Performance Evaluation of Losartan Potassium Tablets of five Different Pharmaceutical Companies in Bangladesh

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DISSERTATION

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Certification

This is to certify that the present project work entitled "Performance Evaluation of Losartan Potassium Tablets from five Different Pharmaceutical Companies in Bangladesh" has been carried out by Mst. Mousume Sultana [ID: 111-29-243] under our direct supervision at the Department of Pharmacy, Daffodil international University, Dhaka, Bangladesh. We recommend that the prepared project work can be accepted in partial fulfillment of the requirements for the degree of **Bachelor of Pharmacy**.

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May, 2015   *The Author*

ABSTRACT

Losartan potassium belongs to a group of medicines known as angiotensin-II receptor antagonists. Losartan potassium is widely produced and marked drug by many Pharmaceutical companies in Bangladesh. The performance evaluation (Namely, some physical parameters, potency, and disintegration and dissolution profile) of Losartan potassium tablets from five different pharmaceutical companies was carried out in order to find out whether they really complied the required standards. As a part of evaluation of physical parameters, the size and shape, specially, thickness of representative samples of each pharmaceutical company was evaluated and they were found to be uniform the tablets from all the companies successfully passed the friability test. Out of the tablets of five evaluated pharmaceutical companies, the potency of Losartan potassium tablets from five companies was found to be satisfactory. The disintegration time of tablets from all the companies were found to be satisfactory. The dissolution profile of the representative sample was determined. The profiles for all the companies were satisfactory. The best profile was showed 90.52% at 30 minutes and 100% at 45.

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INTRODUCTION

INTRODUCTION

An Overview

Hypertension (HTN) is an increasingly important medical and public health problem. In Bangladesh, approximately 20% of adult and 40-65% of elderly people suffer from HTN. High incidence of metabolic syndrome, and lifestyle-related factors like obesity, high salt intake, and less physical activity may play important role in the pathophysiology of HTN.

The association of angiotensin-converting enzyme (ACE) gene polymorphism and low birth weight with blood pressure has been studied inadequately. Studies have found relationship between mass arsenic poisoning and HTN. Hypovitaminosis D presumably plays role in the aetiopathogenesis of HTN in Bangladeshi population. South Asians appear to respond to antihypertensive therapy in a similar manner to the Whites. The latest National Institute for Health and Clinical Excellence guideline advocates a calcium-channel blocker as step 1 antihypertensive treatment to people aged > 55 years and an ACE inhibitor or a low-cost angiotensin-II receptor blocker for the younger people. Angiotensin II receptor antagonists, also known as angiotensin receptor blockers (ARBs), AT_1-receptor antagonists or sartans, are a group of pharmaceuticals that modulate the renin-angiotensin-aldosterone system. Their main uses are in the treatment of hypertension (high blood pressure), diabetic nephropathy (kidney damage due to diabetes) and congestive heart failure.

The follwing drugs are Angiotensin II receptor antagonists

- Candesartan
- Eprosartan
- Irbesartan
- Losartan
- Olmesartan
- Telmisartan
- Valsartan

Tablet Formulation

A tablet is a pharmaceutical dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose. The excipients can include diluents, binders or granulating agents, glidants (flow aids) and lubricants to ensure efficient tabletting; disintegrants to promote tablet break-up in the digestive tract; sweeteners or flavours to enhance taste; and pigments to make the tablets visually attractive. A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance.

The compressed tablet is the most popular dosage form in use today. About two-thirds of all prescriptions are dispensed as solid dosage forms, and half of these are compressed tablets. A tablet can be formulated to deliver an accurate dosage to a specific site; it is usually taken orally, but can be administered sublingually, buccally, rectally or intravaginally. The tablet is just one of the many forms that an oral drug can take such as syrups, elixirs, suspensions, and emulsions. "Welcome" in Britain first use the term „tablet‟ to describe the compressed dosage rm.

Classification of Tablets

Mainly tablets are classified into two classes

      A. Compressed tablets

      B. Molded tablets

Compressed tablets

The compressed tablets usually prepared on large scale production methods, whereas the molded tablets are prepared extemporaneously on small scale . This two main type of tablet are further classified as follows:

Dispersible or effervescent tablets

These tablets are designed to be added to water just prior to swallowing. They are frequently quite large and can contain large amounts of sodium. The size prevents patients from taking many of them, which is helpful for soluble paracetamol products for instance however the sodium content can cause problems in patients where sodium intake is restricted.

Sub-lingual tablets

These tablets are designed to be dissolved under the tongue, are rapidly absorbed through the tongue and therefore work quickly. This is why some tablets for the treatment of angina pain and others for general pain are formulated in this manner. The disadvantages are that they require sufficient saliva production and due to quick absorption are more likely to cause side effects and are more quickly removed from the body.

Buccal tablets

Buccal tablets are intended to be placed on the gum or in the cheek to allow the drug absorbed. Because the medicine can be held for a longer period of time on the gum, medicines which need to be released at a slower rate than sub-lingual tablets can be given via this route. This route is used for anti-nausea drugs and nicotine replacement gums. Anti-nausea medicines are particularly suitable for buccal administration as the nausea itself can cause swallowed tablets to be vomited and therefore rendered ineffective.

Melts

Melt tablets are placed on the tongue and are designed to dissolve directly in the mouth's saliva. The contents are then swallowed with saliva and consequently water does not have to be administered with these medicines. This is particularly useful in patients who are at risk of aspiration and therefore unable to swallow tablets with water concurrently.

Oro-dispersible tablets

Oro-dispersible tablets are similar to melts and are designed to disperse in the mouth and to be washed down with saliva. As with sub-lingual, buccal and melts, oro-dispersible products require an adequate amount of saliva production. Some oro-dispersible tablets consist of coated granules and therefore it is <u>not</u> appropriate to crush the oro-dispersible product prior to dispersion.

Molded tablets
1. Hypodermic tablets
2. Dispensing tablets

Ideal properties of a Tablet (Maynak Sharma Dec23 2011)

Shape and Size of Tablets:

Thickness of the tablets should be controlled within ± 5% variation with a standard value. It may change with die-wall, particle size, distribution, packing of particles and compressive load. The crown thickness of tablets may be measured by micrometer (sliding caliper scale). This test is necessary for packaging of tablets as well as drug content uniformly.

1.Organoleptic properties:

Some tablets may contain organoleptic substances such as flavoring agent, coloring agent and sweetener. Color uniformity of the tablet can be evaluated by reflectance spectrophotometry, tristimulus colorimetry or microref- lectance photometery.

1. Hardness:

Suitable hardness is necessary for handling during manufacturing, packaging and shipping. Hardness of the tablets can be measured by Monsanto tester, Strong-cobb-tester, Pfizer tester and Erweka tester.

2. Friability:

Friability is another measurement of tablet strength as tablet hardness is not an absolute indicator of strength. Roche friabilator is used as laboratory equipment for the determination of friability. It has a plastic chamber that revolves at 25 rpm, tablet drops a distance of six inches with each revolution and operated for 100 revolutions. Compressed should not lose more than 1.0% of their weight.

3. Weight variations:

It is measured to ensure that tablet contains the proper amount of drug and is a satisfactory test for determination of content uniformity of tablets. Usually ten tablets are taken for this test.

4. Disintegration:

Breaking of tablets into smaller particles or granules is known as disintegration and time taken for breaking of tablets in a suitable medium is called disintegration time (DT). IP apparatus consists of 6 glass tubes each 3 inches long, open at top and has 10 mesh screens at the bottom end of basket rack.One tablet is placed in each tube and placed in a one litre beaker of water, simulated gastric fluid or simulated intestinal fluid at $37 \pm 2°C$. It moves up and down through a distance of 5 to 6 cm at 28 to 32 cpm. Uncoated tablets have disintegration times as low as 5 minutes. Majority of tablets have DT of 30 minutes. Disintegration time of enteric coated tablet is one hour in simulated gastric fluid and two hours in simulated intestinal fluid.

