Comparative in vitro Bioequivalence Study of Different Export Brands of Losartan Potassium Tablet

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ID NO: 101-29-159

3rd Batch

DISSERTATION

PHARMACY DEPARTMENT

FACULTY OF ALLIED HEALTH SCIENCE

DAFFODIL INTERNATIONAL UNIVERSITY

BANGLADESH

July 2014

DISSERTATION ACCEPTANCE FORM

DAFFODIL INTERNATIONAL UNIVERSITY

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Certificate

This is to certify that the results of the investigation that are embodied in this project are original and have not been submitted before in substance for any degree or diploma of this university. The entire present work submitted as a project work for the partial fulfillment of the degree of bachelor of pharmacy, is based on the result of author's **(Sujan sarker, id no: 101-29-159)** own investigation.

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ACKNOWLEDGEMENT

Nothing should be performed alone successfully. Contribution of other person must present behind every successful work as boost. So this successful research work is also not exceptional to this natural law. The success and final outcome required a lot of guidance and I am extremely fortunate to have got this all along the completion of my project work. Whatever I have done is only due to such guidance and I would not forget to thank them.

First I would like to praise to the Almighty, God, by the kind of whom I am alive & have got chance to study in this subject & have become enable to complete this research work & finally write up the outcome project work drive towards the fulfillment of the degree of Bachelor of Pharmacy.

I wish to express my profound sense of gratitude from the core of my heart to my most respected Teacher & Supervisor, Mr. KH Ahammad Uz zaman, Lecturer, Pharmacy Department, Daffodil International University for his inspiration, constant guidance, valuable suggestion, instructive advice & unparalleled encouragement during the course of study.

I respect and thank Mr.Arifur Rahman, Assistant Professor for giving me an opportunity to do the project work and providing us all support and guidance which made me complete the project on time. I am extremely grateful to her for providing such a nice support and guidance though she had busy schedule managing the University.

I would thank to our all lab maintenance staff for proving us assistance in various problem encountered during course of our project.

I would like to express my gratitude to my parents, sister & brother for their help, encouragement, admiration & all kinds of logistic support

Date: July, 2014 **The Author**

Dedicated to……

MY PARENTS

ABSTRACT

As a pre-requested requirement for importing any medicine to any country or in Bangladesh point of view for any types of medicines export the company have to submit in-vivo bioequivalence study report. However according to Shargel Waivers of in-vivo Bioequivalence studies (Biowaivers), in some cases, in-vitro dissolution testing may be used in lieu of in-vivo bioequivalence studies. The aim of the present study is to evaluate the bioequivalence quality of different brands of Losartan potassium that are regularly exported to several foreign countries. Three different brands of Losartan potassium of Bangladesh as well as one patented drug are tested according to BP/USP specified procedure where USP apparatus II was used. The result showed that, three brands of Losartan Potassium tablets meet the USP specification. All brands tested, showed a good result for dissolution rate.

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CHAPTER ONE: INTRODUCTION

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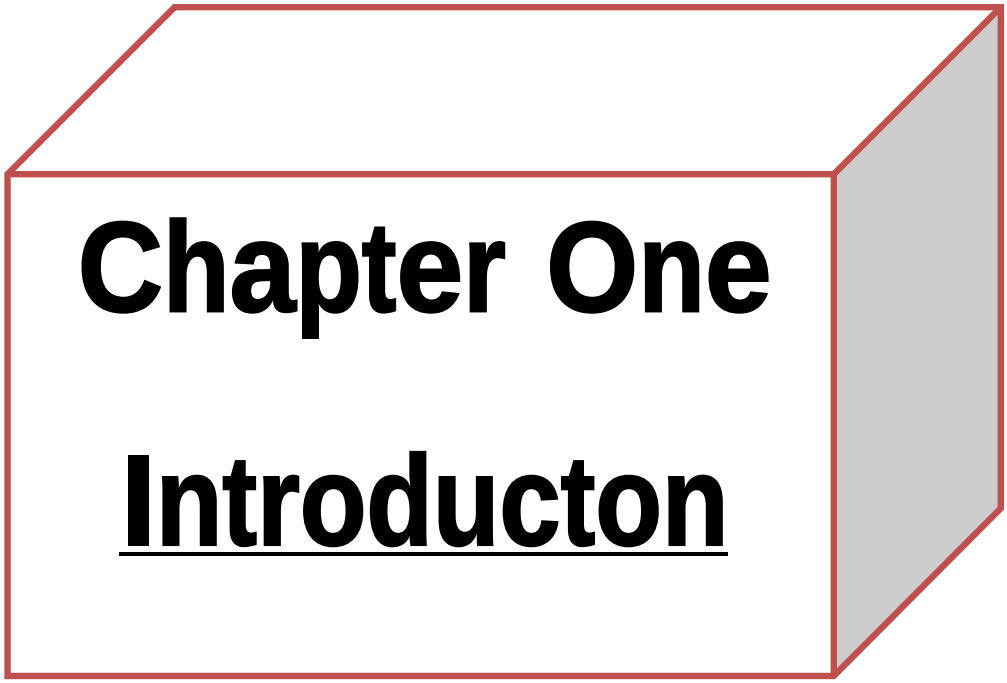

Chapter One
Introducton

1.1 An Overview

There are several sectors on which Bangladesh can be proud of and undoubtedly the pharmaceutical sector is one of these sectors, rather it is the sector, which is the second-largest contributor to the government exchequer. There are about 211 companies in this sector and the approximate total market size is about **Taka 8000 crore** per year of which about 95% of the total requirement of medicines is created by the local companies and the rest 5% is imported. The imported drugs mainly comprise of the cancer drugs, vaccines for viral diseases, hormones etc [1].

In fact, the real growth of local pharmaceutical industries started after the "Drug Control Act" was promulgated in 1982 in Bangladesh to restrict massive import of drugs and to encourage local manufacturing of the same.A lot of multinational companies (MNCs) became unhappy for this development.

There are about 450 generics registered in Bangladesh. Out of these 450 generics, 117 are in the controlled category i.e. in the essential drug list. The remaining 333 generics are in the decontrolled category, the total number of brands /items that are registered in Bangladesh is currently estimated to be 5,300, while the total number of dosage forms and strengths are 8,300. Bangladesh pharmaceutical industry is mainly dominated by domestic manufacturers [2].

From January 01, 2005 onwards, huge export opportunities have already been opened for Bangladesh pharmaceutical sector. As a signatory of WTO/ TRIPs, countries like China and India have already implemented 'Patent Laws' in their countries and hence, these countries are no longer allowed to export patented drugs from their countries. On the contrary, the situation is just reverse for Bangladesh. As a member of LDCs, Bangladesh has already got the exemption from abiding by the patent laws until January 01, 2016, which is going to open the door to 'Enormous Export Opportunities' for the Pharmaceutical Sector of the country. Although, all the 49 LDCs have got this exemption, except Bangladesh all 48 LDCs are basically import based in pharmaceuticals and will not be able to exploit this export opportunity. Bangladesh with its strong manufacturing base in pharmaceuticals is the only country that would really be able to capitalize this opportunity by exporting pharmaceuticals to other LDCs [3].

Needless to mention that, Bangladesh can also ensure huge value addition by pharmaceutical export since the export price is much higher than the local price. For example, in Bangladesh the price of one fluconazole capsule is Tk. 8 whereas fluconazole is exported to Pakistan at a price of Tk. 38. Similarly, the price of paracetamol syrup in Bangladesh is Tk. 13 but it is exported to Russia at a price of Tk. 100. Pharma exports rose around 24 percent year-on-year to $59.82 Million in fiscal 2012-13.

Fig. 1.1: Pharma Export in Millions of Dollar

During the last two decades the pharmaceutical industry of Bangladesh has been taken a newer height. Besides meeting the 97% need of local demand we are exporting the medicines into 72 countries. This sector contributes a lot into the national economy by exporting raw materials and finished goods. Bangladesh is ready to enter the Highly Regulated Market. For this reason different pharmaceutical companies are investing to build high tech pharmaceutical industries. Some renowned companies have already entered the Highly Regulated Market and got the UK MHRA, EU, TGA Australia and GCC approval and some are in the process to get the USFDA & UK MHRA approval. Through this accreditation these companies will be able to export medicine and through contract manufacturing agreement [4].

Asia: Afghanistan, Armenia, Bhutan, Cambodia, Georgia, Hong Kong, Laos, Maldives, Mongolia, Myanmar, Singapore, Sri Lanka, Tajikistan, Turkey, Turkmenistan, Jordan, Macau, Vietnam, Yemen, Iraq, Korea, Malaysia, Nepal, Papua New Guinea, Palau, The Philippines, Pakistan ,Uzbekistan, Vietnam

Africa: Algeria, D. R. Congo, Ethiopia, Ghana,Nigeria, Seychelles, Somalia, Swaziland, Togo, Kenya, Lesotho, Uganda, Mali, Eritrea, Ivory Coast, Libya, Malawi, Mauritania, Mauritius, Mozambique, Somalia, Tanzania,

Europe: UK, Denmark, the Netherlands, Finland, Ukraine,

Central and South America: Belize, Dominican Republic, Honduras, Jamaica, Guyana, Bolivia, Colombia, Venezuela, Costa Rica, and Suriname

Oceania: Fiji, Kiribati, Tonga, Samoa, Solomon Islands & Vanuatu

1.2 Quality and Its Criteria

Quality is an absolute necessity for medicines. The quality of drugs means quality of treatment that ensures the well being of the patients. 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.

