. Phase behavior and solubilization capacity of the microemulsion system were characterized and in vivo nasal absorption of diazepam from microemulsion formulations was investigated in rabbits. A single isotropic region, which is considered as a bicontinuous microemulsion, was found in the pseudo-ternary phase diagrams developed at various Tween 80: propylene glycol: ethanol ratios. With the increase of Tween 80 concentration, the microemulsion region area, microemulsion viscosity, and the amount of H_2O and ethyl laurate solubilized into the microemulsion system increased; however, the increase of ethanol percentage produced opposite effects. Diazepam, a practically water-insoluble drug, displayed a high solubility of 41 mg/ml in a microemulsion consisting of 15% ethyl laurate, 15% H_2O, and 70% (w/w) surfactant/cosurfactant (Tween 80:propylene glycol:ethanol at 1:1:1 weight ratio). Nasal absorption of diazepam from this microemulsion was found to be fairly rapid. At 2 mg/kg dose, the maximum drug plasma concentration was arrived within 2–3 min, and the bioavailability (0–2 h) after nasal spray compared with intravenous injection was about 50%. These results suggest that this ethyl laurate-based microemulsion may be a useful approach for the rapid-onset delivery of diazepam during the emergency treatment of status epilepticus. (Nandi and Kim, 2010)

1.17 Dose

By mouth, anxiety, 2 mg 3 times daily increased if necessary to 15–30 mg daily in divided doses; elderly (or debilitated) half adult dose Insomnia associated with anxiety, 5–15 mg at bedtime .

By intramuscular injection or slow intravenous injection (into a large vein, at a rate of not more than 5 mg/minute), for severe acute anxiety, control of acute panic attacks, and acute alcohol withdrawal, 10 mg, repeated if necessary after not less than 4 hours.

Only use intramuscular route when oral and intravenous routes not possible; emulsion formulation preferred for intravenous injection; special precautions for intravenous injection.

By rectum as rectal solution, acute anxiety and agitation, 500 micrograms/kg repeated after 12 hours as required; elderly 250 micrograms/kg; CHILD not recommended As suppositories, anxiety when oral route not appropriate, 10–30 mg (higher dose divided); dose form not appropriate for less than 10 mg. (BNF, 2011)

1.18 Side effect

Drowsiness and lightheadedness the next day; confusion and ataxia (especially in the elderly); amnesia; dependence; paradoxical increase in aggression muscle weakness; occasionally: headache, vertigo, hypotension, salivation changes, gastro-intestinal disturbances, visual disturbances, dysarthria, tremor, changes in libido, incontinence, urinary retention; blood disorders and jaundice reported; skin reactions; on intravenous injection, pain, thrombophlebitis, and rarely apnoea**.** (BNF, 2011)

1.19 Cautions

Respiratory disease, muscle weakness and myasthenia gravis, history of drug or alcohol abuse, marked personality disorder; reduce dose in elderly and debilitated; avoid prolonged use (and abrupt withdrawal thereafter); special precautions for intravenous injection acute porphyria when given parenterally, close observation required until full recovery from sedation. (BNF, 2011)

1.20 Contraindication

Respiratory depression; marked neuromuscular respiratory weakness including unstable myasthenia gravis; acute pulmonary insufficiency; sleep apnoea syndrome; not for chronic psychosis; should not be used alone in depression or in anxiety with depression; avoid injections containing benzyl alcohol in neonates. (BNF, 2011)

1.21 Adverse effects

Most adverse effects associated with use of the diazepam are related to their ability to produce central nervous system depression. These include drowsiness, excessive sedation, impaired motor coordination, confusion, and memory loss.These effects are most troublesome during the initial week or two of treatment. Subsequently, the patient becomes tolerant and these effects produce less difficulty. Although for most individuals these symptoms are mild, patients should be cautioned against engaging in potentially dangerous tasks such as operating machinery or driving a car during the initial treatment period. Less common adverse effects include blurred vision, hallucinations, and paradoxical reactions consisting of excitement, stimulation, and hyperactivity. Also, a variety of gastrointestinal complaints occur, and blood dyscrasias have been reported, but these are rare.

Diazepam administration during pregnancy, delivery, or lactation has the potential to have adverse effects on the fetus or newborn. As with other central nervous system depressants, the effects of diazepam are additive with those of ethanol. Patients should be warned that ethanolcontaining beverages may produce a more profound depression when taken simultaneously with a diazepam. (Jhon, 2004)

1.22 During pregnency

Diazepam has been assigned to pregnancy category D by the FDA. It has been suggested that there is an increased risk of congenital malformations and other developmental abnormalities associated with the use of benzodiazepine drugs. There may be nonteratogenic risks associated with the use of benzodiazepines during pregnancy. There have been reports of neonatal flaccidity, respiratory and feeding difficulties, and hypothermia in children born to mothers who have been receiving benzodiazepines late in pregnancy. The manufacturer recommends that the use of diazepam in women of childbearing potential, and specifically during known pregnancy, should only be considered when the clinical situation warrants the risk to the fetus. Special care should be taken when diazepam is used during labor and delivery, because high single doses may produce irregularities in the fetal heart rate and hypotonia, poor sucking,

hypothermia, and moderate respiratory depression in the neonate. With newborn infants, the enzyme system involved in the breakdown of the drug is not yet fully developed (especially in premature infants).

Nursing mother

One report on concentrations in breast milk of medications used during general anesthesia has stated that diazepam and nordiazepam were not detectable in any sample of milk or blood. This report stated that the maximum possible infant exposure index for diazepam would be 3%. Therefore, the authors concluded that the amount of diazepam excreted into breast milk when used for general anesthesia does not warrant interruption in breast-feeding. Diazepam is excreted into human milk. Sedation, lethargy and weight loss have been reported in nursing infants. The American Academy of Pediatrics describes diazepam as a drug whose effect on nursing infants is unknown but may be of concern. The manufacturer states that breast-feeding is not recommended in patients receiving diazepam.