5. Dissolution:

The rate of absorption depends on the dissolution of the product. It is directly proportional to the bioavailability of the products. For dissolution study two types of apparatus are used, basket assembly and paddle assembly. It consists of a hemispherical flask of 1000 ml capacity, temperature is maintained at $37 \pm 0.5°C$, t_{90}% obtained within 30 min. is satisfactory.

6. Drug content:

Drug uniformity in tablet is determined by assay. It is calculated on batch to batch or lot to lot basis. It is estimated by the titration, spectrophotometer and HPLC.

Advantages of tablet formulation

1. Cheapest oral dosage form, easy to handle, use and carry out with attractive and elegant appearance.

2. Cheap, easy to swallow and production does not require and additional processing steps.3. Provide protection of medicaments from atmospheric conditions like air, moisture and light etc.

4. Provide prolonged stability to medicaments.

5. Low manufacturing cost as compare to other solid dosage forms and large scale production is possible.

6. Administration of minute dose of drug in accurate amount.

7. Unpleasant taste can be masked by sugar coating.

8. Easy to divide into halves and quarters whenever fraction dose is required.

9. Formulate as a special release products such as enteric or delayed release products.

10. Packing and production is cheap and does not require more space for storage

Quality and Its Criteria (U.S pharmacopial convention)

Medicine quality is critical to patient health: poor quality can lead to treatment failure, adverse effects, prolonged illness, the development of drug resistance, distrust in the healthcare system, waste of limited financial resources, and death. Poor quality medicines fail to meet official standards for strength, quality, purity, packaging, and/or labeling. They are generally classified as

1) substandard (legally registered innovator or generic products that have been improperly produced, handled, or stored)

2) Counterfeit (products whose identity, strength, or source has been deliberately mislabeled).

To help developing countries strengthen QA and QC systems so that they can better monitor drug supply quality and prevent substandard and counterfeit medicines from reaching patients, PQM provides technical assistance to medicine regulatory authorities, national quality control laboratories, and local pharmaceutical manufacturers.According to the WHO World Health Organization), the manufacturers must assume responsibility for the quality of the drugs he produces. A medicinal product must satisfy certain pharmacopoeial standards to claim it to be a quality drug. The principal criteria for a quality drug product are shown in figure-1.1.
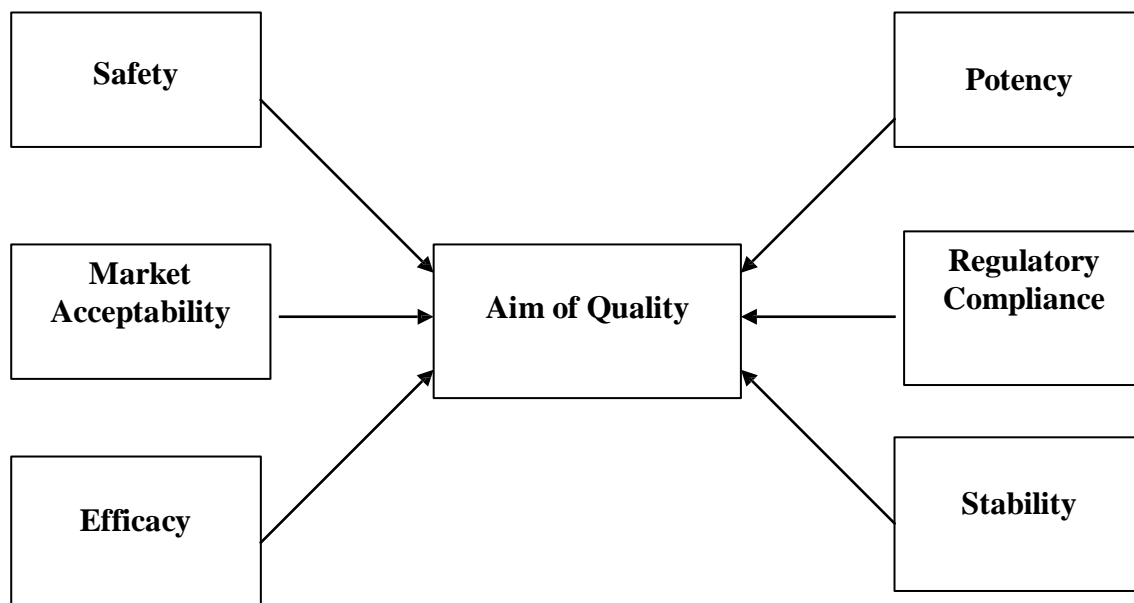
Fig.1.1: The aim for Quality.

(1) Safety

Safety of medicine implies that the drug substance must meet certain safety requirements relating to its intended use. No drug, particularly prescription drugs, can be called absolutely safe. In the real life situation the drug-related risks (side effects) need to be compared with the risk associated with the benefit to the patient to evaluate the risk-benefit ratio. It is this ratio which one must use to judge the drug's therapeutic value. (Nawaz, 1990)

Apart from the serious side-effect which is inherent in the drug itself, such as teratogenicity, a medicinal product can become unsafe due to many other factors such as cross-contamination, contamination with pathogenic organisms, very high or low potency, wrong labeling, inadequate packaging and storage conditions. So a careful and rational evaluation should be needed. (Nawaz, 1990)

(2) Potency

 The product must contain adequate drug substance in its active form. Harmful degradation products must be absent or below defined limits (Nawaz, 1990)

(3) Efficacy

The effectiveness of a drug indicates its biological activity in animals or in human. The active substance should be adequately released from its dosage form. ((Nawaz & Polderman, 1990)

(4) Stability

Pharmaceutical preparations may exhibit chemical or physical instability. This may result in:

(a) educed activity of the drug.

(b) Formation of toxic degradation products and

(c) The drug may become inelegant and thus unacceptable.

The drug substance itself and its dosage form (formation) must be sufficiently stable to retain its minimum potency requirements satisfying the national or international pharmacopoeial monograph. In most western countries now-a-days ±5%, beyond the labeled potency is considered acceptable, unless the manufacturer has sound arguments for a greater variation. The finished product must be marketed in suitable packs to ensure its stability for use up to the expiry date when stored under specified condition (Nawaz, 1990)

(5) Acceptability

Acceptability refers to the consumer or market acceptability. This relates to the organoleptic properties such as its taste, odor, color, mode of use and qualities which are not directly noticeable to patients, e.g., too high a level of microbial contamination. A medicine should have pharmaceutical elegance for market acceptability. ((Nawaz & Polderman, 1990)

(6) Regulatory compliance

Each unit pack of the product must be clearly and correctly labeled. Moreover, the product must fulfill the regulatory requirements. Various information in support of the product such as potency claim, indications, side–effects, precautions, storage conditions, self-life, manufacturing date, batch number, instructions for use etc. must comply with the drug legislation. (Nawaz, 1990)

1.4 Evaluation of Tablets

Non-official tests:

1- *Tablet Hardness:* expressed usually as the load (force) required to crush a tablet placed between two jaws forcing each other, one of which moves towards the other. To measure the force needed for crushing a tablet, different devices available, Monsanto tester, the strong Cobb tester, the Pfizer tester, the Erweka tester and the Schliennger

tester. Hardness value differ with the instrument used allowed values 8-12 Kp. Tablet hardness usually affects drug dissolution and release, and it may affect bioavailability.

2- Tablet Friability: Evaluate the ability of tablets to withstand abrasion, packaging, handling and shipping. It can also be defined as the phenomenon whereby tablet surfaces are damaged and /or show evidence of lamination or breakage when subjected to mechanical shock or attrition.20 tablets are selected randomly, and weighed then placed in the friabilator champer, the tablets are subjected to combined effect of abrasion and shocks by utilizing a plastic chamber that revolve at a speed of 25 rpm drop from height of 6 inch height per revolution for 4 minutes. The 20 tablets are then collected cleaned with a brush and weighed. Then calculate the % of weight loss, %Loss = 100*(weight before − weight after)/weight before

Acceptable if 0.5- 1% of the tablet weight was lost.

