Evaluation of Quality Control Parameters of Two Brands of Diazepam Tablets

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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Certificate

This is to certify that the dissertation entitled “Evaluation of Quality Control Parameters of Two brands of Diazepam Tablets” submitted to the Department of Pharmacy, East West University, Aftabnagar in partial fulfillment of the requirement for the Degree of Bachelor of Pharmacy, was carried out by Sonia Kamal (ID#2008-3-70-095).

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Certificate

This is to certify that the dissertation entitled “Evaluation of Quality Control Parameters of Two Brands of Diazepam Tablets” submitted to the Department of Pharmacy, East West University, Aftabnagar in partial fulfillment of the requirement for the Degree of Bachelor of Pharmacy, was carried out by Sonia Kamal (ID#2008-3-70-095). It is a record of original research work carried out under the supervision and guidance of me 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.

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Dedicated

TO

My Beloved Parents

List of Contents

List of tables

List of figures

Abstract

Quality is something that characterizes a thing and every company strives for it but often it is very difficult to achieve. Quality of Pharmaceutical Product is very important for achieving the therapeutically active and standard drug. It can be achieved by following some parameters that are specified in the respective monograph of the drug. This research work was aimed to investigate the quality control parameters of two brands of diazepam (Seduxen®, Sedil®) which are available in market. This in turn helps to determine whether the two brands of diazepam were manufactured according to the specifications given by British Pharmacopeia (BP). The two brands of diazepam were collected from local market of Bangladesh. Then the brands were subjected to physical parameter tests such as weight variation, hardness, thickness, friability and disintegration. The brands passed the tests as no tablets cross the ±7.5% weight variation. Average thickness of the Seduxen® was 0.252cm with 0% variation and average thickness of Sedil® was 3.155cm with 0.01% variation for 19 tablets and -0.13% for 1 tablet. Average hardness of Sedil® was greater than 5kg which met the specifications but the hardness of the Seduxen® was not within the compendial limit (5 kilograms minimum and 8 kilograms maximum). Percentage friability of the two brands was not more than 1% and thus they met the specifications. All the six tablets of both the brands disintegrated within 15 minutes and thus they complied with the specifications. Last but not the least it can be concluded that, two brands of diazepam were manufactured according to the specifications given by British Pharmacopeia (BP). Due to some technical problems dissolution and potency test were not performed. So, these two parameters were not compared with compendial limit. But we have done other tests required for the determination of the quality control parameters which have shown satisfactory results.

Keywords: Quality, diazepam, weight variation, hardness, thickness, friability, disintegration.

Chapter -1

Introduction

1.1. Quality of Pharmaceutical Products

Quality is something that characterizes a thing and every company strives for it but often it is very difficult to achieve. Quality of pharmaceutical product is very important for achieving the therapeutically active and standard drug. It can be achieved by following some parameters that are specified in the respective monograph of the drug. United States of Pharmacopeia (USP) and British Pharmacopeia (BP) are such two Pharmacopeias that provide the necessary specifications. Quality of pharmaceutical product is very important because drugs must be marketed as safe and therapeutically active formulations whose performance is consistent and predictable. New and better medicinal agents are being produced at an accelerated rate. At the same time more exacting and sophisticated analytical methods are being developed for their evaluation. Quality is a much more complicated term than what it appears. There are a variety of perspectives that can be undertaken in defining quality such as Customers perspectives, Specification based perspectives etc. Quality can be defined as the measurement of excellence or state of being free from defects, deficiencies and significant variations. In Pharmaceutical Industry; Quality is defined as a measure of high degree of managerial, scientific and technical sophistication. (United States Drug Enforcement Administration, 2012)

According to International Standard Organization (ISO); “Quality is defined as the totality of features or characteristics of a product or service that bear on its ability to satisfy stated or implied needs.” (Griffin,R 2012)

There are some dimensions of quality which generally capture the meaning of it. These are:

- Performance
- Features
- Reliability
- Conformance
- Durability
- Aesthetics

- Perceived quality (Griffin R, 2012)

1.2. Views for describing the overall quality of a product

i. Firstly; the view of the manufacturer who is primarily concerned with the design, engineering and manufacturing processes involved in fabricating the product. It is measured by the degree of conformance to predetermined specifications and standards and deviations from these standards can lead to poor quality and low reliability. Efforts for quality improvement are aimed at eliminating defects, the need for scrap and rework, and overall reductions in production costs.

ii. Secondly; the view of the customer or user. To consumer, a high quality product is that one which satisfies their preference and expectations well. This consideration can include a number of characteristics; some of which contribute little or nothing to the functionality of the product but significantly providing customer satisfaction.

iii. Thirdly; this view relating to the quality is to consider the product itself as a system and to incorporate those characteristics that pertain directly to the operation and functionality of the product. This approach should include overlap of the manufacturer and customer view (Mazumder,B 2011).

1.3 Importance of Quality

Quality is essential for the following reasons:

1. The growth and survival of an organization

Quality is essential for the survival and growth of the organization. If a company continuously produces good quality drugs then the customer will be satisfied. As a result, there will be development of belief on the customer's mind about the product of that company which is an important criterion for the survival and growth of the organization.

2. To gain maximum productivity, profitability and customer loyalty

If the quality of the product is low then there will be increased return of the product from the market. As a result profitability and customer loyalty are decreased. On the other hand, there is

no return of the products from the market in case of good quality product that results in increased profitability and customer loyalty.

3. Marketing the drugs as safe and therapeutically active

Drug is a lifesaving product. So, it is responsibility of a pharmaceutical company to ensure the quality of drug. It also serves as a strong marketing tool (Lamba, 2010).

1.4. Quality Objectives

Under the concept of management of objectives the Manager participates in discussing objectives, and these become the basis for planning for results. These objectives are known as quality objectives. Some features of Quality Objectives are:

- A well-defined quality objective helps managers thinking to stimulate action and permit comparison of performance against objectives.
- Objectives may be either for breakthrough or for control.
- In small organizations, the chief executive by personal observation and by direct contact with the people can set quality objectives.
- In a large organization, this personal contact is no more feasible. There are no other alternatives, except the leadership for setting quality objectives and the same is passed on the departmental heads and thus, the quality objective tends to be departmental rather than corporate (Enders, 2000).
- A large company can establish an interdepartmental mechanism to identify potential objectives, assess their economic and other effects and fix a priority in the program of action.
- Proposals from key persons in the organization i.e. managers, supervisors, professionals etc.
- Proposal from suggestion schemes.
- Data from field study of user’s needs, costs;

- Comparison data on performance of the product versus competitor's product.
- Comments of key people outside organization i.e. customers, vendors, critics, press etc.
- Findings or comments of regulatory agency, independent laboratories or reformers (Enders, 2000). (Kanji, 1995)

1.5. Quality Policy

Quality Policy should include the following:

- An expectation to comply with applicable regulatory requirements
- Should facilitate continual improvement of the pharmaceutical quality system.
- Should be communicated to and understood by personnel at all levels
- Should be reviewed periodically for continuing effectiveness.
- Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality (Kanji, 1995).