1.23 Important information about Diazepam

Diazepam is a drug of first choice for treatment of early status epilepticus and acute repetitive seizures and for febrile seizure prophylaxis. It can be administered as an i.v. bolus, as a continuous infusion, or rectally, which enhances its utility in managing seizure emergencies. Four randomized controlled trials support diazepam as a drug of first choice for managing status epilepticus (77–80). Success rates of i.v. diazepam for treating status epilepticus vary. In a randomized double-blind study comparing diazepam and lorazepam, Leppik et al. (80) found that 76% of status epilepticus episodes (25 of 33) were terminated by one or two diazepam doses (5 mg / min). In a randomized, non-blinded trial of patients >15 years of age with status epilepticus, Shaner et al. (78) reported that seizures were aborted in <10 min in 55.6% of patients (10 of 18) treated with diazepam (2 mg / min) and phenytoin (40 mg / min). A randomized, double-blind, multicenter Veterans Affairs cooperative study was designed to compare the effectiveness of four treatments for overt or subtle status epilepticus

Three hundred eighty-four patients with overt status epilepticus and 134 patients with subtle status epilepticus were randomly assigned to receive either diazepam (0.15 mg / kg) followed by phenytoin (18 mg / kg), lorazepam (0.1 mg / kg) alone, phenobarbital (15 mg / kg) alone or phenytoin (18 mg / kg) alone. Treatment with diazepam plus phenytoin was successful in 55.8% of patients (53 of 95) with overt status epilepticus and 8.3% of patients (three of 36) with subtle status epilepticus (79). Alldredge et al. (77) conducted a randomized double-blind trial to determine the effectiveness of i.v. diazepam, lorazepam and placebo on status epilepticus when the drugs were administered by paramedics before patients arrived at the hospital. They found that status epilepticus was terminated by the time of arrival in the emergency department in 42.6% of the 68 patients treated with one or two 5-mg doses of i.v. diazepam (infused over 1–2 min). Limited published data indicate that continuous i.v. infusions of diazepam are safe and effective (82–84).

Use of i.v. diazepam can result in seizure relapse within 2 h of a single injection in approximately 50% of patients (76). Therefore, multiple injections or continuous infusion may be required, which can lead to drug accumulation and possibly to acute respiratory depression, sedation and hypotension (76). The development of tolerance has also been reported for infusions lasting >24 h (85). Recommended dosing guidelines for i.v. diazepam for convulsive status epilepticus are 0.15–0.25 mg / kg in adults and 0.1–1.0 mg / kg in children (86). In placebo-controlled trials, rectal diazepam gel (doses of 0.2–0.5 mg / kg) reduced seizure recurrence in children, adolescents and adults who had clusters of repetitive seizures in a non-medical or home setting (87–90). Rectally administered diazepam may also be effective for short-term prophylaxis (at doses of 5–10 mg or 0.3–0.6 mg / kg in patients weighing <10 kg) in children prone to febrile seizures (91–93), and higher doses of rectal diazepam (20–30 mg) have been used in adult patients with drug-resistant epilepsy who are prone to serial seizures (94, 95). (Riss et al.2008)

1.24 Rational use of diazepam in anxiety

Diazepam prescribed in hypnotic and anxiolytic dieases, depending on the circumstances, is probably the drug of choice. A single dose may be sufficient and it should not be continued for more then 1-2 weeks, followed by tapering if necessary. Lorazepam has

also been widely used in such situations. Single dose of diazepam or lorazepam may also offer appropriate prophylaxis against acute stress reaction in predictably stressful situation (e.g. air travel, dental appointment in phobic patients). Benzodiazepines are not recommended ,except acutely, bereavement because their amnesic action may hinder subsequent adjustments.

In generalized anxiety disorders, panic disorders, agoraphobia and other phobias, benzodiazepines may be prescribed initially (about 4 weeks followed by tapering), to allow time for longer term treatments to take effect. For example, antidepressants can be prescribed concomitantly at the start of benzodiazepine treatment and arrangement made for appropriate psychological therapy. Again, diazepam is probably the the benzodiazepine of first choice because of its long duration of action and relative ease of teparing. Intermittent course of 2-4 weeks can be generalized anxiety often associated with fluctuation of generalized anxiety disorder. (Ashton, 2007)

1.25 Diazepam can be habit-forming

Diazepam can be habit-forming. Do not take a larger dose, take it more often, or for a longer time than your doctor tells you to. Tolerance may develop with long-term or excessive use, making the drug less effective. This medication must be taken regularly to be effective. Do not skip doses even if you feel that you do not need them. Do not take diazepam for more than four months or stop taking this medication without talking to your doctor.

1.26 Withdrawal symptoms of diazepam

Withdrawal of a benzodiazepine should be gradual because abrupt withdrawal may produce confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens. Abrupt withdrawal of a barbiturate is even more likely to have serious effects.The benzodiazepine withdrawal syndrome may develop at any time up to 3 weeks after stopping a long-acting benzodiazepine, but may occur within a day in the case of a short-acting one. It is characterised by insomnia, anxiety, loss of appetite and of body-

weight, tremor, perspiration, tinnitus, and perceptual disturbances. Some symptoms may be similar to the original complaint and encourage further prescribing; some symptoms may continue for weeks or months after stopping benzodiazepines. (BNF, 2011)

1.27 Incompatibilities

Diazepam may enhance the sedative effect of other central nervous system depressants. It also increase the effect of oral anticoagulants of the coumarin group. When taken together with antihypertensives, it produces excessive lowering of the blood pressure. Administered intravenously, it may increase the intensity and prolong the duration of nondepolarizing neuromuscular blocking drugs. It may occasionally antagonize the effect of levodopa. Its serum concentration are decreased by carbamazepine. Cimitidine, isoniazid, and low dose estrogen containing oral contraceptives prolong its elimination half life, because these drug inhibit the hepatic microsomal enzyme responsible for the biotransformation of diazepam. (Korolkovas, 1988)

1.28 Overdose

Symptoms and Signs

Benzodiazepines taken alone cause drowsiness, ataxia, dysarthria, nystagmus, and occasionally respiratory depression, and coma

Treatment

Activated charcoal can be given within 1 hour of ingesting a significant quantity of benzodiazepine, provided the patient is awake and the airway is protected. Benzodiazepines potentiate the effects of other central nervous system depressants taken concomitantly. Use of the benzodiazepine antagonist flumazenil [unlicensed indication] can be hazardous, particularly in mixed overdoses involving tricyclic antidepressants or in benzodiazepine- dependent patients. Flumazenil may prevent the need for ventilation, particularly in patients with severe respiratory disorders; it should be used on expert

advice only and not as a diagnostic test in patients with a reduced level of consciousness. (BNF, 2011)

1.29 Quality

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.