Official tests:

1- Weight variation: Take 20 tablets and weigh them individually, then calculate average tablet weight,

Table 1.1: Percentage deviation for each tablet:

Average tablet weight	Percentage deviation
130 mg or less	10
131-324 mg	7.5
325 mg	5

Accepted tablet:

Not more than two tablets   are outside the percentage limit and no tablet differ by more than two times the percentage limit according to the above table.

Suspected tablet:

Not more than six tablets are outside the percentage limit and no tablet differ by more than two times the percentage limit according to the table.

Rejected tablets:

One tablet differs by more than two times the percentage limit according to the table.

More than six tablets are outside the percentage limit.

2- Tablet Disintegration: It can be defined as the break down of tablets into smaller particles as it contacts with water.

For uncoated tablets and plain coated tablets:

Place 1 tablet in each of the six tubes of the basket and operate the apparatus, using water maintained at $37\text{-}^{+}2\ ^{0}C$ as the immersion fluid unless otherwise specified in the individual monograph. At the end of time specified in the monograph, all the 6 tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets, not less than 16 of 18 disintegrate completely.

3- Content uniformity of the dosage units

a. **Weight determination:** Done on uncoated tablet and film coated tablet, select not fewer than 30 units, take 10 units, weight accurately 10 tablets individually. Calculate the average tablet weight. Crush each tablet and apply the assay procedure in each monograph, calculate the content of active ingredient. Calculate the average content of active ingredient, assuming homogeneous distribution of the active ingredient.

b. **Content uniformity:** select not fewer than 30 units; assay 10 units individually as directed in the assay in the individual monograph. Where a special procedure for content uniformity is specified in the test for uniformity of dosage units in the individual monograph, assay separate A, assay and calculate the weight of active ingredient equivalent to one average dosage unit. P, using the special procedure for content uniformity in the monograph, calculates the weight of active ingredient equivalent to one average dosage obtained by the special procedure. If 100 *(A-P/A) is greater than 10, the use of correction factor is not valid. Calculate F value, F=A/P, a valid correction if F value is between 1.030-1.100 or between 0.900-0.970, calculate the weight of active ingredient in each dosage unit by multiplying each of the weights found using the special procedure by F.

Calculation of relative standard deviation:

s = sample standard deviation, $s = (\Sigma(x_i- X)^2)/(n-1)$

n= number of unit tested, $x_i=$ individual values of the units tested, X= mean of the values obtained from the units tested.

RSD= relative standard deviation (the sample standard deviation expressed as percentage of the mean)

RSD $=100*s/X$

1.4.1 General Appearance

1. General Appearance: The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or absence of odor, taste etc.

2. Size & Shape: It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micrometer or by other device. Tablet thickness should be controlled within a ± 5 % variation of standard value. Krupanidhi College of Pharmacy (Q.A)

Thickness

The thickness of tablets is critical to their therapeutic effectiveness. All tablets, where the active ingredient comprises a major part of the tablet are required to meet a weight variation test. It is assumed that providing the weight of the tablet is kept within defined limits that the amount of active drug available to the user will remain the same. The weight of a compressed tablet is dependent on three factors:density, diameter and thickness. In theory, the density of the powder blend and the diameter of the resultant tablet (which is dictated by the die wall) should remain unchanged. It follows that by monitoring the thickness of the tablets at regular intervals, potential problems relating to tablet weight and hence content uniformity can be detected at an early stage. The thickness of tablet can be dimensionally described, monitored, and controlled.

Procedure-
  A. The crown thickness of individual tablet may be measured with a micrometer, which permits accurate measurements and provide information on the variation between tablets.
  B. Other technique involves placing five or ten tablets in a holding tray where their total crown thickness may be measured with a sliding caliper scale.

The latter Method is much more rapid than measurement with a micrometer (method A).

Problems of un-uniform size and shape-

Tablet thickness should be controlled within a ± 5% variation of a standard value. (Gilbert & Neil, 1986)

- Variation in tablet thickness within a particular lot or between manufacturer's lots should not be apparent to the unaided eye for consumer acceptance of the product.
- Thickness must be controlled to facilitate packaging. Difficulties may be encountered in the use of unit dose and other types of packaging equipment if the volume of the material being packaged is not consistent. (Histand, 1977)
- A secondary packaging problem with variable thickness related to consistent fill levels of the same product container with a given number of dosage unit.

Diameter

The diameter size and shape of tablets depends on the die and punches selected for marking the tablets. The diameter of a tablet is determined with the help of micrometer capillaries or vernier scale. (Gupta)

Organoleptic properties:

Color– Many pharmaceutical tablets use color as a vital means of rapid identification and consumer acceptance. The color of a product must be uniform within a single tablet. (Hamed, 1985)

Odor- The presence of an odor in a batch of tablets could indicate a stability problem, such as the characteristic odor of acetic acid in degrading aspirin tablets; however the presence of an odor could be characteristics of the drugs, added ingredients, or the dosage form.

Taste– Taste is important in consumer acceptance of chewable tablets. Many companies utilize taste panels to judge the performance of different flavors and flavor levels in the development of a product

Hardness

Tablet hardness testing, is a laboratory technique used by the pharmaceutical industry to test the breaking point and structural integrity of a tablet under conditions of storage, transportation, and handling before usage The breaking point of a tablet is based on its shape.

It is similar to friability testing, but they are not the same thing. Tablet hardness testers first appeared in the 1930s.In the 1950s, the Strong-Cobb tester was introduced. It was patented by Robert Albrecht on July 21, 1953.and used an air pump. The tablet breaking force was

based on arbitrary units referred to as Strong-Cobbs.The new one gave readings that were inconsistent to those given by the older testers. Later, electro-mechanical testing machines were introduced. They often include mechanisms like motor drives, and the ability to send measurements to a computer or printer.

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. (Gilbert). Certain tablet such as lozenges and buccal tablets that are intended to dissolve slowly are intentionally made hard; other tablets, such as compressed tablets that are intended to dissolve rapidly are made soft. In general tablet should be sufficiently hard to resist breaking during packaging, shipment, and normal handling and yet soft enough to dissolve or disintegrate properly after administration or to be broken between the figures when a part of a tablet is to be taken. (Lachman *et al.*1985)

The suitability of a tablet in regard to mechanical stability during packaging and shipment can usually be predicted on the basis of hardness. Most manufacturers consider a tablet hardness is minimum 4 kg of uncoated tablets, though some chewable tablets may be somewhat softer. (Ansel *et al.*)

Weight Variation

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 measured to ensure that a tablet contains the proper amount of drug. (Lachman, 1986)

Tablet weight variation in compressing process is not a trivial thing. Moreover, when affecting the uniformity of dosage units.

Tablet weight variation may be caused by:

- Distribution at Hoover caused the vibration. So, small granule pushed, large granules will come out first, because there is a process of consolidation. Therefore, needs to be put a uniform granule size. So, before the compressing process begins better evaluation the particle size distribution first.
- The flow of granules is not good / not free-flowing granules particle distribution is not normal, because the specific gravity is different, so that the flow is bad.
- Lubricant or glidant less or not mixed evenly.

Disintegration

Definition- The process by which a tablet is broken down into smaller particles or granules is known as disintegration. (Lachman, 1986)

Importance of disintegration of drugs from tablets- Disintegration is a process, which causes the tablets to rupture rapidly so as to increase the surface area of the tablet fragments and promote rapid release of the drug.

