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Formulation and Evaluation of Immediate Release Bilayer Film Coated Tablets of Losartan Potassium and Hydrochlorothiazide

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KEYWORDS
Bilayer Tablets, Losartan Potassium, Hydrochlorothiazide, Immediate Release.

ABSTRACT:

The invention relates to a losartan potassium hydrochlorothiazide tablet and a preparation method thereof. The losartan potassium hydrochlorothiazide tablet comprises a core and a film coat layer and is characterized in that the core is composed of the losartan potassium and the hydrochlorothiazide which serve as the medicinal active components, and a medicinally available accessory. The medicinally available accessory is microcrystalline cellulose, pregelatinized starch, lactose monohydrate, polyvinylpyrrolidone K30 and magnesium stearate. The preparation method of the losartan potassium hydrochlorothiazide tablet is as the following: the hydrochlorothiazide is mixed with the easily-dissolvable losartan potassium and lactose monohydrate, and then the mixture is made into grains; the hydrochlorothiazide is dispersed in the easily-dissolvable losartan potassium and lactose monohydrate, and then mixed with the microcrystalline cellulose, the pregelatinized starch and magnesium stearate; then tablets are made and coated.

1. INTRODUCTION:

The oral drug delivery system is regarded as one of the most practical and widely used drug delivery systems. Additionally, due to its ease of consumption, oral medications are typically regarded as the first avenue explored in the discovery and development of new pharmacological entities into pharmaceutical formulations.

- Flexibility in the layout
- Minimal aseptic restrictions
- Avoiding pain
- Economical manufacturing method
- Simple to produce on a vast scale
- Flexibility (to accept different kinds of medication candidates)

However, for therapeutic agents that are poorly absorbed in the gastrointestinal (GI) tract and medications that are unstable to different enzymes, especially proteolytic enzymes, such as peptide and protein pharmaceuticals, the possibility for developing oral dosage forms may be limited.

Numerous physiological, pharmaceutical, and patient compliance issues that are related to the intrinsic physicochemical nature of the medications and/or the variability in Gl conditions—such as pH, food presence, transit times, enzymatic activity in the alimentary canal, and the patient's illness condition—often compromise the oral delivery process as a whole.

Oral drug delivery is still the recommended method of drug delivery in spite of the drawbacks. One key tactic for enhancing oral medication delivery is the manipulation of these issues and difficulties. A comprehensive knowledge of ODDS necessitates the proper integration of physiology, biochemistry, polymer science, pharmacokinetic, and pharmacodynamic concepts with physicochemical principles.

Bilayer Tablet

With multiple features to ensure effective medicine administration, the bi-layer tablet represents a new period

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in controlled release expression development. By physically separating APIs, bi-layer tablets can be the stylish way to help chemical incompatibilities and allow for the creation of distinct medicine release biographies. Bi-layer tablets, which have a lading cure for rapid-fire release and a conservation cure for the alternate subcaste, are applicable for both sustained release and the successional release of two specifics in combination. Bi-layer tablets are now being developed by a number of pharmaceutical companies for a variety of reasons, including effectiveness, rectifiers, and patent extension. Although the fundamentals of tablet manufacturing are still the same, there are numerous further factors to take into account because creating multi-layer tablets requires several constantly inharmonious goods, redundant outfit, and many formulation and operation challenges.

Advantages of multi- layered tablets over conventional tablets:

Conventional Tablets:

There is just one kinetic model for drug release.

There is no method to prevent chemical incompatibilities when multiple drugs are used.

Multilayer tablets:

If there are any chemical incompatibilities, it may be used to combine and separate multiple drugs. There is no method to prevent chemical incompatibilities when multiple drugs are used.

This method may provide multiple drug release kinetics of the same or different medications, such as extended and immediate release, therefore drug release behaviour is not limited to a single type.

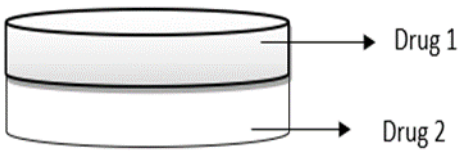

Fig: 1 – In case of combination therapy the drug 1 and drug 2 are different but in case of sustained release the drug 1 is the loading dose whereas the drug 2 is the maintenance dose of a drug

Need of Bilayer Tablets.

Create innovative drug delivery systems, such as chewing devices and floating tablets for gastro-retentive drug delivery; extend the life cycle of drug products; and provide fixed dose combinations of several APIs.

Regulating the rate at which one or more distinct active medicinal ingredients are delivered

To create swellable/erodible barriers for modified release, the entire surface area available for the API layer can be changed by sandwiching it between one or two active layers.

Active pharmaceutical ingredients (APIs) that are incompatible with one another can be separated by using the functional properties of the other layer, such as the osmotic characteristic, to regulate the release of API from one layer.

Advantages of Bilayer Tablets.

The following are the benefits of the tablet lozenge form over the indispensable lozenge forms before going into the advantages of the bilayer tablet

- All the oral lozenge forms, tablets give the stylish comity for the loftiest cure perfection and the least quantum of content variability.
- Compared to other oral cure forms, the price is about cheaper.
- The nature of them is extremely compact.
- Tablet packaging is generally simpler and less precious.
- Tablet swallowing is relatively simple.
- Large- scale product is more applicable for them.
- Tablets are extremely stable physically, chemically, and microbiologically.

The 'bilayer tablet' has the following advantages over other traditional oral solid dose form formulations.

- The tablet can be readily utilized in combination therapy when it contains two distinct layers that contain two different medications.
- Two incompatible substances can be delivered separately using this formulation.
- The case of the tablet's two layers, which contain a loading dosage and a maintenance dose of the

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same, respectively, increases the drug's bioavailability when it comes to medications with short half-lives.

- Lowering the frequency of dosage delivery eventually benefits the patient. Compliance.
- By employing this dosage form, the plasma drug concentration can be maintained at a constant level, which eventually results in a more effective action of the drug. In the case of a conventional dosage form, the plasma drug concentration may vary due to fluctuations in the dosing interval (under or over medication).
- Since formulation in an extended action form can reduce the high blood level peaks that may be noticed after administration of a dose of a high availability medicine, better control of drug absorption can be achieved. High potency medications can have their safety margin expanded, and sensitive patients can experience less systemic and local side effects.