1.30 Quality of pharmaceutical products

Quality is always an imperative 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.

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. Among the dosage forms of the drugs, tablet is the most suitable and famous dosage form. Tablet is mainly known for its characteristics such as easy to swallow, availability, affordability etc. so it is a big issue for the pharmaceutical industries to make

and maintain quality tablets. If a drug of any brand or company is not a quality product than it also causes problems when prescribed to the patients. The patients may suffer from the adverse effects of that drug because of its faulty quality. This would not have happened if the drug was a quality product.

1.31 Quality control

The concept of total quality control refers to the process of striving to produce a perfect product by a series of measures requiring an organized effort by the entire company to prevent or eliminate errors at every stage in 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.

If the specification does not reflect the true quality requirements, the product's quality cannot be guaranteed. For instance, the parameters for a tablet vessel should cover not only the material and dimensions but operating, environmental, safety, reliability and maintainability requirements.

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 et al., 2009)

1.32Quality assurance:

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 et al., 2009)

1.33 Quality control parameters for solid dosage forms

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.

1.34 Standards of the quality

Standards are an important part in the measurement of quality of service to the people. Pharmaceutical products can usually be tested and qualified by various Pharmacopoeias. Current existing pronounced standards include:

- British Pharmacopoeia (BP).
- European Pharmacopoeia (EP).
- Japanese Pharmacopoeia (JP).
- The International Pharmacopoeia (IP).
- United States Pharmacopoeia (USP).

The British Pharmacopoeia

The British Pharmacopoeia (BP) is the official collection of standards for UK medicinal products and pharmaceutical substances. Produced by the British Pharmacopoeia Commission Secretariat of the Medicines and Healthcare products Regulatory Agency, the BP makes a valuable contribution to public health by setting publicly available standards for the quality of medicines. Now used in almost 100 countries, the BP is recognised by the US FDA as an official compendium, and remains an essential reference for anyone working within pharmaceutical research and development, manufacture and quality testing worldwide.

All the standard parameters and procedures which are used in this thesis paper were taken from the BP 2003.

The European Pharmacopoeia

The European Pharmacopoeia (*Ph. Eur.*) of the Council of Europe is a pharmacopoeia, listing a wide range of active substances and excipients used to prepare pharmaceutical products in Europe. It includes more than 2000 specific and general monographs, including various chemical substances, antibiotics, biological substances; Vaccines for human or veterinary use; Immunosera; Radiopharmaceutical preparations; Herbal drugs; Homoeopathic preparations and homoeopathic stocks. The monographs give quality

standards for all the main medicines used in Europe. All medicines sold in the 36 Member States of the European Pharmacopoeia must comply with these quality standards so that consumers have a guarantee for products obtained from pharmacies and other legal suppliers.

The Japanese Pharmacopoeia

Japanese Pharmacopoeia provides the official Japanese standard for the description and quality of drug substances and products. It contains over 1,300 articles regarding: general rules for preparations; processes and apparatus; monographs on drugs; and infrared reference spectra and ultraviolet-visible reference spectra.

The International Pharmacopoeia

The International Pharmacopoeia (Ph. Int.) comprises a collection of quality specifications for pharmaceutical substances (active ingredients and excipients) and dosage forms together with supporting general methods of analysis, that is intended to serve as source material for reference or adaptation by any WHO Member State wishing to establish pharmaceutical requirements. The pharmacopoeia, or any part of it, shall have legal status, whenever a national or regional authority expressly introduces it into appropriate legislation.

The United States Pharmacopoeia

The United States Pharmacopoeia (USP) is the official pharmacopoeia of the United States. USP establishes written (documentary) and physical (reference) standards for medicines, food ingredients, dietary supplement products and ingredients. These standards are used by regulatory agencies and manufacturers to help to ensure that these products are of the appropriate identity, as well as strength, quality, purity, and consistency.

Prescription and over-the-counter medicines available in the United States must, by federal law, meet USP public standards, where such standards exist. Many other

countries use the USP instead of issuing their own pharmacopeia, or to supplement their government pharmacopoeia. USP's standards are recognized and used in more than 130 countries around the globe. These standards have helped to ensure public health throughout the world for close to 200 years.

1.35 Rationale of the study

Today most countries worldwide have requirements for reviewing and approving pharmaceutical products or are currently working to establish them in order to ensure product quality, safety, efficacy, traceability and availability. Over the last couple of decades, significant changes have occurred in the environment of pharmaceutical regulations and these changes have required adjustments to regulatory approaches due to increased number and complexity of products, advances in science and technologies, global harmonization, etc. (Ulman and Rafidison, 2003)

The pharmaceutical industry invests vast amount money and time every year to study the most used solid dosage form also known as tablets. This expense is quite reasonable when one considers the importance of tablet dosage form to the pharmaceutical industry. Tablet dosage form has many advantageous facts such as suitability, well known, availability, affordability etc over the other dosage forms. These facts are the main reasons for the pharmaceutical industries to vastly manufacture tablet.

The process of 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. To maintain manufacturing of the tablet dosage form, quality parameters are necessary. Quality control parameters are the main conditions for a quality product. To improve the quality parameters the tablet manufacturing technology has undergone great improvement and experimentation. Many efforts are given to understand more clearly about the physical parameters and the factors which are considered after the tablet dosage form administered via oral route.

For maintaining the standard quality, many in process quality control tests are done by the pharmaceutical industry. These tests include hardness, thickness, friability, disintegration etc. dissolution and potency tests are also done to ensure the dosage efficacy. The importance of these tests cannot be measure by any means. The main functions of these tests are to ensure uniform quality and purity of the finished dosage forms within a batch and between batches. To have a quality product, quality control tests are immensely needed.