Wagner proposed a scheme, which related tablet breakup to drug dissolution and absorption is shown in the following figure:

Increase in effective surface area of drug
exposed to gastrointestinal fluids

Intact tablet → Disintegration → Granules → De-aggregation → primary drug particles

Low rate of drug dissolution — Moderate rate of drug dissolution — Relatively rapid rate of drug dissolution

Drug in solution in gastrointestinal fluids
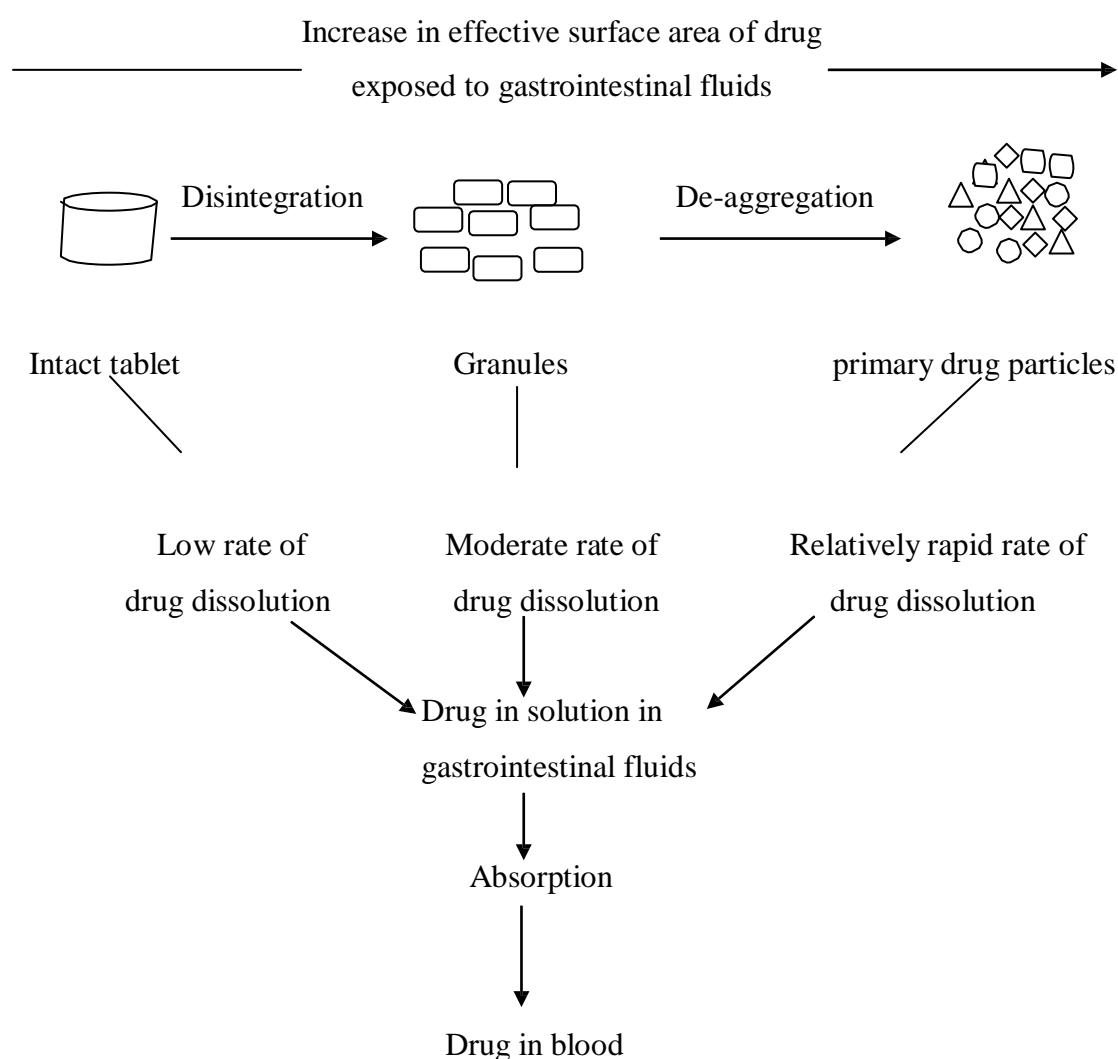
Absorption

Drug in blood

Figure 1.1: Diagrammatic representation of the disintegration and steps prior to absorption of a soluble drug from tablet. (Wagner,1969)

Factors affecting disintegration: Disintegrants used to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet. However, there are several factors affecting disintegration process in tablet, they are:

1. Effect of Fillers
2. Effect of Binder
3. Effect of Lubricants
4. Effect of Surfactant

Effect of fillers

The solubility and compression characteristics of fillers affect the rate and mechanism of disintegration of tablet. If soluble fillers are used then it may cause increase in viscosity of the penetrating fluid which tends to reduce effectiveness of strongly swelling disintegrating agents and as they are water soluble, they are likely to dissolve rather than disintegrate. Insoluble diluents produce rapid disintegration with adequate amount of disintegrants.

Effect of binder

As binding capacity of the binder increases, disintegrating time of tablet increases and this counteract the rapid disintegration. Even the concentration of the binder can also affect the disintegration time of tablet.

Effect of lubricants

Mostly lubricants are hydrophobic and they are usually used in smaller size than any other ingredient in the tablet formulation. When the mixture is mixed, lubricant particles may adhere to the surface of the other particles. This hydrophobic coating inhibits the wetting and consequently tablet disintegration.

Lubricant has a strong negative effect on the water uptake if tablet contains no disintegrants or even high concentration of slightly swelling disintegrants. The disintegration time is hardly affected if there is some strongly swelling disintegrants are present in the tablet. There is one exception, sodium starch glycolate effect remains unaffected in the presence of hydrophobic lubricant.

Effect of surfactants

Surfactant	Remarks
Sodium lauryl sulfate	Good-various drugs Poor - various drugs
Polysorbate 20	Good
Polysorbate 40 & 60	Poor
Polysorbate 80	Good
Tweens	Poor
Poly ethylene glycol	Poor

(Good – decrease in disintegration time, Poor – increase in disintegration time) Sodium lauryl sulphate increased absorption of water by starch or had a variable effect on water penetration in tablets. Surfactants are only effective within certain concentration ranges. Surfactants are recommended to decrease the hydrophobicity of the drugs because the more hydrophobic the tablet the greater the disintegration time.

Disintegrants: A good disintegrants will quickly break up a tablet into primary particles and ensures that the drug molecules are exposed for dissolution. Examples include corn and potato starches, sodium starch glycolate, cellulose derivatives such as sodium carboximethyl cellulose, polyvinyl pyrolidone etc.

1. **Manufacturing process**: The manufacturing processes have great influence on the disintegration behavior of tablets. The total amount of disintegrants is added in two portions. The major part is incorporated to the powders before granulation and the rest part is mixed with the dried granules along with lubricants. Disintegrants added in this manner serves two purposes, those added after granulation breaks the tablet apart into granules and the portion added before granulation breaks the granules into fine particles.(Gupta)

2. **Binders and lubricants**: The concentration of binder and lubricant used in the formulation has effect on disintegration time. At lower concentration of lubricant and binder the disintegration time is lower than that at higher concentration.

Dissolution

Definition- Dissolution can be defined as the processes by which a drug particle dissolves and it is most important for solid dosage form for absorption. (Lachman *et al*) In the pharmaceutical industry, drug dissolution testing is routinely used to provide critical in vitro drug release information for both quality control purposes, i.e., to assess batch-to-batch consistency of solid oral dosage forms such as tablets, and drug development, i.e., to predict in vivo drug release profiles.

Theory- The dissolution phenomenon of drugs can be described by the Noyes and no chemical reaction, the equation can be written as-

$$\frac{dm}{dt} = \frac{DA}{h}(C_s - C) \text{-----------------------------} (1)$$

$\frac{dm}{dt}$ = the rate of dissolution of the drug particles.

D= the dissolution co-efficient of the drug in solution in GI fluid.

A= effective surface area of t he drug particles.

h= thickness of the diffusion layer around each particle.

C_S= the saturation of the drug in the diffusion layer.

C= the concentration of drug in solution of the GI fluids.

C_S-C= the concentration gradient.