Limitations of Bilayer Tablet

From the above-mentioned advantage of bilayer tablets it is quite clear that in pharmaceutical industry it made a great revolution, but there are certain limitations in the formulation and use of bilayer tablets, such as:

- Lack of adequate bonding and adhesion at the interface between the adjacent compacted layers, which frequently results from an interfacial crack and layer separation, is one of the main problems with bilayer formulation.
- Compacted layers that are too soft or too hard will not adhere to one another firmly, which could damage their mechanical integrity and cause the layers to separate.
- Determining the layer sequence order, layer weight ratio, adjacent layer elastic misfit, initial layer tamping force, and interlayer cross contamination are further development obstacles.
- Since a bilayer tablet's neighbouring layers are mechanically connected together, the variables affecting the stress state are crucial. Each layer's and the tablet's mechanical characteristics, compression parameters, specialized methods, and compression conditions all play a significant part in this.
- When a sustained release bilayer pill is administered, treatment cannot be stopped right away.
- The doctor is less able to change the dosage schedules.

Challenges During the Manufacturing of Bilayer Tablet

The following requirements for choosing a bilayer press must be adhered to in order to create a high-quality bi-layer tablet in a verified and GMP manner. Despite their apparent nature, these standards are difficult to meet. The media should to be able be

- Preventing the two separate layers that make up the bi-layer tablet from capping and separating (Lamination)
- Enough tablet hardness
- Keeping the two layers from being contaminated
- Display a distinct visual division between the two layers.
- Producing the goods with a high yield
- Precise and distinct weight regulation of the two layers

Drug Release Mechanism

Drug release from hydrophilic swellable matrices typically depends on the polymer macromolecular coupling, drug diffusion, relaxation, and Narasimaharao Ret al., 2011 (Wadher KJ. et al., 2011; Bhardwaje et al., 2011; Shaikh RP et al., 2010). These factors also affect how quickly water may enter the device.

The fundamentals of the multilayered drug delivery design are the polymer's swelling rate, hydration rate, and matrix modification. These parameters are highly effective during the primary or first phase of drug dissolution; however, as swelling progresses over time, the release profile becomes linearized.

The matrix tablets have been coated with an inert impermeable layer in order to accomplish this goal. Drug release from multilayered preparations is greatly influenced by coating, and there are several possible combinations of coating materials in terms of scheme.

In vitro release rate studies are used to observe the drug's release rate from tablets. The degree of coating has an inverse relationship with the drug's release rate. The polymer's swelling, which is again managed by the coating material's reduction of the drug release surface, is the main factor influencing the drug's release.

Partially coated tablets do not swell; instead, they preserve their original dimensions and form while

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maintaining a constant release retardation throughout the breakdown process. However, when the pill is submerged in water, the inert polymer barrier has a propensity to break and separate from the core in a matter of hours.

This phenomenon is caused by the core's volume expanding when submerged in water as a result of polymer swelling. Stress is created in the outer barrier layer as a result of the outer barrier layer not expanding while the core is swelling. When the exterior barrier is made of a polymer that can be sold, the core and barrier both inflate at the same time throughout the dissolution process without experiencing any internal stress.

Barriers can be applied via a multilayer compression approach. Tablets with two or three layers, where the active substance (active core) is only present in one layer and the other layers are barrier layers, are a prominent illustration of this phenomenon.

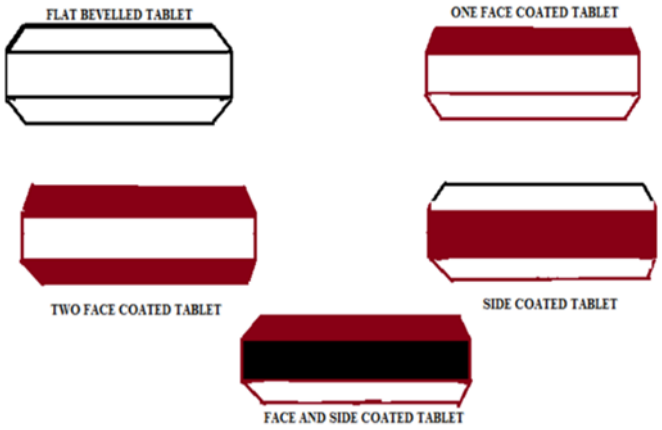

Fig :2 - Schematic representation of the matrix tablet and four partially coated designs

2. LITERATURE SURVEY

Mohanthy et al., (2010) The work investigates and highlights the Losartan potassium tablet formulation and optimization objective was accomplished by preparing and evaluating different formulations of losartan potassium tablets in terms of quality parameters for both the finished products (average weight, weight variation, tablet thickness, friability, hardness, disintegration time, drug content, in vitro dissolution studies) and the granules (loss on drying, bulk density, tapped density, compressibility index, Hausner's ratio). These parameters were used to optimize the formula and compare it to the originator. It was found that the innovator and the optimized losartan potassium tablets were pharmaceutically identical. Stability parameters were found to be good after optimizing tablets for a range of atmospheric conditions.

Natarajan et al., (2005) This work creates a stable immediate-release bilayer tablet formulation of the hypertension medications telmisartan and hydrochlorothiazide, and assessed the dissolution profile in relation to a reference product. Wet granulation was used to start the formulation development process. To increase solubility and drug release, telmisartan was dissolved in an aqueous solution of sodium hydroxide to yield its sodium salt. Microcrystalline cellulose and lactose monohydrate were employed as diluents. The binder was starch paste, which is made with purified water. As a dissolving agent, sodium starch glycolate is used. The lubricant was magnesium stearate. A double-layer compression machine was used to compress the manufactured granules. In vitro release tests revealed that formulation (F-TSH5) was 101.11% and 99.89%, respectively, and that the tablets containing a larger percentage of sodium starch glycolate exhibited good physical properties and were stable. After additional selection and comparison with the innovator product's release profile, the formulation T5H5 was discovered to have a f2 factor that was comparable to the marketed product. The findings point to the viability of creating telmisartan and hydrochlorothiazide bilayer pills for the convenience of hypertension patients.

Noor Alimed VH et al., (2013) In his work he creates a stable formulation of the hydrochlorothiazide and

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telmisartan bilayer tablet, an antihypertensive medication, and examined the dissolution profile. Wet granulation for telmisartan and direct compression for hydrochlorothiazide marked the beginning of the formulation development process. To increase solubility and drug release, telmisartan is dissolved in an aqueous solution of sodium hydroxide to yield its sodium salt. For the adjusted release profile over a three-hour period, several grades of polyethylene oxide were utilized as polymers. Microcrystalline cellulose serves as a binder and crospovidone as a super disintegrant in the direct compression of hydrochlorothiazide. The physical characteristics, drug content, and in vitro drug release of the tablets were assessed. According to FTIR measurements, the excipients utilized in this formulation did not change the drug's physicochemical characteristics. Non-Fickian transport of the medication from the tablets was verified, and this formulation also showed the best fit to zero order kinetics. For the fixed dose combination of telmisartan and hydrochlorothiazide, bilayer tablets made from the optimized formula (T4H5) were determined to be the most effective technique.