1.36 Aim and objectives of the study

The aim and objectives of the study were-

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

CHAPTER - 2

Materials and Methods

2.1 Sample

From the entire Bangladeshi companies produce diazepam tablet, 2 brands were selected from 2 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 diazepam

Company	**Brand**
Opsonin	Easium
Sonear	Relaxen

General appearance two brand of diazepam

The general appearance of a tablet, its visual identity and overall elegance is essential for consumer acceptance, for control lot to lot uniformity and general tablet to tablet uniformity, and for monitoring the trouble free manufacturing. The control of the general appearance of a tablet involves the measurement of a number of attributes such as a tablet size, shape color, presence or absence of an odor, taste, surface texture, physical flows and consistency, and legibility of any identifying markings.

Brand: Easium

Company: opsonin

Uncoated tablet

Round shape

Scored tablet

Absence of odor

Brand: Relaxen

Company: Sonear

Uncoated tablet

Round shape

Scored tablet

Embossed

Absence of odor

2.2 Hardness 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**
VEEGO	India

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. (Banker and Anderson, 2009)

2.3 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 2.3: Name and specification of materials required to friability test.

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

Mathod:

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. (BP, 2009)

Figure 2.1: Friability tester.

2.4 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 2.4: 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.

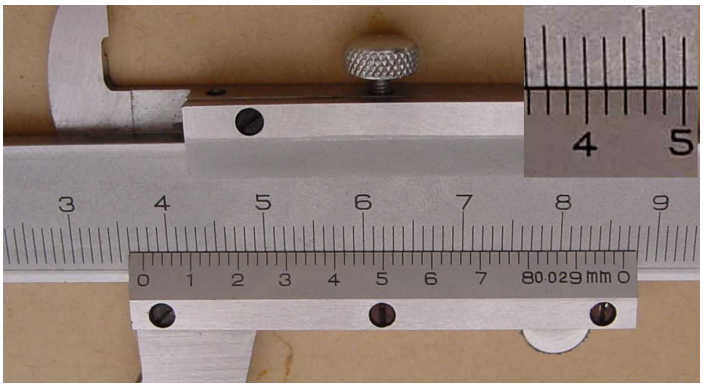

Figure 2.2: Vernier Callipers

2.5 Weight variation test:

The weight variation test would be a satisfactory method of determining the drug content uniformity of tablet if the tablet were all or essentially all (90-95%) active ingredient, or if the uniformity of drug distributed in the granulation or power from which the tablet were made were perfect. With a tablet designed to contain a specific amount of drug in a specific amount of tablet formula, the weight of the tablet being made is routinely measure to help ensure that the tablet contain proper amount of drug. The USP weight variation test is run by weighting 20 tablet individually, calculating the average weight, and comparing the individual tablet weight to the average. The tablet meet the USP test if no more then 2 tablet are outside the percentage limit and if no tablet differs by more then two times the percentage limit. The weight variation tolerances for uncoated tablet differ depending on average tablet weight.

Table 2.5.1: Weight variation tolerances for uncoated tablet

Average weight of tablets(mg)	Maximum percentage difference allowed
130 or less	10
130-324	7.5
More then 324	5

(Banker and Anderson, 2009)

Table 2.5: Name and specification materials required to weight variation test:

Materials	**Specification**
Electronic balance	Shimadzu, Japan

Mathod :

1. Weighting 20 tablet individually.
2. Calculating the average weight.
3. Comparing the individual tablet weight to the average.

2.6 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 2.6: 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 .740 ml 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 . The machine was then operated for the prescribed period.

8 . The entire tablet must disintegrate within the prescribed time. (BP, 2009)

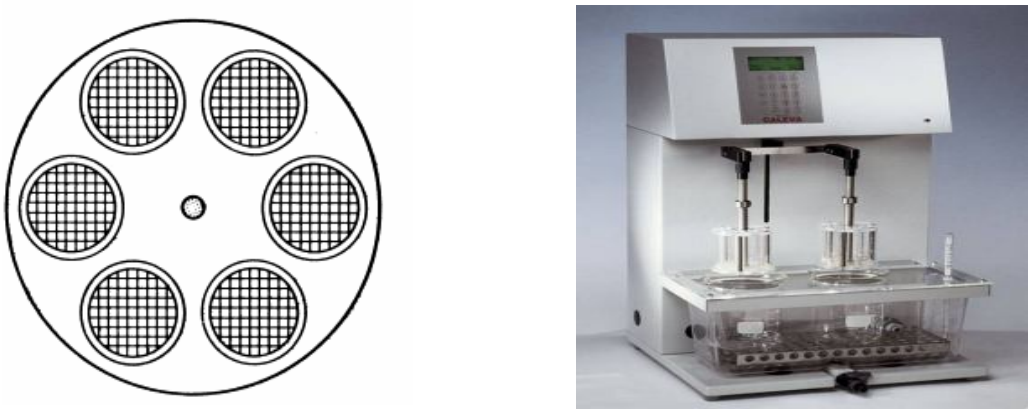

Figure 2.3: Disintegration tester

CHAPTER– 3

Results

3.1 Hardness Test:

Ten tablets from each brand of diazepam were selected to conduct the hardness test.

