

**FORMULATION AND EVALUATION OF LOSARTAN  
POTASSIUM AND HYDROCHLORTHIAZIDE  
CONVENTIONAL TABLETS.**

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## **1.INTRODUCTION**

The oral route of drug administration is the most important route of administering drugs for systemic effect. About 90% of drugs used to produce systemic effects are administered by oral route. When a new drug is discovered one of the first questions a pharmacist asks is whether or not the drug can be effectively administered for its intended effect by the oral route<sup>1</sup>.

The drugs that are administered orally, solid oral dosage form represent the preferred class of products. The reasons for this preference are as follows. Tablet is unit dosage form in which one usual dose of the drug has been accurately placed by compression. Liquid oral dosage forms, such as syrups, suspensions, emulsions, solutions and elixirs are usually designed to contain one dose of medication in 5 to 30 ml and the patient is then asked to measure his or her own medication using teaspoons, tablespoon or other measuring device. Such dosage measurements are typically in error by a factor ranging from 20 to 50% when the drug is self administered by the patient.

### **1.1 TYPES OF TABLETS**

#### **A) Tablets ingested orally<sup>3</sup>**

1. Compressed tablet, e.g. Paracetamol tablet
  - a. Conventional compressed tablet

These tablets are designed to provide rapid disintegration and hence rapid drug release and represent significant proportion of tablets that are clinically used. The manufacture of this tablet involves the compression of granules or powders (both containing the drug) in the required geometry in the ingestion mechanism these tablets allows the drug to dissolve into the gastric fluid and disintegrate in the gastro intestinal tract (stomach) and finally be absorbed systemically.

b. Multiple compressed tablet

2. Repeat action tablets

3. Delayed release tablet, e.g. Enteric coated Bisacodyl tablet

4. Sugar coated tablet, e.g. Multivitamin tablet

5. Film coated tablet, e.g. Metronidazole tablet

6. Chewable tablet, e.g. Antacid tablet

**(B) Tablets used in oral cavity:**

1. Buccal tablet, e.g. Vitamin-C tablet

2. Sublingual tablet, e.g. Vicks Menthol tablet

3. Troches or lozenges

4. Dental cone

**(C) Tablets administered by other route:**

1. Implantation tablet
2. Vaginal tablet, e.g. Clotrimazole tablet

**(D) Tablets used to prepare solution:**

1. Effervescent tablet, e.g. Dispirin tablet (Aspirin)
2. Dispensing tablet, e.g. Enzyme tablet (Digiplex)
3. Hypodermic tablet
4. Tablet triturates e.g. Enzyme tablet (Digiplex)

**1.1.1 Advantages <sup>2</sup>:**

- They are unit dosage forms, they offer greatest capabilities of all oral dosage forms for the greatest dose precision and the least variability.
- Their cost is lowest of all oral dosage forms.
- They are lightest and the most compact among oral dosage forms.
- They are in general the easiest and cheapest to package.
- Product identification is potentially simplest cheapest, requiring no additional processing steps when employing and embossed are monogrammed punch face.
- They may provide the greatest ease of swallowing with the least tendency for “hang-up” above the stomach especially when coated provided the tablet disintegration is not rapid.

- They lend them to certain special release profile products such as enteric or delayed release products.
- They are better suited to large scale production than other unit oral forms.

**1.1.2 Disadvantages:**

- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low density character.
- Drugs with poor wetting, dissolution properties, intermediate to large dosages, optimum absorption high in the GIT or any combination of these features may be difficult to impossible to formulate and manufacture as a tablet that will still provide adequate full drug bioavailability.
- Bitter tasting drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to compression or the tablets may require coating. In such cases, the tablets may offer the best and lowest cost approach.

**1.2 Tablet properties <sup>4</sup>:**

Tablets can be made in virtually any shape, although requirements of patients and tableting machines mean that most are round, oval or capsule shaped. More unusual shapes have been manufactured but patients find these harder to swallow, and they are more vulnerable to chipping or manufacturing problems.

Tablet diameter and shape are determined by the machine tooling used to produce them - a die plus an upper and a lower punch are required. This is called a station of tooling. The thickness is determined by the amount of tablet material and the position of the punches in relation to each other during compression. Once this is done, we can measure the corresponding pressure applied during compression. The shorter the distance between the punches, thickness and the greater the pressure applied during compression and sometimes the harder the tablet. Tablets need to be hard enough that they don't break up in the bottle, yet friable enough that they disintegrate in the gastric tract.

The tablet is composed of the Active Pharmaceutical Ingredient (that is the active drug) together with various excipients. These are biologically inert ingredients which either enhance the therapeutic effect or are necessary to construct the tablet. The filler or diluents (e.g. Lactose or Sorbitol) are a bulking agent, providing a quantity of material which can accurately be formed into a tablet. Binders (e.g. methyl cellulose or gelatin) hold the ingredients together so that they can form a tablet. Lubricants (e.g. magnesium stearate or polyethylene glycol) are added to reduce the friction between the tablet and the punches and dies so that the tablet compression and ejection processes are smooth. Disintegrants (e.g. starch or cellulose) are used to promote wetting and swelling of the tablet so that it breaks up in the gastrointestinal tract; this is necessary to ensure dissolution of the API. Super disintegrants are sometimes used to greatly speed up the disintegration of the tablet. Additional ingredients may also be added such as coloring agents, flavoring agents and coating agents. Formulations are designed using small quantities in a laboratory machine called a Powder Compaction Simulator. This can prove the manufacturing process and provide information.

**1.3 CHOICE OF EXCIPIENTS <sup>5</sup>:**

The choice of excipients in tablet formulations depends on the API, the type of tablet, the desired characteristics, and the manufacturing process used. Several types of tablets are available in the market. These include prompt release, from which the drug dissolves in a very short time (sublingual or buccal tablets), and immediate release and modified release, which includes most of the oral administered tablets that are swallowed. Other types include effervescent, belayed, chewable, multiple compressed topical tablets and tablets for solution. The desired characteristics of a tablet may be achieved by adding colors, pigments, flavours, sweeteners and a sugar or film coating. The types of excipients selected for a formulation depend on the basic process used to manufacture the tablets.

**1.4 Drug-excipient interactions and their effect on absorption <sup>6</sup>:**

Excipients are traditionally thought of as inert but they can have tremendous impact on the ultimate pharmacological availability of a drug substance when added to a formulation. The magnitude of this effect will depend on the characteristics of the drug and on the quantity and properties of the excipients. Excipients have traditionally been classified according to the formulation they perform in a formulation, although many excipients perform multiple functions. Diluents allow the formulation of a practically sized tablet and can form large proportion by weight of a formulated product when, for example, the active ingredient is very potent. The physical characteristics of the diluents are important; for example, triamterene was shown to dissolve more rapidly when it was formulated with hydrophilic fillers such as lactose and starch as compared with insoluble



diluents. Disintegrants tend to swell when wetted and so are added to a formulation to facilitate the breakdown of the dosage form into granules and powder particles. The newer disintegrants, called superdisintegrants, cause an extremely rapid break up of a tablet owing to their ability to swell to many times their original size. Wicking and swelling were found to be the primary mechanisms of actions for tablet disintegrants, while other mechanisms, such as deformation recovery, particle repulsion theory, heat of wetting and evolution of a gas etc., may play a role in particular cases of tablet disintegration (kanig and Rudnic,1984). Co processing is defined as combining or more established excipients by an appropriate. Co processing of excipient could lead to formation of excipients with superior properties compared with the simple physical mixtures of their components or with individual components. A large number of co processed diluents are commercially available. The representative examples are Ludipress, Cellactose and starlac. The use of co processing is totally unexplored avenues in disintegrants. The widely used super disintegrants are SSG, crospovidone and croscarmellose sodium. Like diluents each super disintegrants have strengths and weakness.

### **1.5 Excipients used in tablets <sup>7</sup>:**

Excipients are inert substances used as diluents or vehicles for a drug. In the pharmaceutical industry it is a catch all terms which includes various sub-groups. Comprising diluents or fillers, binders or adhesives, disintegrants, lubricants, glidants or flavours, fragrances and sweeteners. All of these must meet certain criteria as follows:-

1. They must be physiological inert.
2. They must be acceptable to regulatory agencies
3. They must be physiologically and chemically stable.
4. They must be free of any bacteria considered to be pathogenic or otherwise objectionable.
5. They must not interfere with the bioavailability of the drug.
6. They must be commercially available in the form and purity commensurate to pharmaceutical standards.
7. Cost must be relatively inexpensive.
8. They must conform to all current regulatory requirements.

To assure that no excipient interferences with the utilization of the drug, the formulator must carefully and critically evaluate combinations of the drug with each of the contemplated excipients and must ascertain compliance of each ingredient with existing standards and regulations.

The screening of drug-excipients and excipient-excipient interactions should be carried out routinely in preformulation studies.

### **1.5.1 Fillers: (Diluents)**

Tablet fillers of comprise a heterogeneous group of substances. Since they often comprise the bulk of the tablet, selection of a candidate from this group as a carrier for a drug is of prime importance.

### **1.5.2 Binders:**

Binders are the glue that holds powders together to form granules. They are the adhesives that are added to tablet formulations to provide the cohesiveness required for that bonding together of the granules under compaction to form a tablet. The quantity used and the method of application must be carefully regulated, since the tablet must remain intact when swallowed and then release its medicament.

Binders are either sugar or polymeric materials. The latter fall into two classes:

- Natural polymers such as starches or gums include acacia, tragacanth and gelatin.
- Synthetic polymers such as polyvinylpyrrolidone, methyl and ethyl cellulose and hydroxyl propyl cellulose. Binders of both types may be added to the powder mix and the mixture wetted with water, alcohol–water mixtures or a solvent, or binder may be put into solution in the water or solvent and added to the powder. The latter method using the solution of the binder requires much less binding material to achieve the same hardness than if added dry.

- Commonly used binders are gelatin, glucose, methyl cellulose, acacia, starch paste, povidone, alcohol, PVP in water, PVP in alcohol and sorbitol in water

### **1.5.3 Lubricants:**

Lubricants are used in tablet formulation to ease the ejection of the tablet from the die, to prevent sticking of tablets to the punches, and to prevent excessive wear on punches and dies. They function by interposing a film of low shear strength at the interface between the tablet and the die wall and the punch face. Lubricants should be carefully selected for efficiency and for the properties of the tablet formulation.

In selecting a lubricant, the following should be considered:

1. Lubricants markedly reduce the bonding properties of many excipients.
2. Over blending is one of the main causes of lubrication problems. Lubricants should be added last to the granulation and tumble-blended for not more than 10 min.
3. Lubricant efficiency is a function of particle size; therefore, the finest grade available should be used and screened through a 100-300 mesh screen before use.

Examples of lubricants commonly used are magnesium stearali acid, talc, starch.

**1.5.4 Disintegrants:**

Disintegrants are used in tablet preparation to break the tablet faster. But some of the disintegrants are also having property of enhancing solubility of insoluble drug.

**Examples:**

- Crospovidone: Crospovidone is disintegrant, crospovidone also enhances solubility.
- Sodium starch glycollate: sodium starch glycollate is widely used in oral pharmaceuticals and as a disintegrant in capsule.

**1.5.5 Glidants:**

Glidants are materials that improve the flow characteristics of granules by reducing the interparticulate friction. In proper amounts they also serve to assure smooth and uniform flow at all times.

Many of the excipients commonly used in tablet formulations are especially applicable for use in chewable tablets due to their ability to provide the necessary properties of sweetness and chewability. In general; these fall into the sugar category, although a combination of excipients with artificial sweeteners may provide a satisfactory alternative.

Uko-Nne and Mendes reported on the development of dried honey and molasses products marketed for use in chewable tablets. Both are free-flowing compressible materials with characteristics colours, odours and tastes that limit their primary applicability to the vitamin/food supplement field.

#### **1.5.6 Super disintegrants in immediate release tablets:**

A disintegrant is an excipient which is added to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment. This is especially important for immediate release products where rapid release of drug substance is required. A disintegrant can be added to a powder blend for direct compression or encapsulation. It can also be used with products that are wet granulated. While there are some tablets fillers (starch, MCC) which aid in disintegration, there are more effective agents referred to as superdisintegrants.

#### **1.6 Method of addition of disintegrants :**

The requirement placed on the tablet disintegration should be clearly defined. The ideal disintegrant has,

1. Poor solubility.
2. Poor gel formation.
3. Good hydration capacity.

4. Good molding and flow properties.
5. No tendency to form complexes.

Disintegrants are essentially added to tablet granulation for causing the compressed tablet to break or disintegrate when placed in aqueous environment.

There are three methods of incorporating disintegrating agents into tablets:

- Internal addition
- External addition
- Partly internal and external

In external addition method, the disintegrant is added to the sized granulation with mixing prior to compression. In internal addition method, the disintegrant is mixed with other powders before wetting the powder mixture with the granulating fluid. Thus the disintegrant is incorporated within the granules. When these methods are used part of the disintegrants are added internally and part externally. This provides immediate dispersion of the tablet into previous compressed granules while the disintegrating agents within the granules produce further erosion of the granules to the original powder particles. The two stepped method usually produces better and more complete disintegration than the usual method of adding the disintegrant to the granulation surface only.

**1.7 Method of preparation of tablet:**

Compressed tablets may be made by three basic methods.

1. Wet granulation
2. Direct compression
3. Slugging

**1.7.1 Wet granulation <sup>8</sup>:**

Wet granulation forms the granules by binding the powders together with an adhesive, instead of by compaction. The wet granulation technique employs a solution, suspension, or slurry containing a binder, which is usually added to the powder mixture; however, the binder may be incorporated dry into the powder mix, and the liquid may be added by itself. The method of introducing the binder depends on its solubility and on the components of the mixture. Since, in general the mass should merely be moist rather than wet or pasty, there is a limit to the amount of solvent that may be employed. Therefore, when only a small quantity is permissible, the binder is blended in with the dry powders initially; when a large quantity is required, the binder is usually dissolved in the liquid. The solubility of the binder also has an influence on the choice of methods, since the solution should be fluid enough to disperse readily in the mass. The liquid plays a key role in the granulation process. Liquid bridges are developed between particles, and the tensile strength of those bonds increases as the amount of liquid added is increased. These surface tension forces and capillary pressure are primarily responsible for initial granule formation and strength. Once the granulating liquid has been added, mixing continues until a uniform dispersion is attained and all the binder has been activated.



During granulation, practices and agglomerates are subjected to consolidating forces by action of machine parts and of inter particulate forces. Granulation in large blenders requires 15min to an hour. The length of time depends on the powder mixture and the granulating fluid, and upon the efficiency of the mixer. A rough way of determining the end point is to press a portion of the mass in the palm of the hand; if the ball crumbles under moderate pressure, the mixture is ready for the next stage in processing, which is wet screening. Granulation may be considered as a size enlargement process during which small particles are formed into larger, physically strong agglomerates in which original particles can still be identified. High shear forces in high speed mixers are widely used in the pharmaceutical industry for wet granulation. Processing parameters were shown to affect the growth rate of granules in the high-shear wet granulation. The main objective of granulation is to improve flow properties and compression characteristics of the mixture to prevent segregation of the constituents. Though this technique is old for the product of compressed tablet, this method is being used because of the content uniformity.

Granulation is a process of size enlargement whereby small particles are gathered into larger, permanent aggregates in which the original particles can still be identified.<sup>1</sup>

The major reason for granulating the powdered starting material in the manufacture of tablets and granules are to:

- To improve the flow properties so that, the mass uniformity of the dose.
- To prevent segregation of ingredients in the mixture.

- To improve the compression characteristics of the mixture.
- To reduce the environmental hazards for the working personnel due to dust formation from toxic materials.
- To reduce the bulk volume of voluminous powders and make them more convenient for storage and transport.
- To improve the appearance of the product.

The granules being heavier do not blow out of the die and do not clog the lower punch.



**Rapid mixer granulator (RMG) with impeller and chopper**

### **1.8 Drying**

Drying in the Rapid Dryer makes use of the fluidized bed process, a technique similar to the one used in industrial dryers. Ambient air is drawn in through a filter. A blower moves the air around the motor and across heating elements, and ultimately forces it

through the perforated plate and into the detachable drying container. The solid particles are blown upward and agitated and thus kept separate one from another so that their surfaces cannot stick together. The air stream extracts moisture from the particles and then exits through the filter bag in cover of the drying container.

### **1.9 Film coating:**

The Film-coating technology has become well established in the pharmaceutical industry and has made great advances. Improved production equipment and the development of highly efficient film-coating formulations and polymers have accelerated the acceptance of film-coating technologies.

Hydroxypropyl methyl cellulose (HPMC) was typically used in film-coating formulations, as a film forming polymer, and remains in common usage. HPMC is obtained through a sumptuous serial procedure. Firstly, cellulose is extracted from either cotton flock or paper pulp and solubilised in sodium hydroxide solutions to obtain swollen cellulose. Hydroxypropyl methyl cellulose is subsequently obtained by treating the swollen cellulose with methyl chloride and propylene oxide. Finally the mass is dried, comminuted and packaged after removal of dopants. HPMC is typically sold in several grades with different viscosities. To realize high solid matter contents HPMC of low viscosity is commonly used. Optimized formulations however consist of a combination of the different grades to combine their various physical properties. Optimally developed formulations could therefore obtain up to 20 percent solid matter content if further additives (Eg. sugar alcohols) are added. Since the formulation of those multi component systems is quite inconvenient the next generation of film forming polymer came up:

polyvinyl alcohol (PVA). PVA is a film-forming agent produced by the hydrolysis of polyvinyl acetate. An alkali metal or inorganic acid is used as a catalyst in methanol, ethanol or a mixture of ethanol and methyl acetate, to accelerate the hydrolysis of polyvinyl acetate to yield polyvinyl alcohol (PVA). Nowadays, PVA is used as film forming agent in a number of pharmaceutical formulations. An optimized instant release film coating formulation based on PVA, can be applied on the tablets with a solid matter content of up to 25 percent, which is a major step towards achieving highly efficient film coating processes. Besides the increased solids content of the formulations, other properties, like reduced permeability of water vapour or oxygen through a film, have also been achieved. Apart from the film forming polymer and pigments, a plasticizer is typically added to HPMC as well as PVA based formulations. The addition of plasticizer improves physical properties like the flexibility of the film, or lowering of the glass transition temperature ( $T_g$ ). However, these plasticizers might migrate in the film and can cause stability problems of the film respectively the finished dosage form. The latest generation of film coating polymers was developed targeting an improved coating efficiency. An example of this new generation is Kollicoat® IR, which is obtained by grafting polyvinyl alcohol on a polyethylene glycol backbone. The PEG as covalently bonded plasticizer prevents the formulation from instability due to migration of the plasticizer through the film or incompatibilities with actives. Due to the low viscosity compared to all previous film coating materials, formulations based on Kollicoat® IR can be applied in concentrations of up to 30 percent.