Ashutosh Kumar et al. (1990) In his research he Used a Symmetry C18 column (4.6 x 150mm, 5mm, Make: Hypersil) in isocratic mode, a new straightforward, accurate, exact, and repeatable RP-HPLC technique was created for the simultaneous estimation of Losartan Potassium, Ramipril, and Hydrochlorothiazide in bulk and in pharmaceutical dose form. Acetonitrile and potassium dihydrogen phosphate (KH_2PO_4) were combined in a 68:32 (%v/v) ratio to form the mobile phase. At 210 nm, the detection was performed. The percentage recoveries for hydrochlorothiazide, ramipril, and losartan potassium were determined to be 98.9–100.7%, 98.3–101.2%, and 98.0–100.8%, respectively. For Losartan (50.0 ppm-110.0 ppm), Ramipril (1.255 ppm-2.75 ppm), and Hydrochlorothiazide (12.5 ppm-27.5 ppm), the procedure was linear across the concentration range. The standard deviation of the response and the slope (s) of the calibration curve at an approximate level were used to calculate the method's Limit of Detection and Limit of Quantification. The results showed that the limits of detection for hydrochlorothiazide, ramipril, and losartan were 0.01, 0.078, and 0.07 µg/mL, respectively, while the limits of quantification for these three substances were 0.05, 0.27, and 0.24 µg/mL, respectively. The technique's validation was done with ICH- guidelines.

Nithin Kumar P et al., (2012) Developed the bilayer tablets with Metformin hydrochloride for prolonged release and Losartan potassium for instant release using PVP K-30 as a binder and various grades of Hydroxy Propyl Methyl Cellulose (HPMC K4M & HPMC K100M) as hydrophilic polymers. The wet granulation process was used to create the immediate and sustained release layers. The physiochemical characteristics of the pills were assessed. Every value was determined to be within acceptable bounds. Using USP type II paddle apparatus, in vitro release tests were conducted in 0.1N hydrochloric acid (pH 1.2) for the first two hours and phosphate buffer (pH 6.8) for the next eight hours as the dissolving medium.

Thomaset al., (2009) He revealed the simultaneous measurement of hydrochlorothiazide (Hctz), atenolol (Atn), and losartan potassium (Los) in combination tablet dose forms, two straightforward, precise, and repeatable spectrophotometric techniques have been devised. In the first approach, the simultaneous equation method is used to determine the concentration. The sampling wavelengths chosen for Hetz, Atn, and Los are 272.5 mm, 224 nm, and 250 nm, respectively, over the concentration ranges of 0.5-30 microg/ml, 1-50 microg/ml, and 1-60 microg/ml. With linearity in the concentration ranges of 0.5-30 microg/ml, 1-50 microg/ml, and 1-60 microg/ml, respectively, the sampling wavelengths chosen for the determination of Hetz, Atn, and Los are 280.5 nm, 233 nm, and 244 nm. The second approach is the First Order Derivative approach.

Different drug release profiles. Bi-layer tablets, which have a loading dose for rapid release and a maintenance dose for the second layer, are appropriate for both sustained release and the sequential release of two medications in combination. Bi-layer tablet use is therefore significantly different from combination therapy, which is frequently used for anti-hypertensive, diabetic, anti-inflammatory, and analgesic medications. Bi-layer tablets are currently being developed by a number of pharmaceutical companies for a number of purposes, including marketing, therapeutics, and patent extension. Although the fundamentals of tablet manufacture are still the same, there are a lot more

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factors to take into account because producing multi-layer tablets requires a number of frequently incompatible goods, extra equipment, and several formulation and operating difficulties. An overview of bi-layer tablet technology, bi-layer tablet manufacturing challenges, different tablet presses, quality and GMP requirements for their production, bi-layer tabletting techniques, and recent advancements in the field are all covered in this article.

Uday S Rangolectal. (2008) Hydrochlorothiazide is used as a model drug in the formulation and in vitro testing of fast disintegrating tablets employing direct compression technology. Using varying concentrations (2%, 3%, 4%, and 5%) of super disintegrants such as croscarmellose sodium and crospovidone, a fast-dissolving hydrochlorothiazide tablet was created. The Cadmach single punch tablet compression machine was used to prepare each batch utilizing the direct compression method with an 8 mm flat punch. The quickly disintegrating tablet was optimized based on the drug release and disintegration time. The prepared tablets' thickness, hardness, friability, weight uniformity, dissolving studies, and disintegration and wetting times were all assessed. Crospovidone at a concentration of 4% is chosen as the optimal formulation since it exhibits 100% drug release in 14 minutes and quick disintegration in 16 seconds.

Gupta Ankitet al. (2013) developed a flotation drug delivery system for the model drug hydrochlorothiazide and assessed the buyoncy and in vitro drug release tests, among other processing characteristics. Four formulations were created with different ratios of hydrophilic materials like acrypol, gas-generating agents like sodium bicarbonate, and polymers like HPMC K4M and ethylcellulose. For over eight hours, the pills stayed afloat in the release medium. The drug's release varied significantly depending on the polymer compositions. Every formulation demonstrated drug release that was dominated by diffusion and was determined to be stable.

Jaldbara S Patel et al. (2013) According to his thorough analysis, the cost and challenges of launching new drug entities have escalated over the last three decades. As the therapeutic benefits of controlled drug delivery have been recognized, more focus has been placed on creating drugs with sustained or controlled release formulations. With a number of qualities to offer an effective drug delivery mechanism, the bilayer tablet represents a new era in the development of controlled release formulations. For a number of significant medications, controlled release dose forms have been widely utilized to enhance treatment. The use of bilayer tablets differs greatly from that of analgesics and anti-inflammatory drugs. Bi-layer tablets can be used to separate two incompatible substances, release two medications sequentially, or create sustained release tablets with a maintenance dose in the second layer and quick release in the first layer. The upgraded, useful technology of the bilayer tablet addresses the drawbacks of the single-layered tablet. In the case of bilayered tablets, if the medicine is integrated into the upper nonadhesive layer, its administration into the entire oral cavity can be made nearly unidirectional.

Neela M Bhatia et al. (1998) Hydrochlorothiazide and losartan potassium are used together to treat hypertension. Their work focuses on developing a straightforward spectrophotometric approach for the simultaneous measurement of hydrochlorothiazide (HCT) and losartan potassium (LOS) in two-component tablet formulations. First order derivative spectroscopy is the technique used. 20 µg/ml of each of LOS and HCT were scanned in the 200–400 nm range in order to determine the sampling wavelength. In first order derivative spectroscopy, the sampling wavelengths were 257 nm for LOS where HCT exhibited zero crossing point and 243 nm for HCT where LOS showed zero crossing point. Linearity for this technique was found between 2.5 and 22.5 µg/ml for HCT and between 10 and 90 µg/ml for LOS.