Table 3.1: Result of the hardness test

No. of tablet	Easium	Relaxen
1.	6.9	3.2
2.	5.8	5.0
3.	5.2	4.6
4.	5.0	5.6
5.	4.8	3.0
6.	4.2	4.4
7.	5.0	3.6
8.	5.8	4.8
9.	4.8	4.6
10.	5.2	5.0

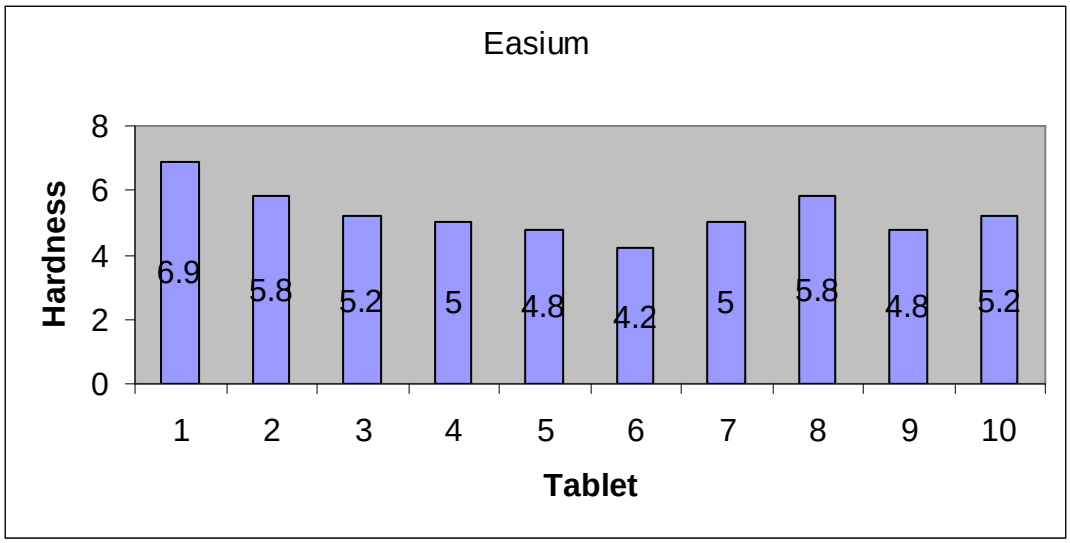

Figure 3.1.1: Hardness test of Easium

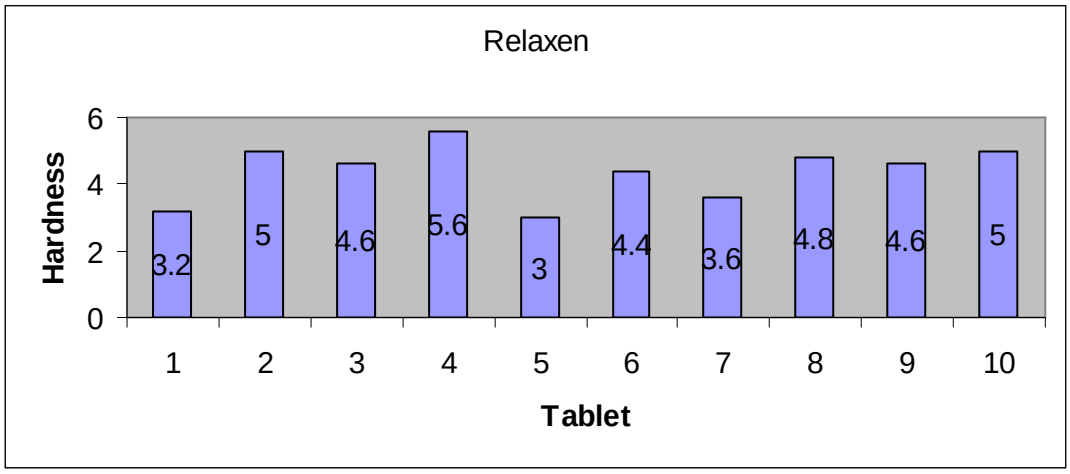

Figure 3.1.2: Hardness test of Relaxen

The highest value of hardness was Easium (6.9) and Relaxen (5.6). The lowest value of hardness was Relaxen (3.0) and Easium (4.2)

3.2 Friability Test:

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

% of friability =(Initial weight –Final weight/Initial weight)×100

Table 3.2: Result of the friability test

Brand	Initial weight of 20 tablets	Final weight of 20 tablets	Friability test (%)
Easium	1.305	1.304	0.198 %
Relaxen	3.378	3.375	0.177 %

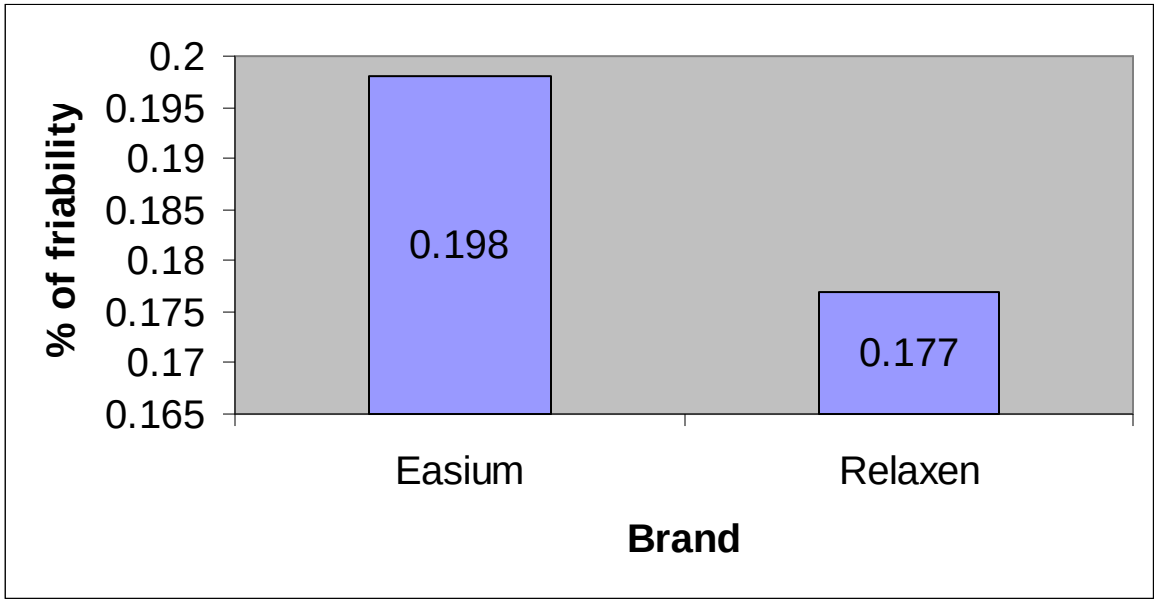

Figure 3.2: Friability test of diazepam.