PEG-PVA grafted polymer formulations are easy to dissolve, form flexible films on tablets and have a similar barrier function for water vapour and oxygen as PVA based

films. Using these types of polymers for film coating purposes, more convenient and more efficient coating formulations have been developed by several suppliers. These coating systems are mixtures of film-forming polymers, plasticizers, colour ingagents and other excipients, which can be easily stirred into water or organic solvents, to produce the dispersion for the film coating of tablets. There are several approaches available in the market: (I) HPMC or PVA based coating systems which are often customized powder blends for every single finished dosage form (II) The PEG-PVA based systems which are sold as a seven base colour system, containing homogeneous granules, which can match hundreds of different colours by combining these coloured granules.

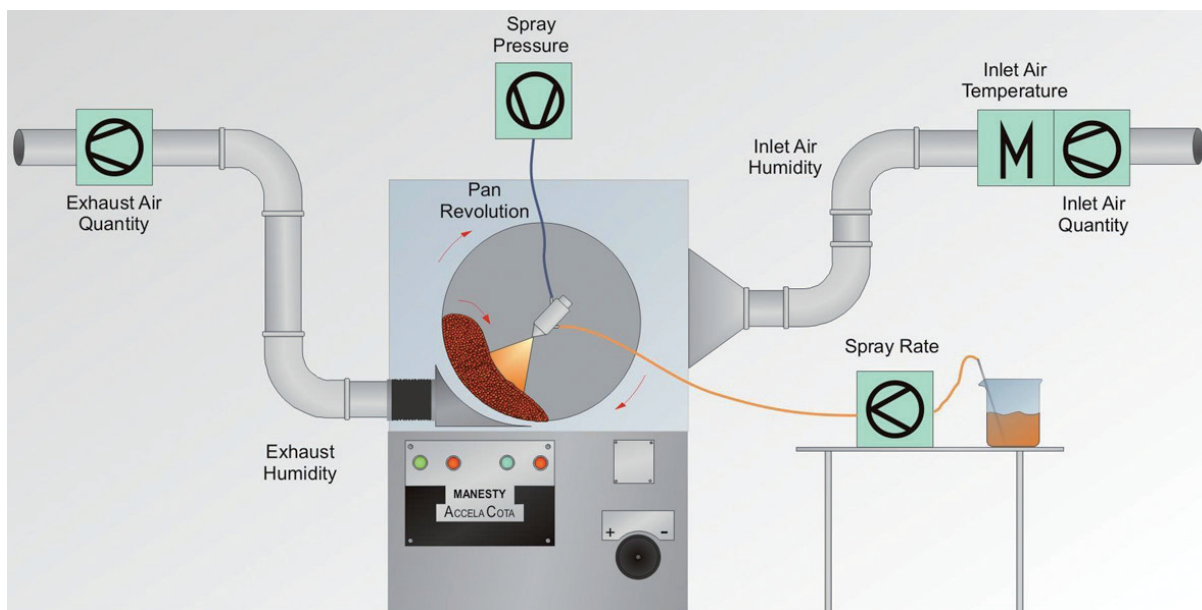
Rapid development of film-coating formulations - in order to improve efficiency - and the increasing interest in optimization of process times and energy consumption, suggests that a comparison of commonly-used coating systems would be in order.

### **1.9.1 Energy flux in coating process**

The thermodynamic model introduced below, potentially describes the energy flux in a model film coating process and helps to provide an understanding of this process. For the calculation of the energy flux in a film coating process, the first law of thermodynamics can be applied. Since the sum of all energies in a closed system remains the same, the total energy can be described as:

$$\begin{aligned} Q_{\text{inlet air}} &= Q_{\text{heat tablets}} + Q_{\text{heat coater}} + Q_{\text{heat solution}} + Q_{\text{evap. solvent}} + Q_{\text{loss}} + \\ &Q_{\text{exhaust air}} \end{aligned}$$

For the film coating process itself various energies are of importance. However, focusing on ecological and economical aspects enthalpies derived from atomizing air and dispersion can be disregarded, as these energies do not depend on energy consumption of heaters. Qinlet air describes the energy introduced into the coating process through the heated and conditioned process air. Yet this amount of energy has to be used for any kind of economical and ecological considerations, as it represents the main amount of energy, introduced in the film coating process. Besides the amount of energy introduced due to the inlet air and atomizing air, energy is also required to revolve the coating drum or to convey the coating dispersion to the spray nozzles. Due to the fact, that the amount of energy for this is minor, compared to the total energy and that the process settings (and hence the required energy) is the same in all compared cases, this energy is not considered in the calculation of energy savings.



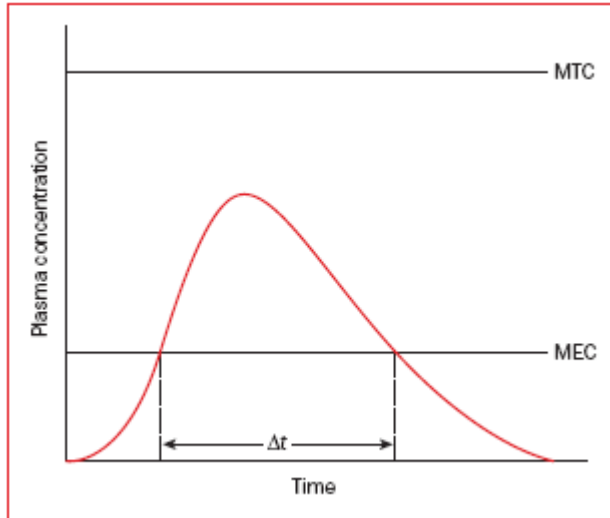
**Figure–1 Sketch of a typical film coating process and its influencing parameters.**

**1.10 Conventional drug delivery system <sup>14</sup>:**

Conventional drug delivery system is defined as – Conventional release tablets are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and other techniques.

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional drug delivery is effective, but some drugs are unstable or toxic and have narrow therapeutic window and solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels as shown in fig. This continuous drug delivery can be achieved by the use of controlled drug delivery systems. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity and improved patient convenience. The main goal of modified drug delivery systems is to improve the effectiveness of drug therapies.

Conventional dosage forms are rapidly absorbed, with the ascending and descending portions of the concentrations versus time curve reflecting primarily the rate of absorption and elimination, respectively. Because of the rapid rate of absorption and elimination from conventional dosage forms, drugs are usually administered more than once daily, with the frequency being dependent on biological half life ( $t_{1/2}$ ) and duration of pharmacological effect. The time of dosing may also be effected by therapeutic index of a drug.



**Figure - 2:** Drug plasma levels after oral administration of a drug from an immediate-release dosage form. The therapeutic range is the concentration interval between the minimal effective concentration (MEC) and the minimum toxic concentration (MTC).  $\Delta t$  is the time interval the drug is in the therapeutic range.

### 1.10.1 Advantages of conventional drug delivery systems:

- Release the drug immediately.
- More flexibility for adjusting the dose.
- It can be prepared with minimum dose of drug.
- There is no dose dumping problem.
- Conventional drug delivery systems used in both initial stage and final stage of disease.
- At the particular site of action the drug is released from the system.



**1.10.2. Disadvantages of conventional drug delivery systems**

- In conventional oral drug delivery systems, there is little or no control over the release of the drug and effective concentration at the target site.
- The dosing pattern in conventional dosage forms results in constantly changing, unpredictable and often sub-therapeutic plasma concentrations leading to marked side effects in some cases.
- Conventional drug delivery system is not suitable for the drugs which cause irritation to the gastric mucosa.

**1.11 Hypertension**

Hypertension is a chronic medical condition in which the blood pressure is elevated. It is also referred to as high blood pressure or shortened to HT, HTN or HPN. The word "hypertension", by itself, normally refers to systemic, arterial hypertension.

Hypertension can be classified as either essential (primary) or secondary. Essential or primary hypertension means that no medical cause can be found to explain the raised blood pressure and represents about 90-95% of hypertension cases. Secondary hypertension indicates that the high blood pressure is a result of (*i.e.*, secondary to) another condition, such as kidney disease or tumours (adrenal adenoma or pheochromocytoma).

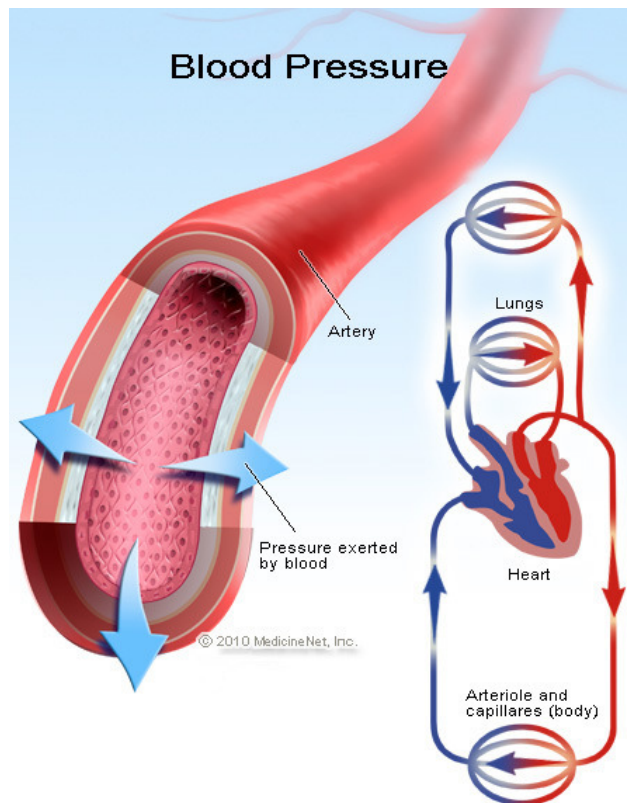
High blood pressure (HBP) or hypertension means high pressure (tension) in the arteries. Arteries are vessels that carry blood from the pumping heart to all the tissues and organs of the body. High blood pressure does not mean excessive emotional tension, although emotional tension and stress can temporarily increase blood pressure. Normal blood pressure is below 120/80; blood pressure between 120/80 and 139/89 is called "pre-hypertension", and a blood pressure of 140/90 or above is considered high.

The top number, the systolic blood pressure, corresponds to the pressure in the arteries as the heart contracts and pumps blood forward into the arteries. The bottom number, the diastolic pressure, represents the pressure in the arteries as the heart relaxes after the contraction. The diastolic pressure reflects the lowest pressure to which the arteries are exposed.

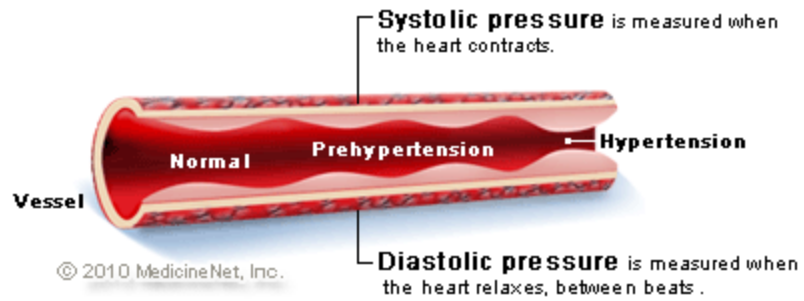
An elevation of the systolic and/or diastolic blood pressure increases the risk of developing heart (cardiac) disease, kidney (renal) disease, hardening of the arteries (atherosclerosis or arteriosclerosis), eye damage, and stroke (brain damage). These complications of hypertension are often referred to as end-organ damage because damage to these organs is the end result of chronic (long duration) high blood pressure. For that reason, the diagnosis of high blood pressure is important so efforts can be made to normalize blood pressure and prevent complications.

It was previously thought that rises in diastolic blood pressure were a more important risk factor than systolic elevations, but it is now known that in people 50 years or older systolic hypertension represents a greater risk.

The American Heart Association estimates high blood pressure affects approximately one in three adults in the United States - 73 million people. High blood pressure is also estimated to affect about two million American teens and children, and the Journal of the American Medical Association reports that many are under-diagnosed. Hypertension is clearly a major public health problem.



**Figure – 3 Blood pressure in blood vessels**



**Figure – 4 Tension in vessels**

### **1.11.1 Symptoms**

Uncomplicated high blood pressure usually occurs without any symptoms (silently) and so hypertension has been labeled "the silent killer." It is called this because the disease can progress to finally develop any one or more of the several potentially fatal complications of hypertension such as heart attacks or strokes. Uncomplicated hypertension may be present and remain unnoticed for many years, or even decades. This happens when there are no symptoms, and those affected fail to undergo periodic blood pressure screening.

Some people with uncomplicated hypertension, however, may experience symptoms such as headache, dizziness, shortness of breath, and blurred vision. The presence of symptoms can be a good thing in that they can prompt people to consult a doctor for treatment and make them more compliant in taking their medications. Often, however, a person's first contact with a physician may be after significant damage to the end-organs

has occurred. In many cases, a person visits or is brought to the doctor or an emergency room with a heart attack, stroke, kidney failure, or impaired vision (due to damage to the back part of the retina). Greater public awareness and frequent blood pressure screening may help to identify patients with undiagnosed high blood pressure before significant complications have developed.

About one out of every 100 (1%) people with hypertension is diagnosed with severe high blood pressure (accelerated or malignant hypertension) at their first visit to the doctor. In these patients, the diastolic blood pressure (the minimum pressure) exceeds 140 mm Hg! Affected persons often experience severe headache, nausea, visual symptoms, dizziness, and sometimes kidney failure. Malignant hypertension is a medical emergency and requires urgent treatment to prevent a stroke (brain damage).

### **1.11.2 Organ damage due to hypertension**

Damage of organs fed by the circulatory system due to uncontrolled hypertension is called end-organ damage. As already mentioned, chronic high blood pressure can lead to an enlarged heart, kidney failure, brain or neurological damage, and changes in the retina at the back of the eyes. Examination of the eyes in patients with severe hypertension may reveal damage; narrowing of the small arteries, small hemorrhages (leaking of blood) in the retina, and swelling of the eye nerve. From the amount of damage, the doctor can gauge the severity of the hypertension.

People with high blood pressure have an increased stiffness, or resistance, in the peripheral arteries throughout the tissues of the body. This increased resistance causes the

heart muscle to work harder to pump the blood through these blood vessels. The increased workload can put a strain on the heart, which can lead to heart abnormalities that are usually first seen as enlarged heart muscle. Enlargement of the heart can be evaluated by chest X-ray, electrocardiogram, and most accurately by echocardiography (an ultrasound examination of the heart). Echocardiography is especially useful in determining the thickness (enlargement) of the left side (the main pumping side) of the heart. Heart enlargement may be a forerunner of heart failure, coronary (heart) artery disease, and abnormal heart rate or rhythms (cardiac arrhythmias). Proper treatment of the high blood pressure and its complications can reverse some of these heart abnormalities.

Blood and urine tests may be helpful in detecting kidney abnormalities in people with high blood pressure. (Remember that kidney damage can be the cause or the result of hypertension.) Measuring the serumcreatinine in a blood test can assess how well the kidneys are functioning. An elevated level of serum creatinine indicates damage to the kidney. In addition, the presence of protein in the urine (proteinuria) may reflect chronic kidney damage from hypertension, even if the kidney function (as represented by the blood creatinine level) is normal. Protein in the urine alone signals the risk of deterioration in kidney function if the blood pressure is not controlled. Even small amounts of protein (microalbuminuria) may be a signal of impending kidney failure and other vascular complications from uncontrolled hypertension. African American patients with poorly controlled hypertension are at a higher risk than Caucasians for most end-organ damage and particularly kidney damage.

Uncontrolled hypertension can cause strokes, which can lead to brain or neurological damage. The strokes are usually due to a hemorrhage (leaking blood) or a blood clot (thrombosis) of the blood vessels that supply blood to the brain. The patient's symptoms and signs (findings on physical examination) are evaluated to assess the neurological damage. A stroke can cause weakness, tingling, or paralysis of the arms or legs and difficulties with speech or vision. Multiple small strokes can lead to dementia (impaired intellectual capacity). The best prevention for this complication of hypertension or, for that matter, for any of the complications, is control of the blood pressure. Recent studies have also suggested the angiotensin receptor blocking drugs may offer an additional protective effect against strokes above and beyond control of blood pressure.

### **1.11.3 High Blood Pressure (Hypertension) At A Glance**

- High blood pressure (hypertension) is designated as either essential (primary) hypertension or secondary hypertension and is defined as a consistently elevated blood pressure exceeding 140/90 mm Hg.
- In essential hypertension (95% of people with hypertension), no specific cause is found, while secondary hypertension (5% of people with hypertension) is caused by an abnormality somewhere in the body, such as in the kidney, adrenal gland, or aortic artery.

- Essential hypertension may run in some families and occurs more often in the African American population, although the genes for essential hypertension have not yet been identified.
- High salt intake, obesity, lack of regular exercise, excessive alcohol or coffee intake, and smoking may all adversely affect the outlook for the health of an individual with hypertension.
- High blood pressure is called "the silent killer" because it often causes no symptoms for many years, even decades, until it finally damages certain critical organs.
- Poorly controlled hypertension ultimately can cause damage to blood vessels in the eye, thickening of the heart muscle and heart attacks, hardening of the arteries (arteriosclerosis), kidney failure, and strokes.
- Heightened public awareness and screening of the population are necessary to detect hypertension early enough so it can be treated before critical organs are damaged.
- Lifestyle adjustments in diet and exercise and compliance with medication regimes are important factors in determining the outcome for people with hypertension.



- Several classes of anti-hypertensive medications are available, including ACE inhibitors, ARB drugs, beta-blockers, diuretics, calcium channel blockers, alpha-blockers, and peripheral vasodilators.
- Most antihypertensive medications can be used alone or in combination: some are used only in combination; some are preferred over others in certain specific medical situations; and some are not to be used (contraindicated) in other situations.
- The goal of therapy for hypertension is to bring the blood pressure down to 140/85 in the general population and to even lower levels in diabetics, African Americans, and people with certain chronic kidney diseases.
- Screening, diagnosing, treating, and controlling hypertension early in its course can significantly reduce the risk of developing strokes, heart attacks, or kidney failure.

#### **1.11.4 Causes of Hypertension**

##### **1.11.4.1 Essential hypertension:**

Essential hypertension is the most prevalent hypertension type, affecting 90-95% of hypertensive patients. Although no direct cause has identified itself, there are many factors such as sedentary lifestyle, stress, visceral obesity, potassium deficiency (hypokalemia), obesity (more than 85% of cases occur in those with a body mass index greater than 25),<sup>[33]</sup> salt (sodium) sensitivity, alcohol intake, and vitamin D deficiency.