1.6. Quality measurement

Quality is measured by the following:

- Customer's experience with the product or
- Service against his or her requirements**.**

In Pharmaceutical sense, quality means checking and directing the degree or grade of excellence of processes and products. To the ethical pharmaceutical manufacturer it implies a detail system of inspection and control covering the production, evaluation, distribution of every drug bearing the companys label. It is the purpose of these operations to produce medication of superior efficacy, safety and elegance and to provide assurance to physician, pharmacists and the consumer that given product performs uniformly and in a manner satisfactory for the purpose for what it is recommended. (Canadian Medical Association, 2007)

- The poor quality of drugs has been linked to counterfeiting of medicines, chemical instability especially in tropical climates, and the poor quality control during manufacture. (WHO, 2012)

1.6.1. Types of tests

There are two types of tests. They are compendial and non compendial tests.

1.6.1.1. Compendial Tests

These tests methods are described in the pharmacopeias like USP (United States Pharmacopeia), BP (British Pharmacopoeia) etc. They are also known as official tests. They include:

Weight variation

Disintegration

Dissolution

Pharmacopeia is an authorized treatise on drugs and their preparation, specially a book containing formulas and information that provide a standard for preparation and dispensation of drugs. At present, many pharmacopoeias are available in the pharmaceutical world. Among them BP and USP are most reliable source for the pharmaceuticals. BP which was introduced in the Great Britain, but now-a-days it is followed overall the world. USP, a pharmacopeia that issued every five years, but with periodic supplements, preapared under the supervision of anational committee of pharmacist, pharmacologist, physician, chemist, biologist and other scientific personnel. It was adopted as standard in 1906 and in 1975 National Formulary was included (Taber's, 2008).

1.6.1.2. Non Compendial Tests

These tests methods are not described in the pharmacopeias and so that are referred as Non Compendial Tests or Non official tests. They include:

Hardness

Friability

1.7. Significance of the Physical Parameter Tests

For determining quality of a drug following physical parameter tests are done in this particular study-

1. Weight Variation Test
2. Thickness test
3. Hardness Test
4. Friability Test
5. Disintegration Test

1.7.1 Weight variation test

Weight Variation test is done to check the uniformity of contents and active ingredients so that a uniform product can be ensured with an elegant appearance. It has direct relation with uniformity of solid dosage forms. A small weight variation does not ensure good content uniformity between dosage units; a large weight variation precludes good content uniformity. So it is one of the most vital and significant quality control parameter tests. Any of the following parameters can produce tablet weight variation:

(1) Poor granulation flow properties, resulting in uneven die fill.

(2) A wide variation in granulation particle size, which result in a variation in die fill density as a function of particle size and particle size distribution at different points in the production run,

(3) Difference in lower punch length, which result in different size die cavities (Anderson, 2009).

Weight Variation is expressed as percentage and it shows to what percentage the weight of an individual tablet deviated from average tablet weight. Tolerance limit of weight variation has been specified in different official compendia.

Limit of weight variation test according to BP (Appendix:VI)

Table 1.1: Limit of weight variation test according to BP

Average Weight	Percentage difference
130 mg or less	±10
More than 130	±7.5
324 mg and above	± 5

(British Pharmacopiea, 2005)

1.7.2. Thickness Test

Tablet Thickness is an important parameter for tablet packaging because very thick tablet affect packaging either in blister or plastic containers. Also for the aesthetic value tablet with uniform thickness is required. So to make an elegant shaped and sized tablet this test is important. 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 (Aulton, 2009).

1.7.3. Hardness Test

Tablet hardness is usually expressed as the load required for crushing a tablet when placed on its edge. Hardness is thus sometimes termed the tablet crushing strength. We measure hardness to determine the need for pressure adjustments on the tableting machine. 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. Hardness also affects the disintegration. If the tablet is too hard, it may not disintegrate in the required period of time. And if the tablet is too soft, it will not withstand the handling during subsequent processing such as coating or packaging. In general, if the tablet hardness is too high, we first check its disintegration before rejecting the batch. And if the disintegration is within limit, we accept the batch. It may also affect tablet friability, drug dissolution, drug release and bioavailability. So this test suggests that the tablet should show sufficient mechanical strength to withstand fracture and erosion during manufacturing, packaging, transporting and handling. (Aulton, 2009)

Factors Affecting the Hardness:

- Compression of the tablet and compressive force.
- Amount of binder. (More binder à more hardness)
- Method of granulation in preparing the tablet (wet method gives more hardness than direct method; Slugging method gives the best hardness).
- Limits: 5 kilograms minimum and 8 kilograms maximum (British Pharmacopiea, 2005).

1.7.4 Friability Test

Friability is a property that is related to the hardness of the tablet. In different operations of tablet preparations like coating, packaging, transport etc. the tablet undergoes a tumbling motion which is not always significant. This may not always break a tablet but may be a part of it gets abraded from the tablet surface. It is the tendency of tablets to powder, chip, or fragment and this can affect the elegance appearance, consumer acceptance of the tablet, and also add to tablet's weight

variation or content uniformity problems. An instrument called friabilator is used to evaluate the ability of the tablet to withstand abrasion in packaging, handling, and shipping. (Aulton, 2009)

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 (Aulton, 2009).

1.7.5 Disintegration Test

Disintegration is the most important step of a drug being under better dissolution. The disintegration test is a measure only of the time required under a given set of conditions for a group of tablets to disintegrate into particles. The breakdown of a drug within its optimum time is the prerequisite for better absorption and consequently for 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 (Aulton, 2009).