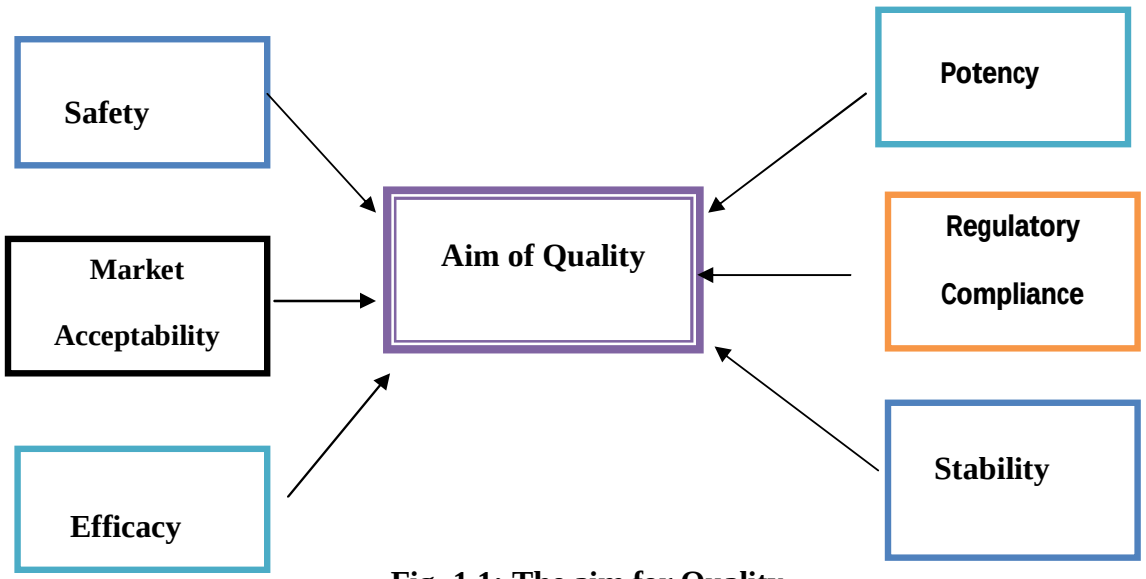


Fig. 1.1: The aim for Quality.

1.3 Quality Control and Quality Assurance

The concept of total quality control refers to the process of striving to produce a perfect product by a series of measures requiring an organized effort by the entire company to prevent or eliminate errors at every stage in production. Although quality assurance personnel are mainly responsible for assuring product quality, it involves many departments and disciplines within a company. Quality must be built in all stages of drug products including plant construction, product research and development, purchasing of materials, production, testing, inspection, labeling, storage and distribution. The essential qualities of good compressed tablets are characterized by a number of specifications which include the size, shape, thickness, weight, hardness, friability, stability, disintegration time, dissolution time and potency. The essential qualities of medicinal syrups are characterized by a number of specifications, which include the color, odor, taste, density, pH, homogeneity and potency [5]. All such qualities are needed to ensure a safe and therapeutically effective dosage forms.

The assurance of product quality depends on more than just proper sampling and adequate testing of various components and the finished dosage form. Prime responsibility of maintaining product quality during production rests with the manufacturing department Removal of responsibility from manufacturing for producing a quality product can result in imperfect composition, such as ingredients missing, sub potent or super potent addition of ingredients, or mix-up of ingredients, mistakes in packaging or filling, such as product contamination, mislabeling, or deficient package; and lack of conformance to product registration. Quality assurance personnel must establish control or checkpoints to monitor the quality of the product as it is processed and upon completion of manufacture. These begin with raw materials and component testing and include in process, packaging, labeling, and finished product testing as well as batch auditing and stability monitoring [6,7].

As a pre-requested requirement for importing any medicine to any country or in Bangladesh point of view for any types of medicines export the company have to submit in-vivo bioequivalence study report.

1.6 Bioequivalence (BE)

Bioequivalence (BE) is a term in pharmacokinetics used to assess the expected in vivo biological equivalence of two proprietary preparations of a drug. If two products are said to be bioequivalent it means that they would be expected to be, for all intents and purposes, the same. During the last two decades the cost of healthcare has been escalating globally, and this has prompted efforts in most countries to reduce those costs. It is known that most of the interventions of healthcare are done through medication. Since the cost of medication has also been escalating through the years, the contribution of drug costs to the overall costs of healthcare has received considerable attention. A major strategy for lowering the cost of medication, and thereby reducing its contribution to total healthcare costs, has been the introduction in global markets of generic equivalents of brand-name drugs (innovator drugs) which is the bioequivalence study. The strategy has been effective. And the regulatory body demands bioequivalence result ok for submission of new drug or generic. The concept of BE and approaches to its assessment were developed in various stages over the last 35 years. During this period, a drug bioequivalence study panel was formed by the Office of Technology Assessment (OTA) to understand the chemical and therapeutic equivalence relationships of drug products. On the basis of the recommendations put forth by this panel, the FDA formulated regulations for the submission of bioavailability data. These regulations are currently incorporated in the 21st volume of Code of Federal Regulation, Part 320 (21CFR320) [8].

The United States Food and Drug Administration (FDA) has defined bioequivalence as, "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

According to World Health Organization (WHO) guidelines, bioavailability is defined as:
"The rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action" (WHO, 1986).

According to Shargel Waivers of in-vivo Bioequivalence studies (Biowaivers)

In some cases, in-vitro dissolution testing may be used in lieu of in-vitro bioequivalence studies. When the drug product is in the same dosage form but in different strengths, and is proportionally similar in active and inactive ingredients, an in-vivo bioequivalence study of one or lower strengths can be waived based on the dissolution test and an in-vivo bioequivalence study on the highest strength. Ideally, if there is a strong correlation between dissolution of the drug and the bioavailability of the drug, then the comparative dissolution tests comparing the test product to the reference product should be sufficient to demonstrate bioequivalence. For most drug product, especially immediate-release tablets and capsules, no strong correlation exists and the FDA requires an in-vivo bioequivalence study may be required to support at least one dose strength of the product. Usually, an in-vivo bioequivalence study is required for the highest dose strength. If the lower dose strength test product is substantially similar in active and inactive ingredients, then only comparison in-vitro dissolution between the test and brand-name formulations may be used. For example, an immediate-release tablet is available in 200mg, 100mg and 50mg strength tablets are made the same way as the highest strength tablet. Human bioequivalence study is performed on the highest or 200mg strength. Comparative in-vitro dissolution studies are performed on the 100mg and 50mg dose strengths. If these drug products have no known bioavailability problems, are well absorbed systemically, are well correlated with in-vitro dissolution, and have a large margin of safety, then arguments for not performing an in-vivo bioavailability study may be valid. The manufacturer does not need to perform additional in-vivo bioequivalence studies on the lower strength products if the products meet all in-vitro criteria [9].

1.4.1 Historical overview of Bioequivalence studies

The concept of bioequivalence and approaches to its assessment were developed in various stages over the last 35 years. In the early 1970s, the "United States Food and Drug Administration" (FDA) became interested in biological availability of new drugs. During this period, a drug bioequivalence study panel was formed by the Office of Technology Assessment (OTA) to understand the chemical and therapeutic equivalence relationships of drug products. On the basis of the recommendations put forth by this panel, the FDA formulated regulations for

the submission of bioavailability data. These regulations are currently incorporated in the 21st volume of Code of Federal Regulation, Part 320 (21CFR320)[4].

In 1984, United States Congress passed the "Drug Price Competition and Patent Term Restoration Act of 1984" that authorized FDA to approve generic drug products through BA and BE studies. As a result of the passage of this act, several activities were initiated by the FDA for the review and approval of generic drug application (Abbreviated New Drug Application, commonly known as ANDA) [10]. During 1984 to 1992, FDA published for the industry a series of drug-specific BA/BE guidance's, general guidance's on conducting studies, and regulatory recommendations and statistical guidance's to document. Consequently, this guidance's helped the industry to conduct BA/BE studies and receive approval of a large number of generic drug products during that period. Since then, and after turn of the century, tremendous advancements have been made by the FDA and other regulatory authorities (national, international, and supranational), and by industry and academia in the area of assessment of bioequivalence. Currently approaches to determine BE of pharmaceutical products has been largely standardized. This has occurred due to discussion and consensus reached among various stakeholders at numerous national and international meetings, conferences, and workshops.

1.4.2 In-vitro-In-vivo correlation

In-vitro-in-vivo correlation (IVIVC) establishes a relationship between a biological property of the drug and a physiochemical property of the drug product containing the drug substance, such as dissolution rate. In order to have an IVIVC, some property of the drug release from the drug product in-vitro, under specified conditions, must relate to in-vitro drug performance. Dissolution tests should be discriminate formulation factors that may affect bioavailability of the drug. In some cases, dissolution tests for immediate-release solid oral drug products may be over discriminating and a clinically acceptable product might perform poorly in the dissolution test. When a proper dissolution method is chosen, the rate of dissolution of the product may be correlated to the rate of absorption of the drug into the body. Well-defined in-vitro-in-vivo (IVIVC) correlations have been reported for modified-release drug products but have been more difficult to predict for immediate -release drug products. An IVIVC should be evaluated to demonstrate that predictability of in-vivo performance of a drug product from its in-vitro dissolution characteristics is maintained over a range of in-vitro dissolution release rates and

manufacturing changes. The in-vitro dissolution characteristics are dependent on the physical properties of the active pharmaceutical ingredients (API), the drug formulation, the hydrodynamics of the dissolution apparatus, and the dissolution medium.IVIVC may be useful for establishing upper and lower dissolution specifications for a solid oral dosage form. Dissolution: The dissolution class is based on the in-vitro dissolution rate of an immediate-release drug product under specified test conditions and is indented to indicate rapid in-vivo dissolution in relation to the average rate of gastric emptying in humans under fasting conditions. An immediate-release drug product is considered rapidly dissolving when not less than 85% of the label amount of drug substance dissolves within 30 minutes using USP apparatus I at 100 rpm or Apparatus II at 50 rpm in a volume of 900ml orin each of the following media: Acidic media such as 0.1 N HCL or simulated Gastric Fluid USP without enzymes A pH 4.5 buffer and A pH 6.8 buffer or simulated Intestinal Fluid USP without enzymes.