Risk also increases with aging, some inherited genetic mutations and family history. An elevation of renin, an enzyme secreted by the kidney, is another risk factor, as is sympathetic nervous system overactivity. Insulin resistance which is a component of syndrome X, or the metabolic syndrome is also thought to contribute to hypertension. Recent studies have implicated low birth weight as a risk factor for adult essential hypertension.

### **1.11.6 Treatment of hypertension:**

#### **1. Diuretics:**

Thiazides: Hydrochlorothiazide, Chlorthalidone, Indapamide.

High ceiling: Furosemide.

K<sup>+</sup>sparing: Spironolactone, Amiloride.

#### **2. ACE inhibitors:**

Captopril, Enalapril, Lisinopril, Perindopril, Ramipril, etc.,

#### **3. Angiotensin blockers:**

Losartan, Candesartan, Irbesartan, Valsartan, Telmesartan.

#### **4. Calcium channel blockers:**

Verapamil, Diltiazem etc.,

#### **5. Adrenergic blockers:**

Propranolol, Labetelol, etc.,

**6. Central sympatholytics:**

Clonidine, Methyl dopa.

**7. Vasodilators:**

**Arteriolar:** Hydralazine, Minoxidil.

**Arteriolar + Venous:** Sodium nitroprusside.

**1.11.7 Angiotensin receptor blockers :**

These are developed as an alternative for ACE inhibitors. Several antagonists of AT<sub>2</sub> receptors as well as combined AT<sub>1</sub> + AT<sub>2</sub> antagonists have been produced.

Pharmacologically these differ from ACE inhibitors in the following ways:

They do not interfere with degradation of bradykinin and other ACE substrates. No rise in level or potentiation of bradykinin occurs. Consequently, ACE inhibitor related cough is rare.

They result in more complete inhibition of AT<sub>1</sub> receptor activation, because alternative pathway of A-II generation and consequent AT<sub>1</sub> receptor activation remain intact with ACE inhibitors.

They result in indirect AT<sub>2</sub> receptor activation. Due to blockade of AT<sub>1</sub> receptor mediated feedback inhibition-more A-II is produced which acts on AT<sub>2</sub> receptors that remain unblocked. ACE inhibitors result in depression of both AT<sub>1</sub> and AT<sub>2</sub> activation.

**1.11.7.1 Mechanism of action**

These substances are AT<sub>1</sub>-receptor antagonists – that is, they block the activation of angiotensin II AT<sub>1</sub> receptors. Blockage of AT<sub>1</sub> receptors directly causes vasodilation,

reduces secretion of vasopressin, and reduces production and secretion of aldosterone, amongst other actions. The combined effect reduces blood pressure.

The specific efficacy of each ARB within this class depends upon a combination of three pharmacodynamic and pharmacokinetic parameters. Efficacy requires three key PD/ PK areas at an effective level; the parameters of the three characteristics will need to be compiled into a table similar to one below, eliminating duplications and arriving at consensus values; the latter are at variance now.

### **1.11.7.2 Pharmacology**

These drugs have very similar effects to angiotensin converting enzyme (ACE) inhibitors and are used for the same indications (hypertension, heart failure, post- myocardial infarction). Their mechanism of action, however, is very different from ACE inhibitors, which inhibit the formation of angiotensin II. ARBs are receptor antagonists that block type 1 angiotensin II (AT<sub>1</sub>) receptors on blood vessels and other tissues such as the heart. These receptors are coupled to the G<sub>q</sub>-protein and IP<sub>3</sub> signal transduction pathway that stimulates vascular smooth muscle contraction. Because ARBs do not inhibit ACE, they do not cause an increase in bradykinin, which contributes to the vasodilation produced by ACE inhibitors and also some of the side effects of ACE inhibitors (cough and angioedema).

ARBs have the following actions, which are very similar to ACE inhibitors:

- Dilate arteries and veins and thereby reduce arterial pressure and preload and afterload on the heart.
- Down regulate sympathetic adrenergic activity by blocking the effects of angiotensin II on sympathetic nerve release and reuptake of norepinephrine.

- Promote renal excretion of sodium and water (natriuretic and diuretic effects) by blocking the effects of angiotensin II in the kidney and by blocking angiotensin II stimulation of aldosterone secretion.
- Inhibit cardiac and vascular remodeling associated with chronic hypertension, heart failure, and myocardial infarction.

**1.11.8.3 Uses:**

The ARBs have the same overall range of clinical utility as ACE inhibitors, but the suitability efficacy of one over the other is not clearly defined. It may depend on the condition being treated and specific features of the patient. The value of their combination versus monotherapy is also still unsettled.

**1.11.8 Diuretics****1.11.8.1 Mechanisms of diuretic drugs**

Diuretic drugs increase urine output by the kidney (i.e., promote diuresis). This is accomplished by altering how the kidney handles sodium. If the kidney excretes more sodium, then water excretion will also increase. Most diuretics produce diuresis by inhibiting the reabsorption of sodium at different segments of the renal tubular system. Sometimes a combination of two diuretics is given because this can be significantly more effective than either compound alone (synergistic effect). The reason for this is that one nephron segment can compensate for altered sodium reabsorption at another nephron segment; therefore, blocking multiple nephron sites significantly enhances efficacy.

**Thiazide diuretics**, which are the most commonly used diuretic, inhibit the sodium-chloride transporter in the distal tubule. Because this transporter normally only reabsorbs

about 5% of filtered sodium, these diuretics are less efficacious than loop diuretics in producing diuresis and natriuresis. Nevertheless, they are sufficiently powerful to satisfy most therapeutic needs requiring a diuretic. Their mechanism depends on renal prostaglandin production.

Because loop and thiazide diuretics increase sodium delivery to the distal segment of the distal tubule, this increases potassium loss (potentially causing *hypokalemia*) because the increase in distal tubular sodium concentration stimulates the aldosterone-sensitive sodium pump to increase sodium reabsorption in exchange for potassium and hydrogen ion, which are lost to the urine. The increased hydrogen ion loss can lead to *metabolic alkalosis*. Part of the loss of potassium and hydrogen ion by loop and thiazide diuretics results from activation of the renin-angiotensin-aldosterone system that occurs because of reduced blood volume and arterial pressure. Increased aldosterone stimulates sodium reabsorption and increases potassium and hydrogen ion excretion into the urine.

There is a third class of diuretic that is referred to as **potassium-sparing diuretics**. Unlike loop and thiazide diuretics, some of these drugs do not act directly on sodium transport. Some drugs in this class antagonize the actions of aldosterone (**aldosterone receptor antagonists**) at the distal segment of the distal tubule. This causes more sodium (and water) to pass into the collecting duct and be excreted in the urine. They are called K<sup>+</sup>-sparing diuretics because they do not produce hypokalemia like the loop and thiazide diuretics. The reason for this is that by inhibiting aldosterone-sensitive sodium reabsorption, less potassium and hydrogen ion are exchanged for sodium by this transporter and therefore less potassium and hydrogen are lost to the urine. Other potassium-sparing diuretics directly inhibit sodium channels associated with the

aldosterone-sensitive sodium pump, and therefore have similar effects on potassium and hydrogen ion as the aldosterone antagonists. Their mechanism depends on renal prostaglandin production.

## 2. LITERATURE REVIEW

**Paul R. Conlin *et al.*,** <sup>20</sup> in 2001 Studied the current treatment options for hypertension, with particular emphasis on the angiotensin receptor blockers (ARBs). *Losartan*, the most widely studied agent of this class, is also discussed. In hypertensive patients, *losartan* has been compared with other antihypertensive agents, including enalapril, amlodipine, and nifedipine gastrointestinal therapeutic system. In each case, an antihypertensive regimen of losartan once daily with or without hydrochlorothiazide showed comparable blood pressure-lowering effects. Losartan has also consistently demonstrated an excellent tolerability profile, with an overall incidence of adverse effects similar to that of placebo.

**Javier dfez *et al.*,** in 2006<sup>21</sup> Studied the *Losartan* Intervention For Endpoint reduction in hypertension (LIFE) study found that a *losartan*-based regimen, compared with an atenolol based regimen, resulted in a significantly lower risk of stroke in hypertensive patients with left ventricular hypertrophy, despite similar reductions in blood pressure. The purpose of this work was to examine the molecular and pharmacologic mechanisms that may be associated with the different outcomes observed in the LIFE study. Losartan's significant effect on stroke may be related to several possible mechanisms that are independent of blood-pressure reductions. These include improvements in endothelial function and vascular structure; decreases in vascular oxidative stress; reductions in left ventricular hypertrophy, reductions in myocardial fibrosis, or both; and modulation of atherosclerotic disease progression.



**N.N.RAJENDRAN *et al.***,<sup>22</sup> in 2010 investigated 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 hydrochlorothiazide 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 *hydrochlorothiazide and losartan potassium* showed an enhanced dissolution of *hydrochlorothiazide* 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.

**Mauro Cavinato *et al.***,<sup>23</sup> in 2011 determined the effects of some important drug properties (such as particle size distribution, hygroscopicity and solubility) and process variables on the granule growth behaviour and final drug distribution in high shear wet granulation. Results have been analyzed in the light of widely accepted theories and some recently developed approaches. A mixture composed of drug, some excipients and a dry binder was processed using a lab-scale highshear mixer. Three common active pharmaceutical ingredients (paracetamol, caffeine and acetylsalicylic acid) were used within the initial formulation. Drug load was 50% (on weight basis). Influences of drug particle properties (e.g. particle size and shape, hygroscopicity) on the granule growth behaviour were evaluated. Particle size distribution (PSD) and granule morphology were monitored during the entire process

through sieve analysis and scanning electron microscope (SEM) image analysis. Resistance of the wet mass to mixing was furthermore measured using the impeller torque monitoring technique.

**NILS ROTTMANN *et al.***,<sup>24</sup> in 2009 studied that Nowadays the buzzword “process optimization” has an unprecedented importance. This can be on one hand attributed to increasing cost pressure in pharmaceutical production and on the other hand, to an increasing environmental awareness in the industry. However, to address this concern, we have considered one of the most energy consuming processes in the industry – the film-coating process – with respect to the efficiency of several instant release film coating formulations, based on HPMC, PVA and a PEG-PVA graft co-polymer. By choosing an appropriate coating polymer or formulation, a process time reduction of more than 30 percent is achievable, a result that serves the purpose of both, cost reduction as well as environmental protection.

**SchreimerT *et al.***, in 2005<sup>25</sup> investigated about the mechanism of immediate drug release from solid oral dosage forms. They found that starch and cellulose substances favoured the matrix disintegration and the generation of effective dissolution surface of the drug substances. They developed a mathematical model suitable for the characterization and optimization of immediate drug release by the choice and modification of excipients.

**Sameer Late Get *al.***,<sup>26</sup> in 2009 investigated the effects of disintegration promoting agent, lubricants, on optimized fast disintegrating tablets. Results of multiple linear regression analysis revealed that concentration of lubricant was found to be important for tablet dis- integration and hardness.

**Van Kamp HVet al.**, in 2005 studied about the improvement of tableting properties of super disintegrants by wet granulation. The crushing strength, disintegration and dissolution properties of tablets, made by wet granulation with lactose as filler, gelatin as binder, potato starch as disintegrant and magnesium stearate as lubricant would be markedly improved when potato starch (20%) was replaced by much lower concentration(4%) of an insoluble super disintegrant, such as SSG or crospovidone.

**Magnus Alwuagwnet al.**,<sup>27</sup> in 2003 studied the disintegrant ability of *Pleurotustuber-regium* in comparison with maize starch in preparation of paracetmol tablets via wet granulation method. The results indicated that *P.tuber-regium* and maize starch have similar true, bulk and tapped density values.

**Makino Todashi et al.**,<sup>28</sup> in 2000 studied on the effects of binder distribution of granules and granule hardness on the compressibility of granules for tablets manufactured by wet granulation. This study suggested that uniform binder distribution of granules on wet granulation is important for the excellent compressibility of granules for tablets.

**Satia MC., et al** in 1995<sup>29</sup> has reported on *Losartan*, an angiotenisis-II receptor antagonist, and a few of its congeners; A new therapeutic class in the management of hypertension.

**JakobKristensenet et al., in**<sup>30</sup> 2000 studied on comparison of granule and tablet properties prepared by wet granulation in a rotary processor and a conventional fluid bed. This study is indicated that rotary processor gave rise to more dense granules with better flow properties than fluid bed granules.

**Maja Lusina et al.**, in 2005<sup>31</sup> studied the stability of *losartan potassium* and hydrochlorothiazide tablets. The purpose of stability testing is to investigate how the quality of a drug product changes with time under the influence of environmental factors, to establish a shelf life for the product and to recommend storage conditions. Stability study of *losartan/hydrochlorothiazide* tablets is presented. Losartan (angiotensin II receptor antagonist) and hydrochlorothiazide (diuretic) are successfully used in association in the treatment of hypertension. Stability study of *losartan/hydrochlorothiazide* tablets consisted of three steps: stress test (forced degradation study), preliminary testing (selection of packaging) and formal stability testing. The results of stress test suggested that *losartan/hydrochlorothiazide* tablets are sensitive to moisture. It was demonstrated that the developed analytical methods are stability indicating. Additional preliminary testing was performed in order to select appropriate packaging for *losartan/hydrochlorothiazide* tablets.

**G.K. Aulakh et al.**, in 2007<sup>32</sup> studied about the non-peptide angiotensin receptor antagonists. The renin–angiotensin–aldosterone-system (RAAS) is an important regulator of blood pressure and fluid-electrolyte homeostasis. RAAS has been implicated in pathogenesis of hypertension, congestive heart failure, and chronic renal failure. Aliskiren is the first non-peptide orally active renin inhibitor approved by FDA. Angiotensin Converting Enzyme (ACE) Inhibitors are associated with frequent side effects such as cough and angio-oedema. Recently, the role of ACE2 and neutral endopeptidase (NEP) in the formation of an important active metabolite/mediator of RAAS, ang 1–7, has initiated attempts towards development of ACE2 inhibitors and combined ACE/NEP inhibitors.

**Jennifer Wang *et al.*, in 2010<sup>33</sup> studied** the lubrication in tablets. Theoretical aspects and practical considerations of lubrication in tablet compression are reviewed in this paper. Properties of the materials that are often used as lubricants, such as magnesium stearate, in tablet dosage form are summarized. The manufacturing process factors that may affect tablet lubrication are discussed. As important as the lubricants in tablet formulations are, their presence can cause some changes to the tablet physical and chemical properties. Furthermore, a detailed review is provided on the methodologies used to characterize lubrication process during tablet compression with relevant process analytical technologies. Finally, the Quality-by-Design considerations for tablet formulation and process development in terms of lubrication are discussed.

### **3. AIM AND OBJECTIVE**

The main objective of this work is to formulate an conventional release oral solid dosage form of *Losartan potassium and Hydrochlorthiazide* which is considered to be stable, robust quality and pharmaceutically equivalent to that of the reference [marketed] product for the treatment of Hypertension.

The aim is to develop and evaluate immediate release tablets with different compositions of excipients which will meet the standards to that of the reference product with the subsequent achievement of invitro correlation with the reference product.

## **4. PLAN OF WORK**

### **1. Literature review**

### **2. Pre compression studies:-**

- a. Bulk density
- b. Tapped density
- c. Compressibility index
- d. Angle of repose
- e. Hausner's ratio

### **3. Formulation of tablets by wet granulation method**

### **4. Evaluation of Formulated tablets**

- Appearance
- Hardness
- Weight variation test
- Friability
- Thickness

- Disintegration
- Dissolution
- Drug content
- Stability studies .



**4. MATERIALS AND METHODS****Table: 1      Materials**

<b>S.NO</b>	<b>RAW MATERIALS</b>	<b>MANUFACTURER</b>
1	Losartan potassium	aurobindopharmaltd.,Hyderabad
2	Hydrochlorthiazide	aurobindopharmaltd.,Hyderabad
3	Aerosil 200 pharma	Signet Chemicals, Mumbai
4	Lactose Monohydrate	Colorcon, Mumbai
5	Avicel 102	Signet Chemicals, Mumbai
6	HPMC	Aurolab, Madurai
7	Starch 1500	Signet Chemicals, Mumbai
8	Avicel 101	Signet Chemicals, Mumbai
9	Low substituted hydroxyl propyl cellulose	Colorcon Verna Industrial estate area, Goa
10	Magnesium stearate	SD Fine Chemicals limited, Mumbai

Table:2 List of Equipments

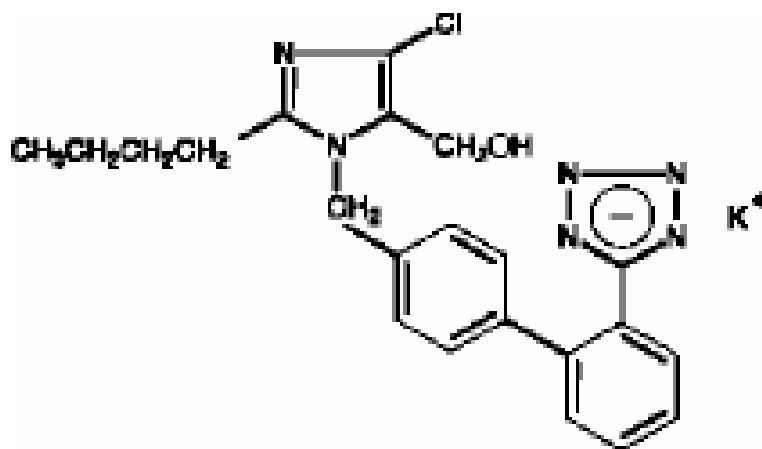
S. No.	EQUIPMENT	MANUFACTURER	Model NO
1	Electronic Balance	Shimadzu	AUX220
2	Sieves	United Engineering Ltd.	ASL00
3	Tap density Tester	Electrolab	ETD-020
4	Laboratory Stirrer	Remi	RQT-124A
5	Rapid dryer	Retsch	TG-200
6	Dissolution test apparatus	Electro lab USP XXII	TDT-08L
7	Disintegration Tester	Electrolab	ED-2L
8	Hardness tester	Pharmatest	PTB-311E
9	Friabilator	Electrolab	EF-1W
10	Tablet Compression machine-16Station	Cadmch Machinery co. Pvt.Ltd	CM D3-16
11	Thickness tester(vernier calipers)	Pharmatest	ET-1P

## 4.1 DRUG PROFILE

### LOSARTAN POTASSIUM :

Losartan potassium<sup>42,43</sup> is an angiotensin II receptor (type AT<sub>1</sub>) antagonist. Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted into a carboxylic acid metabolite. Losartan metabolites have been identified in human plasma and urine. In addition to the carboxylic acid metabolite, several metabolites are formed.