Liquids used in disintegration are:

- Water
- Simulated gastric fluid (P^H = 1.2 HCl),
- Simulated intestinal fluid (P^H = 7.5, KH_2PO_4 (phosphate buffer) + pancreatic enzyme +NaOH)

1.8. Description of Diazepam

The Diazepam is the drug of Benzodiazepine family. The benzodiazepine family of depressants is used therapeutically to produce sedation, to induce sleep, to relieve anxiety, muscle spasms and to prevent seizures. In general, benzodiazepines act as hypnotics in high doses, anxiolytics in moderate doses, and sedatives in low doses. Of the drugs marketed in the United States that affect central nervous system function, benzodiazepines are among the most widely prescribed

medications. Fifteen members of this group are presently marketed in the United States, and about 20 additional benzodiazepines are marketed in other countries. Short-acting benzodiazepines are generally used for patients with sleep-onset insomnia (difficulty falling asleep) without daytime anxiety. (Reeder, 1961)

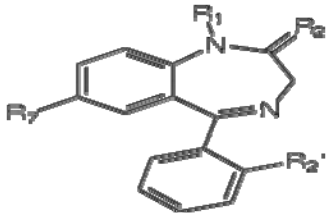

Figure 1.1: General structure of Benzodiazepines

Among the short-acting benzodiazepines include estazolam, flurazepam, temazepam and triazolam, midazolam. Midazolam is also utilized for sedation, anxiety, and amnesia in critical care settings and prior to anesthesia. It is available in the United States as an injectable preparation and as syrup (primarily for pediatric patients) (Tripathi, 2008).

Benzodiazepines with a longer duration of action are utilized to treat insomnia in patients with daytime anxiety. These benzodiazepines include alprazolam, chlordiazepoxide, clorazepate, diazepam, halazepam, lorzepam, oxazepam, prazepam, and quazepam. Clonazepam, diazepam, and clorazepate are also used as anticonvulsants

Repeated use of large doses or; in some cases, daily use of therapeutic doses of benzodiazepines is associated with amnesia, hostility, irritability, and vivid or disturbing dreams, as well as tolerance and physical dependence. The withdrawal syndrome is similar to that of alcohol and may require hospitalization. Abrupt cessation of benzodiazepines is not recommended and tapering-down the dose eliminates many of the unpleasant symptoms (Islam, 2007).

Given the millions of prescriptions written for benzodiazepines (about 100 million in 1999), relatively few individuals increase their dose on their own initiative or engage in drug-seeking behavior. Those individuals who do abuse benzodiazepines often maintain their drug supply by getting prescriptions from several doctors, forging prescriptions, or buying diverted pharmaceutical products on the illicit market. Abuse is frequently associated with adolescents

and young adults who take benzodiazepines to obtain a "high." This intoxicated state results in reduced inhibition and impaired judgment. Concurrent use of alcohol or other depressant with benzodiazepines can be life threatening. Abuse of benzodiazepines is particularly high among heroin and cocaine abusers. A large percentage of people entering treatment for narcotic or cocaine addiction also report abusing benzodiazepines. Alprazolam and diazepam are the two most frequently encountered benzodiazepines on the illicit market (National Institute of Health, 2006).

Flunitrazepam is a benzodiazepine that is not manufactured or legally marketed in the United States, but is smuggled in by traffickers. In the mid-1990s, flunitrazepam was extensively trafficked in Florida and Texas. Known as "rophies," "roofies," and "roach," flunitrazepam gained popularity among younger individuals as a "party" drug. It has also been utilized as a "date rape" drug. In this context, flunitrazepam is placed in the alcoholic drink of an unsBPecting victim to incapacitate them and prevent resistance from sexual assault. The victim is frequently unaware of what has happened to them and often does not report the incident to authorities. A number of actions by the manufacturer of this drug and by government agencies have resulted in reducing the availability and abuse of flunitrazepam in the United States (United States Drug Enforcement Administration 2012).

1.8.1 Mechanism of action of Benzodiazepines

All benzodiazepines act by enhancing the actions of a natural brain chemical, GABA (gamma-aminobutyric acid). GABA is a neurotransmitter, an agent which transmits messages from one brain cell (neuron) to another. The message that GABA transmits is an inhibitory one that is it tells the neurons that it contacts to slow down or stop firing. Since about 40% of the millions of neurons all over the brain respond to GABA, this means that GABA has a general quietening influence on the brain and it is in some ways the body's natural hypnotic and tranquillizer. This natural action of GABA is augmented by benzodiazepines which thus exert an extra (often excessive) inhibitory influence on neurons (Reeder, 1961).

The way in which GABA sends its inhibitory message is by a clever electronic device. Its reaction with special sites (GABA-receptors) on the outside of the receiving neuron opens a channel, allowing negatively charged particles (chloride ions) to pass to the inside of the neuron.

These negative ions "supercharge" the neuron making it less responsive to other neurotransmitters which would normally excite it. Benzodiazepines also react at their own special sites (benzodiazepine receptors), situated actually on the GABA-receptor. Combination of a benzodiazepine at this site acts as a booster to the actions of GABA, allowing more chloride ions to enter the neuron, making it even more resistant to excitation. Various subtypes of benzodiazepine receptors have slightly different actions. One subtype (alpha 1) is responsible for sedative effects, another (alpha 2) for anti-anxiety effects, and both alpha 1 and alpha 2, as well as alpha 5, for anticonvulsant effects. All benzodiazepines combine, to a greater or lesser extent, with all these subtypes and all enhance GABA activity in the brain. As a consequence of the enhancement of GABA's inhibitory activity caused by benzodiazepines, the brain's output of excitatory neurotransmitters, including norepinephrine (noradrenaline), serotonin, acetyl choline and dopamine, is reduced. Such excitatory neurotransmitters are necessary for normal alertness, memory, muscle tone and co-ordination, emotional responses, endocrine gland secretions, heart rate and blood pressure control and a host of other functions, all of which may be impaired by benzodiazepines. Other benzodiazepine receptors, not linked to GABA, are present in the kidney, colon, blood cells and adrenal cortex and these may also be affected by some benzodiazepines. These direct and indirect actions are responsible for the well-known adverse effects of dosage with benzodiazepines. (Aston, 2011)

1.8.2. Introductions to Diazepam

1.8.2.1 Chemical Structure

The chemical structure of diazepam is given below-

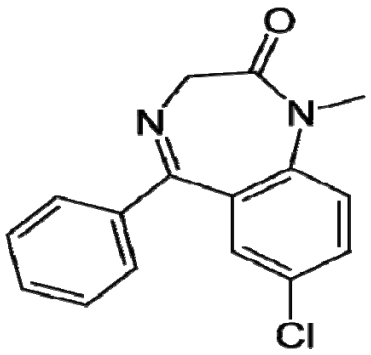

Figure 1.2: Chemical structure of diazepam

1.8.2.2. Indications

It is used for the treatment of-

- Anxiety disorders
- Status epilepticus (as anti convulsant)
- Convulsive disorder (as skeletal muscle relaxant)
- Anesthetic premedication
- Night terrors

1.8.2.3. Diazepam Chemistry

Table 1.2: Overview of Diazepam chemistry (Aston, 2011)