1.4.3 The importance of bioequivalence studies in pharmaceutical products

According to World Health Organization (WHO) "before a new innovator product reaches the market, its efficacy and safety is thoroughly investigated in a large number of pre-clinical and clinical studies. For a Generic or Multisource Product, Bioequivalence (BE) studies can serve as a surrogate for costly and time consuming traditional efficacy and safety studies. In a BE study, the systemic exposure profile of the Generic Product (test) is compared to a reference product, for which there is sufficient efficacy and safety data (usually the innovator product). If the test product shows the same rate and extent of absorption as the reference product, the products are considered bioequivalent and the efficacy and safety data obtained with the reference product can be extrapolated to the Generic Product". The measurement of absorption rate and extent of assay in systematic circulation after a drug is being taken is called bioequivalence. Occasionally one drug is produced by several companies and release to market. Quality assurance, efficacy and safety of one product are the most important responsibility of pharmaceutical companies which can be achieved by bioequivalence studies. Production method, formulation and quality of raw material and exceptions have a direct effect on its bioequivalence. Drug absorption is relied on dissolution in *in vivo* and absorption by gastrointestinal tract. Adding exceptions in order to achieve the most stable, desired form is necessary however these exceptions would increase or decrease the bioequivalence of active material. Therefore for the efficacy of such pharmaceutical

product the bioequivalence study is necessary. Bioequivalence studies are very important for the development of a pharmaceutical preparation in the pharmaceutical industry. Their rationale is the monitoring of pharmacokinetic and pharmacodynamic parameters after the administration of tested drugs. The target of such study is to evaluate the therapeutic compatibility of tested drugs (pharmaceutical equivalents or pharmaceutical alternatives). The importance of bioequivalence studies is increasing also due to the large growth of the production and consumption of generic products. Generic products represent approximately 50 % of the whole consumption in many European countries and USA. The search output of bioequivalence study is together with the pharmaceutical quality data of medical product one of the main part of the registration file submitted to a national regulatory authorities. We can perform the bioequivalence study by in vitro dissolution method**.**

Compared to the in vivo bioequivalence tests, conventional in vitro studies are less complicated, fast, economic and useful quality control tool and evaluate more directly drug absorption than in vivo bioequivalence studies. On the other hand, for all products except formulation C the drug delivery was satisfactory since at least 80% was dissolved in 30 min. Therefore results confirm the bioequivalence of the analyzed brands and reference (patented) product is almost same. This study shows that the generic products assessed do not qualify for biowaiver; therefore, in vivo bioequivalence studies are required to ascertain BE. In vivo BE are expensive studies that, if performed, will increase the cost of drugs. Without bioequivalence studies, whether in vivo or in vitro, the therapeutic equivalence of generics is in doubt. Therefore, to use in vitro dissolution as a surrogate for bioequivalence studies for regulatory purposes, manufacturers of generic products need to consider factors that affect solubility and permeability of their products when formulating them. Keeping in view the health-care cost, the pharmaceutical companies are manufacturing and marketing cheaper generic drug products. It is vital for the regulatory authorities of every country to ensure the efficacy and safety of these generic formulations. Carefully planned and designed bioequivalence studies are the only way to ensure uniformity in standards of quality, efficacy and safety of pharmaceutical products [9].

1.5 Dissolution

A Proces in which a solid substance is solubilised in a given solvent that is mass transfer from solid surface to liquid phase.

The administration of drugs via oral dosage forms is one of the most common and effective means of delivering treatments to patients. When a dosage form is swallowed, the rate at which it releases the active ingredient is critical to ensure that the drug is delivered properly. The rate at which the drug is released is called the dissolution rate.

One of the problems facing pharmaceutical manufacturers is to how optimize the amount of drug available to the body, i.e. its bioavailability. Inadequacies in bioavailability can mean that the treatment is ineffective and at worst potentially dangerous (toxic overdose). All kinds of factors affect this from the formulation of the dosage form, size, shape, excipients, bindings and other physical characteristics, to the pH, temperature and so on.

The actual drug release in the human body can be measured in-vivo by measuring the plasma or urine concentrations in the patient. However, there are certain obvious impracticalities involved in employing such techniques on a routine basis. These difficulties have led to the introduction of official in-vitro tests which are now rigorously and comprehensively defined in the respective Pharmacopoeia and recent harmonization between the various Pharmacopoeias (notably the USP, BP, EP and JP) has lead to global standardization in the measurement of drug release rates.

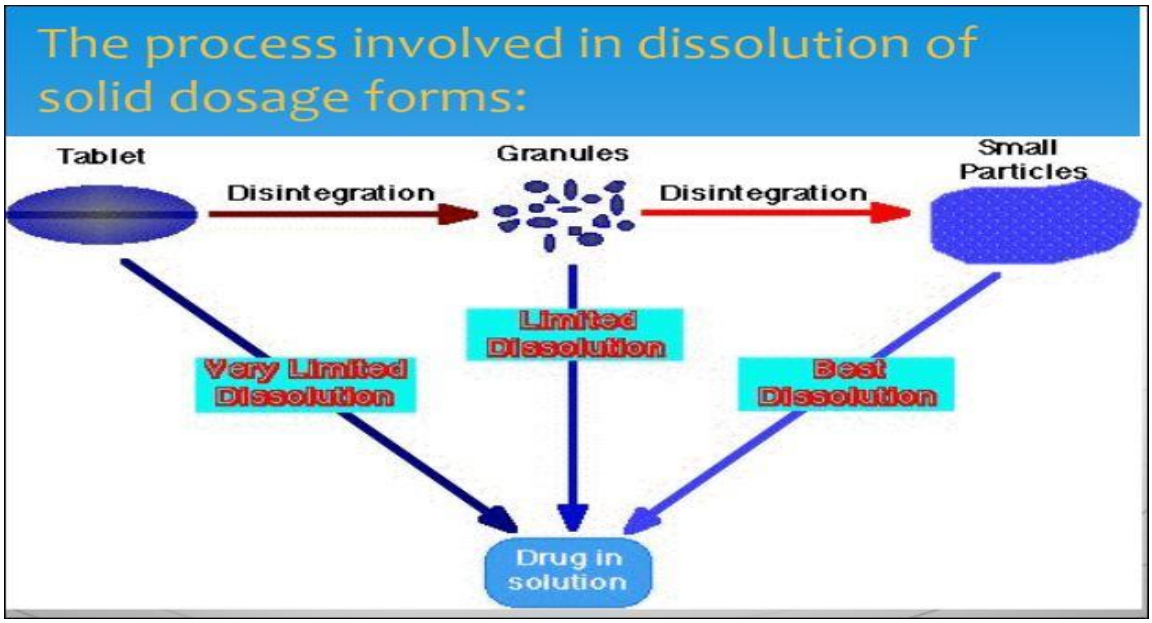


Fig. 1.3: The process involed in dissolution

1.5.1 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 .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) [11].

- 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, 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.

Many middle / small graded manufacturers still perform only the disintegration test for their product to save time and expenditure. So many marketed solid dosage forms do not show standard dissolution profile. The ultimate result is fewer drugs in solution, less drugs in absorption and thus the bioavailability and pharmacological action is not as predicted even if they include the claimed amount of drug.

In case of enteric coated tablet, the dissolution process get special importance because in such case, the drug cannot be dissolved in gastric pH and have to be dissolved within specified time in intestinal pH.

1.5.2 Tablet Dissolution Testing

When it comes to measuring the release rates of drugs in a manufacturing environment then the technique of Tablet Dissolution testing is employed.

Tablet Dissolution is a standardized method for measuring the rate of drug release from a dosage form and the key word here is "standardization" because for any results to be meaningful, it is

essential that all the apparatus used for the testing, produces the same sets of results given all other parameters are equal.

There are many discussions about how good dissolution testing may or may not be compared with the actual in-vivo effects, but without a standardized test it is impossible to gain comparative data

The principle function of the dissolution test may be summarized as follows [12]:

- Optimization of therapeutic effectiveness during product development and stability assessment.
- Routine assessment of production quality to ensure uniformity between production lots.
- Assessment of 'bioequivalence', that is to say, production of the same biological availability from discrete batches of products from one or different manufacturers.
- Prediction of in-vivo availability, i.e. bioavailability (where applicable).

1.5.3 Why Test?

From a manufacturing objective, the aim is to:

"Manufacture a dosage form in such a way that the active ingredient is released from the dosage form in a predictable way and within a reasonable time in order for it to be absorbed by the body". Drugs also need to be released in the right area of the body - in the intestine instead of the stomach for example. Most routine dissolution testing is used to confirm the statement above.

When a dosage form is manufactured, there are a number of parameters which need to be checked:

- That the active ingredient is released in the predicted way
- That the manufactured batch is the same as previous batches and falls within the required levels.
- That he product can be stored for the specified shelf life without deterioration
- To ensure that the dosage form does not break up in transit
- To confirm that the drug is stable over time.

1.5.4 Dissolution Rates of Dosage Forms

There are many kinds of dosage forms of course and all of them have a dissolution rate. The dissolution time can range from seconds to hours or even days for implants.

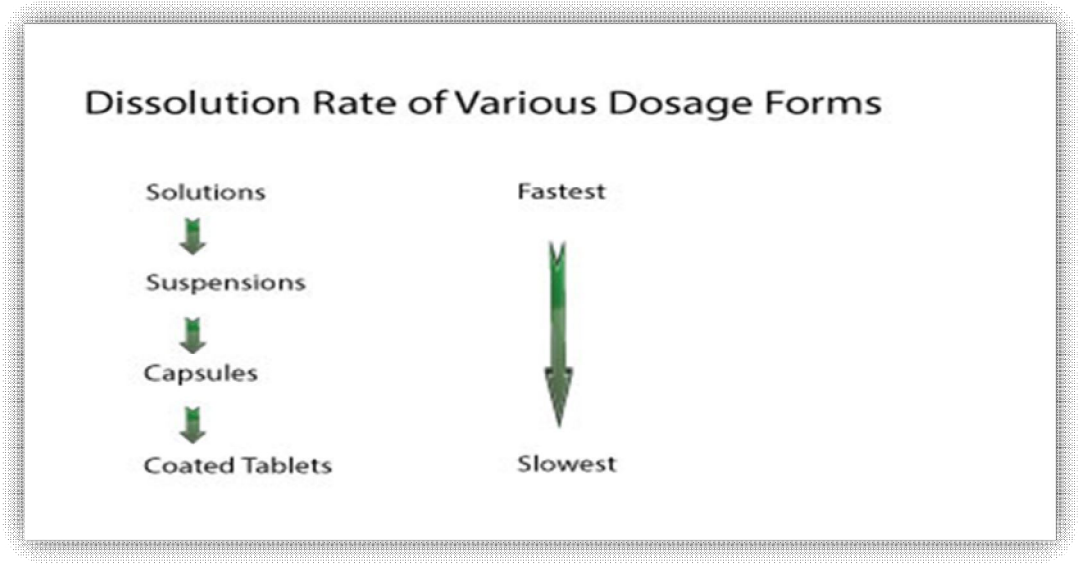


Fig. 1.4: Dissolution rate of various dosage forms

Of course there are other dosage forms such as patches, implants, creams etc. but the principles remain the same. The interface between the dosage form, and in particular the particles after disaggregation and the dissolution media is critical and is known as the Shear Rate.