The value of friability was Easium (0.198%) and Relaxen (0.177%). Two brands of diazepam has a in standard range friability values.

3.3 Thickness Test:

Twenty tablets from each brand of diazepam were selected to conduct the thickness test.

% Of thickness variation = Main scale reading + (Vernier scale reading × Vernier constant) ± Error

Table 3.3.1: Result of the thickness test of easium

Brand	Reading of cm scale (cm)	Reading of vernier scale(mm)	Vernier constant (mm)	Vernier error (mm)	Thickness of the tablet (mm)
Easium	0.25	4	0.1	0	0.402
	0.25	4	0.1	0	0.402
	0.25	4	0.1	0	0.402
	0.25	4	0.1	0	0.402
	0.25	5	0.1	0	0.502
	0.25	5	0.1	0	0.502
	0.25	4	0.1	0	0.402
	0.25	4	0.1	0	0.402
	0.26	5	0.1	0	0.502
	0.26	5	0.1	0	0.502
	0.25	4	0.1	0	0.402
	0.25	5	0.1	0	0.502
	0.25	4	0.1	0	0.402
	0.25	4	0.1	0	0.402
	0.26	5	0.1	0	0.502
	0.25	4	0.1	0	0.402
	0.25	4	0.1	0	0.402
	0.25	4	0.1	0	0.402
	0.25	4	0.1	0	0.402
	0.26	5	0.1	0	0.502

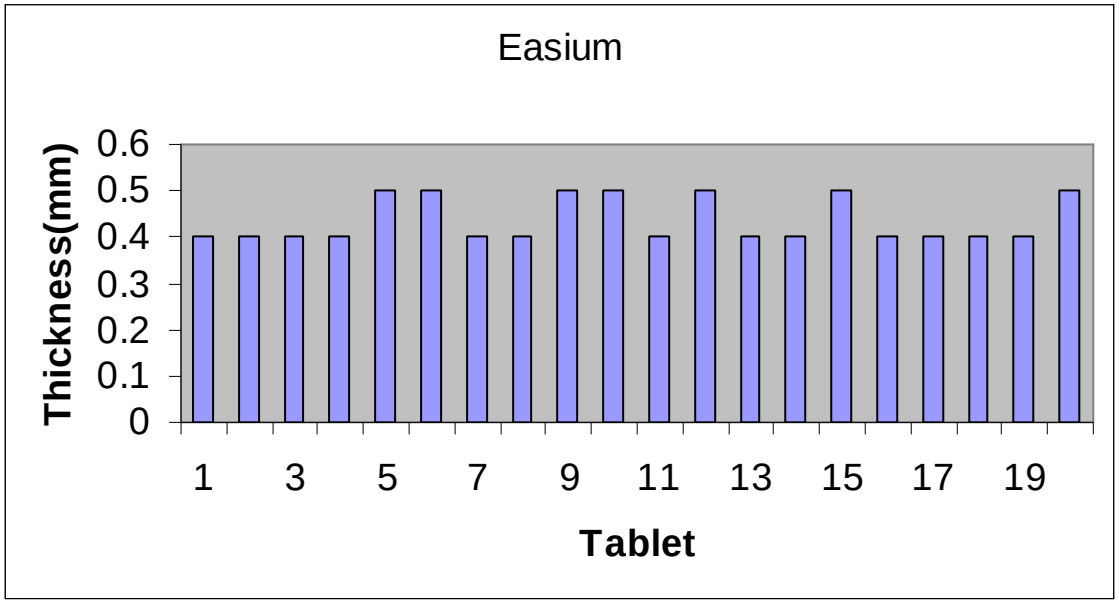

Figure 3.3.1: Thickness test of Easium

Table 3.3.2: Result of the thickness test of relaxen

Brand	Reading of cm scale (cm)	Reading of vernier scale(mm)	Vernier constant (mm)	Vernier error (mm)	Thickness of the tablet (mm)
Relaxen	0.23	3	0.1	0	0.302
	0.23	3	0.1	0	0.302
	0.23	3	0.1	0	0.302
	0.23	3	0.1	0	0.302
	0.24	3	0.1	0	0.302
	0.24	3	0.1	0	0.302
	0.24	3	0.1	0	0.302
	0.25	4	0.1	0	0.402
	0.24	3	0.1	0	0.302
	0.23	3	0.1	0	0.302
	0.25	5	0.1	0	0.502
	0.24	3	0.1	0	0.302
	0.24	3	0.1	0	0.302
	0.24	3	0.1	0	0.302
	0.24	3	0.1	0	0.302
	0.23	3	0.1	0	0.302
	0.24	3	0.1	0	0.302