Brand Name	Diazepam, Valium
Chemical name	7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one
Chemical formula	$C_{16}H_{13}ClN_2O$
Molecular formula	284.7445

1.8.2 4. Physical properties

Diazepam occurs as solid white or yellow crystals and has a melting point of 131.5 to 134.5 °C. It is odorless, and has a slightly bitter taste. The British Pharmacopoeia lists diazepam as being

very slightly soluble in water, soluble in alcohol and freely soluble in chloroform. The United States Pharmacopoeia lists diazepam as soluble 1 in 16 ethyl alcohol, 1 in 2 of chloroform, 1 in 39 ether, and practically insoluble in water. The P^H of diazepam is neutral (i.e., P^H = 7). Diazepam has a shelf-life of 5 years for oral tablets and 3 years for IV/IM solution. Diazepam should be stored at room temperature (15–30°C). The solution for parenteral injection should be protected from light and kept from freezing. The oral forms should be stored in air-tight containers and protected from light.

Diazepam can absorb into plastic and so diazepam solution is not stored in plastic bottles or syringes etc. It can absorb into plastic bags and tubing used for intravenous infusions. Absorption appears to be dependent on several factors such as temperature, concentration, flow rates, and tube length. Diazepam should not be administered if a precipitate has formed and will not dissolve. (Online Drug information, 2000)

1.8.2.5. Clinical Pharmacology

Diazepam exerts anxiolytic, sedative, muscle-relaxant, anticonvulsant and amnestic effects. Most of these effects are thought to result from a facilitation of the action of gamma amino butyric acid (GABA), an inhibitory neurotransmitter in the central nervous system.

1.8.2.6. Pharmacokinetics (Tripathi, 2008)

1.8.2.6.1. Absorption

After oral administration >90% of diazepam is absorbed and the average time to achieve peak plasma concentrations is 1 - 1.5 hours with a range of 0.25 to 2.5 hours. When administered with a moderate fat meal absorption is delayed and decreased. In the presence of food mean lag times are approximately 45 minutes as compared with 15 minutes when fasting. There is also an increase in the average time to achieve peak concentrations to about 2.5 hours in the presence of food as compared with 1.25 hours when fasting. This results in an average decrease in Cmax of 20% in addition to a 27% decrease in AUC (range 15% to 50%) when administered with food.

1.8.2.6.2. Distribution

Diazepam and its metabolites are highly bound to plasma proteins (diazepam 98%). Diazepam and its metabolites cross the blood-brain and placental barriers and are also found in breast milk in concentrations approximately one tenth of those in maternal plasma (day's 3 to 9 post-partum). In young healthy males, the volume of distribution at steady-state is 0.8 to 1.0 L/kg. The decline in the plasma concentration-time profile after oral administration is biphasic. The initial distribution phase has a half-life of approximately 1 hour, although it may range up to >3 hours.

1.8.2.6.3. Metabolism

Diazepam is N-demethylated by CYP3A4 and 2C19 to the active metabolite N-desmethyldiazepam, and is hydroxylated by CYP3A4 to the active metabolite temazepam. N-desmethyldiazepam and temazepam are both further metabolized to oxazepam. Temazepam and oxazepam are largely eliminated by glucuronidation.

1.8.2.6.4. Elimination

The initial distribution phase is followed by a prolonged terminal elimination phase (half-life up to 48 hours). The terminal elimination half-life of the active metabolite N-desmethyldiazepam is up to 100 hours. Diazepam and its metabolites are excreted mainly in the urine, predominantly as their glucuronide conjugates. The clearance of diazepam is 20 to 30 mL/min in young adults. Diazepam accumulates upon multiple dosing and there is some evidence that the terminal elimination half-life is slightly prolonged.

1.8.2.7. Pharmacokinetics in Special Populations (Islam, 2007)

1.8.2.7.1. Children

In children of 3 - 8 years old, the mean half-life of diazepam has been reported to be 18 hours.

1.8.2.7.2. Newborns

In full term infants, elimination half-lives around 30 hours have been reported, with a longer average half-life of 54 hours reported in premature infants of 28 - 34 weeks gestational age and 8 - 81 days post-partum. In both premature and full term infants the active metabolite

desmethyldiazepam shows evidence of continued accumulation compared to children. Longer half-lives in infants may be due to incomplete maturation of metabolic pathways.

1.8.2.7.3. Geriatric

Elimination half-life increases by approximately 1 hour for each year of age beginning with a half-life of 20 hours at 20 years of age. This appears to be due to an increase in volume of distribution with age and a decrease in clearance. Consequently, the elderly may have lower peak concentrations, and on multiple dosing higher trough concentrations. It will also take longer to reach steady-state. Conflicting information has been published on changes of plasma protein binding in the elderly. Reported changes in free drug may be due to significant decreases in plasma proteins due to causes other than simply aging.

1.8.2.8. Brands found in Bangladesh

There many companies those have Diazepam in the market. Some of the company's names are listed below.

Table 1.3: Companies in Bangladesh producing Diazepam

Company name	**Brand names**
Opsonin Pharmaceuticals	Easium
Aristopharma	Evalin
Sanofi Aventis	Fizepam
Navana Pharmaceuticals	Rozam
Amico Pharmaceutical Limited	Sedapen

Square Pharmaceuticals	Sedil
Jayson Pharma	Sedulin
Ambee Pharmaceutical Limited	Seduxen

(MIMS, 2007

1.9. Literature Review

Table 1.4: Literature review

Title	Name of the authors	References
Study of effects of post-compression curing on kollidon® SR based floating tablets	SK Jain and V.J Kadam.	Sunil K Jain, V. J (2011) Study of effects of post-compression curing on kollidon® SR based floating tablets *International Journal of Pharmacy and Pharmaceutical Sciences*, 90-93.
Emerging Liquisolid Compact Technology for Solubility Enhancement of BCS Class-II Drug	PG Manogar, BNV Hari *et al.*	P Gowree Manogar, B. V. (2011). Emerging Liquisolid Compact Technology for Solubility Enhancement of BCS Class-II Drug. *Journal of Pharmaceutical Science and Research*, 1604-1611.
An approach for rapid disintegrating tablet: a review	T Khan, S Nazim, S Shaikh, A Shaikh	T Khan *et. al.* (2011) An approach for rapid disintegrating tablet: a review. *International Journal of Pharmaceutical Research & Development*, 170-183.