### Structure :



**Molecular Formula :** C<sub>22</sub>H<sub>22</sub>ClKN<sub>6</sub>O

**Molecular Weight :** 461.0

**Chemical name :**

2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol  
monopotassium salt.

**Limits :**

Losartan potassium contains not less than 98.5 % and not more than equivalent of 101.0 % of calculated with reference to the anhydrous substance.

**Properties :**

APPEARANCE : white to off-white free-flowing crystalline powder.

**Solubility :**

It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.

**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 block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT<sub>1</sub>receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT<sub>2</sub> 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 AT<sub>1</sub> receptor and have much greater affinity (about 1000-fold) for the AT<sub>1</sub> receptor than for the AT<sub>2</sub>

receptor. *In vitro* binding studies indicate that Losartan is a reversible, competitive inhibitor of the AT<sub>1</sub> receptor.

**Pharmacokinetics:**

Losartan is readily absorbed from the gastrointestinal tract following oral administration. It undergoes first pass metabolism to form a carboxylic acid metabolite E-3174 (EXP-3174). The terminal elimination half lives of Losartan and is about 1.5 to 2.5 hours. Losartan's bioavailability is about 32%. Following oral administration, 6 % of Losartan is excreted unchanged in the urine. After oral administration peak plasma levels are attained at 1hr for losartan and 3-4hrs for E3174. Both compounds are 98% plasma protein bound. The plasma t<sub>1/2</sub> of losartan is 2hr, but that of E3174 is 6-9hr.

**Dose :**

Dosing must be individualized. The usual starting dose of Losartan potassium 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 can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

**Storage:**

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep container tightly closed. Protect from light.

**Adverse Reactions:**

Adverse effects of Losartan have been reported to be usually mild and transient, and include dizziness and dose-related orthostatic hypotension. Hypotension may occur particularly patients with volume depletion (for example those who have high dose diuretics). Hyperkalaemia has been reported. It appears less lightly than angiotensin-converting enzyme (ACE) inhibitors to cause cough.

**Uses and Administration:**

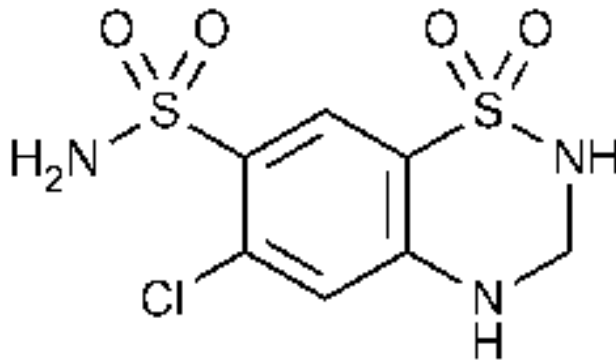
Losartan is an angiotensin II receptor antagonist with antihypertensive activity due mainly to selectively blockade of AT<sub>1</sub> receptors and the consequent reduced pressor effect of angiotensin II. It is given by mouth as the potassium salt in the management of hypertension. It has also been tried in heart failure.

In hypertension dose is 50 mg once daily. The maximum effect is achieved in about 3-6 weeks after initiating treatment. The dose may increased, if necessary, to 100 mg once daily. An initial dose of 25 mg once daily is suggested for the elderly over 75 years-of-age, and for patients with moderate to severe renal impairment (creatinine clearance less than 20 ml per minute ), or intravascular fluid depletion. A reduced dose should also be considered for patients with hepatic impairment.

**Availability:** Trade names of Losartan potassium

COZAAR 50 mg,

COZAAR 100 mg

**HYDROCHLORTHIAZIDE :****Structure :****Molecular Formula :** C<sub>7</sub>H<sub>8</sub>ClN<sub>3</sub>O<sub>4</sub>S<sub>2</sub>**Molecular Weight :** 297.74**Chemical name :**

2H-1,2,4-Benzothiadiazine-7-sulfonamide,6-chloro-3,4-dihydro-,1,1-dioxide.

6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide [58-93-5].

**Solubility:** Very slightly soluble in water, soluble in aqueous solutions of inorganic bases, e.g. sodium hydroxide / ammonium hydroxide, and in organic bases like n-butylamine**Limits :**Hydrochlorothiazide contains not less than 98.0percent and not more than 102.0percent of C<sub>7</sub>H<sub>8</sub>ClN<sub>3</sub>O<sub>4</sub>S<sub>2</sub>,calculated on the dried basis.

**Uses :**

This medication is used to treat high blood pressure. Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. Hydrochlorothiazide is a "water pill" (diuretic) that causes you to make more urine. This helps your body get rid of extra salt and water. This medication also reduces extra fluid in the body (edema) caused by conditions such as heart failure, liver disease, or kidney disease. This can lessen symptoms such as shortness of breath or swelling in your ankles or feet.

**Mechanism of action:**

Hydrochlorothiazide belongs to the thiazide class of diuretics. It reduces blood volume by acting on the kidneys to reduce sodium (Na) reabsorption in the distal convoluted tubule. The major site of action in the nephron appears on an electroneutral Na<sup>+</sup>-Cl<sup>-</sup> co-transporter by competing for the chloride site on the transporter. By impairing Na transport in the distal convoluted tubule, hydrochlorothiazide induces a natriuresis and concomitant water loss. Thiazides increase the reabsorption of calcium in this segment in a manner unrelated to sodium transport.<sup>[6]</sup> Additionally, by other mechanisms, HCTZ is believed to lower peripheral vascular resistance.

**Pharmacokinetics:**

The bioavailability of hydrochlorothiazide from 50-mg oral tablet doses was examined in healthy male volunteers under fasting and nonfasting conditions. Bioavailability was examined from plasma levels and urinary excretion of unchanged drug. The pharmacokinetics of hydrochlorothiazide in plasma could be described in terms of a triexponential function, and the mean drug half-lives determined from the



three exponents were 1.0, 2.2, and 9.0 hr. Changing the accompanying fluid volume had no significant effect on hydrochlorothiazide absorption in fasted subjects. Plasma drug levels were significantly reduced in nonfasted individuals, compared with those in fasted individuals. A similar trend was observed in the urinary excretion of hydrochlorothiazide, but differences between treatments were not significant ( $p > 0.05$ ). Mean 48-hr urinary recovery of hydrochlorothiazide was 70.5% of the dose in nonfasted subjects, and 73.5 and 75.0% of the dose in fasted subjects receiving the drug with 20 and 250 ml of water, respectively.

**Dosage:**

For high blood pressure control with HCTZ, dosage recommendations typically start at 25 mg once a day. Depending on your response to the medication, your healthcare provider may adjust your dosage accordingly. The suggested dosage for treating water retention varies between 25 mg and 100 mg, taken in a single dose or divided and taken more frequently. Generally, the recommended HCTZ dosage for infants and children is 0.5 mg to 1 mg per pound of body weight each day.

**Storage:**

Store in a well closed container, at room temperature. Protect from Moisture and Heat.

Store Below 40°C. Protect from Sunlight and Heat.

**Stability:**

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 36 months has been set, which is satisfactory. Storage conditions are “Do not store above 30°C”, “Store in the original packaging”.

## 4.2 EXCIPIENTS PROFILE

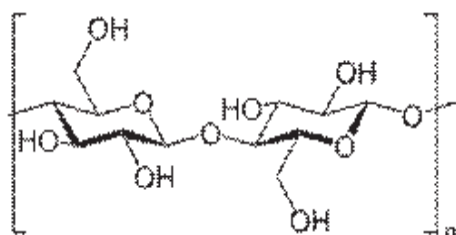
### MICRO CRYSTALLINE CELLULOSE<sup>43</sup>

**Synonyms:** Avicel PH, Celex, cellulose gel, celphere.

**Empirical formula and molecular weight:**  $(C_6H_{10}O_5)_n = 36000W$

Where,  $n = 220$ .

**Structure:**



**Functional category:** Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrant.

**Description:** Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

**pH** : 5.0 - 7.5

**Melting point:** 260 - 270<sup>0</sup>C

**Stability:** It is stable though hygroscopic material.

**Storage:** Should be stored in well closed container in a cool, dry place.

**Safety :** Non- toxic and non-irritant material. Consumption of large quantities of cellulose may have a laxative effect

**Handling precautions:** It may be irritant to eyes. Gloves, eye protection and a dust mask is recommended.

**Applications in pharmaceutical formulation or technology:**

- Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.
- In addition to its use as binder/diluents, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

**MAGNESIUM STEARATE<sup>44</sup>**

**Synonyms:** Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid.

**Chemical Name:** Octadecanoic acid magnesium salt.

**Empirical Formula:**  $C_{36}H_{70}MgO_4$

**Description :** Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

**Molecular Weight:** 591.34

**Functional category:** Tablet and capsule lubricant.

**Stability and Storage Conditions:** It is stable and should be stored in a well closed container in a cool, dry place

**Safety :** Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

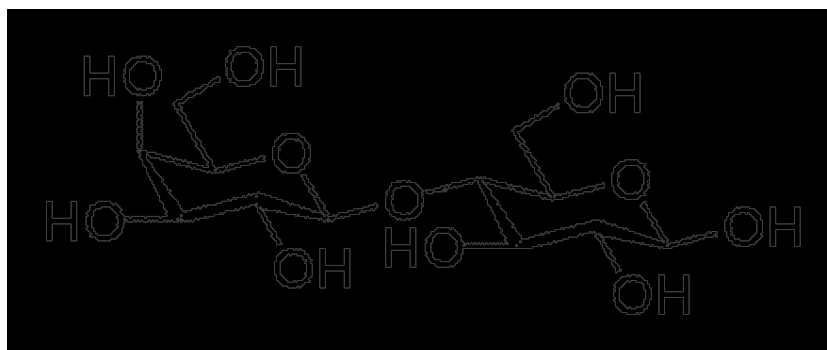
**Applications in Pharmaceutical Formulation or Technology:**

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as an lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

## LACTOSE

**Synonyms:**Pharmatose,milk sugar,prismalac.

**Structure:**



**Molecular weight:**360.31

**Functional category:**Tablet and capsule diluent, diluents for dry power inhalers.

**Description:** Lactose occurs white to off crystalline particles or powder. It is odorless aslightly sweet tasting.

**Stability and storage conditions:**

Mold growth occurs under humid conditions (80% relative humidity and above). It may develop a brown coloration on storage. It should be stored in a well closed container in a cool, dry place

**Applications:**

Lactose is widely used as filler or diluents in capsules and tablets and to a more limited extent in lyophilized products and infant feed formulas. Usually fine grades of lactose are used in the preparation of tablets by the wet granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredient and utilizes the binder more efficiently.

**STARCH :**

**Nonproprietary Names**

- BP: Maize starch
- Potato starch
- Rice starch
- Tapioca starch
- Wheat starch
- JP: Corn starch
- Potato starch
- Rice starch

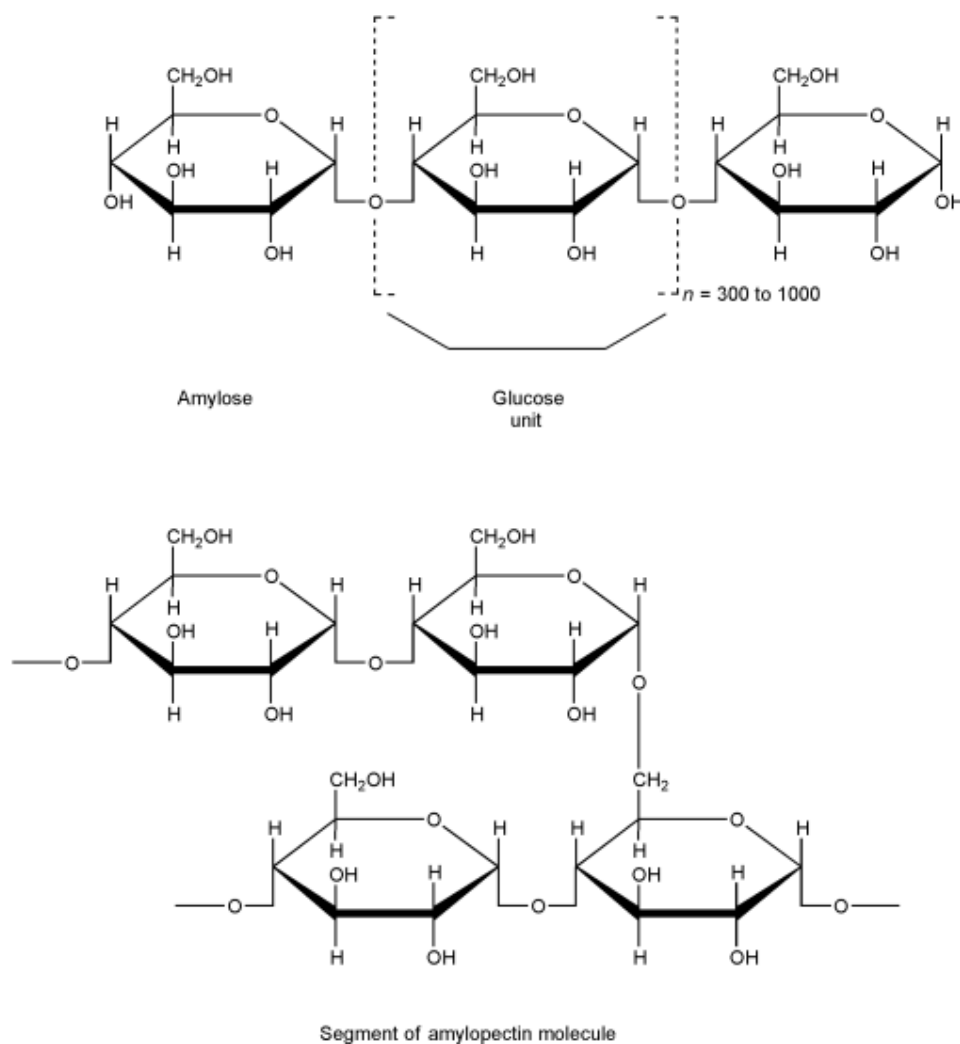
- Wheat starch
- PhEur: *Maydis amyllum* (maize starch)
- *Solani amyllum* (potato starch)
- *Oryzae amyllum* (rice starch)
- *Tritici amyllum* (wheat starch)
- USPNF: Corn starch
- Potato starch
- Tapioca
- Wheat starch
- Note that the USPNF 23 has individual monographs for corn (*Zea mays*), potato (*Solanum tuberosum*), tapioca (*Manihot utilissima* Pohl) and wheat starch (*Triticum aestivum*). The PhEur 2005 has monographs for each of these starches, except tapioca starch, along with an additional monograph for rice starch, *Oryza sativa*. Also note that the PhEur 2005 Suppl 5.0 contains an updated monograph for maize (corn) starch. The BP 2004 similarly describes maize, potato, rice, tapioca (cassava), and wheat starch in individual monographs, tapioca starch being obtained from the rhizomes of *Manihot utilissima* Pohl. The JP 2001
- similarly describes corn (maize), rice, potato and wheat starch in separate monographs.

### Synonyms

*Amido; amidon; amilo; amyllum; Aytex P; C\*PharmGel; Fluftex W; Instant Pure-Cote; Melojel; Meritena; Paygel 55; Perfectamyl D6PH; Pure-Bind; Pure-Cote; Pure-Dent; Pure-Gel; Pure-Set; Purity 21; Purity 826; Tablet White.*

**Chemical Name and CAS Registry Number**

Starch [9005-25-8]

**Empirical Formula and Molecular Weight** $(C_6H_{10}O_5)_n$  50 000–160 000where  $n = 300$ –1000.Starch consists of amylose and amylopectin, two polysaccharides based on  $\alpha$ -glucose.**Structural Formula**

**Functional Category**

Glidant; tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

**Applications in Pharmaceutical Formulation or Technology**

Starch is used as an excipient primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.

As a diluent, starch is used for the preparation of standardized triturates of colorants or potent drugs to facilitate subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix.

In tablet formulations, freshly prepared starch paste is used at a concentration of 5–25% w/w in tablet granulations as a binder. Selection of the quantity required in a given system is determined by optimization studies, using parameters such as granule friability, tablet friability, hardness, disintegration rate, and drug dissolution rate.

Starch is one of the most commonly used tablet disintegrants at concentrations of 3–15% w/w. However, unmodified starch does not compress well and tends to increase tablet friability and capping if used in high concentrations. In granulated formulations, about half the total starch content is included in the granulation mixture and the balance as part of the final blend with the dried granulation. Also, when used as a disintegrant, starch exhibits type II isotherms and has a high specific surface for water sorption.

Starch has been investigated as an excipient in novel drug delivery systems for nasal, oral, periodontal, and other site-specific delivery systems.



Starch is also used in topical preparations; for example, it is widely used in dusting powders for its absorbency, and is used as a protective covering in ointment formulations applied to the skin. Starch mucilage has also been applied to the skin as an emollient, has formed the base of some enemas, and has been used in the treatment of iodine poisoning.

### **COLLIDAL SILICONE DIOXIDE**

**Synonyms** : Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica;

**Description** : Colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.

**Functional categories** : Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

**Solubility** : Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water. For Aerosil, solubility in water is 150 mg/L at 25°C (pH 7).

**pH** : 3.5-5.5 for a 4% w/w aqueous solution

**Bulk Density** : 0.029–0.042 g/cm<sup>3</sup>

**Melting Point** : 1600 °C

**Stability and storage conditions** : Colloidal silicon dioxide is hygroscopic but

adsorbs large quantities of water without liquefying at a pH greater than 7.5 the viscosity increasing properties of colloidal silicon dioxide are reduced.

**Incompatibility** : Incompatible with diethylstilbestrol preparations

**Applications** : Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations. (5) Colloidal silicon dioxide is also used as an adsorbent during the preparation of wax microspheres; as a thickening agent for topical preparations; and has been used to aid the freeze-drying of nanocapsules and nanosphere suspensions.

#### **HYPROMELLOSE (HPMC K4M)**

Hypromellose<sup>45</sup> is a white or slightly off-white, fibrous or granular powder. Swells in water and produces a clear to opalescent, viscous, colloidal mixture. Insoluble in dehydrated alcohol, ether and in chloroform.

#### **NF Category :**

Coating agent, suspending and/or viscosity increasing agent, tablet binder.

Hypromellose is propylene glycol ether of methylcellulose. When dried to 105°C for 2 hours, it contains methoxy (-OCH<sub>3</sub>) and hydroxypropoxy (-OCH<sub>2</sub>CHOHCH<sub>3</sub>) groups conforming to the limits for the types of Hypromellose (hydroxypropylmethylcellulose).

Substitution type	Methoxy (percent)		Hydroxypropoxy(percent)	
	Minimum	Maximum	Minimum	Maximum
2208	19.0	24.0	4.0	12.0

**Storage:**

Hypromellose should be stored in a well closed container, in a cool, dry place.