AIM AND PLAN OF THE WORK:

AIM:

The aim of the present study is to formulate and evaluate bilayer film coated tablets of Losartan Potassium and hydrochlorothiazide.

PLAN OF WORK:

To Perform Preformulation studies:

- Identification study
- Solubility
- Ph
- Melting point
- Angle of repose

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- Bulk density
- Tapped density
- Carr's index
- Hausner's ratio
- Compatibility studies

Formulation of Bilayer Tablets:

- Optimization of formulation parameters using appropriate methods.
- Preparation of Losartan Potassium granules.
- Preparation of Hydrochlorothiazide granules.
- Compression of bilayer tablets containing Losartan Potassium and Hydrochlorothiazide.
- Coating of bilayer tablets containing Losartan Potassium and Hydrochlorothiazide

Evaluation:

Granules:

- Blend Uniformity Analysis for granules.

Compressed Bilayer tablets:

- Description
- Size and shape
- Weight variation
- Hardness
- Thickness
- Friability
- Content Uniformity
- Disintegration time.
- To develop suitable analytical method for the estimation of the drug
- Dissolution
- Assay

Accelerated stability studies of the most satisfactory formulation will be carried out as per ICH guidelines.

METHODS

Preformulation Studies

Preformulation is a phase of the development process where researchers define the mechanical, chemical, and physical characteristics of the drug material to create a dosage form that is safe, stable, and effective. Therefore, in order to properly design the drug delivery system, preformulation studies are necessary to characterize the drug. Among the preformulation investigations conducted for this project are those by Lachman L. et al. (1987).

Identification Study

It is intended to use FT-IR to conduct identification studies for both hydrochlorothiazide and losartan potassium.

Melting Point test:

The melting point of the drug is determined by using the melting point apparatus.

Organoleptic Properties:

Organoleptic characters of drug were observed and recorded by using descriptive terminology.

Drug-Excipients Compatibility Studies:

In the tablet dosage form, the medicine comes into close contact with one or more excipients, which may have an impact on the drug's stability. Therefore, formulators can choose the right excipients with the use of knowledge about drug-excipient interactions.

Methods: Compatibility studies were conducted by creating compatibility blends using the medicine and various excipient ratios based on the approximate average weight. The mixes were kept in accelerated storage at 40°C, 2°C, and 75±5% relative humidity.

The samples were stored in double-lined poly bags, and the medication to excipient ratio ranges from 1:1 to 1:5, depending on the intended application. Using a controlled sample that was kept at 40 degrees Celsius for 30 days, the sample was assessed for any changes in physical characterisation.

Physicochemical Interaction of drug and Excipients:

By using the Fourier Transform Infra-red spectrophotometer (FTIR) for the identification test, the physicochemical interaction of drag and excipients will be performed for both Losartan potassium and hydrochlorothiazide in accordance with USP.

Bulk density: Bulk density, expressed in grams per milliliter, is the ratio of a powder's weight to the bulk volume it occupies (Baloğlu E. et al., 2010). A weighed amount of a powder blend that had been shaken to break up any agglomerates was added to a powder blend whose volume had already been recorded.

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Tapped density: A measuring cylinder was filled with a weighed amount of powder blend that had been shaken to break up any agglomerates before the volume was recorded. In order to achieve a fixed drop of 3mm (±10%) at a nominal rate of 250 drops per hour, the cylinder was placed in the tapped density apparatus and allowed to fall onto a hard fice (USP-II) under its own weight. The tapping continued till the loudness didn't fluctuate any more. The following formula was utilized to determine the taped density.

Carr's Index: One significant metric that can be derived from the bulk and tapped densities is the Carr's Index. Theoretically, a material is more flowable the less compressible it is. A material is considered free flowing if its value is less than 20. The following is the formula for the Carr's Index

Hausner's Ratio: It is determined by the ratio of the tapped density to the bulk density and shows the powder's flow characteristics.

Angle of Repose: The frictional forces between granule particles are shown by the angle of repose. The angle of repose is the greatest angle that can exist between the granule pile's surface and the horizontal plane.

Assay

Calibration curve of Losartan Potassium and Hydrochlorothiazide.

A 100 ml volumetric flask was filled with precisely weighed 40 mg of Losartan potassium and 10 mg of Hydrochlorothiazide working standard, which were then dissolved in diluent (50 percent of the flask's capacity).It was diluted using Buffer A, which contains 0.4 mg/ml of losartan potassium and 0.1 mg/ml of hydrochlorothiazide.

Buffer Preparation: 0.5% Ammonium acetate in water. Filter and degas.

Mobile Phase Preparation: Mix 0.5% Ammonium acetate buffer and Acetonitrile in the ratio of 50:50.

Diluent Preparation: Mix water and acetonitrile in the ratio 50:50.

Standard Stock Preparation:

Solution A: Accurately weigh 50 mg of the working standard for losartan potassium in a 100 ml volumetric flask. Use diluent to dissolve and dilute to the mark. (500 parts per million)

Solution B: Accurately weigh 25 mg of the working standard hydrochlorothiazide in a 100 ml volumetric flask. Use diluent to dissolve and dilute to the mark. (250 parts per million)

Standard Preparation: Ten milliliters of solution A and five milliliters of solution B were pipetted into a 100-milliliter volumetric flask. Set the volume up to the diluent mark.

FORMULATION:

Losartan Potassium and Hydrochlorothiazide Bilayer Tablets:

Preparation of Losartan Part:

Mesh 308 was used for the weighing and sifting of Losartan Potassium, Microcrystalline Cellulose Plain, Starch Plain, and Polyplasdone XL10. The binder solution was moved to the granulated section along with the sifted materials. For fifteen minutes, the sifted material was combined in the quick mixer's main bowl (Prajapati SK. et al, 2012).

The main bowl of FBD received the sifted materials. At 50 degrees Celsius, the granules are dry. Using knives moving at a medium speed, the semi-dried granules were filtered through Mesh 208 and the remaining granules were then run through a Multi-Mill equipped with a 1.0 mm screen (Behera AK. et al., 2010). The milled granules were moved into the FBD bowl after

being semi-dried and sifted. dried till the necessary LOD was reached at 50 degrees Celsius. Verify the granules' LOD (Limit: 2.0–4.0% w/w at 105 C).