Aims and objectives

The aims and objectives of this study was to find out whether the two brands of diazepam (Seduxen, Sedil) met the specifications given by British Pharmacopeia (BP) when they were subjected to physical parameter tests such as

- Weight variation,
- Hardness,
- Thickness,
- Friability
- Disintegration

Rationale of the Study

The pharmaceutical industry, as a vital segment of the health care system conducts research, manufacturing and marketing of pharmaceuticals and biological products and medicinal devices used for the diagnosis and treatment of diseases. The poor qualities of medicines are not only a health hazard, but also a waste of money for both government and individual consumers. Therefore, the maintenance of quality with continuous improvement in facilities is very important in pharmaceutical industries. The pursuit of quality being approached through the concept of total quality management (TQM) system which is aimed at prevention of defects rather than detection of defects. The concept of total quality control refers to the process 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 responsibilities for assuring product quality belong primarily to quality assurance personnel, it involves many department and disciplines within a pharmaceutical company. To be effective, it must be supported by a team effort. Quality must be built into a pharmaceutical product during product and process design and it is influenced by the physical plant design, space, ventilation, cleanliness and sanitation during routine production. The assurance of quality of the product depends on more than just proper sampling and adequate testing of various components and finished dosage forms (products). Prime responsibility of maintaining the product quality during production rests with the manufacturing department. Quality assurance personnel must establish control or check points to monitor the quality of the product as it is processed and up to completion of manufacturing. This begins with raw materials and component testing and includes in-process packaging, labeling and finished product testing as well as batch auditing and stability monitoring. Quality assurance policy, therefore, become the most important goal of pharmaceutical industry. The concept of quality assurance and quality control develops and follows standard operating procedures (SOP) directed towards assuring the quality, safety and efficacy. World Health Organization (WHO) has issued a primary or fundamental regulation to pharmaceutical industries entitled good manufacturing practice (GMP) for pharmaceuticals. Based on WHOGMP, many countries have formulated their own requirements for GMP. In USA, as the Food and Drug Administration (FDA) has a mandate that the marketed drug product be safe effective, the drug product must meet certain criteria for quality and purity. The FDA has issued regulatory guidelines known as current good manufacturing practice (cGMP) and good

laboratory practice (GLP) to assure the public that the marketed drug product has been properly manufactured and clinically tested respectively. According to FDA regulations, a drug product that does not meet the GMP requirements is considered unacceptable. Thus, quality is critically important ingredient to organizational success today which can be achieved by total quality management (TQM) in an organization wide approach that focuses on quality as an overarching goal. The basis of this approach is the organizational units should be working harmoniously to satisfy the customer. Since the customer's needs are in constant flux, the organization must strive to continuously improve its system and practices. The TQM perspective views quality as the central purpose of the organization, in contrast to the focus on efficiency advocated by the operational perspective (Mazumder, 2011).

Quality is a very commonly used term but can be described very vaguely. Quality is an unusually slippery concept, easy to visualize and yet difficult to define. It is a matter of feeling and the definition varies from person to person depending on the perspective in which defined. Quality has been defined in different ways by the quality gurus as – conformance to standards or specifications; fitness for use; meeting customer's requirements or expectations; delighting the customer etc. The code defines as 'quality therefore is the totality of features and characteristics of a product/service that bears on its ability to satisfy given needs. If we are selecting a tablet for purchasing, we shall compare the different brands of that particular tablet on the basis of their therapeutic efficacy and side-effects, color and odors. Thus a customer/user of a product makes a comparison of features or attributes of the product and also the absence of deficiency in it, while comparing the quality. Thus the quality, for a product or service, has two aspects, both of which together make for an appropriate definition of the term. The first relates to the features and attributes of the product or service. These ensure that the product or the services meets the needs of the user. The second aspect concerns the absence of deficiencies in the product. The eight dimensions of quality, which is a critically important ingredient to organizational success, are as follows (Das M, 2008).

1. Performance: Product's primary operating characteristics.
2. Features: Supplements to a product's basic functioning characteristics.
3. Reliability: A probability of not malfunctioning during a specified period.
4. Conformance: The degree to which a product's design and operating characteristics meet established standards.

5. Durability: A measure of product life.

6. Serviceability: The speed and ease of repair.

7. Aesthetics: How a product looks, feel, tastes.

8. Perceived quality: As seen by a customer.

Quality indicates the degree of excellence of a product or service. Quality of any Pharmaceutical Product is important for obtaining the therapeutic activity of drug. It is influenced by the inputs and control during manufacture. Validated methods of testing and approved standards of the drug are necessary to evaluate the quality. Qualities of the products are monitored by analyzing the constituents by analytical laboratory (QC lab). So if the quality of the drug is not maintained then the drug will be a substandard drug. As a result the quality control studies which include physical parameters such as weight variation, thickness, hardness, friability, disintegration, dissolution evaluates the physical characteristics and ensure that the quality of drug and thereby impart optimum therapeutic activity. This study explores the physical parameter of two brands of Diazepam (Seduxen, Sedil) which are available in the pharma market of Bangladesh. Diazepam is an anti-anxiety medication in the benzodiazepine family. This drug is widely used for the treatment of anxiety disorders. It is preferred more than the others because it has rapid onset of action, long acting, and rapid absorption from gastrointestinal tract. Also because when its metabolic products are used they are active, they develop less withdrawal symptoms after chronic use, a specific antagonist is available etc. It also decreases nocturnal gastric secretion and prevents stress ulcers. On occasional use it is free of residual effects. It is also used for the treatment of agitation, tremors, delirium, seizures, and hallucinations resulting from alcohol withdrawal. In some neurological diseases it is used for the treatment of seizures and relief of muscle spasms. It is used in chronic insomnia, short- term insomnia with anxiety, frequent nocturnal awakening and night before operation. (Tripathi, 2008)

Diazepam is considered as the first line therapy for the treatment of anxiety by the physicians. Overdose of this drug sometimes may be life threatening on the other hand sub therapeutic dose of this drug would not help to cure anxiety. So, it is very important to determine the physical parameter of its tablet form.

Chapter- 2

Materials and Methods

2.1 Sample Collection

There are approximately seven brands of diazepam tablets in the pharma market of Bangladesh. (MIMS, 2007)Among them Seduxen® and Sedil® were selected for the study.

2.2 Physical Parameter

2.2.1. General Appearance

General Appearance of a tablet, its visual identity and overall elegance is essential for consumer acceptance, for control of lot-to-lot uniformity, and general tablet-to-tablet uniformity. The control of general appearance of a tablet involves the measurement of a number of attributes such as the following-

Size, shape, and thickness: The size, shape, and thickness of a tablet are important to facilitate packaging and to decide which tablet compressing machine to use.