Several dissolution apparatuses exist. In United States Pharmacopeia(USP) General

Chapter <711> Dissolution, there are four dissolution apparatuses standardized and specified.They are:

• USP Dissolution Apparatus 1 - Basket (37°C)
• USP Dissolution Apparatus 2 - Paddle (37°C)
• USP Dissolution Apparatus 3 - Reciprocating Cylinder (37°C)
• USP Dissolution Apparatus 4 - Flow-Through Cell (37°C)
USP Dissolution Apparatus 2 is the most widely used apparatus among these four

Importance of dissolution of drugs from tablets- In order for a drug to be absorbed, it must be dissolved in the fluid at the absorption site. For instance, a drug administered orally in tablet or capsule form cannot be absorbed until the drug particles are dissolved by the fluids

at some point within the GIT (Safiullah & Roy). That is why; dissolution is a process, which can affect the absorption of the drug particles and thus the bioavailability and also pharmacological response of the drug. From the Wagner's schematic representation one can easily understand how absorption is greatly influenced by dissolution.

In in-vitro testing procedures, dissolution is the only test that can more or less indirectly correlate the in vivo bioavailability (United States Pharmacopoeia, 1980) Other than bioavailability two objectives can be fulfilled through dissolution testing which are to show (Tripathi, 1999)-

- ❖ That the release of the drug from the tablet is as close as possible to 100% and
- ❖ That the rate of drug release is uniform from batch-to-batch and is same as the release rate from those batches proven to be bioavailable and clinically effective.

For many years, it was assumed that disintegration test is intimately related to dissolution and to predict the release rate of active ingredient from solid dosage form, only disintegration test was performed (Shahidi, 2004) but now-a-days, it has been apparent that the disintegration test is not itself a wholly adequate criterion for predicting the dissolution characteristics of tablets.

Factors affecting dissolution- The amorphous form of novobiocin has a greater solubility and higher dissolution rate than the crystalline form (Poole *et al*, 1967)

The following (influence) the dissolution of a substance:

1. Temperature.
2. Particular size of solute
3. Agitation (concentration of the solvent)
4. Solvent selection (properties of solvent)

EX: - water of oily.

Temperature: - In most cases of dissolution of sold (solute) in a liquid involves the absorption of heat. If the temperature is increased then the dissolution will be more & if the temperature is decreased than the dissolution will be less. So, dissolution depends on the temperature.

Particle Size: - The dissolution rate of (d) depends on its particle size. small particle size, dissolution will be more and large particle size , dissolution will be less. The absorption depends upon the dissolution rate of (d). So determination of dissolution rate of any solute (d) is very important.

Agitation: - Dissolution also depends on the concentration of the solvent. If the solvent is more concentrated dissolution will be less. If the solvent is less concentrated dissolution will be more.

Solvent selection: - Dissolution also depends on the concentration of the solvent. In water dissolution rate will be more than oily solvent.

Potency

In the field of pharmacology, potency is a measure of drug activity expressed in terms of the amount required to produce an effect of given intensity. A highly potent drug (e.g., morphine, alprazolam, risperidone) evokes a larger response at low concentrations, while a drug of lower potency (ibuprofen, acetylsalicylic acid) evokes a small response at low concentrations. It is proportional to affinity and efficacy. For highly potent, low dose drugs such as digitoxin, this range is usually not less than 90% and not more than 110% of the labeled amount. For most other larger dose drugs in tablet form the official potency range that is permitted is not less than 95% and not more than 105% of the labeled amount (Tripathi, 1999)

1.5 Information about Losartan potassium Under Analysis

Losartan is an angiotensin II receptor antagonist drug used mainly to treat high blood pressure (hypertension). It was the first angiotensin II antagonist to be marketed. Losartan potassium is marketed by Merck & Co. In. under the trade name Cozaar, and is available in generic form. Losartan has been found to downregulate the expression of transforming growth factor beta (TGF-β) types I and II receptors in the kidney of diabetic rats, which may partially account for its nephroprotective effects. Effects on TGF-β expression may also account for its potential efficacy in Marfan syndrome and Duchenne muscular dystrophy– losartan has been shown to prevent aortic aneurysm and certain pulmonary complications in a mouse model of the disease.

Losartan is being studied for use in the treatment of the 20% of breast cancer tumors positive for AGTR1. The University of Michigan Comprehensive Cancer Center announced in 2009 the result of an animal study which found losartan to "block" - reverse neoplastic changes – caused by this gene. In 2003, losartan was studied on 32 subjects for its use in the treatment of aortic enlargement in Marfan and related syndromes such as Loeys-Dietz syndrome. Losartan is being researched as a possible protection against loss of damaged or old muscle. Losartan has recently been found to be a cognitive enhancer. It improved memory in people with normal blood pressure under standard conditions, as well as during memory-impaired tasks (coadministration of scopolamine). Losartan has been found to prevent smoking-related lung damage in mice, and trials are underway for the potential treatment of smoking-related chronic obstructive pulmonary disease, the long-term consequence of smoking and for which, until now, no potential treatments to prevent or repair the resulting lung damage are known.

Action and use

Angiotensin II receptor antagonist

Preparations
Losartan potassium
Systematic (IUPAC) name (2-butyl-4-chloro-1-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}- 1H-imidazol-5-yl)methanol
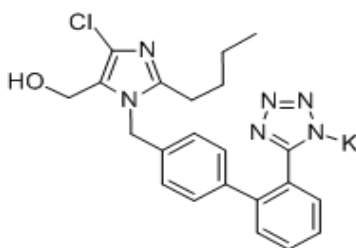
Physiochemical Properties
Physical properties (RxList, 2004)
Losartan potassium is a white to off-white powder
Molecular weight : 461.01
It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone

The structural formula is as follows:

1.2 Structure of Losartan potassium

Chemical properties

Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt. Its empirical formula is $C_{22}H_{22}ClKN_6O$

Pharmacokinetic data

Bioavailability :25–35%

Protein binding :99.7% (primarily albumin)

Metabolism Hepatic: (CYP2C9, CYP3A4 Half-

life: 1.5–2 hours

Excretion Renal: 13–25%,

Biliary: 50–60%

Mechanism of Action (Edwin, 2001)

Mechanism of Action

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)], is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT1 receptor and have much greater affinity (about 1000-fold) for the AT1 receptor than for the AT2 receptor. In vitro binding studies indicate that losartan is a reversible, competitive inhibitor of the AT1 receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT1 receptor.

Neither losartan nor its active metabolite inhibits ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin); nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Indication of losartan potassium(Web Mediplus drug information)

Losartan is used alone or in combination with other medications to treat high blood pressure. Losartan is also used to decrease the risk of stroke in people who have high blood pressure and a heart condition called left ventricular hypertrophy (enlargement of the walls of the left side of the heart). Losartan may not decrease the risk of stroke in African Americans who have these conditions. This medication is also used to treat kidney disease in people who have type 2 diabetes (condition in which the body does not use insulin normally and therefore cannot control the amount of sugar in the blood) and high blood pressure.

Losartan is in a class of medications called angiotensin II receptor antagonists. It works by blocking the action of certain natural substances that tighten the blood vessels, allowing the blood to flow more smoothly and the heart to pump more efficiently.

High blood pressure is a common condition, and when not treated it can cause damage to the brain, heart, blood vessels, kidneys, and other parts of the body. Damage to these organs may cause heart disease, a heart attack, heart failure, stroke, kidney failure, loss of vision, and other problems. In addition to taking medication, making lifestyle changes will also help to control your blood pressure. These changes include eating a diet that is low in fat and salt, maintaining a healthy weight, exercising at least 30 minutes most days, not smoking, and using alcohol in moderation.

Drug Interaction (Web Mediplus drug information)

1. Losartan, administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin.

2. Losartan did not affect the pharmacokinetics of oral or intravenous digoxin.

3. Coadministration of Losartan and cimetidine led to an increase of about 18% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite.

4. Coadministration of Losartan and phenobarbital led to a reduction of about 20% in the AUC of Losartan and that of its active metabolite.

5. Greater interaction (approximately 40% reduction in the AUC of active metabolite and approximately 30% reduction in the AUC of Losartan) has been reported with rifampin.

Fluconazole, an inhibitor of cytochrome P450 2C9, decreased the AUC of the active metabolite by approximately 40%, but increased the AUC of Losartan by approximately 70% following multiple doses.

6. Conversion of Losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4.

Dose (Ridwan, 2004)

Adult Hypertensive Patients

Losartan potassium tablets may be administered with other antihypertensive agents, and with or without food.