1.4.5 In Vitro Dissolution Testing for Solid Oral Dosage Forms

Dissolution testing is a requirement for all solid oral dosage forms and is used in all phases of development for product release and stability testing. It is a key analytical test used for detecting physical changes in an active pharmaceutical ingredient (API) and in the formulated product.

At early stages of development, in vitro dissolution testing guides the optimization of drug release from formulations. Over the past 50 years, dissolution testing has also been employed as a quality control (QC) procedure, in R&D to detect the influence of critical manufacturing variables and in comparative studies for in vitro-in vivo correlation (IVIVC).

The FDA guidance on dissolution testing for immediate release solid oral dosage forms1 includes the use of the Biopharmaceutics Classification System (BCS) guidelines for bio relevant dissolution tests, which is based upon API solubility and permeability. According to the BCS

guidelines, in vitro dissolution testing may be a useful tool to forecast the in vivo performance of drug products and potentially reduce the number of bioavailability/bioequivalence studies required. The FDA guidance on scale-up and post-approval changes (SUPAC) for immediate release oral dosage forms recommends the use of in vitro dissolution to justify post-approval changes.

The development of a dissolution procedure involves selecting the dissolution media, apparatus type and hydrodynamics (agitation rate) appropriate for the product. This overview article will focus on the most commonplace (USP 1 and 2) dissolution apparatus and present an overview of typical method parameters that should be considered during dissolution development.

Dissolution testing is an in vitro method that characterizes how an API is extracted out of a solid dosage form. It can indicate the efficiency of in vivo dissolution but does not provide any information on drug substance absorption. Pharmacokinetic data supplements and provides additional information regarding API absorption rate.

Selection of the appropriate in vitro conditions (media and hydrodynamics) that simulate the in vivo conditions can lead to the generation of successful IVIVC or at the very least, in vitro-in vivo relations (IVIVR). Conditions that are optimal for QC purposes may not be applicable for establishing IVIVC so it may be necessary to use two dissolution tests to meet different objectives such as development needs or regulatory demands.

1.5.6 Factor Affecting Dissolution

There are several factors that must be considered in the design of dissolution test. They are –

i. Factors relating to the dissolution apparatus such as – the design, the size of the container (several ml to several litres), the shape of the container (round bottomed or flat), nature of agitation (stirring, rotating or oscillating methods), speed of agitation performance precision of the apparatus, etc.

ii. Factors relating to the dissolution fluid such as – composition (water, 0.1 N HCl, Phosphate buffer, simulated gastric fluid, simulated intestinal fluid, etc.), viscosity, volume (generally larger temperature (general 37o C) and maintenance of sink (drug

concentration in solution maintained constant at a low level) or non-sink conditions (gradual increase in the drug concentration in the dissolution medium).

iii. Process parameters such as method of introduction of dosage form, sampling techniques, changing the dissolution fluid, etc.

1.5.7 Dissolution Apparatus

1.5.7.1 The ideal features of a dissolution apparatus are -

1.Simple in design, easy to operate and usable under a variety of conditions.

2. Fabrication dimensions and positioning of all components are precisely specified and reproducible, run-to-run.

3. provides an easy way of introducing the dosage form into the dissolution medium and once immersed, holding it in a regular and reliable fashion.

4. Permits controlled variable intensity of mild, uniform, non-turbulent liquid agitation.

5. Provides minimum mechanical abrasion to the dosage form during the test period to avoid disruption of the microenvironment surrounding the dissolving form.

6. Maintains nearly perfect sink conditions.

7. Prevents / eliminates evaporation of the dissolution medium and maintains it at a fixed temperature within a specified narrow range. Most apparatuses are thermostatically controlled at around 37o C.

8. Ease of drawing samples for automatic or manual analysis without interrupting the flow characteristics of the liquid.

9. Facilitates good inter-laboratory agreement.

10. Sensitive enough to reveal process changes and formulation differences but still yield repeatable results under identical conditions.

11. Permits evaluation of disintegrating, non-disintegrating, dense or floating tablets or capsules, and finely powdered drugs.

The dissolution apparatus has evolved gradually and considerably from a simple beaker type to a highly versatile and fully automated instrument.

1.5.7.2 Types of Dissolution Apparatus

The devices can be classified in a number of ways. Based on the absence or presence of sink conditions, there are two principal types of dissolution apparatuses:

1. Closed-compartment apparatus

It is basically a limited-volume apparatus operating under non-sink conditions. The dissolution fluid is restrained to the size of the container, e.g. beaker type apparatuses such as the rotating basket and the rotating paddle apparatus.

2. Open-compartment (continuous flow-through) apparatus

It is the one in which the dosage form is contained in a column which is brought in continuous contact with fresh, flowing dissolution medium (perfect sink condition).

A third type called as dialysis systems are used for very poorly aqueous soluble drugs for which maintenance of sink conditions would otherwise require large volume of dissolution fluid. Only the official or compendial methods (USP methods) will be discussed here briefly.

USP dissolution apparatus (official)

i. Basket type
ii. Paddle type
iii. Reciprocating cylinder
iv. Flow through cell
v. Paddle over disc
vi. Rotating cylinder
vii. Reciprocating disc

USP dissolution apparatus (non-official)

i. Rotating bottle method.
ii. Diffusion cell.
iii. Peristalisis method.
iv. Intrinsic dissolution method.

IP dissolution apparatus

i. Paddle type
ii. Basket type
iii. BP dissolution apparatus:
iv. Basket type apparatus
v. Paddle type apparatus
vi. Flow through cell

1.5.7.3 Rotating Basket Apparatus (USP Apparatus 1 / IP Apparatus 2)

First described by Pernarowski et al, it is basically a closed-compartment, beaker type apparatus comprising of a cylindrical glass vessel with hemispherical bottom of one litre capacity partially immersed in a water bath to maintain the temperature at 37o C. A cylindrical basket made of 22 meshes to hold the dosage form is located centrally in the vessel at a distance of 2 cm from the bottom and rotated by a variable speed motor through a shaft.

The basket should remain in motion during drawing of samples. The apparatus consists a metallic drive shaft connected to the cylindrical basket. The basket is positioned inside a vessel made of glass or other inert, transparent material. The temperature inside the vessel is kept at a constant temperature by being placed inside a water bath or heating jacket. The solution in the vessels stirred smoothly by the rotating stirring element.

The Rotating Basket Suppository Basket Standard 40 Mesh Basket

Fig. 1.5: Rotating Basket Apparatus

1.5.7.4 Rotating Paddle Apparatus (IP Apparatus 1 / USP Apparatus 2)

The assembly is same as that for apparatus 1 except that the rotating basket is replaced with a paddle which acts as a stirrer. The method was first described by Levy and Hayes. The dosage form is allowed to sink to the bottom of the vessel. Sinkers are recommended to prevent floating of capsules and other floatable forms. A small, loose, wire helix may be attached to such preparations to prevent them from floating.

Fig. 1.6: Rotating Paddle Apparatus

1.5.7.5 Reciprocating Cylinder Apparatus (USP Apparatus 3)

This apparatus consists of a set of cylindrical flat-bottomed glass vessels equipped with reciprocating cylinders. The apparatus is particularly used for dissolution testing of controlled-release bead-type (pellet) formulations.

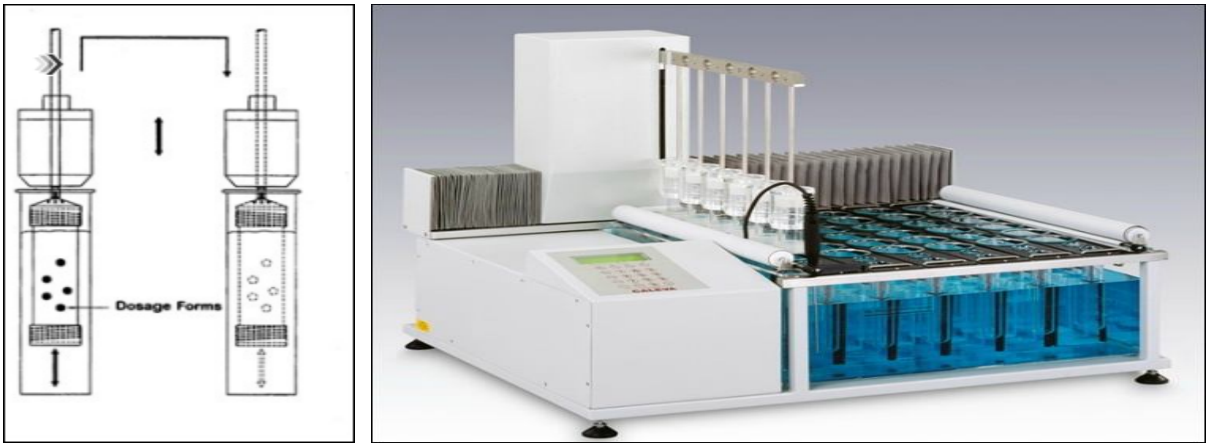


Fig. 1.7: Reciprocating Cylinder Apparatus

1.5.7.6 Flow-Through Cell Apparatus (USP Apparatus 4)

The flow-through apparatus consists of reservoir for the dissolution medium and a pump that forces dissolution medium through the cell holding the test sample.

It may be used in either:

-Closed-mode where the fluid is re circulated and, by necessity, is of fixed volume, or

-Open-mode when there is continuous replenishment of the fluids.

The material under test (tablet, capsules, or granules) is placed in the vertically mounted dissolution cell, which permits fresh solvent to be pumped in (between 240 and 960 ml/h) from the bottom.