2.2.2. Organoleptic properties

These properties are also important as they include color and odor of the tablets. Many pharmaceutical tablets use color as a vital means of rapid identification and consumer's acceptance. Taste is also important in consumer acceptance of chewable tablets (Anderson, 2009).

Figure 2.1: Diazepam Tablet

2.2.3. Weight Variation test

1) The experiment has been started with 20 tablets and all tablets were weighed at one time by electronic balance (Shimadzu, Japan).

2) Then the composite weight was divided by 20 provided in order to get an average weight.

Average weight, $X= (X_1+X_2 +X_3+\ldots+ Xz)/20$

3) Then each tablet selected at random was weighed individually such as X_1, X_2, $X_{3.....}Xz$ and was observed whether the individual weight are within the range or not.

4) As per BP weight variation test procedure, individual weight was compared to the average weight.

5) The tablets meet the BP test if not more than two tablets are outside the percentage limit and if no tablet differ by more than two times the percentage limit.

The equation for calculation of percentage weight variation is given below:

Percentage weight variation= (average weight - individual weight)/ individual weight x 100%

6) The same procedure was followed for the other brand and the results were documented.None of the tablets deviated from the average weight by more than ±7.5% (British Pharmacopiea, 2005).

2.2.4. Tablet Thickness Test

1. Tablets have been placed between two jaws of Vernier calipers 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
4. The equation for calculation of thickness of tablet is given below:

Total reading = Main scale reading + (Vernier scale reading X Vernier constant)

(Anderson, 2009).

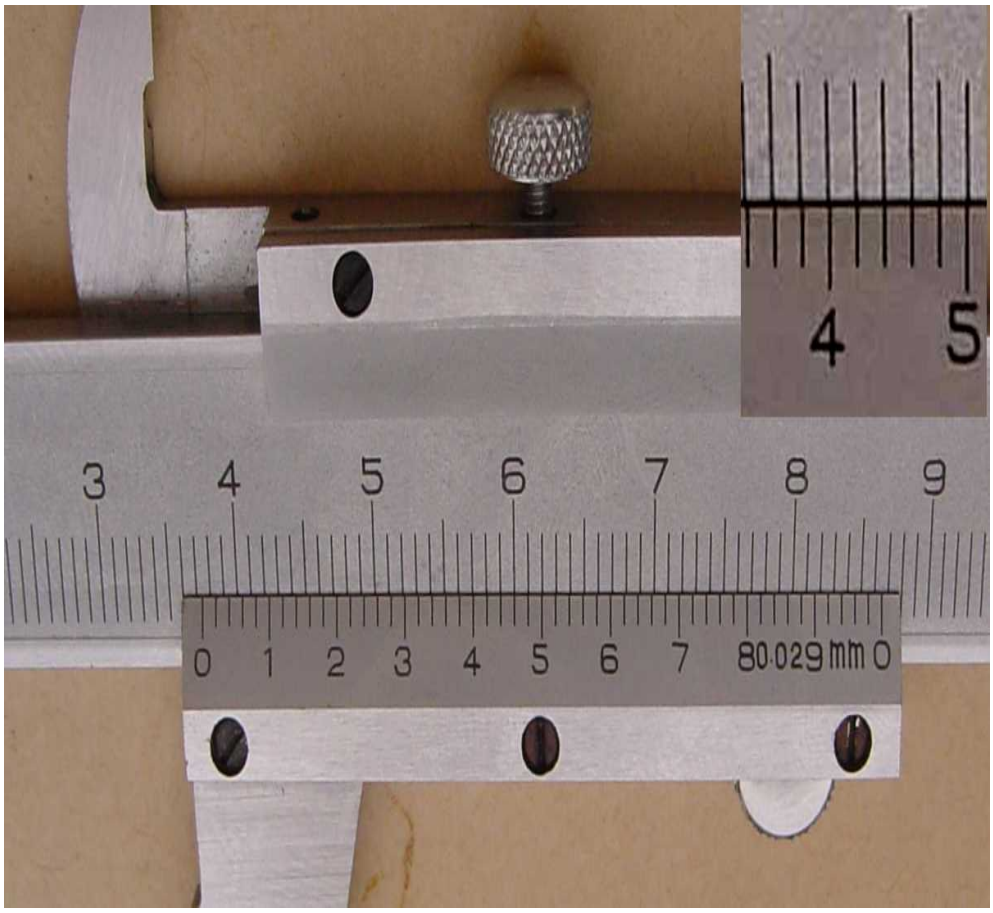

Figure 2.2: Vernier calipers

2.2.5. Hardness Test

- The crushing strength of the tablets was measured using a hardness tester.
- At first 10 tablets were picked randomly from 20 tablets.
- The sliding scale of hardness tester has been set off to zero.
- The tablets have been placed vertically between the two jaws.
- Force has been applied with the screw thread and spring until the tablets has been fractured.
- A force of about 5kg is considered to be the minimum for hardness.
- 1 kg =9.81 Newton (Anderson, 2009)

2.2.6. Friability Test

- The experiment has been started by weighing 10 tablets altogether which is considered as the initial weight, W_1.
- All the tablets has been placed in the drum of friability tester and the equipment was rotated 100 rpm for 4 min (i.e. = 25 rpm for 1 min).
- Then the tablets were taken out, deducted, and reweighed (only the intact ones).This is considered as the final weight,W_2
- Then the percentage loss of weight of the tablets was calculated by using following equation-

Percentage friability= {(Initial weight- Final weight)/ Initial weight} x100

- According to BP the tablets should not lose more than 1% of their total weight.
  So friability (% loss) must be less than or equal to1% but if more we do not reject the tablets as this test is non-official.

2.2.7. Disintegration Test

- The disintegration tester was assembled .An arbitrary figure appeared in the digital display.
- Then the time and temperature was set at prescribed in specification.
- 710 ml of the water was placed in each 1000ml beaker (N.B: The volume of the liquid is such that when the assembly is in the highest position the wire mesh is at least 15mm below the surface of the liquid and when the assembly is in the lowest position the wire mesh is at least 25 mm above the bottom of the beaker and the upper open ends of the tubes remain above the surface of the liquid).