	0.23	3	0.1	0	0.302
	0.24	3	0.1	0	0.302
	0.26	6	0.1	0	0.602

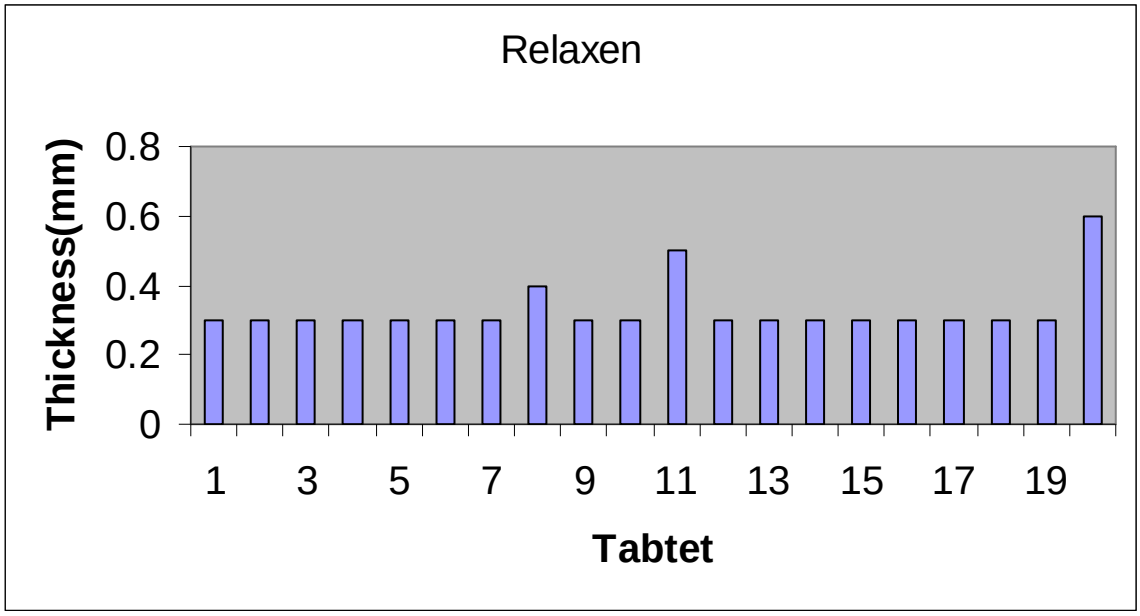

Figure 3.3.2: Thickness test of relaxen

The thickness of easium and relaxen brands of diazepam was complied with the BP standards. Because tablet thickness is controlled within 5 percent of standard value.

3.4 Weight variation test:

Twenty tablets from each brand of diazepam were selected to conduct the weight variation test.

% Of weight variation = (Average weight – individual weight / Individual weight) × 100

Table 3.4.1: Result of the weight variation test of easium

Brand	Individual weight (gm)	Average weight (gm)	% of Weight variation (mg)
Easium	0.0667	0.0665	1.799
	0.0659		-0.606
	0.0661		-0.907
	0.0661		-0.907
	0.0656		-0.152
	0.0647		1.236
	0.0655		0
	0.0653		0.306
	0.0659		-0.606
	0.0663		-1.206
	0.0656		-0.152
	0.0662		-1.206
	0.0659		-0.606
	0.0656		-0.152
	0.0652		0.460
	0.0653		0.306
	0.0661		-0.907
	0.0645		1.550
	0.0661		-0.907
	0.0654		0.152

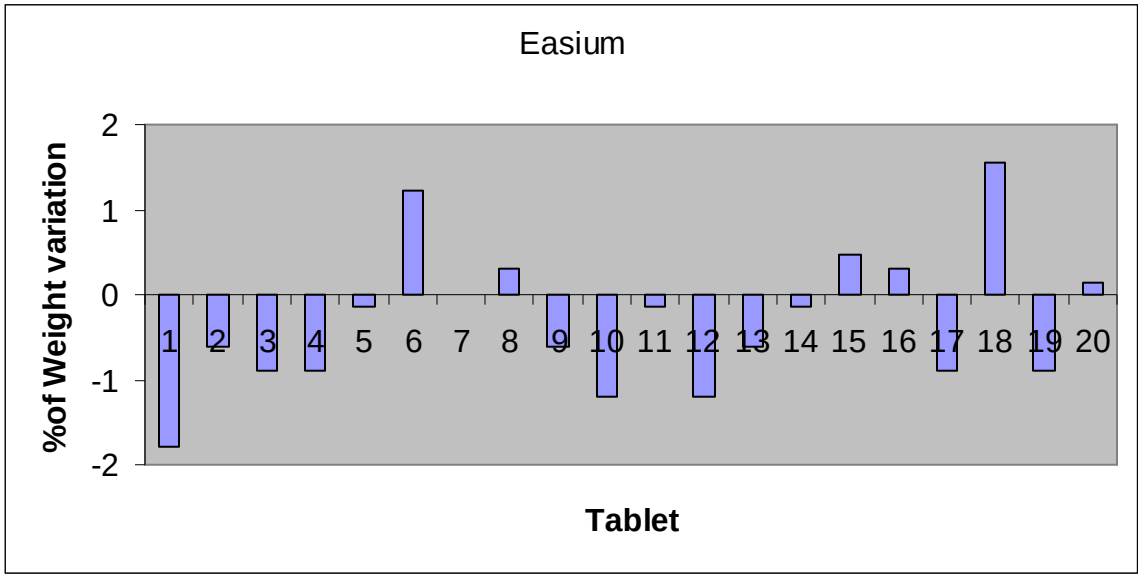

Figure 3.4.1: Weight variation test of easium

Table 3.4.2: Result of the weight variation test of relaxen

Brand	Individual weight (gm)	Average weight (gm)	Weight variation (mg)
Relaxen	0.1726	0.1705	-1.216
	0.1703		0.117
	0.1670		2.095
	0.1701		0.235
	0.1672		1.973
	0.1670		2.095
	0.1676		1.730
	0.1713		-0.467
	0.1693		1.548
	0.1673		6.363
	0.1700		0.294
	0.1744		-2.236
	0.1670		2.095
	0.1659		2.772
	0.1699		0.353
	0.1669		2.156
	0.1720		-0.872
	0.1866		-8.628
	0.1789		-4.695
	0.1750		-2.571