Dosing must be individualized. The usual starting dose of Losartan potassium tablets is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume (e.g., patients treated with diuretics) and patients with a history of hepatic impairment. Losartan potassium tablets can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response. The effect of Losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks.

If blood pressure is not controlled by Losartan potassium alone, a low dose of a diuretic may be added. Hydrochlorothiazide has been shown to have an additive effect.

No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis.

Pediatric Hypertensive Patients ≥ 6 years of age

The usual recommended starting dose is 0.7 mg/kg once daily (up to 50 mg total) administered as a tablet or a suspension Dosage should be adjusted according to blood pressure response. Doses above 1.4 mg/kg (or in excess of 100 mg) daily have not been studied in pediatric patients.

Losartan potassium is not recommended in pediatric patients <6 years of age or in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m2

Side effect (Web Mediplus drug information**)**

- swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs
- hoarseness
- difficulty breathing or swallowing
- chest pain

Losartan may cause other side effects

- leg, knee, or back pain
- muscle cramps or weakness
- diarrhea
- heartburn
- decreased sensitivity to touch

Storage (Web mediplus drug information)

1. Keep this medication in the container it came in, tightly closed, and out of reach of children.
2. Store it at room temperature and away from excess heat, light, and moisture (not in the bathroom).
3. Throw away any medication that is outdated or no longer needed.

SOME MARKET PREPARATIONS AVAILABLE IN BANGLADESH

(Ridwan, 2004)

Table 1.2:Different brand of losartan potassium available in Bangladesh.

Name of the company	Brand name	Dosage form available
Sandoz	Lopass	Tab: 50 mg
Square	Angiloc	Tab: 50mg
Popular	Losatan	Tab: 50 mg
Sunpharma	RePACE	Tab: 50 mg
SK-F	Cardon	Tab: 50mg
General Pharmaceutical Ltd.	ANREB	Tab: 50 mg
Unimed & Unihealth Manufacturers Ltd	ARATEN	Tab: 50 mg
Hallmark Pharmaceuticals Ltd.	COZARIL	Tab: 50 mg
E-TAN	Edruc Ltd.	Tab: 50 mg
LARB	Opsonin Pharma Ltd.	Tab: 50 mg
LOK-50	Globe Pharmaceuticals Ltd.	Tab: 5 0mg
LOPO	Bio Pharma Laboratories Ltd	Tab: 25 mg

Chapter - 2

Purpose of the Study

2.Purpose of this work

The main objectives of this presentation described below

- To evalualution of different brands of losartan potassium availabe in Bangladesh
- The major purpose of this project work is to find out the current status of the quality of the marketed Losartan potassium preparations available in Bangladesh.
- This project work makes awareness among the peoples health, health practitioners and drug control authority so that pharmaceutical manufacturers produce quality medicine and people may not waste their hard earning money by buying low quality product.
- This project work provides a comprehensive knowledge about the hardness, friability, weight variation, disintegration, dissolution, percentage of potencies of Losartan potassium market preparations and compares these values with their specifications.
- This project work will help both health practitioners and consumers to select quality products. Also this work can provide some information for Drug Control Authority of Bangladesh to evaluate the overall quality status of potassium Losartan preparation

Chapter - 3

Materials & Methods

MATERIALS AND METHODS

3.1 MATERIALS

3.1.1. Sample Collection

There are about 40 brands of Losartan (tablets) in Bangladesh. Samples were collected from retail medicine shop of different areas.During that period the following were considered:

1. The samples were properly checked for their physical appearance, name of the manufacturer, batch number, manufacturing data, expiry date, manufacturing license number, D.A.R. number and maximum retail price at the time of purchase.

2. No samples were bought and analyzed whom date of expiry had already been passed. Collected samples also covered small, medium and big companies.

3. The samples were then coded with ethics for analysis.

Packaging of the Samples

The status of purchased Losartan potassium market preparations were as follows:

1. Every company had packed 30 of Losartan potassium tablet in each inner carton.

2. Each strip contain 10tablets.except Lopass which contain 14tablets.

3. Tablets were round,or heart or triangle in shape.

Then Tablets of 5 different available brands of various manufacturers were purchased for the analytical studies.

Reference Standard

The BP reference standard of Losartan was obtained from S-KF Bangladesh. The purity of the reference standard was 99.45%

Coding of Tablet

 5 Losartan potassium tablet brands collected from 5 different pharmaceutical companies were coded as

- LP-A
- LP-B
- LP-C
- LP-D
- LP-E

Labeling On the Inner Carton / Container of Tablets of the Collected Samples

Each of the containers of tablets labeled with the following particulars:

(a) Brand name of the product

(b) Name of the manufacturer

(c) Composition of the product

(d) Batch number

(e) Manufacturing date

(f) Expiry date

(g) Manufacturing license number

(h) D.A.R. number

(i) Maximum retail price (M.R.P.)

Reagents

Distilled Water

0.1 N HCl (Merck, India)

Hydrochloride (HCl)

HCl: 32%w/w

3.1.7 Apparatus Used in This Study

Table 3.1: Name of glassware

Name of the glass ware	Manufacturer / Source
Volumetric flask (50 ml, 100 ml , 250 ml, 1000 ml)	Wheel Brand, China.
Beaker (100 ml)	Gilin Brand, China.
Pipette (1 ml ,2 ml ,5 ml ,10 ml)	Precicolor (HBG), Germany.
Funnel (75 mm)	Wheel Brand, China.
Filter paper	India.

Table 3.2: Name of the Instrument

Name of the instrument	Manufacturer
Analytical balance	Mettler, Toleds, Switzerland.
UV-Spectrophotometer	Thermospectronic type: Helias Gamma, England.
Tablet hardness tester	India.
Dissolution test apparatus	India.
Disintegration test apparatus	India.
UV-Spectrophotometer	Thermospectionic type:PG
pH meter	Switzerland.
Slide calipers	Shanghai, China.

METHODS

3.2.1Preparation of the Reagents

3.2.1.2 Preparation of 0.1N Hydrochloride

1. At first,9.84 ml of HCl was taken in a voluemetruic flask

2. Then added to distilled water in a 1000-ml volumetric flask and diluted to 1000 ml with distilled water.

3.2.2PHYSICAL ANALYSIS

Color variation test of tablets

1. The tablets were tested visually at day light under a white background.

2. Color of the tablets was determined.

3. Shapes of Different brands was observed

In this way color of the 5 different brands of tablets were determined and observed result for each sample was recorded.

Thickness test of tablets

1. Thickness of 10 tablets of each sample was measured with a slide calipers.

2. Slide calirpers reading was carefully observed

3. The average thickness of the tablets was determined and then thickness variation was calculated.

In this way the thickness variation of 5 different brands of tablets was determined and the observed result for each sample was recorded.

Diameter tests of tablets

Ten tablets were taken and determined individual diameter, average diameter and standard deviation.

Weight variation test of tablets

The weight variation is routinely measured to help ensured that a tablet contains proper amount of drug.

Procedure

1. At first 10 tablets were taken and weighed individually by an analytical balance.

2. The weight was carefully observed.

3. Then another was placed carefully one by one.

4. The average weight of the tablets was calculated.

Then % of weight variation is calculated by using the following formula.

$$\% \text{ of weight variation} = \frac{\text{Individual weight} - \text{average weight}}{\text{Average weight}} \times 100$$

In this way the weight variation for 5 different brands of tablets were measured and the observed value for each sample was recorded.

Note

1. Not more than two tablets should fall outside the limit.

2. No tablet should differ by more than two times the allowed % limit.

Disintegration time test of tablets

Disintegration time is the length of time required for causing disintegration of tablet. This test is important to evaluate a tablet since it directly influences the onset of action. This test not only evaluates the quality but also the bioavailability and effectiveness of tablets.

Procedure

1. USP disintegration apparatus contains 6 glass tubes that are 3 inches long, open at the top and held against a 10-mesh screen at the bottom end of the basket rack assembly.

2. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1 liter beaker of water at $37°c \pm 2°c$, such that the tablets remain 2.5 cm below the surface of the liquid on their upward movement and descent not closer than 2.5 cm from the bottom of the beaker.

3. A standard motor driven device is used to move the basket assembly containing tablets up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute.

4. Perforated plastic discs may also be used in the test.

5. These are placed on the top of the tablets and impart an abrasive action to the tablets. The discs may or may not the meaningful or impart more sensitivity to the test but they are useful for tablets that float.

6. To comply with USP standards, the tablets must disintegrate and all particles fall through the 10-mesh screen in the time specified. If any residue remains, it must have a soft mass with no palpably firm core.

7. The disintegration time of each tablet was determined and the average disintegration time was calculated.

In this way disintegration time was determined for 5 different brands of tablets and the observed result for each sample was recorded.

Dissolution rate test of tablets

Dissolution is the property or tendency of a drug to undergo solution, which affects the rate of drug absorption.

Medium: Normal water

Apparatus

1. USP dissolution apparatus 1
2. Whatman filter paper
3. Pipette
4. Volumetric flask
5. UV-visible spectrophotometer

USP dissolution apparatus

In general, a single tablet is placed in a small wire mesh basket fastened to the bottom of the shaft connected to a variable speed motor. The basket is emerged in the dissolution medium (Normal water; 900 ml) contained in a 1000 ml flask. The flask is cylindrical with a hemispherical bottom. The flask is maintained at a 37 °c ± 0.5°c by a constant temperature bath. The motor is adjusted to turn at the specified speed.

Procedure

1. The flask was filled with 900 ml of Normal water
2. The dissolution medium was heated up to 37 °c ±0.05°c by an auto heater.
3. One tablet was put in to the basket and stirred immediately at 100 r.p.m.
4. 5 ml of sample was withdrawn from the flask after 15-45 minutes.
5. The dissolved Losartan potassium was determined from UV absorbance at the wavelength of maximum absorbance at about 250 nm of filtered portion of the solution under test, suitably diluted with in comparison with a standard Losartan potassium having known concentration of BP Losartan WS in the same medium.

In this way the dissolution rates of 5 different brands of tablets were determined and the observed value for each sample was recorded. (British Pharmacopoeia)

3.2.3 CHEMICAL ANALYSIS

Preparation of standard curve

1. At first,100 mg of standard Losartan potassium was weighed accurately and was taken in a 100-ml volumetric flask.

2.50-60 ml of 0.1N HCL solution was added and shakes mechanically.

3. Then the volume was adjusted to 100 ml by 0.1N HLC solution and standard stock solution was prepared.

4. Then 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1 ml, 1.2 ml, 1.4 ml and 1.6 ml of stock solutions were taken in a series of separated 100-ml volumetric flask and each of them was diluted up to 100 ml with 0.1N HCL solution.

5.Thus a series of standard solutions with different concentration of standard Losartan potassium e.g., 2 mcg/ml, 4 mcg/ml, 6 mcg/ml, 8 mcg/ml, 10 g/ml, 12 mcg/ml, 14 mcg/ml and 16mcg/ml were obtained.

6. Then absorbance were taken at 250 nm against blank for each solution and the average was calculated which has been given in table.

7. The measured absorbance were plotted against the respective concentrations of the standard solutions which give a straight line in the concentration range of 2 mcg/ml to 16 mcg/ml (Fig.3.1)

Table 3.1: Absorbance of different concentration of standard Losartan potassium solution measured at 250 nm

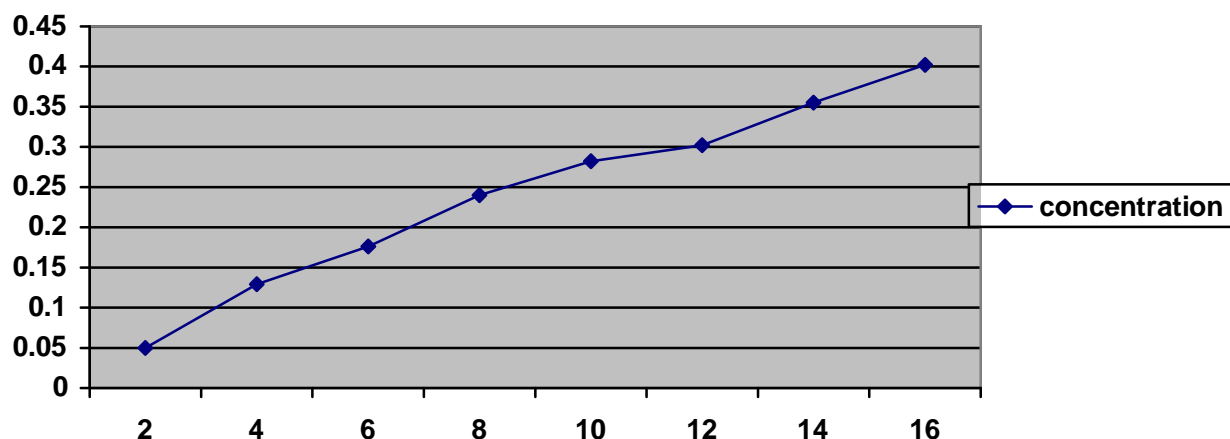| Concentration (mcg/ml)	Absorbance	Average of the absorbance
2	0.050 0.051 0.050	0.051
4	0.100 0.102 0.104	0.102
6	0.165 0.169 0.171	0.169
8	0.240 0.240 0.240	0.240
10	0.262 0.263 0.264	0.263
12	0.304 0.301 0.299	0.301
14	0.355 0.355 0.357	0.355
16	0.402 0.401 0.400	0.401

Figure 1.3: Standard curve of Losartan potassium

Potency determination of tablets

3.2.3.2.1 Preparation of standard solution

1. At first,100 mg of standard Losartan potassium was weighed accurately in an analytical balance and was taken in a 100-ml volumetric flask.

2.70 ml of 0.1 N HCL solutions was added and was shaken mechanically.

3. The volume was made upto the mark with the same solvent.

4.1ml of the above solution was diluted to 100 ml with the same solvent.

3.2.3.2.2 Preparation of assay solution

1. At first,4 tablets were weighed and powdered in a mortar with a pestle.

2. An amount of powder equivalent to 100 mg of Losartan potassium was transferred in a 100-ml volumetric flask.

3.5.70 ml of 0.1 N HCl solutions was added and was shaken for 45 minutes.

4. The volume was made upto the mark with the same solvent and filtered the solution with Whatman filter paper.

5.1ml of the filtered solution was diluted to 100 ml with the same solvent.

3.2.3.2.3 Measurement

The absorbance of both standard and sample were measured in a suitable UV-VIS spectrophotometer at 250 nm using 0.1 N HCL. Each sample was run in triplicate and average of the results was taken in to consideration.

Calculation

$$\text{Potency of sample} = \frac{\text{Absorbance of sample } \times \text{ Weight of standard}}{\text{Absorbance of standard } \times \text{ Weight of sample}} \times \text{ Purity of standard}$$

In this way, the potency of 5 brands of tablets was determined and the observed value for each sample was recorded.

Chapter - 4

Results and Discussion

RESULTS AND DISCUSSION

4.1GENERAL APPEARANCE OF THE TABLETS

The general appearance of 5 brands of Losartan potassium tablets were thoroughly analyzed according to the procedure.

Table: 4.1 General appearances of the tablets

Sample code	Shape	Color	Surface Texture	Identifying markings
LP-A	Heart	Green	Smooth	Company name
LP-B	Round	Green	Smooth	Company name
LP-C	Round	Ass	Smooth	Company name
LP-D	Round	Green	Rough	Company name
LP-E	Round	White	Smooth	Company name

4.2 PHYSICAL ANALYSIS

4.2.1 Weight Variation Test Losartan potassium Tablets

The weight variation of 5 different brands of Losartan potassium tablets were determined according to the procedure.