Ingredient	**L_1 (Mg/tab)**	**L_2 (Mg/tab)**	**L_3 (Mg/tab)**	**L_4 (Mg/tab)**	**L_5 (Mg/tab)**	**L_6 (Mg/tab)**	**L_7 (Mg/tab)**	**L_8 (Mg/tab)**
Losartan Potassium	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00

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MCC Plain	175.00	165.00	148.00	139.00	127.00	110.50	104.00	95.00
Starch Plain	-	10.00	10.00	15.00	15.00	25.00	25.00	30.00
Polyplasdone XL 10	-	-	5.00	5.00	7.00	7.00	9.00	11.00
P. Water(For Granulation)	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s
LUBRICATION								
Pregelatinized Starch	-	-	7.50	7.50	15.00	20.00	22.50	22.50
Polyplasdone XL 10	-	-	4.50	9.00	11.00	13.00	15.00	17.00
Magnesium Stearate	4.50	4.50	4.50	4.50	4.50	4.50	4.50	4.50
Total Weight	230.0	230.0	230.0	230.0	230.0	230.0	230.0	230.0

Preparation of Hydrochlorothiazide:

Weighed and sieved through Mesh30 were hydrochlorothiazide pregelatinized starch, microcrystalline cellulose PH 102, cross carmellose sodium, and colloidal silicon dioxide. After passing through Mesh100g, brilliant blue lake was added to the blend mentioned above. moved the medication solution and the sifted materials to the granulated area. After loading the sifted material into the main bowl, put it to the blender along with the above mixture and mix for an additional five minutes.

Using a rotary compression machine, the lubricated granules of both parts were compressed to an average weight of 380.00 mg. utilizing a normal concave 13/32-inch punch. moved the isopropyl alcohol into a sanitized stainless steel container. Incorporate Brilliant Blue Jake into a portion of isopropyl alcohol, run it through a colloid mill, and then combine it with the remaining isopropyl alcohol. Add insta coat to the aforesaid solution while stirring constantly, and then add methylene chloride while stirring continuously. Make sure that the solution doesn't form any lumps. Visually strain the aforementioned solution using a 100% nylon cloth.

Ingredients	**H_1 (Mg/tab)**	**H_2 (Mg/tab)**	**H_3 (Mg/tab)**	**H_4 (Mg/tab)**	**H_5 (Mg/tab)**	**H_6 (Mg/tab)**
Hydrochlorothiazide	12.50	12.502	12.503	12.504	12.505	12.506
MCC pH102	111.00	101.00	84.00	82.00	78.50	76.50
Pregelatinized Starch	25.00	35.00	50.00	50.00	50.00	50.00
Colloidal silicon dioxide	-	-	-	1.50	1.50	1.50
Croscarmellose sodium	-	-	2.00	2.00	6.00	8.00
Brilliant Blue Lake	0.50	0.50	0.50	0.50	0.50	0.50
Magnesium Stearate	1.00	1.00	1.00	1.00	1.00	1.00
Total	137. 50	137. 50	137. 50	137. 50	137. 50	137. 50

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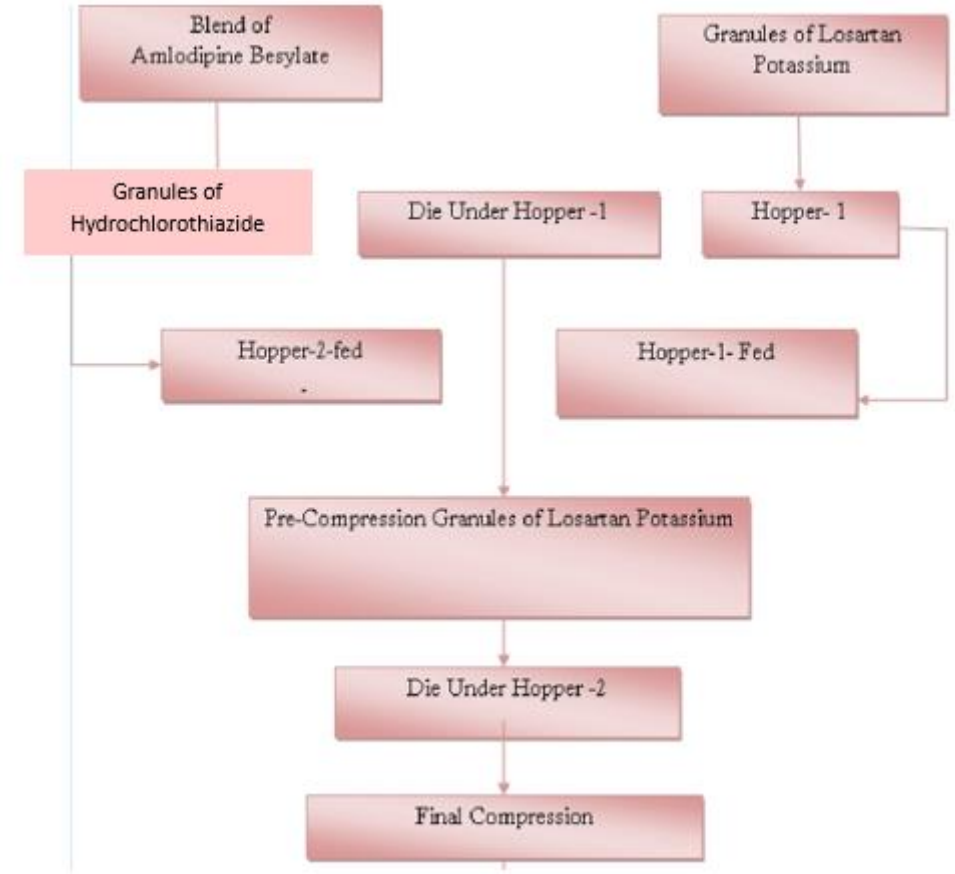
Compression of Bi-layer Tablet:

Using 13/32-inch circular standard plain punches, 27 stationary double rotary compression machines (Cadmach, India) were used to mildly compress the amount of granules for the immediate-release layer. 2012; Nithi Kumar, P. et al. To create a bilayer tablet of immediate release of hydrochlorothiazide and immediate release of losartan potassium, the necessary amount of the second immediate release layer was layered on top of this compressed layer and crushed until the hardness was between 6 and 8 kg/cm². Next, an evaluation was conducted on the compressed bilayer tablets. DP. Pattanayak et al. (2011).



Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
LOSARTAN POTASSIUM LAYER								
Losartan Potassium	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00
MCC Plain	175.00	165.00	148.00	139.00	127.00	110.50	104.00	95.00
Starch Plain	-	10.00	10.00	15.00	15.00	25.00	25.00	30.00
Polyplasdone XL 10	-	-	5.00	5.00	7.00	7.00	9.00	11.00
P.Water(For Granulation)	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s
LUBRICATION								

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Pregelatinized Starch	-	-	7.50	7.50	15.00	20.00	22.50	22.50
Polyplasdone XL 10	-	-	4.50	9.00	11.00	13.00	15.00	17.00
Magnesium Stearate	4.50	4.50	4.50	4.50	4.50	4.50	4.50	4.50
HYDROCHLOROTHIAZIDE LAYER								
Hydrochlorothiazide	12.50	12.502	12.503	12.504	12.505	12.506	12.506	12.506
MCC pH102	111.00	101.00	84.00	82.00	78.50	76.50	76.50	76.50
Pregelatinized Starch	25.00	35.00	50.00	50.00	50.00	50.00	50.00	50.00
Colloidal silicon dioxide	-	-	-	1.50	1.50	1.50	1.50	1.50
Croscarmellose sodium	-	-	2.00	2.00	6.00	8.00	8.00	8.00
Brilliant Blue Lake	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
LUBRICATION								
Magnesium Stearate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Total	380.00	380.00	380.00	380.00	380.00	380.00	380.00	380.00

7.4 – EVALUATION:

7.4.1 – Evaluation of Granules:

Blend Uniformity Analysis:

Following blending, the granules will be weighed from various blender positions to determine their drug concentration. The weight of each granule will be equivalent to the average weight of the tablet.

7.4.2 – Evaluation of Tablets.

Evaluation of Physical Characteristics:

The formulated tablets were evaluated for the following physical parameters

Thickness: Die filling and the physical characteristics of the material to be compressed determine thickness. There is a chance that each tablet in a batch will vary slightly in thickness. However, it shouldn't be visible to the naked eye. A verniercaliper can be used to measure the diameter and thickness.

Hardness: The tablet needs to be strong enough or hard enough to be measured by a Monsanto hardness tester. From each formulation, ten tablets were chosen at random, and their hardness—which may be represented in kg/cm²—was assessed.

Friability: The Roche friabilator can be used to perform friability. Ten tablets that had been previously weighed were added to the friabilator. After that, the machine was turned 100 times. With every revolution, tablets were falling from a six-inch distance. After that, the tablets were reweighed and dusted. Weight loss of less than 1% is seen as acceptable and falling within the parameters.

Weight variation Test: A total of twenty tablets were chosen at random and weighed separately. Determine the average weight of each tablet and compare it to the average. None of the individual weights differ from the average weight by more than twice the percentage, and no two diverge from the average weight by more than the percentage indicated in the table.

Table: -USP Specification for weight variation

Average weight of Tablet (mg)	**Percentage different allowed**
130 or less	10

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From 130 Through 324	7.5
324 or more	5

Disintegration Time: USP disintegration test equipment was used to calculate the in-vitro disintegration time. One disk was added to each of the apparatus's six tubes, and one tablet was put into each tube. It was measured in seconds how long it took for the tablet to completely dissolve and leave no discernible mass in the sieve or mesh.

Analytical development: To develop suitable analytical method for the estimation of the drug using HPLC.

Dissolution Test: The purpose of this test is to ascertain if solid Josage forms taken orally comply with the dissolving requirements. The test is designed for tablets or capsules. Unless instructed otherwise, use Apparatus 1. all of the equipment's components that could interact with the preparation.

They are chemically inert, meaning they don't adsorb, react, or obstruct the preparation being examined or the dissolving media. To guarantee that they don't react or obstruct the preparation being examined or the dissolution medium, all metal components of the apparatus that might come into contact with them must be made of stainless steel, type 316 or an equivalent, or coated with an appropriate substance. Beyond what is caused by the smoothly rotating element, no component of the assembly—including the surroundings in which it is placed—contributes appreciably to motion, agitation, or vibration. It is better to use a device that allows you to watch the preparation being tested as well as the stirrer.

A cylindrical tank with a hemispherical bottom, a nominal capacity of 1000 rni, and an internal diameter of 98–106 mm that is constructed of borosilicate glass or any other appropriate transparent material. The vessel has an upper rim that is flanged, and it has a cover with several apertures, including a central one.

A motor with a speed regulator that can keep the paddle's rotational speed within 4% of the specific monograph's specified limit. The motor has a stirring element that is made up of a paddle-shaped blade and drive shaft.

Stability study: According to ICH recommendations, the impact of temperature and humidity on the medications' chemical and physical properties will be assessed. The pills will be stored in a stability chamber (Oswald, Mumbai) for three months at 40°C/75% RH and 25°C/60% RH in blister packaging. Tablets were removed after a month and assessed for appearance, average weight, assay, and in vitro drug release.

7.5 – FILM COATING

A film coating is a thin layer of polymer-based material that is applied to a tablet or other solid dosage form. Such coatings typically range in thickness from 20 to 100 µm. If the film structure is closely examined, it appears to be relatively non-uniform and significantly different from a film formed by casting a polymer solution on a flat surface.

Film Coating Formulations:

- Polymer
- Plasticizer
- Colourants/Opacifiers
- Solvent/Vehicle

8. RESULT AND DISCUSSION

8.1 PREFORMULATION STUDIES:

Evaluation of API

It was determined as per procedure given in the methodology.

		Losartan Potassium	**Hydrochlorothiazide**
S. No	**Test**	**Observation**	**Observation**
1	Description	White to off-white	White to off-white crystalline powder

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		crystalline powder	
2	Water Content	NMT 2%	NMT 2%
3	Loss on drying	NMT 1.0 – 1.5%	NMT 1.0 – 1.5%
4	Solubility	Freely soluble in water and slightly soluble in ethanol (95%)	Freely soluble in water and slightly soluble in ethanol 95%)
5	Particle size distribution	Moderately coarse powder	Moderately coarse powder
6	Hygroscopicity	Non - hygroscopic	Non - hygroscopic
7	Melting Point	145 degree Celsius.	145 degree Celsius.

8.2 – DRUG – EXCIPIENTS COMPACTIBILITY STUDIES

It was determined as per procedure given in the methodology the results were tabulated as follows illustrates. (NCC- No Characteristic Change.)