Advantages of this apparatus include –

1. Ease of maintaining of sink conditions during dissolution which is often required for drugs having limited aqueous solubility.
2. Feasibility of using large volume of dissolution fluid.
3. Feasibility for automation of apparatus.

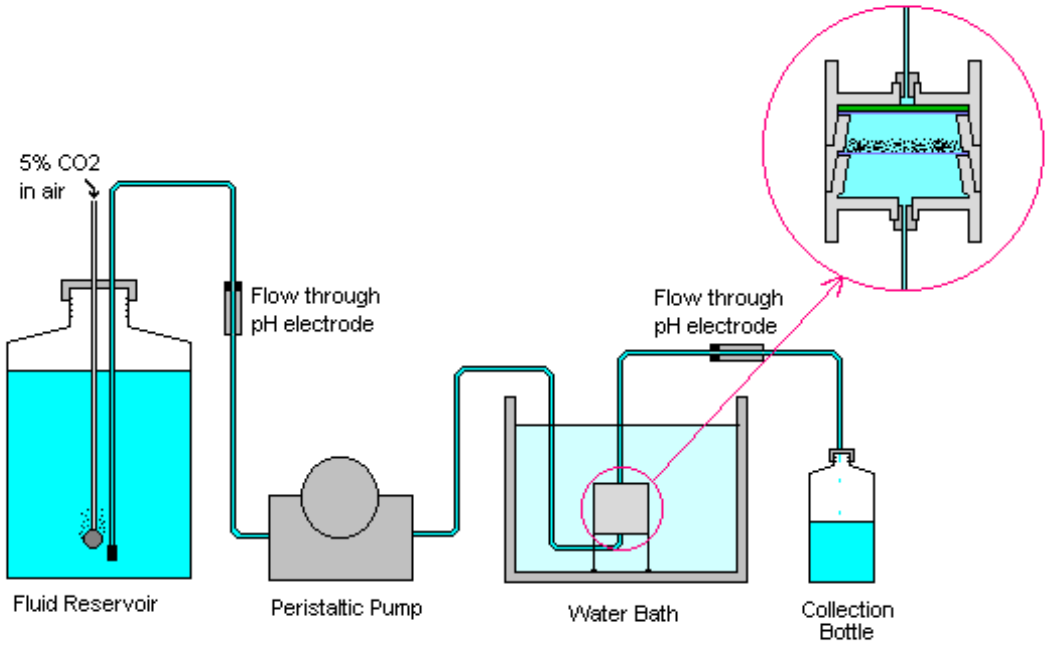


Fig. 1.8: Flow-Through Cell Apparatus

1.5.7.7 Paddle over Disc Apparatus (USP Apparatus 5)

This apparatus is used for evaluation of transdermal products and consists of a sample holder or disc that holds the product. The disc is placed at the bottom of apparatus 2 and the apparatus operated in the usual way.

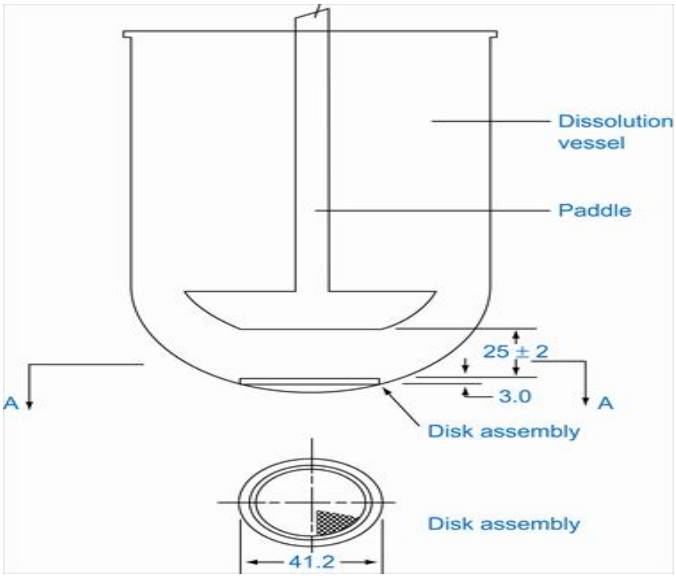


Fig. 1.9: Paddle over Disc Apparatus

1.5.7.8 Cylinder Apparatus (USP Apparatus 6)

This apparatus is also used for evaluation of transdermal products and is similar to apparatus 1. Instead of basket, a stainless steel cylinder is used to hold the sample. The sample is mounted on an inert porous cellulosic material and adhered to the cylinder.

Fig. 1.10: Cylinder Apparatus

Reciprocating Disc Apparatus (USP Apparatus 7)

This apparatus is used for evaluation of transdermal products as well as non-disintegrating controlled-release oral preparations. The samples are placed on disc-shaped holders using inert porous cellulosic support which reciprocates vertically by means of a drive inside a glass container containing dissolution medium. The test is carried out at 32oC and reciprocating frequency of 30 cycles/min.

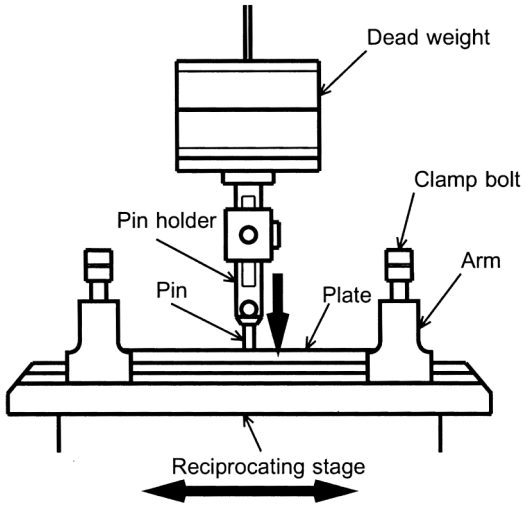


Fig. 1.11: Reciprocating Disc Apparatus

1.6 Information about the Drug under Analysis

1.6.1 Losartan Potassium

Losartan Potassium, the first of a new class of antihypertensive, is an angiotensin II receptor (type AT1) antagonist. Angiotensin II is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. Losartan and its principal active metabolite block the vasoconstriction and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues. Losartan potassium is now regarded as the first-line therapy option for treating high blood pressure.

1.6.2 History

In 1898, the physiologist Robert Tigerstedt and his student, Per Bergman, experimented with rabbits by injecting them with kidney extracts. Their results suggested the kidneys produced a protein, which they named renin, that caused a rise in blood pressure. In the 1930s, Goldblatt conducted experiments where he constricted the renal blood flow in dogs; he found the ischaemic kidneys did in fact secrete a chemical that caused vasoconstriction. In 1939, renin was found not to cause the rise in blood pressure, but was an enzyme which catalyzed the formation of the substances that were responsible, namely, angiotensin I (Ang I) and Ang II.

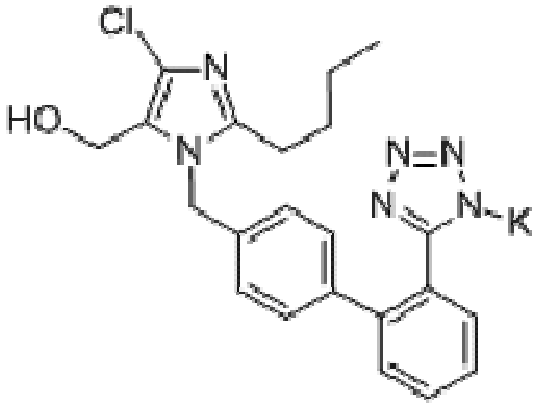
In the 1970s, scientists first observed Ang II to harm the heart and kidneys, and individuals with high levels of renin activity in plasma were at increased risk of myocardial infarction and stroke. With the introduction of angiotensin converting enzyme (ACE) inhibitors in the late 1970s it was confirmed that Ang II plays an important role in regulating blood pressure and electrolyte and fluid balance.

Before that attempts had been made to develop useful Ang II receptor antagonists and initially, the main focus was on angiotensin peptide analogues. Saralasin and other Ang II analogues were potent Ang II receptor blockers but the main problem was a lack of oral bioavailability.

In the early 1980s it was noted that a series of imidazole-5-acetic acid derivatives diminished blood pressure responses to Ang II in rats. Two compounds, S-8307 and S-8308, were later found to be highly specific and promising non-peptide Ang II receptor antagonists but using molecular modeling it was seen that their structures would have to mimic more closely the pharmacophore of Ang II. Structural modifications were made and the orally active, potent and selective nonpeptide AT1 receptor blocker losartan was developed. In 1995 losartan was approved for clinical use in the United States and since then six additional ARBs have been approved. These drugs are known for their excellent side-effects profiles, which clinical trials have shown to be similar to those of placebos.

1.6.3 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 C22H22ClKN6O



Structural formula

1.6.4 Pharmacokinetics [13]

Absorption

Well absorbed. Food decreases absorption but has only minor effects on losartan AUC or AUC of active metabolite. Systemic bioavailability is about 33%. T max is 1 h (losartan) and 3 to 4 h (metabolite). While C max of drug and active metabolite are equal, metabolite AUC is 4 times greater than that of losartan.

Distribution

Linear pharmacokinetics. Vd is 34 L (losartan) and 12 L (metabolite). Losartan and active metabolite are highly bound to plasma proteins, primarily albumin. Neither losartan or metabolite accumulates in plasma upon repeated daily dosing.

Metabolism

Undergoes substantial first-pass metabolism by CYP-450 2C9 and 3A4 enzymes. Fourteen percent of an oral dose is converted to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonist activity.

Elimination

The t ½ is 2 h (losartan) and 6 to 9 h (metabolite). Renal Cl is 75 mL/min (losartan) and 25 mL/min (metabolite). Total plasma Cl is 600 mL/min (losartan) and 50 mL/min (metabolite). Biliary excretion contributes to the elimination of losartan and metabolite. About 4% is excreted unchanged in the urine and 6% excreted as active metabolite in urine.

1.6.5 Indications

Losartan is indicated for the treatment of all grades of hypertension, chronic heart failure, Stroke risk reduction in hypertension & LVH and Nephropathy in type 2 Diabetes. It may be used alone or in combination with other antihypertensive agents. It is an effective alternative for patients who have to discontinue an ACE inhibitor because of persistent dry cough.