Table 4.2: **Weight variation of various brands of Losartan potassium tablets**

Sample code	Number of tablets taken	Average weight per tablet (mg)	Weight variation	
			Number of tablets within BP/USP range	Number of tablets out of BP/USP range
LP-A	10	190.0	10	0
LP-B	10	217.0	10	0
LP-C	10	156.0	10	0
LP-D	10	190.0	10	0
LP-E	10	164.0	10	0

BP/USP specification for weight variation.

Allowed range of variation for 0 to 130 mg tablets: ±5% (w/w). It is observed from the above result that all brands complied with the specification. The weight variation test is a satisfactory method of determining the drug content uniformity of tablets (Gilbert and Neil, 1991).

Weights variations may result from, poor granulation flow properties, resulting in uneven die fill. A wide variation in granules particle size which results in a variation in die fill density as a function of particle size distribution at different points in the production run. Differences in lower punch length which result in different size die cavities. Improper incorporation of glidant, granulation flow promoters. Tablet machines in mechanically poor condition or dirty which prevent free punch movement.

When the weight variation is within the specifications the tablets are thought to contain uniform active ingredient to give desired therapeutic response. But when the weight variation is out of the specification the tablets are thought to contain less or more active ingredient to give ineffective therapeutic response or toxic effect respectively.

4.2.2 Thickness Test of Tablets

The thickness of 5 different brands of Losartan potassium tablets was measured according to the procedure and the observed results shown in the table 4.3

Table 4.3: Thickness of various brands Losartan potassium of tablets

Sample code	Number of tablets taken	Average thickness per tablet (mm)	Number of tablets within BP / USP range	Number of tablets out of BP / USP range
LP-A	10	3.13	10	0
LP-B	10	2.85	10	0
LP-C	10	3.35	10	0
LP-D	10	3.31	10	0
LP-E	10	2.50	10	0

BP / USP specification of thickness variation: ±5%.

It is found from the above results that none of the samples exceeded the specification for thickness variation. Therefore, it can be said that the entire studied sample complied with the BP / USP specification for thickness variation.

The thickness of a 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, and with tablet weight, while with a constant die fill, thickness varies with variations in compressive load. (Gilbert and Neil, 1991**).** Tablet thickness may be controlled by –

- Controlling the physical properties of raw materials.
- Standardizing the upper and lower punch lengths.
- Controlling the granulation properties including density particle size, and particle size distribution.

Tablet thickness cannot be controlled independently, since it is related to tablet weight compaction, density friability and possibly drug release (Lewis) .In addition, tablet thickness must be controlled to facilitate packaging.

4.2.3 Diameter Test of Tablets

The diameter of 5 different brands of Losartan potassium tablets was measured according to the procedure described in section and the observed results are shown in the table

Table 4.4: Diameter of various brands of Losartan potassium tablets

Sample code	Number of tablets taken	Average diameter per tablet (mm)	Number of tablets within BP / USP range	Number of tablets out of BP / USP range
LP-A	10	7.31	10	0
LP-B	10	5.99	10	0
LP-C	10	6.08	10	0
LP-D	10	7.15	10	0
LP-E	10	6.02	10	0

BP / USP specification of diameter variation: ±5%.

It is found from the above results (Tables 4.3) that none of the samples exceeded the specification for diameter variation. Therefore, it can be said that the entire studied sample complied with the BP / USP specification for diameter variation

4.2.4 Disintegration Time Test of Tablets

The disintegration times of 5 different brands of Losartan potassium tablets were measured according to the procedure and the observed results are shown in the table 4.6

Table 4.5 Disintegration time of various brands of Losartan potassium tablets.

Sample code	No. of tablets	Disintegration time (min)
LP-A	5	3.40
LP-B	5	3.59
LP-C	5	3.10
LP-D	5	4.00
LP-E	5	2.55

BP/USP specification of disintegration time: Not more than 30 minutes for uncoated or film coated tablets. Enteric coated are to show no evidence of disintegration after one hour in simulated gastric fluid and are to disintegrate in two hours plus the time specified in the monograph in the intestinal fluid .(Gilbert and Neil,1991) .

To be compliance with USP standards, the tablets must disintegrate, and all particles must pass through the 3 inches long glass tubes and held against a 10-mesh screen in the time specified (Gilbert and Neil, 1991).

The onset of action of a dosage form of a drug depends on the time to be taken by the tablets to release the active ingredients into the digestive fluid. The tablets should be disintegrated in the appropriate time, otherwise the prescribed course will be affected and the drug may not exert its effect properly. Therefore, it can be said that all the studied samples complied with the BP/USP specification for tablet disintegration time.

4.3 CHEMICAL ANALYSIS

4.3.1 Potency determination of Losartan potassium tablets

The potency of 5 different brands of Losartan potassium tablets were determined within their shelf-life according to the procedure and obtained results are shown in the table 4.7

Table 4.6: Potency of Losartan potassium Tablet.

Sample code	Potency (% w/w)	BP specification
LP-A	99.00	specified
LP-B	98.16	Specified
LP-C	96.26	Specified
LP-D	95.93	Specified
LP-E	97.53	Specified

BP Specification: 95-105% for losartan potassium tablet.

The ingredients of tablets exert the therapeutic effect. The deficient potency will result in less therapeutic response or even the product may be ineffective. From the above result (Table 4.7), it is observed that all brands of tablets meet the specification of potency.

From the above table it is shown that 5 brands meet the BP specification but one brand fails.

4.3.2 Dissolution Rate Test of Tablets

The dissolution rates of 5 different brands of Losartan potassium tablets were measured according to the procedure and observed results are shown in the table 4.8

Table 4.7: Dissolution Rate of Various Brands of Losartan potassium Tablets

Sample code	% of drug release after 15 minutes	% of drug release after 30 minutes	%of drug release after 45 minutes
LP-A	34.00	83.09	98
LP-B	35.8	89.90	100
LP-C	36.7	90.02	98
LP-D	35.22	89.77	100
LP-E	36.33	90.52	99

BP specification of dissolution percentage:

To be compliance with BP standard at least 90% of the tablets must be dissolved within 45 minutes.

The rate of dissolution may be directly related to the efficacy of the tablet product, as well as to bioavailability differences between formulations .Therefore, an evaluation as to whether or not a tablet releases its drug contents when placed in the environment of the gastrointestinal tract is often of fundamental concern to the tablet formulator (Gilbert and Neil, 1991).

Chapter-5

Conclusion

CONCLUSION

At present about 95% of the essential drugs are being produced in our country. Now only 5% drugs are imported which include different types of vaccines and drugs which require high technology for manufacturing. About 90.8% drugs are manufactured by the National companies and the rest of the drugs are manufactured by multinational companies. Although overall quality of the drug products in our country is satisfactory but some spurious and substandard drugs are also supplied by some of the pharmaceutical companies.

There is no alternative to quality medicine for good health. After the implementation of National Drug Policy in 1982, no doubt, the quality of medicine is improved, but not as expected. This project work was designed to evaluate the current status of the marketed Losartan Potassium dosages forms because very often we found in various news media about the spurious and substandard drug in Bangladesh.

From the above result it is assumed that although most of the brands meet with specification. So the Drug Control Authority should take proper measure to control quality of marketed drug in any situation.

Sub-standard drugs cause not only wastage of money but also are responsible for health hazards which are sometimes so acute that may cause death. So the drug control authority should strengthen their visiting team to visit frequently the manufacturing plant and establish more effective analytical measures to analyze the marketed drugs.

In our country, in most cases, quality of drugs still means the amount of active ingredient present in the dosage form. But there are many other important parameters (like disintegration, dissolution etc) which are directly associated with the quality of medicine. So the drug control authority of our country should consider all of the quality parameters so that manufacturers are bound to ensure their quality.

The present study although performed on a limited scale, yet on the basis of professional judgment, the data reported in this project paper can help the Drug Control Authority to get an idea about the quality status of Losartan potassium preparations in Bangladesh.

I am hopeful that the results of this project work will awake the drug control authority to take appropriate steps to ensure quality medicine thereby assuring good health

Chapter-6

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