S. No	**Composition**	**Initial**	**Condition**			
			40 C ± 2 C / 75 ± 5% RH			
			7 Days	**14 Days**	**30 Days**	**Conclusion**
1	Losartan Potassium	White Crystalline Powder	NCC	NCC	NCC	Complies
2	Losartan Potassium + Crospovidone XL 10	White or White crystalline powder	NCC	NCC	NCC	Complies
3	Losartan Potassium + Micro crystalline cellulose Plain		NCC	NCC	NCC	Complies
4	Losartan Potassium + Starch Plain		NCC	NCC	NCC	Complies
5	Losartan Potassium +Magnesium Stearate		NCC	NCC	NCC	Complies
6	Hydrochlorothiazide + Pregelatinized Starch		NCC	NCC	NCC	Complies
7	Hydrochlorothiazide + Micro crystalline cellulose PH 102		NCC	NCC	NCC	Complies
8	Hydrochlorothiazide + Croscarmellose sodium		NCC	NCC	NCC	Complies

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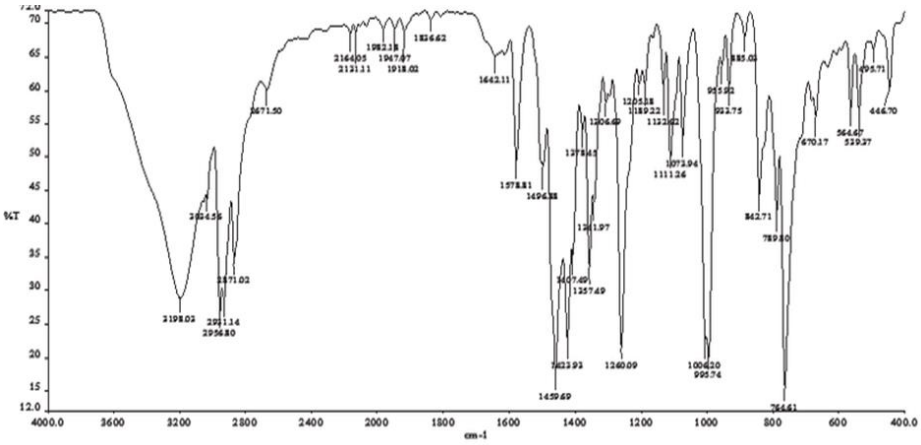
9	Hydrochlorothiazide + Magnesium Stearate		NCC	NCC	NCC	Complies
10	Hydrochlorothiazide + Colloidal silicon dioxide		NCC	NCC	NCC	Complies

8.3 – DRUG – EXCIPIENT INTERACTION STUDY



S:NO	WAVE NUMBER	SINGLE ASSIGNMENT
1	3197	OH - Stretch
2	3178	NH - Stretch
3	2956	C- H Aliphatic Stretch
4	754	C – CL Stretch
5	997	C – O Stretch
6	1615	C = N Stretch
7	1518	C = C Stretch
8	1008	C – N Stretch

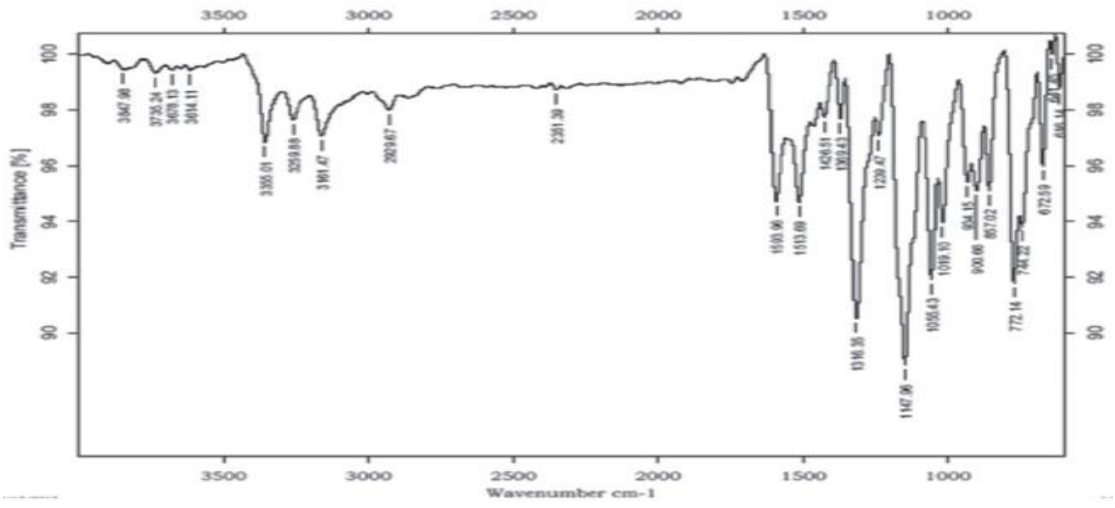


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Table: - FT- IR Spectral Value of Hydrochlorothiazide

S. No	Wave Number (Cm^{-1})	Signal Assignment
1	3363	N- H Stretch
2	3093	Aromatic C- H
3	2945	C- H Aliphatic Stretch
4	1604	C = C Stretch
5	1190	S = O Stretch
6	777	C – Cl Stretch
7	1508	C – N Stretch

8.4 - PRECOMPRESSION PARAMETER

It was determined as per procedure given in the methodology. The results were tabulated as follows.

Table: -Precompression parameters for Losartan Potassium layer blend

Formulation Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Hauner's Ratio	Carr's Index (%)	Angle of Respose (Ɵ)	Moisture content (%)
L1	0.488±0.002	0.605±0.002	1.17±0.01	19.39±0.89	30.4°±1.40	4.3±0.2
L2	0.479±0.003	0.604±0.006	1.25±0.01	20.60±1.12	31.7°±1.23	4.4±0.2
L3	0.491±0.001	0.617±0.001	1.26±0.03	20.89±1.45	32.5°±0.95	4.5±0.1
L4	0.487±0.002	0.612±0.002	1.25±0.01	20.41±1.23	31.8°±0.89	4.2±0.2
L5	0.490±0.007	0.599±0.002	1.09±0.02	18.19±1.16	26.2°±1.15	4.5±0.1
L6	0.479±0.008	0.605±0.001	1.26±0.01	20.82±1.31	29.9°±1.63	4.1±0.2
L7	0.486±0.009	0.609±0.003	1.25±0.02	20.32±0.93	29.4°±1.34	4.3±0.1
L8	0.477±0.005	0.600±0.004	1.25±0.02	20.51±0.96	30.3°±0.90	4.2±0.1

All the values are expressed as mean ±standard deviation; n=3

It was referred that all the pre compression parameters (bulk density, tapped density, hausner's ratio, Carr's index, angle of repose & moisture content) of all trials (L1 to LS) of losartan potassium blend were within the limit.