- The temperature of the liquid was maintained at 35-39^{0}C.
- In each of the 6 tubes one tablet was placed.
- The machine was then operated for the prescribed period.
- The entire tablet must disintegrate within the prescribed time. (Anderson, 2009)

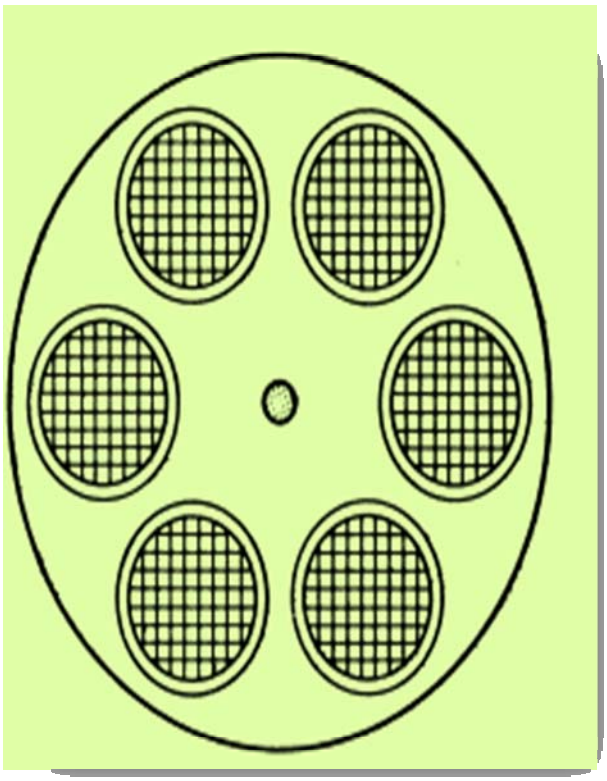

Figure 2.3: Disintegration tester

2.2.7.1. Limit of Disintegration test

Table 1.5: Limit of disintegration test

Source	Medium	Temperature	Time limit
According to B.P	Water	37^{o}C	Not exceed 15min

Chapter- 3

Results and Discussion

3.1. Physical Appearance

Brand: Seduxen

Company: Ambee Pharmaceutical Limited

Color: White

Other: Uncoated, Scored.

Brand: Sedil

Company: Square Pharmaceutical Limited

Color: Cream

Other: Uncoated, Scored.

3.2. Weight Variation Test

Weight variation of tablets is an important in-process control measurement. Its specification is given in different pharmacopeias. The weight of a tablet being compressed is determined by the amount of granulation in the die prior to compression. Therefore, anything that can alter the die filling process can alter the tablet weight and weight variation.

3.2.1. Seduxen

Table 3.1: Result of weight variation test of Seduxen

Tablet Sample	Tablet No	Weight of diazepam	Average	Variation

		tablet (gm)	weight (gm)	%
Diazepam tablet Brand name- Seduxen	1	0.1836	0.18393	0.18%
	2	0.1827		0.67%
	3	0.1872		-1.75%
	4	0.1796		2.41%
	5	0.1865		-1.38%
	6	0.183		0.51%
	7	0.1881		-2.22%
	8	0.1842		-0.15%
	9	0.1827		0.67%
	10	0.1822		0.95%
	11	0.1825		0.78%
	12	0.1848		-0.47%
	13	0.1829		0.56%
	14	0.1828		0.62%
	15	0.1846		-0.36%
	16	0.1844		-0.25%
	17	0.1827		0.67%
	18	0.1849		-0.52%
	19	0.1861		-1.17%
	20	0.1831		0.45%

3.2.2 Sedil

Table 3.2: Result of weight variation test of Sedil

Tablet Sample	Tablet No	Weight of diazepam tablet (gm)	Average weight (gm)	Variation %
	1	0.1741		0.76%

Diazepam tablet Brand name- Sedil	2	0.1754	0.17543	0.02%
	3	0.1778		-1.33%
	4	0.1772		-1.00%
	5	0.1770		-0.89%
	6	0.1767		-0.72%
	7	0.1740		0.82%
	8	0.1741		0.76%
	9	0.1754		0.02%
	10	0.1759		-0.27%
	11	0.1747		0.42%
	12	0.1761		-0.38%
	13	0.1728		1.52%
	14	0.1754		0.02%
	15	0.1746		0.48%
	16	0.1761		-0.38%
	17	0.1752		0.13%
	18	0.1749		0.30%
	19	0.1750		0.25%
	20	0.1762		-0.44%

3.3. Discussion of Weight Variation Test

Table 3.3: Limit of weight variation test according to BP

Average Weight	**Percentage difference**
130 mg or less	±10
More than 130	±7.5
324 mg and above	± 5

(British Pharmacopiea, 2005)

The weight variation of the tablets within the compendial limit is primary indication of the content uniformity. If the weight variation is out of the compendia limit then it is quite impossible to maintain the content uniformity.

The tablets having the average weight of 0.18393 gm. or 183.93 mg. According to the BP, the tablets having the weight more than 130 mg should have weight variation within ± 7.5 (Anderson, 2009). So, we can say that all of the Seduxen tablets having weight variation within the compendial limit.

The tablets having the average weight of 0.17543 gm. or 175.43 mg. According to the BP, the tablets having the weight more than 130 mg should have weight variation within ± 7.5 (Anderson, 2009). From the results shown above, we can say that all of the Sedil tablets having weight variation within the compendial limit.

3.4. Thickness Test

The size and shape of the tablet can be dimensionally described, monitored and controlled. A compressed tablet's shape and dimensions are determined by the tooling during the compression process. The thickness of the tablet is the only dimensional variable related to the process. At a constant compressive load, tablet thickness varies with changes in die fill, with particle size distribution and packing of the particle mix being compressed.

3.4.1 Seduxen

Table 3.4: Result of thickness of Seduxen

Tab No#	Reading of Main cm Scale(cm)	Reading of Vernier scale(mm)	Vernier constant(mm)	Thickness of the tablet(cm)	Percent variation (Average weight-Initial weight)/Initial weight
1	0.25	4	0.05	0.252	0

2	0.25	4	0.05	0.252	0
3	0.25	4	0.05	0.252	0
4	0.25	4	0.05	0.252	0
5	0.25	4	0.05	0.252	0
6	0.25	4	0.05	0.252	0
7	0.25	4	0.05	0.252	0
8	0.25	4	0.05	0.252	0
9	0.25	4	0.05	0.252	0
10	0.25	4	0.05	0.252	0
11	0.25	4	0.05	0.252	0
12	0.25	4	0.05	0.252	0
13	0.25	4	0.05	0.252	0
14	0.25	4	0.05	0.252	0
15	0.25	4	0.05	0.252	0
16	0.25	4	0.05	0.252	0
17	0.25	4	0.05	0.252	0
18	0.25	4	0.05	0.252	0
19	0.25	4	0.05	0.252	0
20	0.25	4	0.05	0.252	0

3.4.2 Sedil

Table 3.5: Result of thickness of Sedil

Tab No#	Reading of Main cm Scale(cm)	Reading of Vernier scale(mm)	Vernier constant(mm)	Thickness of the tablet(cm)	Percent variation (Average weight-Initial weight)/Initial weight