1.6.6 Dosage & Administration

Hypertension: The usual starting dose is 50 mg once daily. In patients with possible depletion of intravascular volume or patients with a history of hepatic impairment, starting dose is 25 mg once daily. Losartan can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg. No initial dosage adjustment is necessary for elderly or renal impairment patients. If blood pressure is not controlled by Losartan, a low dose of a diuretic (Hydrochlorothiazide) may be added. Losartan may be administered with or without food.

Chronic heart failure: 12.5 mg once daily, increased at weekly intervals to 50 mg once daily if tolerated,

Stroke risk reduction in hypertension & LVH: 50 mg once daily. Hydrochlorothiazide 12.5 mg daily should added. Maximum dose-Losartan 100 mg followed by Hydrochlorothiazide 25 mg once daily.

Nephropathy in type 2 Diabetes: 50 mg once daily. Maximum dose-100 mg once daily.

1.6.7 Side Effects

Overall incidence of adverse effects of Losartan potassium is comparable to placebo in clinical studies. The most common adverse events occuring with Losartan potassium at a rate of >1% above placebo were upper respiratory infection (7.9% vs 6.9%), dizziness (3.5% vs 2.1%) and leg pain (1.0% vs 0.0%).

1.6.8 Contraindications

Losartan potassium is contraindicated in patients who are hypersensitive to the active ingredient or any component of the drug.

1.6.9 Use in Pregnancy & Lactation

Losartan potassium must be discontinued as soon as possible when pregnancy is detected. It should not be prescribed during lactation as there is no information in humans on the passage of Losartan (Losartan potassium) into breast milk.

1.6.10 Drug Interaction

No drug interactions of clinical significance have been identified. Drugs which have been studied in clinical pharmacokinetic trials include –

(1) Hydrochlorothiazide,
(2) Digoxin,
(3) Warfarin,
(4) Cimetidine,
(5) Ketoconazole and
(6) Phenobarbital.

1.6.11 Precautions

Losartan potassium should be used with caution in patients with known hypersensitivity to the drugs that act through renin-angiotensin system. Special precaution should be taken when it is administered to the patients with renal and hepatic impairment. Safety and effectivenss of Losartan potassium in pediatric patients have not been established.

1.6.12 Storage

To store this medicine:

- Keep out of the reach of children.
- Store away from heat and direct light.
- Do not store in the bathroom, near the kitchen sink, or in other damp places. Heat or moisture may cause the medicine to break down.
- Keep the oral liquid form of this medicine from freezing.
- Do not keep outdated medicine or medicine no longer needed. Be sure that any discarded medicine is out of the reach of children.

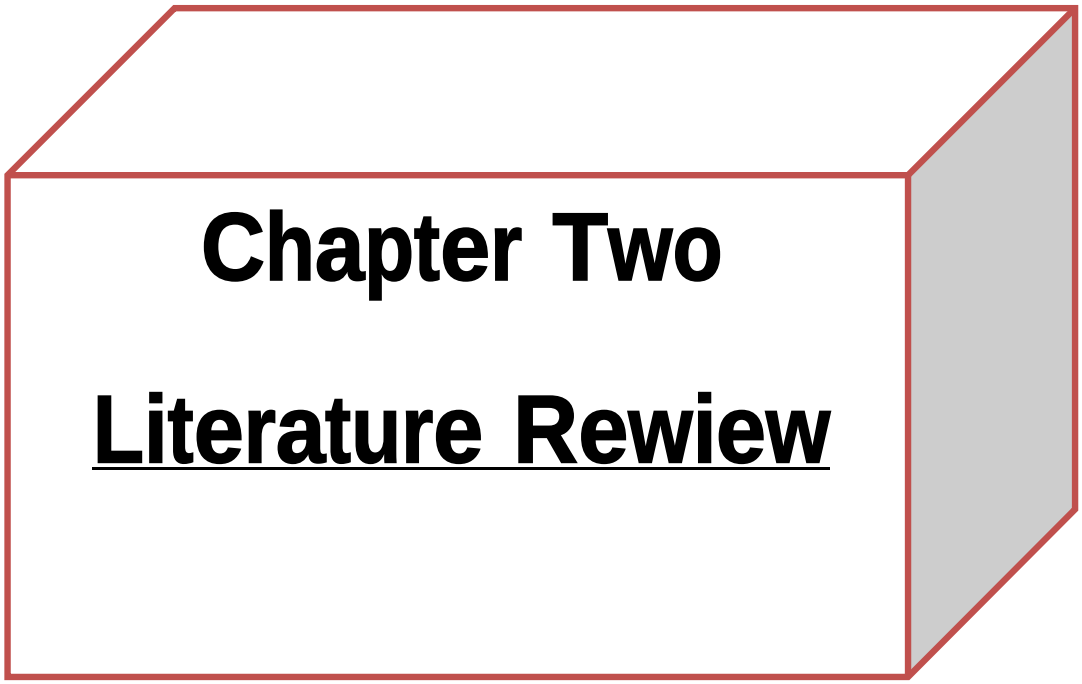
1.1: SOME MARKET PREPARATIONS OF LOSARTAN POTASSIUM

Name of the company	Brand name	Dosage form available
Incepta Pharmaceuticals Ltd.	Osartil	25, 50, 100 mg tablet
Beximco Pharmaceuticals Ltd.	Prosan	25, 50, mg tablet
Square Pharmaceuticals Ltd.	Angilock	25, 50, 100 mg tablet
Aristopharma Ltd	Osartan	25, 50, mg tablet
Opsonin Pharma Limited	Larb	25, 50, 100 mg tablet
ACI Limited	Rosatan	25, 50, mg tablet
Eskayef Bangladesh Ltd.	CARDON	25 mg & 50 mg tablet

Purpose of this work

The main objectives of this work described below

- The major purpose of this project work is to find out the quality of the exported medicine available in Bangladesh. Representated by Losartan potassium.
- This project work ensures the quality of medicine and awareness among the people's health, health practitioners and drug control authority.
- To find out the growth rate of pharma market of bangladesh in global market.
- To find out the growth chance of pharma market in global market.
- Substandard or spurious drugs could endanger patient's life. After the implementation of the National Drug Policy 1982, the quality of marked drugs, no doubt, improved, but not improved as expected. This realization makes this project thesis to evaluate the Losartan potassium market preparations.
- This project work provides a comprehensive knowledge about the 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 Frusemide preparations.


Chapter Two
Literature Rewiew

TITLE: DEVELOPMENT AND OPTIMIZATION OF LOSARTAN POTASSIUM TABLETS (A. K. BEHERA, A. K. NAYAK2, B. R. MOHANTY, B. B. BARIK)

The present investigation highlighted the formulation and optimization of losartan potassium tablets. To achieve this goal, various formulation of losartan potassium tablets were prepared and evaluated with respect to the various quality parameters both in process parameters for granules (loss on drying, bulk density, tapped density, compressibility index, Hausner's ratio) and parameters for finished products (average weight, weight variation, tablet thickness, friability, hardness, disintegration time, drug content, *in vitro* dissolution studies). On the basis of these parameters, the formula was optimized and compared with the innovator. It was observed that the optimized losartan potassium tablet was pharmaceutically equivalent with the innovator. The stability of optimized tablets at various atmospheric conditions was done and stability parameters were satisfactory.

TITLE: A NOVEL DRUG-DRUG SOLID DISPERSION OF HYDROCHLORO THIAZIDE LOSARTAN POTASSIUM (M.PANNEERSELVAM, R.NATRAJAN, S.SELVARAJ AND N.N.RAJENDRAN)

To investigate the effect of a novel drug- drug solid dispersion approach on the dissolution of Hydrochlorothiazide in a fixed dose combination with Losartan potassium. Solid dispersion of Hydrochloro thiazide and losartan potassium (12.5mg: 50mg) was prepared by co-precipitation Method. Solid dispersions were characterized by differential scanning calorimetry, x-ray diffractometry and dissolution tests and the results were compared with that of pure drugs and physical mixtures.Solid dispersion as well as physical mixture were then compressed into tablets and evaluated for physicochemical, stability and dissolution characteristics and the results compared with commercial tablets. Both solid dispersion and solid dispersion tablets of hydrochloro thiazide and losartan potassium showed an enhanced dissolution of hdrochloro thiazide compared with pure hydrochlorothiazide, physical mixture, and commercial tablets. The solubility of hydrochlorothiazide increased with increase in concentration of losartan potassium as observed from the phase solubility study. Stability study on the tablets showed no changes either in the drug content or in the dissolution profile. The results of present study suggest that the novel drug-drug solid dispersion approach is promising for improving dissolution of poorly soluble drugs presented in a fixed dose combination with soluble drugs.

TITLE: FORMULATION AND CHARACTERIZATION OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM OF LOSARTAN POTASSIUM(MANISH JAIMINI, YUVERAJ SINGH TANWAR, BIRENDRA SRIVASTAVA)

Floating matrix tablets of losartan potassium were developed with an aim to prolong its gastric residence time and increase the bioavailability of drug. Rapid gastrointestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. The tablets were prepared by wet granulation technique, using polymers Methocel K15 and Methocel K100 in combination with other standard excipients. Sodium bicarbonate was incorporated as gas generating agent. The effects of sodium bicarbonate and polymers on drug release profile and floating properties were investigated. It was found that viscosity of Methocel K15 and Methocel K100 along with sodium bicarbonate had significant impact on the release and floating properties of the delivery system. The decrease in the release rate was observed with an increase in the viscosity of the polymeric system. Polymer with high viscosity Methocel K100 was shown to be beneficial than low viscosity polymer Methocel K15 in improving the floating properties of gastric floating drug delivery system (GFDDS). The observed difference in the drug release and floating properties of GFDDS could be attributed to the difference in the basic properties of two polymers, Methocel K15 and Methocel K100 due to their water uptake potential and functional group substitution. The release mechanism were explored and described with zero-order, first-order and Korsmeyer-Peppas equations. The drug release profiles and buoyancy of the floating tablets were stable when stored at 40°C/75% RH for 6 months.