**Pharmaceutical Applications:**

- Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.
- Low viscosity grades of HPMC are used in aqueous film coating in tablet formulations.
- High viscosity grades are used in solvent film coating.
- 2.5 % high viscosity grades are used to retard the release of water soluble drugs as binder in tablet granules.
- As thickening agent added to vehicles of eye drops and artificial tear solutions at 0.45-1.0 % concentrations.
- It is also used as protective colloid to prevent droplets and particles from coalescing or agglomerating.
- It is used as emulsifier, suspending agent, stabilizer in gels and in ointments.
- It is also used as an additive in plastic bandages.
- It is also widely used in cosmetics and food products.

**Typical Viscosity:**

<b>Methocel product</b>	<b>USP 28 designation</b>	<b>Nominal viscosity (mPa s)</b>
Methocel K4M	2208	4000
Methocel K15M	2208	15000

Table-3 Formulae

Sl.No.	Chemicals	F1	F2	F3	F4	F5	F6	F7
1	Losartan potassium	100	100	100	100	100	100	100
2	HCTZ	12.5	12.5	12.5	12.5	12.5	12.5	12.5
3	Avicel 101	70	70	60	50	40	30	30
4	L- HPC	-	-	-	-	12.5	15.0	15.0
5	Avicel 200	-	-	-	10	20	30	30
6	Starch 1500	10.0	12.5	15.0	20.0	25.0	25.0	30.0
7	HPMC	10	10	10	12.5	-	-	-
8	Aerosil 200 Pharma	90	90	90	-	-	-	-
9	Pharmatose DCL 11	-	-	-	80	80	80	80
10	Magnesium Stearate	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Granulating fluid								
11	Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s

### 4.3 MANUFACTURING:

#### 4.3.1 Manufacture of the Tableting Blend<sup>38</sup>:

In the tablet pressing process, the main guideline is to ensure that the appropriate amount of active ingredient is in each tablet. Hence, all the ingredients should be well-mixed. If a sufficiently homogenous mixture of the components cannot be obtained with simple blending processes, the ingredients must be granulated prior to compression to assure an even distribution of the active compound in the final tablet. Two basic techniques are used to granulate powders for compression into a tablet: wet granulation and dry granulation. Powders that can be mixed well do not require granulation and can be compressed into tablets through direct compression.

#### 4.4 Preparation of LOSARTAN/HCTZ tablets by wet granulation method <sup>39</sup> :

##### 4.4.1 Sifting:

Microcrystalline Cellulose (Avicel PH 101) and Lactose Monohydrate (Pharmatose 200M) sifted separately through # 40 mesh (ASTM, 425 μm) in both batches. In 1<sup>st</sup> batch losartan potassium sifted through #40 mesh and in 2<sup>nd</sup> batch through #30 mesh to improve the sifting process.

##### 4.4.2 Dry Mixing:

Sifted materials were loaded into Rapid Mixer Granulator and dry mixing was carried out for 5+5+5 minutes in 1<sup>st</sup> batch and in 2<sup>nd</sup> batch for 10 min with Impeller at slow speed. Unit dose samples were collected and submitted for analysis. The results found to be satisfactory within the acceptable limits.

**4.4.3 Granulation:**

Granulation fluid(Purified water-fluid uptake-10%) was added over a period of 5-6 min with impeller at slow speed in 1<sup>st</sup> batch and in 2<sup>nd</sup> batch the fluid was added in 3min10sec.Kneading was done for 2 min in 1<sup>st</sup> batch and in 2<sup>nd</sup> batch to have better granules Kneading was done for 30 sec with impeller at slow speed in both batches.

**4.4.4 Drying:**

Drying was carried out in Fluidized Bed Drier at an inlet temperature of  $55\pm 5^{\circ}\text{c}$  in 1<sup>st</sup> batch and in 2<sup>nd</sup> batch drying was carried out with an inlet temperature of  $60\pm 5^{\circ}\text{c}$  to have a better control of drying.Loss on Drying of the granules at the end of drying was found to be 3.98%w/w(lot I) and 3.81%w/w(Lot II) in 1<sup>st</sup> batch and in 2<sup>nd</sup> batch 3.85%w/w against limit of 3.0-5.0%w/w.

**4.4.5 Sifting & Milling:**

Dried granules were sifted through #30 mesh(ASM,600 $\mu\text{m}$ ) & retentions milled through 1.0mm screen at medium speed,knives forward configuration.Milled granules were sifted through #30 mesh(ASM<600 $\mu\text{m}$ ).The retentions were milled through 1.0mm screen at fast speed,knives forward.Ensured all the material passed through 30 mesh(ASM<600 $\mu\text{m}$ ) in both batches.

**4.4.6 Extra granular Materials Sifting:**

Microcrystalline Cellulose(Avicel PH 200)sifted through #30 sieve(ASM 600 $\mu\text{m}$ ), Pregelatinized Starch(stach 1500) & Low Substituted HYDROXYPROPYL Cellulose(L-HPC(LH-11)) sifted through #40 sieve(ASM 425 $\mu\text{m}$ ) Magnesium stearate was sifted through #60 mesh(ASM,25.0 $\mu\text{m}$ ) in both batches.

**4.4.7 Prelubrication:**

Sifted Extra granular material was added into Octagonal Blender and mixed for 5+5+5 min in 1<sup>st</sup> batch and in 2<sup>nd</sup> batch for 10 min in which unit dose samples were collected and submitted for analysis. The results found to be satisfactory within the acceptable limits.

**4.4.8 Lubrication:**

Sifted magnesium stearate was added into Octagonal blender and mixed for 3 min in both batches. Unit dose samples were collected and submitted for analysis. The results found to be satisfactory within the acceptable limits.

In process blend analysis is complying with the proposed specifications.

**4.4.9 Compression:**

Compression was done on 16-station compression machine. All physical parameters were found consistent.

**4.4.10 WET GRANULATION PROCESS<sup>40</sup>:**

Wet granulation forms the granules by binding the powders together with an adhesive, instead of by compaction. In this process the excipients are weighed and are sifted through 30# and these ingredients are loaded in the rapid mixer granulator and are mixed for about two minutes with impeller at slow speed. Then the drug is mixed along with all the excipients which are mixed previously at the speeds of the impeller slow for about six minutes and thereafter the ingredients with drug is mixed in the rapid mixer granulator at impeller and chopper fast for about two minutes. These two minutes the impeller and chopper are in fast speed as they have to mix all the ingredients along with the granulating fluid which is purified water the

impeller is used to mix the granules properly and the chopper is used to break the agglomerates properly and then the final blend is checked whether the granules are formed. Then after the granules are formed they are to be dried that the LOD should be less than 3% the granules are dried for about 15 minutes with an inlet temperature of  $50 \pm 5^{\circ}$  C. then the granules are milled to break the agglomerates present in the final blend or granules. The screen size of the mill is 40 and after breaking all the agglomerates i.e., after collecting all the material the granules are blended in an octagonal blender for 10 minutes by adding the magnesium stearate.

The total weight of granules formed is 150gm from which the 500 tablets are punched using caddmach 16 stn punching machine with 8.5 mm circular punches, which is used in the further process like coating. The process of coating is done with opadry white as coating material used for film coating. The coating process is done in NEOCOTA. For the optimized batch coating is done by using coating solution (50 mg with 200 ml of purified water).

#### **4.4.11 Coating <sup>41</sup>:**

In the first batch, during coating gun jamming, rough surface and shade variation was observed. As recommended by the formulation research from second batch onwards %w/w solids was decreased from 12%w/w to 10%w/w and coating efficiency was decreased from 90% to 80%. Coated tablets are complying with the drug product release specifications.

#### **Coating procedure:**

Pan Speed (RPM)

10-14



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Air Pressure (kg/cm <sup>2</sup> )	2-2.5
Blower Air Volume (CFM)	30
Solid Content (%)	12-15
Baffels	4
Tablet Weight	150gm
Bed Temperature (°C)	35-40
Spray Nozzle (mm)	1
No. of Spray Gun	1
Inlet Air temperature(°C )	70

#### 4.5 Drug-excipient compatibility studies<sup>42</sup>:

The proper design and the formulation of a dosage form require consideration of the physical, chemical and biological characteristics of the drug and excipients used in fabricating the product. The drug and excipients must be compatible with one another to produce a product i.e. stable, efficacious, attractive, easy to administer and safe.

The compatibility studies provide the frame work for the drugs combination with the excipients in the fabrication of the dosage form. The study was carried out to establish that the therapeutically active drug has not undergone any changes, after it has been subjected to processing steps during formulation of tablets.

Compatibility studies are carried out by mixing definite properties of drug and excipient and kept in glass vials, which is stored at 55°C for one month.

## 4.6 Preformulation Studies<sup>33</sup>

### 4.6.1 Bulk Density<sup>34</sup>:

It refers to a measurement to describe packing of particles. Bulk density is used to determine the amount of drug that occupies the volume in mg/ml

$$P_i = m/v_i$$

Where,

m = mass of the blend

v<sub>i</sub> = untapped volume

#### Procedure:

Weighed quantity of API was transferred into 100 ml measuring cylinder without tapping during transfer. The volume occupied by DRUG was measured. Bulk density was measured by using formula

$$P_i = m/v_i$$

### 4.6.2 Tapped Density<sup>34</sup>:

#### Procedure:

Weighed quantity of API was taken into a graduated cylinder. Volume occupied by DRUG was noted down. Then the cylinder was subjected to 500, 750 & 1250 taps in tap density tester (Electro Lab USP II). According to USP, the blend was subjected for 500 taps. % Volume variation was calculated and subjected for additional 750 taps. % Variation is calculated.

$$P_t = m/v_t$$

#### 4.6.3 Compressibility Index<sup>35</sup>:

Weighed API was transferred to 100ml-graduated cylinder and subjected to 500,750&1250 taps in tap density tester (Electro lab). The difference between two taps should be less than 2%. The %of compressibility index calculated using formula

$$CI = v_i - v_t / v_i \times 100$$

#### Limits :

S.No	Compressibility index	Flow
1	5-12	Free flow
2	12-16	Good flow
3	18-21	Fair
4	23-25	Poor
5	33-38	Verypoor
6	>40	Extremelypoor

#### 4.6.4 Hausner's Ratio<sup>36</sup>:

It is measurement of frictional resistance of the drug. The ideal range should be 1.2 –1.5.it is the determined by the ratio of tapped density and bulk density.

$$\text{Hausner's ratio} = v_i / v_t$$

Where  $v_t$  = Tapped volume

$v_i$  = untapped volume

**Limits:**

S.No	Hausner' ratio	Flow
1	1-1.2	Free flowing
2	1.2-1.6	Cohesive powder

**4.6.5 Angle of Repose<sup>37</sup>: -**

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

$$\tan \theta = h / r$$

$$\theta = \tan^{-1} h / r$$

Where,  $\theta$  = angle of repose, h = height, r = radius.

A funnel was fixed at a height approximately of 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the cone of the powder formed. Determine the angle of repose by measuring the height of the cone of powder and radius of the heap of powder.

**Flow Properties and Corresponding Angles of Repose**

<b>Flow Property</b>	<b>Angle of Repose (degrees)</b>
Excellent	25–30
Good	31–35
Fair - aid not needed	36–40
Passable - may hang up	41–45
Poor - must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

**4.6.6 Particle size distribution:** The size was determined by using eye piece micrometer. The eye piece micrometer was calibrated using stage micrometer. A smear of drug was prepared on a glass slide and utilizing eye piece micrometer the particle size was determined.

**4.6.7 Solubility:** Freely soluble in water.

Soluble in alcohol and

Slightly soluble in acetonitrile and methyl ethyl ketone

**4.7 EVALUATION OF TABLETS<sup>43</sup>:**

To design tablets and later monitor tablet production quality, quantitative evaluation and assessment of tablet chemical, physical and bioavailability properties must be made.

The important parameters in the evaluation of tablets can be divided into physical and chemical parameters.

**4.7.1 Physical appearance:**

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, color, presence or absence of odor, taste, surface texture and consistency of any identification marks.

**4.7.2 Hardness test:**

This is the force required to break a tablet in a diametric compression. Hardness of the tablet is determined by Stock's Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moves along the gauze in the barrel fracture. The tablet hardness of 5 kg is considered as suitable for handling the tablet. (Values are given in Table No:14)

**4.7.3 Tablet size and Thickness:**

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by Vernier Calipers scale. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a  $\pm 5\%$ . In addition thickness must be controlled to facilitate packaging. (Values are given in Table No:15)

**4.7.4 Friability:**

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the friabilator, rotating at 25rpm for 4min. The difference in the weight

is noted and expressed as percentage. It should be preferably between 0.5 to 1.0%.  
(Values are given in Table No: 16)

#### 4.7.5 Average weight of Tablets:

It is desirable that all the tablets of a particular batch should be uniform in weight. If any weight variation is there, that should fall within the prescribed limits:

±10% for tablets weighing 300mg or less

±7.5% for tablets weighing 300mg to 315mg

±5% for tablets weighing more than 315mg

Twenty tablets were taken randomly and weighed accurately. The average weight is calculated by -

$$\text{Average weight} = \frac{\text{weight of 20 tablets}}{20}$$

20

#### 4.7.6 Disintegration test:

For most tablets the first important step toward solution is break down of tablet into smaller particles or granules, a process known as disintegration. This is one of the important quality control tests for disintegrating type tablets. Six tablets are tested for disintegration time using USP XXII apparatus. Disintegration type conventional release tablets are tested for disintegrating time. (Values are given in Table No:18 )

#### 4.7.7 Construction of Calibration curve of Losartan Potassium

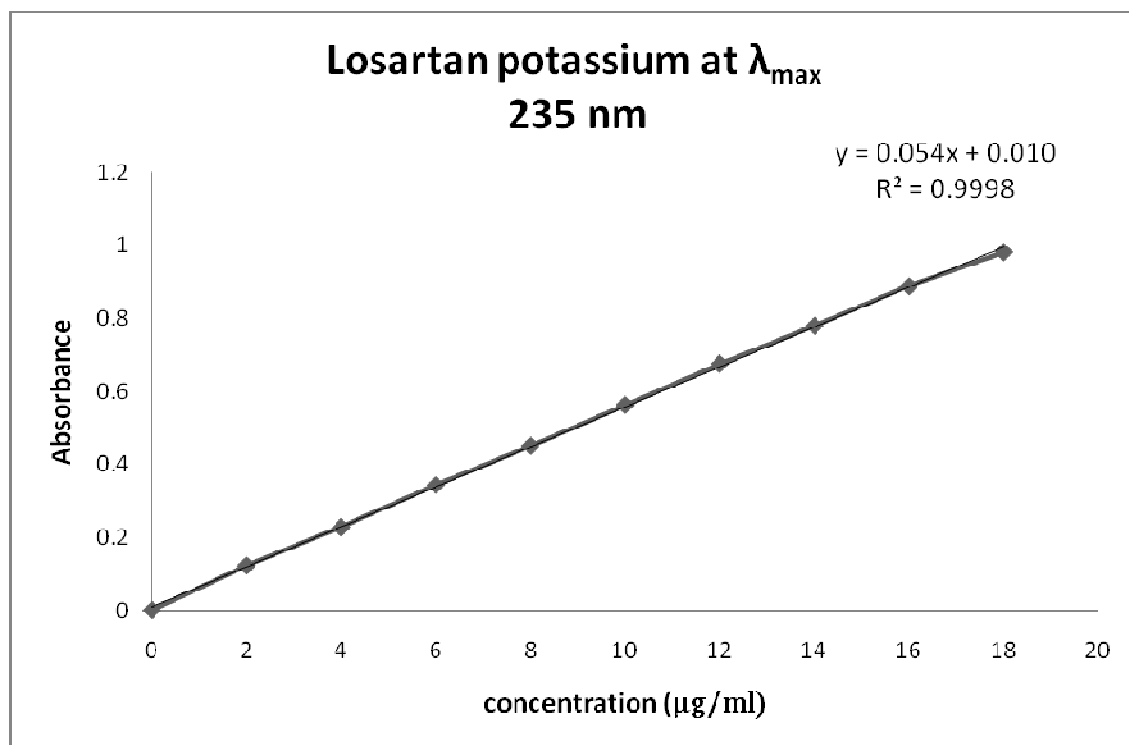
Accurately weighed 100 mg of Losartan potassium and transferred into 100 ml of volumetric flask and dissolved in small quantity of methanol and diluted with 6.8 phosphate buffer up to the mark to give stock solution 1 mg/ml. 1 ml was taken from

stock solution in another volumetric flask and diluted up to 100 ml to give a stock solution 10 µg/ml. Further dilutions were made from 2-40 µg/ml with 6.8 phosphate buffer and absorbance was measured at 235 nm.

**Table-4 : Calibration curve of Losartan potassium in pH 6.8 phosphate buffer at 235 nm**

S.No.	Concentration	Absorbance
1	2 µg/ml	0.122
2	4 µg/ml	0.227
3	6 µg/ml	0.343
4	8 µg/ml	0.450
5	10 µg/ml	0.562
6	12 µg/ml	0.670
7	14 µg/ml	0.779
8	16 µg/ml	0.887
9	18 µg/ml	0.981
10	20 µg/ml	1.074





**Fig. No:5 Calibration curve of Losartan potassium**

#### 4.7.7 INVITRO DISSOLUTION STUDIES OF TABLETS<sup>45</sup>:

Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP XXVII paddle method and 900ml of pH 6.8 phosphate buffer as the dissolution medium. The medium was allowed to equilibrate to temp of  $37^\circ\text{c} \pm 0.5^\circ\text{c}$ . Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 1 hr in pH 6.8 phosphate buffer at 50 rpm. At definite time intervals of 5 ml of the aliquot of sample was with drawn periodically and the volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 235 nm using uv-spectrophotometer.

##### 4.7.7.1 Dissolution parameters:

Apparatus	--	USP-II,
Dissolution Medium	--	pH 6.8 phosphate buffer

RPM	--	50
Sampling intervals	--	5, 10, 15, 20, 30 and 45.
Temperature	--	37°C ± 0.5°C

#### 4.7.8 Release Kinetics <sup>46</sup>

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to five popular release models such as zero-order, first-order, diffusion and exponential equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first order kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation, erosion equation and Peppas-Korsmeyer equation. The results are given in Table 26.

##### 4.7.8.1 Zero Order Release Kinetics:

It defines a linear relationship between the fraction of drug released versus time.

$$Q = k_0 t$$

Where, Q is the fraction of drug released at time t and  $k_0$  is the zero order release rate constant.

A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

**4.7.8.2 First Order Release Kinetics:**

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is

$$\ln (1-Q) = - K_1t$$

Where, Q is the fraction of drug released at time t and  $k_1$  is the first order release rate constant.

Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

**4.7.8.3 Higuchi's equation:**

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$$Q=K_2t^{1/2}$$

Where,  $K_2$  is the release rate constant.

A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependant.

**4.7.8.4 Power Law:**

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppas and Korsmeyer equation (Power Law).

$$M_t/M_\alpha = K.t^n$$

Where,  $M_t$  is the amount of drug released at time  $t$  and  $M_\alpha$  is the amount released at time  $\alpha$ , thus the  $M_t/M_\alpha$  is the fraction of drug released at time  $t$ ,  $k$  is the kinetic constant and  $n$  is the diffusional exponent. To characterize the mechanism for both solvent penetration and drug release  $n$  can be used as abstracted in Table-6. A plot between  $\log$  of  $M_t/M_\alpha$  against  $\log$  of time will be linear if the release obeys Peppas and Korsmeyer equation and the slope of this plot represents “ $n$ ” value.

**Table 5: Diffusion exponent and solute release mechanism for cylindrical shape**

Diffusion Exponent	Overall solute diffusion mechanism
0.45	Fickian diffusion
$0.45 < n < 0.89$	Anomalous (non-fickian) diffusion
0.89	Case II transport
$n > 0.89$	Super Case II transport

## 4.8 STABILITY STUDIES<sup>46, 47</sup>

### 4.8.1. Introduction

The purpose of stability testing is to provide evidence on how the quality of an active substance or pharmaceutical product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. In addition, product-related factors influence the stability, e.g. the chemical and physical properties of the active substance and the pharmaceutical excipients, the dosage form and its composition, the manufacturing process, the nature of the container-closure system, and the properties of the packaging materials. Also, the stability of excipients that may contain or form reactive degradation products, have to be considered.

**Table- 6: Objectives of Stability Testing:**

OBJECTIVE	TYPE OF STUDY	USE
To select adequate (from the viewpoint of stability) formulations and container-closure systems	Accelerated	Development of the product
To determine shelf-life and storage conditions	Accelerated and real-time	Development of the product and of the registration dossier
To substantiate the claimed shelf-life	Real-time	Registration dossier
To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product	Accelerated and real-time	Quality assurance in general, including quality control.

**Climatic Zones and Conditions**

WHO has issued guidelines, where it is stated that the world is divided into four zones based on the prevailing annual climatic conditions for the purpose of stability testing.

Zone I: temperate

Zone II: subtropical with possible high humidity

Zone III: hot/dry

Zone IV: hot/humid

**Table-7: Mean climatic conditions: measured data in the open air and in the storage room**

Climatic Zone	Measured data in the Open Air		Measured data in storage room	
	°C	%RH	°C	%RH
I	10.9	75	18.7	45
II	17.0	70	21.1	52
III	24.4	39	26.0	54
IV	26.5	77	28.4	70

So for example if a manufacturer plans to sell his products in zone-III he/she should do real time studies at 30°C and 35%RH. If a manufacturer wants to apply for the registration of a new drug, i.e. if he is applying for a (1) Investigative New Drug Application (IND) or (2) New Drug Application (NDA) or (3) Abbreviated New Drug Application (ANDA) then he has to assure the FDA regarding the drug's/drug product's safety, quality and efficacy. For this he has to carry out stability tests and submit stability data. How he should do this is specified by Q1A (R2).

#### 4.8.2 Selection of Batches

Data from formal stability studies should be provided on at least three primary batches of the drug substance. These batches should be made to a minimum of pilot scale by the same synthetic route as that of the production batches.

Specifications which include testing methods and acceptance criteria should be fixed.

<b>Testing frequency</b>	<b>Months</b>
Long term:	0, 3, 6, 9, 12, 18, 24
Accelerated storage:	0, 3, 6
Storage conditions recommended	

**Table-8 : Testing frequency for different storage conditions**

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25 <sup>0</sup> C + 2 <sup>0</sup> C/60% RH + 5% RH or 30 <sup>0</sup> C + 2 <sup>0</sup> C/65% RH + 5% RH	12 months
Intermediate**	30 <sup>0</sup> C + 2 <sup>0</sup> C/65% RH + 5% RH	6 months
Accelerated	40 <sup>0</sup> C + 2 <sup>0</sup> C/75% RH + 5% RH	6 months

\* It is up to the applicant to decide whether long term stability studies are performed at 25 + 2<sup>0</sup>C/60% RH + 5% RH or 30<sup>0</sup>C + 2<sup>0</sup>C/65% RH + 5% RH.

\*\* If 30<sup>0</sup>C + 2<sup>0</sup>C/65% RH + 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25<sup>0</sup>C+ 2<sup>0</sup>C/60% RH + 5% RH and “significant change” occurs at any time during 6 months’ testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria (ICH, 2003)

“Significant change” for a drug substance is defined as failure to meet its specification.

**Table -9 : Drug substances intended for storage in a refrigerator**

<b>Study</b>	<b>Storage condition</b>	<b>Minimum time period covered by data at submission</b>
Long term	5 <sup>0</sup> C + 3 <sup>0</sup> C	12 months
Accelerated	25 <sup>0</sup> C + 2 <sup>0</sup> C/60% RH + 5% RH	6 months

**Table-10 : Drug substances intended for storage in a freezer**

<b>Study</b>	<b>Storage condition</b>	<b>Minimum time period covered by data at submission</b>
Long term	20 <sup>0</sup> C + 5 <sup>0</sup> C	12 months

#### 4.8.3 Stability Testing for Established Drug Substances

WHO has issued guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage form. The stability of finished pharmaceutical products depends on environmental factors and on product related factors. So stability considerations should be given, the highest priority in the design and formulation of a product. The shelf life should be established with due regard to the climatic zones. To ensure both patient safety and the rational management of drug supplies, it is important that the expiry date and storage conditions are properly indicated on the label.



#### **4.8.4 Accelerated stability testing**

These are the studies designed to increase the rate of chemical degradation and physical change of a drug by using exaggerated storage conditions as part of the formal stability testing programme. The data thus obtained, in addition to those derived from real – time stability studies, may be used to assess longer – term chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes. These are also known as stress testing studies.

#### **4.8.5 Expiry date**

The date given on the individual container of a drug product up to and including which the product is expected to remain within specifications if stored correctly. It is established for each batch by adding the shelf-life period to the date of manufacture.

#### **4.8.6 Real time (Long term) stability studies**

Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of a drug, during and beyond the expected shelf life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the shelf life, to confirm the projected shelf life and to recommend storage conditions.

#### **4.8.7 Stability tests**

A series of tests designed to obtain information on the stability of a pharmaceutical product in order to define its shelf-life and utilization period under specified packaging and storage conditions. The following table gives the main objectives and uses the different types of stability testing (ICH, 1995)

**5. RESULTS & DISCUSSION****TABLE -11 : DRUG-EXCIPIENTS COMPATIBILITY STUDIES**

S.NO	EXCIPIENTS	RATIO	DESCRIPTION	
			Initial	Final
1	Losartan potassium – API	1:1	White to off white powder	White to off white powder
2	API – Lactose	1:1	Off white coloured powder	Off white coloured powder
3	API – Microcrystalline cellulose	1:1	Off white coloured powder	Off white coloured powder
4	API – Aerosil 200	1:1	Off white coloured powder	Off white coloured powder
5	API – Magnesium stearate	1:1	Off white coloured powder	Off white coloured powder
6	API – starch 1500	1:1	Off white coloured powder	Off white coloured powder
7	API – HCTZ	1:1	Off white coloured powder	Off white coloured powder

TABLE 12 : API RESULTS:

BULK DENSITY gm/ml	TAPPED DENSITY gm/ml	CARR'S INDEX (%)	HAUSNER'S RATIO	ANGLE OF REPOSE ( $\Theta$ )
0.362	0.612	42	1.64	30.1

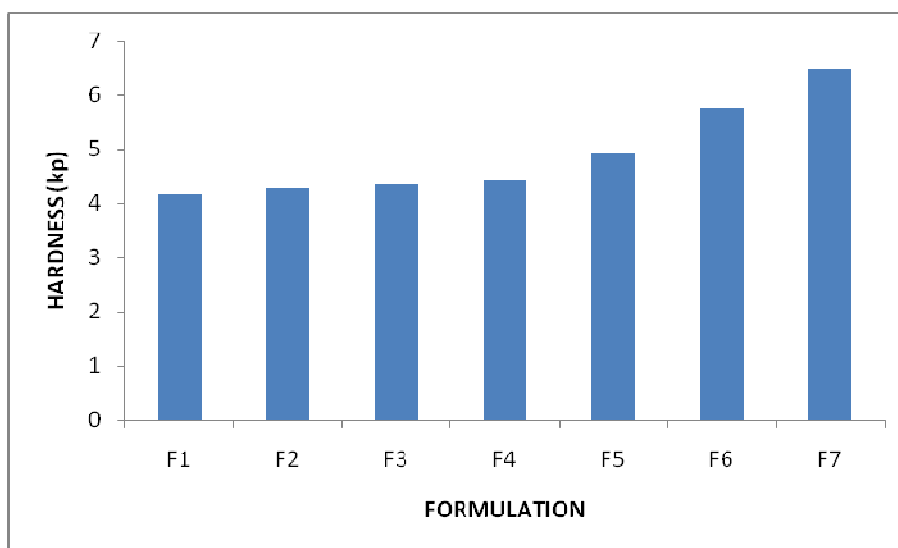
TABLE -13 : BULK DENSITY, COMPRESSIBILITY INDEX, HAUSNER'S RATIO, ANGLE OF REPOSE OF LOSARTAN/HCTZ BLEND

S.N O	FORMULA TION CODE	BULK DENSITY(g/ml)		COMPRESSIBI LITY INDEX (%)	HAUSNE R'S RATIO	ANGLE OF REPOSE (DEGRE ES)
		Untap ped	Tap ped			
1	F <sub>1</sub>	0.382	0.439	34.46	1.56	25.0
2	F <sub>2</sub>	0.410	0.461	36.39	1.59	28.6
3	F <sub>3</sub>	0.428	0.486	38.43	1.62	29.3
4	F <sub>4</sub>	0.431	0.457	44.6	1.72	28.6
5	F <sub>5</sub>	0.426	0.460	40.35	1.65	30.5
6	F <sub>6</sub>	0.412	0.491	41.8	1.67	32.6
7	F <sub>7</sub>	0.391	0.445	40.17	1.65	29.1

**TABLE-14 : HARDNESS OF *LOSARTAN* And *HCTZ* TABLETS FOR DIFFERENT FORMULATIONS**

S.NO	FORMULATION CODE	HARDNESS OF TABLETS(KP)
1	F1	4.18
2	F2	4.28
3	F3	4.35
4	F4	4.42
5	F5	4.90
6	F6	5.76
7	F7	6.48

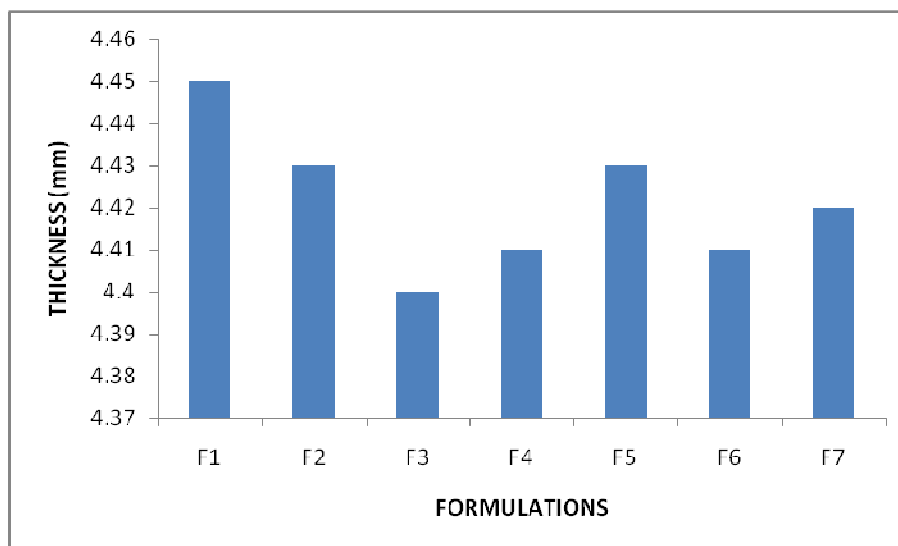
Specifications : 4 – 8 kp

**FIG - 6: HARDNESS OF *LOSARTAN* And *HCTZ* TABLETS FOR DIFFERENT FORMULATIONS**

**TABLE -15 THICKNESS OF *LOSARTAN* And *HCTZ* TABLETS FOR DIFFERENT FORMULATIONS**

S.NO	FORMULATION CODE	THICKNESS OF TABLETS(mm)
1	F1	4.45
2	F2	4.43
3	F3	4.40
4	F4	4.41
5	F5	4.43
6	F6	4.41
7	F7	4.42

specification 4.20+/- 0.3

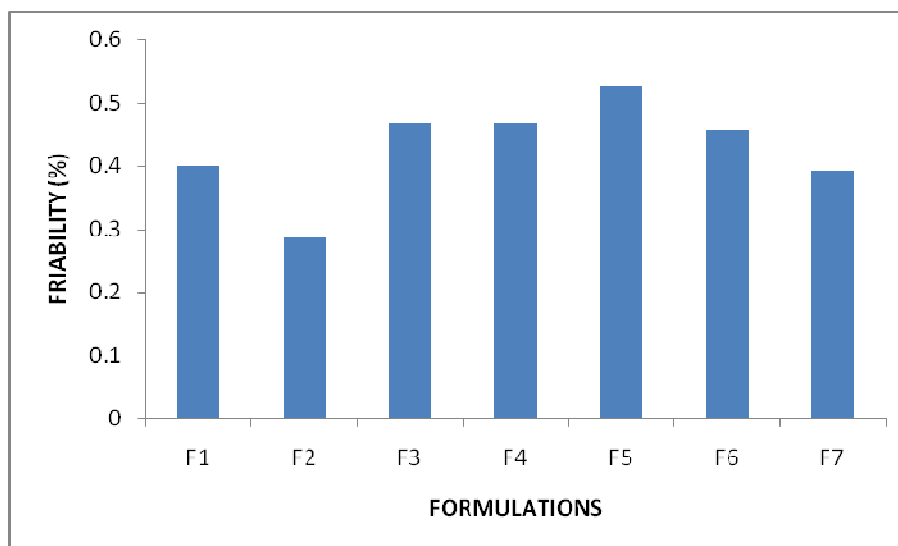


**FIG - 7 : THICKNESS OF *LOSARTAN* And *HCTZ* TABLETS FOR DIFFERENT FORMULATIONS**

**TABLE -16 FRIABILITY OF *LOSARTAN* And *HCTZ* TABLETS FOR DIFFERENT FORMULATIONS**

S.NO	FORMULATION CODE	FRIABILITY OF TABLETS (%)
1	F1	0.400
2	F2	0.286
3	F3	0.467
4	F4	0.466
5	F5	0.525
6	F6	0.458
7	F7	0.393

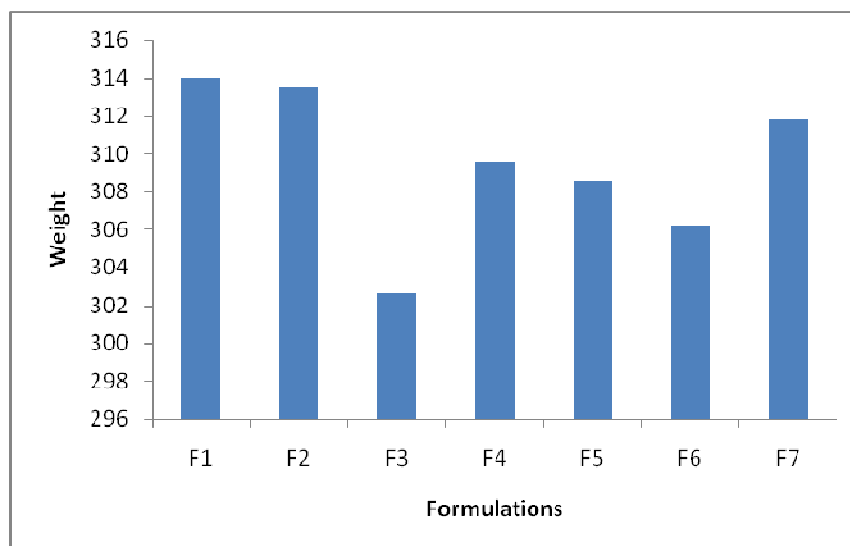
Specifications : Less than 0.8%

**FIG - 8: FRIABILITY OF *LOSARTAN* and *HCTZ* TABLETS FOR DIFFERENT FORMULATIONS**

**TABLE - 17 AVERAGE WEIGHT OF *LOSARTAN* And *HCTZ* TABLETS FOR DIFFERENT FORMULATIONS**

S.NO	FORMULATION CODE	AVERAGE WEIGHT OF TABLETS (mg)
1	F1	314.0
2	F2	313.5
3	F3	302.6
4	F4	309.6
5	F5	308.6
6	F6	306.2
7	F7	311.8

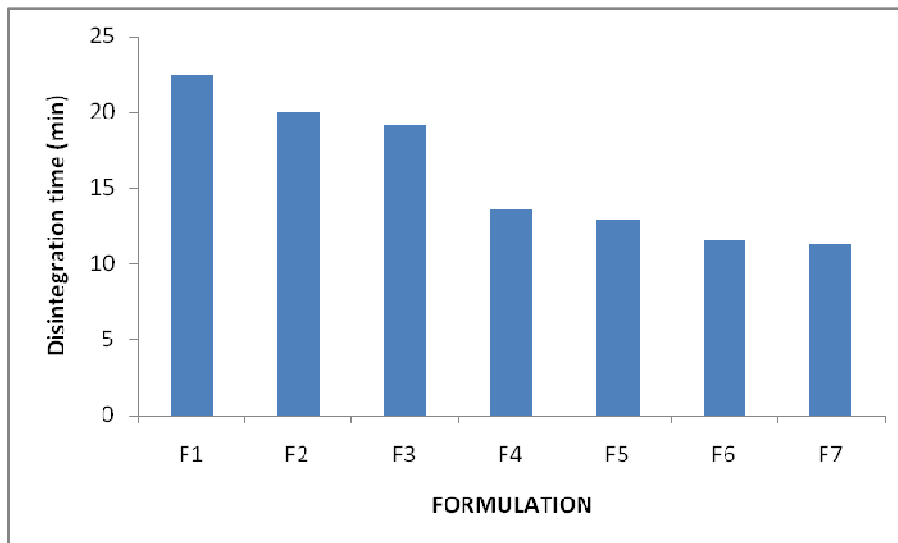
Specifications : 309.00 +/- 2.0%  
(302.82 – 315.18)