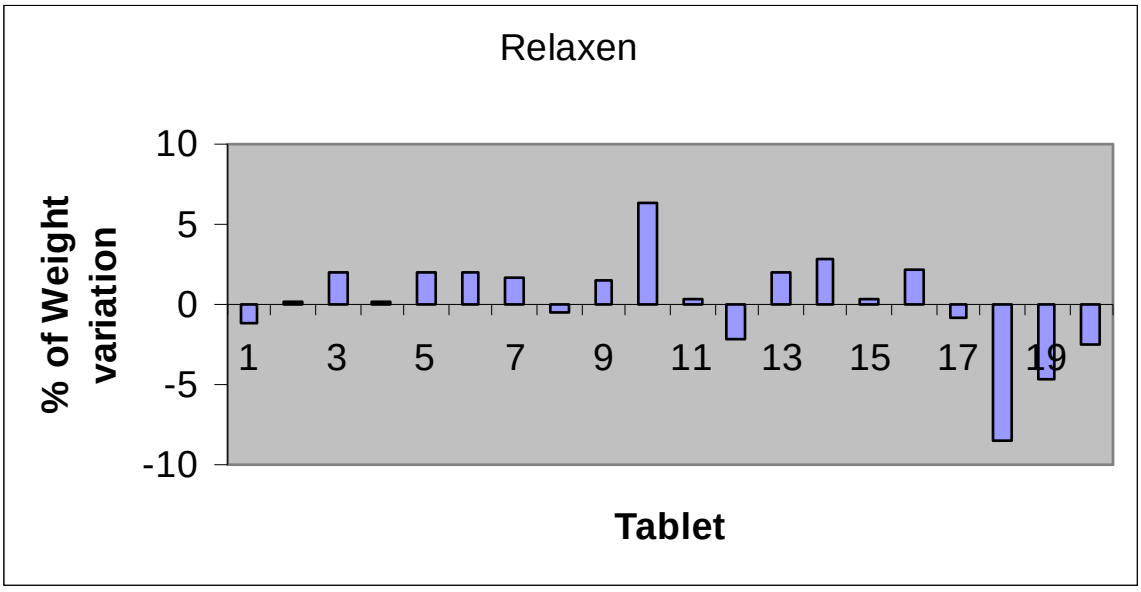

Figure 3.4.2: Weight variation test of relaxen

The weight variation of easium and relaxen brands of diazepam was complied with the BP standards. The tablet meet the USP test if no more then 2 tablet are outside the

percentage limit and if no tablet differs by more then two times the percentage limit. The average weight of Easium (6.55 mg) and Relaxen (17.05 mg).

3.5 Disintegration Test:

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

Table 3.5: Result of the disintegration test

Brand	Sample 01	Sample 02	Sample 03
Easium	4:26 min	3:46 min	3:09 min
Relaxen	0:42 min	0:39 min	0:38 min

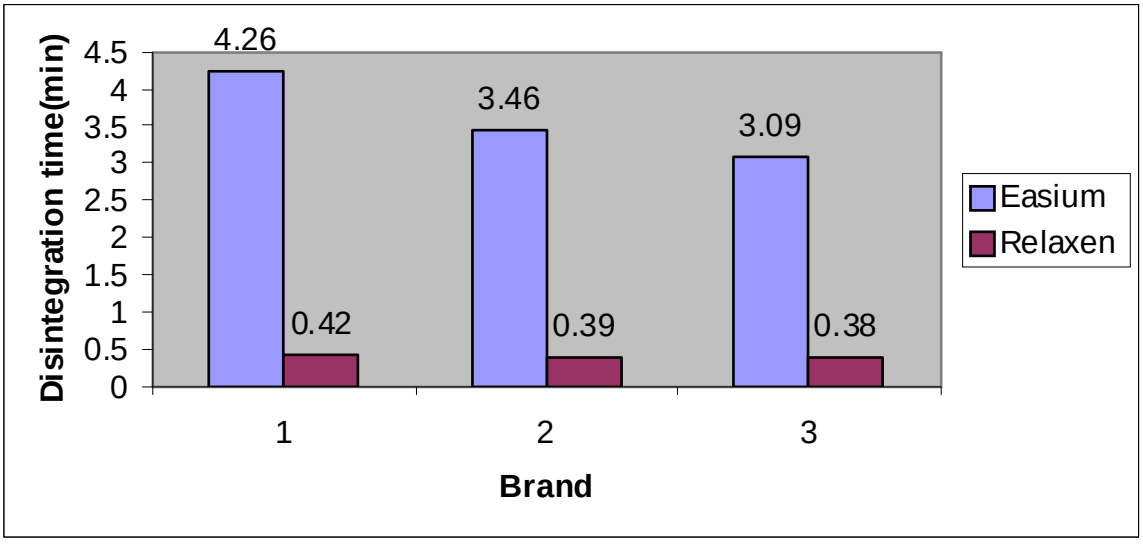

Figure 3.5: Disintegration test of diazepam.

The disintegration test results of two brands showed in range disintegration time which represents a quality product. The average value was Easium (3:68 min) and the average value was Relaxen (0:51 min).

CHAPTER - 04

Discussion and Conclusion

Discussion

Quality is never an accident; it is always the result of high intention, sincere effort, intelligent direction and skillful execution; it represents the wise choice of many alternatives. Quality of product is the main precursor for any pharmaceutical industry to maintain its existence. 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, weight variation or disintegration.

Tablet hardness has been defined as the force required breaking a tablet in a diametric compression test. 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 diazepam, the highest value of hardness was showed by brand Easium (6.9). The lowest hardness value was showed by the brand Relaxen (3.0). Easium brands of diazepam have a high hardness value. High hardness causes the tablets to break slowly in the system, which is a major drawback for the tablets to work efficiently. A force of about 4-5 kg is considered to be the minimum for hardness according to The British Pharmacopoeia.

Friability is an indicator of the strength of a tablet to resist breakdown through attrition. Friability tests helps to measure whether a tablet posses specific amount of strength to withstand mechanical shocks of handling in manufacture, packaging or shipping. Conventional compressed tablets that lose less than 0.5 to 1 % of their weight are considered acceptable. The value of friability was Easium (0.198%) and Relaxen (0.177%). We can view that the % friability values for two brands were within acceptable range.

Thickness is a physical parameter of tablets, which is often evaluated. Tablet thickness test provides an idea about the compressive strength during compression process. The value of thickness Easium and Relaxen was 0.30 and 0.40 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 can not be swallowed by an average person. On the other hand, if the tablet is less thick then it can breakdown easily.

Weight variation is also a physical parameter of tablets. With a tablet designed to contain a specific amount of drug in a specific amount of tablet formula, the weight of the tablet being made is routinely measure to help ensure that the tablet contain proper amount of drug. The tablet meet the USP test if no more then 2 tablet are outside the percentage limit and if no tablet differs by more then two times the percentage limit. The average weight of Easium brand was (6.55 mg) and Relaxen brand was (17.05). The maximum percentage difference allowed 10 for no more then two tablet. We can view that the % of weight variation values for two brands were within acceptable range.

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 value of disintegration test was 3:68 min (Easium) and the value of disintegration test was 0:51 min (Relaxen). Uncoated USP tablet have disintegration time standard as low as 5 min. 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, the brands of diazepam tablet showed an in standard range of disintegration value.

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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.

CHAPTER- 05

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