1	0.25	3.5	0.05	0.25175	-0.13
2	0.25	3	0.05	0.2515	0.01
3	0.25	3	0.05	0.2515	0.01
4	0.25	3	0.05	0.2515	0.01
5	0.25	3	0.05	0.2515	0.01
6	0.25	3	0.05	0.2515	0.01
7	0.25	3	0.05	0.2515	0.01
8	0.25	3	0.05	0.2515	0.01
9	0.25	3	0.05	0.2515	0.01
10	0.25	3	0.05	0.2515	0.01
11	0.25	3	0.05	0.2515	0.01
12	0.25	3	0.05	0.2515	0.01
13	0.25	3	0.05	0.2515	0.01
14	0.25	3	0.05	0.2515	0.01
15	0.25	3	0.05	0.2515	0.01
16	0.25	3	0.05	0.2515	0.01
17	0.25	3	0.05	0.2515	0.01
18	0.25	3	0.05	0.2515	0.01
19	0.25	3	0.05	0.2515	0.01
20	0.25	3	0.05	0.2515	0.01

3.5. Discussion of Thickness Test

In general, tablet thickness is controlled within 5 percent of average value.

Thickness is the dimensional variable related to the process. Major variation in thickness can destroy the consumer acceptance of the produce. It also creates problems in packaging of the product. As a result, packaging may not be uniform and packaging equipment is also hampered. A secondary packaging problem with tablets of variable thickness relates to consistent fill levels of the same product container with a given number of dosage units.

So, from the results of the thickness of Seduxen® tablets we can say that the tablets were uniform in their thickness.

From the table mentioned above we can say that 19 of 20 tablets are within range. So, we can say that the Sedil® tablets were uniform in their thickness.

3.6. Hardness Testing

In general, tablets should be sufficiently hard to resist breaking during normal handling, packaging and shipping, and yet soft enough to disintegrate properly after swallowing. Hardness of the tablet is controlled by (or is affected by) the degree of the pressure applied during the compression stage. The Hardness test is therefore performed to measure the degree of force required to break a tablet. The greater the pressure needed to be applied, the harder the tablet. The Hardness testers apply increasing pressure on the tablets until the tablet breaks.

3.6.1. Seduxen

Table 3.6: Hardness variation of Seduxen

Seduxen				
Tab No	Hardness (Kg)	Average (Kg)	Hardness (N)	Average (N)
1	3.15	3.85	30.90	37.769
2	5		49.05	
3	3.6		35.32	
4	4.2		41.20	
5	3		29.43	
6	4.6		45.13	
7	2.65		26	
8	4.25		41.69	

9	4.6		45.13	
10	3.45		33.84	

3.6.2. Sedil

Table 3.7: Hardness variation of Sedil

Sedil				
Tab No	Hardness (Kg)	Average (Kg)	Hardness (N)	Average (N)
1	6.7	6.235	65.73	61.167
2	6.4		62.78	
3	6.75		66.22	
4	5.85		57.39	
5	5.6		54.94	
6	5.85		57.39	
7	5.85		57.39	
8	6.6		64.75	
9	6.15		60.33	
10	6.6		64.75	

3.7. Discussion of Hardness Test

Tablets require a certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packaging and shipping. Monitoring of tablet harness is important for drug products that possess real or potential bioavailability problems or that a sensitive to altered dissolution release profile as function of the compressive force employed.

The hardness of the Seduxen tablet is out of the limit in most of the cases except sample 2. The limit of hardness is 5 kilograms minimum and 8 kilograms maximum.

The hardness of the Sedil tablet is within the limit i.e. 5 kilograms minimum and 8 kilograms maximum.

3.8. Friability Testing

Friability is the tendency of the tablet to crumble. It is important for the tablet to resist attrition. During manufacturing and handling, tablets are subjected to stresses from collision and tablet sliding towards one another and other solid surfaces, which can result in the removal of small fragments and particles from the tablet surface. Friability test is performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting.

Table 3.8: Percentage friability of diazepam

Tab sample	Initial Weight of 20 tablets (gm)	Final weight of 10 tablet (gm)	% Friability
Seduxen® Batch no# 0118	3.7031	3.6820	0.570%
Sedil® Batch no# 0060115	3.5053	3.4947	0.302%

3.9. Discussion of Friability Test

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.

Friability is the tendency of the tablet to crumble. It is important for the tablet to resist attrition. During manufacturing and handling, tablets are subjected to stresses from collision and tablet sliding towards one another and other solid surfaces, which can result in the removal of small fragments and particles from the tablet surface. Friability test is performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting 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 (Seitz, J. A., 1965).

For Seduxen Tablets % friability was 0.570% which is in the acceptable limit.

For Sedil Tablets % friability was 0.302% which is in the acceptable limit. So, the friability in both cases was in acceptable limit.

3.10. Disintegration Test

For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration. The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 mesh screen. Generally, the test is useful as a quality assurance tool for conventional dosage forms.

Table No 3.9: Disintegration time of diazepam tablet

Tab No	Seduxen®		Sedil® Batch	
1	49 sec		3min 20 sec	
2	45 sec		3min	
3	55 sec		3 min 50 sec	
4	42 sec	46.83 sec	3 min	3 min 18 sec
5	47 sec		3min 2 sec	
6	43 sec		3 min 15 sec	

3.11. Discussion of Disintegration Test

The rate of drug absorption as well as the therapeutic efficacy of the drug is dependent upon the disintegration time. If the disintegration time is not perfect we cannot say that effectiveness of the drug is good.

The disintegration time of the Seduxen® Tablets was found to be 46.83 sec which is within compendial limit.

The disintegration time of the Seduxen® Tablets was found to be 3 min 18 sec

CHAPTER-4

CONCLUSION

4. Conclusion

In this study it was observed that in most case the two brands have passed. For example, in weight variation test all the tablets have passed. All the two brands have passed hardness and friability tests. There was no significant variation into the thickness of tablets. Disintegration time of the tablets was under acceptable range. Various limitations were faced throughout the whole of the study process, such as, due to some technical problems dissolution test and potency test were not performed. If those studies were performed then we could say more precisely about the physical parameters of the drug. In spite of all the limitations faced, it was possible to undertake the overall experimental procedure quite smoothly. As all drugs substances are lifesaving so both overdose and subtherapeutic dose of the drug is harmful for the patients. As a result, more care should be given by the Pharmaceutical Company during the production and marketing of medicine because pharmaceutical companies are dealing with the life of human.

Chapter-5

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