**FIG - 9: AVERAGE WEIGHT OF *LOSARTAN* And *HCTZ* TABLETS FOR DIFFERENT FORMULATIONS**

**TABLE - 18 DISINTEGRATION TIME OF *LOSARTAN* And *HCTZ* TABLETS FOR DIFFERENT FORMULATIONS**

S.NO	FORMULATION CODE	DISINTEGRATION OF TABLETS (min)
1	F1	22.50
2	F2	20.03
3	F3	19.11
4	F4	13.55
5	F5	12.85
6	F6	11.52
7	F7	11.25

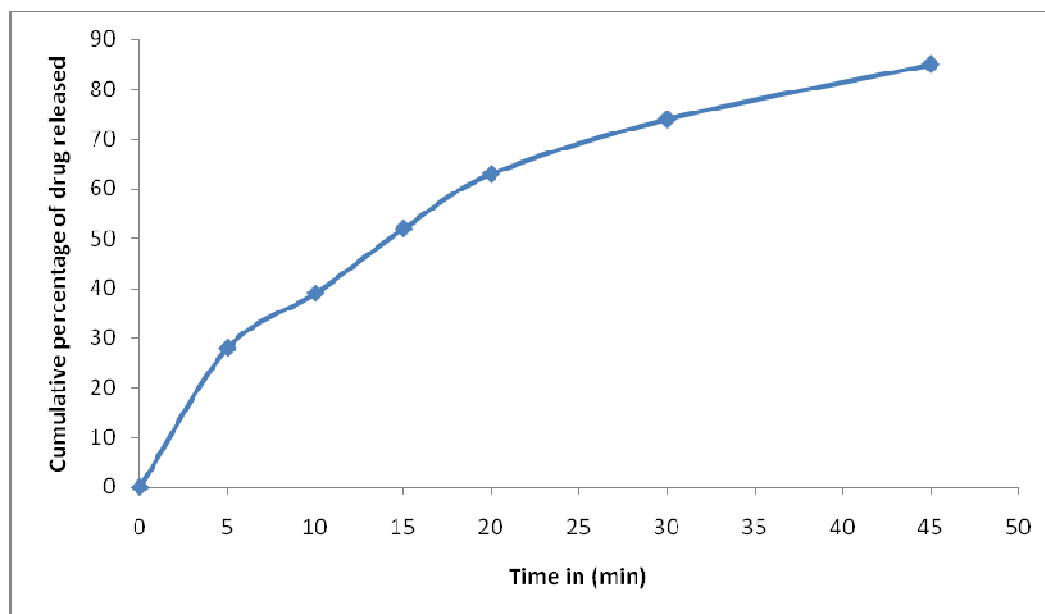
**Specifications :**Not more than 20

**FIG - 10: DISINTEGRATION OF *LOSARTAN* And *HCTZ* TABLETS FOR DIFFERENT FORMULATIONS**



**Table – 19 : INVITRO DISSOLUTION PROFILE OF FORMULATION F1 IN PHOSPATE BUFFER MEDIUM**

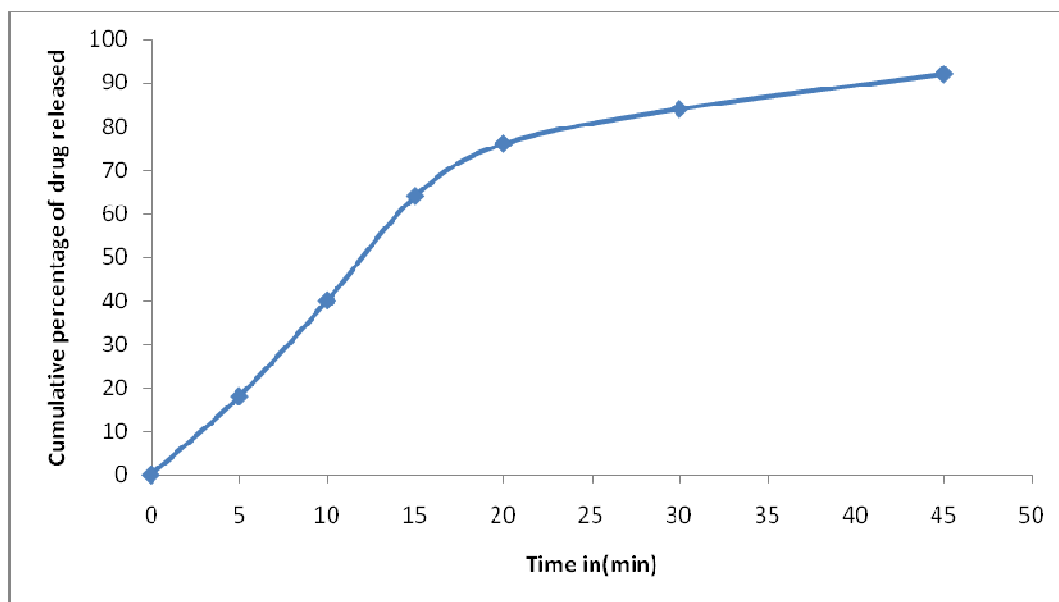
Slno	Tablet weight(mg)	5 Min	10Min	15Min	20Min	30Min	45Min
1	308.2	26	35	48	59	72	85
2	311.4	31	42	58	62	75	88
3	314.1	34	49	61	72	79	84
4	316.4	25	35	51	63	75	82
5	312.1	22	34	46	59	71	80
6	309.1	28	39	48	61	75	89
Mean	311.8	28	39	52	63	74	85
SD	-	1.18	1.55	0.90	0.62	1.17	2.36



**Fig no - 11 INVITRO DISSOLUTION PROFILE OF FORMULATION F1 IN PHOSPATE BUFFER MEDIUM**

**Table – 20 : INVITRO DISSOLUTION PROFILE OF FORMULATION F2 IN PHOSPATE BUFFER MEDIUM**

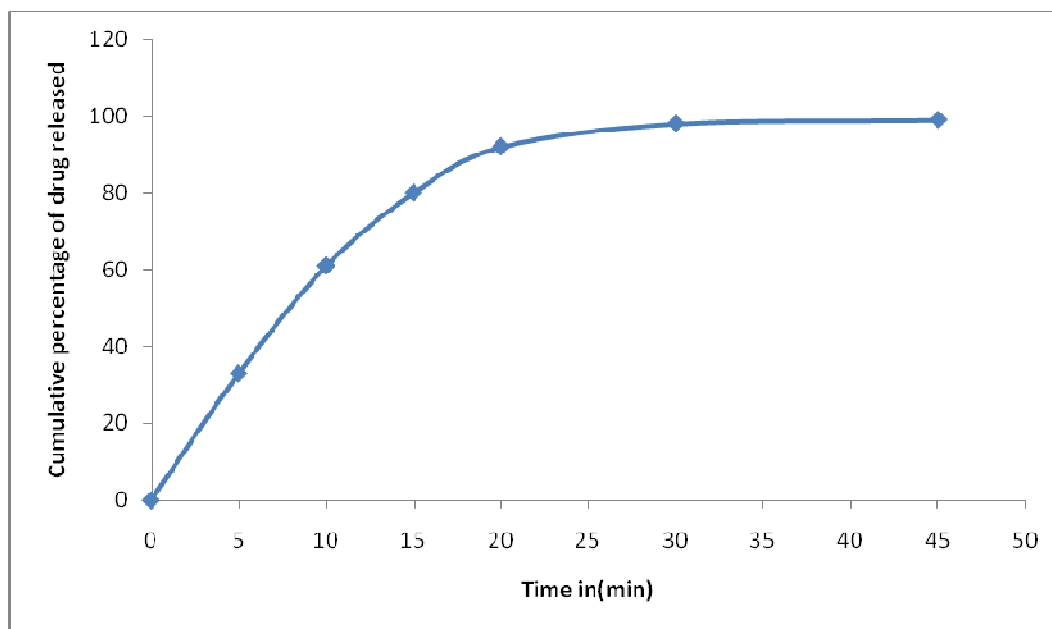
Slno	Tablet weight(mg)	5 Min	10Min	15Min	20Min	30Min	45Min
1	304.2	15	38	64	75	82	89
2	311.2	17	41	68	79	84	92
3	299.8	21	45	69	75	86	94
4	302.9	16	37	59	72	84	91
5	314.3	23	42	63	78	86	93
6	305.2	19	40	62	76	83	95
Mean	306.2	18	40	64	76	84	92
SD	-	1.18	1.55	0.90	0.62	1.17	2.36



**Fig no- 12 : INVITRO DISSOLUTION PROFILE OF FORMULATION F2 IN PHOSPATE BUFFER MEDIUM**

**Table – 21 : INVITRO DISSOLUTION PROFILE OF FORMULATION F3 IN PHOSPATE BUFFER MEDIUM**

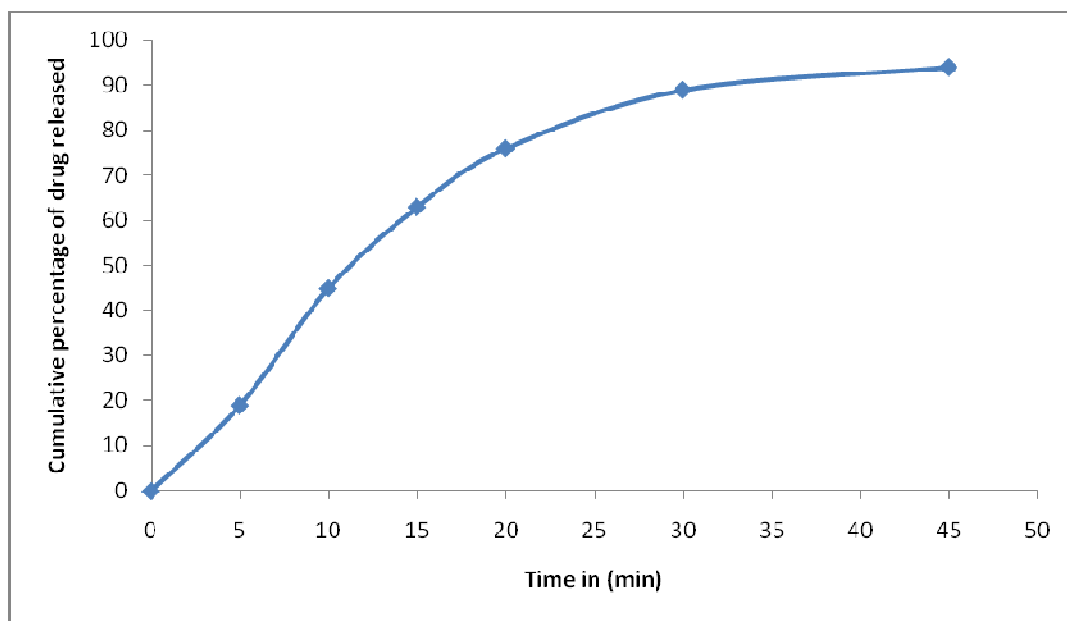
Slno	Tablet weight(mg)	5 Min	10Min	15Min	20Min	30Min	45Min
1	304.1	20	47	71	84	95	96
2	312.0	36	68	86	96	102	102
3	314.6	33	55	73	87	95	97
4	305.4	34	64	88	97	98	98
5	310.9	37	65	82	94	96	97
6	304.8	36	65	81	91	100	102
Mean	308.6	33	61	80	92	98	99
SD	0	1.18	1.55	0.90	0.62	1.17	2.36



**Fig no.-13: INVITRO DISSOLUTION PROFILE OF FORMULATION F3 IN PHOSPATE BUFFER MEDIUM**

**Table – 22 : INVITRO DISSOLUTION PROFILE OF FORMULATION F4 IN PHOSPATE BUFFER MEDIUM**

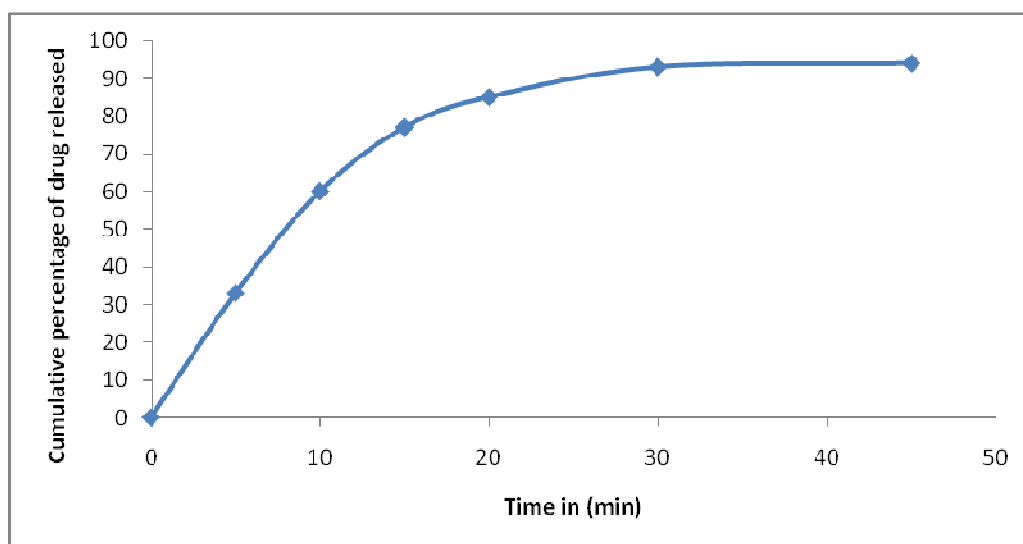
Slno	Tablet weight(mg)	5 Min	10Min	15Min	20Min	30Min	45Min
1	312.9	14	32	58	76	92	95
2	309.3	24	52	69	83	95	96
3	306.0	10	32	50	66	84	91
4	310.8	19	48	64	73	83	91
5	309.1	19	47	64	76	88	93
6	309.2	26	52	72	82	94	96
MEAN	309.6	19	45	63	76	89	94
SD	0	1.18	1.55	0.90	0.62	1.17	2.36



**Fig no- 14 : INVITRO DISSOLUTION PROFILE OF FORMULATION F4 IN PHOSPATE BUFFER MEDIUM**

**Table – 23 : INVITRO DISSOLUTION PROFILE OF FORMULATION F5 IN PHOSPATE BUFFER MEDIUM**

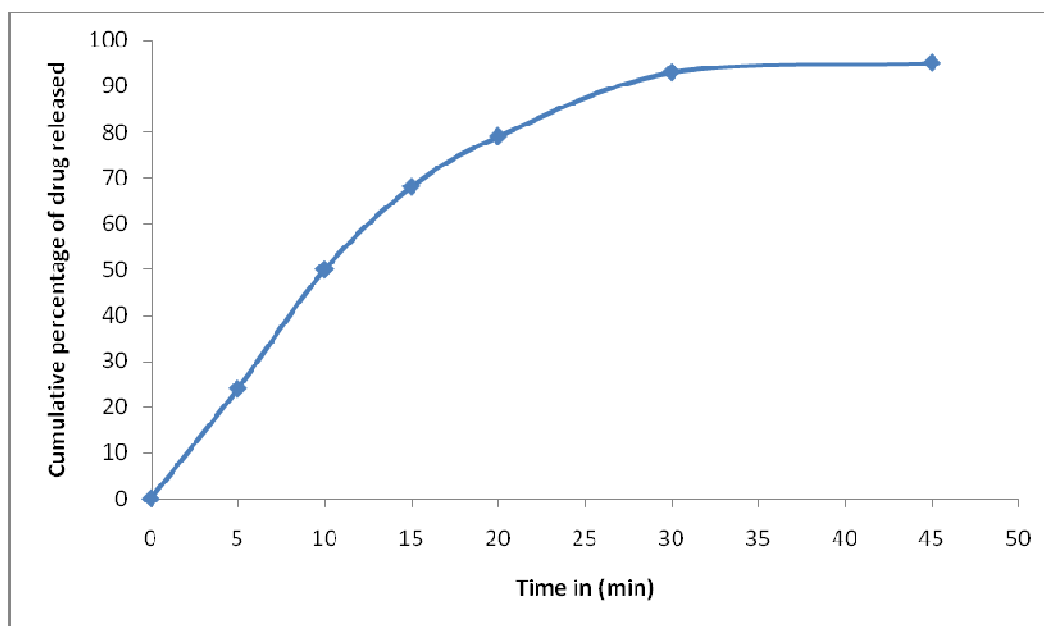
Slno	Tablet weight(mg)	5 Min	10Min	15Min	20Min	30Min	45Min
1	304.2	25	58	74	84	92	94
2	299.7	33	57	73	82	93	97
3	304.2	32	59	75	85	93	94
4	299.8	35	61	80	89	95	95
5	302.9	43	67	83	90	92	92
6	304.5	30	56	74	84	93	94
Mean	302.6	33	60	77	85	93	94
SD	0	1.18	1.55	0.90	0.62	1.17	2.36



**Fig no.- 15 : INVITRO DISSOLUTION PROFILE OF FORMULATION F5 IN PHOSPATE BUFFER MEDIUM**

**Table – 24 : INVITRO DISSOLUTION PROFILE OF FORMULATION F6 IN PHOSPATE BUFFER MEDIUM**

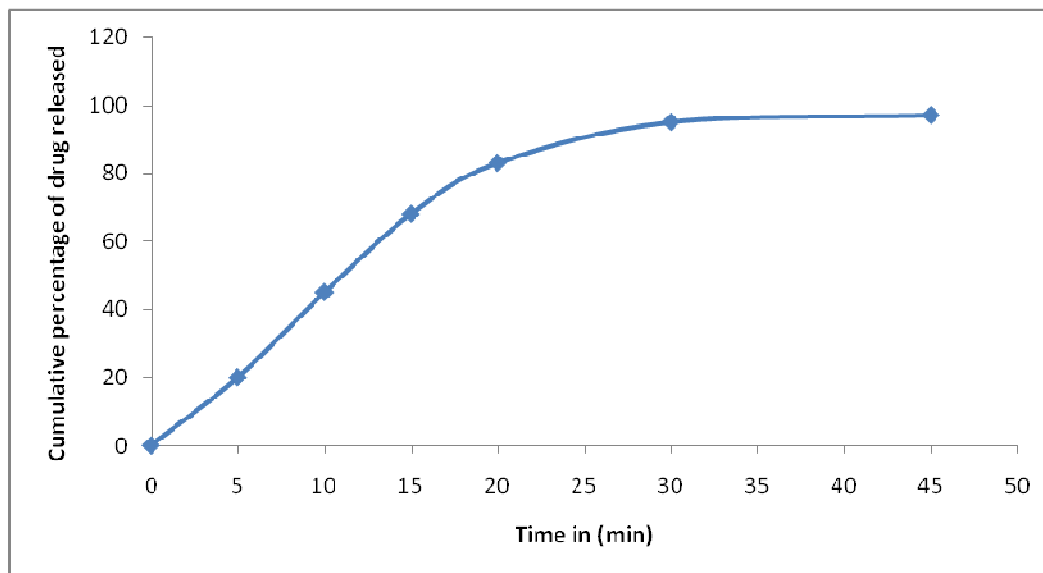
Slno	Tablet weight(mg)	5 Min	10Min	15Min	20Min	30Min	45Min
1	308.9	23	51	68	79	92	94
2	315.0	19	45	66	77	93	95
3	311.7	29	53	74	86	96	97
4	313.1	24	47	67	78	91	96
5	314.9	26	53	68	78	90	94
6	317.4	21	49	67	78	93	95
Mean	313.5	24	50	68	79	93	95
SD	0	1.18	1.55	0.90	0.62	1.17	2.36