TITLE: SIMULTANEOUS DETERMINATION AND METHOD DEVELOPMENT FOR ASSAY OF LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE DRUGS IN SOLID DOSAGE FORM BY RP-HPLC (KHAN M. RIZWAN1, SHAIKH ANIS1, THAKER A.K.)

A simple, specific, accurate and precise RP HPLC method has been developed for the simultaneous determination of Losartan Potassium (LOS) and Hydrochlorothiazide (HCTZ) from combined dosage form by reverse phase C18 column (Zorbax CN (250mm x 4.6mm) 5µ). The sample was analysed using Triethylamine: Acetonitrile: Methanol in the ratio of 33:27:40(pH adjusted to 7.0 with phosphric acid) as a mobile phase at a flow rate of 1.0ml/min

and detection at 270nm. The retention time for Losartan potassium (LOS) and Hydrochlorothiazide (HCTZ) was found to be 11.869 min and 7.893 min respectively. The stability assay was performed for this combination and was validated for accuracy, precision, linearity, specificity and sensitivity in accordance with ICH guidelines. Validation revealed the method is specific, rapid, accurate, precise, reliable, and reproducible.Calibration plots were linear over the 70%-130% concentration ranges for both the drugs of LOS and HCTZ respectively, and recoveries from combined dosage form were between 98 and 102%. The method can be used for estimation of combination of these drugs in combined dosage form.

Chapter Three

Materials And Methods

3.1 Materials

3.1.1 Collection of Sample

Samples from four pharmaceutical companies were randomly selected,one of the sample is patent sample. Samples were collected from retail medicine shop of Bangladesh.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. No samples were bought and analyzed whom date of expiry had already been passed. The samples were then coded with ethics for analysis.

3.1.2 Status of the Samples

The status of purchased Losartan Potassium market preparations were as follows:
Three different available brands of various manufacturers and patent of tablet were purchased for the analytical studies.

3.1.3 Coding of tablet

Five brands collected from five different pharmaceutical companies were coded as

- LT- P
- LT-01
- LT-02
- LT- 03

3.1.4 Apparatus Used in This Study

Table 3.1: Name of glassware

Name of the glass ware	Manufacturer / Source
Measuring cylinder (50 ml)	India.
Beaker (50 ml ,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	Elder.
UV-Spectrophotometer	Shimadzu.
Dissolution tester	Minhua

3.2 Methods

3.2.1 Chemical analysis

3.2.1.1 Preparation of standard solution

To prepare a standard solution, 25mg of standard was measured by the electronic balance and placed in 100ml volumetric flask. Then aseries of standard solution of standard eg, , .5µg/ml, 1µg/ml, 1.25µg/ml, 2.5µg/ml,µg/ml,etc were prepared by proper dilution by using distilled water.

3.2.1.2 Chemical analysis

A series of standard solution of standard eg, .5µg/ml, 1µg/ml, 1.25µg/ml, 2.5µg/ml,µg/ml,etc. were check for Absorbance at 250nm against a blank for each solution by UV-spectrophotometer (Shimadzu). The measured absorbances were plotted against the respective concentration of the standard solutions which give a straight line.

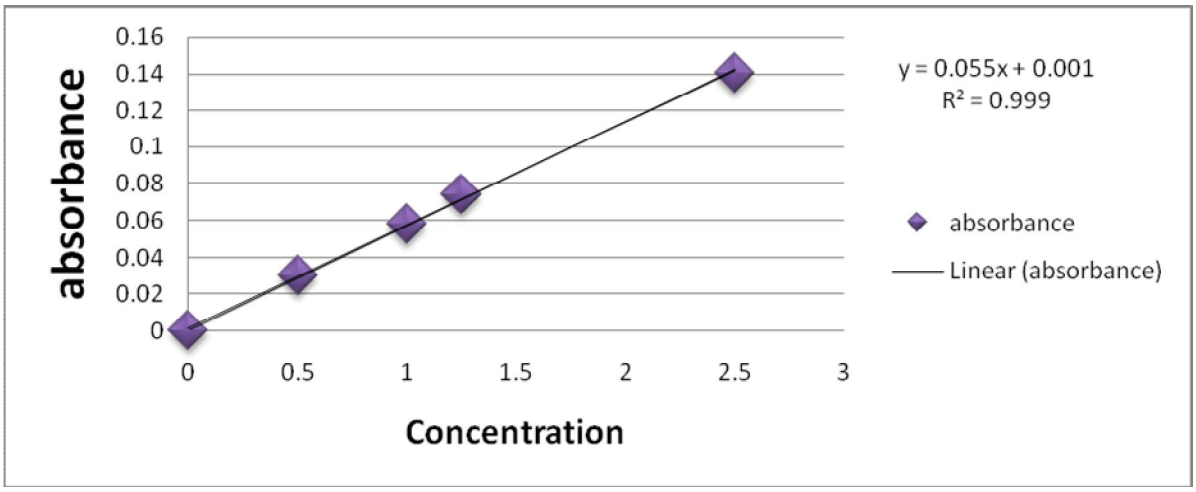


Fig.3.1: Standard curve of Losartan potassium

3.2.2 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

- USP dissolution Apparatus 2
- Whatman filter paper
- Pipette
- Volumetric flask
- UV-visible spectrophotometer

Procedure

1. The flask was filled with 900 ml of Normal water
2. The dissolution medium was heated up to 37 ℃ ±0.05℃ 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.

Calculation

$$\textbf{\% of drug release} = \frac{\text{Absorbance of sample} \times \text{Dilution factor of standard}}{\text{Absorbance of standard} \times \text{Dilution factor of sample}} \times \text{Potency} \times 100$$

In this way, % of drug release four brands of tablet was determined and the observed value for each sample was recorded.