Table: - Precompression parameters for Hydrochlorothiazide blend

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's Ratio	Carr's Index %	Angle of Repose (Ɵ)
H1	0.434±0.002	0.540±0.001	1.24± 0.01	19.62±0.65	26.30.98 ±°
H2	0.423±0.001	0.554±0.003	1.30± 0.01	23.64±0.87	29.81.17 ±°
H3	0.478±0.002	0.522±0.004	1.09± 0.03	08.42±1.11	28.80.75 ±°
H4	0.495±0.004	0.558±0.002	1.12± 0.01	16.66±0.87	28.6±0.88°
H5	0.478±0.001	0.557±0.002	1.18± 0.02	16.16±0.45	29.4±1.24°
H6	0.498±0.003	0.587±0.003	1.17± 0.02	15.16±0.72	28.4±1.32°

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All the values are expressed as mean standard deviation; n=3

It was referred that all the pre compression parameters (bulk density, tapped density, hausner's ratio, Carr's index, angle of repose & moisture content) of all trials (L1 to L8) of losartan potassium blend were within the limit.

Table: - Precompression parameters for Hydrochlorothiazide blend

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's Ratio	Carr's Index %	Angle of Repose (Ɵ)
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H3	0.478±0.002	0.522±0.004	1.09± 0.03	08.42±1.11	28.80.75 ±°
H4	0.495±0.004	0.558±0.002	1.12± 0.01	16.66±0.87	28.6±0.88°
H5	0.478±0.001	0.557±0.002	1.18± 0.02	16.16±0.45	29.4±1.24°
H6	0.498±0.003	0.587±0.003	1.17± 0.02	15.16±0.72	28.4±1.32°

All the values are expressed as mean standard deviation; n=3

It was referred that all the pre compression parameters (bulk density, tapped density, hausner's ratio, Carr's index, angle of repose & moisture content) of all trials (L1 to L8) of losartan potassium blend were within the limit.

Table: - Post compression parameters for core bilayer tablets

Batch	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintegration Time (minutes & sec)
F-1	4.81±0.011	2.4±0.57	1.22	11.53
F-2	4.78±0.015	4.3±0.73	1.19	10.14
F-3	4.80±0.014	5.8±0.34	1.13	19.40
F-4	4.77±0.012	6.9±0.69	0.09	17.47
F-5	4.77±0.011	6.5±0.76	0.15	15.18
F-6	4.78±0.010	6.4±0.43	0.22	14.41
F-7	4.74±0.011	6.9±0.67	0.18	13.25
F-8	4.74±0.013	6.1±0.82	0.17	5.30

In F1 formulation the hardness was very low 2.3 kg/cm² and friability was high. The F2 & F3 formulation was improved with hardness but friability & disintegration time was not within the limit.F4 & F5 formulation satisfied all the parameters except the disintegration time, further batches from F6 to F8 showed satisfactory results

Table: -Post compression parameters for coated tablets.

Batch	Thickness (mm)	Disintegration Time (minutes & sec)	Assay
F -7	4.97 ± 0.011	14.44	L-98.9%
			H – 100.9 %
F -8	4.91 ± 0.014	7.45	L – 102.5%
			H – 103.9%

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Table: -Weight Variation Test

Batch	F1	F2	F3	F4	F5	F6	F7	F8
Average weight	392±0.71	391±0.84	394±0.71	399±0.78	398±0.63	395±0.82	390±0.68	393±0.69
% max Positive deviation	+1.98	+3.23	+ 2.76	+ 1.98	+ 2.41	+ 3.14	+ 2.23	+ 2.65
% min Negative deviation	-1.34	-2.75	-1.87	-2.75	-2.63	-2.25	-1.87	-1.98

Table: -Evaluation Parameter of bilayer Film Coated Tablets.

Batch	Thickness (mm)	Disintegration time (min & sec)	Weight variation (mg)	Drug Release (%)	Assay (%)
F7	4.97 ± 0.011	14.44 ± 0.25	390 ± 0.68	L – 81. 0	L – 98.9
				H – 83. 40	H – 100.9
F8	4. 91 ± 0.014	7.45 ± 0.25	393 ± 0.68	L – 87.9	L – 102. 5
				H – 90. 0	H – 103. 9

All the values are expressed as mean's, n= 3.

Inference:

F7 Formulation the percentage of drug release was failed (81% to 48%).

F8 Formulation was improved with dissolution enhancer.

Table: -Evaluation data of Uncoated and Film coated Losartan Potassium and Hydrochlorothiazide.

Batch	Thickness	Disintegration time. (minutes & sec)	Weight variation (mg)	Drug release (%)	Assay (%)
F8 Film Coated	4.91± 0.014	7.45±0.25	393±0.69	L – 87.9	L – 102.5
				H – 90.0	H- 103.9
F8 Un Coated	4.71±0.013	5.30+0.15	390±0.68	L – 89.2	L – 103.1
				H – 94.8	H – 104. 0

All the values are expressed as mean's, n= 3.

9. SUMMARY AND CONCLUSION

Losartan Potassium is a selective angiotensin II receptor blocking agent. It is useful mainly in the treatment of hypertension. It has a short biological half-life of 2 hours and its dose 40-80mg daily in divided doses.

The thiazide class of diuretics includes hydrochlorothiazide. By exerting pressure on the kidneys to decrease sodium (Na) reabsorption in the distal convoluted tubule, it lowers blood volume. Water loss and natriuresis are caused by hydrochlorothiazide. Furthermore, HCTZ is thought to reduce peripheral vascular resistance through additional pathways. A combination of hydrochlorothiazide and losartan potassium was recommended for the effective management of anti-diuretics and hypertension.

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The present research was carried out to develop a Immediate Release Bilayer tablet of Losartan Potassium and Hydrochlorothiazide and in this study an attempt was made to prepare Bilayer tablet of Losartan Potassium and Hydrochlorothiazide with excipients like MCC plain, Crosspovidone XL 10, Starch & Magnesium stearate for Losartan Potassium release layer and pre gelatinised starch, CCS, aerosil & Magnesium stearate for hydrochlorothiazide release layer.

The preformulation studies were carried out which ruled out the interaction between the drug and excipients used in the formulations. Eight formulations were prepared and were evaluated for hardness, friability, weight variation, drug content uniformity, in vitro drug release and stability studies. Six formulations (F1-F6) were failed as evaluation parameters did not match with the USP specifications. Finally F7 and F8 Formulation were selected for coating and evaluation.

Film coating was performed using conventional coating pan and the formulation characteristics such as, thickness, hardness, friability drug content and in vitro drug release were evaluated. Among the formulation, F8 ((5%) of Crosspovidone XL 10 for losartan release and CCS (4%) for Hydrochlorothiazide release) showed acceptable pharmaco-technical propertiesand complied with the internal specification for weight variation, thickness, hardness, friability, drug content and in vitro drug release. Stability profile of bilayer tablets were found to be satisfactory Reproducibility was checked by intra batch variability study and found no pronounced variation was observed.

Hence, it was finally concluded that, the Bilayer tablet technology can be successfully applied for Losartan Potassium and Hydrochlorothiazide release for once daily administration.

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