**Fig no.-16 : INVITRO DISSOLUTION PROFILE OF FORMULATION F6 IN PHOSPATE BUFFER MEDIUM**

**Table -25 : INVITRO DISSOLUTION PROFILE OF FORMULATION F7 IN PHOSPATE BUFFER MEDIUM**

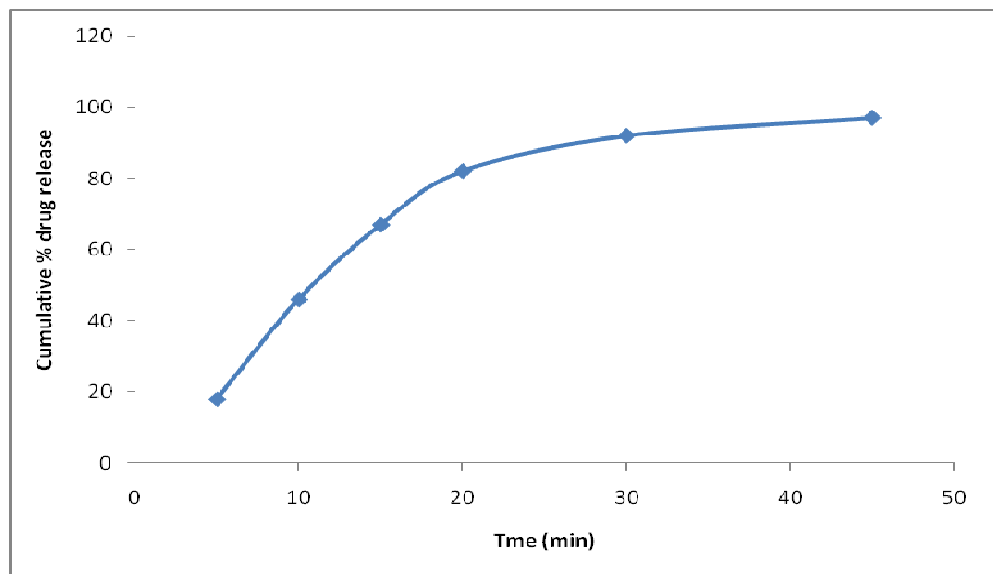
Slno	Tablet weight(mg)	5 Min	10Min	15Min	20Min	30Min	45Min
1	317.8	18	44	69	83	99	99
2	314.4	21	48	68	88	97	99
3	311.4	19	44	64	79	92	95
4	318.1	21	46	70	87	98	99
5	312.7	18	39	63	78	93	95
6	309.3	25	49	72	85	93	97
MEAN	314.0	20	45	68	83	95	97
SD	0	1.18	1.55	0.90	0.62	1.17	2.36



**Fig no. -17 : INVITRO DISSOLUTION PROFILE OF FORMULATION F7 IN PHOSPATE BUFFER MEDIUM**

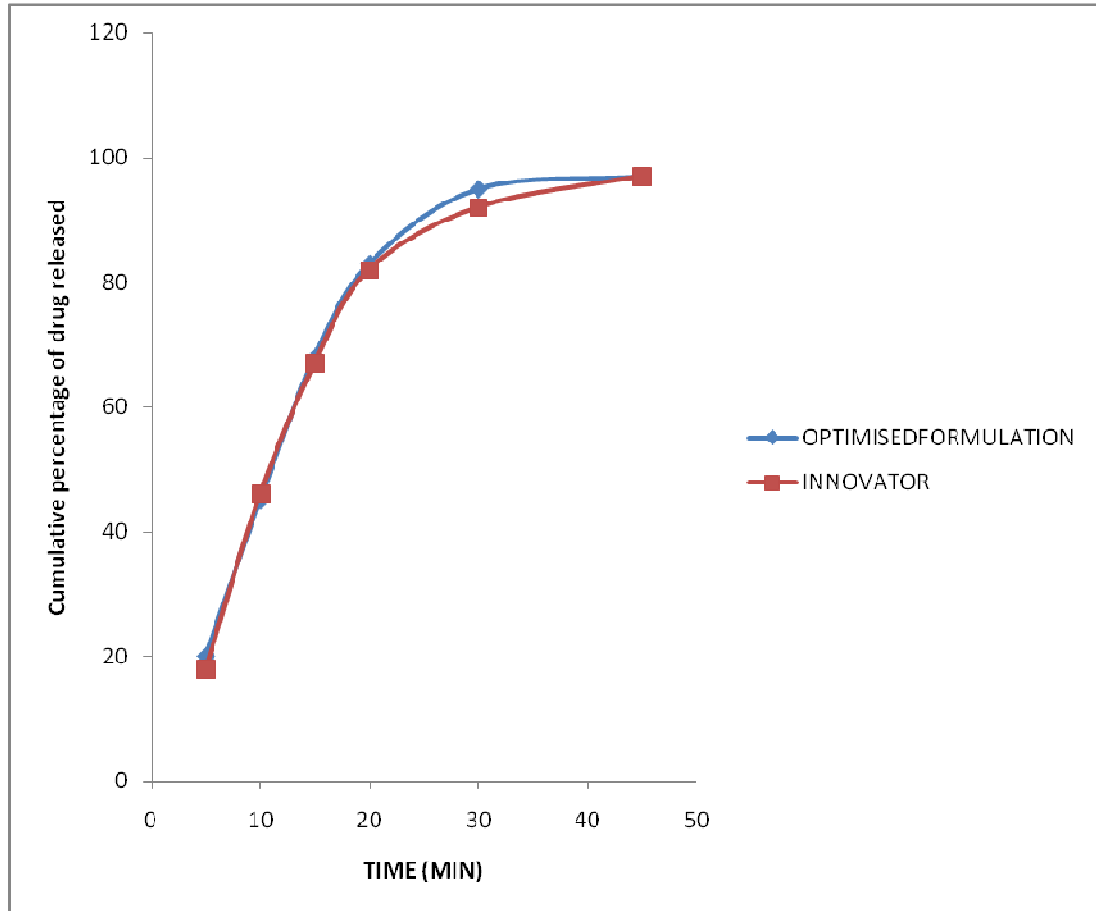
**Table -26 : INVITRO DISSOLUTION PROFILE OF INNOVATOR IN PHOSPATE BUFFER MEDIUM**

Sl.no.	5min	10min	15min	20min	30min	45min
1	18	44	65	81	95	98
2	17	45	67	84	98	99
3	19	45	69	85	92	95
4	18	46	64	83	91	94
5	16	43	71	82	98	99
6	20	47	72	83	96	97
Mean	18	46	67	82	95	97
SD	1.18	1.55	0.90	0.62	1.17	2.36



**Fig no. -18 : INVITRO DISSOLUTION PROFILE OF INNOVATOR IN PHOSPATE BUFFER MEDIUM**





**Fig no. -19 :COMPARISON OF *INVITRO* DISSOLUTION PROFILE OF INNOVATOR VS OPTIMISED FORMULATION IN PHOSPATE BUFFER MEDIUM**

**TABLE -27 : COEFFICIENT CORRELATION (r) VALUES FROM *INVITRO* DISSOLUTION RATE TEST OF LOSARTAN POTASSIUM AND HYDROCHLORTHIAZIDE CONVENTIONAL TABLETS**

<b>Formulation Code</b>	<b>Zero Order</b>	<b>First Order</b>	<b>Higuchi's</b>	<b>Peppas's</b>
<b>F1</b>	0.9037	0.9704	0.9809	0.9769
<b>F2</b>	0.9541	0.9581	0.9679	0.9885
<b>F3</b>	0.9888	0.9751	0.9695	0.9882
<b>F4</b>	0.9689	0.8169	0.9834	0.9913
<b>F5</b>	0.9277	0.99555	0.9797	0.9568
<b>F6</b>	0.8330	0.9388	0.9512	0.9160
<b>F7</b>	0.9308	0.9886	0.9876	0.9459

**Stability results:****Table – 28: Percentage Cumulative release of stability studies of optimized formulation (F7) at 40<sup>0</sup>C / 75% RH and 50<sup>0</sup>C for 1 month**

Time (Min)	Cumulative % drug release		
	Initial	50 <sup>0</sup> C	40 <sup>0</sup> C / 75% RH
0	0	0	0
5	20±5.0	19±4.5	19±4.1
10	45±4.9	44±4.1	43±3.5
15	68±4.0	67±3.2	67±2.9
20	83±3.2	82±4.1	82±1.8
30	95±2.1	95±4.0	94±1.1
45	97±2.0	96±2.1	95±1.0

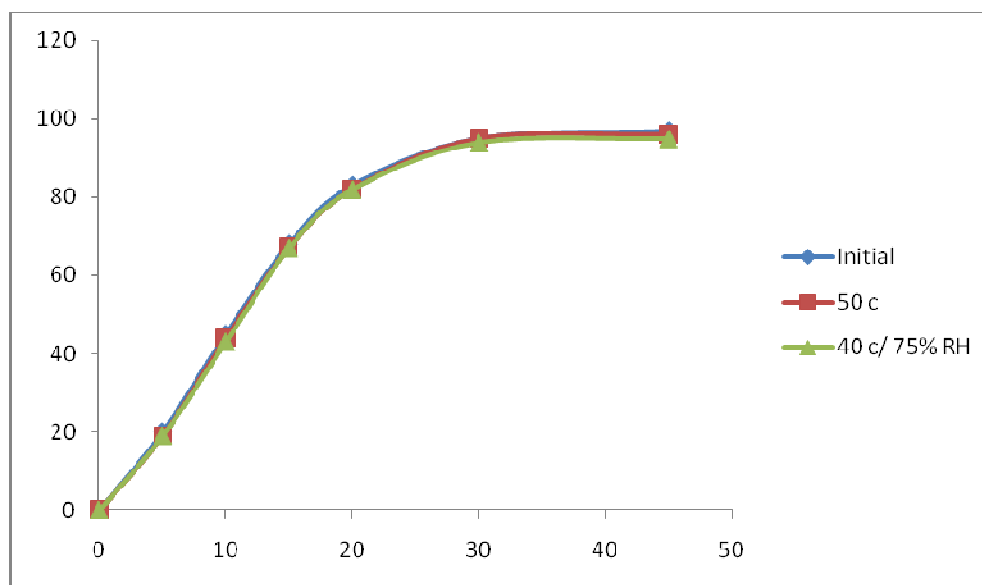
**Fig no.-20: Dissolution profiles of 1 month stability samples at different conditions**

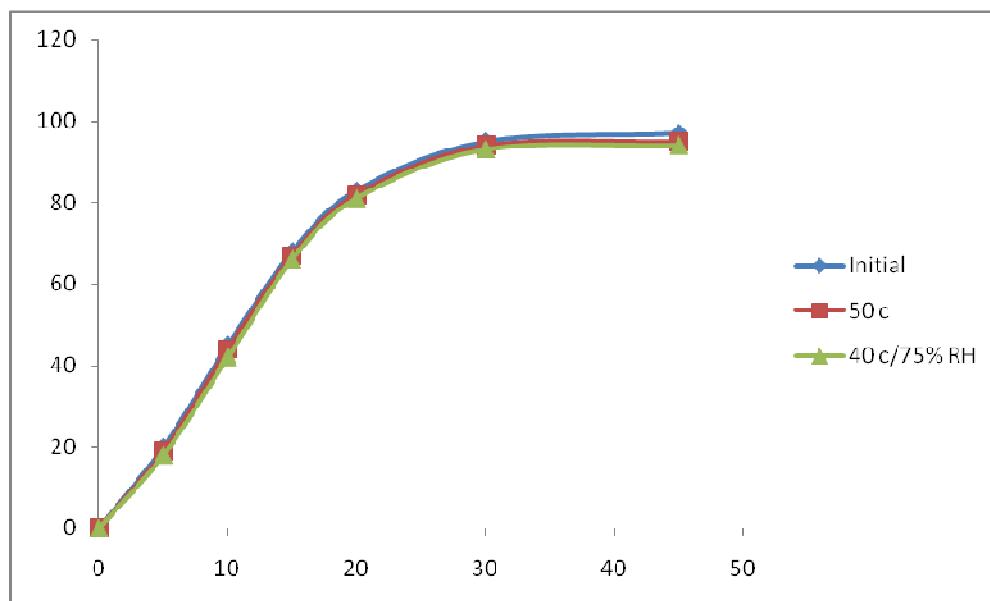
Table – 29 : Physical evaluation for stability studies of optimized formulations

Parameter	Initial	50°C	40°C / 75% RH
Color	White	White	White
Surface	Smooth	Smooth	Smooth
Thickness (mm)	4.40 mm	4.41 mm	4.42 mm
Hardness (kp)	4.0-6.5	4.0-6.0	4.0-6.0
Wight (mg)	300 ± 0.11	300 ± 0.76	300 ± 1.89
Assay	99.12%	98.16%	97.98%

**AFTER 3 MONTHS :**

Table – 30 : Percentage Cumulative release of stability studies of optimized formulation (F7) at 40°C / 75% RH and 50°C for three months

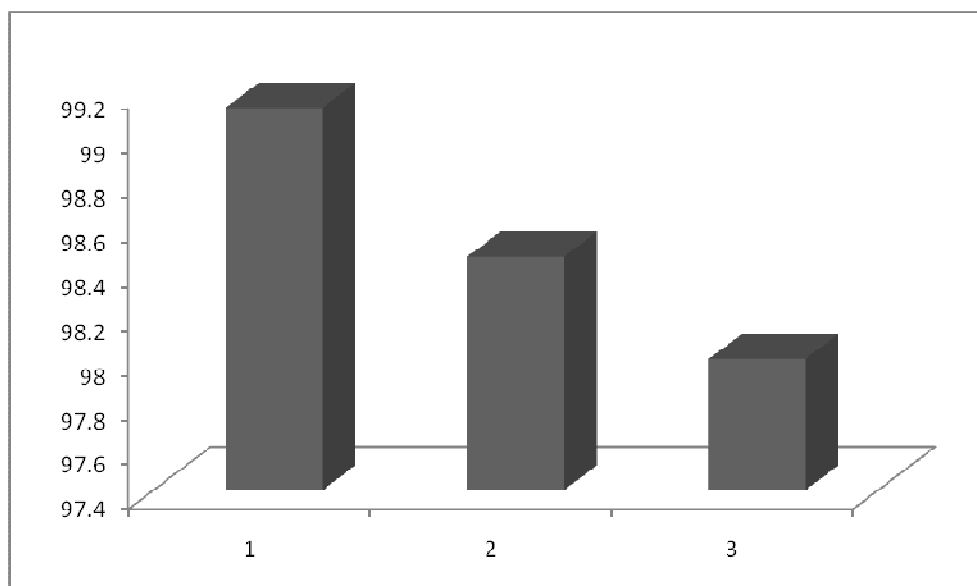
Time (hr)	Cumulative % drug release		
	Initial	50°C	40°C / 75% RH
0	0	0	0
5	20±5.0	19±4.8	18±5.1
10	45±4.9	44±4.1	42±5.2
15	68±4.0	67±3.5	66±2.6
20	83±3.2	82±2.1	81±4.2
30	95±2.1	94±2.0	93±2.9
45	97±2.0	95±1.8	94±1.2



**Fig no. – 21: Dissolution profiles of 3 months stability samples at different conditions**

**Table – 31: Physical evaluation for stability studies of optimized formulations**

Parameter	Initial	50°C	40°C / 75% RH
Color	White	White	White
Surface	Smooth	Smooth	Smooth
Thickness (mm)	4.40 mm	4.42 mm	4.42 mm
Hardness (kp)	4.0-6.5	4.0-6.0	4.0-5.5
Wight (mg)	300 ± 0.11	300 ± 0.76	300 ± 1.89
Assay	99.12%	98.45%	97.99%



**Fig no.- 22 Drug content of tablets after 3 months stability studies at different condition.**

## **7. SUMMARY**

- For the treatment of hypertension losartan potassium and hydrochlorthiazide conventional tablets are formulated. The hydrochlorthiazide added to the formulation to potentiate the activity of the losartan potassium.
- The drugs are found to be stable and there is no any interaction between these two drugs and are producing synergistic activity. Also confirmed that there is no interaction between the drug and the excipients as a result of incompatibility results in different ratios.
- The resulted tablets are evaluated for their hardness, weight variation, thickness, friability, disintegration, dissolution etc.,
- In F1 batch the granules are cohesive even after drying for about 20 min. the loss on drying greater than 3%. The compressed tablets are evaluated for disintegration, the disintegration time in deviating from specifications.
- In F2 batch to overcome these problems the binder concentration increased so that the agglomerates are decreased than the F1 trial.
- In F3 futher concentration of binder is increased to decrease the moisture content present in the final blend.

- In F4 the microcrystalline cellulose 101 and 200 are added in various concentrations and the amount of starch is further increased to avoid problems like cohesive mass and to obtain LOD less than 3%.
- In F5 the disintegrant is changed to low substituted hydroxyl propyl cellulose as it is found to be better than the previous and even the binder is increased.
- In F6 the microcrystalline cellulose 101 and 200 are added in equal concentration to overcome the cohesive mass. The results are found to be satisfactory.
- Even though the results are satisfactory in F6 the concentration of binder is further increased in F7 to obtain the better results and the results are good.
- The tablets from F7 comply with all the specifications for the evaluation tests. The dissolution profile of F7 batch was compared with the innovator and found to be equal with that of innovator.
- Then the F7 batch samples are kept for stability studies and are found to be good after three months.



## **CONCLUSION**

- The stable robust quality of losartan potassium and hydrochlorthiazide conventional tablets are formulated. The formulated tablets are compared with the specifications of the innovator and the optimised formulation complies with the specifications.
- The disintegrant used in the formulation is low substituted hydroxyl propyl cellulose which is different from that of the innovator and even the binder differs from the innovator even though the specifications of the evaluation are complied as per the specifications.
- The optimised formulation is kept for stability studies and the results are good

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