Chapter Four

Result And Discussion

4.1 Dissolution rate test of tablets

Table 4.1: Dissolution rate after 10 minute

Sample	% of drug release
LT-P	51.2
LT-01	49.8
LT-02	48.6
LT-03	49.2

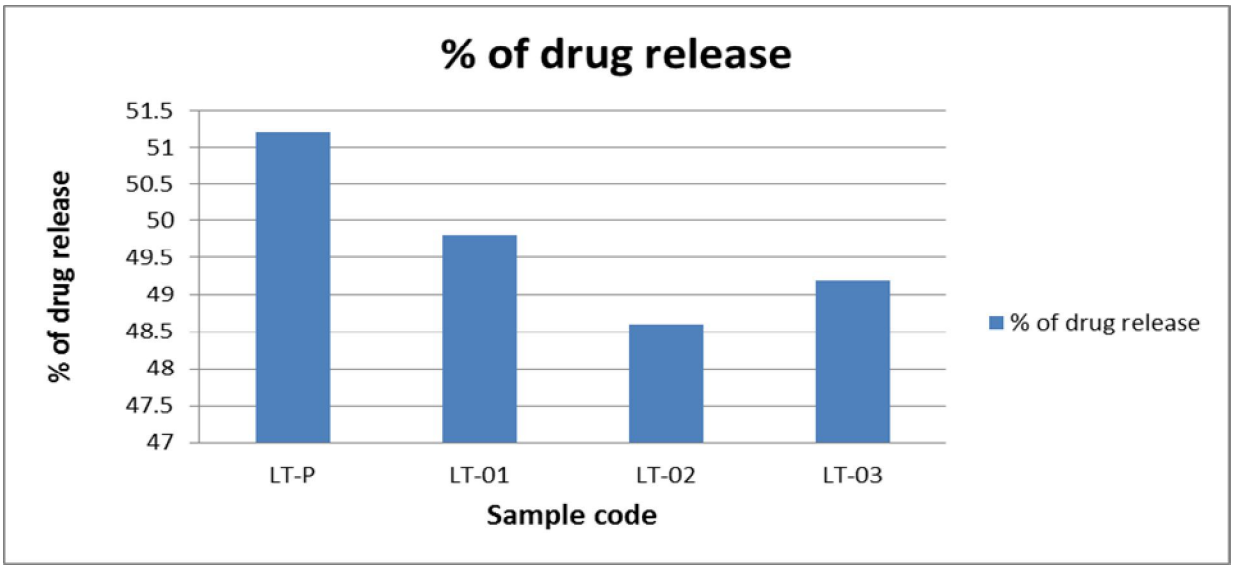


Fig. 4.1: Dissolution rate after 10 minute

Table 4.2: Dissolution rate after 20 minute

Sample	% of drug release
LT-P	72.6
LT-01	71.4
LT-02	73.8
LT-03	71.4

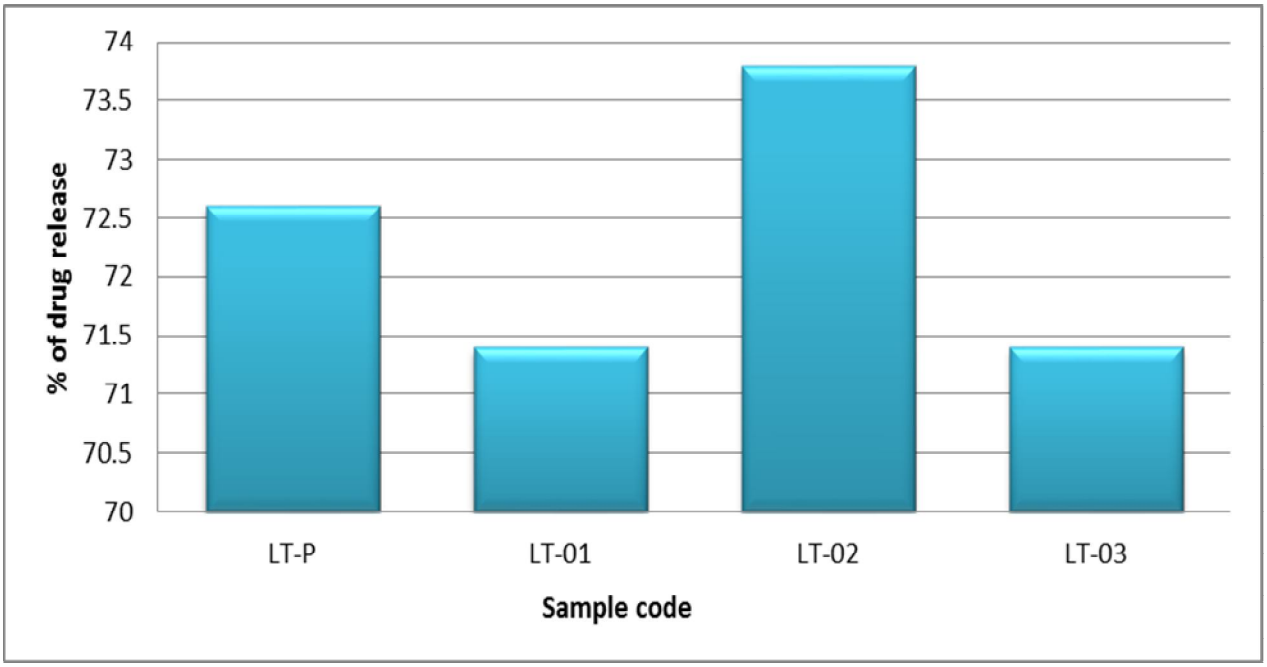


Fig. 4.2: Dissolution rate after 20 minute

Table 4.3: Dissolution rate after 30 minute

Sample	% of drug release
LT-P	81.6
LT-01	79.8
LT-02	82.6
LT-03	82.8

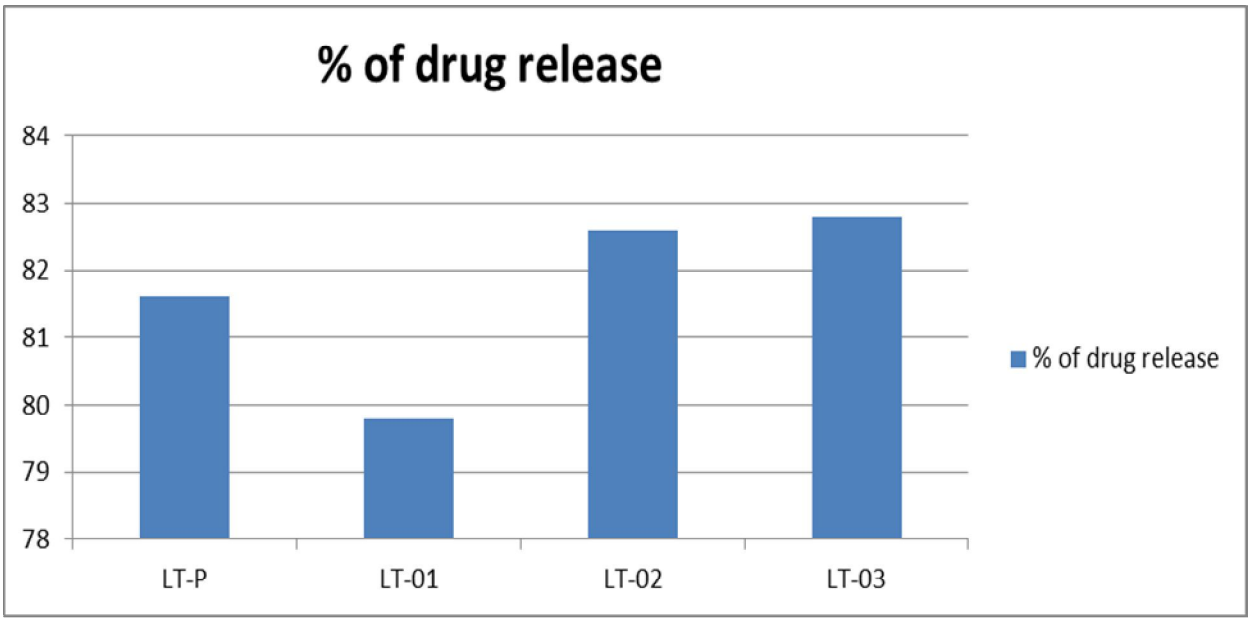


Fig. 4.3: Dissolution rate after 30 minute

Table 4.4: Dissolution rate after 45 minute

Sample	% of drug release
LT-P	94.8
LT-01	93
LT-02	92.4
LT-03	91.2

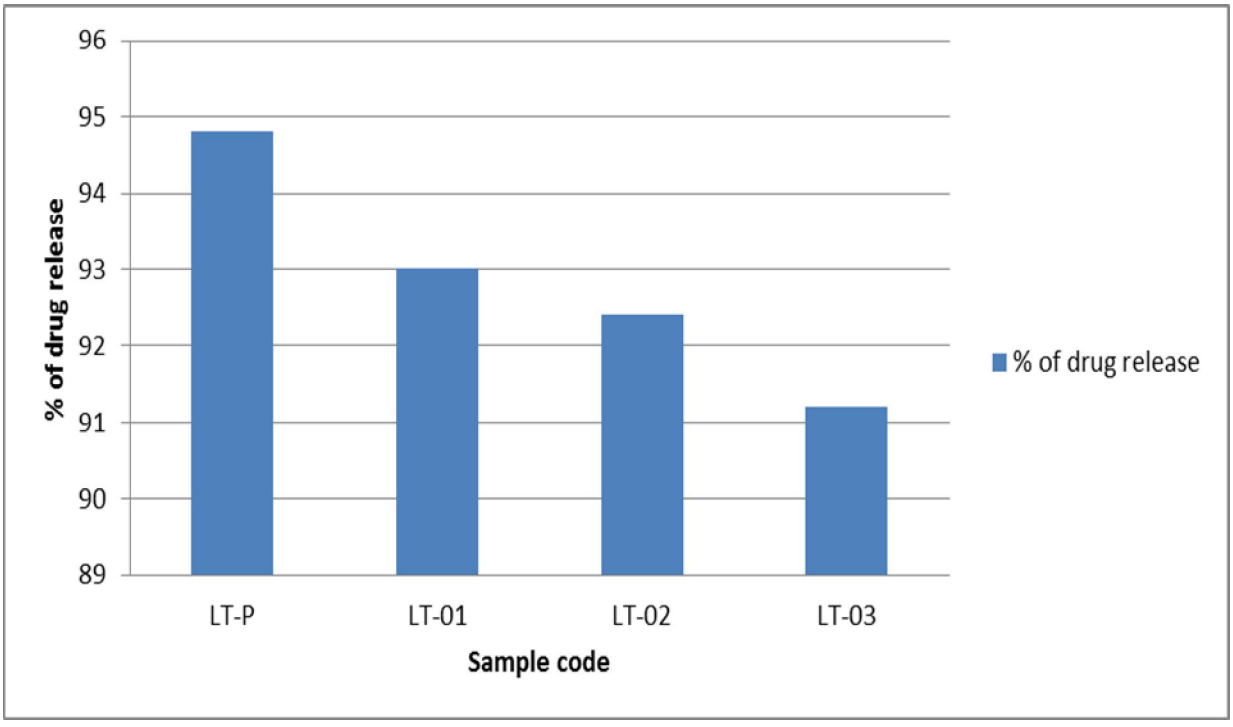


Fig. 4.4: Dissolution rate after 45 minute

4.2 Discussion

To be compliance with BP standard at least 90% of the tablets must be dissolved within 45 minutes. All the sample meet the BP standard and the quality of the all sample are same as patent quality.

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) [14].

Chapter Five

Conclusion

Conclusion

Huge export opportunities have already been opened for Bangladesh pharmaceutical sector. Growth rate of pharma market is very high because, The quality of our product meet the standard.

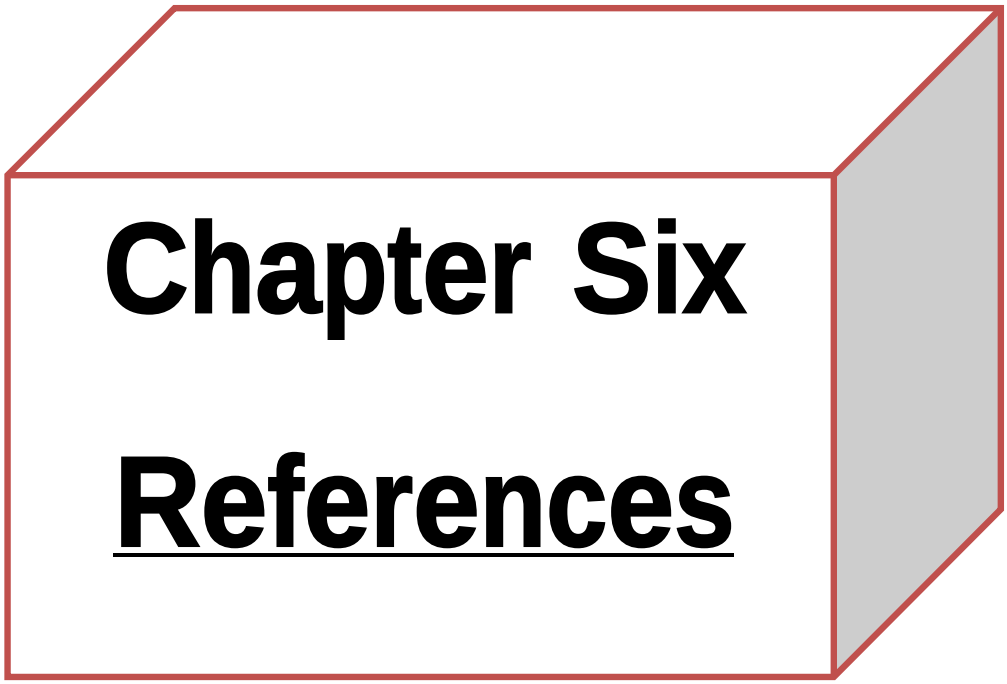
Some renowned companies have already entered the Highly Regulated Market and got the UK MHRA, EU, TGA Australia and GCC approval and some are in the process to get the USFDA & UK MHRA approval.

The present work reports the comparative study of in vitro bioequivalence of tablets formulated by different pharmaceutical companies and FDA approved patented drugs. It was observed that there was some variation in the dissolution rates but there was no much variation of the product compare with patent medicine.

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 present the actual scenario of our pharmaceutical market (medicine) which is much positive in product quality point of view that ultimately assure good health of the public.


Chapter Six
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